Bibliographie sur les maladies neuromusculaires

Bibliography of neuromuscular disorders

n° 2021-09-1 du 27 août au 9 septembre 2021 (August 27 to September 9, 2021)

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COVID-19 et maladies neuromusculaires – *COVID-19 and neuromuscular diseases*

1. Neuromuscul Disord . 2021 May 7;S0960-8966(21)00122-X.Online ahead of print.

A web-based questionnaire survey on the influence of coronavirus disease-19 on the care of patients with muscular dystrophy

Tsuyoshi Matsumura [1], Hiroto Takada [2], Michio Kobayashi [3], Takashi Nakajima [4], Katsuhisa Ogata [5], Akinori Nakamura [6], Michinori Funato [7], Satoshi Kuru [8], Kiyonobu Komai [9], Naonobu Futamura [10], Yoshiki Adachi [11], Hajime Arahata [12], Takayasu Fukudome [13], Masatoshi Ishizaki [14], Shugo Suwazono [15], Masashi Aoki [16], Tohru Matsuura [17], Masanori P Takahashi [18], Yoshihide Sunada [19], Kouzou Hanayama [20], Hiroya Hashimoto [21], Harumasa Nakamura [22]

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- [5] Dept. of Clinical Research, NHO Higashisaitama Hosp., Kurohama 4147, Hasuda, Saitama 349-0196, Japan.
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- [9] Dept. of Neurology, NHO Iou Hosp., 2-73-1 Iwade-machi, Kanazawa, Ishikawa 920-0171, Japan.
- [10] Dept. of Neurology, NHO Hyogo-Chuo Hosp., 1314 Ohara, Sanda, Hyogo 669-1516, Japan.
- [11] Dept. of Clinical Research, NHO Matsue Medical Center, 5-8-31 Agenoki, Matsue, Shimane 690-8556, Japan.
- [12] Dept. of Neurology, NHO Omuta Hosp., Omuta, Fukuoka 837-0911, Japan.
- [13] Dept. of Neurology, NHO Nagasaki Kawatana Medical Center, 2005-1 Shimogumigo, Kawatana, Nagasaki-1 859-3615, Japan.
- [14] Dept. of Neurology, NHO Kumamoto Saishunso Medical Center, 2659 Suya, Goushi, Kumamoto 861-1196, Japan.
- [15] Dept. of Neurology, NHO Okinawa Hosp., 3-20 Ganeko, Ginowan, Okinawa 901-2214, Japan.
- [16] Dept. of Neurology, Tohoku Univ. School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.
- [17] Dept. of Neurology, Jichi Medical Univ., 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan.
- [18] Dept. of Functional Diagnostic Science, Osaka Univ. Graduate School of Medicine, 1-7 Yamadaoka, Suita, Osaka 565-0871, Japan.
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- PMID: 34462178
- PMCID: PMC8102088
- DOI: 10.1016/j.nmd.2021.04.008

To clarify the influence of coronavirus disease-19 (COVID-19) on the care of muscular dystrophy patients, we performed a questionnaire survey that was posted on the internet on May 11, 2020. By the end of July 2020, 542 responses had been collected. Approximately 30% of patients postponed regular consultations, and one-quarter of patients who received consultation more than once a month used telephone consultations. Two of 84 patients with Duchenne muscular dystrophy had reduced their steroid doses. A shortage of ventilator accessories and infection protection equipment occurred following the onset of COVID-19, and this shortage had a serious impact on medical care and infection prevention measures. Reductions in rehabilitation and other services, and avoidance of outings, led to a decrease in exercise and an increase in caregiver burden. Inpatients were restricted from going out and visiting family members. More than 20% of patients reported physical or mental complaints; however, few required treatment. COVID-19 has seriously affected the activities and quality of life of patients with muscular dystrophy. We will continue this survey and analyze the longitudinal changes.

Keywords: Activities of daily living; Coronavirus disease-19; Muscular dystrophy; Quality of life; Respiratory care; Undersupply.

ELSEVIER FULL-TEXT ARTICLE

2. Cleve Clin J Med . 2021 Sep 1;88(9):484-486. doi: 10.3949/ccjm.88a.20204.

Dermatomyositis-related interstitial lung disease mimicking COVID-19 pneumonia

Satoshi Hayano [1], Kenichiro Tokunaga [2], Yusuke Imamura [3], Hideto Oshikawa [3]

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- PMID: 34470751
- DOI: 10.3949/ccjm.88a.20204

No abstract available

Amyotrophies bulbospinales – *Bulbospinal amyotrophies*

3. J Laryngol Otol . 2021 Sep 9;1-23. doi: 10.1017/S0022215121002395. Online ahead of print.

The audiovestibular profile of Brown-Vialetto-Van Laere syndrome

R Omar [1], K Rajput [2], T Sirimanna [2], S Rajput [3], W Pagarkar [2]

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- PMID: 34496984
- DOI: 10.1017/S0022215121002395

No abstract available

Review

4. Curr Opin Neurobiol . 2021 Sep 3;72:39-47. doi: 10.1016/j.conb.2021.07.001. Online ahead of print.

Polyglutamine diseases

Emma L Bunting [1], Joseph Hamilton [1], Sarah J Tabrizi [2]

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- PMID: 34488036
- DOI: 10.1016/j.conb.2021.07.001

Polyglutamine diseases are a collection of nine CAG trinucleotide expansion disorders, presenting with a spectrum of neurological and clinical phenotypes. Recent human, mouse and cell studies of Huntington's disease have highlighted the role of DNA repair genes in somatic expansion of the CAG repeat region, modifying disease pathogenesis. Incomplete splicing of the HTT gene has also been shown to occur in humans, with the resulting exon 1 fragment most probably contributing to the Huntington's disease phenotype. In the spinocerebellar ataxias, studies have converged on transcriptional dysregulation of ion channels as a key disease modifier. In addition, advances have been made in understanding how increased levels of toxic, polyglutamine-expanded proteins can arise in the spinocerebellar ataxias through post-transcriptional and -translational modifications and autophagic mechanisms. Recent studies in spinal and bulbar muscular atrophy implicate similar pathogenic pathways to the more common polyglutamine diseases, highlighting autophagy stimulation as a potential therapeutic target. Finally, the therapeutic use of antisense oligonucleotides in several polyglutamine diseases has shown preclinical benefits and serves as potential future therapies in humans.

Keywords: CAG repeat; Huntington's disease; Polyglutamine; Repeat expansion; Spinal and bulbar muscular atrophy; Spinocerebellar ataxias.

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n° 2021-09-1 du 27 août au 9 septembre 2021 (August 27 to September 9, 2021)

Amyotrophies spinales – *Spinal amyotrophies*

5. Am J Phys Med Rehabil . 2021 Sep 2. doi: 10.1097/PHM.0000000000001869. Online ahead of print.

Systematic review of motor function scales and patient reported outcomes in spinal muscular atrophy

Jennifer W Wu [1], Laura Pepler, Bridget Maturi, Alexandria C F Afonso, Janice Sarmiento, Renee Haldenby

- [1] From Hoffmann-La Roche Limited, Mississauga, Ontario, Canada (JW, LP, BM, RH); and Synapse Medical Communications Inc., Oakville, Ontario, Canada (AA, JS).

- PMID: 34483260
- DOI: 10.1097/PHM.0000000000001869

Spinal muscular atrophy (SMA) is a heterogeneous disease that results in loss of motor function. In an evolving treatment landscape, establishing the suitability and limitations of existing motor function scales and patient-reported outcomes (PROs) used to monitor patients with this disease is important. A systematic review was conducted to examine utility of motor function scales and PROs in evaluating patients with SMA. Published literature was reviewed up to June 2021 with no start date restriction. Of the reports screened, 122 were deemed appropriate for inclusion and are discussed in this review (including 24 validation studies for motor function scales or patient reported outcomes). Fifteen motor function scales and PROs were identified to be commonly used (≥5 studies), of which 11 had available validation assessments. Each instrument has its strengths and limitations. It is imperative that the patient population (e.g., age, mobility), goals of treatment, and outcomes or endpoints of interest be considered when selecting the appropriate motor function scales and PROs for clinical studies.

Amyotrophie spinale proximale liée à SMN1 – *SMN1-related spinal muscular atrophy (SMA)*

Review

6. Neurol Clin Pract . 2021 Aug;11(4):e524-e536. doi: 10.1212/CPJ.0000000000000872.

Molecular Biomarkers for Spinal Muscular Atrophy: A Systematic Review

Angela Navarrete-Opazo [1], Sheldon Garrison [1], Mindy Waite [1]

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- PMID: 34484951
- PMCID: **PMC8382389** (available on 2022-08-01)
- DOI: 10.1212/CPJ.0000000000000872

Background: There is an unmet need for reliable biomarkers to predict disease severity, prognosis, and treatment effect in patients with spinal muscular atrophy (SMA). The purpose of this review is to evaluate the clinical utility of blood-based biomarkers in patients with SMA.

Methods: A systematic review of MEDLINE, DARE, PEDro, PsycINFO, Cochrane Database, LILACS, OTSeeker, SpeechBITE, CINAHL, Scopus, Science Direct, clinicaltrial.gov, OpenGrey, and Google Scholar was performed with the last search data of June 30, 2019.

Results: Survival motor neuron (SMN)-related biomarkers showed an important interpatient and cell variability with a wide overlap between SMA phenotypes and healthy controls. Several plasma protein analytes correlated with motor scores; however, validation studies are needed to rule out false positives. DNA methylation analysis distinguished between patients with mild/moderate SMA and healthy controls. Plasma phosphorylated neurofilament heavy chain (pNF-H) levels increased with disease severity and declined considerably after nusinersen treatment.

Conclusion: There is no sufficient evidence to support the clinical utility of SMN-related biomarkers to predict disease severity in SMA. pNF-H appears to be a promising biomarker of disease activity and treatment effect in SMA. Further studies should include longitudinal assessments of patients with SMA across functional groups and comparisons with age-matched healthy controls to evaluate the stability of putative biomarkers over time and in response to SMA therapeutics. PROSPERO registration: CRD42019139050.

7. Ann Clin Transl Neurol . 2021 Sep 4. doi: 10.1002/acn3.51449. Online ahead of print.

Serum neurofilament light chain in pediatric spinal muscular atrophy patients and healthy children

Elisa Nitz [1], Martin Smitka [1], Jens Schallner [1], Katja Akgün [2], Tjalf Ziemssen [2], Maja von der Hagen [1], Victoria Tüngler [1,3]

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- PMID: 34482646
- DOI: 10.1002/acn3.51449

Objective: The aim of this study was to evaluate neurofilament light chain as blood biomarker for disease activity in children and adolescents with different types of spinal muscular atrophy (SMA) and establish pediatric reference values.

Methods: We measured neurofilament light chain levels in serum (sNfL) and cerebral spinal fluid (cNfL) of 18 children with SMA and varying numbers of SMN2 copies receiving nusinersen by single-molecule array (SiMoA) assay and analyzed correlations with baseline characteristics and motor development. Additionally, we examined sNfL in 97 neurologically healthy children.

Results: Median sNfL levels in treatment-naïve SMA patients with 2 SMN2 copies are higher than in those with >2 SMN2 copies ($P < 0.001$) as well as age-matched controls ($P = 0.010$) and decline during treatment. The median sNfL concentration of healthy controls is 4.73 pg/mL with no differences in sex ($P = 0.486$) but age ($P < 0.001$). In all children with SMA, sNfL levels correlate strongly with cNfL levels ($r = 0.7$, $P < 0.001$). In children with SMA and 2 SMN2 copies, sNfL values correlate with motor function ($r = -0.6$, $P = 0.134$), in contrast to older SMA children with >2 SMN2 copies ($r = -0.1$, $P = 0.744$).

Interpretation: Reference sNfL values of our large pediatric control cohort may be applied for future studies. Strong correlations between sNfL and cNfL together with motor function suggest that sNfL may be a suitable biomarker for disease activity in children with 2 SMN2 copies and those with >2 SMN2 copies within their initial stages during early childhood.

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8. Orphanet J Rare Dis . 2021 Sep 4;16(1):375. doi: 10.1186/s13023-021-02015-9.

Growth patterns in children with spinal muscular atrophy

Ramona De Amicis [1], Giovanni Baranello [2,3], Andrea Foppiani [4], Alessandro Leone [4], Alberto Battezzati [4], Giorgio Bedogni [4], Simone Ravella [4], Ester Giaquinto [5], Chiara Mastella [6], Caterina Agosto [7], Enrico Bertini [8], Adele D'Amico [8], Marina Pedemonte [9], Claudio Bruno [10], Jonathan C Wells [11], Mary Fewtrell [11], Simona Bertoli [12,13]

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- PMID: 34481516
- PMCID: PMC8418717
- DOI: 10.1186/s13023-021-02015-9

Background: Spinal muscular atrophy (SMA) is a neuromuscular disorder characterized by muscle atrophy and weakness. SMA type 1 (SMA1) is the most severe form: affected infants are unable to sit unaided; SMA type 2 (SMA2) children can sit, but are not able to walk independently. The Standards of Care has improved quality of life and the increasing availability of disease-modifying treatments is progressively changing the natural history; so, the clinical assessment of nutritional status has become even more crucial. Aims of this multicenter study were to present the growth pattern of treatment-naïve SMA1 and SMA2, and to compare it with the general growth standards.

Results: Body Weight (BW, kg) and Supine Length (SL, cm) were collected using a published standardized procedure. SMA-specific growth percentiles curves were developed and compared to the WHO reference data. We recruited 133 SMA1 and 82 SMA2 (48.8% females). Mean ages were 0.6 (0.4-1.6) and 4.1 (2.1-6.7) years, respectively. We present here a set of disease-specific percentiles curves of BW, SL, and BMI-for-age for girls and boys with SMA1 and SMA2. These curves show that BW is significantly lower in SMA than healthy peers, while SL is more variable. BMI is also typically lower in both sexes and at all ages.

Conclusions: These data on treatment-naïve patients point toward a better understanding of growth in SMA and could be useful to improve the clinical management and to assess the efficacy of the available and forthcoming therapies not only on motor function, but also on growth.

Keywords: Growth; Nutritional status; Percentiles; Spinal muscular atrophy.

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9. Neurol Clin Pract . 2021 Jun;11(3):e317-e327. doi: 10.1212/CPJ.0000000000001033.

Nusinersen Treatment in Adults With Spinal Muscular Atrophy

Tina Duong [1], Connie Wolford [1], Michael P McDermott [1], Chelsea E Macpherson [1], Amy Pasternak [1], Allan M Glanzman [1], William B Martens [1], Elizabeth Kichula [1], Basil T Darras [1], Darryl C De Vivo [1], Zarazuela Zolkipli-Cunningham [1], Richard S Finkel [1], Michael Zeineh [1], Max Wintermark [1], Jacinda Sampson [1], Katharine A Hagerman [1], Sally Dunaway Young [1], John W Day [1]

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- PMID: 34476123
- PMCID: PMC8382360
- DOI: 10.1212/CPJ.0000000000001033

Objective: To determine changes in motor and respiratory function after treatment with nusinersen in adults with spinal muscular atrophy (SMA) during the first two years of commercial availability in the USA.

Methods: Data were collected prospectively on adult (age >17 years at treatment initiation) SMA participants in the Pediatric Neuromuscular Clinical Research (PNCR) Network. Baseline assessments of SMA outcomes including the Expanded Hammersmith Functional Rating Scale (HFMSE), Revised Upper Limb Module (RULM), and 6-Minute Walk Test (6MWT) occurred <5 months before treatment, and post-treatment assessments were made up to 24 months after nusinersen initation. Patient-reported experiences, safety laboratory tests and adverse events were monitored. The mean annual rate of change over time was determined for outcome measures using linear mixed effects models.

Results: Forty-two adult SMA participants (mean age: 34 years, range 17-66) receiving nusinersen for a mean of 12.5 months (range 3-24 months) were assessed. Several motor and respiratory measures showed improvement distinct from the progressive decline typically seen in untreated adults. Participants also reported qualitative improvements including muscle strength, stamina, breathing and bulbar related outcomes. All participants tolerated nusinersen with normal surveillance labs and no significant adverse events.

Conclusions: Trends of improvement emerged in functional motor, patient-reported, and respiratory measures, suggesting nusinersen may be efficacious in adults with SMA. Larger well-controlled studies and additional outcome measures are needed to firmly establish the efficacy of nusinersen in adults with SMA.

Classification of evidence: This study provides Class IV evidence regarding nusinersen tolerability and efficacy based on reported side effects and pulmonary and physical therapy assessments in an adult SMA cohort.

10. BMJ Neurol Open . 2021 Aug 12;3(2):e000164. doi: 10.1136/bmjno-2021-000164. eCollection 2021.

Persistent neuromuscular junction transmission defects in adults with spinal muscular atrophy treated with nusinersen

W David Arnold [1], Steven Severyn [2], Songzhu Zhao [3], David Kline [3], Matthew Linsenmayer [4], Kristina Kelly [1], Marco Tellez [1], Amy Bartlett [1], Sarah Heintzman [1], Jerry Reynolds [1], Gary Sterling [1], Tristan Weaver [2], Kiran Rajneesh [1], Arthur H M Burghes [5], Stephen J Kolb [1 5], Bakri Elsheikh [1]

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- PMID: 34466806
- PMCID: PMC8362737
- DOI: 10.1136/bmjno-2021-000164

Objective: Spinal muscular atrophy (SMA) is a motor neuron disease caused by low levels of survival motor neuron (SMN) protein. Prior work in models and patients has demonstrated electrophysiological and morphological defects at the neuromuscular junction (NMJ). Therapeutic development has resulted in clinically available therapies to increase SMN protein levels in patients and improve muscle function. Here we aimed to investigate the effect of SMN restoration (via nusinersen) on NMJ transmission in adults with SMA.

Methods: Participants undergoing nusinersen treatment underwent 3 Hz repetitive nerve stimulation (RNS) of the spinal accessory nerve to assess compound muscle action potential amplitude decrement. Maximum voluntary isometric contraction (MVICT), Revised Upper Limb Module (RULM), and 6 min walk test (6MWT) were assessed for correlations with decrement.

Results: Data from 13 ambulatory (7 men/6 women, mean age 40±11 years) and 11 non-ambulatory (3 men/8 women, mean age 38±12 years) participants were analysed. Cross-sectional analyses of RNS decrement were similar at 14 months of nusinersen (-14.2%±11.5%, n=17) vs baseline (-11.9%±8.3%, n=15) (unpaired t-test, p=0.5202). Longitudinal comparison of decrement in eight participants showed no change at 14 months (-13.9%±6.7%) vs baseline (-16.9%±13.4%) (paired t-test, p=0.5863). Decrement showed strong correlations with measures of MVICT, RULM and 6MWT but not age or disease duration.

Conclusion: Adults with SMA had significant NMJ transmission defects that were not corrected with 14 months of nusinersen treatment. NMJ defects were negatively associated with physical function, and thus may represent a promising target for additive or combinatorial treatments.

Keywords: EMG; neuromuscular; spinal muscular atrophy.

11. Front Cell Dev Biol . 2021 Aug 11;9:639904. doi: 10.3389/fcell.2021.639904. eCollection 2021.

Fluorescence Correlation Spectroscopy Reveals Survival Motor Neuron Oligomerization but No Active Transport in Motor Axons of a Zebrafish Model for Spinal Muscular Atrophy

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- [2] Department of Biochemistry, Theodor-Boveri-Institut für Biowissenschaften (Biozentrum), University of Wuerzburg, Wuerzburg, Germany.
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- PMID: 34458251
- PMCID: PMC8385639
- DOI: 10.3389/fcell.2021.639904

Spinal Muscular Atrophy (SMA) is a progressive neurodegenerative disease affecting lower motor neurons that is caused by a deficiency in ubiquitously expressed Survival Motor Neuron (SMN) protein. Two mutually exclusive hypotheses have been discussed to explain increased motor neuron vulnerability in SMA. Reduced SMN levels have been proposed to lead to defective snRNP assembly and aberrant splicing of transcripts

that are essential for motor neuron maintenance. An alternative hypothesis proposes a motor neuron-specific function for SMN in axonal transport of mRNAs and/or RNPs. To address these possibilities, we used a novel *in vivo* approach with fluorescence correlation spectroscopy (FCS) in transgenic zebrafish embryos to assess the subcellular dynamics of Smn in motor neuron cell bodies and axons. Using fluorescently tagged Smn we show that it exists as two freely diffusing components, a monomeric, and a complex-bound, likely oligomeric, component. This oligomer hypothesis was supported by the disappearance of the complex-bound form for a truncated Smn variant that is deficient in oligomerization and a change in its dynamics under endogenous Smn deficient conditions. Surprisingly, our FCS measurements did not provide any evidence for an active transport of Smn in axons. Instead, our *in vivo* observations are consistent with previous findings that SMN acts as a chaperone for the assembly of snRNP and mRNP complexes.

Keywords: active transport; fluorescence correlation spectroscopy; motor axons; smn oligomerization; spinal muscular atrophy; survival motion neuron; zebrafish.

OPEN ACCESS frontiers

12. Brain Dev . 2021 Aug 24;S0387-7604(21)00152-2. doi: 10.1016/j.braindev.2021.08.002. Online ahead of print.

Epidemiological investigation of spinal muscular atrophy in Japan

Mayuri Ito [1], Akemi Yamauchi [1], Mari Urano [1], Tamaki Kato [1], Mari Matsuo [1], Kenji Nakashima [2], Kayoko Saito [3]

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- PMID: 34452804
- DOI: 10.1016/j.braindev.2021.08.002

Background: International reporting of epidemiological surveys of spinal muscular atrophy (SMA) in Japan has been limited to Shikoku, despite the epidemiology of the disease in countries worldwide becoming clearer. Treatments of 5q-SMA have been developed, and epidemiological studies are needed.

Purpose: This study aimed to conduct a nationwide epidemiological survey of SMA in Japan to clarify the actual situation of SMA in Japan.

Method: Patients with all clinical types of SMA, including neonates and adults, were selected from 1,005 medical facilities in Japan.

Results: As of December 2017, the actual number of reported patients with SMA was 658 and the genetic testing rate was 79.5%. The estimated number of patients was 1,478 (95% confidence interval (CI), 1,122-1,834), with a prevalence of 1.17 (95%CI, 0.89-1.45) per 100,000 people and an incidence of 0.51 (95%CI, 0.32-0.71) per 10,000 live births. Incidence rates of 5q-SMA by clinical type were 0.27 (95%CI, 0.17-0.38) and 0.08 (95%CI, 0.04-0.11) per 10,000 live births for type 1 and 2, respectively, in cases with a definitive diagnosis by genetic testing. We found that 363 cases (82.7%) occurred less than 2 years and 88 (20.0%) occurred age of 2 months old or under.

Conclusion: This study clarifies the prevalence and incidence of SMA in Japan. As infantile onset accounts for most cases of SMA, newborn screening and subsequent treatment are important to save lives.

Keywords: Epidemiology; Genetic testing; Incidence; Prevalence; Spinal muscular atrophy.

ELSEVIER FULL-TEXT ARTICLE

13. Int J Neonatal Screen . 2021 Jul 21;7(3):47. doi: 10.3390/ijns7030047.

Novel Modification of a Confirmatory SMA Sequencing Assay that Can Be Used to Determine *SMN2* Copy Number

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- PMID: 34449530
- PMCID: PMC8395917
- DOI: 10.3390/ijns7030047

Promising treatments for spinal muscular atrophy (SMA), the leading genetic cause of infant mortality, prompted calls for inclusion in newborn screening (NBS). In January 2018, the New England Newborn Screening Program (NENSP) began statewide screening for SMA using a tiered algorithm looking for the absence of *SMN1* Exon 7. When results from the first and second tier needed reconciliation, we developed and validated a third tier DNA sequencing assay to ensure the presence or absence of *SMN1* Exon 7. All nine infants referred to specialty centers through NBS showed single base substitution of c.840C>T, and were confirmed to have SMA. Further, a minor sequencing protocol modification allowed the estimation of *SMN2* copy number in SMA affected patients; we developed and validated a copy-number assay yielding 100% match with seven previously characterized specimens of SMA patients. All nine SMA-affected infants found through NBS were also assayed for *SMN2* copy number. Results were comparable but not 100% matched with those that were reported by independent diagnostic laboratories. In conclusion, a sequencing protocol confirms NBS findings from real-time qPCR, and its modified application allows NBS programs that have sequencing capabilities to provide *SMN2* copy numbers without the need for additional instrumentation.

Keywords: SMA; SMN2; copy number; newborn screening; sequencing.

FULL TEXT OPEN ACCESS MDPI

14. Int J Neonatal Screen . 2021 Aug 11;7(3):53. doi: 10.3390/ijns7030053.

Newborn Screening for 5q Spinal Muscular Atrophy: Comparisons between Real-Time PCR Methodologies and Cost Estimations for Future Implementation Programs

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- PMID: 34449526
- PMCID: PMC8396021
- DOI: 10.3390/ijns7030053

Since the approval of modifying therapies for Spinal Muscular Atrophy (SMA), several protocols aiming to screen *SMN1* homozygous deletion in a neonatal context have been published. However, no work has compared different methodologies along with detailed implementation costs for centers where the neonatal screening of SMA has not yet been implemented. Therefore, our work compared different qualitative real-time PCR approaches for SMA screening and the estimated costs of test implementation. Using Brazilian blood samples, the presence and absence (P/A) and melt curve protocols were analyzed. MLPA was used as a confirmatory test. The costs were calculated for the simplex and multiplex tests plus equipment. The test workflow was based on the present experience and literature report. The accuracy of the P/A protocol was 1 (95% CI 0.8677-1) using dried blood spots (DBS). The melt curve protocol also achieved 100% concordance. The consumable costs ranged from USD 1.68 to 4.42 and from USD 2.04 to 12.76 per reaction, for the simplex and multiplex tests, respectively. The equipment acquisition costs ranged from USD 44,817.07 to 467,253.10, with several factors influencing this value presented. Our work presents a framework for decision-making, with a project demonstration of the different assays that will be useful in dealing with the issues of cost and availability of reagents. Moreover, we present a literature review and discussion of important concerns regarding treatment policies. We take the first step towards a future SMA NBS pilot program where it is not yet a reality.

Keywords: SMN1; genetic diagnosis; neonatal screening; real-time PCR; screening test; spinal muscular atrophy.

FULL TEXT OPEN ACCESS MDPI

Review

15. Int J Mol Sci . 2021 Aug 21;22(16):9029. doi: 10.3390/ijms22169029.

The Importance of Digging into the Genetics of *SMN* Genes in the Therapeutic Scenario of Spinal Muscular Atrophy

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- PMID: 34445733
- PMCID: PMC8396600
- DOI: 10.3390/ijms22169029

After 26 years of discovery of the determinant survival motor neuron 1 and the modifier survival motor neuron 2 genes (*SMN1* and *SMN2*, respectively), three SMN-dependent specific therapies are already approved by FDA and EMA and, as a consequence, worldwide SMA patients are currently under clinical investigation and treatment. Bi-allelic pathogenic variants (mostly deletions) in *SMN1* should be detected in SMA patients to confirm the disease. Determination of *SMN2* copy number has been historically employed to correlate with the phenotype, predict disease evolution, stratify patients for clinical trials and to define those eligible for treatment. In view that discordant genotype-phenotype correlations are present in SMA, besides technical issues with detection of *SMN2* copy number, we have hypothesized that copy number determination is only the tip of the iceberg and that more deepen studies of variants, sequencing and structures of the *SMN2* genes are necessary for a better understanding of the disease as well as to investigate possible influences in treatment responses. Here, we highlight the importance of a comprehensive approach of *SMN1* and *SMN2* genetics with the perspective to apply for better prediction of SMA in positive neonatal screening cases and early diagnosis to start treatments.

Keywords: genotype-phenotype correlations; hybrid structure; spinal muscular atrophy; survival motor neuron 1; survival motor neuron 2; variants.

FULL TEXT OPEN ACCESS MDPI

Review

16. Int J Mol Sci . 2021 Aug 20;22(16):8962. doi: 10.3390/ijms22168962.

Drug Discovery of Spinal Muscular Atrophy (SMA) from the Computational Perspective: A Comprehensive Review

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- DOI: 10.3390/ijms22168962

Spinal muscular atrophy (SMA), one of the leading inherited causes of child mortality, is a rare neuromuscular disease arising from loss-of-function mutations of the survival motor neuron 1 (*SMN1*) gene, which encodes the SMN protein. When lacking the SMN protein in neurons, patients suffer from muscle weakness and atrophy, and in the severe cases, respiratory failure and death. Several therapeutic approaches show promise with human testing and three medications have been approved by the U.S. Food and Drug Administration (FDA) to date. Despite the shown promise of these approved therapies, there are some crucial limitations, one of the most important being the cost. The FDA-approved drugs are high-priced and are shortlisted among the most expensive treatments in the world. The price is still far beyond affordable and may serve as a burden for patients. The blooming of the biomedical data and advancement of computational approaches have opened new possibilities for SMA therapeutic development. This article highlights the present status of computationally aided approaches, including *in silico* drug repurposing, network driven drug discovery as well as artificial intelligence (AI)-assisted drug discovery, and discusses the future prospects.

Keywords: SMA; artificial intelligence; computational aided drug discovery; drug discovery; drug therapy; in silico drug repurposing; neuromuscular disorder; spinal muscular atrophy.

FULL TEXT OPEN ACCESS MDPI

17. Int J Mol Sci . 2021 Aug 6;22(16):8494. doi: 10.3390/ijms22168494.

What Genetics Has Told Us and How It Can Inform Future Experiments for Spinal Muscular Atrophy, a Perspective

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- DOI: 10.3390/ijms22168494

Proximal spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder characterized by motor neuron loss and subsequent atrophy of skeletal muscle. SMA is caused by deficiency of the essential *survival motor neuron* (SMN) protein, canonically responsible for the assembly of the spliceosomal small nuclear ribonucleoproteins (snRNPs). Therapeutics aimed at increasing SMN protein levels are efficacious in treating SMA. However, it remains unknown how deficiency of SMN results in motor neuron loss, resulting in many reported cellular functions of SMN and pathways affected in SMA. Herein is a perspective detailing what genetics and biochemistry have told us about SMA and SMN, from identifying the SMA determinant region of the genome, to the development of therapeutics. Furthermore, we will discuss how genetics and biochemistry have been used to understand SMN function and how we can determine which of these are critical to SMA moving forward.

Keywords: SMA; SMN function; SMN missense mutants; biochemistry; genetics; motor neuron; spinal muscular atrophy; suppressor screen; survival motor neuron.

FULL TEXT OPEN ACCESS MDPI

18. Int J Mol Sci . 2021 Aug 4;22(16):8378. doi: 10.3390/ijms22168378.

High Concentration of an ISS-N1-Targeting Antisense Oligonucleotide Causes Massive Perturbation of the Transcriptome

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- PMID: 34445083
- PMCID: PMC8395096
- DOI: 10.3390/ijms22168378

Intronic splicing silencer N1 (ISS-N1) located within *Survival Motor Neuron 2* (*SMN2*) intron 7 is the target of a therapeutic antisense oligonucleotide (ASO), nusinersen (Spinraza), which is currently being used for the treatment of spinal muscular atrophy (SMA), a leading genetic disease associated with infant mortality. The discovery of ISS-N1 as a promising therapeutic target was enabled in part by Anti-N1, a 20-mer ASO that restored *SMN2* exon 7 inclusion by annealing to ISS-N1. Here, we analyzed the transcriptome of SMA patient cells treated with 100 nM of Anti-N1 for 30 h. Such concentrations are routinely used to demonstrate the efficacy of an ASO. While 100 nM of Anti-N1 substantially stimulated *SMN2* exon 7 inclusion, it also caused massive perturbations in the transcriptome and triggered widespread aberrant splicing, affecting expression of essential genes associated with multiple cellular processes such as transcription, splicing, translation, cell signaling, cell cycle, macromolecular trafficking, cytoskeletal dynamics, and innate immunity. We validated our findings with quantitative and semiquantitative PCR of 39 candidate genes associated with diverse pathways. We also showed a substantial reduction in off-target effects with shorter ISS-N1-targeting ASOs. Our findings are significant for implementing better ASO design and dosing regimens of ASO-based drugs.

Keywords: ISS-N1; SMA; SMN; Spinraza; antisense oligonucleotide; nusinersen; off-target effect; spinal muscular atrophy; splicing; survival motor neuron.

FULL TEXT OPEN ACCESS MDPI

19. Children (Basel) . 2021 Aug 16;8(8):703. doi: 10.3390/children8080703.

Sagittal Plane Deformities in Children with SMA2 following Posterior Spinal Instrumentation

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- PMID: 34438594
- PMCID: PMC8394982
- DOI: 10.3390/children8080703

This is a retrospective radiographic review to assess post-operative sagittal plane deformities in patients with Spinal Muscular Atrophy type 2 that had been treated with posterior spinal instrumentation. Thirty-two patients with a history of either spinal fusion (N = 20) or growing rods (N = 12) were identified with an average of 7.6 (2.1-16.6) years post-operative follow-up. Forty percent (13/32) of the patients were identified as having obvious "tucked chin" (N = 4), "tipped trunk" (N = 9), or both (N = 3). Sacral incidence was the only parameter that was statistically significant change between pre-operative or immediate post-operative measurements (66.9° vs. 55.2° $p = 0.03$). However, at final follow-up, the post-operative thoracic kyphosis had decreased over time in those that developed a subsequent sagittal deformity (24.2°) whereas it increased in those that did not (44.7°, $p = 0.008$). This decrease in thoracic kyphosis throughout the instrumented levels, resulted in a greater lordotic imbalance (30.4° vs. 5.6°, $p = 0.001$) throughout the instrumented levels in the group that developed the subsequent cervical or pelvic sagittal deformities. In conclusion, sagittal plane deformities commonly develop outside the instrumented levels in children with SMA type 2 following posterior spinal instrumentation and may be the result of lordotic imbalance that occurs through continued anterior growth following posterior instrumentation.

Keywords: kyphosis; posterior spinal fusion; sagittal plane deformity; spinal muscular atrophy.

FULL TEXT OPEN ACCESS MDPI

20. Children (Basel) . 2021 Aug 12;8(8):694. doi: 10.3390/children8080694.

Views of the General Population on Newborn Screening for Spinal Muscular Atrophy in Japan

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- PMID: 34438585
- PMCID: PMC8391323
- DOI: 10.3390/children8080694

Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder that results in progressive muscle atrophy and weakness. As new therapies for SMA have been developed, newborn screening for SMA can lead to early diagnosis and treatment. The objective of this study was to gather the general population's view on screening of SMA in newborns in Japan. A questionnaire survey was conducted on two general population groups in Japan. A total of 269 valid responses were obtained. In the general population, about half of the participants had no knowledge about SMA, and more than 90% did not know about new therapies for SMA. Conversely, more than 95% of the general population agreed with screening newborns for SMA because they believed that early diagnosis was important, and treatments were available. This study revealed that the general population in Japan mostly agreed with screening for SMA in newborns even though they did not know much about SMA. Newborn screening for SMA is promising, but it is in very early stages. Therefore, SMA newborn screening should be performed with sufficient preparation and consideration in order to have a positive impact on SMA patients and their families.

Keywords: general population; newborn screening; public intention; spinal muscular atrophy.

FULL TEXT OPEN ACCESS MDPI

Amyotrophies spinales distales – *Distal spinal muscular atrophies*

Case Reports

21. Brain Dev . 2021 Aug 26;S0387-7604(21)00154-6. doi: 10.1016/j.braindev.2021.08.004. Online ahead of print.

A patient with early-onset SMAX3 and a novel variant of ATP7A

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- PMID: 34456088
- DOI: 10.1016/j.braindev.2021.08.004

Objective: To describe clinical and genetic studies on a patient with early-onset spinal muscular atrophyX3 (SMAX3) with novel variant of ATP7A.

Methods: Clinical, neurophysiological, neuroimaging and pathological examinations were performed. Whole exome sequencing was applied to search genetic bases of this patient.

Results: The patient had gait abnormality from early infantile period. Muscle imaging at 42 years old showed predominant involvement of proximal muscles as compared to the distal muscles. The patient had a novel variant of ATP7A, which was the fourth genotype of ATP7A exhibited as SMAX3. Contrary to previous reports of distal motor neuropathy, the clinical and neuroimaging findings in this case revealed dominant involvement in the proximal portion of the extremities and trunk, which is similar to patients with type III SMA.

Conclusion: The dominant involvement of proximal motor system in this patient may expand the phenotypic variability of SMAX3. We need to be aware of this disorder in differential diagnosis of patients with type III SMA-like phenotype.

Keywords: ATP7A; Motor neuron disease; SMAX3; Type III SMA.

ELSEVIER FULL-TEXT ARTICLE

Canalopathies musculaires – *Muscular channelopathies*

22. J Gen Physiol . 2021 Nov 1;153(11):e202112946. doi: 10.1085/jgp.202112946. Epub 2021 Aug 31.

Gating pore currents occur in CaV1.1 domain III mutants associated with HypoPP

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- PMID: 34463712
- DOI: 10.1085/jgp.202112946

Mutations in the voltage sensor domain (VSD) of CaV1.1, the α1S subunit of the L-type calcium channel in skeletal muscle, are an established cause of hypokalemic periodic paralysis (HypoPP). Of the 10 reported mutations, 9 are missense substitutions of outer arginine residues (R1 or R2) in the S4 transmembrane segments of the homologous domain II, III (DIII), or IV. The prevailing view is that R/X mutations create an anomalous ion conduction pathway in the VSD, and this so-called gating pore current is the basis for paradoxical depolarization of the resting potential and weakness in low potassium for HypoPP fibers. Gating pore currents have been observed for four of the five CaV1.1 HypoPP mutant channels studied to date, the one exception being the charge-conserving R897K in R1 of DIII. We tested whether gating pore currents are detectable for the other three HypoPP CaV1.1 mutations in DIII. For the less conserved R1 mutation, R897S, gating pore currents with exceptionally large amplitude were observed, correlating with the severe clinical phenotype of these patients. At the R2 residue, gating pore currents were detected for R900G but not R900S. These findings show that gating pore currents may occur with missense mutations at R1 or R2 in S4 of DIII and that the magnitude of this anomalous inward current is mutation specific.

JGP >

Dystrophies musculaires congénitales – *Congenital muscular dystrophies*

23. Neuromuscul Disord . 2021 Jul 1;S0960-8966(21)00166-8. doi: 10.1016/j.nmd.2021.06.012. Online ahead of print.

Whole-body muscle MRI characteristics of LAMA2-related congenital muscular dystrophy children: An emerging pattern

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- PMID: 34481707
- DOI: 10.1016/j.nmd.2021.06.012

Merosin-deficient or LAMA2-related congenital muscular dystrophy (CMD) belongs to a group of muscle diseases with an overlapping diagnostic spectrum. MRI plays an important role in the diagnosis and disease-tracking of muscle diseases. Whole-body MRI is ideal for describing patterns of muscle involvement. We intended to analyze the pattern of muscle involvement in merosin-deficient CMD children employing whole-body muscle MRI. Ten children with merosin-deficient CMD underwent whole-body muscle MRI. Eight of which were genetically-confirmed. We used a control group of other hereditary muscle diseases, which included 13 children (mean age was 13 SD +/- 5.5 years), (8 boys and 5 girls) for comparative analysis. Overall, 37 muscles were graded for fatty infiltration using Mercuri scale modified by Fischer et al. The results showed a fairly consistent pattern of muscle fatty infiltration in index group, which differs from that in control group. There was a statistically significant difference between the two groups in regard to the fatty infiltration of the neck, serratus anterior, intercostal, rotator cuff, deltoid, triceps, forearm, gluteus maximus, gluteus medius, gastrocnemius and soleus muscles. Additionally, the results showed relative sparing of the brachialis, biceps brachii, gracilis, sartorius, semitendinosus and extensor muscles of the ankle in index group, and specific texture abnormalities in other muscles. There is evidence to suggest that whole-body muscle MRI can become a useful contributor to the differential diagnosis of children with merosin deficient CMD. The presence of a fairly characteristic pattern of involvement was demonstrated. MRI findings should be interpreted in view of the clinical and molecular context to improve diagnostic accuracy.

Keywords: Congenital muscular dystrophy type 1; Genetic muscular diseases; LAMA2 gene; Laminin Alpha-2 congenital muscular dystrophy; Merosin-deficient congenital muscular dystrophy.

ELSEVIER FULL-TEXT ARTICLE

24. Neuromuscul Disord . 2021 Jul 28;S0960-8966(21)00191-7. Online ahead of print.

Congenital muscular dystrophies: What is new?

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- PMID: 34470717
- DOI: 10.1016/j.nmd.2021.07.009

Congenital muscular dystrophies (CMDs) are a group of inherited conditions defined by muscle weakness occurring before the acquisition of ambulation, delayed motor milestones, and characterised by muscle dystrophic pathology. A large number of genes - at least 35- are responsible for CMD phenotypes, and it is therefore not surprising that CMDs comprise a wide spectrum of phenotypes, with variable involvement of cardiac/respiratory muscles, central nervous system, and ocular structures. The identification of several new genes over the past few years has further expanded both the clinical and the molecular spectrum underlying CMDs. Comprehensive gene panels allow to arrive at a final diagnosis in around 60% of cases, suggesting that both new genes, and unusual mutations of the currently known genes are likely to account for the remaining cases. The aim of this review is to present the most recent advances in this field. We will

outline recent natural history studies that provide additional information on disease progression, discuss recently discovered genes and the current status of the most promising therapeutic options.

Keywords: Alpha-dystroglycan; COL6-RD; Congenital muscular dystrophy; LAMA2-RD; Lamin a/c; Natural history; Review; SEPN1; Treatments.

ELSEVIER FULL-TEXT ARTICLE

Dystrophinopathies, dystrophie musculaire de Duchenne, dystrophie musculaire de Becker – *Dystrophinopathies*

25. J Neuropathol Exp Neurol . 2021 Sep 8;nlab088. doi: 10.1093/jnen/nlab088. Online ahead of print.

High-Throughput Digital Image Analysis Reveals Distinct Patterns of Dystrophin Expression in Dystrophinopathy Patients

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- PMID: 34498054
- DOI: 10.1093/jnen/nlab088

Duchenne muscular dystrophy (DMD) is an incurable disease caused by out-of-frame DMD gene deletions while in frame deletions lead to the milder Becker muscular dystrophy (BMD). In the last decade several antisense oligonucleotides drugs have been developed to induce a partially functional internally deleted dystrophin, similar to that produced in BMD, and expected to ameliorate the disease course. The pattern of dystrophin expression and functionality in dystrophinopathy patients is variable due to multiple factors, such as molecular functionality of the dystrophin and its distribution. To benchmark the success of therapeutic intervention, a clear understanding of dystrophin expression patterns in dystrophinopathy patients is vital. Recently, several groups have used innovative techniques to quantify dystrophin in muscle biopsies of children but not in patients with milder BMD. This study reports on dystrophin expression using both Western blotting and an automated, high-throughput, image analysis platform in DMD, BMD, and intermediate DMD/BMD skeletal muscle biopsies. Our results found a significant correlation between Western blot and immunofluorescent quantification indicating consistency between the different methodologies. However, we identified significant inter- and intradisease heterogeneity of patterns of dystrophin expression in patients irrespective of the amount detected on blot, due to variability in both fluorescence intensity and dystrophin sarcolemmal circumference coverage. Our data highlight the heterogeneity of the pattern of dystrophin expression in BMD, which will assist the assessment of dystrophin restoration therapies.

Keywords: Becker muscular dystrophy; Duchenne muscular dystrophy; Dystrophin; High–throughput digital analysis; Muscle biopsy; Skeletal muscle.

OXFORD ACADEMIC

26. Neuroreport. 2021 Sep 6. doi: 10.1097/WNR.0000000000001710. Online ahead of print.

The variability in neurological deficits in Duchenne muscular dystrophy patients may be explained by differences in dystrophin glycoprotein complexes in the brain and muscle

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- PMID: 34494993
- DOI: 10.1097/WNR.0000000000001710

Duchenne muscular dystrophy (DMD) is an X-linked recessive genetic neuromuscular disorder. The variability in neurologic deficits in DMD patients may be explained by the fact that (1) dystrophin containing complexes in the brain are more stable than dystrophin containing complexes in the muscle (2) neurons are not affected by the same stresses as muscle and (3) neurons have a greater capacity to buffer increases in intracellular calcium levels. In the muscle, the loss of dystrophin and subsequent loss of dystrophin-associated proteins (DAPs) affects the stability of the dystrophin-glycoprotein complex and calcium ion channels. It causes the sarcolemma of the muscle to tear and calcium ion leak. The subsequent calcium influx leads to calcium dependant proteolysis. In the brain, the structure of the dystrophin-containing complexes is completely different from the muscle. There are several dystrophin isoforms that combine with a completely different set of proteins compared to the muscle to form several different dystrophin-containing complexes. In addition, the loss of dystrophin does not affect the expression of DAPs. The heterogeneity of dystrophin-containing complexes and the continued expression of DAPs will result in more stable dystrophin-containing complexes in the DMD brain. Muscles are under more stress than neurons as they undergo contractions. This combined with txhe fact that the neurons have a better ability to buffer increases in calcium would suggest that neurons are less likely to be damaged despite the loss of dystrophin.

27. Neurology . 2021 Sep 7;10.1212/WNL.0000000000012724. Online ahead of print.

Association of Elbow Flexor MRI Fat Fraction With Loss of Hand-to-Mouth Movement in Patients With Duchenne Muscular Dystrophy

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- PMID: 34493619
- DOI: 10.1212/WNL.0000000000012724

Objective: To study the potential of quantitative MRI (qMRI) fat fraction (FF) as biomarker in non-ambulant Duchenne muscular dystrophy (DMD) patients, we assessed the additive predictive value of elbow flexor FF to age on loss of hand-to-mouth movement.

Methods: Non-ambulant DMD patients (≥8 years) were included. 4-point Dixon MRI scans of the right upper arm were performed at baseline and at 12, 18 or 24 months follow-up. Elbow flexor FFs were determined from five central slices. Loss of hand-to-mouth movement was determined at study visits and by phone-calls every four months. FFs were fitted to a sigmoidal curve using a mixed model with random slope to predict individual trajectories. The added predictive value of elbow flexor FF to age on loss of hand-to-mouth movement was calculated from a Cox model with the predicted FF as a time varying covariate, yielding a hazard ratio.

Results: Forty-eight MRIs of 20 DMD patients were included. The hazard ratio of a percent-point increase in elbow flexor FF for the time to loss of hand-to-mouth movement was 1.12 (95%-confidence interval 1.04-

1.21; p=0.002). This corresponded to a 3.13-fold increase of the instantaneous risk of loss of hand-to-mouth movement in patients with a 10 percent-points higher elbow flexor FF at any age.
Conclusion: In this prospective study, elbow flexor FF predicted loss of hand-to-mouth movement independent of age. qMRI measured elbow flexor FF can be used as surrogate endpoint or stratification tool for clinical trials in non-ambulant DMD patients.
Classification of evidence: This study provides Class II evidence that qMRI FF of elbow flexor muscles in patients with DMD predicts loss of hand-to-mouth movement independent of age.

Neurology

Review

28. Front Cell Dev Biol . 2021 Aug 19;9:689533. doi: 10.3389/fcell.2021.689533. eCollection 2021.

Current Pharmacological Strategies for Duchenne Muscular Dystrophy

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- PMCID: PMC8417245
- DOI: 10.3389/fcell.2021.689533

Duchenne muscular dystrophy (DMD) is a lethal, X-linked neuromuscular disorder caused by the absence of dystrophin protein, which is essential for muscle fiber integrity. Loss of dystrophin protein leads to recurrent myofiber damage, chronic inflammation, progressive fibrosis, and dysfunction of muscle stem cells. There is still no cure for DMD so far and the standard of care is principally limited to symptom relief through glucocorticoids treatments. Current therapeutic strategies could be divided into two lines. Dystrophin-targeted therapeutic strategies that aim at restoring the expression and/or function of dystrophin, including gene-based, cell-based and protein replacement therapies. The other line of therapeutic strategies aims to improve muscle function and quality by targeting the downstream pathological changes, including inflammation, fibrosis, and muscle atrophy. This review introduces the important developments in these two lines of strategies, especially those that have entered the clinical phase and/or have great potential for clinical translation. The rationale and efficacy of each agent in pre-clinical or clinical studies are presented. Furthermore, a meta-analysis of gene profiling in DMD patients has been performed to understand the molecular mechanisms of DMD.

Keywords: Duchenne muscular dystrophy; fibrosis; inflammation; meta-analysis; pharmacological therapeutics; regeneration; skeletal muscle.

OPEN ACCESS frontiers

29. Neuromuscul Disord . 2021 Jun 10;S0960-8966(21)00155-3. Online ahead of print.

Health related quality of life in young, steroid-naïve boys with Duchenne muscular dystrophy

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- PMID: 34489153
- DOI: 10.1016/j.nmd.2021.06.001

Knowledge of health related quality of life (HRQOL) in the immediate phase following DMD diagnosis has not been well-characterized. It is important to understand HRQOL early in disease for both clinical care and studies of treatment. The relationship between parent-proxy and child self-report HRQOL and their associations with medical, psycho-social and behavioral symptoms deserve study. In this study HRQOL was measured using the PedsQL inventory in parent/caregiver and corticosteroid-naïve boys (ages 4 to 7 years) participating in the FOR-DMD study. Agreement between the parent-proxy report and the boys' self-report HRQOL was measured using intraclass correlation coefficients (ICCs). Factors associated with HRQOL, including standardized psychosocial and behavioral measures in this cross-sectional sample, were explored using correlations. The results showed that the level of agreement between 70 dyads of child self-report and parent-proxy ratings of HRQOL was poor for the generic PedsQL total score (ICC=0.48, 95% CI (0.23,

0.66)) and its subscale scores, and was similarly low for the neuromuscular disease module (ICC=0.24, 95% CI (0.00, 0.45)). Parents rated their child's HRQOL as poorer than the children rated themselves in all scales. Psychosocial outcome measures were more highly associated with HRQOL measures than disease severity or patient demographic variables. In the early phases of DMD, child and parent-proxy HRQOL ratings were discordant. In early DMD, psychosocial and behavioral aspects appear to be more relevant to HRQOL than disease severity factors.

Keywords: Duchenne muscular dystrophy; Health related quality of life; Psychosocial.

ELSEVIER FULL-TEXT ARTICLE

30. Mol Ther Methods Clin Dev . 2021 Jun 4;22:122-132. doi: 10.1016/j.omtm.2021.05.014. eCollection 2021 Sep 10.

A consolidated AAV system for single-cut CRISPR correction of a common Duchenne muscular dystrophy mutation

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- PMCID: PMC8397837
- DOI: 10.1016/j.omtm.2021.05.014

Duchenne muscular dystrophy (DMD), caused by mutations in the X-linked dystrophin gene, is a lethal neuromuscular disease. Correction of DMD mutations in animal models has been achieved by CRISPR/Cas9 genome editing using *Streptococcus pyogenes* Cas9 (*Sp*Cas9) delivered by adeno-associated virus (AAV). However, due to the limited viral packaging capacity of AAV, two AAV vectors are required to deliver the *Sp*Cas9 nuclease and its single guide RNA (sgRNA), impeding its therapeutic application. We devised an efficient single-cut gene-editing method using a compact *Staphylococcus aureus* Cas9 (*Sa*Cas9) to restore the open reading frame of exon 51, the most commonly affected out-of-frame exon in DMD. Editing of exon 51 in cardiomyocytes derived from human induced pluripotent stem cells revealed a strong preference for exon reframing via a two-nucleotide deletion. We adapted this system to express *Sa*Cas9 and sgRNA from a single AAV9 vector. Systemic delivery of this All-In-One AAV9 system restored dystrophin expression and improved muscle contractility in a mouse model of DMD with exon 50 deletion. These findings demonstrate the effectiveness of CRISPR/*Sa*Cas9 delivered by a consolidated AAV delivery system in the correction of DMD *in vivo*, representing a promising therapeutic approach to correct the genetic causes of DMD.

Keywords: AAV; CRISPR/Cas; Duchenne muscular dystrophy; SaCas9; exon reframing; exon skipping; gene editing; induced pluripotent stem cells; sgRNA.

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31. Neurol Clin Pract . 2021 Aug;11(4):311-317. doi: 10.1212/CPJ.0000000000000970.

Achieving Life Milestones in Duchenne/Becker Muscular Dystrophy: A Retrospective Analysis

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- PMCID: PMC8382433 (available on 2022-08-01)
- DOI: 10.1212/CPJ.0000000000000970

Objective: To understand the milestones achieved in the transition from childhood to adulthood for patients with Duchenne and Becker muscular dystrophies (DMD/BMD).

Methods: We performed a retrospective chart review on patients aged 15 years or older with a clinical diagnosis of DMD/BMD who received care from January 1, 2008, to January 1, 2018 at the University of Kansas Medical Center and the University of Rochester Medical Center. Participants were identified using local Muscular Dystrophy Asssociation-funded clinic lists, neuromuscular research databases, and electronic medical record review. Data were abstracted using a uniform template on education, employment,

community resources, relationships, and end-of-life discussions and is presented as mean, median, or frequency with associated 95% confidence interval (CI).
Results: A total of 109 patients were identified: patients ranged in age from 15 to 56 years with a median of 24, and covered a 5-state region and Ontario, Canada. Seventy-eight percent of patients had DMD and were, on average, 8.5 years younger than patients with BMD. Over half (56.9%, 95% CI 47.6-66.2) were high school graduates or beyond. Sixteen percent did not have their highest level of education documented. Only 20.0% had an occupation (95% CI 12.7-27.7), most frequently in education and administrative support (34%). The majority were still living with parents (80.7%, 95% CI 73.3-88.1). A minority reported having end-of-life discussions (17.4%, 95% CI 10.3-24.6).
Conclusions: Psychosocial elements reflecting the transition to adulthood are inconsistently reported in clinical documentation. A prospective study will further elucidate this transition.

32. Exp Neurobiol . 2021 Aug 31;30(4):263-274. doi: 10.5607/en21008.

Altered Gene Expression Profiles in Neural Stem Cells Derived from Duchenne Muscular Dystrophy Patients with Intellectual Disability

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- PMID: 34483141
- DOI: 10.5607/en21008

Intellectual disability (ID) is a neurodevelopmental disorder defined by below-average intelligence (intelligence quotient of <70) accompanied by adaptive behavior deficits. Defects in the functions of neural stem cells during brain development are closely linked to the pathogenesis of ID. To understand the molecular etiology of ID, we examined neural stem cells from individuals with Duchenne muscular dystrophy (DMD), a genetic disorder in which approximately one-third of the patients exhibit ID. In this study, we generated induced pluripotent stem cells from peripheral blood mononuclear cells from a normal individual and DMD patients with and without ID to identify ID-specific functional and molecular abnormalities. We found defects in neural ectoderm formation in the group of DMD patients with ID. Our transcriptome analysis of patient-derived neural stem cells revealed altered expression of genes related to the hippo signaling pathway and neuroactive ligand-receptor interaction, implicating these in the pathogenesis of ID in patients with DMD.

Keywords: Duchenne muscular dystrophy; Gene expression; Induced pluripotent stem cell; Intellectual disability.

en Experimental Neurobiology FREE FULL TEXT

33. Skelet Muscle . 2021 Sep 3;11(1):21. doi: 10.1186/s13395-021-00276-3.

Simvastatin does not alleviate muscle pathology in a mouse model of Duchenne muscular dystrophy

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- PMCID: PMC8414747
- DOI: 10.1186/s13395-021-00276-3

Background: Duchenne muscular dystrophy (DMD) is an incurable disease, caused by the mutations in the DMD gene, encoding dystrophin, an actin-binding cytoskeletal protein. Lack of functional dystrophin results in muscle weakness, degeneration, and as an outcome cardiac and respiratory failure. As there is still no cure for affected individuals, the pharmacological compounds with the potential to treat or at least attenuate the symptoms of the disease are under constant evaluation. The pleiotropic agents, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, known as statins, have been suggested to exert beneficial effects in the mouse model of DMD. On the other hand, they were also reported to induce skeletal-muscle myopathy. Therefore, we decided to verify the hypothesis that simvastatin may be considered a potential therapeutic agent in DMD.

Methods: Several methods including functional assessment of muscle function via grip strength measurement, treadmill test, and single-muscle force estimation, enzymatic assays, histological analysis of muscle damage, gene expression evaluation, and immunofluorescence staining were conducted to study simvastatin-related alterations in the mdx mouse model of DMD.

Results: In our study, simvastatin treatment of mdx mice did not result in improved running performance, grip strength, or specific force of the single muscle. Creatine kinase and lactate dehydrogenase activity, markers of muscle injury, were also unaffected by simvastatin delivery in mdx mice. Furthermore, no significant changes in inflammation, fibrosis, and angiogenesis were noted. Despite the decreased percentage of centrally nucleated myofibers in gastrocnemius muscle after simvastatin delivery, no changes were noticed in other regeneration-related parameters. Of note, even an increased rate of necrosis was found in simvastatin-treated mdx mice.

Conclusion: In conclusion, our study revealed that simvastatin does not ameliorate DMD pathology.

Keywords: 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors; Angiogenesis; DMD; Duchenne muscular dystrophy; Simvastatin; mdx.

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34. Pak J Med Sci . Sep-Oct 2021;37(5):1376-1381. doi: 10.12669/pjms.37.5.3104.

Induced pluripotent stem cells derived cardiomyocytes from Duchenne Muscular Dystrophy patients in vitro

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- PMID: 34475915
- PMCID: PMC8377888
- DOI: 10.12669/pjms.37.5.3104

Objective: This study aimed at the in vitro generation of DMD-cardiomyocytes from patient-specific induced pluripotent stem cells derived from a Pakistani patient for future work on DMD in vitro disease modeling and drug testing for efficacy and toxicity.

Methods: This in vitro experimental study was carried out from December 2018 to January 2019 at Stem Cells and Regenerative Medicine Lab (SCRML) at Dow Research Institute of Biotechnology and Biomedical Sciences (DRIBBS), Dow University of Health Sciences (DUHS) Urine derived DMD-iPSCs were used which had been generated previously from a Pakistani DMD patient who had been selected through non-random purposive sampling. These were differentiated towards cardiomyocytes using Cardiomyocytes Differentiation media having specified growth factors and then the molecular characterization of the differentiated cells was done using immunofluorescence.

Results: Pakistani patient's DMD-Cardiomyocytes were generated and their identity was confirmed by positive immunofluorescence for the expression of cardiac markers NKX2-5 and TNNT-2.

Conclusion: This study aimed for in vitro generation of DMD cardiomyocytes for future application in disease modeling, new drug testing for efficacy and toxicity, as well as for drug-testing for tailored personalized

therapy. To the best of our knowledge, this was the first time DMD-Cardiomyocytes were generated from Pakistani DMD patients using their own induced pluripotent stem cells.

Keywords: Duchenne muscular dystrophy; Human induced pluripotent stem cells; In vitro cardiomyocytes.

35. Clin Rehabil . 2021 Sep 2;2692155211043265. doi: 10.1177/02692155211043265. Online ahead of print.

The effect of trunk training on trunk control, upper extremity, and pulmonary function in children with Duchenne muscular dystrophy: A randomized clinical trial

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- PMID: 34474581
- DOI: 10.1177/02692155211043265

Objectives: To investigate the effect of trunk training on trunk control, arm, and pulmonary function in children with Duchenne muscular dystrophy.

Design: A randomised controlled trial.

Settings: Neuromuscular diseases clinic of university hospital.

Subjects: Twenty-six children with Duchenne muscular dystrophy aged 5-16 were included in the study.

Intervention: Participants were randomly allocated into two groups. The study group (N = 13) exercised with the trunk-oriented exercise program and the conventional exercise program, whereas the control group (N = 13) underwent the conventional exercise program for eight weeks.

Main measures: The primary outcomes were trunk control was assessed using the Trunk Control Measurement Scale, the arm function was assessed using Performance of Upper Limb, and respiratory function using the pulmonary function test. Data collection was conducted at baseline, and eighth week. The differences in trunk control scores, arm function scores, and respiratory function values before and after the training were calculated for the intergroup comparison.

Results: The mean age of the participants was 11.6 (2.6) in the study group and 10.6 (3.4) in the control group. The changes between trunk control score, arm function score (total and distal level score), and respiratory function value (Forced Vital Capacity, Forced Expiratory Volume in one second, and Peak Expiratory Flow Volume percentage values) were compared and significant differences were found after eight week periods in the study and control groups.

Conclusions: Trunk-oriented exercise program in Duchenne muscular dystrophy might be effective for trunk control, arm, and respiratory function.

Keywords: Duchenne muscular dystrophy; arm function; respiratory function; trunk control; trunk-oriented exercises.

36. Biosci Rep . 2021 Sep 2;BSR20211325. doi: 10.1042/BSR20211325. Online ahead of print.

miRNome profiling in Duchenne Muscular Dystrophy; Identification of Asymptomatic and Manifesting Female Carriers

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- PMID: 34472584
- DOI: 10.1042/BSR20211325

Duchenne muscular dystrophy (DMD) is a fatal neuromuscular disorder that occurs due to inactivating mutations in DMD gene, leading to muscular dystrophy. Prediction of pathological complications of DMD and the identification of female carriers are important research points that aim to reduce disease burden. Herein, we describe a case of a late DMD patient and his immediate female family members, who all carry same DMD mutation and exhibited varied degrees of symptoms. In our study, we sequenced the whole miRNome in leukocytes and plasma of the family members and results were validated using Real-Time PCR. Our results highlighted the role of miR-409-3p, miR-424-5p, miR-144-3p as microRNAs that show correlation

with the extent of severity of muscular weakness and can be used for detection of asymptomatic carriers. Cellular and circulating levels of miR-494-3p had showed significant increase in symptomatic carriers, which may indicate significant roles played by this miRNA in the onset of muscular weakness. Interestingly, circulating levels of miR-206 and miR-410-3p were significantly increased only in the severely symptomatic carrier. In conclusion, our study highlighted several miRNA species, which could be used in predicting the onset of muscle and/or neurological complications in DMD carriers.

Keywords: Carriers; Duchenne muscular dystrophy; Next generation sequencing; microRNA.

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37. J Cell Sci. 2021 Sep 2;jcs.258429. doi: 10.1242/jcs.258429. Online ahead of print.

Myofiber / pro-inflammatory macrophage interplay controls muscle damage in mdx mice

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- PMID: 34471933
- DOI: 10.1242/jcs.258429

Duchenne Muscular Dystrophy is a genetic muscle disease characterized by chronic inflammation and fibrosis, mediated by a pro-fibrotic macrophage population expressing pro-inflammatory markers. Our aim was to characterize cellular events leading to the alteration of macrophage properties, and to modulate macrophage inflammatory status using the gaseous mediator H2S. Using co-culture experiments, we first showed that myofibers derived from mdx mice strongly skewed the polarization of resting macrophages towards a pro-inflammatory phenotype. Treatment of mdx mice with NaHS, an H2S donor, reduced the number of pro-inflammatory macrophages in skeletal muscle, which was associated with a decreased number of nuclei per fiber, together with a reduced myofiber branching and fibrosis. Finally, we established the metabolic sensor AMPK as a critical NaHS target in muscle macrophages. These results identify an interplay between myofibers and macrophages where dystrophic myofibers contribute to the maintenance of a highly inflammatory environment sustaining a pro-inflammatory macrophage status, in turn favoring myofiber damage, myofiber branching and fibrosis establishment. They also identify H2S donors as a potential therapeutic strategy to improve dystrophic muscle phenotype by dampening chronic inflammation.

Keywords: AMPK; Duchenne muscular dystrophy; Fibrosis; Macrophage; Myofiber branching.

Journal of Cell Science

38. J Musculoskelet Neuronal Interact . 2021 Sep 1;21(3):343-350.

Efficacy of two intervention approaches on functional walking capacity and balance in children with Duchene muscular dystrophy

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- PMID: 34465672
- PMCID: PMC8426654

Objectives: Children with Duchene muscular dystrophy have weak muscles, which may impair postural adjustments. These postural adjustments are required for gait and dynamic balance during the daily living activities. The aim was to compare between the effect of bicycle ergometer versus treadmill on functional walking capacity and balance in children with Duchenne muscular dystrophy.

Methods: Thirty boys aged from 6 to 10 years old diagnosed as Duchene muscular dystrophy participated in this study. Children were assigned randomly into two groups (A&B). Children in group (A) underwent a designed program of physical therapy plus aerobic exercise training in form of bicycle ergometer while, group (B) received the same program as group (A) and aerobic exercise training by treadmill for one hour, at three times a week for three successive months. Functional walking capacity and balance were assessed

before and after treatment by using the 6-minute walk test and Biodex balance system equipment respectively.
Results: The post treatment results revealed significant difference in all measured variables (P<0.05) as compared with its pre-treatment results. Post-treatment values indicated that there was a significant difference in all measured variables in favor of group B.
Conclusions: treadmill training as an aerobic exercise can improve walking capacity and balance more effectively than bicycle ergometer in children with Duchenne muscular dystrophy.
Keywords: Balance; Bicycle Ergometer; Duchene Muscular Dystrophy; Functional Walking Capacity; Treadmill.
JMNI ismni.org Full text PDF

39. Stat Med. 2021 Aug 31. doi: 10.1002/sim.9178. Online ahead of print.

Penalized regression calibration: A method for the prediction of survival outcomes using complex longitudinal and high-dimensional data

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- PMID: 34464990
- DOI: 10.1002/sim.9178

Longitudinal and high-dimensional measurements have become increasingly common in biomedical research. However, methods to predict survival outcomes using covariates that are both longitudinal and high-dimensional are currently missing. In this article, we propose penalized regression calibration (PRC), a method that can be employed to predict survival in such situations. PRC comprises three modeling steps: First, the trajectories described by the longitudinal predictors are flexibly modeled through the specification of multivariate mixed effects models. Second, subject-specific summaries of the longitudinal trajectories are derived from the fitted mixed models. Third, the time to event outcome is predicted using the subject-specific summaries as covariates in a penalized Cox model. To ensure a proper internal validation of the fitted PRC models, we furthermore develop a cluster bootstrap optimism correction procedure that allows to correct for the optimistic bias of apparent measures of predictiveness. PRC and the CBOCP are implemented in the R package pencal, available from CRAN. After studying the behavior of PRC via simulations, we conclude by illustrating an application of PRC to data from an observational study that involved patients affected by Duchenne muscular dystrophy, where the goal is predict time to loss of ambulation using longitudinal blood biomarkers.
Keywords: Duchenne muscular dystrophy; high-dimensionality; longitudinal data analysis; optimism correction; penalized regression calibration; risk prediction modeling; survival analysis.

40. Genome Med . 2021 Aug 28;13(1):137. doi: 10.1186/s13073-021-00937-4.

Functional significance of gain-of-function H19 lncRNA in skeletal muscle differentiation and anti-obesity effects

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- PMCID: PMC8403366
- DOI: 10.1186/s13073-021-00937-4

Background: Exercise training is well established as the most effective way to enhance muscle performance and muscle building. The composition of skeletal muscle fiber type affects systemic energy expenditures, and perturbations in metabolic homeostasis contribute to the onset of obesity and other metabolic dysfunctions. Long noncoding RNAs (lncRNAs) have been demonstrated to play critical roles in diverse cellular processes and diseases, including human cancers; however, the functional importance of lncRNAs in muscle performance, energy balance, and obesity remains elusive. We previously reported that the lncRNA H19 regulates the poly-ubiquitination and protein stability of dystrophin (DMD) in muscular dystrophy.

Methods: Here, we identified mouse/human H19-interacting proteins using mouse/human skeletal muscle tissues and liquid chromatography-mass spectrometry (LC-MS). Human induced pluripotent stem-derived skeletal muscle cells (iPSC-SkMC) from a healthy donor and Becker Muscular Dystrophy (BMD) patients were utilized to study DMD post-translational modifications and associated proteins. We identified a gain-of-function (GOF) mutant of H19 and characterized the effects on myoblast differentiation and fusion to myotubes using iPSCs. We then conjugated H19 RNA gain-of-function oligonucleotides (Rgof) with the skeletal muscle enrichment peptide agrin (referred to as AGR-H19-Rgof) and evaluated AGR-H19-Rgof's effects on skeletal muscle performance using wild-type (WT) C57BL/6 J mice and its anti-obesity effects using high-fat diet (HFD)- and leptin deficiency-induced obese mouse models.

Results: We demonstrated that both human and mouse H19 associated with DMD and that the H19 GOF exhibited enhanced interaction with DMD compared to WT H19. DMD was found to associate with serine/threonine-protein kinase MRCK alpha (MRCKα) and α-synuclein (SNCA) in iPSC-SkMC derived from BMD patients. Inhibition of MRCKα and SNCA-mediated phosphorylation of DMD antagonized the interaction between H19 and DMD. These signaling events led to improved skeletal muscle cell differentiation and myotube fusion. The administration of AGR-H19-Rgof improved the muscle mass, muscle performance, and base metabolic rate of WT mice. Furthermore, mice treated with AGR-H19-Rgof exhibited resistance to HFD- or leptin deficiency-induced obesity.

Conclusions: Our study suggested the functional importance of the H19 GOF mutant in enhancing muscle performance and anti-obesity effects.

Keywords: Dystrophin; H19; Long noncoding RNA; Obesity; RNA therapy; Skeletal muscle.

41. Ann Clin Transl Neurol . 2021 Aug 28. doi: 10.1002/acn3.51417. Online ahead of print.

Upper limb disease evolution in exon 53 skipping eligible patients with Duchenne muscular dystrophy

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- PMID: 34453498
- DOI: 10.1002/acn3.51417

Objective: To understand the natural disease upper limb progression over 3 years of ambulatory and non-ambulatory patients with Duchenne muscular dystrophy (DMD) using functional assessments and quantitative magnetic resonance imaging (MRI) and to exploratively identify prognostic factors.

Methods: Forty boys with DMD (22 non-ambulatory and 18 ambulatory) with deletions in dystrophin that make them eligible for exon 53-skipping therapy were included. Clinical assessments, including Brooke score, motor function measure (MFM), hand grip and key pinch strength, and upper limb distal coordination and endurance (MoviPlate), were performed every 6 months and quantitative MRI of fat fraction (FF) and lean muscle cross sectional area (flexor and extensor muscles) were performed yearly.

Results: In the whole population, there were strong nonlinear correlations between outcome measures. In non-ambulatory patients, annual changes over the course of 3 years were detected with high sensitivity standard response mean (|SRM| ≥0.8) for quantitative MRI-based FF, hand grip and key pinch, and MFM. Boys who presented with a FF<20% and a grip strength >27% were able to bring a glass to their mouth and retained this ability in the following 3 years. Ambulatory patients with grip strength >35% of predicted value and FF <10% retained ambulation 3 years later.

Interpretation: We demonstrate that continuous decline in upper limb strength, function, and MRI measured muscle structure can be reliably measured in ambulatory and non-ambulatory boys with DMD with high SRM and strong correlations between outcomes. Our results suggest that a combination of grip strength and FF can be used to predict important motor milestones.

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42. Muscle Nerve . 2021 Aug 27. doi: 10.1002/mus.27406. Online ahead of print.

Occurrence of symptoms in different stages of Duchenne muscular dystrophy and their impact on social participation

Saskia L S Houwen-van Opstal [1,2,3,4], Lotte Heutinck [2,4], Merel Jansen [2], Yvonne D Krom [4,5], Edith H C Cup [2], Jos G M Hendriksen [4,6], Michel A A P Willemsen [1,2], Jan J G M Verschuuren [4,5], Erik H Niks [4,5], Imelda J M de Groot [1,2,4]

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- PMID: 34453345
- DOI: 10.1002/mus.27406

Introduction/aims: As life expectancy improves for patients with Duchenne muscular dystrophy (DMD), new symptoms are likely to arise. This aims of this study are: (1) to explore the prevalence of a broad variety of symptoms in the various stages of DMD (with and without steroid use); (2) to explore the prevalence of common secondary diagnoses; and (3) to evaluate the social participation level of patients with DMD older than 16 y of age; and to explore correlations between social participation and symptoms.

Methods: A cross-sectional self-report questionnaire, including questions on functional level and health status, as well as a standardized participation scale was distributed among Dutch patients with DMD.

Results: Eighty-four male patients with a mean age of 22.0 (SD = 10.0) y were enrolled. The most prevalent and limiting symptoms were difficulty coughing (58%), coldness of hands (57%), contractures (51%), stiffness (49%), fatigue (40%), myalgia (38%), and low speech volume (33%). Prevalent secondary diagnoses included cardiac disease (14%), neurobehavioral diagnosis (13%), low blood pressure (13%), and arthrosis (5%). Social participation correlated negatively with coldness of hands ($r = -.29$; $P < .03$), decreased intelligibility ($r = -.40$; $P < .003$), and chewing problems ($r = -.33$; $P < .02$).

Discussion: The prevalence of a broad spectrum of symptoms and secondary diagnoses is high in patients with DMD, and some of these symptoms are correlated with social participation. Growing awareness of new symptoms and secondary diagnoses among patients, caregivers, and professionals can enhance their recognition, possibly facilitating prevention and early treatment.

Keywords: Duchenne muscular dystrophy; aging; signs and symptoms; social participation; symptoms.

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Review

43. Pharmaceuticals (Basel). 2021 Aug 13;14(8):798. doi: 10.3390/ph14080798.

Genetic Modifiers and Phenotype of Duchenne Muscular Dystrophy: A Systematic Review and Meta-Analysis

Carlos Pascual-Morena [1], Iván Cavero-Redondo [1,2], Alicia Saz-Lara [1], Irene Sequí-Domínguez [1], Maribel Lucerón-Lucas-Torres [1], Vicente Martínez-Vizcaíno [1,3]

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- PMID: 34451895
- PMCID: PMC8401629
- DOI: 10.3390/ph14080798

The transforming growth factor beta (TGFβ) pathway could modulate the Duchenne muscular dystrophy (DMD) phenotype. This meta-analysis aims to estimate the association of genetic variants involved in the TGFβ pathway, including the latent transforming growth factor beta binding protein 4 (LTBP4) and secreted phosphoprotein 1 (SPP1) genes, among others, with age of loss of ambulation (LoA) and cardiac function in patients with DMD. Meta-analyses were conducted for the hazard ratio (HR) of LoA for each genetic variant. A subgroup analysis was performed in patients treated exclusively with glucocorticoids. Eight studies were included in the systematic review and four in the meta-analyses. The systematic review suggests a protective effect of LTBP4 haplotype IAAM (recessive model) for LoA. It is also suggested that the SPP1 rs28357094 genotype G (dominant model) is associated with early LoA in glucocorticoids-treated patients. The meta-analysis of the LTBP4 haplotype IAAM showed a protective association with LoA, with an HR = 0.78 (95% CI: 0.67-0.90). No association with LoA was observed for the SPP1 rs28357094. The LTBP4 haplotype IAAM is associated with a later LoA, especially in the Caucasian population, while the SPP1 rs28357094 genotype G could be associated with a poor response to glucocorticoids. Future research is suggested for SPP1 rs11730582, LTBP4 rs710160, and THBS1 rs2725797.

Keywords: Duchenne muscular dystrophy; LTBP4; SPP1; TGFβ; meta-analysis; polymorphism; systematic review.

FULL TEXT OPEN ACCESS MDPI

Review

44. Pharmaceuticals (Basel) . 2021 Aug 9;14(8):785. doi: 10.3390/ph14080785.

Ataluren-Promising Therapeutic Premature Termination Codon Readthrough Frontrunner

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- PMID: 34451881
- PMCID: PMC8398184
- DOI: 10.3390/ph14080785

Around 12% of hereditary disease-causing mutations are in-frame nonsense mutations. The expression of genes containing nonsense mutations potentially leads to the production of truncated proteins with

residual or virtually no function. However, the translation of transcripts containing premature stop codons resulting in full-length protein expression can be achieved using readthrough agents. Among them, only ataluren was approved in several countries to treat nonsense mutation Duchenne muscular dystrophy (DMD) patients. This review summarizes ataluren's journey from its identification, via first in vitro activity experiments, to clinical trials in DMD, cystic fibrosis, and aniridia. Additionally, data on its pharmacokinetics and mechanism of action are presented. The range of diseases with underlying nonsense mutations is described for which ataluren therapy seems to be promising. What is more, experiments in which ataluren did not show its readthrough activity are also included, and reasons for their failures are discussed.

Keywords: ataluren; nonsense mutation; readthrough.

FULL TEXT OPEN ACCESS MDPI

45. J Pediatr Nurs. 2021 Aug 24;61:298-304. doi: 10.1016/j.pedn.2021.08.003. Online ahead of print.

Emergency planning as part of healthcare transition preparation for patients with Duchenne muscular dystrophy

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- PMID: 34450470
- DOI: 10.1016/j.pedn.2021.08.003

Background: Emergency care planning is an important component of healthcare transition, particularly for patients with medical complexity. Duchenne muscular dystrophy (DMD) is a complex, progressive pediatric-onset disease affecting multiple organ systems including impairment of cardiac and pulmonary function, high risk for fractures, fat embolism, adrenal crisis and malignant hyperthermia. Appropriate interdisciplinary emergency management is critical for survival for these patients. The purpose of this quality improvement project was to develop a process to reliably share an individualized emergency care plan (ECP) with patients and their families as part of a larger plan to develop an integrated transition program.

Methods: An interdisciplinary team of nurses and clinicians used the principles of quality improvement to develop a reliable process to assure patients with DMD received an individualized, multidisciplinary ECP at routine interdisciplinary clinic visits. Additionally, the project used surveys to assess patient and family satisfaction with the letter and whether it improved their knowledge of emergency care.

Results: Sixty-two patients were seen during the study timeframe. All received an ECP. Sixty-two surveys were sent and twenty-three surveys were returned. Of those that responded, the majority stated the ECP increased their knowledge of emergency care.

Conclusion: ECPs can be developed and disseminated to patients with DMD and their caregivers. This tool can potentially promote timely and appropriate emergency care for these patients with unique and complex medical needs.

Keywords: Duchenne muscular dystrophy; Emergency care plan; Health care transition; Quality improvement.

ELSEVIER FULL-TEXT ARTICLE

Review

46. Int J Mol Sci. 2021 Aug 19;22(16):8954. doi: 10.3390/ijms22168954.

Multiomic Approaches to Uncover the Complexities of Dystrophin-Associated Cardiomyopathy

Aoife Gowran [1], Maura Brioschi [2], Davide Rovina [1], Mattia Chiesa [3,4], Luca Piacentini [3], Sara Mallia [1], Cristina Banfi [2], Giulio Pompilio [1,5,6], Rosaria Santoro [1,4]

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- PMID: 34445659
- PMCID: PMC8396646
- DOI: 10.3390/ijms22168954

Despite major progress in treating skeletal muscle disease associated with dystrophinopathies, cardiomyopathy is emerging as a major cause of death in people carrying dystrophin gene mutations that remain without a targeted cure even with new treatment directions and advances in modelling abilities. The reasons for the stunted progress in ameliorating dystrophin-associated cardiomyopathy (DAC) can be explained by the difficulties in detecting pathophysiological mechanisms which can also be efficiently targeted within the heart in the widest patient population. New perspectives are clearly required to effectively address the unanswered questions concerning the identification of authentic and effectual readouts of DAC occurrence and severity. A potential way forward to achieve further therapy breakthroughs lies in combining multiomic analysis with advanced preclinical precision models. This review presents the fundamental discoveries made using relevant models of DAC and how omics approaches have been incorporated to date.

Keywords: dystrophin-associated cardiomyopathy; dystrophinopathies; multiomic analysis; muscular dystrophy; preclinical precision models.

FULL TEXT OPEN ACCESS MDPI

47. Life (Basel). 2021 Aug 13;11(8):827. doi: 10.3390/life11080827.

Validation of Chemokine Biomarkers in Duchenne Muscular Dystrophy

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- PMID: 34440571
- PMCID: PMC8401931
- DOI: 10.3390/life11080827

Duchenne muscular dystrophy (DMD) is a progressive muscle disease involving complex skeletal muscle pathogenesis. The pathogenesis is triggered by sarcolemma instability due to the lack of dystrophin protein expression, leading to Ca^{2+} influx, muscle fiber apoptosis, inflammation, muscle necrosis, and fibrosis. Our lab recently used two high-throughput multiplexing techniques (e.g., SomaScan® aptamer assay and tandem mass tag-(TMT) approach) and identified a series of serum protein biomarkers tied to different pathobiochemical pathways. In this study, we focused on validating the circulating levels of three proinflammatory chemokines (CCL2, CXCL10, and CCL18) that are believed to be involved in an early stage of muscle pathogenesis. We used highly specific and reproducible MSD ELISA assays and examined the association of these chemokines with DMD pathogenesis, age, disease severity, and response to glucocorticoid treatment. As expected, we confirmed that these three chemokines were significantly elevated in serum and muscle samples of DMD patients relative to age-matched healthy controls (p-value < 0.05, CCL18 was not significantly altered in muscle samples). These three chemokines were not

significantly elevated in Becker muscular dystrophy (BMD) patients, a milder form of dystrophinopathy, when compared in a one-way ANOVA to a control group but remained significantly elevated in the age-matched DMD group ($p < 0.05$). CCL2 and CCL18 but not CXCL10 declined with age in DMD patients, whereas all three chemokines remained unchanged with age in BMD and controls. Only CCL2 showed significant association with time to climb four steps in the DMD group ($r = 0.48$, $p = 0.038$) and neared significant association with patients' reported outcome in the BMD group ($r = 0.39$, $p = 0.058$). Furthermore, CCL2 was found to be elevated in a serum of the mdx mouse model of DMD, relative to wild-type mouse model. This study suggests that CCL2 might be a suitable candidate biomarker for follow-up studies to demonstrate its physiological significance and clinical utility in DMD.

Keywords: Becker muscular dystrophy; Duchenne muscular dystrophy; chemokines; disease severity; inflammatory biomarkers; validation studies.

FULL TEXT OPEN ACCESS MDPI

48. Life (Basel). 2021 Aug 5;11(8):791. doi: 10.3390/life11080791.

Skeletal Effects of Bone-Targeted TGFbeta Inhibition in a Mouse Model of Duchenne Muscular Dystrophy

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- PMID: 34440535
- PMCID: PMC8401157
- DOI: 10.3390/life11080791

Duchenne muscular dystrophy (DMD) is a severe progressive muscle disease that is frequently associated with secondary osteoporosis. Previous studies have shown that TGFbeta inactivating antibody improves the muscle phenotype in *mdx* mice, a model of DMD. In the present study, we assessed the skeletal effects of treatment with a bone-targeted TGFbeta antibody (PCT-011) in *mdx* mice. Micro-computed tomography showed that 8 weeks of intraperitoneal administration of PCT-011 (10 mg per kg body mass, 3 times per week) was associated with more than twofold higher trabecular bone volume at the distal femur, which was explained by a higher trabecular number. At the femoral midshaft, PCT-011 exposure increased cortical thickness but did not significantly affect the results of three-point bending tests. Histomorphometric analyses of the lumbar vertebra 4 showed that PCT-011 treatment led to a lower bone formation rate. In conclusion, treatment with the TGFbeta antibody PCT-011 had a positive effect on bone development in *mdx* mice. Inhibiting TGFbeta activity thus appears to be a promising approach to treat bone fragility in the context of DMD.

Keywords: Duchenne muscular dystrophy; bone remodeling; fractures; transforming growth factor beta.

FULL TEXT OPEN ACCESS MDPI

49. Life (Basel). 2021 Jul 30;11(8):772. doi: 10.3390/life11080772.

Prevalence of Bladder and Bowel Dysfunction in Duchenne Muscular Dystrophy Using the Childhood Bladder and Bowel Dysfunction Questionnaire

Judith M Lionarons [1,2], Imelda J M de Groot [3,4], Johanna M Fock [5], Sylvia Klinkenberg [1], Desiree M J Vrijens [6], Anita C E Vreugdenhil [7,8], Evita G Medici-van den Herik [9], Inge Cuppen [10], Bregje Jaeger [11], Erik H Niks [4,12], Rinske Hoogerhuis [13], Nicky Platte-van Attekum [13], Frans J M Feron [14], Catharina G Faber [1,2], Jos G M Hendriksen [4,15], Johan S H Vles [2]

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- PMCID: PMC8399211
- DOI: 10.3390/life11080772

Introduction: Lower urinary tract symptoms (LUTS) and gastrointestinal (GI) problems are common in Duchenne muscular dystrophy (DMD), but not systematically assessed in regular care. We aimed to determine the prevalence of bladder and bowel dysfunction (BBD) in DMD patients compared with healthy controls (HC).

Methods: The Childhood Bladder and Bowel Dysfunction Questionnaire (CBBDQ) based on the International Rome III criteria and the International Children's Continence Society was filled out by 57 DMD patients and 56 HC. Additionally, possible associations of BBD with, for example, medication use or quality of life were evaluated in an additional questionnaire developed by experts.

Results: In 74% of patients versus 56% of HC ≥ 1 LUTS (n.s.) were reported, 68% of patients versus 39% of HC reported ≥1 bowel symptom (p = 0.002) and 53% of patients versus 30% of HC reported combined LUTS and bowel symptoms (p = 0.019). A negative impact of BBD on daily life functioning was reported by 42% of patients.

Conclusions: These data underscore that standard screening for BBD is needed and that the CBBDQ could be of added value to optimize DMD care.

Keywords: Duchenne muscular dystrophy; bladder and bowel dysfunction; constipation; lower urinary tract symptoms; urinary incontinence.

FULL TEXT OPEN ACCESS MDPI

50. Life (Basel). 2021 Jul 27;11(8):752. doi: 10.3390/life11080752.

Influence of Different Types of Corticosteroids on Heart Rate Variability of Individuals with Duchenne Muscular Dystrophy-A Pilot Cross Sectional Study

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- PMID: 34440496
- PMCID: PMC8398672
- DOI: 10.3390/life11080752

Individuals with Duchenne Muscular Dystrophy (DMD) have an impairment of cardiac autonomic function categorized by parasympathetic reduction and sympathetic predominance. The objective of this study was to assess the cardiac autonomic modulation of individuals with DMD undergoing therapy with Prednisone/Prednisolone and Deflazacort and compare with individuals with DMD without the use of these medications and a typically developed control group. Methods: A cross-sectional study was completed, wherein 40 boys were evaluated. The four treatment groups were: Deflazacort; Prednisone/Prednisolone; no corticoid use; and typical development. Heart Rate Variability (HRV) was investigated via linear indices (Time Domain and Frequency Domain) and non-linear indices Results: The results of this study revealed that individuals with DMD undertaking pharmacotherapies with Prednisolone demonstrated HRV comparable to the Control Typically Developed (CTD) group. In contrast, individuals with DMD undergoing pharmacotherapies with Deflazacort achieved lower HRV, akin to individuals with DMD without any medications, as demonstrated in the metrics: RMSSD; LF (n.u.), HF (n.u.), LF/HF; SD1, α1, and α1/α2, and a significant effect for SD1/SD2; %DET and Ratio; Shannon Entropy, 0 V%, 2 LV% and 2 ULV%. Conclusions: Corticosteroids have the potential to affect the cardiac autonomic modulation in adolescents with DMD. The use of Prednisone/Prednisolone appears to promote improved responses in terms of sympathovagal activity as opposed to Deflazacort.

Keywords: Duchenne Muscular Dystrophy (DMD); Heart Rate Variability (HRV); autonomic nervous system; deflazacort; prednisone.

FULL TEXT OPEN ACCESS MDPI

51. Antioxidants (Basel). 2021 Aug 3;10(8):1241. doi: 10.3390/antiox10081241.

A Blood Biomarker for Duchenne Muscular Dystrophy Shows That Oxidation State of Albumin Correlates with Protein Oxidation and Damage in Mdx Muscle

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- PMID: 34439489
- PMCID: PMC8389308
- DOI: 10.3390/antiox10081241

Duchenne muscular dystrophy (DMD) is a severe X-linked muscle wasting disease with no cure. While the precise mechanisms of progressive dystropathology remain unclear, oxidative stress caused by excessive generation of oxidants is strongly implicated. Blood biomarkers that could track oxidant levels in tissues would be valuable to measure the effectiveness of clinical treatments for DMD; our research has focused on developing such biomarkers. One target of oxidants that has the potential to be harnessed as a clinical biomarker is the thiol side chain of cysteine 34 (Cys34) of the blood protein albumin. This study using the *mdx* mouse model of DMD shows that in plasma, albumin Cys34 undergoes thiol oxidation and these changes correlate with levels of protein thiol oxidation and damage of the dystrophic muscles. A comparison with the commonly used biomarker protein carbonylation, confirmed that albumin thiol oxidation is the more sensitive plasma biomarker of oxidative stress occurring in muscle tissue. We show that plasma albumin oxidation reflects muscle dystropathology, as increased after exercise and decreased after taurine treatment of *mdx* mice. These data support the use of albumin thiol oxidation as a blood biomarker of dystropathology to assist with advancing clinical development of therapies for DMD.

Keywords: Cys34 albumin; Duchenne muscular dystrophy; ageing; biomarkers; exercise; mdx mice; oxidative stress; taurine; thiol oxidation.

FULL TEXT OPEN ACCESS MDPI

Dystrophies musculaires des ceintures – *Limb-girdle muscular dystrophies*

52. Neurodegener Dis Manag . 2021 Sep 2. doi: 10.2217/nmt-2020-0066. Online ahead of print.

Unmet needs and evolving treatment for limb girdle muscular dystrophies

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- PMID: 34472379
- DOI: 10.2217/nmt-2020-0066

Limb-girdle muscular dystrophies (LGMDs) represent a major group of muscle disorders. Treatment is sorely needed and currently expanding based on safety and efficacy adopting principles of single-dosing gene therapy for monogenic autosomal recessive disorders. Gene therapy has made in-roads for LGMD and this review describes progress that has been achieved for these conditions. This review first provides a background on the definition and classification of LGMDs. The major effort focuses on progress in LGMD gene therapy, from experimental studies to clinical trials. The disorders discussed include the LGMDs where the most work has been done including calpainopathies (LGMD2A/R1), dysferlinopathies (LGMD2B/R2) and sarcoglycanopathies (LGMD2C/R5, LGMD2D/R3, LGMD2E/R4). Early success in clinical trials provides a template to move the field forward and potentially apply emerging technology like CRISPR/Cas9 that may enhance the scope and efficacy of gene therapy applied to patient care.

Keywords: AAV; gene therapy; limb-girdle muscular dystrophy.

Plain Language Summary

Lay abstract Limb-girdle muscular dystrophy is a term that is applied to a group of relatively rare forms of muscular dystrophy. The term 'LGMD' was introduced in the 1950's, but there were no strict rules for defining the condition. This changed as a result of the 229th European Neuromuscular Center International Workshop in 2017 providing a clear definition and classification discussed in this article. Limb-girdle muscular dystrophy is now recognized as a genetic muscle disease with an elevated serum creatine kinase and dystrophic changes on muscle histology. Most treatments up to now rely on supportive measures for heart and lungs and assisting the physical limitations. Medications have not proven to be beneficial to stop progression of disease. This article focuses on new innovations of treatment that target the effected gene and the use special methods to replace the abnormal gene.

Case Reports

53. Brain Sci . 2021 Jul 31;11(8):1020. doi: 10.3390/brainsci11081020.

Sarcotubular Myopathy Due to Novel *TRIM32* Mutation in Association with Multiple Sclerosis

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- DOI: 10.3390/brainsci11081020

Azerbaijani 28-year-old female showed weakness (MRC (Medical Research Council Scale for Muscle Strength) grade 4 in the proximal part of the upper and MRC grade 2-3 in the lower extremities), difficulty in stair lifting, positive symptom of Hoover's rising, «waddling gait», decline deep reflexes symmetrical, lack of surface reflexes, positive Babinsky's reflex on the right, urinary incontinence during sneezing, prolonged walking and exercise from puberty. Additional methods made it possible to identify minor violations of conduction of the left ventricle, electromyography signs of primary muscular disease with predominant involvement of the proximal muscles of the lower extremities, elevation of serum creatine kinase (746.81

U/l), active foci of demyelination in the left frontal lobe, intrathecal synthesis of oligoclonal IgG bands (type 2) in cerebrospinal fluid, atrophy and fatty degeneration of all muscles of the shins, homozygous Variant of Uncertain Significance (VUS) c.1855C > T (p.Pro619Ser) in TRIM32 gene and heterozygous VUS c.2300C > G (p.Thr767Arg) in KIF5A, c.2840G > A (p.Arg947Lys) in MYH2, c.1502G > C (p.Gly501Ala) in POMT1 genes. Comparison of the phenotypes of the mutations that have been identified with the clinical picture of the patient suggests that VUS c.1855C > T (p.Pro619Ser) in the TRIM32 gene can be pathological. Summarizing, it can be argued that the cause of the identified disorders is a homozygous variant c.1855C > T (p.Pro619Ser) in TRIM32 gene that causes LGMDR8 in a patient with MS.

Keywords: Hoover's rising; LGMD R8; LGMD2H; Limb-Girdle Muscular Dystrophy 2H; TRIM32; multiple sclerosis; muscular dystrophy; next-generation sequencing; sarcotubular myopathy; waddling gait.

FULL TEXT OPEN ACCESS MDPI

Dysferlinopathies – *Dysferlinopathies*

Case Reports

54. J Musculoskelet Neuronal Interact . 2021 Sep 1;21(3):397-400.

Mutation at a new allele of the dysferlin gene causes Miyoshi myopathy: A case report

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- PMID: 34465679
- PMCID: PMC8426653

Miyoshi myopathy (MM) is a rare autosomal recessive disorder caused by dysferlin (DYSF) gene mutation. Miyoshi myopathy-inducing mutation sites in the DYSF gene have been discovered worldwide. In the present study, a patient with progressive lower extremity weakness is reported, for which MM was diagnosed according to clinical manifestations, muscle biopsy, and immunohistochemistry. In addition, the DYSF gene of the patient and his parents was sequenced and analyzed and two heterozygous mutations of the DYSF gene (c.4756C> T and c.5316dupC) were discovered. The first mutation correlated with MM while the second was a new mutation. The patient was diagnosed with a compound heterozygous mutation. The mutation site is a new member of pathogenic MM gene mutations.

Keywords: Dysferlin; Gene Mutation; Miyoshi Myopathy; Muscle; Recessive Inheritance.

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Dystroglycanopathies – *Dystroglycanopathies*

Case Reports

55. Front Pediatr . 2021 Aug 18;9:710553. doi: 10.3389/fped.2021.710553. eCollection 2021.

Case Report: *ISPD* Gene Mutation Leads to Dystroglycanopathies: Genotypic Phenotype Analysis and Treatment Exploration

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- PMID: 34485198
- PMCID: PMC8416436
- DOI: 10.3389/fped.2021.710553

ISPD gene mutation-related diseases have high clinical and genetic heterogeneity, and no studies have yet reported any effective treatments. We describe six patients with dystroglycanopathies caused by ISPD gene mutations and analyze their genotypes and phenotypes to explore possible effective treatments. Our results confirm that the phenotype of limb-girdle muscular dystrophies can be easily misdiagnosed as Duchenne muscular dystrophy and that exon deletions of ISPD gene are relatively common. Moreover, low-dose

prednisone therapy can improve patients' exercise ability and prolong survival and may be a promising new avenue for ISPD therapy.

Keywords: Duchenne muscular dystrophy; ISPD gene; dystroglycanopathies; limb-girdle muscular dystrophies; pediatric.

OPEN ACCESS frontiers

Dystrophie musculaire facioscapulohumérale – *Facioscapulohumeral muscular dystrophy (FSHD)*

56. J Neurol . 2021 Sep 6. doi: 10.1007/s00415-021-10786-1. Online ahead of print.

Diagnostic magnetic resonance imaging biomarkers for facioscapulohumeral muscular dystrophy identified by machine learning

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- PMID: 34486074
- DOI: 10.1007/s00415-021-10786-1

Background: The diagnosis of facioscapulohumeral muscular dystrophy (FSHD) can be challenging in patients not displaying the classical phenotype or with atypical clinical features. Despite the identification by magnetic resonance imaging (MRI) of selective patterns of muscle involvement, their specificity and added diagnostic value are unknown.

Methods: We aimed to identify the radiological features more useful to distinguish FSHD from other myopathies and test the diagnostic accuracy of MRI. A retrospective cohort of 295 patients (187 FSHD, 108 non-FSHD) studied by upper and lower-limb muscle MRI was analyzed. Scans were evaluated for the presence of 15 radiological features. A random forest machine learning algorithm was used to identify the most relevant for FSHD diagnosis. Different patterns were created by their combination and diagnostic accuracy of each of them was tested.

Results: The combination of trapezius involvement and bilateral subscapularis muscle sparing achieved the best diagnostic accuracy (0.89, 95% Confidence Interval [0.85-0.92]) with 0.90 [0.85-0.94] sensitivity and 0.88 [0.80-0.93] specificity. This pattern correctly identified 91% atypical FSHD patients of our cohort. The combination of trapezius involvement, bilateral subscapularis and iliopsoas sparing and asymmetric involvement of upper and lower-limb muscles was pathognomonic for FSHD, yielding a specificity of 0.99 [0.95-1.00].

Conclusions: We identified MRI patterns that showed a high diagnostic power in promptly discriminating FSHD from other muscle disorders, with comparable performance irrespective of typical or atypical clinical features. Upper girdle in addition to lower-limb muscle imaging should be extensively implemented in the diagnostic workup to support or exclude a diagnosis of FSHD.

Keywords: Biomarkers; Facioscapulohumeral muscular dystrophy; Machine learning; Muscle MRI.

SpringerLink FULL-TEXT ARTICLE

57. Mol Ther Nucleic Acids . 2021 Jun 1;25:342-354. doi: 10.1016/j.omtn.2021.05.020. eCollection 2021 Sep 3.

Adenine base editing of the *DUX4* polyadenylation signal for targeted genetic therapy in facioscapulohumeral muscular dystrophy

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- PMID: 34484861
- PMCID: PMC8399085
- DOI: 10.1016/j.omtn.2021.05.020

Facioscapulohumeral muscular dystrophy (FSHD) is caused by chromatin relaxation of the D4Z4 repeat resulting in misexpression of the D4Z4-encoded *DUX4* gene in skeletal muscle. One of the key genetic requirements for the stable production of full-length *DUX4* mRNA in skeletal muscle is a functional polyadenylation signal (ATTAAA) in exon three of *DUX4* that is used in somatic cells. Base editors hold great promise to treat DNA lesions underlying genetic diseases through their ability to carry out specific and rapid nucleotide mutagenesis even in postmitotic cells such as skeletal muscle. In this study, we present a simple and straightforward strategy for mutagenesis of the somatic *DUX4* polyadenylation signal by adenine base editing in immortalized myoblasts derived from independent FSHD-affected individuals. We show that mutating this critical *cis*-regulatory element results in downregulation of *DUX4* mRNA and its direct transcriptional target genes. Our findings identify the somatic *DUX4* polyadenylation signal as a therapeutic target and represent the first step toward clinical application of the CRISPR-Cas9 base editing platform for FSHD gene therapy.

Keywords: CRISPR-Cas9; DUX4; base editing; facioscapulohumeral muscular dystrophy; gene therapy; polyadenylation signal.

58. PLoS Comput Biol . 2021 Aug 30;17(8):e1009263. doi: 10.1371/journal.pcbi.1009263. Online ahead of print.

A multi-objective genetic algorithm to find active modules in multiplex biological networks

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- PMID: 34460810
- DOI: 10.1371/journal.pcbi.1009263

The identification of subnetworks of interest-or active modules-by integrating biological networks with molecular profiles is a key resource to inform on the processes perturbed in different cellular conditions. We here propose MOGAMUN, a Multi-Objective Genetic Algorithm to identify active modules in MUltiplex biological Networks. MOGAMUN optimizes both the density of interactions and the scores of the nodes (e.g., their differential expression). We compare MOGAMUN with state-of-the-art methods, representative of different algorithms dedicated to the identification of active modules in single networks. MOGAMUN identifies dense and high-scoring modules that are also easier to interpret. In addition, to our knowledge, MOGAMUN is the first method able to use multiplex networks. Multiplex networks are composed of different layers of physical and functional relationships between genes and proteins. Each layer is associated to its own meaning, topology, and biases; the multiplex framework allows exploiting this diversity of biological networks. We applied MOGAMUN to identify cellular processes perturbed in Facio-Scapulo-Humeral muscular Dystrophy, by integrating RNA-seq expression data with a multiplex biological network. We identified different active modules of interest, thereby providing new angles for investigating the pathomechanisms of this disease. Availability: MOGAMUN is available at https://github.com/elvanov/MOGAMUN and as a Bioconductor package at https://bioconductor.org/packages/release/bioc/html/MOGAMUN.html. Contact: anais.baudot@univ-amu.fr.

59. J Neuromuscul Dis . 2021 Aug 21. doi: 10.3233/JND-210711. Online ahead of print.

Identification of Serum Interleukin 6 Levels as a Disease Severity Biomarker in Facioscapulohumeral Muscular Dystrophy

Marilyn Gros [1], Andreia M Nunes [2], Douglas Daoudlarian [3], Jonathan Pini [1], Emanuela Martinuzzi [3], Susana Barbosa [3], Monique Ramirez [2], Angela Puma [1], Luisa Villa [1], Michele Cavalli [1], Nicolae Grecu [1], Jérémy Garcia [4], Gabriele Siciliano [5], Guilhem Solé [6], Raul Juntas-Morales [7], Peter L Jones [2], Takako Jones [2], Nicolas Glaichenhaus [3], Sabrina Sacconi [1 8 9]

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- PMID: 34459413
- DOI: 10.3233/JND-210711

Background: Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common myopathies in adults, displaying a progressive, frequently asymmetric involvement of a typical muscles' pattern. FSHD is associated with epigenetic derepression of the polymorphic D4Z4 repeat on chromosome 4q, leading to DUX4 retrogene toxic expression in skeletal muscles. Identifying biomarkers that correlate with disease severity would facilitate clinical management and assess potential FSHD therapeutics' efficacy.

Objectives: This study purpose was to analyze serum cytokines to identify potential biomarkers in a large cohort of adult patients with FSHD.

Methods: We retrospectively measured the levels of 20 pro-inflammatory and regulatory cytokines in sera from 100 genetically confirmed adult FSHD1 patients. Associations between cytokine concentrations and various clinical scores were investigated. We then measured serum and muscle interleukin 6 (IL-6) levels in a validated FSHD-like mouse model, ranging in severity and DUX4 expression.

Results: IL-6 was identified as the only cytokine with a concentration correlating with several clinical severity and functional scores, including Clinical Severity Score, Manual Muscle Testing sum score, Brooke and Vignos scores. Further, FSHD patients displayed overall IL-6 levels more than twice high as control, and patients with milder phenotypes exhibited lower IL-6 serum concentration than those with severe muscular weakness. Lastly, an FSHD-like mouse model analysis confirmed that IL-6 levels positively correlate with disease severity and DUX4 expression.

Conclusions: Serum IL-6, therefore, shows promise as a serum biomarker of FSHD severity in a large cohort of FSHD1 adult patients.

Keywords: Facioscapulohumeral muscular dystrophy (FSHD); Interleukin-6; cytokines; disease biomarkers.

IOS Press Full Text

Case Reports

60. Neuromuscul Disord . 2021 Jun 18;S0960-8966(21)00160-7. Online ahead of print.

Facioscapulohumeral Muscular Dystrophy and Poliomyelitis followed by Multiple Sclerosis: A "triple trouble" case report and review of the literature on the association of MS and muscle disorders

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- PMID: 34446310
- DOI: 10.1016/j.nmd.2021.06.006

We describe herein a "triple trouble" case of a patient affected by Facioscapulohumeral Muscular Dystrophy type 1 (FSHD1), with a previous history of poliomyelitis, who later developed Multiple Sclerosis (MS). Association of muscle disorders and MS is uncommon; in fact, there are only three case reports of this unusual co-occurrence. As regard as this combination, some hypotheses have been raised about the role of immunological factors. Genetic basis of FSHD1 is a deletion of a critical number of macrosatellite repeats (D4Z4) in the subtelomeric region of chromosome 4q35, resulting in transcriptional de-repression of a gene DUX4. This molecular change could induce an alteration of immune responses, likely conferring susceptibility to both diseases. In this case, poliomyelitis could have delayed the FSHD1 diagnosis and likely acted as a trigger for MS onset. Association of multiple neurological disorders has to be kept in mind to avoid misinterpretation of symptoms and diagnostic delays.

Keywords: Facioscapulohumeral dystrophy type 1; Multiple sclerosis; Myopathy; Poliomyelitis.

ELSEVIER FULL-TEXT ARTICLE

61. Diagnostics (Basel) . 2021 Aug 13;11(8):1469. doi: 10.3390/diagnostics11081469.

Precise Epigenetic Analysis Using Targeted Bisulfite Genomic Sequencing Distinguishes FSHD1, FSHD2, and Healthy Subjects

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- PMID: 34441403
- PMCID: PMC8393475
- DOI: 10.3390/diagnostics11081469

The true prevalence of facioscapulohumeral muscular dystrophy (FSHD) is unknown due to difficulties with accurate clinical evaluation and the complexities of current genetic diagnostics. Interestingly, all forms of FSHD are linked to epigenetic changes in the chromosome 4q35 D4Z4 macrosatellite, suggesting that epigenetic analysis could provide an avenue for sequence-based FSHD diagnostics. However, studies assessing DNA methylation at the FSHD locus have produced conflicting results; thus, the utility of this technique as an FSHD diagnostic remains controversial. Here, we critically compared two protocols for epigenetic analysis of the FSHD region using bisulfite genomic sequencing: Jones et al., that contends to be individually diagnostic for FSHD1 and FSHD2, and Gaillard et al., that can identify some changes in DNA methylation levels between groups of clinically affected FSHD and healthy subjects, but is not individually diagnostic for any form of FSHD. We performed both sets of assays on the same genetically confirmed samples and showed that this discrepancy was due strictly to differences in amplicon specificity. We propose that the epigenetic status of the FSHD-associated D4Z4 arrays, when accurately assessed, is a diagnostic for genetic FSHD and can readily distinguish between healthy, FSHD1 and FSHD2. Thus, epigenetic diagnosis of FSHD, which can be performed on saliva DNA, will greatly increase accessibility to FSHD diagnostics for populations around the world.

Keywords: D4Z4; DNA methylation; DUX4; FSHD; epigenetics; muscular dystrophy.

FULL TEXT OPEN ACCESS MDPI

Dystrophies myotoniques – *Myotonic dystrophies*

62. Front Cell Dev Biol . 2021 Aug 19;9:710112. doi: 10.3389/fcell.2021.710112. eCollection 2021.

Inhibition of *Postn* Rescues Myogenesis Defects in Myotonic Dystrophy Type 1 Myoblast Model

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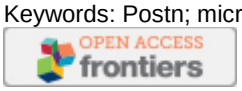
- PMID: 34490258
- PMCID: PMC8417118
- DOI: 10.3389/fcell.2021.710112

Myotonic dystrophy type 1 (DM1) is an inherited neuromuscular disease caused by expanded CTG repeats in the 3' untranslated region (3'UTR) of the DMPK gene. The myogenesis process is defective in DM1, which is closely associated with progressive muscle weakness and wasting. Despite many proposed explanations for the myogenesis defects in DM1, the underlying mechanism and the involvement of the extracellular microenvironment remained unknown. Here, we constructed a DM1 myoblast cell model and reproduced the myogenesis defects. By RNA sequencing (RNA-seq), we discovered that periostin (Postn) was the most significantly upregulated gene in DM1 myogenesis compared with normal controls. This difference in Postn was confirmed by real-time quantitative PCR (RT-qPCR) and western blotting. Moreover, Postn was found to be significantly upregulated in skeletal muscle and myoblasts of DM1 patients. Next, we knocked down Postn using a short hairpin RNA (shRNA) in DM1 myoblast cells and found that the myogenesis defects in the DM1 group were successfully rescued, as evidenced by increases in the myotube area, the fusion index, and the expression of myogenesis regulatory genes. Similarly, Postn knockdown in normal myoblast cells enhanced myogenesis. As POSTN is a secreted protein, we treated the DM1 myoblast cells with a POSTN-neutralizing antibody and found that DM1 myogenesis defects were successfully rescued by POSTN neutralization. We also tested the myogenic ability of myoblasts in the skeletal muscle injury mouse model and found that Postn knockdown improved the myogenic ability of DM1 myoblasts. The activity of the TGF-β/Smad3 pathway was upregulated during DM1 myogenesis but repressed when inhibiting Postn with a Postn shRNA or a POSTN-neutralizing antibody, which suggested that the TGF-β/Smad3 pathway might mediate the function of Postn in DM1 myogenesis. These results suggest that Postn is a potential therapeutical target for the treatment of myogenesis defects in DM1.

Keywords: Postn; microenvironment; myoblast; myogenesis; myotonic dystrophy type 1.



Review

63. Biochim Biophys Acta Gen Subj . 2021 Nov;1865(11):129996.129996. Epub 2021 Aug 30.

What's new about CNBP? Divergent functions and activities for a conserved nucleic acid binding protein

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- PMID: 34474118
- DOI: 10.1016/j.bbagen.2021.129996

Background: Cellular nucleic acid binding protein (CNBP) is a conserved single-stranded nucleic acid binding protein present in most eukaryotes, but not in plants. Expansions in the CNBP gene cause myotonic dystrophy type 2. Initially reported as a transcriptional regulator, CNBP was then also identified acting as a translational regulator.

Scope of review: The focus of this review was to link the CNBP structural features and newly reported biochemical activities with the recently described biological functions, in the context of its pathological significance.

Major conclusions: Several post-translational modifications affect CNBP subcellular localization and activity. CNBP participates in the transcriptional and translational regulation of a wide range of genes by remodeling

single-stranded nucleic acid secondary structures and/or by modulating the activity of trans-acting factors. CNBP is required for proper neural crest and heart development, and plays a role in cell proliferation control. Besides, CNBP has been linked with neurodegenerative, inflammatory, and congenital diseases, as well as with tumor processes.

General significance: This review provides an insight into the growing functions of CNBP in cell biology. A unique and robust mechanistic or biochemical connection among these roles has yet not been elucidated. However, the ability of CNBP to dynamically integrate signaling pathways and to act as nucleic acid chaperone may explain most of the roles and functions identified so far.

Keywords: Cell proliferation; Craniofacial development; G-Quadruplex; Inflammatory response; Nucleic acid chaperone; Viral infection.

ELSEVIER FULL-TEXT ARTICLE

Case Reports

64. Lung India . Sep-Oct 2021;38(5):486-488. doi: 10.4103/lungindia.lungindia_25_21.

Mediastinal and pleural lipomatosis as a manifestation of myotonic dystrophy type 1

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- PMID: 34472530
- DOI: 10.4103/lungindia.lungindia_25_21

Mediastinal and pleural lipomatosis is a rare but usually benign and asymptomatic disease. Mediastinal lipomatosis is associated with steroid use, obesity, hyperlipidemia, diabetes, or Cushing syndrome. In some cases, it becomes symptomatic manifesting with dyspnea, thoracic pain, coughing, dysphonia, dysphagia, supraventricular tachycardia, or persistent pneumonia. Mediastinal lipomatosis has not been reported in association with myotonic dystrophy type 1 (MD1). In a 65yo male with a long-term history of progressive muscle weakness, hyper-creatine-kinase-emia, bilateral cataract, sleep apnea syndrome, gynecomastia, hepatic steatosis, arterial hypertension, atrioventricular block 1, QTc prolongation, hyperlipidemia, hyperuricemia, and hepatopathy, MD1 was diagnosed upon the clinical presentation and a heterozygous CTG repeat expansion of 1200-1400 repeats in DMPK. Work-up for dyspnea and leg edema revealed heart failure and mediastinal and pleural lipomatosis. Upon standard treatment, heart failure resolved. In conclusion, mediastinal and pleural lipomatosis can be a rare manifestation of MD1 and can manifest with heart failure. In patients with mediastinal lipomatosis, MD1 should be excluded.

Keywords: CTG repeats; Cardiac involvement; lipomatosis; multisystem; myotonic dystrophy.

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65. Ann Indian Acad Neurol . May-Jun 2021;24(3):429-430. doi: 10.4103/aian.AIAN_473_20. Epub 2021 Jan 11.

Type 1 Myotonic Dystrophy Presenting with Bulbar Weakness without Myotonia

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- PMID: 34447014
- PMCID: PMC8370145
- DOI: 10.4103/aian.AIAN_473_20

No abstract available

66. Int J Mol Sci . 2021 Aug 10;22(16):8607. doi: 10.3390/ijms22168607.

Transcriptome Analysis in a Primary Human Muscle Cell Differentiation Model for Myotonic Dystrophy Type 1

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- PMID: 34445314
- PMCID: PMC8395314
- DOI: 10.3390/ijms22168607

Myotonic dystrophy type 1 (DM1) is caused by CTG-repeat expansions leading to a complex pathology with a multisystemic phenotype that primarily affects the muscles and brain. Despite a multitude of information, especially on the alternative splicing of several genes involved in the pathology, information about additional factors contributing to the disease development is still lacking. We performed RNAseq and gene expression analyses on proliferating primary human myoblasts and differentiated myotubes. GO-term analysis indicates that in myoblasts and myotubes, different molecular pathologies are involved in the development of the muscular phenotype. Gene set enrichment for splicing reveals the likelihood of whole, differentiation stage specific, splicing complexes that are misregulated in DM1. These data add complexity to the alternative splicing phenotype and we predict that it will be of high importance for therapeutic interventions to target not only mature muscle, but also satellite cells.

Keywords: human primary muscle cell culture; myotonic dystrophy type 1; splicing; transcriptomics.

FULL TEXT OPEN ACCESS MDPI

Fibrodysplasie ossifiante progressive (FOP) – Fibrodysplasia ossificans progressiva

67. Intractable Rare Dis Res . 2021 Aug;10(3):179-189. doi: 10.5582/irdr.2021.01012.

Rare and intractable fibrodysplasia ossificans progressiva shows different PBMC phenotype possibly modulated by ascorbic acid and propranolol treatment

Deborah Ribeiro Nascimento [1], Suzana Lopes Bomfim Balaniuc [1], Durval Batista Palhares [1], Adam Underwood [2], Marilene Garcia Palhares [1], Fabiana Alves [3,4], Francisco Oliveira Vieira [3,4], Elaine Maria Souza-Fagundes [3], Liane De Rosso Giuliani [1], Paula Cristhina Niz Xavier [1], Helen Lima Del Puerto [3], Robson Augusto Souza Santos [3], Amy Milsted [2], Jose Mauro Brum [5], Iandara Schettert Silva [1], Almir Sousa Martins [1,3]

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- PMID: 34466340
- PMCID: PMC8397826
- DOI: 10.5582/irdr.2021.01012

Fibrodysplasia Ossificans Progressiva (FOP) is a rare congenital intractable disease associated with a mutation in *ACVR1* gene, characterized by skeleton malformations. Ascorbic acid (AA) and propranolol (PP) in combination is reported to minimize flare-ups in patients. FOP leukocyte phenotype may possibly be modulated by AA and PP treatment. In this study, expression of 22 potential target genes was analyzed by RT-PCR in peripheral blood mononuclear cells culture (PBMC) from FOP patients and controls to determine effectiveness of the combination therapy. PBMC were treated with AA, PP and AA+PP combination. Basal expression of 12 of the 22 genes in FOP PBMC was statistically different from controls. *ACVR1*, *ADCY2*, *ADCY9* and *COL3* were downregulated while *COL1* was upregulated. *ADRB1*, *ADRB2*, *RUNX2*, *TNF-α* and *ACTB*, were all overexpressed in FOP PBMC. In control, AA upregulated *COL1, SVCT1, ACTB, AGTR2* and downregulated *ADCY2*. In FOP cells, AA upregulated *ACVR1, BMP4, COL1, COL3, TNF-α*, *ADCY2, ADCY9, AGTR2* and *MAS*, while downregulated *ADBR2, RUNX2, ADCY1, SVCT1* and *ACTB*. PP increased *ADBR1* and decreased *RUNX2, TNF-α, AGTR1, ACTB* and *CHRNA7* genes in treated control PBMC compared to untreated. PP upregulated *ADBR1, ADBR2* and *MAS*, and downregulated *TNF-α* and *ACTB* in treated FOP PBMC versus untreated. AA+PP augmented *ADRB1* and *ADRB2* expressions in control PBMC. In FOP PBMC, AA+PP augmented *ACVR1, COL1, COL3, ADBR1, AGTR2* and *MAS* expression and downregulated *ADBR2, RUNX2, ACTB* and *MRGD*. These data show distinct gene expression modulation in leukocytes from FOP patients when treated with AA and or PP.

Keywords: FOP; FOPCON; gene expression modulation; peripheral blood mononuclear cells.

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Case Reports

68. Genes (Basel) . 2021 Jul 30;12(8):1187. doi: 10.3390/genes12081187.

Fibrodysplasia Ossificans Progressiva: A Challenging Diagnosis

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- PMID: 34440363
- PMCID: PMC8391109
- DOI: 10.3390/genes12081187

Fibrodysplasia ossificans progressiva (FOP) is an ultrarare genetic condition characterized by extraskeletal bone formation. Most of the musculoskeletal characteristics of FOP are related to dysregulated chondrogenesis, with heterotopic ossification being the most typical feature. Activating mutations of activin receptor A type I (ACVR1), a bone morphogenetic protein (BMP) type I receptor, are responsible for the skeletal and nonskeletal features. The clinical phenotype is always consistent, with congenital bilateral hallux valgus malformation and early-onset heterotopic ossification occurring spontaneously or, more frequently, precipitated by trauma. Painful, recurrent soft-tissue swellings (flare-ups) precede localized heterotopic ossification that can occur at any location, typically affecting regions near the axial skeleton and later progressing to the appendicular bones. A diagnosis of FOP is suspected in a proband presenting with hallux valgus malformation, heterotopic ossification, and confirmed by the identification of a heterozygous pathogenic variant in the *ACVR1/ALK2* gene. Avoiding unnecessary surgical procedures, prescribing prophylactic corticosteroids, preventing falls, and using protective headgear represent essential interventions for care management. Different classes of medications to contain acute inflammation flare-ups have been proposed, with high dose corticosteroids and nonsteroidal anti-inflammatory drugs usually utilized. Here, we report on two FOP patients, with typical clinical features summarizing the principal aspects of FOP, and we aim to provide comprehensive information outlining some unusual findings, possibly contributing to FOP's definition and management.

Keywords: ACVR1; ACVR1/ALK2; CNS; FOP; MRI; fibrodysplasia ossificans progressiva; heterotopic ossification.

FULL TEXT OPEN ACCESS MDPI

Maladie de Charcot-Marie-Tooth – *Charcot-Marie-Tooth disease*

69. Stem Cell Res . 2021 Aug 26;56:102520. doi: 10.1016/j.scr.2021.102520. Online ahead of print.

Generation and characterization of an endogenously tagged SPG11-human iPSC line by CRISPR/Cas9 mediated knock-in

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- PMID: 34479069
- DOI: 10.1016/j.scr.2021.102520

Pathogenic bi-allelic variants in the SPG11 gene result in rare motor neuron disorders such as Hereditary Spastic Paraplegia type 11, Charcot-Marie Tooth, and Juvenile Amyotrophic Lateral Sclerosis-5. The main

challenge in SPG11-linked disease research is the lack of antibodies against SPG11 encoded spatacsin. Here, we describe the CRISPR/Cas9 mediated generation and validation of an endogenously tagged SPG11-human iPSC line that contains an HA tag at the C-terminus of SPG11. The line exhibits multi-lineage differentiation potential and holds promise for studying the role of spatacsin and for the elucidation of SPG11-associated pathogenesis. Resource Table.

ELSEVIER OPEN ACCESS

Review

70. J Peripher Nerv Syst . 2021 Sep 9. doi: 10.1111/jns.12467. Online ahead of print.

HEREDITARY NEUROPATHIES, A PATHOLOGICAL PERSPECTIVE

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- PMID: 34499384
- DOI: 10.1111/jns.12467

Hereditary neuropathies may result from mutations in genes expressed by Schwann cells or neurons that affect selectively the peripheral nervous system, or may represent a minor or major component of complex inherited diseases that involve also the central nervous system and/or other organs and tissues. The chapter is constantly expanding and reworking thanks to advances of molecular genetics; next-generation sequencing is identifying a plethora of new genes and is revolutionizing the diagnostic approach. In the past, diagnostic sural nerve biopsies paved the way to the discovery and elucidation of major genes and molecular pathways associated to most frequent hereditary motor-sensory neuropathies. Nowadays, a sural nerve biopsy may prove useful in selected cases for the differential diagnosis of an acquired neuropathy when clinical examination, nerve conduction studies and molecular tests are not sufficiently informative. Skin biopsy has emerged as a minimally invasive window on the peripheral nervous system which may provide biomarkers of progression and clues to the physiopathology and molecular pathology of inherited neuropathies. The aim of our review is to illustrate the pathological features of more frequent and paradigmatic hereditary neuropathies and to highlight their correlations with the roles of the involved genes and functional consequences of related molecular defects.

Keywords: Charcot-Marie-Tooth disease; Hereditary amyloid neuropathy; Inherited complex neuropathies; Nerve biopsy; Skin biopsy.

WILEY Full Text Article

71. J Peripher Nerv Syst . 2021 Sep 9. doi: 10.1111/jns.12463. Online ahead of print.

Nerve pathology in animal models of neuropathies

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- PMID: 34498774
- DOI: 10.1111/jns.12463

To understand the pathology of axonal degeneration and demyelination in peripheral neuropathy, histological investigations in different animal models that mimic some aspects of human peripheral neuropathy are needed. Thus, in the following section of this special issue, the main pathological features of experimental autoimmune neuritis, animal models of chemotherapy-induced peripheral neuropath and of human inherited peripheral neuropathies (IPNs) will be illustrated. When possible, micrographs from animal models and selected human biopsy will be shown side by side.

Keywords: Charcot-Marie-Tooth; chemotherapy-induced peripheral neuropathy; experimental autoimmune neuritis; inherited peripheral neuropathies.

WILEY Full Text Article

72. Neuroradiology . 2021 Sep 9. doi: 10.1007/s00234-021-02730-x. Online ahead of print.

Structural and functional brain changes in X-linked Charcot-Marie-Tooth disease: insights from a multimodal neuroimaging study

Efstratios Karavasilis [1], Foteini Christidi [2], Eirini Pantou [3], Georgia Angelopoulou [4], Dimitrios Kasselimis [4], Marianthi Breza [4], Zoi Kontogeorgiou [5], Dimitrios Filippiadis [3], Constantin Potagas [4], Georgia Karadima [5], Georgios Koutsis [# 5], Georgios Velonakis [# 3]

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- PMID: 34498107
- DOI: 10.1007/s00234-021-02730-x

Purpose: Brain involvement in X-linked Charcot-Marie-Tooth disease (CMTX) has been previously reported. We studied the brain structural and functional integrity using a multimodal neuroimaging approach in patients with no current central nervous system (CNS) symptoms, in order to further delineate the disease's phenotype.

Methods: Seventeen CMTX patients with no current CNS symptoms and 24 matched healthy controls underwent brain magnetic resonance imaging (MRI). Structural integrity was evaluated performing Gray matter analysis with voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) of diffusion tensor imaging (DTI). Functional integrity was evaluated with resting-state functional MRI (rs-fMRI).

Results: Decreased gray matter density was detected in CMTX patients compared to healthy controls in bilateral hippocampus, left thalamus, left postcentral gyrus, left superior parietal lobule, left cerebellum crus I and II, and vermis VI. DTI analysis showed increased fractional anisotropy and radial diffusivity in the right anterior insula and increased axial diffusivity in right cerebellum crus I in CMTX patients. rs-fMRI revealed decreased spontaneous neural activity on left precentral gyrus in patients compared to healthy controls.

Conclusion: Advanced magnetic resonance (MR) neuroimaging techniques in CMTX patients revealed structural and functional involvement of multiple motor and extra-motor brain areas. MR neuroimaging techniques have the potential to delineate the CNS phenotype of a peripheral neuropathy like CMTX.

Keywords: Charcot-Marie-Tooth; Diffusion tensor imaging; Gray matter volumetry; Neuroimaging; Resting-state fMRI.

SpringerLink FULL-TEXT ARTICLE

73. Neurology . 2021 Sep 7;10.1212/WNL.0000000000012725. Online ahead of print.

Association Between Body Mass Index and Disability in Children With Charcot-Marie-Tooth Disease

Gabrielle A Donlevy [1 2], Sarah P Garnett [3 2], Kayla M D Cornett [4 2], Marnee J McKay [4], Jennifer N Baldwin [5], Rosemary R Shy [6], Sabrina W Yum [7 8], Timothy Estilow [8 9], Isabella Moroni [10], Maria Foscan [10], Emanuela Pagliano [10], Davide Pareyson [10], Matilde Laura [11], Trupti Bhandari [12], Francesco Muntoni [12], Mary M Reilly [11], Richard S Finkel [13], Janet E Sowden [14], Katy J Eichinger [14], David N Herrmann [14], Michael E Shy [15], Joshua Burns [4 2], Manoj P Menezes [3 2]

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- PMID: 34493614
- DOI: 10.1212/WNL.0000000000012725

Objective: This study examined the association between body mass index (BMI) and disability in children with Charcot-Marie-Tooth disease (CMT).

Methods: We conducted a cross-sectional analysis of 477 patients with CMT aged 3-20 years from the Inherited Neuropathy Consortium, and 316 age-and-sex matched healthy children from the 1000 Norms Project. BMI was categorised according to the International Obesity Task Force (IOTF) criteria, and BMI categorisation was compared with healthy children. IOTF categories (adult equivalent BMI cut points) were: severely underweight (BMI<17kg/m2); underweight (BMI≥17 to <18.5kg/m2); healthy weight (BMI≥18.5 to <25kg/m2); overweight (BMI ≥25 to <30kg/m2); obese (BMI ≥30kg/m2). Scores on the 0-44 point CMT Pediatric Scale (CMTPedS), a well-validated measure of disability, were examined in relation to BMI.

Results: There was a higher proportion of children with CMT categorised as severely underweight (5.7%vs0.3%), underweight (10.3%vs5.1%), and obese (7.3%vs3.8%) (p<0.05). Fewer children with CMT were categorised as healthy weight (61.8%vs74.4%) (p<0.05), and the proportion of overweight (14.9%vs16.5%) between groups was similar. CMTPedS scores (mean ± SD) for weight categories were: severely underweight (27±9), underweight (20±8), healthy weight (17±9), overweight (17±9) obese (22 ±10). Compared to healthy weight children with CMT, being severely underweight was associated with being more disabled (p<0.001), as was being obese (p=0.015).

Conclusion: The proportion of underweight and obese children with CMT is higher compared to age-and sex-matched healthy children. Children with CMT who are underweight or obese are associated with greater disability than compared children with CMT of healthy weight.

Neurology

74. J Cell Sci . 2021 Sep 6;jcs.258559. doi: 10.1242/jcs.258559. Online ahead of print.

Tubular microdomains of Rab7-endosomes retrieve TrkA, a mechanism disrupted in Charcot-Marie-Tooth 2B

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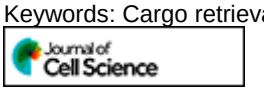
- PMID: 34486665
- DOI: 10.1242/jcs.258559

Axonal survival and growth requires signalling from tropomyosin receptor kinases (Trks). To transmit their signals, receptor-ligand complexes are endocytosed and retrogradely trafficked to the soma where downstream signalling occurs. Vesicles transporting neurotrophic receptors to the soma are reported to be Rab7-positive late endosomes/multi vesicular bodies where receptors localize within so-called intraluminal vesicles. Therefore, one challenging question is how downstream signalling is possible given the insulating properties of intraluminal vesicles. In this study, we report that Rab7-endosomes/multi vesicular bodies retrieve TrkA through tubular microdomains. Interestingly, this phenotype is absent for the EGF-receptor.

Further, we found that EndophilinA1, EndophilinA2 and EndophilinA3 together with WASH1 are involved in the tubulation process. In Charcot-Marie-Tooth 2B, a neuropathy of the peripheral nervous system, this tubulating mechanism is disrupted. In addition, the ability to tubulate correlates with the phosphorylation levels of TrkA as well as with neurite length in neuronal cultures from dorsal root ganglia. In all, we report a new retrieval mechanism of late Rab7-endosomes, which enables TrkA signalling and sheds new light onto how neurotrophic signalling is disrupted in CMT2B.

Keywords: Cargo retrieval; Charcot-Marie-Tooth disease 2B; Endosomes; Neurotrophins; Signalling.



75. Front Cell Dev Biol . 2021 Aug 16;9:723023. doi: 10.3389/fcell.2021.723023. eCollection 2021.

Allele-Specific Gene Editing Rescues Pathology in a Human Model of Charcot-Marie-Tooth Disease Type 2E

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- PMID: 34485306
- PMCID: PMC8415563
- DOI: 10.3389/fcell.2021.723023

Many neuromuscular disorders are caused by dominant missense mutations that lead to dominant-negative or gain-of-function pathology. This category of disease is challenging to address via drug treatment or gene augmentation therapy because these strategies may not eliminate the effects of the mutant protein or RNA. Thus, effective treatments are severely lacking for these dominant diseases, which often cause severe disability or death. The targeted inactivation of dominant disease alleles by gene editing is a promising approach with the potential to completely remove the cause of pathology with a single treatment. Here, we demonstrate that allele-specific CRISPR gene editing in a human model of axonal Charcot-Marie-Tooth (CMT) disease rescues pathology caused by a dominant missense mutation in the neurofilament light chain gene (*NEFL*, CMT type 2E). We utilized a rapid and efficient method for generating spinal motor neurons from human induced pluripotent stem cells (iPSCs) derived from a patient with CMT2E. Diseased motor neurons recapitulated known pathologic phenotypes at early time points of differentiation, including aberrant accumulation of neurofilament light chain protein in neuronal cell bodies. We selectively inactivated the disease *NEFL* allele in patient iPSCs using Cas9 enzymes to introduce a frameshift at the pathogenic N98S mutation. Motor neurons carrying this allele-specific frameshift demonstrated an amelioration of the disease phenotype comparable to that seen in an isogenic control with precise correction of the mutation. Our results validate allele-specific gene editing as a therapeutic approach for CMT2E and as a promising strategy to silence dominant mutations in any gene for which heterozygous loss-of-function is well tolerated. This highlights the potential for gene editing as a therapy for currently untreatable dominant neurologic diseases.

Keywords: CRISPR-Cas9; Charcot-Marie-Tooth; dominant; gene editing; induced pluripotent stem cells; motor neurons; neuropathy.

Review

76. Front Mol Neurosci . 2021 Aug 16;14:695294. doi: 10.3389/fnmol.2021.695294. eCollection 2021.

Held Up in Traffic-Defects in the Trafficking Machinery in Charcot-Marie-Tooth Disease

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- PMID: 34483837
- PMCID: PMC8415527
- DOI: 10.3389/fnmol.2021.695294

Charcot-Marie-Tooth disease (CMT), also known as motor and sensory neuropathy, describes a clinically and genetically heterogenous group of disorders affecting the peripheral nervous system. CMT typically arises in early adulthood and is manifested by progressive loss of motor and sensory functions; however, the mechanisms leading to the pathogenesis are not fully understood. In this review, we discuss disrupted intracellular transport as a common denominator in the pathogenesis of different CMT subtypes. Intracellular transport via the endosomal system is essential for the delivery of lipids, proteins, and organelles bidirectionally to synapses and the soma. As neurons of the peripheral nervous system are amongst the longest neurons in the human body, they are particularly susceptible to damage of the intracellular transport system, leading to a loss in axonal integrity and neuronal death. Interestingly, defects in intracellular transport, both in neurons and Schwann cells, have been found to provoke disease. This review explains the mechanisms of trafficking and subsequently summarizes and discusses the latest findings on how defects in trafficking lead to CMT. A deeper understanding of intracellular trafficking defects in CMT will expand our understanding of CMT pathogenesis and will provide novel approaches for therapeutic treatments.

Keywords: Charcot-Marie-Tooth; endosomal system; signaling; trafficking; transport.

77. Lab Med . 2021 Sep 4;lmab060. doi: 10.1093/labmed/lmab060. Online ahead of print.

A Novel Mutation of the Membrane Metallo-Endopeptidase Gene Related to Late-Onset Hereditary Polyneuropathy: Case Report and Review of the Literature

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- PMID: 34480178
- DOI: 10.1093/labmed/lmab060

The advent of next generation sequencing has revolutionized diagnostic approaches to hereditary polyneuropathies. Recently, mutations on the membrane metallo-endopeptidase (MME) gene, encoding neprilysin, have been related to the development of late-onset Charcot-Marie-Tooth disease type 2 (CMT2). Here, we report the first Greek patient presenting with a slowly progressive late-onset axonal polyneuropathy and a novel, likely pathogenic, heterozygous variant in the MME gene. In addition, we have performed a systematic review of all published case reports of patients with MME mutations. The results of the studies show that MME variants can be inherited as both fully penetrant autosomal-recessive and incompletely penetrant autosomal-dominant traits. A number of heterozygous variants characterized as incompletely penetrant impose an increased risk of developing a CMT2-like phenotype late in life, identical to the case study described here. Greater mutation numbers in different populations and mutation-specific functional studies will be essential to identify the pathogenicity and inheritance of more MME variants.

Keywords: CD10; HMSN; MME; late-onset CMT; membrane metallo-endopeptidase; neprilysin.

78. Neurol Genet . 2021 Aug 31;7(5):e621. doi: 10.1212/NXG.0000000000000621. eCollection 2021 Oct.

Genetic Survey of Autosomal Recessive Peripheral Neuropathy Cases Unravels High Genetic Heterogeneity in a Turkish Cohort

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Neurology, Istanbul Faculty of Medicine, Istanbul University, Turkey; and Molecular Medicine Center (A.J.), Department of Medical Chemistry and Biochemistry, Medical University-Sofia, Bulgaria.

- PMID: 34476298
- PMCID: PMC8409130
- DOI: 10.1212/NXG.0000000000000621

Background and objectives: Inherited peripheral neuropathies (IPNs) are a group of genetic disorders of the peripheral nervous system in which neuropathy is the only or the most predominant clinical feature. The most common type of IPN is Charcot-Marie-Tooth (CMT) disease. Autosomal recessive CMT (ARCMT) is generally more severe than dominant CMT and its genetic basis is poorly understood due to high clinical and genetic diversity. Here, we report clinical and genetic findings from 56 consanguineous Turkish families initially diagnosed with CMT disease.

Methods: We initially screened the GDAP1 gene in our cohort as it is the most commonly mutated ARCMT gene. Next, whole-exome sequencing and homozygosity mapping based on whole-exome sequencing (HOMWES) analysis was performed. To understand the molecular impact of candidate causative genes, functional analyses were performed in patient primary fibroblasts.

Results: Biallelic recurrent mutations in the GDAP1 gene have been identified in 6 patients. Whole-exome sequencing and HOMWES analysis revealed 16 recurrent and 13 novel disease-causing alleles in known IPN-related genes and 2 novel candidate genes: 1 for a CMT-like disease and 1 for autosomal recessive cerebellar ataxia with axonal neuropathy. We have achieved a potential genetic diagnosis rate of 62.5% (35/56 families) in our cohort. Considering only the variants that meet the American College for Medical Genetics and Genomics (ACMG) classification as pathogenic or likely pathogenic, the definitive diagnosis rate was 55.35% (31/56 families).

Discussion: This study paints a genetic landscape of the Turkish ARCMT population and reports additional candidate genes that might help enlighten the mechanism of pathogenesis of the disease.

79. J Genet . 2021;100:58.

Novel compound heterozygous missense mutations in *GDAP1* cause Charcot-Marie-Tooth type 4A

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- PMID: 34470922

Homozygous or compound heterozygous mutations in the *GDAP1* gene cause Charcot-Marie-Tooth (CMT4A) that are consistent with an autosomal recessive mode of inheritance. The case reported in this study is clinically and genetically diagnosed with recessive CMT4A that is caused by a compound novel heterozygous *GDAP1* mutation. The genomic DNA of the proband with the clinical diagnosis of CMT was screened for *GDAP1* mutations using a targeted next-generation sequencing (NGS) gene-panel that comprised of 27 CMT genes. Two novel compound heterozygous amino acid changing variants were identified in the *GDAP1* gene, c.246C>G p.His82Gln in exon 2 and c.614T>G p.Leu205Trp in exon 5. The two amino acid changing variants were not previously reported in the 1000 Genome, Mutation Taster and gnomAD. Our findings expand the phenotypic characterization of the two novel heterozygous mutations associated with CMT4A (AR-CMT1A) and add to the repertoire of *GDAP1* mutations related to autosomal recessive CMT in Chinese populations.

80. J Neuromuscul Dis . 2021 Aug 24. doi: 10.3233/JND-210681. Online ahead of print.

Early Changes in Skeletal Muscle of Young C22 Mice, A Model of Charcot-Marie-Tooth 1A

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- PMID: 34459411
- DOI: 10.3233/JND-210681

Background: The C22 mouse is a Charcot-Marie-Tooth 1A transgenic model with minimal axonal loss.

Objective: To analyse early skeletal muscle changes resulting from this dysmyelinating neuropathy.
Methods: Histology of tibialis anterior muscles of C22 mice and wild type litter mate controls for morphometric analysis and (immuno-)histochemistry for known denervation markers and candidate proteins identified by representational difference analysis (RDA) based on mRNA from the same muscles; quantitative PCR and Western blotting for confirmation of RDA findings.
Results: At age 10 days, morphometry was not different between groups, while at 21 days, C22 showed significantly more small diameter fibres, indicating the onset of atrophy at an age when weakness becomes detectable. Neither (immuno-)histochemistry nor RDA detected extrajunctional expression of acetylcholine receptors by age 10 and 21 days, respectively. RDA identified some mRNA up-regulated in C22 muscles, among them at 10 days, prior to detectable weakness or atrophy, integral membrane protein 2a (Itm2a), eukaryotic initiation factor 2, subunit 2 (Eif2s2) and cytoplasmic phosphatidylinositol transfer protein 1 (Pitpnc1). However, qPCR failed to measure significant differences. In contrast, Itm2a and Eif2s2 mRNA were significantly down-regulated comparing 21 versus 10 days of age in both groups, C22 and controls. Western blotting confirmed significant down-regulation of ITM2A protein in C22 only.
Conclusion: Denervation-like changes in this model develop slowly with onset of atrophy and weakness at about three weeks of age, before detection of extrajunctional acetylcholine receptors. Altered Itm2a expression seems to being early as an increase, but becomes distinct as a decrease later.

Keywords: Skeletal muscle; beta subunit; charcot-marie-tooth disease; cytoplasmic 1; demyelination; eukaryotic initiation factor 2; gene expression profiling; integral membrane protein 2A; muscle denervation; phosphatidylinositol transfer protein.

IOS Press Full Text

81. Cells . 2021 Aug 20;10(8):2147. doi: 10.3390/cells10082147.

Identifying the Effects of Reactive Oxygen Species on Mitochondrial Dynamics and Cytoskeleton Stability in *Dictyostelium discoideum*

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- PMID: 34440916
- PMCID: PMC8392674
- DOI: 10.3390/cells10082147

Defects in mitochondrial dynamics, fission, fusion, and motility have been implicated in the pathogenesis of multiple neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, Huntington's disease, and Charcot-Marie-Tooth disease. Another key feature of neurodegeneration is the increase in reactive oxygen species (ROS). Previous work has shown that the cytoskeleton, in particular the microtubules, and ROS generated by rotenone significantly regulate mitochondrial dynamics in *Dictyostelium discoideum.* The goal of this project is to study the effects of ROS on mitochondrial dynamics within our model organism *D. discoideum* to further understand the underlying issues that are the root of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. We chose three likely ROS inducers, cumene hydroperoxide, hydroxylamine hydrochloride, and Antimycin A. Our work demonstrates that alteration of the microtubule cytoskeleton is not required to alter dynamics in response to ROS and there is no easy way to predict how mitochondrial dynamics will be altered based on which ROS generator is used. This research contributes to the better understanding of the cellular mechanisms that induce the pathogenesis of incurable neurodegenerative diseases with the hope that it will translate into developing new and more effective treatments for patients afflicted by them.

Keywords: ROS; fission; fusion; microtubules; mitochondrial dynamics; motility.

FULL TEXT OPEN ACCESS MDPI

82. Biomedicines . 2021 Aug 2;9(8):945. doi: 10.3390/biomedicines9080945.

GDAP1 Involvement in Mitochondrial Function and Oxidative Stress, Investigated in a Charcot-Marie-Tooth Model of hiPSCs-Derived Motor Neurons

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- PMID: 34440148
- PMCID: PMC8393985
- DOI: 10.3390/biomedicines9080945

Mutations in the ganglioside-induced differentiation associated protein 1 (*GDAP1*) gene have been associated with demyelinating and axonal forms of Charcot-Marie-Tooth (CMT) disease, the most frequent hereditary peripheral neuropathy in humans. Previous studies reported the prevalent *GDAP1* expression in neural tissues and cells, from animal models. Here, we described the first GDAP1 functional study on human induced-pluripotent stem cells (hiPSCs)-derived motor neurons, obtained from normal subjects and from a CMT2H patient, carrying the *GDAP1* homozygous c.581C>G (p.Ser194*) mutation. At mRNA level, we observed that, in normal subjects, *GDAP1* is mainly expressed in motor neurons, while it is drastically reduced in the patient's cells containing a premature termination codon (PTC), probably degraded by the nonsense-mediated mRNA decay (NMD) system. Morphological and functional investigations revealed in the CMT patient's motor neurons a decrease of cell viability associated to lipid dysfunction and oxidative stress development. Mitochondrion is a key organelle in oxidative stress generation, but it is also mainly involved in energetic metabolism. Thus, in the CMT patient's motor neurons, mitochondrial cristae defects were observed, even if no deficit in ATP production emerged. This cellular model of hiPSCs-derived motor neurons underlines the role of mitochondrion and oxidative stress in CMT disease and paves the way for new treatment evaluation.

Keywords: CMT disease; GDAP1; hiPSCs; mitochondria; motor neurons.

FULL TEXT OPEN ACCESS MDPI

Review

83. Children (Basel) . 2021 Aug 9;8(8):687. doi: 10.3390/children8080687.

Differential Diagnosis of Acquired and Hereditary Neuropathies in Children and Adolescents-Consensus-Based Practice Guidelines

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- PMID: 34438578
- PMCID: PMC8392610
- DOI: 10.3390/children8080687

Disorders of the peripheral nerves can be caused by a broad spectrum of acquired or hereditary aetiologies. The objective of these practice guidelines is to provide the reader with information about the differential diagnostic workup for a target-oriented diagnosis. Following an initiative of the German-speaking Society of Neuropaediatrics, delegates from 10 German societies dedicated to neuroscience worked in close co-operation to write this guideline. Applying the Delphi methodology, the authors carried out a formal consensus process to develop practice recommendations. These covered the important diagnostic steps both for acquired neuropathies (traumatic, infectious, inflammatory) and the spectrum of hereditary Charcot-Marie-Tooth (CMT) diseases. Some of our most important recommendations are that: (i) The indication for further diagnostics must be based on the patient's history and clinical findings; (ii) Potential toxic neuropathy also has to be considered; (iii) For focal and regional neuropathies of unknown aetiology, nerve sonography and MRI should be performed; and (iv) For demyelinated hereditary neuropathy, genetic diagnostics should first address PMP22 gene deletion: once that has been excluded, massive parallel sequencing including an analysis of relevant CMT-genes should be performed.

Keywords: Charcot–Marie–Tooth disease; adolescents; children; inflammatory neuropathy; metabolic neuropathy; neuropathy; traumatic neuropathy.

FULL TEXT OPEN ACCESS MDPI

Review

84. GeneReviews® [Internet]. 1998 Sep 28 [**updated 2021 Sep 9**].

Charcot-Marie-Tooth (CMT) Hereditary Neuropathy Overview

Thomas D Bird [1]
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- PMID: 20301532
- Bookshelf ID: NBK1358

MYOBASE link : https://www.myobase.org/index.php?lvl=notice_display&id=69456

The purpose of this overview is to increase the awareness of clinicians regarding Charcot-Marie-Tooth (CMT) hereditary neuropathy, its causes, and its management.

The following are the goals of this overview.

Goal 1: Describe the clinical characteristics of CMT hereditary neuropathy.

Goal 2: Review the causes of CMT hereditary neuropathy.

Goal 3: Provide an evaluation strategy to identify the cause of CMT hereditary neuropathy in a proband (when possible).

Goal 4: Inform genetic counseling of family members of an individual with CMT hereditary neuropathy.

Goal 5: Review management of CMT hereditary neuropathy.

Myasthénie autoimmune – *Myasthenia gravis*

85. Neurologist . 2021 Sep 7;26(5):175-177. doi: 10.1097/NRL.0000000000000339.

MuSK Myasthenia Gravis Presenting with Bilateral Vocal Cord Abduction Paresis: A Case Report and Literature Review

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- PMID: 34491934
- DOI: 10.1097/NRL.0000000000000339

Introduction: Approximately 39% to 49% of patients with previously diagnosed acetylcholine receptor antibody-negative myasthenia gravis have been found to be muscle-specific tyrosine kinase (MuSK) antibody positive. These patients have a presentation that typically includes oculobulbar weakness, poorer response to cholinesterase inhibitors, and higher risk for acute clinical decompensation that necessitates plasma exchange. MuSK patients can require more aggressive maintenance immunosuppression earlier-on to maintain stability, often with rituximab.

Case report: The authors report the case of a 45-year-old woman who presented with months of worsening hoarseness and exertional dyspnea. Laryngoscopy revealed limited abduction of vocal cords bilaterally as

the source of the complaint. Examination revealed ophthalmoparesis and fatigable proximal muscle weakness. She was found to have elevated MuSK antibodies that, along with evidence of neuromuscular junction transmission defect on nerve conduction studies, confirmed the diagnosis of MuSK myasthenia gravis. She experienced no improvement with pyridostigmine and decompensated despite receiving oral steroids, requiring intubation. However, she dramatically improved with plasma exchange and has since been doing well on rituximab therapy.
Conclusion: Dysphonia with hoarse quality secondary to vocal cord abduction paresis is a rare presentation of myasthenia gravis, as opposed to the typical flaccid dysarthria seen in bulbar myasthenia and should raise suspicion for MuSK antibody positivity. MuSK myasthenia gravis cases can be more refractory to treatment with cholinesterase inhibitors and are more likely to cause exacerbations and myasthenia crisis. Therefore, early and accurate diagnosis with appropriate antibody testing is imperative to avoid delays in treatment to prevent potentially life-threatening outcomes.

Wolters Kluwer

86. J Neurol . 2021 Sep 4. doi: 10.1007/s00415-021-10759-4. Online ahead of print.

Long-term outcome in patients with myasthenia gravis: one decade longitudinal study

Ivo Bozovic [1], Jelena Ilic Zivojinovic [2], Stojan Peric [1], Marko Kostic [3], Vukan Ivanovic [1], Dragana Lavrnic [1], Ivana Basta [4]

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- PMID: 34480608
- DOI: 10.1007/s00415-021-10759-4

Introduction: Even treated, myasthenia gravis (MG) continues to represent a significant burden and might continuously affect patients' quality of life (QoL). The aim of our longitudinal study was to analyze QoL in a large cohort of MG patients after a 10-year follow-up period.
Methods: This study comprised 78 MG patients (60% females, 50 ± 16 years old at baseline, 70% AchR positive) who were retested after 10 years. Disease severity was evaluated by MGFA classification. QoL was assessed using SF-36 questionnaire and Myasthenia Gravis-specific Questionnaire (MGQ). Hamilton rating scales for depression and anxiety (HDRS and HARS), Multidimensional Scale of Perceived Social Support (MSPSS) and Acceptance of Illness Scale (AIS) were also used.
Results: Similar percentage of patients was in remission at both time points (42% and 45%). However, at baseline all patients were treated, while 32% were treatment-free at follow-up. SF-36, MGQ, MSPSS and AIS scores were similar at baseline and retest. Mean HDRS and HARS scores worsened during time ($p < 0.05$), although percentage of patients with depression and anxiety did not change significantly. Significant predictors of worse SF-36 score at retest were depression ($\beta = - 0.45$, $p < 0.01$), poor disease acceptance ($\beta = - 0.44$, $p < 0.01$) and older age ($\beta = - 0.30$, $p < 0.01$). Significant predictors of worse MGQ score at retest were poor disease acceptance ($\beta = - 0.40$, $p < 0.01$), retirement ($\beta = - 0.36$, $p < 0.01$), lower education ($\beta = 0.25$, $p < 0.01$), and depression ($\beta = - 0.18$, $p < 0.05$).
Conclusions: Although after 10 years, a significant number of MG patients were in remission, their QoL was still reduced. Neurologists should be aware that patients' perception of poor QoL may persist even if MG is well treated from a physician's perspective.

Keywords: Depression; Disease acceptance; Longitudinal study; Myasthenia gravis; Quality of life.

SpringerLink FULL-TEXT ARTICLE

87. Lung India . Sep-Oct 2021;38(5):496-498. doi: 10.4103/lungindia.lungindia_433_19.

Steroid dependence in acute asthma due to myasthenia gravis

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- PMID: 34472534
- DOI: 10.4103/lungindia.lungindia_433_19

No abstract available

88. J Gastrointest Cancer . 2021 Aug 31. doi: 10.1007/s12029-021-00702-1. Online ahead of print.

A Case of Myasthenia Gravis with Two Primary Tumors: Paraneoplastic or Incidental?

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- PMID: 34463912
- DOI: 10.1007/s12029-021-00702-1

No abstract available

89. J Transl Autoimmun . 2021 Aug 10;4:100111. doi: 10.1016/j.jtauto.2021.100111. eCollection 2021.

Calprotectin as potential novel biomarker in myasthenia gravis

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- PMID: 34458711
- PMCID: PMC8379505
- DOI: 10.1016/j.jtauto.2021.100111

Myasthenia gravis (MG) is the most common autoimmune disease affecting the neuromuscular junction by specific autoantibodies. The etiology of MG and its heterogeneity in clinical courses are poorly understood, although it was recently shown that gut microbial dysbiosis plays a critical role. Since levels of Calprotectin (CLP) seem to correlate with level of dysbiosis, we hypothesize that CLP may serve as potential disease activity biomarker in MG. Sera from 251 patients with MG and 90 controls were analyzed in an explorative, cross-sectional design. Prospectively, we tested CLP levels in MG patients up to 3 years. Association of CLP levels with socio-demographics, disease activity (quantitative myasthenia gravis (QMG) score, myasthenia gravis-specific Activities of Daily Living scale (MG-ADL)), antibody (Abs) status, history of myasthenic crisis, treatment regime, and history of thymectomy were investigated using univariate analysis. Mean baseline serum levels of CLP were significantly higher in MG patients compared to controls (4.3 µg/ml vs. 2.1 µg/ml; $p < 0.0001$). Higher levels of CLP were associated with a higher clinical disease severity measured by MGFA classification and QMG score. Nevertheless, the only weak correlation of CLP with clinical outcome parameters needs confirmation in future studies. Currently, there are no validated blood biomarkers for MG. The significantly elevated CLP and mild correlation with parameters of disease activity suggests that CLP holds promise as a biomarker for measurement of individual disease severity.

Keywords: Biomarker; Calprotectin; Disease severity; Microbial dysbiosis; Myasthenia gravis.

Review

90. Front Immunol . 2021 Aug 11;12:715036. doi: 10.3389/fimmu.2021.715036. eCollection 2021.

Clinical Efficacy and Safety of Eculizumab for Treating Myasthenia Gravis

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- PMID: 34456922
- PMCID: PMC8384962
- DOI: 10.3389/fimmu.2021.715036

Myasthenia gravis (MG) is an autoimmune disease primarily mediated by acetylcholine receptor antibodies (AChR-Ab), cellular immune dependence, and complement system involvement. Since the AChR on the postsynaptic membrane is destroyed by an immune attack, sufficient endplate potential cannot be generated, resulting in the development of a synaptic transmission disorder at the neuromuscular junction and in muscle weakness. The role of the complement system in MG has been demonstrated in animal models and clinical tests, and it has been determined that complement inhibition in patients with MG can prevent disease induction and reverse its progression. Eculizumab is a humanized monoclonal antibody that inhibits the cleavage of complement protein C5 and prevents autoimmune damage; additionally, it has received subsequent approval by the Federal Drug Administration of the United States for MG treatment. However, various concerns regarding the use of eculizumab persist. In this review, we have discussed the treatment time, cost effectiveness, long-term efficacy, and tolerability of eculizumab for MG treatment. We have also summarized historical information and have presented perspectives on this new therapeutic modality.

Keywords: clinical; eculizumab; generalized myasthenia gravis; mechanism; systematic review.

OPEN ACCESS frontiers

91. Clin Immunol . 2021 Aug 24;231:108830. doi: 10.1016/j.clim.2021.108830. Online ahead of print.

Cellular changes in eculizumab early responders with generalized myasthenia gravis

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- PMID: 34450290
- DOI: 10.1016/j.clim.2021.108830

Eculizumab (ECU), a C5 complement inhibitor, is approved to treat acetylcholine receptor autoantibody positive generalized myasthenia gravis (AChR MG). The clinical effect of ECU relies on inhibition of the terminal complement complex; however, the effect of ECU on lymphocytes is largely unknown. We evaluated innate and adaptive immunity among AChR MG patients (N = 3) before ECU and ≥3 months later while on stable therapy, and found reduced activation markers in memory $CD4^+$ T cell subsets, increased regulatory T cell populations, and reduced frequencies of $CXCR5^+HLA\text{-}DR^+CCR7^+$ Tfh subsets and $CD11b^+$ migratory memory B cells. We observed increases within $CD8^+$ T cell subsets that were terminally differentiated and senescent. Our data suggest complement inhibition with ECU modulates the adaptive immunity in patients with MG, consistent with preclinical data showing changes in complement-mediated signaling by T- and antigen-presenting cells. These findings extend our understanding of ECU's mechanism of action when treating patients with MG.

Keywords: Complement C5; Complement inactivating agents; Flow cytometry; Lymphocytes; Myasthenia gravis.

ELSEVIER FULL-TEXT ARTICLE

92. Brain Sci . 2021 Aug 11;11(8):1057. doi: 10.3390/brainsci11081057.

Myasthenia Gravis-An Analysis of Multimodal Evoked Potentials

Edyta Dziadkowiak [1], Marta Waliszewska-Prosół [1], Małgorzata Wieczorek [2], Joanna Bladowska [3], Sławomir Budrewicz [1], Maria Ejma [1]

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- PMID: 34439676
- PMCID: PMC8392656
- DOI: 10.3390/brainsci11081057

Introduction: The aim of this study is a comprehensive analysis of the parameters of exogenous evoked potentials (visual, brainstem auditory, and somatosensory) in patients with myasthenia gravis (MG), a prototype of both neuromuscular junction disease and autoimmune disease. The study also seeks to isolate electrophysiological changes that may indicate disorders within the central and/or peripheral nervous system.

Methods: A total of forty-two consecutive patients with myasthenia gravis (24 women, 18 men) were included in the study. All of the patients underwent EP examination. MR images were also analyzed.

Results: In the group of MG patients, the latency of P100 (113.9 ± 13.9; $p < 0.0001$) VEP, wave III (3.92 ± 0.29; $p = 0.015$), wave V (5.93 ± 0.32; <0.0001), interlatency III-V (2.00 ± 0.12; $p < 0.0001$), interlatency I-V (4.20 ± 0.28; $p < 0.001$) BAEP, and all components of SEP (N9, P10, N13, P16, N20, P22) were significantly longer. Mean wave I and V amplitude BAEP were relatively lower.

Conclusions: The results of the study suggest the presence of disturbances in the bioelectric activities of the central and peripheral nervous system in MG patients.

Keywords: brainstem auditory evoked potentials; myasthenia gravis; somatosensory evoked potentials; visual evoked potentials.

FULL TEXT OPEN ACCESS MDPI

Case Reports

93. BMC Gastroenterol . 2021 Aug 26;21(1):333. doi: 10.1186/s12876-021-01904-4.

A rare case of nivolumab-related myasthenia gravis and myocarditis in a patient with metastatic gastric cancer

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- PMID: 34445963
- PMCID: PMC8393464
- DOI: 10.1186/s12876-021-01904-4

Background: Although rare, several immune-related adverse effects can be life-threatening. Here, we describe a metastatic gastric cancer patient presenting with nivolumab-related myasthenia gravis and myocarditis, a previously unreported adverse effect of gastric cancer treatment.

Case presentation: A 66-year-old man with metastatic gastric cancer visited the emergency department because of dizziness after the first dose of nivolumab. Diagnoses of nivolumab-related myasthenia gravis and myocarditis were established. Myocardial biopsy results and anti-acetylcholine receptor antibody positivity confirmed the diagnoses. Despite plasma exchange and intravenous methylprednisolone and immunoglobulin administration, the patient's general condition gradually worsened, and he died.

Conclusions: Strict monitoring for cardiac and neuromuscular symptoms after nivolumab administration is necessary to rapidly treat these adverse effects.

Keywords: Gastric cancer; Myasthenia gravis; Myocarditis; Nivolumab; Programmed cell death-1 receptor.

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Myopathies congénitales – *Congenital myopathies*

94. Intractable Rare Dis Res . 2021 Aug;10(3):220-222. doi: 10.5582/irdr.2021.01034.

Mild congenital myopathy due to a novel variation in *SPEG* gene

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- PMID: 34466346
- PMCID: PMC8397816
- DOI: 10.5582/irdr.2021.01034

Centronuclear myopathies (CNMs) are a subgroup of congenital myopathies (CMs) characterized by muscle weakness, genetic heterogeneity, and predominant type 1 fibers and increased central nuclei in muscle biopsy. Mutations in CNM-causing genes such as *MTM1*, *DNM2*, *BIN1*, *RYR1*, *CACNA1S*, *TTN*, and extraordinary rarely *SPEG* (striated muscle preferentially expressed protein kinase) have been identified for about 60-80% of patients. Herein, we report a case of CM due to a novel variation in the *SPEG* gene, manifested by mild neonatal hypotonia, muscle weakness, delayed motor milestones, and ophthalmoplegia, without dilated cardiomyopathy. We identified a novel variation [c.153C>T (p.Asn51=) in exon 1] in the *SPEG* gene with whole-exome sequencing and confirmed by Sanger sequencing. Mild intellectual disability has not been associated with SPEG-related CM in the previous reports. We suggest that this report expands the phenotypic spectrum of SPEG-related CM, and further case reports are required to expand the genotype-phenotype correlations.

Keywords: SPEG; centronuclear myopathy; congenital myopathy; intellectual disability; striated muscle preferentially expressed protein kinase.

95. Clin Genet . 2021 Aug 31. doi: 10.1111/cge.14054. Online ahead of print.

Clinical, genetic and histological features of Centronuclear Myopathy in the Netherlands

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- PMID: 34463354
- DOI: 10.1111/cge.14054

Centronuclear myopathy (CNM) is a genetically heterogeneous congenital myopathy characterized by muscle weakness, atrophy and variable degrees of cardiorespiratory involvement. The clinical severity is largely explained by genotype (DNM2, MTM1, RYR1, BIN1, TTN and other rarer genetic backgrounds), specific mutation(s) and age of the patient. The histopathological hallmark of CNM is the presence of internal centralized nuclei on muscle biopsy. Information on the phenotypical spectrum, subtype prevalence and phenotype-genotype correlations is limited. To characterize CNM more comprehensively, we retrospectively assessed a national cohort of 48 CNM patients (mean age = 32 ± 24 years, range 0-80, 54% males) from the Netherlands clinically, histologically, and genetically. All information was extracted from entries in the patient's medical records, between 2000 and 2020. Frequent clinical features in addition to muscle weakness and hypotonia were fatigue and exercise intolerance in more mildly affected cases.

Genetic analysis showed variants in four genes (18 DNM2, 14 MTM1, 9 RYR1 and 7 BIN1), including 16 novel variants. In addition to central nuclei, histologic examination revealed a large variability of myopathic features in the different genotypes. The identification and characterization of these patients contributes to trial readiness.

Keywords: BIN1; Centronuclear myopathy; DNM2; MTM1; Netherlands; RYR1; cohort.

WILEY Full Text Article

96. Acta Neuropathol . 2021 Oct;142(4):785-788. doi: 10.1007/s00401-021-02363-7. Epub 2021 Sep 1.

A recurrent homozygous ACTN2 variant associated with core myopathy

Michio Inoue [1,2], Satoru Noguchi [3,4,5], Kyuto Sonehara [6,7], Keiko Nakamura-Shindo [8], Akira Taniguchi [9], Hiroyuki Kajikawa [10], Hisayoshi Nakamura [2], Keiko Ishikawa [2], Megumu Ogawa [1], Shinichiro Hayashi [1,2], Yukinori Okada [6,7,11], Satoshi Kuru [12], Aritoshi Iida [2], Ichizo Nishino [1,2]

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- PMID: 34471957
- PMCID: PMC8423689
- DOI: 10.1007/s00401-021-02363-7

No abstract available

SpringerLink FULL-TEXT ARTICLE

Myopathies oculopharyngodistales – *Oculopharyngodistal myopathies*

97. eNeurologicalSci . 2021 Jun 4;24:100348. doi: 10.1016/j.ensci.2021.100348. eCollection 2021 Sep.

Neuropathy/intranuclear inclusion bodies in oculopharyngodistal myopathy: A case report

Tomoyasu Matsubara [1], Yuko Saito [1], Takashi Kurashige [2], Mana Higashihara [2], Fumio Hasegawa [1], Masashi Ogasawara [3,4], Aritoshi Iida [4], Ichizo Nishino [3,4], Tadashi Adachi [1], Akatsuki Kubota [5], Shigeo Murayama [1,2,6]

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- PMID: 34466670
- PMCID: PMC8385282
- DOI: 10.1016/j.ensci.2021.100348

No abstract available

Keywords: LRP12, lipoprotein receptor-related protein 12 gene; Low-density lipoprotein receptor-related protein 12 gene (LRP12); NIID, neuronal intranuclear inclusion disease; Neuropathy; OPDM, oculopharyngodistal myopathy; OPML, oculopharyngeal myopathy with leukoencephalopathy; Oculopharyngodistal myopathy; Trinucleotide repeat diseases.

ELSEVIER OPEN ACCESS

Myopathies inflammatoires – *Inflammatory myopathies*

98. Curr Opin Rheumatol . 2021 Aug 26. doi: 10.1097/BOR.0000000000000832. Online ahead of print.

Anti-HMGCR myopathy: clinical and histopathological features, and prognosis

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- PMID: 34456255
- DOI: 10.1097/BOR.0000000000000832

Purpose of review: This review aims to describe clinical and pathological features, prognosis and treatment in patients with anti-HMGCR antibody positive immune-mediated necrotizing myopathy (HMGCR-IMNM) based on recent findings.

Recent findings: Using advances in diagnostic modalities that can confirm the presence of anti-HMGCR antibody, the clinical and pathological manifestations of HMGCR-IMNM were found to be broader than previously reported. Although only a small percentage of HMGCR-IMNM patients present with atypical manifestations, some of these patients show slow disease progression and clinical symptoms, which are similar to those of limb-girdle muscular dystrophies. Other atypical HMGCR-IMNM patients have skin conditions similar to dermatomyositis-like skin rush or dermatological presentations of Jessner-Kanoff disease or cutaneous lymphoma, whose pathological changes including CD8-positive and bcl-2-positive lymphocytic accumulations, similar to Jessner-Kanoff lymphocytic infiltration of skin or low-grade cutaneous lymphoma, which are observed in muscle and skin.

Summary: Anti-HMGCR autoantibodies define unique populations of IMNM patients. Recent studies have revealed that clinicopathological manifestations of HMGCR-IMNM, especially extramuscular symptoms and pathological manifestations, are more common than previously recognized.

Wolters Kluwer

99. Acta Neuropathol . 2021 Sep 9. doi: 10.1007/s00401-021-02365-5. Online ahead of print.

A network of core and subtype-specific gene expression programs in myositis

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- PMID: 34499219
- DOI: 10.1007/s00401-021-02365-5

Myositis comprises a heterogeneous group of skeletal muscle disorders which converge on chronic muscle inflammation and weakness. Our understanding of myositis pathogenesis is limited, and many myositis patients lack effective therapies. Using muscle biopsy transcriptome profiles from 119 myositis patients (spanning major clinical and serological disease subtypes) and 20 normal controls, we generated a co-expression network of 8101 dynamically regulated transcripts. This network organized the myositis transcriptome into a map of gene expression modules representing interrelated biological processes and disease signatures. Universally myositis-upregulated network modules included muscle regeneration, specific cytokine signatures, the acute phase response, and neutrophil degranulation. Universally myositis-suppressed pathways included a specific subset of myofilaments, the mitochondrial envelope, and nuclear isoforms of the anti-apoptotic humanin protein. Myositis subtype-specific modules included type 1 interferon signaling and titin (dermatomyositis), RNA processing (antisynthetase syndrome), and vasculogenesis (inclusion body myositis). Importantly, therapies exist to target influential proteins in many myositis-dysregulated modules, and nearly all modules contained understudied proteins and non-coding RNAs - many of which were extraordinarily dysregulated in myositis and may represent novel therapeutic targets. Finally, we apply our network to patient classification, finding that a deep learning algorithm trained on patient-level network "images" successfully assigned patients to clinical groups and further into molecular subclusters. Altogether, we provide a global resource to probe and contextualize differential gene expression in myositis.

Keywords: Co-expression; Deep learning; Myopathy; Myositis; Network; Transcriptome.

100.Rheumatology (Oxford) . 2021 Sep 8;keab681. doi: 10.1093/rheumatology/keab681. Online ahead of print.

Nailfold capillaries and myositis specific antibodies in anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis

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- PMID: 34498053
- DOI: 10.1093/rheumatology/keab681

Objectives: This study aimed to quantify nailfold capillary (NFC) abnormalities in anti-melanoma differentiation-associated gene 5 (MDA5)-positive dermatomyositis (DM) patients and to evaluate the association with clinical parameters, including serum biomarkers. In addition, we aimed to clarify the period leading to remission of NFC abnormalities during immunosuppressive treatment in patients with DM.

Methods: A prospective observational study was conducted including patients (n = 10) who first visited Hiroshima University Hospital and were diagnosed with DM or clinically amyopathic dermatomyositis (CADM) with anti-MDA5 antibodies. We compared the NFC abnormalities detected by nailfold-video capillaroscopy (NVC), physical findings, blood tests, respiratory function tests, and vascular-related growth factors measured using a LEGENDplexTM Multi-Analyte Flow Assay Kit.

Results: NFC abnormalities improved in all patients from 2-17 weeks after the initiation of immunosuppressive treatment. The NVC scores were inversely correlated with anti-MDA5 antibody titres at baseline. NVC scores and forced vital capacity (FVC) were positively correlated. Baseline with macrophage colony-stimulating factor (M-CSF) and stem cell factor (SCF) was correlated with anti-MDA-5 titres.

Conclusion: Our study suggests that NVC scores and disease activity are inversely correlated before treatment. Vascular-related growth factors, such as M-CSF and SCF, may be associated with the disease mechanism in patients with anti-MDA5 antibody-positive DM.

Keywords: anti-melanoma differentiation gene-5; capillaroscopy; dermatomyositis; macrophage; nailfold capillary.

101. Curr Opin Rheumatol . 2021 Sep 7. doi: 10.1097/BOR.0000000000000837. Online ahead of print.

Polymyositis: does it really exist as a distinct clinical subset?

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- DOI: 10.1097/BOR.0000000000000837

Purpose of review: To summarize information on polymyositis; diagnosis, definitions, published data and opinions.

Recent findings: Polymyositis originally referred to inflammatory muscle diseases presenting with muscle weakness and inflammatory cell infiltrates on muscle tissue visible by microscopy. Over time and with improved technology to immunophenotype infiltrating inflammatory cells and characterize muscle fibres, the meaning of polymyositis changed and became more specific. There is ongoing controversy over the term polymyositis, with proponents for a strict definition based on histopathological and immunohistochemical features on muscle biopsies whereas others advocate for a broader clinical and histopathological phenotype. Over the past decades, the discovery of several myositis-specific autoantibodies together with distinct histopathological features have enabled the identification of new subsets previously labelled as polymyositis notably the antisynthetase syndrome and the immune-mediated necrotizing myopathies thus reducing the number of patients classified as polymyositis.

Summary: There are still a small number of patients among the idiopathic inflammatory myopathies that can be classified as polymyositis as discussed in this review but the entity is now considered relatively rare.

102. Indian J Dermatol Venereol Leprol . 2021 Aug 24;1-4. doi: 10.25259/IJDVL_1306_20. Online ahead of print.

Immunotherapy-intensified paraneoplastic dermatomyositis

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- PMID: 34491672
- DOI: 10.25259/IJDVL_1306_20

No abstract available

103. Indian J Dermatol Venereol Leprol . 2021 Aug 24;1-9. doi: 10.25259/IJDVL_297_20. Online ahead of print.

Juvenile dermatomyositis in Thai children: Retrospective review of 30 cases from a tertiary care center

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- PMID: 34491668
- DOI: 10.25259/IJDVL_297_20

Background: Juvenile dermatomyositis is a rare condition, but it is the most common idiopathic inflammatory myopathy in pediatric patients.

Aim: To study the clinical manifestations, investigations, treatment, clinical course, and outcomes of juvenile dermatomyositis in Thai children.

Method: This retrospective study included juvenile dermatomyositis patients treated at Siriraj Hospital, a 2,300-bed national tertiary referral center in Bangkok, Thailand, from 1994 to 2019.

Results: Thirty patients (22 females and 8 males) were included with a female to male ratio of 2.7:1. Median age at diagnosis was 5.1 years (range, 2.6-14.8 years). Median duration of illness before diagnosis was 6.5

months (range, 0.3-84.0 months). Acute and subacute onset occurred in the majority of patients. Presenting symptoms included muscle weakness in 27/30 (90%), skin rash in 26/30 (86.7%), muscle pain in 17/26 (65.4%), and arthralgia in 4/18 (22.2%) of patients. Dermatologic examination revealed Gottron's rash, heliotrope rash, and periungual telangiectasia in 25/30 (83.3%), 21/30 (70.0%), and 15/24 (62.5%) of patients, respectively. Interestingly, scalp dermatitis was found in 8/21 (38.1%) of patients. The most commonly used treatment regimen in this series was a combination of prednisolone and methotrexate. During the median follow-up of 3.1 years (range, 0.0-18.5 years), only one-third of patients were seen to have monocyclic disease. Extraskeletal osteosarcoma at a previous lesion of calcinosis cutis was observed in one patient at 12 years after juvenile dermatomyositis onset.

Limitations: This was a retrospective single-center study, and our results may not be generalizable to other healthcare settings. Prospective multicenter studies are needed to confirm the findings of this study.

Conclusion: juvenile dermatomyositis usually poses a diagnostic and therapeutic challenge, which can be compounded by the ethnic variations in the clinical presentation, as observed in this study. Asian patients tend to present with acute or subacute onset of disease, and arthralgia and/or arthritis are less common than in Caucasian patients. Scalp dermatitis is not uncommon in pediatric juvenile dermatomyositis patients. An association between juvenile dermatomyositis and malignancy, though rare, can occur.

Keywords: JDM; Juvenile dermatomyositis; Thai; calcinosis cutis; children; osteosarcoma; pediatric.

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Case Reports

104. Clin Case Rep . 2021 Aug 30;9(9):e04750. doi: 10.1002/ccr3.4750. eCollection 2021 Sep.

An itchy rash and muscle weakness

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- PMID: 34484777
- PMCID: PMC8405535
- DOI: 10.1002/ccr3.4750

Dermatomyositis is a rare disease affecting primarily skin and muscles and is associated with malignancies, especially in at-risk patients. Clinical presentations vary widely but proximal muscle weakness and typical skin findings should prompt consideration of the diagnosis. Immunosuppressive therapy is required, as is continued screening for malignant disease during follow-up.

Keywords: dermatomyositis; muscle weakness; myopathy; rash.

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Case Reports

105. Ann Thorac Med . Jul-Sep 2021;16(3):294-298. doi: 10.4103/atm.atm_739_20. Epub 2021 Jul 20.

Fatal rapidly progressive interstitial lung disease in a patient with amyopathic dermatomyositis

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- PMID: 34484446
- PMCID: PMC8388568
- DOI: 10.4103/atm.atm_739_20

Interstitial lung disease (ILD) is a well-established common manifestation of idiopathic inflammatory myopathies. Yet, till now, the pathogenetic mechanisms are still poorly understood, classification is evolving and prognosis is variable. A refractory and rapidly progressive ILD (RPILD) that is associated with dermatomyositis (DM) with minimal muscle weakness and normal creatine kinase (termed clinically amyopathic DM) is increasingly being recognized, with more incidence in Asians. However, we are not aware of reports of the Arab region. Herein, we present a 38-year-old male with this condition that ended with a fatal outcome despite aggressive therapy, with a review of recent literature.

Keywords: Amyopathic dermatomyositis; connective tissue disease; idiopathic inflammatory myopathy; interstitial lung disease.

106.Curr Opin Rheumatol . 2021 Sep 1. doi: 10.1097/BOR.0000000000000836. Online ahead of print.

Differential diagnosis of necrotizing myopathy

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- PMID: 34482348
- DOI: 10.1097/BOR.0000000000000836

Purpose of review: Necrotizing myopathy is a broad term. It includes patients with the recently described immune-mediated necrotizing myopathies (IMNM) who have specific antibodies, such as anti-hydroxy-3-methylglutaryl-CoA reductase or anti-signal recognition particle, seronegative phenotypes that can be associated with cancer, and other types of myositis and connective tissue diseases involving necrotic muscle fibers as a characteristic pathologic feature. Necrotizing myopathies that are not immune-mediated, such as those caused by drugs, dystrophies, infections, or even hypothyroidism are also included. The purpose of this review is to address the differential diagnosis of these disorders.

Recent findings: New IMNM have been described over the last few years, some of them related with checkpoint inhibitors, drugs that are being increasingly used in cancer treatment. Necrotizing myopathy has also been reported in association with specific phenotypes and autoantibodies (e.g. anti-Mi2 dermatomyositis, antisynthetase syndrome, and myositis associated with antimitochondrial antibodies). Rarer cases associated with graft-versus-host disease and severe acute respiratory syndrome coronavirus 2 infection are also emerging.

Summary: Differentiation between patients with IMNM and those without the superimposed autoimmune phenomena helps clinicians determine the best individualized approach to use and the appropriate immunosuppressive therapy, whenever needed.

107.Arthritis Res Ther . 2021 Sep 4;23(1):232. doi: 10.1186/s13075-021-02606-8.

High incidence and mortality of Pneumocystis jirovecii infection in anti-MDA5-antibody-positive dermatomyositis: experience from a single center

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- PMID: 34481528
- PMCID: PMC8417987
- DOI: 10.1186/s13075-021-02606-8

Background: Idiopathic inflammatory myopathies (IIM) are associated with a significantly higher risk of opportunistic infections including Pneumocystis jirovecii pneumonia (PJP), a potentially fatal opportunistic infection. However, no prior studies have evaluated PJP infection in subtypes of IIM.

Objectives: To investigate the prevalence and mortality rate of PJP infection in subgroups of IIM patients stratified according to myopathy-specific antibodies.

Methods: In the first part of the study, 463 consecutive patients with IIM were prospectively followed for a period of at least 1 year to analyze the incidence of PJP. In the second part of the study, we enrolled 30 consecutive PJP patients with any rheumatic disease in order to identify the mortality rate and risk factors by Cox regression analysis. The Kaplan-Meier method with log-rank testing was used to assess differences in survival.

Results: The prevalence of PJP in IIM patients was found to be 3.0/100 person-years, while in MDA5+ DM patients it was 7.5/100 person-years and in MDA5- IIM patients 0.7/100 person-years (P < 0.05). PJP typically occurred in the first 2 months in the case of MDA5+ DM patients who had a significant decrease in their CD4+ T cell counts and lymphocyte counts (P < 0.05). In PJP patients, 3-month mortality was higher for MDA5+ DM patients than in those with other rheumatic diseases (83.3% vs 38.9%, P < 0.05). Alarmingly, MDA5+ DM patients seemed not to benefit from prompt anti-PJP treatment, unlike patients with other rheumatic diseases whose survival improved when anti-PJP treatment was started within 6 days (P < 0.05). Conclusion: PJP has an alarming high incidence and mortality in MDA5+ DM patients. Timely treatment for PJP seems not to improve the prognosis of patients with this particular subtype. Hence, there remains a crucial unmet need to develop PJP prophylaxis for MDA5+ DM patients.

Keywords: Anti-MDA5-antibody-positive dermatomyositis; Incidence; Mortality; Pneumocystis jirovecii pneumonia; Treatment.

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108.Arthritis Rheumatol . 2021 Sep 4. doi: 10.1002/art.41964. Online ahead of print.

Performance of the 2017 EULAR/ACR classification criteria for inflammatory myopathies in patients with myositis-specific autoantibodies

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- PMID: 34480833
- DOI: 10.1002/art.41964

Background: The objectives of the study were to (1) determine the sensitivity of EULAR/ACR criteria to properly classify myositis-specific autoantibody (MSA) positive myositis patients, (2) describe the phenotype and muscle involvement over time in different MSA-positive patients, and (3) compare MSAs with the EULAR/ACR subgroups to predict clinical phenotypes.

Methods: The study included 524 MSA-positive myositis patients from the Johns Hopkins Myositis Center. Each patient was classified using the EULAR/ACR classification criteria. Patient phenotypes were summarized using factor analysis of mixed data (FAMD). We compared the ability of MSAs with the EULAR/ACR subgroups to predict the phenotype of patients by applying the Akaike information criterion (AIC) and the Bayesian information criteria (BIC) to the linear regression models.

Results: Overall, 91% of MSA-positive patients met EULAR/ACR criteria to be classified as myositis. However, 20% of anti-HMGCR and 50% of anti-PL7 patients were incorrectly classified as not myositis. Furthermore, ~10% of anti-SRP and anti-HMGCR patients were misclassified as having inclusion body myositis. FAMD demonstrated that patients within each MSA-defined group had similar phenotypes. Application of both the AIC and BIC to the linear regression models revealed that MSAs better predict myositis phenotypes than the subgroups defined by the EULAR/ACR criteria.

Conclusions: Although the EULAR/ACR criteria successfully classified 91% of MSA-positive myositis patients, certain MSA-defined subgroups, including those with autoantibodies against HMGCR, SRP, and PL7, are frequently misclassified. In myositis patients with MSAs, autoantibodies outperform the EULAR/ACR-defined subgroups to predict clinical phenotypes. These findings underscore the need to include MSAs in a revised myositis classification scheme.

Keywords: Autoimmune diseases; autoantibodies; classification; muscle disease; myositis.

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109.JBJS Case Connect . 2021 Sep 2;11(3). doi: 10.2106/JBJS.CC.21.00328.

Surgically Managed Malakoplakia of the Spine: A Case Report

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- PMID: 34473660
- DOI: 10.2106/JBJS.CC.21.00328

Case: A 66-year-old woman with polymyositis and recurrent urinary tract infections presented with lumbar pain and progressive lower extremity neuropathy. Imaging showed lytic destruction of the vertebral bone from L2 to L4 with extension into adjacent musculature. Histological examination demonstrated Michaelis-Gutmann bodies consistent with malakoplakia. The patient underwent revision T12-sacrum posterior fusion, L2-5 laminectomy, and anterior L3-4 corpectomy, followed by L2-4 anterior stabilization and a 6-week course of ceftriaxone. At 3 months postoperatively, she was asymptomatic without recurrence.

Conclusion: Malakoplakia of bone should be considered in the differential diagnosis of lytic bone lesions and can be effectively treated with surgical debulking with penetrative antibiotics.

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Review

110.Ther Adv Musculoskelet Dis . 2021 Aug 28;13:1759720X211037519. eCollection 2021.

Natural history and screening of interstitial lung disease in systemic autoimmune rheumatic disorders

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- PMID: 34471427
- PMCID: PMC8404673
- DOI: 10.1177/1759720X211037519

Interstitial lung disease (ILD) is a relatively frequent manifestation of systemic autoimmune rheumatic disorders (SARDs), including systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myopathies (IIM), systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), and anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis. Interstitial pneumonia with autoimmune features (IPAF) has been proposed to describe patients with ILD who have clinical or serological findings compatible with SARDs but they are not sufficient for a definite diagnosis. ILD may present with different patterns among patients with SARDs, but most commonly as nonspecific interstitial pneumonia (NSIP), with the exception of RA and ANCA vasculitis that more often present with usual interstitial pneumonia (UIP). The natural history of ILD is quite variable, even among patients with the same SARD. It may present with subclinical features following a slow progressively course or with acute manifestations and clinically significant rapid progression leading to severe deterioration of pulmonary function and respiratory failure. The radiographic pattern of ILD, the extent of the disease, the baseline pulmonary function, the pulmonary function deterioration rate over time and clinical variables related to the primary SARD, such as age, sex and the clinical phenotype, are considered prognostic factors for SARDs-ILD associated with adverse outcomes and increased mortality. Different modalities can be employed for ILD detection including clinical evaluation, pulmonary function tests, high resolution computed tomography and novel techniques such as lung ultrasound and serum biomarkers. ILD may determine the clinical outcome of SARDs, since it is associated with significant morbidity and mortality and therefore screening of patients with SARDs for ILD is of great clinical importance.

Keywords: Sjögren's syndrome; anti-synthetase syndrome; dermatomyositis; interstitial lung disease; interstitial pneumonia with autoimmune features; natural history; polymyositis; rheumatoid arthritis; screening; systemic lupus erythematosus; systemic sclerosis; vasculitis.

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111.Scand J Rheumatol . 2021 Sep 1;1-9. doi: 10.1080/03009742.2021.1941243. Online ahead of print.

Re-evaluation of the prognostic significance of oropharyngeal dysphagia in idiopathic inflammatory myopathies

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- PMID: 34470549
- DOI: 10.1080/03009742.2021.1941243

Objective: To investigate the prognostic significance of videofluorographic swallowing study (VFSS)-confirmed oropharyngeal dysphagia in idiopathic inflammatory myopathies (IIMs).

Method: We reviewed the medical records of patients who were diagnosed with IIM between 2009 and 2020 at Seoul St Mary's Hospital. All oropharyngeal dysphagia cases were limited to VFSS-confirmed dysphagia found during the initial diagnostic work-up for IIM. We described the findings on VFSS and the course of the dysphagic symptoms. Logistic regression and survival analyses were performed to evaluate the risk of pneumonia and mortality, respectively.

Results: We found 88 patients with IIM who met the criteria. Among them, 17 patients (19%) had oropharyngeal dysphagia. Except for two cases lost to follow-up and one deceased case, all of the patients with dysphagia (14 of 14) had swallowing function restored within 6 months. The risk of pneumonia within 3 months from the diagnosis of IIM was significant [odds ratio = 4.49, 95% confidence interval (CI) 1.07-18.88]. The median follow-up duration was 34 and 27 months for the groups without and with dysphagia, respectively. The survival analysis failed to demonstrate that the presence of oropharyngeal dysphagia increased the risk of death (hazard ratio = 0.77, 95% CI: 0.085-7.00).

Conclusions: Oropharyngeal dysphagia found at the initial diagnosis of IIM improved within 3-6 months in nearly all cases. Furthermore, IIM patients who had oropharyngeal dysphagia at the initial diagnosis of IIM were not likely to have shorter survival, even if the risk of pneumonia was increased in the short term.

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Case Reports

112.Neuromuscul Disord . 2021 Jul 8;S0960-8966(21)00179-6. doi: 10.1016/j.nmd.2021.07.002. Online ahead of print.

A rare case of sporadic inclusion body myositis and rheumatoid arthritis exhibiting ectopic lymphoid follicle-like structures: a case report and literature review

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- PMID: 34465502
- DOI: 10.1016/j.nmd.2021.07.002

Sporadic inclusion body myositis (sIBM) is a degenerative, intractable, inflammatory myopathy with an immune pathomechanism. We report on a case of a 44-year-old Japanese man who began developing progressive muscle weakness at age 40. Rheumatoid arthritis symptoms manifested at 43 with strongly positive anti-cyclic citrullinated peptide antibodies. Along with typical sIBM pathology, a muscle biopsy revealed dramatic inflammation with prominent perivascular B-cell infiltration forming ectopic lymphoid follicle-like structures (ELFLSs). Exome sequencing identified no causative variants of hereditary myopathy or immune disorders. A combination of immunotherapy slowed the progression of the muscular symptoms. This unusual form of sIBM, including earlier age at onset, a partial response to immunotherapy, and a

histopathology presenting B-cell infiltrate with ectopic lymphoid follicle-like structures, indicates a possible association of rheumatoid arthritis and heterogeneity with the autoimmune involvement of sIBM. We review the clinical and pathological features of patients with rheumatoid arthritis associated sIBM in the literature.

Keywords: Ectopic lymphoid follicle-like structure; Perivascular B-cell infiltration; Rheumatoid arthritis; Sporadic inclusion body myositis.

ELSEVIER FULL-TEXT ARTICLE

113.Curr Opin Rheumatol . 2021 Aug 27. doi: 10.1097/BOR.0000000000000829. Online ahead of print.

Physical exercise for the management of systemic autoimmune myopathies: recent findings, and future perspectives

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- PMID: 34456254
- DOI: 10.1097/BOR.0000000000000829

Purpose of review: The aim of this review is to present the main pieces of evidence, recent literature and to present future perspectives on the use of exercise/physical training in the treatment and improvement of the quality of life of patients with systemic autoimmune myopathies.

Recent findings: In the last decades, knowledge about the relevance of physical exercise training in preventing and treating chronic diseases and improving quality of life has grown. Following the global trend exemplified by the expression 'exercise is medicine', the importance of exercise/physical training has also grown in myopathies. However, the science of exercise has a lot to collaborate on and improve patients' quality of life with myopathies by appropriating new technological tools, including accessible and low-cost devices and smartphone apps.

Summary: Physical exercise, as already consolidated in the literature, is an effective, well tolerated, and low-cost strategy for patients with myopathies. The use of wearable devices, smartphone apps, and online training prescriptions must accompany the global scenario, bringing new research fields and expanding the options for access to training for the individualized basis, and prescribed by qualified professionals.

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114.Respir Med . 2021 Aug 21;187:106581. doi: 10.1016/j.rmed.2021.106581. Online ahead of print.

Diagnosis of myositis-associated interstitial lung disease: Utility of the myositis autoantibody line immunoassay

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- PMID: 34454312
- DOI: 10.1016/j.rmed.2021.106581

Objectives: The detection of myositis autoantibodies (MA) in patients with interstitial lung disease (ILD) has major implications for diagnosis and management, especially amyopathic and forme frustes of idiopathic inflammatory myositis-associated ILD (IIM-ILD). Use of the MA line immunoblot assay (MA-LIA) in non-rheumatological cohorts remains unvalidated. We assessed the diagnostic performance of the MA-LIA and explored combined models with clinical variables to improve identification of patients with IIM-ILD.

Methods: Consecutive patients referred to a specialist ILD clinic, with ILD-diagnosis confirmed at multidisciplinary meeting, and MA-LIA performed within six months of baseline were included. Pre-specified MA-LIA thresholds were evaluated for IIM-ILD diagnosis.

Results: A total 247 ILD patients were included (IIM-ILD n = 12, non-IIM connective tissue disease-associated ILD [CTD-ILD] n = 52, idiopathic interstitial pneumonia [IIP] n = 115, other-ILD n = 68). Mean age was 64.8 years, with 45.3% female, mean FVC 75.5% and DLCO 59.2% predicted. MA were present in 13.8% overall and 83.3% of IIM-ILD patients. The most common MA in IIM-ILD and non-IIM ILD patients were anti-Jo-1 (prevalence 40%) and anti-PMScl (29.2%) autoantibodies respectively. The pre-specified low-positive threshold (>10 signal intensity) had the highest discriminative capacity for IIM-ILD (AUC 0.86). Combining MA-LIA with age, gender, clinical CTD-manifestations and an overlap non-specific interstitial pneumonia/organising pneumonia pattern on HRCT improved discrimination for IIM-ILD (AUC 0.96).

Conclusion: The MA-LIA is useful to support a diagnosis of IIM-ILD as a complement to multi-disciplinary ILD assessment. Clinical interpretation is optimised by consideration of the strength of the MA-LIA result together with clinical and radiological features of IIM-ILD.

Keywords: Autoimmune disease; Connective tissue disease; Immunoblot; Interstitial lung disease; Myositis autoantibody.

ELSEVIER FULL-TEXT ARTICLE

Case Reports

115.S D Med . 2021 Jun;74(6):272-276.

Statin Associated Muscle Adverse Effects: From Presentation to Management

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- PMID: 34449167

Statins inhibit β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase, an enzyme involved in cholesterol synthesis, and are widely used for primary and secondary prevention of cardiovascular events. They are generally well tolerated but may cause muscle symptoms ranging from myalgias, myopathy, myositis to rhabdomyolysis. More recently, studies have reported autoimmune necrotizing myopathy associated with statin use, characterized by progressive symmetric weakness even after discontinuation of statins, often warranting immunosuppressive treatment. We describe the spectrum of statin associated muscle adverse effects for primary care physician including the clinical presentation, etiology, diagnostic workup, and appropriate management.

116.Mediterr J Rheumatol . 2021 Jun 30;32(2):134-142. doi: 10.31138/mjr.32.2.134. eCollection 2021 Jun.

High Prevalence of Active Tuberculosis in Adults and Children with Idiopathic Inflammatory Myositis as Compared with Systemic Lupus Erythematosus in a Tuberculosis Endemic Country: Retrospective Data Review from a Tertiary Care Centre in India

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- PMID: 34447909
- PMCID: PMC8369275
- DOI: 10.31138/mjr.32.2.134

Aim: Infections are the leading cause of morbidity and mortality in idiopathic inflammatory myositis (IIM) with India being endemic for Tuberculosis (TB). We compared and contrasted the prevalence, clinical profile and outcomes of active TB in IIM with systemic lupus erythematosus (SLE).

Methods: Medical records were reviewed for adults and children with IIM (Bohan and Peter criteria) and SLE (ACR criteria) at a tertiary care hospital in India from January 2015 to October 2017. Follow-up was recorded until February 2020 for all those who had developed active TB.

Results: Of 167 (132 adults and 35 juvenile) IIM and 280 (131 adults and 149 juvenile) SLE, active TB occurred in 24 (14.4%) IIM (22 (16.7% of 132) adults; 2 (5.71% of 35) juvenile) and 18 (6.4%) SLE [(8 (6.1% of 131) adults; 10 (6.7% of 149) juvenile, p-value < 0.01]. Patients with IIM had higher odds of developing TB as compared with SLE [OR 2.24 (CI 1.5-5.5), p=0.007]. The risk of developing active TB was 68-fold and 30.4-fold higher in patients with IIM and SLE, respectively, as compared with the general population. Extrapulmonary forms were more common (14/24). Nearly half developed TB during active IIM, at a glucocorticoid dose of 0.25 (0-1.5) mg/kg/day. Over a follow-up duration of 27 months (8-184), all were cured of TB, though prolonged course of anti-tuberculous treatment was required in 25%, and five IIM relapsed during treatment.

Conclusion: Patients with IIM have increased risk of active TB, with common extrapulmonary forms, slow response, and relapses during treatment.

Keywords: India; Myositis; dermatomyositis; glucocorticoids; infections; lupus; tuberculosis.

117.Front Med (Lausanne) . 2021 Aug 10;8:708432. doi: 10.3389/fmed.2021.708432. eCollection 2021.

Nailfold Capillaroscopy Abnormalities Correlate With Disease Activity in Adult Dermatomyositis

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- PMCID: PMC8382972
- DOI: 10.3389/fmed.2021.708432

Objectives: The aim of this study was to determine the relationship between disease activity in adult patients with dermatomyositis (DM) and other biomarkers of disease activity such as C-reactive protein creatinine kinase and nailfold video capillaroscopy (NVC).

Methods: We performed a prospective single center study of 15 adult patients with DM. Study participants underwent two assessments at least 9 months apart including clinical, laboratory and NVC evaluations. Patients received immunosuppressive medications for their dermatomyositis, and ongoing disease activity was measured by the Myositis Intention to Treat Index (MITAX). NVC evaluation included assessment of capillary density, capillary apical diameter (mm), and the number of microhemorrhages per digit.

Results: Microvascular abnormalities were present in most DM patients. Of these, capillary density (4.71 vs. 6.84, p = 0.006) and mean apical diameter (56.09 vs. 27.79 µm, p = 0.003) significantly improved over the

study period in concordance with improving disease control (MITAX 8.53 vs. 2.64, p = 0.002). Longitudinal analysis demonstrated that capillary density was independently associated with MITAX (β = -1.49 [CI -2.49, -0.33], p = 0.013), but not other parameters such as C-reactive protein and creatinine kinase.
Conclusions: Nailfold capillary density is a dynamic marker of global disease activity in adult DM. NVC may be utilized as a non-invasive point-of-care tool to monitor disease activity and inform treatment decisions in patients with DM.

Keywords: CK; capillary density; dermatomyositis; disease activity; nailfold capillaroscopy.

118.J Clin Med . 2021 Aug 22;10(16):3730. doi: 10.3390/jcm10163730.

Serum Amphiregulin and Heparin-Binding Epidermal Growth Factor as Biomarkers in Patients with Idiopathic Inflammatory Myopathy

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- PMID: 34442026
- PMCID: PMC8396848
- DOI: 10.3390/jcm10163730

Background: The epidermal growth factors amphiregulin (AREG) and heparin-binding epidermal growth factor (HB-EGF) are implicated in the pathogenesis of several autoimmune diseases, but their clinical and pathological roles in idiopathic inflammatory myopathy (IIM) are unclear.
Methods: Serum AREG and HB-EGF levels were measured by ELISA in patients with IIM (n = 37), systemic sclerosis (n = 17), and rheumatoid arthritis (n = 10), and for seven age- and sex-matched healthy controls (HCs). Associations between serum AREG or HB-EGF levels and the clinical parameters were analyzed.
Results: Serum AREG levels in IIM patients were significantly elevated compared to those in HCs (median, 20.7 and 10.7 pg/mL, respectively; p = 0.025). In particular, serum AREG levels in IIM patients with interstitial lung disease (ILD) were higher than those of HCs (22.4 pg/mL, p = 0.027). The disease duration in patients with elevated serum AREG levels was significantly shorter compared to those who had normal serum AREG levels (7 and 21 months, respectively; p = 0.0012). Serum HB-EGF levels were significantly increased in IIM patients with elevated CK levels (136.2 pg/mL; p = 0.020) and patients with anti-Mi-2 antibody (183.7 pg/mL; p = 0.045) compared to those in HCs (74.9 pg/mL).
Conclusion: These results suggested that AREG could be a promising biomarker associated with early-phase IIM-related ILD, and that HB-EGF expression was associated with muscle injury and regeneration in IIM.

Keywords: amphiregulin; heparin-binding epidermal growth factor; idiopathic inflammatory myopathy; interstitial lung disease.

Maladie de Pompe – *Pompe disease*

119.Intractable Rare Dis Res . 2021 Aug;10(3):190-197. doi: 10.5582/irdr.2021.01091.

The usage of enzyme replacement treatments, economic burden, and quality of life of patients with four lysosomal storage diseases in Shanghai, China

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- PMID: 34466341
- PMCID: PMC8397822
- DOI: 10.5582/irdr.2021.01091

Lysosomal storage diseases (LSDs) are a group of rare diseases that cause progressive physical dysfunction and organ failure, which significantly affected patients' quality of life. The objective of this study was to explore the characteristics and usage of Enzyme Replacement Treatments (ERTs), which is the only specific

therapy for LSDs, of patients with the four different LSDs (Gaucher, Fabry, Pompe disease and Mucopolysaccharidosis) in Shanghai, and then evaluate the economic burden and quality of life of these patients. A total of 31patients, involving 5, 14, 4 and 8 patients with Gaucher, Fabry, Pompe disease and Mucopolysaccharidosis, respectively, were included in analysis. The result showed that only five Gaucher disease (GD) patients in Shanghai used Imiglucerase in 2019, while the other 26 patients with the other three LSDs did not receive ERTs. The total health expenditure of GD patients was 2,273,000CNY on average mainly resulted by the high cost of Imiglucerase. The total health expenditure of the other 26 patients was 37,765CNY on average. Though the cost-sharing mechanism between basic medical insurance, charity fund and patients had been explored for Gaucher disease in Shanghai, the out-of-pocket part, which was 164,301 CNY, still laid a heavy economic burden on the patients and their families. The mean EQ-VAS score of GD patients was 76.4 ± 15.5, which was higher than that of the other three LSDs. It is recommended that the scope of drug reimbursement list and the reimbursement level should be further expanded and raised to help improve the living conditions of patients with LSDs.

Keywords: Rare diseases; Shanghai; disease burden; enzyme replacement treatment; lysosomal storage diseases; patient survey; quality of life.

J-STAGE FREE

120.J Clin Med . 2021 Aug 16;10(16):3617. doi: 10.3390/jcm10163617.

Assessment of Dysphonia in Children with Pompe Disease Using Auditory-Perceptual and Acoustic/Physiologic Methods

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- PMID: 34441913
- PMCID: PMC8396833
- DOI: 10.3390/jcm10163617

Bulbar and respiratory weakness occur commonly in children with Pompe disease and frequently lead to dysarthria. However, changes in vocal quality associated with this motor speech disorder are poorly described. The goal of this study was to characterize the vocal function of children with Pompe disease using auditory-perceptual and physiologic/acoustic methods. High-quality voice recordings were collected from 21 children with Pompe disease. The Grade, Roughness, Breathiness, Asthenia, and Strain (GRBAS) scale was used to assess voice quality and ratings were compared to physiologic/acoustic measurements collected during sustained phonation tasks, reading of a standard passage, and repetition of a short phrase at maximal volume. Based on ratings of grade, dysphonia was present in 90% of participants and was most commonly rated as mild or moderate in severity. Duration of sustained phonation tasks was reduced and shimmer was increased in comparison to published reference values for children without dysphonia. Specific measures of loudness were found to have statistically significant relationships with perceptual ratings of grade, breathiness, asthenia, and strain. Our data suggest that dysphonia is common in children with Pompe disease and primarily reflects impairments in respiratory and laryngeal function; however, the primary cause of dysphonia remains unclear. Future studies should seek to quantify the relative contribution of deficits in individual speech subsystems on voice quality and motor speech performance more broadly.

Keywords: GRBAS; acoustic; auditory-perceptual; dysphonia; pompe disease; respiratory; speech; voice.

FULL TEXT OPEN ACCESS MDPI

Myopathies métaboliques – *Metabolic myopathies*

121.EMBO Mol Med . 2021 Sep 6;e14554. doi: 10.15252/emmm.202114554. Online ahead of print.

Alleviation of a polyglucosan storage disorder by enhancement of autophagic glycogen catabolism

Or Kakhlon [1], Hilla Vaknin [2], Kumudesh Mishra [1], Jeevitha D'Souza [2], Monzer Marisat [2], Uri Sprecher [2], Shane Wald-Altman [2], Anna Dukhovny [2], Yuval Raviv [2], Benny Da'adoosh [3], Hamutal Engel [3], Sandrine Benhamron [1 4], Keren Nitzan [1 4], Sahar Sweetat [1 4], Anna Permyakova [5], Anat Mordechai [1], Hasan Orhan Akman [6], Hanna Rosenmann [1 4], Alexander Lossos [1], Joseph Tam [5], Berge A Minassian [7], Miguel Weil [2]

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- PMID: 34486811
- DOI: 10.15252/emmm.202114554

This work employs adult polyglucosan body disease (APBD) models to explore the efficacy and mechanism of action of the polyglucosan-reducing compound 144DG11. APBD is a glycogen storage disorder (GSD) caused by glycogen branching enzyme (GBE) deficiency causing accumulation of poorly branched glycogen inclusions called polyglucosans. 144DG11 improved survival and motor parameters in a GBE knockin ($Gbe^{ys/ys}$) APBD mouse model. 144DG11 reduced polyglucosan and glycogen in brain, liver, heart, and peripheral nerve. Indirect calorimetry experiments revealed that 144DG11 increases carbohydrate burn at the expense of fat burn, suggesting metabolic mobilization of pathogenic polyglucosan. At the cellular level, 144DG11 increased glycolytic, mitochondrial, and total ATP production. The molecular target of 144DG11 is the lysosomal membrane protein LAMP1, whose interaction with the compound, similar to LAMP1 knockdown, enhanced autolysosomal degradation of glycogen and lysosomal acidification. 144DG11 also enhanced mitochondrial activity and modulated lysosomal features as revealed by bioenergetic, image-based phenotyping and proteomics analyses. As an effective lysosomal targeting therapy in a GSD model, 144DG11 could be developed into a safe and efficacious glycogen and lysosomal storage disease therapy.

Keywords: adult polyglucosan body disease; autophagy; glycogen; lysosomes; polyglucosan.

EMBO Molecular Medicine FREE

122.JIMD Rep . 2021 Jun 14;61(1):60-66. doi: 10.1002/jmd2.12232. eCollection 2021 Sep.

Energy metabolism during exercise in patients with β-enolase deficiency (GSDXIII)

Astrid Emilie Buch [1], Olimpia Musumeci [2], Ralph Wigley [3], Mads Peter Godtfeldt Stemmerik [1], Anne-Sofie Vibæk Eisum [1], Karen Lindhardt Madsen [1], Nicolai Preisler [1], David Hilton-Jones [4], Ros Quinlivan [5], Antonio Toscano [2], John Vissing [1]

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- PMID: 34485019
- PMCID: PMC8411107
- DOI: 10.1002/jmd2.12232

Aim: To investigate the in vivo skeletal muscle metabolism in patients with β-enolase deficiency (GSDXIII) during exercise, and the effect of glucose infusion.

Methods: Three patients with GSDXIII and 10 healthy controls performed a nonischemic handgrip test as well as an incremental cycle ergometer test measuring maximal oxidative consumption (VO2max) and a 1-

hour submaximal cycle test at an intensity of 65% to 75% of VO2max. The patients repeated the submaximal exercise after 2 days, where they received a 10% iv-glucose supplementation.
Results: Patients had lower VO2max than healthy controls, and two of three patients had to stop prematurely during the intended 1-hour submaximal exercise test. During nonischemic forearm test, all patients were able to produce lactate in normal amounts. Glucose infusion had no effect on patients' exercise capacity.
Conclusions: Patients with GSDXIII experience exercise intolerance and episodes of myoglobinuria, even to the point of needing renal dialysis, but still retain an almost normal anaerobic metabolic response to submaximal intensity exercise. In accordance with this, glucose supplementation did not improve exercise capacity. The findings show that GSDXIII, although causing episodic rhabdomyolysis, is one of the mildest metabolic myopathies affecting glycolysis.

Keywords: GSDXIII; exercise intolerance; exercise metabolism; maximal exercise capacity; metabolic myopathy; β-enolase deficiency.

SpringerLink FULL-TEXT ARTICLE

Lipidoses musculaires – *Lipid myopathies*

Case Reports
123.JIMD Rep . 2021 May 7;61(1):12-18. doi: 10.1002/jmd2.12223. eCollection 2021 Sep.

Abnormal VLCADD newborn screening resembling MADD in four neonates with decreased riboflavin levels and VLCAD activity

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- PMID: 34485012
- PMCID: PMC8411102
- DOI: 10.1002/jmd2.12223

Early detection of congenital disorders by newborn screening (NBS) programs is essential to prevent or limit disease manifestation in affected neonates. These programs balance between the detection of the highest number of true cases and the lowest number of false-positives. In this case report, we describe four unrelated cases with a false-positive NBS result for very-long-chain acyl-CoA dehydrogenase deficiency (VLCADD). Three neonates presented with decreased but not deficient VLCAD enzyme activity and two of them carried a single heterozygous *ACADVL* c.1844G>A mutation. Initial biochemical investigations after positive NBS referral in these infants revealed acylcarnitine and organic acid profiles resembling those seen in multiple acyl-CoA dehydrogenase deficiency (MADD). Genetic analysis did not reveal any pathogenic mutations in the genes encoding the electron transfer flavoprotein (ETF alpha and beta subunits) nor in ETF dehydrogenase. Subsequent further diagnostics revealed decreased levels of riboflavin in the newborns and oral riboflavin administration normalized the MADD-like biochemical profiles. During pregnancy, the mothers followed a vegan, vegetarian or lactose-free diet which probably caused alimentary riboflavin deficiency in the neonates. This report demonstrates that a secondary (alimentary) maternal riboflavin deficiency in combination with reduced VLCAD activity in the newborns can result in an abnormal VLCADD/MADD acylcarnitine profile and can cause false-positive NBS. We hypothesize that maternal riboflavin deficiency contributed to the false-positive VLCADD neonatal screening results.

Keywords: MADD; VLCADD; newborn screening; riboflavin deficiency.

SpringerLink FULL-TEXT ARTICLE

124.Clin Chem . 2021 Sep 1;67(9):1290-1292. doi: 10.1093/clinchem/hvab096.

An Unusually High Excretion of Ethylmalonic Acid in a Patient with Multiple Acyl-CoA Dehydrogenase Deficiency

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- PMID: 34470039
- DOI: 10.1093/clinchem/hvab096

No abstract available

Keywords: gas chromatography–mass spectrometry; multiple acyl-CoA dehydrogenase deficiency; newborn screening; urine organic acids.

Review

125.J Med Case Rep . 2021 Sep 1;15(1):441. doi: 10.1186/s13256-021-03013-y.

A novel mutation in ACADVL causing very long-chain acyl-coenzyme-A dehydrogenase deficiency in a South Asian pediatric patient: a case report and review of the literature

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- PMID: 34465376
- PMCID: PMC8407922
- DOI: 10.1186/s13256-021-03013-y

Background: Very long-chain acyl-coenzyme-A dehydrogenase deficiency is a rare, severe life-threatening metabolic disorder of mitochondrial fatty acid oxidation, caused by mutations in ACADVL gene. Here we present a genetically confirmed case of a South Asian baby girl with severe, early-onset form of very long-chain acyl-coenzyme-A dehydrogenase deficiency due to a novel mutation in ACADVL gene.

Case presentation: Index case was the second baby girl of second-degree consanguineous South Asian parents. She had an uncomplicated antenatal period and was born by spontaneous vaginal delivery at term with a birth weight of 2910 g. She had been noted to have fair skin complexion, hypotonia, and 3 cm firm hepatomegaly. Since birth, the baby developed grunting, poor feeding, and recurrent episodes of symptomatic hypoglycemia and convulsions with multiple semiology. Her septic screening and urine ketone bodies were negative. The baby had high anion gap metabolic acidosis and elevated transaminases and serum creatine phosphokinase levels. Echocardiogram at 4 months revealed bilateral ventricular hypertrophy. Acylcarnitine profile revealed elevated concentrations of tetradecanoylcarnitine (C14), tetradecanoylcarnitine C14:1, and C14:1/C16. Unfortunately, the baby died due to intercurrent respiratory illness at 4 months of age. Sequence analysis of ACADVL gene in perimortem blood sample revealed homozygous frame shift novel variant NM_001270447.1, c.711_712del p.(Phe237Leufs*38), which confirmed the diagnosis of very long-chain acyl-coenzyme-A dehydrogenase deficiency.

Conclusions: This case demonstrates the importance of early diagnosis and management of very long-chain acyl-coenzyme-A dehydrogenase deficiency in improving the outcome of the patients. Implementation of newborn screening using tandem mass spectrometry in Sri Lanka will be beneficial to reduce the morbidity and mortality of treatable disorders of inborn errors.

Keywords: ACADVL; Convulsions; High anion gap metabolic acidosis; Hypoketonemic hypoglycemia; Very long-chain acyl-CoA dehydrogenase deficiency.

Case Reports

126.Neuromuscul Disord . 2021 Jul 18;S0960-8966(21)00188-7. Online ahead of print.

Infant with early onset bilateral facial and bulbar weakness: Successful treatment of riboflavin in multiple acyl-CoA dehydrogenase deficiency caused by biallelic nonsense FLAD1 variants

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- PMID: 34454814
- DOI: 10.1016/j.nmd.2021.07.006

Multiple acyl-CoA dehydrogenase deficiency (MADD) is a heterogeneous group of inborn error of metabolic disease affecting the oxidation of fatty acids and amino acids, and choline metabolism. Genes involved in electrons transfer to the mitochondrial respiratory chain typically induce MADD. Recently, FLAD1, which encodes flavin adenine dinucleotide synthase, has also been reported as a cause of MADD. Here, we present a case of a 28-month girl with progressive weakness in facial and bulbar muscle. She has been suffering from feeding difficulty and recurrent respiratory distress. Lipid storage myopathy was evident from muscle biopsy. Furthermore, whole exome sequencing identified homozygous variant of c.745C > T (p.Arg249*) in FLAD1, confirming the diagnosis of FLAD1-related MADD. The patient showed improvements in her symptoms and exhibited catch-up growth following the supplementation of riboflavin. Lipid storage myopathy with FLAD1-related MADD is potentially treatable. Therefore, we should have high clinical suspicion, even though the diagnosis is challenging.

Keywords: FLAD1; Multiple acyl-CoA dehydrogenase deficiency; Riboflavin: Vacuolar myopathy.

ELSEVIER FULL-TEXT ARTICLE

Case Reports

127.Int J Neonatal Screen . 2021 Aug 13;7(3):55. doi: 10.3390/ijns7030055.

Detection of Early Onset Carnitine Palmitoyltransferase II Deficiency by Newborn Screening: Should CPT II Deficiency Be a Primary Disease Target?

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- PMID: 34449523
- PMCID: PMC8395870
- DOI: 10.3390/ijns7030055

Early-onset carnitine palmitoyltransferase II deficiency (CPT II deficiency) (OMIM 600650) can result in severe outcomes, which are often fatal in the neonatal to infantile period. CPT II deficiency is a primary target in the Maritime Newborn Screening Program. We report a case of neonatal-onset CPT II deficiency identified through expanded newborn screening with tandem mass spectrometry. Identification through newborn screening led to early treatment interventions, avoidance of metabolic decompensation, and a better clinical outcome. Newborn screening for CPT II deficiency is highly sensitive and specific with no false positives identified. The only screen positive case detected identified a true positive case. This experience illustrates the importance of newborn screening for CPT II deficiency and demonstrates why reconsideration should be taken to add this disease as a primary newborn screening target.

Keywords: CPT II deficiency; carnitine; newborn; screening; transferase; treatment.

FULL TEXT OPEN ACCESS MDPI

128.Genes (Basel) . 2021 Jul 28;12(8):1140. doi: 10.3390/genes12081140.

Multiple Acyl-CoA Dehydrogenase Deficiency with Variable Presentation Due to a Homozygous Mutation in a Bedouin Tribe

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- PMID: 34440319
- PMCID: PMC8393905
- DOI: 10.3390/genes12081140

Multiple acyl-CoA dehydrogenase deficiency (MADD) is a fatty acid and amino acid oxidation defect caused by a deficiency of the electron-transfer flavoprotein (ETF) or the electron-transfer flavoprotein dehydrogenase (ETFDH). There are three phenotypes of the disease, two neonatal forms and one late-onset. Previous studies have suggested that there is a phenotype-genotype correlation. We report on six patients from a single Bedouin tribe, five of whom were sequenced and found to be homozygous to the same variant in the *ETFDH* gene, with variable severity and age of presentation. The variant, NM_004453.3 (*ETFDH*): c.524G>A, p.(R175H), was previously recognized as pathogenic, although it has not been reported in the literature in a homozygous state before. R175H is located near the FAD binding site, likely affecting the affinity of FAD for EFT:QO. The single homozygous *ETFDH* pathogenic variant was found to be causing MADD in this cohort with an unexpectedly variable severity of presentation. The difference in severity could partly be explained by early diagnosis via newborn screening and early treatment with the FAD precursor riboflavin, highlighting the importance of early detection by newborn screening.

Keywords: electron-transfer flavoprotein (ETF); electron-transfer flavoprotein dehydrogenase (ETFDH); genotype; multiple acyl-CoA dehydrogenase deficiency (MADD); phenotype.

FULL TEXT OPEN ACCESS MDPI

Myopathies mitochondriales – *Mitochondrial myopathies*

129.J Clin Med . 2021 Aug 5;10(16):3471. doi: 10.3390/jcm10163471.

Two Novel Variants in *YARS2* Gene Are Responsible for an Extended MLASA Phenotype with Pancreatic Insufficiency

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- PMID: 34441767
- PMCID: PMC8397107
- DOI: 10.3390/jcm10163471

Pathogenic variants in the mitochondrial tyrosyl-tRNA synthetase gene (*YARS2*) were associated with myopathy, lactic acidosis, and sideroblastic anemia (MLASA). However, patients can present mitochondrial myopathy, with exercise intolerance and muscle weakness, leading from mild to lethal phenotypes. Genes

implicated in mtDNA replication were studied by Next Generation Sequencing (NGS) and whole exome sequence with the TruSeq Rapid Exome kit (Illumina, San Diego, CA, USA). Mitochondrial protein translation was studied following the Sasarman and Shoubridge protocol and oxygen consumption rates with Agilent Seahorse XF24 Analyzer Mitostress Test, (Agilent, Santa Clara, CA, USA). We report two siblings with two novel compound heterozygous pathogenic variants in *YARS2* gene: a single nucleotide deletion in exon 1, c.314delG (p.(Gly105Alafs*4)), which creates a premature stop codon in the amino acid 109, and a single nucleotide change in exon 5 c.1391T>C (p.(Ile464Thr)), that cause a missense variant in amino acid 464. We demonstrate the pathogenicity of these new variants associated with reduced *YARS2* mRNA transcript, reduced mitochondrial protein translation and dysfunctional organelle function. These pathogenic variants are responsible for late onset MLASA, herein accompanied by pancreatic insufficiency, observed in both brothers, clinically considered as Pearson's syndrome. Molecular study of *YARS2* gene should be considered in patients presenting Pearson's syndrome characteristics and MLASA related phenotypes.

Keywords: Pearson's syndrome; mitochondrial aminocyl-tRNA synthetase; novel pathogenic variant.

FULL TEXT OPEN ACCESS MDPI

Myopathies myofibrillaires – *Myofibrillar myopathies*

130.Front Physiol . 2021 Aug 19;12:706806. doi: 10.3389/fphys.2021.706806. eCollection 2021.

Biomechanical Properties of the Sarcolemma and Costameres of Skeletal Muscle Lacking Desmin

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- PMID: 34489727
- PMCID: PMC8416993
- DOI: 10.3389/fphys.2021.706806

Intermediate filaments (IFs), composed primarily by desmin and keratins, link the myofibrils to each other, to intracellular organelles, and to the sarcolemma. There they may play an important role in transfer of contractile force from the Z-disks and M-lines of neighboring myofibrils to costameres at the membrane, across the membrane to the extracellular matrix, and ultimately to the tendon ("lateral force transmission"). We measured the elasticity of the sarcolemma and the connections it makes at costameres with the underlying contractile apparatus of individual fast twitch muscle fibers of desmin-null mice. By positioning a suction pipet to the surface of the sarcolemma and applying increasing pressure, we determined the pressure at which the sarcolemma separated from nearby sarcomeres, $P_{separation}$, and the pressure at which the isolated sarcolemma burst, $P_{bursting}$. We also examined the time required for the intact sarcolemma-costamere-sarcomere complex to reach equilibrium at lower pressures. All measurements showed the desmin-null fibers to have slower equilibrium times and lower $P_{separation}$ and $P_{bursting}$ than controls, suggesting that the sarcolemma and its costameric links to nearby contractile structures were weaker in the absence of desmin. Comparisons to earlier values determined for muscles lacking dystrophin or synemin suggest that the desmin-null phenotype is more stable than the former and less stable than the latter. Our results are consistent with the moderate myopathy seen in desmin-null muscles and support the idea that desmin contributes significantly to sarcolemmal stability and lateral force transmission.

Keywords: contractile apparatus; dystrophin; elastimetry; intermediate filaments; lateral force transmission; myopathy; sarcomere; synemin.

Myosinopathies – *Myosinopathies*

131.J Neonatal Perinatal Med . 2021 Aug 25. doi: 10.3233/NPM-210780. Online ahead of print.

Novel mutation in the MYH2 gene in a symptomatic neonate with a hereditary myosin myopathy

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- PMID: 34459418
- DOI: 10.3233/NPM-210780

Introduction: Hereditary myosin myopathies are muscle disorders caused by mutations in myosin heavy chain genes. The MYH2 gene encodes the fast 2A skeletal muscle isoform, and mutations manifest as joint contractures, muscle weakness, and external ophthalmoplegia. Muscle biopsy shows decreased type 2A fibers, and vacuoles are sometimes present in adults with progressive disease.
Presentation of case: This case describes a full term baby boy with hypotonia, dysmorphic features, dysphagia, and aspiration. Whole genome sequencing detected a novel heterozygous variant in the MYH2 gene. Muscle biopsy showed decreased type 2A fibers and vacuoles in myofibers.
Discussion: Hypotonia and dysphagia are common in infants with a MYH2 myopathy. However, dysmorphic features and vacuoles on biopsy have not previous been described in infants with MYH2 myopathies.
Conclusion: This case reports an unusual phenotype of a rare neonatal-onset congenital myopathy associated with a novel heterozygous variant in MYH2.
Keywords: Dysphagia; hereditary myosin myopathies; hypotonia; myofiber vacuoles myosin heavy chain genes; neonatal-onset congenital myopathy.
IOS Press Full Text

Syndrome de Lambert-Eaton – *Lambert-eaton myasthenic syndrome*

132. Clin Biochem . 2021 Aug 24;S0009-9120(21)00225-3. Online ahead of print.

Discordant SOX-1 antibodies results in paraneoplastic Lambert-Eaton syndrome diagnosis by the clinical laboratory

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- PMID: 34450126
- DOI: 10.1016/j.clinbiochem.2021.08.004

Background: Anti-Sry-like high mobility group box 1 (anti SOX-1) proteins are rare onconeural antibodies associated with paraneoplastic Lambert-Eaton myasthenic syndrome (LEMS). Few patients with anti-SOX-1 antibodies and negative anti-glial nuclear antibody reactivity have been described to date.
Case subject and methods: Our case involves a 72-year-old female patient with progressive girdle weakness, sensation of heaviness in the lower limbs, predominantly distal and associated with circulatory problems together with instability when walking, with a high suspicion of an autoimmune myopathic disorder. Immunoblot test for autoimmune myopathies antibodies detection were all negative. Onconeuronal antibodies were determined in serum by indirect immunofluorescence being negative as well. Given the high suspicion, we also checked for the presence of other antineuronal antibodies whose patterns are not visible by IIF.
Results: Onconeuronal antibodies by immunoblot for the following antibodies: Hu, Ri, Yo, Zic4, Tr, PCA-2, MA-TA, CV2, GAD65, Zic4, Titin, SOX1, Recoverin and Amp, revealed an unexpected clear band in SOX-1, which are highly suggestive of paraneoplastic LEMS.
Discussion: We hypothesize that discordant onconeuronal antibodies results were due to the fact that positivity in IIF is associated with other SOX-B group proteins (normally related to cases of non-paraneoplastic neuropathy), while negativity in IIF and subsequent confirmed presence of specific SOX1 antibody by immunoblot could indicate an underlying tumor.
Keywords: Lambert-Eaton myasthenic syndrome. MeSH Unique ID: D015624; Paraneoplastic syndromes, Nervous system. MeSH Unique ID: D020361; SOX-1 antibodies; Small cell lung carcinoma. MeSH Unique ID: D055752.
ELSEVIER FULL-TEXT ARTICLE

Review

133. Brain Sci . 2021 Aug 3;11(8):1035. doi: 10.3390/brainsci11081035.

Presynaptic Paraneoplastic Disorders of the Neuromuscular Junction: An Update

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- PMID: 34439654
- PMCID: PMC8392118
- DOI: 10.3390/brainsci11081035

The neuromuscular junction (NMJ) is the target of a variety of immune-mediated disorders, usually classified as presynaptic and postsynaptic, according to the site of the antigenic target and consequently of the neuromuscular transmission alteration. Although less common than the classical autoimmune postsynaptic myasthenia gravis, presynaptic disorders are important to recognize due to the frequent association with cancer. Lambert Eaton myasthenic syndrome is due to a presynaptic failure to release acetylcholine, caused by antibodies to the presynaptic voltage-gated calcium channels. Acquired neuromyotonia is a condition characterized by nerve hyperexcitability often due to the presence of antibodies against proteins associated with voltage-gated potassium channels. This review will focus on the recent developments in the autoimmune presynaptic disorders of the NMJ.

Keywords: CASPR2; Lambert Eaton myasthenic syndrome; immune checkpoint inhibitors; neuromuscular junction; neuromyotonia; paraneoplastic syndrome; presynaptic disorders.

FULL TEXT OPEN ACCESS MDPI

Maladies du motoneurone (plusieurs pathologies) – *Motor neuron diseases (Multiple)*

Review

134.Front Neurol . 2021 Aug 16;12:723450. doi: 10.3389/fneur.2021.723450. eCollection 2021.

Frontotemporal Pathology in Motor Neuron Disease Phenotypes: Insights From Neuroimaging

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- PMID: 34484106
- PMCID: PMC8415268
- DOI: 10.3389/fneur.2021.723450

Frontotemporal involvement has been extensively investigated in amyotrophic lateral sclerosis (ALS) but remains relatively poorly characterized in other motor neuron disease (MND) phenotypes such as primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), spinal muscular atrophy (SMA), spinal bulbar muscular atrophy (SBMA), post poliomyelitis syndrome (PPS), and hereditary spastic paraplegia (HSP). This review focuses on insights from structural, metabolic, and functional neuroimaging studies that have advanced our understanding of extra-motor disease burden in these phenotypes. The imaging literature is limited in the majority of these conditions and frontotemporal involvement has been primarily evaluated by neuropsychology and post mortem studies. Existing imaging studies reveal that frontotemporal degeneration can be readily detected in ALS and PLS, varying degree of frontotemporal pathology may be captured in PMA, SBMA, and HSP, SMA exhibits cerebral involvement without regional predilection, and there is limited evidence for cerebral changes in PPS. Our review confirms the heterogeneity extra-motor pathology across the spectrum of MNDs and highlights the role of neuroimaging in characterizing anatomical patterns of disease burden *in vivo*. Despite the contribution of neuroimaging to MND research, sample size limitations, inclusion bias, attrition rates in longitudinal studies, and methodological constraints need to be carefully considered. Frontotemporal involvement is a quintessential clinical facet of MND which has important implications for screening practices, individualized management strategies, participation in clinical trials, caregiver burden, and resource allocation. The academic relevance of imaging frontotemporal pathology in MND spans from the identification of genetic variants, through the ascertainment of presymptomatic changes to the design of future epidemiology studies.

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n° 2021-09-1 du 27 août au 9 septembre 2021 (August 27 to September 9, 2021)

Keywords: ALS; MND; MRI; PET; PLS; PMA; SBMA; SMA.

Review

135. Front Cell Dev Biol . 2021 Aug 12;9:681122. doi: 10.3389/fcell.2021.681122. eCollection 2021.

Profilin Isoforms in Health and Disease - All the Same but Different

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- PMID: 34458253
- PMCID: PMC8387879
- DOI: 10.3389/fcell.2021.681122

Profilins are small actin binding proteins, which are structurally conserved throughout evolution. They are probably best known to promote and direct actin polymerization. However, they also participate in numerous cell biological processes beyond the roles typically ascribed to the actin cytoskeleton. Moreover, most complex organisms express several profilin isoforms. Their cellular functions are far from being understood, whereas a growing number of publications indicate that profilin isoforms are involved in the pathogenesis of various diseases. In this review, we will provide an overview of the profilin family and "typical" profilin properties including the control of actin dynamics. We will then discuss the profilin isoforms of higher animals in detail. In terms of cellular functions, we will focus on the role of Profilin 1 (PFN1) and Profilin 2a (PFN2a), which are co-expressed in the central nervous system. Finally, we will discuss recent findings that link PFN1 and PFN2a to neurological diseases, such as amyotrophic lateral sclerosis (ALS), Fragile X syndrome (FXS), Huntington's disease and spinal muscular atrophy (SMA).

Keywords: Fragile X syndrome; Huntington's disease; actin; amyotrophic lateral sclerosis; central nervous system; cytoskeleton; profilin; spinal muscular atrophy.

Dystrophies musculaires (plusieurs pathologies) – *Muscular dystrophies (Multiple)*

136. J Neuroeng Rehabil . 2021 Sep 3;18(1):131. doi: 10.1186/s12984-021-00926-z.

Reaching higher: External scapula assistance can improve upper limb function in humans with irreversible scapula alata

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- PMID: 34479574
- PMCID: PMC8414749
- DOI: 10.1186/s12984-021-00926-z

Background: Scapular dyskinesis, i.e., the deviant mobility or function of the scapula, hampers upper limb function in daily life. A typical sign of scapular dyskinesis is a scapula alata-a protrusion of the shoulder blade during arm elevation. While some reversible causes of scapula alata can be treated with therapy, other, irreversible causes require invasive surgical interventions. When surgery is not an option, however, severe limitations arise as standard approaches for assisting the scapula in daily life do not exist. The aim of this study was to quantify functional improvements when external, i.e., non-invasive, scapula assistance is provided.

Methods: The study was designed as a randomized controlled crossover trial. Eight participants with a scapula alata due to muscular dystrophy performed arm elevations in shoulder flexion and abduction while unassisted (baseline), externally assisted by a trained therapist, and externally assisted by a novel, textile-based scapula orthosis.

Results: With therapist assistance, average arm elevation increased by 17.3° in flexion ($p < 0.001$, 95% confidence interval of the mean [Formula: see text]), and by 11.2° in abduction ($p < 0.01$, [Formula: see text]), constituting the potential of external scapula assistance. With orthosis assistance, average arm elevation increased by 6.2° in flexion ([Formula: see text]) and by 5.8° in abduction ([Formula: see text]). Remarkably, in three participants, the orthosis was at least as effective as the therapist. Moreover, orthosis assistance reduced average perceived exertion by 1.25 points (Borg Scale) when elevating a filled bottle during a simulated daily living task.

Conclusion: These findings indicate a large potential for future advancements in orthotics. Already now, the textile-based scapula orthosis presented here is a feasible tool for leveraging the benefits of external scapula assistance when a therapist is unavailable, as encountered in daily life scenarios.

Trial Registration ClincalTrials.gov (ID NCT04154098). Registered: November 6th 2019, https://clinicaltrials.gov/ct2/show/NCT04154098?term=scapula+orthosis&draw=2&rank=1.

Keywords: Daily life; Muscle weakness; Muscular dystrophy; Scapula Assistance Test; Scapula alata; Scapula orthosis; Scapular fusion; Winging scapula.

Review

137.Biomed Pharmacother . 2021 Aug 25;142:112021. doi: 10.1016/j.biopha.2021.112021. Online ahead of print.

Hidden pharmacological activities of valproic acid: A new insight

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- PMID: 34463268
- DOI: 10.1016/j.biopha.2021.112021

Valproic acid (VPA) is an approved drug for managing epileptic seizures, bipolar disorders, and migraine. VPA has been shown to elevate the level of gamma-aminobutyric acid (GABA) in the brain through competitive inhibition of GABA transaminase, thus promoting the availability of synaptic GABA and facilitating GABA-mediated responses. VPA, which is a small chain of fatty acids, prevents histone deacetylases (HDACs). HDACs play a crucial role in chromatin remodeling and gene expression through posttranslational changes of chromatin-associated histones. Recent studies reported a possible effect of VPA against particular types of cancers. This effect was partially attributed to its role in regulating epigenetic modifications through the inhibition of HDACs, which affect the expression of genes associated with cell cycle control, cellular differentiation, and apoptosis. In this review, we summarize the current information on the actions of VPA in diseases such as diabetes mellitus, kidney disorders, neurodegenerative diseases, muscular dystrophy, and cardiovascular disorders.

Keywords: Cardiac remodeling; Diabetes mellitus; Histone deacetylases; Muscular dystrophy; Renal protection; Valproic acid.

Maladies neuromusculaires (plusieurs pathologies) – *Neuromuscular diseases (Multiple)*

138.Genes (Basel) . 2021 Jul 31;12(8):1199. doi: 10.3390/genes12081199.

An Integrated Clinical-Biological Approach to Identify Interindividual Variability and Atypical Phenotype-Genotype Correlations in Myopathies: Experience on A Cohort of 156 Families

Raul Juntas Morales [1,2], Aurélien Perrin [3,4], Guilhem Solé [5], Delphine Lacourt [3], Henri Pegeot [3], Ulrike Walther-Louvier [6], Pascal Cintas [7], Claude Cances [8], Caroline Espil [9], Corinne Theze [3], Reda Zenagui [3], Kevin Yauy [3], Elodie Cosset [2], Dimitri Renard [10], Valerie Rigau [11], Andre Maues de Paula [12], Emmanuelle Uro-Coste [13], Marie-Christine Arne-Bes [7], Marie-Laure Martin Négrier [14], Nicolas Leboucq [15], Blandine Acket [7], Edoardo Malfatti [16,17], Valérie

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- PMID: 34440373
- PMCID: PMC8392536
- DOI: 10.3390/genes12081199

Diagnosis of myopathies is challenged by the high genetic heterogeneity and clinical overlap of the various etiologies. We previously reported a Next-Generation Sequencing strategy to identify genetic etiology in patients with undiagnosed Limb-Girdle Muscular Dystrophies, Congenital Myopathies, Congenital Muscular Dystrophies, Distal Myopathies, Myofibrillar Myopathies, and hyperCKemia or effort intolerance, using a large gene panel including genes classically associated with other entry diagnostic categories. In this study, we report the comprehensive clinical-biological strategy used to interpret NGS data in a cohort of 156 pediatric and adult patients, that included Copy Number Variants search, variants filtering and interpretation according to ACMG guidelines, segregation studies, deep phenotyping of patients and relatives, transcripts and protein studies, and multidisciplinary meetings. Genetic etiology was identified in 74 patients, a diagnostic yield (47.4%) similar to previous studies. We identified 18 patients (10%) with causative variants in different genes (*ACTA1, RYR1, NEB, TTN, TRIP4, CACNA1S, FLNC, TNNT1,* and *PAPBN1*)

that resulted in milder and/or atypical phenotypes, with high intrafamilial variability in some cases. Mild phenotypes could mostly be explained by a less deleterious effect of variants on the protein. Detection of inter-individual variability and atypical phenotype-genotype associations is essential for precision medicine, patient care, and to progress in the understanding of the molecular mechanisms of myopathies.

Keywords: atypical phenotype-genotype associations; deep phenotyping; inter-individual variability; myopathies; next generation sequencing.

FULL TEXT OPEN ACCESS MDPI

139.J Perinat Med . 2021 Sep 9. doi: 10.1515/jpm-2021-0435. Online ahead of print.

Postnatal gene therapy for neuromuscular diseases - opportunities and limitations

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- PMID: 34499826
- DOI: 10.1515/jpm-2021-0435

During the last decade a number of innovative treatments including gene therapies have been approved for the treatment of monogenic inherited diseases. For some neuromuscular diseases these approaches have dramatically changed the course of the disease. For others relevant challenges still remain and require disease specific approaches to overcome difficulties related to the immune response and the efficient transduction of target cells. This review provides an overview of the current development status of mutation specific treatments for neuromuscular diseases and concludes with on outlook on future developments and perspectives.

Keywords: Duchenne muscular dystrophy; antisense oligonucleotide; gene therapy; myotubular myopathy; spinal muscular atrophy; viral vector.

DE GRUYTER

Review

140.Arch Dis Child . 2021 Aug 30;archdischild-2020-320908. Online ahead of print.

Gene therapy for neuromuscular disorders: prospects and ethics

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- PMID: 34462265
- DOI: 10.1136/archdischild-2020-320908

Most childhood neuromuscular disorders are caused by mutations causing abnormal expression or regulation of single genes or genetic pathways. The potential for gene therapy, gene editing and genetic therapies to ameliorate the course of these conditions is extraordinarily exciting, but there are significant challenges associated with their use, particularly with respect to safety, efficacy, cost and equity. Engagement with these novel technologies mandates careful assessment of the benefits and burdens of treatment for the patient, their family and their society. The examples provided by spinal muscular atrophy and Duchenne muscular dystrophy illustrate the potential value and challenges of gene and genetic therapies for paediatric neurological conditions. The cost and complexity of administration of these agents is a challenge for all countries. Jurisdictional variations in availability of newborn screening, genetic diagnostics, drug approval and reimbursement pathways, treatment and rehabilitation will affect equity of access, nationally and internationally. These challenges will best be addressed by collaboration by governments, pharma, clinicians and patient groups to establish frameworks for safe and cost-effective use of these exciting new therapies.

Keywords: ethics; genetics; neurology; therapeutics.

BMJ Online First

Review

141.Biomolecules . 2021 Jul 28;11(8):1109. doi: 10.3390/biom11081109.

How Inflammation Pathways Contribute to Cell Death in Neuro-Muscular Disorders

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- PMID: 34439778
- PMCID: PMC8391499
- DOI: 10.3390/biom11081109

Neuro-muscular disorders include a variety of diseases induced by genetic mutations resulting in muscle weakness and waste, swallowing and breathing difficulties. However, muscle alterations and nerve depletions involve specific molecular and cellular mechanisms which lead to the loss of motor-nerve or skeletal-muscle function, often due to an excessive cell death. Morphological and molecular studies demonstrated that a high number of these disorders seem characterized by an upregulated apoptosis which significantly contributes to the pathology. Cell death involvement is the consequence of some cellular processes that occur during diseases, including mitochondrial dysfunction, protein aggregation, free radical generation, excitotoxicity and inflammation. The latter represents an important mediator of disease progression, which, in the central nervous system, is known as neuroinflammation, characterized by reactive microglia and astroglia, as well the infiltration of peripheral monocytes and lymphocytes. Some of the mechanisms underlying inflammation have been linked to reactive oxygen species accumulation, which trigger mitochondrial genomic and respiratory chain instability, autophagy impairment and finally neuron or muscle cell death. This review discusses the main inflammatory pathways contributing to cell death in neuro-muscular disorders by highlighting the main mechanisms, the knowledge of which appears essential in developing therapeutic strategies to prevent the consequent neuron loss and muscle wasting.

Keywords: cell death; innate immune system; motor neuron disorders; neuro-muscular diseases; neuroinflammation.

FULL TEXT OPEN ACCESS MDPI

142.Can Respir J . 2021 Aug 23;2021:5554765. doi: 10.1155/2021/5554765. eCollection 2021.

Intermittent Abdominal Pressure Ventilation: An Alternative for Respiratory Support

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- PMID: 34471441
- PMCID: PMC8405303
- DOI: 10.1155/2021/5554765

Intermittent abdominal pressure ventilation is a positive pressure ventilation technique that works with abdominal compressions. It has been known since 1938; however, for many years, it was out of production. In recent years, a new device has been produced that has captured the attention to this old respiratory support technique. We considered eight patients with respiratory failure secondary to a neuromuscular disease (congenital myopathy, Duchenne dystrophy, and amyotrophic lateral sclerosis) intolerant to daytime noninvasive ventilation (NIV). IAPV was proposed as an alternative to NIV. We performed baseline and post-IAPV respiratory function assessment. All patients, two years later, are still using intermittent abdominal ventilation. Intermittent positive abdominal mechanical ventilation can be a valid alternative to noninvasive mechanical ventilation with a nasal or face mask. It improves gas exchange, symptoms, and quality of life, decreases the incidence of pneumonia, and can avert the need for intubation and tracheotomy.

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Review

143.Biomolecules . 2021 Aug 20;11(8):1246. doi: 10.3390/biom11081246.

Circulating Biomarkers in Neuromuscular Disorders: What Is Known, What Is New

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- PMID: 34439911
- PMCID: PMC8393752
- DOI: 10.3390/biom11081246

The urgent need for new therapies for some devastating neuromuscular diseases (NMDs), such as Duchenne muscular dystrophy or amyotrophic lateral sclerosis, has led to an intense search for new potential biomarkers. Biomarkers can be classified based on their clinical value into different categories: diagnostic biomarkers confirm the presence of a specific disease, prognostic biomarkers provide information about disease course, and therapeutic biomarkers are designed to predict or measure treatment response. Circulating biomarkers, as opposed to instrumental/invasive ones (e.g., muscle MRI or nerve ultrasound, muscle or nerve biopsy), are generally easier to access and less "time-consuming". In addition to well-known creatine kinase, other promising molecules seem to be candidate biomarkers to improve the diagnosis, prognosis and prediction of therapeutic response, such as antibodies, neurofilaments, and microRNAs. However, there are some criticalities that can complicate their application: variability during the day, stability, and reliable performance metrics (e.g., accuracy, precision and reproducibility) across laboratories. In the present review, we discuss the application of biochemical biomarkers (both validated and emerging) in the most common NMDs with a focus on their diagnostic, prognostic/predictive and therapeutic application, and finally, we address the critical issues in the introduction of new biomarkers.

Keywords: antibody; biomarker; creatine kinase; microRNA; neurofilament; neuromuscular disease.

FULL TEXT OPEN ACCESS MDPI

144.Adapt Phys Activ Q . 2021 Sep 3;1-21. doi: 10.1123/apaq.2020-0133. Online ahead of print.

Singing and Dancing With Neuromuscular Conditions: A Mixed-Methods Study

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- PMID: 34480007
- DOI: 10.1123/apaq.2020-0133

The purpose of this study was to assess the safety and meaningfulness of a 15-week recreational dance and singing program for people with neuromuscular conditions. Within a transformative mixed-methods design, pulmonary function tests, plethysmography through wearable technology (Hexoskin vests), individualized neuromuscular quality-of-life assessments (version 2.0), and semistructured interviews were used. The interviews were analyzed through inductive, semantic thematic analysis. Although the sample sizes were small (six people with neuromuscular conditions), the authors found no evidence of safety concerns. There was evidence of respiratory improvements and reported improvements in swallowing and speech. The most notable quality-of-life changes included improvements related to weakness, swallowing, relationships, and leisure. The participants shared that the program offered meaningful social connection and embodied skills and safe and pleasurable physical exertion. The authors learned that recreational singing and dancing programs could be a safe and deeply meaningful activity for those with neuromuscular conditions that impact respiration.

Keywords: disability; muscular dystrophy; qualitative methods; quality of life; respiration; wearable technology.

HUMAN KINETICS JOURNALS View full text

145.Elife . 2021 Aug 27;10:e70490. doi: 10.7554/eLife.70490. Online ahead of print.

MACF1 controls skeletal muscle function through the microtubule-dependent localization of extra-synaptic myonuclei and mitochondria biogenesis

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- PMID: 34448452
- DOI: 10.7554/eLife.70490

Skeletal muscles are composed of hundreds of multinucleated muscle fibers (myofibers) whose myonuclei are regularly positioned all along the myofiber's periphery except the few ones clustered underneath the neuromuscular junction (NMJ) at the synaptic zone. This precise myonuclei organization is altered in different types of muscle disease, including centronuclear myopathies (CNMs). However, the molecular machinery regulating myonuclei position and organization in mature myofibers remains largely unknown. Conversely, it is also unclear how peripheral myonuclei positioning is lost in the related muscle diseases. Here, we describe the microtubule-associated protein, MACF1, as an essential and evolutionary conserved regulator of myonuclei positioning and maintenance, in cultured mammalian myotubes, in *Drosophila* muscle, and in adult mammalian muscle using a conditional muscle-specific knockout mouse model. *In vitro*, we show that MACF1 controls microtubules dynamics and contributes to microtubule stabilization during myofiber's maturation. In addition, we demonstrate that MACF1 regulates the microtubules density specifically around myonuclei, and, as a consequence, governs myonuclei motion. Our *in vivo* studies show that MACF1 deficiency is associated with alteration of extra-synaptic myonuclei positioning and microtubules network organization, both preceding NMJ fragmentation. Accordingly, MACF1 deficiency results in reduced muscle excitability and disorganized triads, leaving voltage-activated sarcoplasmic reticulum Ca^{2+} release and maximal muscle force unchanged. Finally, adult MACF1-KO mice present an improved resistance to fatigue correlated with a strong increase in mitochondria biogenesis.

Keywords: D. melanogaster; cell biology; developmental biology; mouse.

Case Reports

146.Front Cardiovasc Med . 2021 Aug 16;8:714460. doi: 10.3389/fcvm.2021.714460. eCollection 2021.

Case Report: The Neuromusclar Triad of Immune Checkpoint Inhibitors: A Case Report of Myositis, Myocarditis, and Myasthenia Gravis Overlap Following Toripalimab Treatment

Yue-Bei Luo [1], Weiting Tang [1], Qiuming Zeng [1], Weiwei Duan [1], Shuyu Li [1], Xiaosu Yang [1], Fangfang Bi [1]

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- PMID: 34485412
- PMCID: PMC8415306
- DOI: 10.3389/fcvm.2021.714460

The neuromuscular adverse events of immune checkpoint inhibitor (ICI) treatment include myositis, polymyalgia rheumatica, myocarditis, and myasthenia syndrome. We report a 47-year old female presenting with external ophthalmoplegia, generalized muscle weakness, and third-degree atrioventricular block 4 weeks after toripalimab treatment for metastatic thymoma. Creatine kinase was elevated to 25,200 U/l and cardiac troponin I to 2.796 ng/ml. Autoantibody profiling shows positive anti-ryanodine receptor and anti-acetylcholine receptor antibodies and negative myositis specific antibodies. Repetitive nerve stimulation did not reveal decrement of compound muscle action potentials. Pulse methylprednisolone and immunoglobulin infusion, together with temporary pacemaker insertion normalized her muscle enzyme levels and cardiac rhythm. This is the first report of overlaping neuromuscular adverse event of toripalimab.

Keywords: PD-1; myasthenia gravis; myocarditis; myositis; toripalimab.

147.Neurol Clin Pract . 2021 Jun;11(3):242-248. doi: 10.1212/CPJ.0000000000000923.

Pneumocystis jirovecii Pneumonia in Neurologic Disorders: Is Prophylaxis Necessary?

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- PMID: 34484891
- PMCID: PMC8382367 (available on 2022-06-01)
- DOI: 10.1212/CPJ.0000000000000923

Background: The incidence of Pneumocystis jirovecii pneumonia (PJP) in patients with underlying neurologic conditions is not well established, and the necessity of PJP prophylaxis for immunocompromised patients with neurologic disorders is uncertain.

Methods: Single-center retrospective analysis of non-HIV PJP patients at a tertiary referral center from 2007 to 2016 to determine the incidence of PJP in patients with primary neurologic disorders.

Results: The study included 142 patients with PJP without HIV. Twenty patients had primary neurologic diagnoses, and 122 had non-neurologic conditions. Associated neurologic diagnoses included brain malignancies (N = 14), myasthenia gravis (MG) (N = 2), myopathy (N = 2), neuromyelitis optica (NMO) (N = 1), and CNS vasculitis (N = 1). Estimated incidences of PJP were 0.7% for patients with NMO and 0.3% for patients with MG for the 10-year study period, whereas 4.6% of patients with NMO and 3.8% of patients with MG were placed on PJP prophylaxis. A survey of 24 neurologists who prescribe immunotherapy or chemotherapy confirmed an infrequent occurrence of PJP in their practice. Malignancy or parenchymal organ failure was present in 90% of neurologic patients with PJP, and coexisting infections occurred in 45%.

Conclusions: The overall incidence of PJP in patients with non-neoplastic neurologic disorders is exceedingly low, raising doubt about the value of routine PJP prophylaxis in neurologic patients outside neuro-oncology. PJP infection occurs frequently in patients with malignancy or parenchymal organ failure, indicating that overall health status may serve as a predisposing factor for PJP.

148.Ont Health Technol Assess Ser . 2021 Aug 12;21(11):1-96. eCollection 2021.

Stance-Control Knee-Ankle-Foot Orthoses for People With Knee Instability: A Health Technology Assessment

Ontario Health (Quality)

- Ontario Health (Quality):

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- PMID: 34484485
- PMCID: PMC8376152

Background: Knee instability can arise from various causes and conditions such as neuromuscular disease, central nervous system conditions, and trauma. For people with knee instability, knee orthosis devices are prescribed to help with standing, walking, and performing tasks. We conducted a health technology assessment of stance-control knee-ankle-foot orthoses (SCKAFOs) for people with knee instability, which included an evaluation of the effectiveness, safety, and budget impact of publicly funding SCKAFOs, as well as patient preferences and values.

Methods: We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the Risk of Bias in Nonrandomized Studies (RoBANS) tool and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and also analyzed the budget impact of publicly funding SCKAFOs in people with knee instabilities in Ontario. We did not conduct a primary economic evaluation as there was limited comparative clinical evidence to inform an economic model. Our reference case budget impact analysis was done from the perspective of the Ontario Ministry of Health; it compared the total costs of a basic mechanical SCKAFO and locked KAFO (LKAFO) for people with knee instability. We also performed scenario analyses varying the following parameters: the price of all classes of SCKAFO (mechanical, electronic, and microprocessor), and the uptake of SCKAFO. To contextualize the potential value of SCKAFO, we spoke with people with knee instability.

Results: We included four studies in the clinical evidence review. We are uncertain if SCKAFOs improve walking ability, energy consumption, or activities of daily living compared with LKAFOs (GRADE: Very low).

Our economic evidence review identified one costing analysis that suggested that the costs of orthotic devices such as LKAFOs and SCKAFOs are highly variable according to the cost of materials, professional time, and customization required by the individual patient. The budget impact of publicly funding mechanical SCKAFOs in Ontario over the next 5 years (at a full device cost of $10,784) ranged from an additional $0.50 million in year 1 (at an uptake rate of 30% in the target population [429 eligible people]) to $0.83 million in year 5 (at an uptake rate of 50%), with a total budget impact of $3.34 million over 5 years. We found that the greatest increase in budget impact in the scenario analysis came from the microprocessor SCKAFO device, which had an additional cost of $10.07 million in year 1, increasing to $16.78 million in year 5. When we decreased the cost of a mechanical SCKAFO device (to $7,384), this reduced the 5-year budget impact to $0.89 million (vs. $3.34 million in the reference case). The people with knee instability with whom we spoke reported that they preferred a device that would provide a more typical gait, but starting with this type of device would be easier than switching from an existing LKAFO.
Conclusions: We are uncertain if SCKAFOs improve walking ability, reduce energy consumption, or improve activities of daily living compared with LKAFOs. We estimate that the additional cost to provide public funding for a mechanical SCKAFO in people with knee instability would range from about $0.50 million in year 1 to $0.83 million in year 5, yielding a total budget impact of $3.34 million over 5 years. Depending on the class of SCKAFO and the uptake rate for the device, the budget impact may vary. People who met the criteria for the use of a SCKAFO did have a strong preference for it over an LKAFO.

149. Pharmacoecon Open . 2021 Sep 1. doi: 10.1007/s41669-021-00299-y. Online ahead of print.

Budget Impact of the Vest™ High Frequency Chest Wall Oscillation System for Managing Airway Clearance in Patients with Complex Neurological Disorders: A US Healthcare Payers' Perspective Analysis

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- PMID: 34468966
- DOI: 10.1007/s41669-021-00299-y

Objective: As a recognized therapy to improve airway clearance, high-frequency chest wall oscillation (HFCWO) is used to manage reduced vital capacity in patients with complex neuromuscular disorders (cNMD). This study aimed to investigate the budget impact of HFCWO versus chest wall physical therapy (CWPT) from a US-commercial payer perspective.
Methods: In combination with a previously developed cost-effectiveness model, a budget impact model was developed to evaluate the incremental budgetary impact associated with introducing a HFCWO device over a 5-year time horizon. The model compared the cost implications associated with the commonly used CWPT procedure, as the current scenario, with a new scenario consisting of 80% of market share for HFCWO. The resource use and costs included in the analyses were costs associated with the HFCWO device (Vest™ System) and its consumables, patient training, and medical services such as hospitalization, medications, emergency room, and outpatient visits. The primary outcome measures included total and incremental budgetary impact per member per year (PMPY).
Results: In a hypothetical plan of 1,000,000 members (men: 49.2%), 2099 patients with cNMD were estimated to be eligible to receive airway clearance services over 5 years. The new scenario (HFCWO and CWPT [US$24 PMPY]) was cost-saving compared with the current scenario (CWPT only [$34 PMPY]) with a cost reduction of US$9.46 PMPY. The model estimated a net cost-saving of US$1,594,131 and US$9,591,343 over 1 and 5 years, respectively.

Conclusion: This study suggests the HFCWO technique to manage the reduction in vital capacity in patients with cNMD would lead to favorable budget impact results.

SpringerLink FULL-TEXT ARTICLE

Divers – *Miscellaneous*

150.Hum Gene Ther . 2021 Sep 8. doi: 10.1089/hum.2021.191. Online ahead of print.

Recent progress in genome editing for gene therapy applications: the French perspective

Mario Amendola [1], Aurélie Bedel [2], Ana Buj Bello [3], Mathieu Carrara [4], Jean-Paul Concordet [5], Giacomo Frati [6], David Gilot [7], Carine Giovannangeli [8], Alejandra Guttierrez [9], Marine Laurent [10], Annarita Miccio [11] [12], François Moreau-Gaudry [13], Célia Sourd [14], Julien Valton [15], Els Verhoeyen [16]

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- PMID: 34494480
- DOI: 10.1089/hum.2021.191

Recent advances in genome editing tools, especially the novel developments in the clustered regularly interspaced short palindrome repeats associated protein (CRISPR/Cas)-derived editing machinery have revolutionized not only basic science but, importantly, also the gene therapy field. Their flexibility and ability to introduce precise modifications in the genome in order to disrupt or correct genes or insert expression cassettes in safe harbors in the genome underlines their potential applications as a medicine of the future to cure many genetic diseases. In this review, we give an overview of the recent progress made by French researchers in the field of therapeutic genome editing while putting their work in the general context of advances made in the field. We focus on recent hematopoietic stem cell gene editing strategies for blood diseases affecting the red blood cells or blood coagulation as well as lysosomal storage diseases. We report on a genome editing based therapy for a muscular dystrophy and the potency of T cell gene editing to increase anti-cancer activity of chimeric antigen receptor (CAR) T cells to combat cancer. We will also discuss technical obstacles and side-effects such as unwanted editing activity that need to be surmounted on the way towards a clinical implementation of genome editing. We propose here improvements developed today, including by French researchers to overcome the editing related genotoxicity and improve editing precision by the use of novel recombinant nuclease-based systems such as nickases, base editors and prime editors. Finally, a solution is proposed to resolve the cellular toxicity induced by the systems employed for gene editing machinery delivery.

Mary Ann Liebert

151. Acta Biochim Pol . 2021 Aug 31;68(3):359-375. doi: 10.18388/abp.2020_5805.

Gene therapy. The legacy of Wacław Szybalski

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- PMID: 34464044
- DOI: 10.18388/abp.2020_5805

Seminal demonstration of the possibility of stable genetic modification of mammalian cells performed by Wacław and Elisabeth Szybalski opened the doors for gene therapy, the term coined by Wacław Szybalski already in 1962. In the next 60 years, numerous tools for gene delivery have been developed and applied for clinical research, culminating in the registration of several genetic therapies in Europe and the USA. Some of these strategies, aimed to treat severe combined immunodeficiencies, inherited forms of blindness, spinal muscular atrophy, some cancers, and genetic anemias, are the real hope for patients suffering from previously incurable diseases or the ones whose treatment was not effective. On the approaching 60th anniversary of gene therapy, combined with the 100th anniversary of the birth of Professor Wacław Szybalski (September 9th, 1921), who passed away on December 16, 2020, here I present the summary of the most important aspects of clinical applications of genetic therapies.

Review

152. Muscle Nerve . 2021 Aug 27. doi: 10.1002/mus.27380. Online ahead of print.

Comparison of the United Kingdom and United States approaches to approval of new neuromuscular therapies

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- PMID: 34448221
- DOI: 10.1002/mus.27380

Many novel therapies are now available for rare neuromuscular conditions that were previously untreatable. Hereditary transthyretin amyloidosis and spinal muscular atrophy are two examples of diseases with new medications that have transformed our field. The United States and the United Kingdom have taken disparate approaches to the approval and coverage of medications, despite both providing incentives to develop therapies targeting rare diseases. The US requires less evidence for approval when compared with medications for common diseases and does not have a mechanism to ensure or even encourage cost-effectiveness. The Institute of Clinical and Economic Review provides in-depth cost-effectiveness analyses in the US, but does not have the authority to negotiate drug costs. In contrast, the UK has maintained a similar scientific threshold for approval of all therapies, while requiring negotiation with National Institute for Health and Care Excellence to ensure that medications are cost-effective for rare diseases. These differences have led to approval of medications for rare diseases in the US that have less evidence than required for common diseases. Importantly, these medications have not been approved in the UK. Even when medications meet traditional scientific thresholds, they uniformly arrive with high list prices in the US, whereas they are available at cost-effective prices in the UK. The main downsides to the UK approach are that cost-effective medications are often available months later than in the US, and some medications remain unavailable.

Review

153. Biologics . 2021 Aug 21;15:353-361. doi: 10.2147/BTT.S326422. eCollection 2021.

Mechanism and Applications of CRISPR/Cas-9-Mediated Genome Editing

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- PMCID: PMC8388126
- DOI: 10.2147/BTT.S326422

Clustered regularly interspaced short palindromic repeat (CRISPR) and their associated protein (Cas-9) is the most effective, efficient, and accurate method of genome editing tool in all living cells and utilized in many applied disciplines. Guide RNA (gRNA) and CRISPR-associated (Cas-9) proteins are the two essential components in CRISPR/Cas-9 system. The mechanism of CRISPR/Cas-9 genome editing contains three steps, recognition, cleavage, and repair. The designed sgRNA recognizes the target sequence in the gene of interest through a complementary base pair. While the Cas-9 nuclease makes double-stranded breaks at a site 3 base pair upstream to protospacer adjacent motif, then the double-stranded break is repaired by either non-homologous end joining or homology-directed repair cellular mechanisms. The CRISPR/Cas-9 genome-editing tool has a wide number of applications in many areas including medicine, agriculture, and biotechnology. In agriculture, it could help in the design of new grains to improve their nutritional value. In medicine, it is being investigated for cancers, HIV, and gene therapy such as sickle cell disease, cystic fibrosis, and Duchenne muscular dystrophy. The technology is also being utilized in the regulation of specific genes through the advanced modification of Cas-9 protein. However, immunogenicity, effective delivery systems, off-target effect, and ethical issues have been the major barriers to extend the technology in clinical applications. Although CRISPR/Cas-9 becomes a new era in molecular biology and has countless roles ranging from basic molecular researches to clinical applications, there are still challenges to rub in the practical applications and various improvements are needed to overcome obstacles.

Keywords: CRISPR; Cas-9; applications; gene-editing; mechanism; sgRNA.

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Review

154.Life Sci . 2021 Aug 25;284:119908. doi: 10.1016/j.lfs.2021.119908. Online ahead of print.

Applications of CRISPR as a potential therapeutic

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- PMID: 34453943
- DOI: 10.1016/j.lfs.2021.119908

Genetic disorders and congenital abnormalities are present in 2-5% of births all over the world and can cause up to 50% of all early childhood deaths. The establishment of sophisticated and controlled techniques for customizing DNA manipulation is significant for the therapeutic role in such disorders and further research on them. One such technique is CRISPR that is significant towards optimizing genome editing and therapies, metabolic fluxes as well as artificial genetic systems. CRISPR-Cas9 is a molecular appliance that is applied in the areas of genetic and protein engineering. The CRISPR-CAS system is an integral element of prokaryotic adaptive immunity that allows prokaryotic cells to identify and kill any foreign DNA. The Gene editing property of CRISPR finds various applications like diagnostics and therapeutics in cancer, neurodegenerative disorders, genetic diseases, blindness, etc. This review discusses applications of CRISPR as a therapeutic in various disorders including several genetic diseases (including sickle cell anemia, blindness, thalassemia, cystic fibrosis, hereditary tyrosinemia type I, duchenne muscular dystrophy, mitochondrial disorders), Cancer, Huntington's disease and viral infections (like HIV, COVID, etc.) along with the prospects concerning them. CRISPR-based therapy is also being researched and defined for COVID-19. The related mechanism of CRISPR has been discussed alongside highlighting challenges involved in therapeutic applications of CRISPR.

Keywords: COVID-19; CRISPR; Gene therapy; Genetic diseases; Genome editing; cancer.

ELSEVIER FULL-TEXT ARTICLE

Certaines références présentées par maladies sont triées ci-dessous **par spécialités**.
*Some of citations presented by diseases are sorted below **by specialties**.*

Cardiologie – *Cardiology*

Review Int J Mol Sci. 2021 Aug 19;22(16):8954. doi: 10.3390/ijms22168954.

Multiomic Approaches to Uncover the Complexities of Dystrophin-Associated Cardiomyopathy

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- PMCID: PMC8396646
- DOI: 10.3390/ijms22168954

Despite major progress in treating skeletal muscle disease associated with dystrophinopathies, cardiomyopathy is emerging as a major cause of death in people carrying dystrophin gene mutations that remain without a targeted cure even with new treatment directions and advances in modelling abilities. The reasons for the stunted progress in ameliorating dystrophin-associated cardiomyopathy (DAC) can be explained by the difficulties in detecting pathophysiological mechanisms which can also be efficiently targeted within the heart in the widest patient population. New perspectives are clearly required to effectively address the unanswered questions concerning the identification of authentic and effectual readouts of DAC occurrence and severity. A potential way forward to achieve further therapy breakthroughs lies in combining multiomic analysis with advanced preclinical precision models. This review presents the fundamental discoveries made using relevant models of DAC and how omics approaches have been incorporated to date.

Keywords: dystrophin-associated cardiomyopathy; dystrophinopathies; multiomic analysis; muscular dystrophy; preclinical precision models.

FULL TEXT OPEN ACCESS MDPI

Life (Basel). 2021 Jul 27;11(8):752. doi: 10.3390/life11080752.

Influence of Different Types of Corticosteroids on Heart Rate Variability of Individuals with Duchenne Muscular Dystrophy-A Pilot Cross Sectional Study

Rodrigo Martins Dias [1], Rosangela Akemi Hoshi [2], Luiz Carlos Marques Vanderlei [3], Carlos Bandeira de Mello Monteiro [4], Mayra Priscila Boscolo Alvarez [4,5], Tânia Brusque Crocetta [6], Luis Fernando Grossklauss [7], Deborah Cristina Gonçalves Luiz Fernani [8], Maria Tereza Artero Prado Dantas [8], Fabiana Paula Almeida Martins [9], David M Garner [10], Luiz Carlos Abreu [11], Celso Ferreira [1], Talita Dias da Silva [1,4,12]

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- PMID: 34440496
- PMCID: PMC8398672
- DOI: 10.3390/life11080752

Individuals with Duchenne Muscular Dystrophy (DMD) have an impairment of cardiac autonomic function categorized by parasympathetic reduction and sympathetic predominance. The objective of this study was to assess the cardiac autonomic modulation of individuals with DMD undergoing therapy with Prednisone/Prednisolone and Deflazacort and compare with individuals with DMD without the use of these medications and a typically developed control group. Methods: A cross-sectional study was completed, wherein 40 boys were evaluated. The four treatment groups were: Deflazacort; Prednisone/Prednisolone; no corticoid use; and typical development. Heart Rate Variability (HRV) was investigated via linear indices (Time Domain and Frequency Domain) and non-linear indices Results: The results of this study revealed that individuals with DMD undertaking pharmacotherapies with Prednisolone demonstrated HRV comparable to the Control Typically Developed (CTD) group. In contrast, individuals with DMD undergoing pharmacotherapies with Deflazacort achieved lower HRV, akin to individuals with DMD without any medications, as demonstrated in the metrics: RMSSD; LF (n.u.), HF (n.u.), LF/HF; SD1, α1, and α1/α2, and a significant effect for SD1/SD2; %DET and Ratio; Shannon Entropy, 0 V%, 2 LV% and 2 ULV%. Conclusions: Corticosteroids have the potential to affect the cardiac autonomic modulation in adolescents with DMD. The use of Prednisone/Prednisolone appears to promote improved responses in terms of sympathovagal activity as opposed to Deflazacort.

Keywords: Duchenne Muscular Dystrophy (DMD); Heart Rate Variability (HRV); autonomic nervous system; deflazacort; prednisone.

FULL TEXT OPEN ACCESS MDPI

Pak J Med Sci . Sep-Oct 2021;37(5):1376-1381. doi: 10.12669/pjms.37.5.3104.

Induced pluripotent stem cells derived cardiomyocytes from Duchenne Muscular Dystrophy patients in vitro

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- PMCID: PMC8377888
- DOI: 10.12669/pjms.37.5.3104

Objective: This study aimed at the in vitro generation of DMD-cardiomyocytes from patient-specific induced pluripotent stem cells derived from a Pakistani patient for future work on DMD in vitro disease modeling and drug testing for efficacy and toxicity.

Methods: This in vitro experimental study was carried out from December 2018 to January 2019 at Stem Cells and Regenerative Medicine Lab (SCRML) at Dow Research Institute of Biotechnology and Biomedical Sciences (DRIBBS), Dow University of Health Sciences (DUHS) Urine derived DMD-iPSCs were used which had been generated previously from a Pakistani DMD patient who had been selected through non-random purposive sampling. These were differentiated towards cardiomyocytes using Cardiomyocytes Differentiation media having specified growth factors and then the molecular characterization of the differentiated cells was done using immunofluorescence.

Results: Pakistani patient's DMD-Cardiomyocytes were generated and their identity was confirmed by positive immunofluorescence for the expression of cardiac markers NKX2-5 and TNNT-2.

Conclusion: This study aimed for in vitro generation of DMD cardiomyocytes for future application in disease modeling, new drug testing for efficacy and toxicity, as well as for drug-testing for tailored personalized therapy. To the best of our knowledge, this was the first time DMD-Cardiomyocytes were generated from Pakistani DMD patients using their own induced pluripotent stem cells.

Keywords: Duchenne muscular dystrophy; Human induced pluripotent stem cells; In vitro cardiomyocytes.

Case Reports BMC Gastroenterol . 2021 Aug 26;21(1):333. doi: 10.1186/s12876-021-01904-4.

A rare case of nivolumab-related myasthenia gravis and myocarditis in a patient with metastatic gastric cancer

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- PMID: 34445963
- PMCID: PMC8393464
- DOI: 10.1186/s12876-021-01904-4

Background: Although rare, several immune-related adverse effects can be life-threatening. Here, we describe a metastatic gastric cancer patient presenting with nivolumab-related myasthenia gravis and myocarditis, a previously unreported adverse effect of gastric cancer treatment.

Case presentation: A 66-year-old man with metastatic gastric cancer visited the emergency department because of dizziness after the first dose of nivolumab. Diagnoses of nivolumab-related myasthenia gravis and myocarditis were established. Myocardial biopsy results and anti-acetylcholine receptor antibody positivity confirmed the diagnoses. Despite plasma exchange and intravenous methylprednisolone and immunoglobulin administration, the patient's general condition gradually worsened, and he died.

Conclusions: Strict monitoring for cardiac and neuromuscular symptoms after nivolumab administration is necessary to rapidly treat these adverse effects.

Keywords: Gastric cancer; Myasthenia gravis; Myocarditis; Nivolumab; Programmed cell death-1 receptor.

Gastroentérologie / Nutrition – *Gastroenterology / Nutrition*

Life (Basel). 2021 Jul 30;11(8):772. doi: 10.3390/life11080772.

Prevalence of Bladder and Bowel Dysfunction in Duchenne Muscular Dystrophy Using the Childhood Bladder and Bowel Dysfunction Questionnaire

Judith M Lionarons [1 2], Imelda J M de Groot [3 4], Johanna M Fock [5], Sylvia Klinkenberg [1], Desiree M J Vrijens [6], Anita C E Vreugdenhil [7 8], Evita G Medici-van den Herik [9], Inge Cuppen [10], Bregje Jaeger [11], Erik H Niks [4 12], Rinske Hoogerhuis [13], Nicky Platte-van Attekum [13], Frans J M Feron [14], Catharina G Faber [1 2], Jos G M Hendriksen [4 15], Johan S H Vles [2]

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- DOI: 10.3390/life11080772

Introduction: Lower urinary tract symptoms (LUTS) and gastrointestinal (GI) problems are common in Duchenne muscular dystrophy (DMD), but not systematically assessed in regular care. We aimed to determine the prevalence of bladder and bowel dysfunction (BBD) in DMD patients compared with healthy controls (HC).

Methods: The Childhood Bladder and Bowel Dysfunction Questionnaire (CBBDQ) based on the International Rome III criteria and the International Children's Continence Society was filled out by 57 DMD patients and 56 HC. Additionally, possible associations of BBD with, for example, medication use or quality of life were evaluated in an additional questionnaire developed by experts.

Results: In 74% of patients versus 56% of HC ≥ 1 LUTS (n.s.) were reported, 68% of patients versus 39% of HC reported ≥1 bowel symptom (p = 0.002) and 53% of patients versus 30% of HC reported combined LUTS and bowel symptoms (p = 0.019). A negative impact of BBD on daily life functioning was reported by 42% of patients.

Conclusions: These data underscore that standard screening for BBD is needed and that the CBBDQ could be of added value to optimize DMD care.

Keywords: Duchenne muscular dystrophy; bladder and bowel dysfunction; constipation; lower urinary tract symptoms; urinary incontinence.

FULL TEXT OPEN ACCESS MDPI

Neurology . 2021 Sep 7;10.1212/WNL.0000000000012725. Online ahead of print.

Association Between Body Mass Index and Disability in Children With Charcot-Marie-Tooth Disease

Gabrielle A Donlevy [1 2], Sarah P Garnett [3 2], Kayla M D Cornett [4 2], Marnee J McKay [4], Jennifer N Baldwin [5], Rosemary R Shy [6], Sabrina W Yum [7 8], Timothy Estilow [8 9], Isabella Moroni [10], Maria Foscan [10], Emanuela Pagliano [10], Davide Pareyson [10], Matilde Laura [11], Trupti Bhandari [12], Francesco Muntoni [12], Mary M Reilly [11], Richard S Finkel [13], Janet E Sowden [14], Katy J Eichinger [14], David N Herrmann [14], Michael E Shy [15], Joshua Burns [4 2], Manoj P Menezes [3 2]

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- PMID: 34493614
- DOI: 10.1212/WNL.0000000000012725

Objective: This study examined the association between body mass index (BMI) and disability in children with Charcot-Marie-Tooth disease (CMT).

Methods: We conducted a cross-sectional analysis of 477 patients with CMT aged 3-20 years from the Inherited Neuropathy Consortium, and 316 age-and-sex matched healthy children from the 1000 Norms Project. BMI was categorised according to the International Obesity Task Force (IOTF) criteria, and BMI categorisation was compared with healthy children. IOTF categories (adult equivalent BMI cut points) were:

severely underweight (BMI<17kg/m2); underweight (BMI≥17 to <18.5kg/m2); healthy weight (BMI≥18.5 to <25kg/m2); overweight (BMI ≥25 to <30kg/m2); obese (BMI ≥30kg/m2). Scores on the 0-44 point CMT Pediatric Scale (CMTPedS), a well-validated measure of disability, were examined in relation to BMI.
Results: There was a higher proportion of children with CMT categorised as severely underweight (5.7%vs0.3%), underweight (10.3%vs5.1%), and obese (7.3%vs3.8%) (p<0.05). Fewer children with CMT were categorised as healthy weight (61.8%vs74.4%) (p<0.05), and the proportion of overweight (14.9%vs16.5%) between groups was similar. CMTPedS scores (mean ± SD) for weight categories were: severely underweight (27±9), underweight (20±8), healthy weight (17±9), overweight (17±9) obese (22 ±10). Compared to healthy weight children with CMT, being severely underweight was associated with being more disabled (p<0.001), as was being obese (p=0.015).
Conclusion: The proportion of underweight and obese children with CMT is higher compared to age-and sex-matched healthy children. Children with CMT who are underweight or obese are associated with greater disability than compared children with CMT of healthy weight.

Neurology

Imagerie médicale – *Medical imaging*

Neuromuscul Disord . 2021 Jul 1;S0960-8966(21)00166-8. doi: 10.1016/j.nmd.2021.06.012. Online ahead of print.

Whole-body muscle MRI characteristics of LAMA2-related congenital muscular dystrophy children: An emerging pattern

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- PMID: 34481707
- DOI: 10.1016/j.nmd.2021.06.012

Merosin-deficient or LAMA2-related congenital muscular dystrophy (CMD) belongs to a group of muscle diseases with an overlapping diagnostic spectrum. MRI plays an important role in the diagnosis and disease-tracking of muscle diseases. Whole-body MRI is ideal for describing patterns of muscle involvement. We intended to analyze the pattern of muscle involvement in merosin-deficient CMD children employing whole-body muscle MRI. Ten children with merosin-deficient CMD underwent whole-body muscle MRI. Eight of which were genetically-confirmed. We used a control group of other hereditary muscle diseases, which included 13 children (mean age was 13 SD +/- 5.5 years), (8 boys and 5 girls) for comparative analysis. Overall, 37 muscles were graded for fatty infiltration using Mercuri scale modified by Fischer et al. The results showed a fairly consistent pattern of muscle fatty infiltration in index group, which differs from that in control group. There was a statistically significant difference between the two groups in regard to the fatty infiltration of the neck, serratus anterior, intercostal, rotator cuff, deltoid, triceps, forearm, gluteus maximus, gluteus medius, gastrocnemius and soleus muscles. Additionally, the results showed relative sparing of the brachialis, biceps brachii, gracilis, sartorius, semitendinosus and extensor muscles of the ankle in index group, and specific texture abnormalities in other muscles. There is evidence to suggest that whole-body muscle MRI can become a useful contributor to the differential diagnosis of children with merosin deficient CMD. The presence of a fairly characteristic pattern of involvement was demonstrated. MRI findings should be interpreted in view of the clinical and molecular context to improve diagnostic accuracy.

Keywords: Congenital muscular dystrophy type 1; Genetic muscular diseases; LAMA2 gene; Laminin Alpha-2 congenital muscular dystrophy; Merosin-deficient congenital muscular dystrophy.

ELSEVIER FULL-TEXT ARTICLE

Neurology . 2021 Sep 7;10.1212/WNL.0000000000012724. Online ahead of print.

Association of Elbow Flexor MRI Fat Fraction With Loss of Hand-to-Mouth Movement in Patients With Duchenne Muscular Dystrophy

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- PMID: 34493619
- DOI: 10.1212/WNL.0000000000012724

Objective: To study the potential of quantitative MRI (qMRI) fat fraction (FF) as biomarker in non-ambulant Duchenne muscular dystrophy (DMD) patients, we assessed the additive predictive value of elbow flexor FF to age on loss of hand-to-mouth movement.

Methods: Non-ambulant DMD patients (≥8 years) were included. 4-point Dixon MRI scans of the right upper arm were performed at baseline and at 12, 18 or 24 months follow-up. Elbow flexor FFs were determined from five central slices. Loss of hand-to-mouth movement was determined at study visits and by phone-calls every four months. FFs were fitted to a sigmoidal curve using a mixed model with random slope to predict individual trajectories. The added predictive value of elbow flexor FF to age on loss of hand-to-mouth movement was calculated from a Cox model with the predicted FF as a time varying covariate, yielding a hazard ratio.

Results: Forty-eight MRIs of 20 DMD patients were included. The hazard ratio of a percent-point increase in elbow flexor FF for the time to loss of hand-to-mouth movement was 1.12 (95%-confidence interval 1.04-1.21; p=0.002). This corresponded to a 3.13-fold increase of the instantaneous risk of loss of hand-to-mouth movement in patients with a 10 percent-points higher elbow flexor FF at any age.

Conclusion: In this prospective study, elbow flexor FF predicted loss of hand-to-mouth movement independent of age. qMRI measured elbow flexor FF can be used as surrogate endpoint or stratification tool for clinical trials in non-ambulant DMD patients.

Classification of evidence: This study provides Class II evidence that qMRI FF of elbow flexor muscles in patients with DMD predicts loss of hand-to-mouth movement independent of age.

Neurology

Ann Clin Transl Neurol . 2021 Aug 28. doi: 10.1002/acn3.51417. Online ahead of print.

Upper limb disease evolution in exon 53 skipping eligible patients with Duchenne muscular dystrophy

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- PMID: 34453498
- DOI: 10.1002/acn3.51417

Objective: To understand the natural disease upper limb progression over 3 years of ambulatory and non-ambulatory patients with Duchenne muscular dystrophy (DMD) using functional assessments and quantitative magnetic resonance imaging (MRI) and to exploratively identify prognostic factors.
Methods: Forty boys with DMD (22 non-ambulatory and 18 ambulatory) with deletions in dystrophin that make them eligible for exon 53-skipping therapy were included. Clinical assessments, including Brooke score, motor function measure (MFM), hand grip and key pinch strength, and upper limb distal coordination and endurance (MoviPlate), were performed every 6 months and quantitative MRI of fat fraction (FF) and lean muscle cross sectional area (flexor and extensor muscles) were performed yearly.
Results: In the whole population, there were strong nonlinear correlations between outcome measures. In non-ambulatory patients, annual changes over the course of 3 years were detected with high sensitivity standard response mean (|SRM| ≥0.8) for quantitative MRI-based FF, hand grip and key pinch, and MFM. Boys who presented with a FF<20% and a grip strength >27% were able to bring a glass to their mouth and retained this ability in the following 3 years. Ambulatory patients with grip strength >35% of predicted value and FF <10% retained ambulation 3 years later.
Interpretation: We demonstrate that continuous decline in upper limb strength, function, and MRI measured muscle structure can be reliably measured in ambulatory and non-ambulatory boys with DMD with high SRM and strong correlations between outcomes. Our results suggest that a combination of grip strength and FF can be used to predict important motor milestones.

J Neurol . 2021 Sep 6. doi: 10.1007/s00415-021-10786-1. Online ahead of print.

Diagnostic magnetic resonance imaging biomarkers for facioscapulohumeral muscular dystrophy identified by machine learning

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- PMID: 34486074
- DOI: 10.1007/s00415-021-10786-1

Background: The diagnosis of facioscapulohumeral muscular dystrophy (FSHD) can be challenging in patients not displaying the classical phenotype or with atypical clinical features. Despite the identification by magnetic resonance imaging (MRI) of selective patterns of muscle involvement, their specificity and added diagnostic value are unknown.
Methods: We aimed to identify the radiological features more useful to distinguish FSHD from other myopathies and test the diagnostic accuracy of MRI. A retrospective cohort of 295 patients (187 FSHD, 108 non-FSHD) studied by upper and lower-limb muscle MRI was analyzed. Scans were evaluated for the presence of 15 radiological features. A random forest machine learning algorithm was used to identify the most relevant for FSHD diagnosis. Different patterns were created by their combination and diagnostic accuracy of each of them was tested.
Results: The combination of trapezius involvement and bilateral subscapularis muscle sparing achieved the best diagnostic accuracy (0.89, 95% Confidence Interval [0.85-0.92]) with 0.90 [0.85-0.94] sensitivity and

0.88 [0.80-0.93] specificity. This pattern correctly identified 91% atypical FSHD patients of our cohort. The combination of trapezius involvement, bilateral subscapularis and iliopsoas sparing and asymmetric involvement of upper and lower-limb muscles was pathognomonic for FSHD, yielding a specificity of 0.99 [0.95-1.00].
Conclusions: We identified MRI patterns that showed a high diagnostic power in promptly discriminating FSHD from other muscle disorders, with comparable performance irrespective of typical or atypical clinical features. Upper girdle in addition to lower-limb muscle imaging should be extensively implemented in the diagnostic workup to support or exclude a diagnosis of FSHD.
Keywords: Biomarkers; Facioscapulohumeral muscular dystrophy; Machine learning; Muscle MRI.

Neuroradiology. 2021 Sep 9. doi: 10.1007/s00234-021-02730-x. Online ahead of print.

Structural and functional brain changes in X-linked Charcot-Marie-Tooth disease: insights from a multimodal neuroimaging study

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- PMID: 34498107
- DOI: 10.1007/s00234-021-02730-x

Purpose: Brain involvement in X-linked Charcot-Marie-Tooth disease (CMTX) has been previously reported. We studied the brain structural and functional integrity using a multimodal neuroimaging approach in patients with no current central nervous system (CNS) symptoms, in order to further delineate the disease's phenotype.
Methods: Seventeen CMTX patients with no current CNS symptoms and 24 matched healthy controls underwent brain magnetic resonance imaging (MRI). Structural integrity was evaluated performing Gray matter analysis with voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) of diffusion tensor imaging (DTI). Functional integrity was evaluated with resting-state functional MRI (rs-fMRI).
Results: Decreased gray matter density was detected in CMTX patients compared to healthy controls in bilateral hippocampus, left thalamus, left postcentral gyrus, left superior parietal lobule, left cerebellum crus I and II, and vermis VI. DTI analysis showed increased fractional anisotropy and radial diffusivity in the right anterior insula and increased axial diffusivity in right cerebellum crus I in CMTX patients. rs-fMRI revealed decreased spontaneous neural activity on left precentral gyrus in patients compared to healthy controls.
Conclusion: Advanced magnetic resonance (MR) neuroimaging techniques in CMTX patients revealed structural and functional involvement of multiple motor and extra-motor brain areas. MR neuroimaging techniques have the potential to delineate the CNS phenotype of a peripheral neuropathy like CMTX.
Keywords: Charcot-Marie-Tooth; Diffusion tensor imaging; Gray matter volumetry; Neuroimaging; Resting-state fMRI.

Médecine physique et de réadaptation – *Physical and rehabilitation medicine*

Clin Rehabil. 2021 Sep 2;2692155211043265. doi: 10.1177/02692155211043265. Online ahead of print.

The effect of trunk training on trunk control, upper extremity, and pulmonary function in children with Duchenne muscular dystrophy: A randomized clinical trial

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- PMID: 34474581
- DOI: 10.1177/02692155211043265

Objectives: To investigate the effect of trunk training on trunk control, arm, and pulmonary function in children with Duchenne muscular dystrophy.

Design: A randomised controlled trial.

Settings: Neuromuscular diseases clinic of university hospital.

Subjects: Twenty-six children with Duchenne muscular dystrophy aged 5-16 were included in the study.

Intervention: Participants were randomly allocated into two groups. The study group (N = 13) exercised with the trunk-oriented exercise program and the conventional exercise program, whereas the control group (N = 13) underwent the conventional exercise program for eight weeks.

Main measures: The primary outcomes were trunk control was assessed using the Trunk Control Measurement Scale, the arm function was assessed using Performance of Upper Limb, and respiratory function using the pulmonary function test. Data collection was conducted at baseline, and eighth week. The differences in trunk control scores, arm function scores, and respiratory function values before and after the training were calculated for the intergroup comparison.

Results: The mean age of the participants was 11.6 (2.6) in the study group and 10.6 (3.4) in the control group. The changes between trunk control score, arm function score (total and distal level score), and respiratory function value (Forced Vital Capacity, Forced Expiratory Volume in one second, and Peak Expiratory Flow Volume percentage values) were compared and significant differences were found after eight week periods in the study and control groups.

Conclusions: Trunk-oriented exercise program in Duchenne muscular dystrophy might be effective for trunk control, arm, and respiratory function.

Keywords: Duchenne muscular dystrophy; arm function; respiratory function; trunk control; trunk-oriented exercises.

SAGE journals

J Musculoskelet Neuronal Interact . 2021 Sep 1;21(3):343-350.

Efficacy of two intervention approaches on functional walking capacity and balance in children with Duchene muscular dystrophy

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- PMID: 34465672
- PMCID: PMC8426654

Objectives: Children with Duchene muscular dystrophy have weak muscles, which may impair postural adjustments. These postural adjustments are required for gait and dynamic balance during the daily living activities. The aim was to compare between the effect of bicycle ergometer versus treadmill on functional walking capacity and balance in children with Duchenne muscular dystrophy.

Methods: Thirty boys aged from 6 to 10 years old diagnosed as Duchene muscular dystrophy participated in this study. Children were assigned randomly into two groups (A&B). Children in group (A) underwent a designed program of physical therapy plus aerobic exercise training in form of bicycle ergometer while, group (B) received the same program as group (A) and aerobic exercise training by treadmill for one hour, at three times a week for three successive months. Functional walking capacity and balance were assessed before and after treatment by using the 6-minute walk test and Biodex balance system equipment respectively.

Results: The post treatment results revealed significant difference in all measured variables ($P<0.05$) as compared with its pre-treatment results. Post-treatment values indicated that there was a significant difference in all measured variables in favor of group B.

Conclusions: treadmill training as an aerobic exercise can improve walking capacity and balance more effectively than bicycle ergometer in children with Duchenne muscular dystrophy.

Keywords: Balance; Bicycle Ergometer; Duchene Muscular Dystrophy; Functional Walking Capacity; Treadmill.

JMNI ismni.org Full text PDF

Curr Opin Rheumatol . 2021 Aug 27. doi: 10.1097/BOR.0000000000000829. Online ahead of print.

Physical exercise for the management of systemic autoimmune myopathies: recent findings, and future perspectives

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- PMID: 34456254
- DOI: 10.1097/BOR.0000000000000829

Purpose of review: The aim of this review is to present the main pieces of evidence, recent literature and to present future perspectives on the use of exercise/physical training in the treatment and improvement of the quality of life of patients with systemic autoimmune myopathies.

Recent findings: In the last decades, knowledge about the relevance of physical exercise training in preventing and treating chronic diseases and improving quality of life has grown. Following the global trend exemplified by the expression 'exercise is medicine', the importance of exercise/physical training has also grown in myopathies. However, the science of exercise has a lot to collaborate on and improve patients' quality of life with myopathies by appropriating new technological tools, including accessible and low-cost devices and smartphone apps.

Summary: Physical exercise, as already consolidated in the literature, is an effective, well tolerated, and low-cost strategy for patients with myopathies. The use of wearable devices, smartphone apps, and online training prescriptions must accompany the global scenario, bringing new research fields and expanding the options for access to training for the individualized basis, and prescribed by qualified professionals.

Wolters Kluwer

Ophtalmologie – *Ophthalmology*

eNeurologicalSci . 2021 Jun 4;24:100348. doi: 10.1016/j.ensci.2021.100348. eCollection 2021 Sep.

Neuropathy/intranuclear inclusion bodies in oculopharyngodistal myopathy: A case report

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- PMID: 34466670
- PMCID: PMC8385282
- DOI: 10.1016/j.ensci.2021.100348

No abstract available

Keywords: LRP12, lipoprotein receptor-related protein 12 gene; Low-density lipoprotein receptor-related protein 12 gene (LRP12); NIID, neuronal intranuclear inclusion disease; Neuropathy; OPDM, oculopharyngodistal myopathy; OPML, oculopharyngeal myopathy with leukoencephalopathy; Oculopharyngodistal myopathy; Trinucleotide repeat diseases.

ELSEVIER OPEN ACCESS

Pneumologie – *Pulmonogy*

Cleve Clin J Med . 2021 Sep 1;88(9):484-486. doi: 10.3949/ccjm.88a.20204.

Dermatomyositis-related interstitial lung disease mimicking COVID-19 pneumonia

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- PMID: 34470751
- DOI: 10.3949/ccjm.88a.20204

No abstract available

Lung India . Sep-Oct 2021;38(5):496-498. doi: 10.4103/lungindia.lungindia_433_19.

Steroid dependence in acute asthma due to myasthenia gravis

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- PMID: 34472534
- DOI: 10.4103/lungindia.lungindia_433_19

No abstract available

Case Reports Ann Thorac Med . Jul-Sep 2021;16(3):294-298. doi: 10.4103/atm.atm_739_20. Epub 2021 Jul 20.

Fatal rapidly progressive interstitial lung disease in a patient with amyopathic dermatomyositis

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- PMID: 34484446
- PMCID: PMC8388568
- DOI: 10.4103/atm.atm_739_20

Interstitial lung disease (ILD) is a well-established common manifestation of idiopathic inflammatory myopathies. Yet, till now, the pathogenetic mechanisms are still poorly understood, classification is evolving and prognosis is variable. A refractory and rapidly progressive ILD (RPILD) that is associated with dermatomyositis (DM) with minimal muscle weakness and normal creatine kinase (termed clinically amyopathic DM) is increasingly being recognized, with more incidence in Asians. However, we are not aware of reports of the Arab region. Herein, we present a 38-year-old male with this condition that ended with a fatal outcome despite aggressive therapy, with a review of recent literature.

Keywords: Amyopathic dermatomyositis; connective tissue disease; idiopathic inflammatory myopathy; interstitial lung disease.

Review Ther Adv Musculoskelet Dis . 2021 Aug 28;13:1759720X211037519. eCollection 2021.

Natural history and screening of interstitial lung disease in systemic autoimmune rheumatic disorders

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- PMID: 34471427
- PMCID: PMC8404673
- DOI: 10.1177/1759720X211037519

Interstitial lung disease (ILD) is a relatively frequent manifestation of systemic autoimmune rheumatic disorders (SARDs), including systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myopathies (IIM), systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), and anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis. Interstitial pneumonia with autoimmune features (IPAF) has been proposed to describe patients with ILD who have clinical or serological findings compatible with SARDs but they are not sufficient for a definite diagnosis. ILD may present with different patterns among patients with SARDs, but most commonly as nonspecific interstitial pneumonia (NSIP), with the exception of RA and ANCA vasculitis that more often present with usual interstitial pneumonia (UIP). The natural history of ILD is quite variable, even among patients with the same SARD. It may present with

subclinical features following a slow progressively course or with acute manifestations and clinically significant rapid progression leading to severe deterioration of pulmonary function and respiratory failure. The radiographic pattern of ILD, the extent of the disease, the baseline pulmonary function, the pulmonary function deterioration rate over time and clinical variables related to the primary SARD, such as age, sex and the clinical phenotype, are considered prognostic factors for SARDs-ILD associated with adverse outcomes and increased mortality. Different modalities can be employed for ILD detection including clinical evaluation, pulmonary function tests, high resolution computed tomography and novel techniques such as lung ultrasound and serum biomarkers. ILD may determine the clinical outcome of SARDs, since it is associated with significant morbidity and mortality and therefore screening of patients with SARDs for ILD is of great clinical importance.

Keywords: Sjögren's syndrome; anti-synthetase syndrome; dermatomyositis; interstitial lung disease; interstitial pneumonia with autoimmune features; natural history; polymyositis; rheumatoid arthritis; screening; systemic lupus erythematosus; systemic sclerosis; vasculitis.

SAGE journals
Open access full text

Respir Med . 2021 Aug 21;187:106581. doi: 10.1016/j.rmed.2021.106581. Online ahead of print.

Diagnosis of myositis-associated interstitial lung disease: Utility of the myositis autoantibody line immunoassay

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- PMID: 34454312
- DOI: 10.1016/j.rmed.2021.106581

Objectives: The detection of myositis autoantibodies (MA) in patients with interstitial lung disease (ILD) has major implications for diagnosis and management, especially amyopathic and forme frustes of idiopathic

inflammatory myositis-associated ILD (IIM-ILD). Use of the MA line immunoblot assay (MA-LIA) in non-rheumatological cohorts remains unvalidated. We assessed the diagnostic performance of the MA-LIA and explored combined models with clinical variables to improve identification of patients with IIM-ILD.
Methods: Consecutive patients referred to a specialist ILD clinic, with ILD-diagnosis confirmed at multidisciplinary meeting, and MA-LIA performed within six months of baseline were included. Pre-specified MA-LIA thresholds were evaluated for IIM-ILD diagnosis.
Results: A total 247 ILD patients were included (IIM-ILD n = 12, non-IIM connective tissue disease-associated ILD [CTD-ILD] n = 52, idiopathic interstitial pneumonia [IIP] n = 115, other-ILD n = 68). Mean age was 64.8 years, with 45.3% female, mean FVC 75.5% and DLCO 59.2% predicted. MA were present in 13.8% overall and 83.3% of IIM-ILD patients. The most common MA in IIM-ILD and non-IIM ILD patients were anti-Jo-1 (prevalence 40%) and anti-PMScl (29.2%) autoantibodies respectively. The pre-specified low-positive threshold (>10 signal intensity) had the highest discriminative capacity for IIM-ILD (AUC 0.86). Combining MA-LIA with age, gender, clinical CTD-manifestations and an overlap non-specific interstitial pneumonia/organising pneumonia pattern on HRCT improved discrimination for IIM-ILD (AUC 0.96).
Conclusion: The MA-LIA is useful to support a diagnosis of IIM-ILD as a complement to multi-disciplinary ILD assessment. Clinical interpretation is optimised by consideration of the strength of the MA-LIA result together with clinical and radiological features of IIM-ILD.

Keywords: Autoimmune disease; Connective tissue disease; Immunoblot; Interstitial lung disease; Myositis autoantibody.

ELSEVIER FULL-TEXT ARTICLE

Can Respir J . 2021 Aug 23;2021:5554765. doi: 10.1155/2021/5554765. eCollection 2021.

Intermittent Abdominal Pressure Ventilation: An Alternative for Respiratory Support

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- PMID: 34471441
- PMCID: PMC8405303
- DOI: 10.1155/2021/5554765

Intermittent abdominal pressure ventilation is a positive pressure ventilation technique that works with abdominal compressions. It has been known since 1938; however, for many years, it was out of production. In recent years, a new device has been produced that has captured the attention to this old respiratory support technique. We considered eight patients with respiratory failure secondary to a neuromuscular disease (congenital myopathy, Duchenne dystrophy, and amyotrophic lateral sclerosis) intolerant to daytime noninvasive ventilation (NIV). IAPV was proposed as an alternative to NIV. We performed baseline and post-IAPV respiratory function assessment. All patients, two years later, are still using intermittent abdominal ventilation. Intermittent positive abdominal mechanical ventilation can be a valid alternative to noninvasive mechanical ventilation with a nasal or face mask. It improves gas exchange, symptoms, and quality of life, decreases the incidence of pneumonia, and can avert the need for intubation and tracheotomy.

Hindawi FREE Full Text Article

Clin Rehabil . 2021 Sep 2;2692155211043265. doi: 10.1177/02692155211043265. Online ahead of print.

The effect of trunk training on trunk control, upper extremity, and pulmonary function in children with Duchenne muscular dystrophy: A randomized clinical trial

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- PMID: 34474581
- DOI: 10.1177/02692155211043265

Objectives: To investigate the effect of trunk training on trunk control, arm, and pulmonary function in children with Duchenne muscular dystrophy.

Design: A randomised controlled trial.
Settings: Neuromuscular diseases clinic of university hospital.
Subjects: Twenty-six children with Duchenne muscular dystrophy aged 5-16 were included in the study.
Intervention: Participants were randomly allocated into two groups. The study group (N = 13) exercised with the trunk-oriented exercise program and the conventional exercise program, whereas the control group (N = 13) underwent the conventional exercise program for eight weeks.
Main measures: The primary outcomes were trunk control was assessed using the Trunk Control Measurement Scale, the arm function was assessed using Performance of Upper Limb, and respiratory function using the pulmonary function test. Data collection was conducted at baseline, and eighth week. The differences in trunk control scores, arm function scores, and respiratory function values before and after the training were calculated for the intergroup comparison.
Results: The mean age of the participants was 11.6 (2.6) in the study group and 10.6 (3.4) in the control group. The changes between trunk control score, arm function score (total and distal level score), and respiratory function value (Forced Vital Capacity, Forced Expiratory Volume in one second, and Peak Expiratory Flow Volume percentage values) were compared and significant differences were found after eight week periods in the study and control groups.
Conclusions: Trunk-oriented exercise program in Duchenne muscular dystrophy might be effective for trunk control, arm, and respiratory function.

Keywords: Duchenne muscular dystrophy; arm function; respiratory function; trunk control; trunk-oriented exercises.