Neuropathies sensitives

Ataxie proprioceptive

- Marche instable
- Chutes avec embardées
- Tremblements au maintien d’attitude
- ROT +/-
- Pieds creux tardifs souvent pieds plats valgus
- Scoliose <10 ans

- IRM cérébrale normale

Anna 5 ans

- Ataxie proprioceptive
  - Neuropathie sensitive à l'EMG
  - IRM cérébrale normale
  - PL normale
  - FO normal
  - Pas de nystagmus
- Evolution
  - Perte de la marche
  - Scoliose
  - Neuropathie tj sensitive pure

- Bilan métabo ?

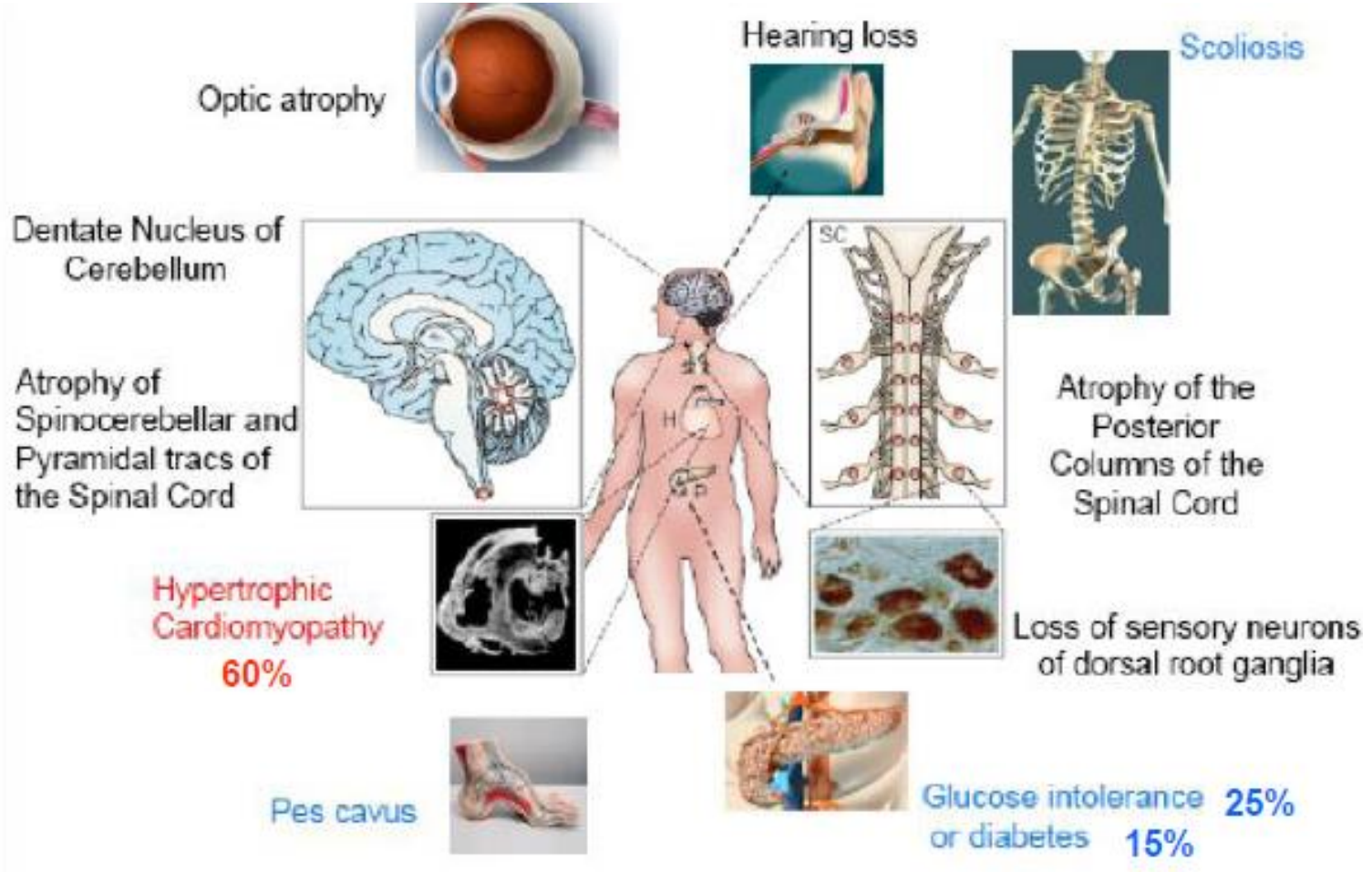
  …….
- Echo cœur?
- Autres??
- Génétique
  - Mitochondriale?
  - NGS neuropathies
  - Exome

Frataxine tj…..y penser

- Diagnostic par whole génome
  - Cas1: triplet sur un allèle et mutation ponctuelle sur l’autre allèle de novo (5% des cas)
  - Cas 2: mutation ponctuelle sur un allèle et délétion emportant Frataxine sur l’autre
  - Cas 3 : Triplet non vu en exome avec inversion d’un intron sur l’autre allèle

Ataxie de Freidreich

- Cause fréquente d' **ataxie recessive autosomique**
- Prevalence: 1/50000; frequence porteur: 1:90
- Homozygote **GAA répétitions (70 to >1000) expansion** in *FXN (frataxin)* (chr 19q13)
- Frataxin: Protéine mitochondriale > régultaion de l'homéostasie cellulaire du fer
- Symptomes associés



Diagnostics différentiels de l'ataxie de Friedreich

Name	Gene	Clinical features	Biomarkers	Treatment
Ataxia with vitamine E deficiency (onset 2-50 ans)	-Biallelic pathogenic variants in TTPA -Fat malabsorptive conditions	**Mimicking Friedreich's ataxia**	**Vitamin E deficiency**	**Vitamin E supplementation.**
Ataxia télangiectasia (onset<5y)	ATM (Defective DNA repair)	Ocular telangiectasia Dystonia Neuropathy ?	**Elevated alpha-fetoprotein (AFP) levels** IgA deficiency	**Predisposition to tumors** **Control and prevention of infections**
AOA1 (onset 1-20y)	Biallelic pathogenic variants in APTX	Ataxia/dystonia **OMA** Axonal sensorimotor neuropathy	**Hypoalbuminemia**	**-**
AOA2 (onset 7-25y)	Biallelic pathogenic variants in SETX	Ataxia/dystonia **OMA** Axonal sensorimotor neuropathy	**Elevated alpha-fetoprotein (AFP) levels**	-

Carla

- **13 ans : troubles de l’équilibre + Ataxie sensitive**

- **ATCD**: Prématurité (32 SA), entérocolite ulcéronécrosante, traitée chirurgicalement (colectomie totale et resection partielle de l’ileus)

- **Premiers symptomes :** ataxie, diminution de force membres inférieurs, ROT absents mbes inf.

CAS 2

Motor nerves conduction results

Nerve	Recording site	Latency (ms)	Velocity (m/s)	Amplitude (mV)
Median	Thenar	3.2	49	8.2
Tibial	Ankle	6.5	**35**	**1.3**
Peroneal	EDB	5.7	**34**	**0.2**

Sensory nerves conduction results

Nerve	Recording site	Latency (ms)	Velocity (m/s)	Amplitude (µV)
Median	Wrist	4.2	43	**6.4**
Sural	Ankle	-	-	-

Needle EMG: (TA) acute denervation

Sensory and motor axonal neuropathy

CAS 2

- PL (J27) : hyperproteinorachie (0,59g/L), celulles normales
- IRM cérébrale : normale
- Suspicion de polyradiculonévrite subaigue :
- Essai de traitement pat IgIV et steroids : sans bénéfice…
- J40 : nouveau résultat biologique …

CAS 2

- PL (J27) : hyperproteinorachie (0,59g/L), celulles normales
- IRM cérébrale : normale
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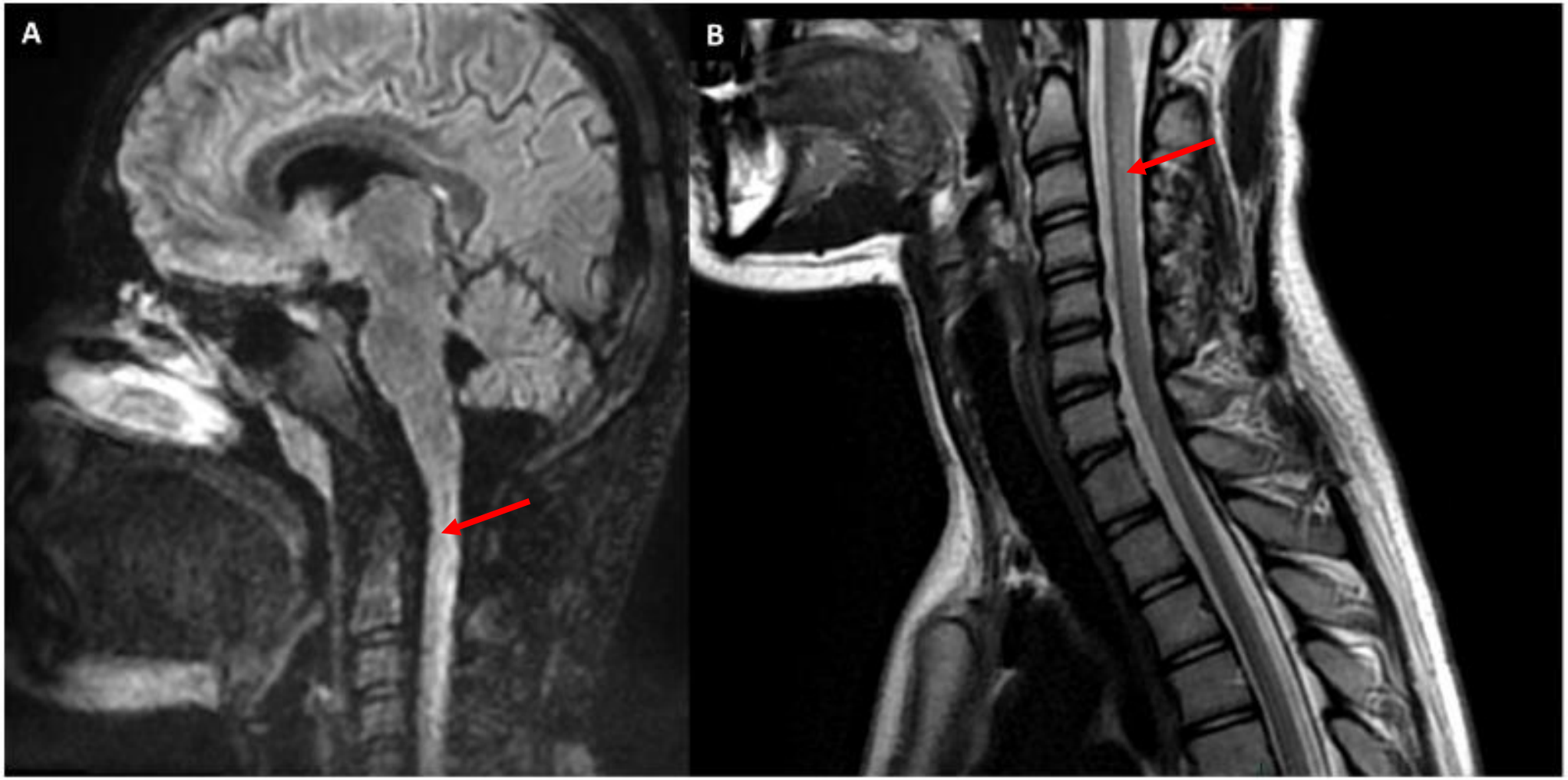
Serum vitamin B12 diminué et AMM élevé

CAS 2

Midline sagittal image of the cervical spinal cord demonstrate abnormal increase T2 FLAIR (A) and T2 (B) increased signal intensity.



Dégénerescence combinée subaigue de la moelle épinière

Complication neurologique du déficit en Vit. B12

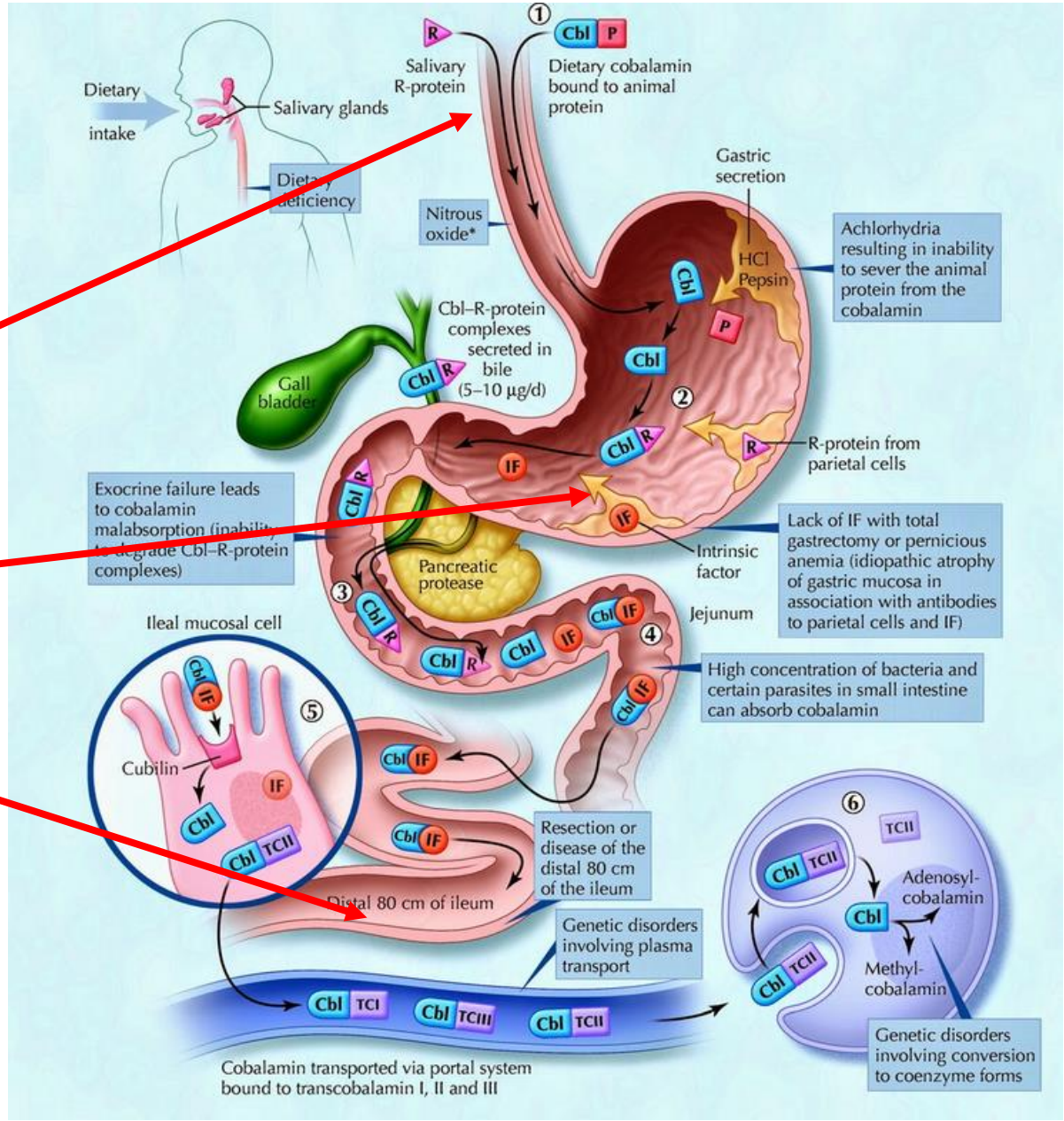
- **Causes**:

- Défaut d'apport (véganisme)

- Défaut IF (gastrectomie, pernicious anemia)

- Défaut d'absorption de l'ileon terminal (**resection**, Crohn disease)

- **Traitement**: Vit B12 supplementation IM 1/ sem pendant 1 mois puis 1/mois (1 mg)



Usage récréatif du protoxyde d'azote > inhibition de la methionine synthase

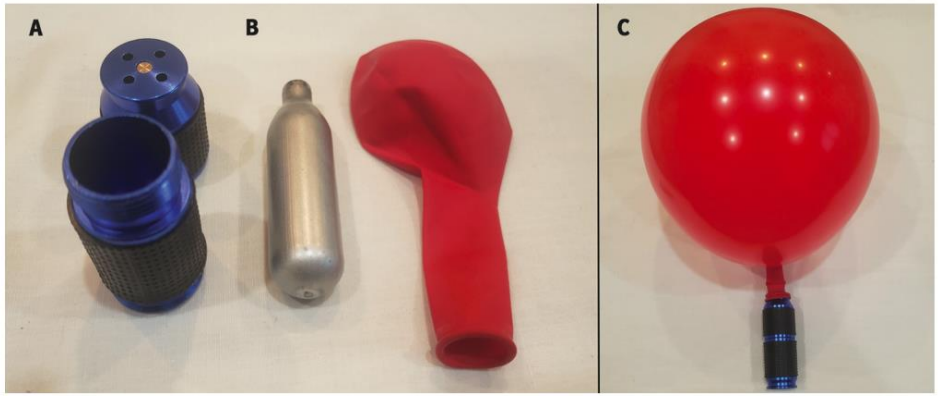
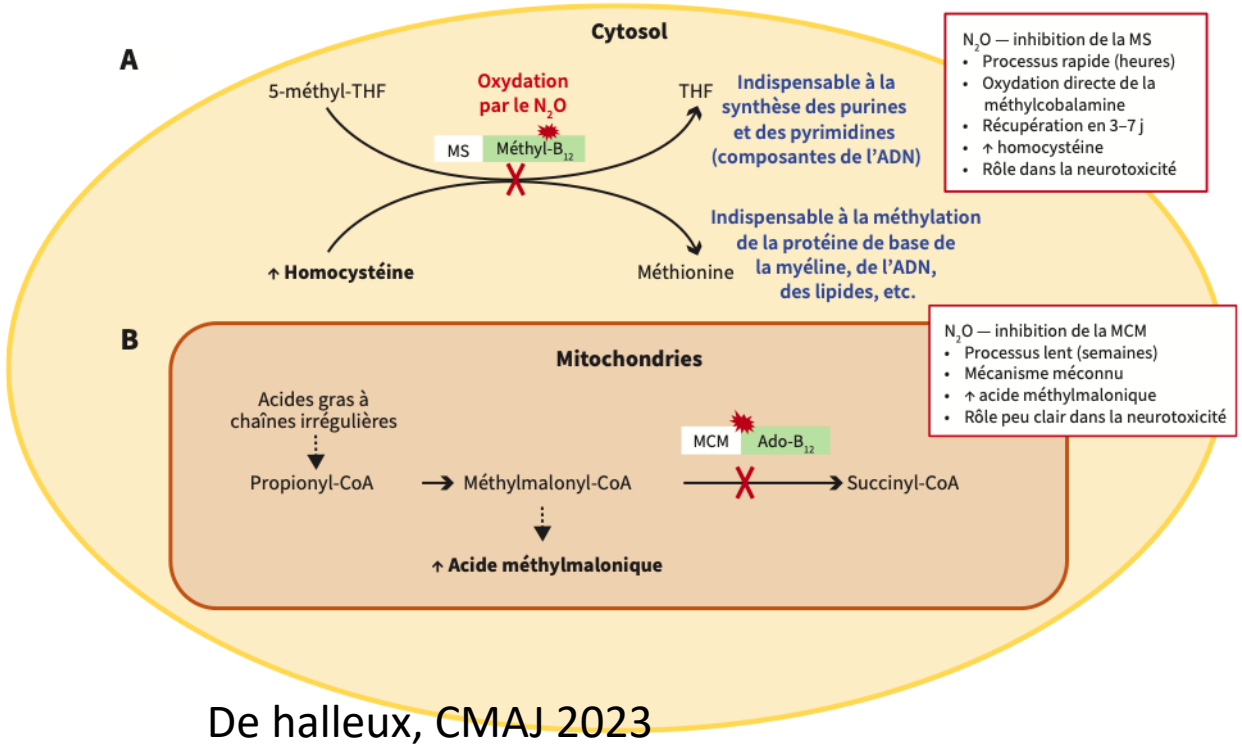


Figure 1 : Dispositif pour l'utilisation du protoxyde d'azote à des fins récréatives. La cartouche de protoxyde d'azote (B) est placée dans un « cracker » (A), qui perce la cartouche et permet de libérer le gaz dans le ballon (C).

20 OCTOBRE 2021 Le Monde.fr ÉDITION GLOBALE

Le protoxyde d'azote ne fait plus rire : nouvelle mise en garde de la communauté médicale internationale

- Homocystéine et AMM élevés
- Vitamine B12 bas dans 54-72%



De halleux, CMAJ 2023

Neuropathie sensitive et vomissements cycliques

- Trouble de la marche , ataxie à 4 ans post infection
- Bilan
  - IRM cérébrale et médullaire Normale
  - PL: prot 0.6 g/l
  - EMG: neuropathie sensitive
- Absence de réponse aux IG
- Bilan métabo…..
- Vomissements cycliques +++
  - KT central
  - Echec de renutrition
- Evolution
  - Atrophie optique
  - Dégradation motrice
  - Décès

TABLE 1 Clinical findings.

	Patient 1	Patient 2	Patient 3	Patient 4
Consanguinity	yes	yes	yes	yes
Age at first symptom	4 Y	4 Y	4 Y	3 Y
Mild Cognitive delay	5 Y	5 Y	no	no
Pyramidal signs	5 Y	4 Y	6 Y	no
Optic atrophy	6 Y	6 Y	6 Y	10 Y
Neuropathy	8 Y mixed	8 Y mixed	5 Y mixed	7 Y mixed
Ambulation	with support at 14 Y	loss at 10 Y	loss at 5 Y	with support
				at 17 Y
Biochemical analysis*	N	N	N	Abnormal
				Elevated 3-OH-valeric acid
First line genetic analyses**	N	N	N	N
Cardiac	Wolf Parkinson	no	no	no
Brain and medullar MRI including MRSI	normal except OA	OA, WM occipital Ab	cortical atrophy	normal except OA
Lower limb contractures	severe	severe	severe	severe distal
Epilepsy	no	no	no	no
Growth delay	no	8 Y	5 Y	8 Y/11 Y
Cyclic vomiting	8 Y	6 Y	4 Y	12 Y
CIPO	no	7 Y	5 Y	12 Y
Parenteral nutrition	no	13 Y (3 m)	5 Y	13 Y
Enteral nutrition	no	13 Y (6 m)	5 Y	13 Y
Bladder palsy	no	no	5 Y	recurrent acute at 13 Y
High blood pressure	no	no	no	13 Y
Medical treatment	amitriptylin	amitriptylin	amitriptylin	amitriptylin + oxcarbazepin; gabapentin
Vitamines uptake	no	no	low doses	beflavine at 13Y B5/B7/lipoic acid high doses at 22 Y
			carnitine	
Long term follow up	15 Y	14 Y	death at 7 Y	23 Y

Motor nerve conduction		Normal value	R	L	R	L	R	L	R	L	R	L	R	L
DML (ms)	Median	< 4.2	NR	3.10	3.60	3.33	4.91	6.41	A	NR	8.4	5.9	A	A
	Ulnar	< 3.5	NR	2.90	4.5	NR	4.30	3.46	A	NR	3.1	5.9	3.7	3.8
	Common Peroneal	< 5.0	NR	4.91	NR	NR	NR	NR	NR	NR	5.2	A	A	A
	Tibial	<5.5	6.88	5.38	4.37	6.01	NR	NR	A	NR	5.5	6.3	A	A
CMAP (mV)	Median	> 5	NR	5.0	3.5	4.7	0.29	0.18	A	NR	0.24	0.77	A	A
	Ulnar	>5	NR	4.1	2.5	NR	0.24	1.63	A	NR	5.48	6.19	1.53	1.08
	Common Peroneal	>3	NR	0.61	NR	NR	NR	NR	NR	NR	0.32	A	A	A
	Tibial	>3	0.85	1.02	0.05	0.19	NR	NR	A	NR	0.17	0.06	A	A
MNCV (m/s)	Median	> 50	NR	39.5	30.7	34.1	18.1	NR	A	NR	NR	34	A	A
	Ulnar	> 50	NR	55.4	32.6	NR	NR	43.7	A	NR	41	41	37	39
	Common Peroneal	> 42	NR	32.9	NR	NR	NR	NR	NR	NR	41	40	A	A
	Tibial	> 42	36.8	31.6	28.9	NR	NR	NR	A	NR	NR	NR	A	A
Sensory nerve conduction		Normal value	R	L	R	L	R	L	R	L	R	L	R	L
SNCV (m/s)	Median (transcarpal)	> 45	NR	39.5	39.8	39.3	32.5	NR	A	NR	A	34	A	A
	Ulnar	> 45	NR	NR	NR	NR	NR	NR	NR	NR	36	35	A	A
	Radial	> 45	NR	NR	NR	NR	NR	NR	NR	NR	34	30	36	30
	Sural	> 40	A	A	33.8	NR	NR	NR	A	NR	A	A	A	A
	Superficial peroneal	>40	NR	NR	NR	NR	NR	NR	NR	NR	35	38	30	38
	Median (transcarpal)	> 15	NR	2.5	12.0	18.7	6.2	NR	A	NR	A	2	A	A
SNAP (μV)	Ulnar	> 8	NR	NR	NR	NR	NR	NR	NR	NR	6.1	0.7	A	A
	Radial	> 10	NR	NR	NR	NR	NR	NR	NR	NR	3.6	0.6	2.3	1.9
	Sural	> 10	A	A	10.1	NR	NR	NR	A	NR	A	A	A	A
	Superficial peroneal	>10	NR	NR	NR	NR	NR	NR	NR	NR	2	6.7	2.1	2.1

OPEN ACCESS

EDITED BY
Jared C. Roach,
Institute for Systems Biology (ISB), United States

REVIEWED BY
Matthew Chau,
Baylor College of Medicine, United States
Haowei Du,
Baylor College of Medicine, United States

*CORRESPONDENCE
Lamisse Mansour-Hendili,
lamisse.mansour-hendili@aphp.fr

RECEIVED 07 December 2023

Recurrent "outsider" intronic variation in the *SLC5A6* gene causes severe mixed axonal and demyelinating neuropathy, cyclic vomiting and optic atrophy in 3 families from Maghreb

Lamisse Mansour-Hendili[1,2]*, Cyril Gitiaux[3,4],

CAS 5

- Garçon de 12 ans, a marché à 18 mois, langage normal
- 5 ans : épilepsie **myoclonique**
- 6 ans : ataxie progressive et chronique

- Examen à 12 ans :
    - Ataxie sensitive et cerebelleuse
    - Oculomotricité normale
    - ROT absents
    -Signe de Babinski
    -Pieds creux

CAS 5

Motor nerves conduction results

Nerve	Recording site	Latency (ms)	Velocity (m/s)	Amplitude (mV)
Median	Thenar	2.25	50.6	8.7
Peroneal	EDB	3.6	45.5	2.2
Tibial	Ankle	3.3	46.3	9.7

Sensory nerves conduction results

Nerve	Recording site	Latency (ms)	Velocity (m/s)	Amplitude (µV)
Median	Wrist	2.9	48.5	**7.9**
Sural	Ankle	3.2	41.5	**4.0**

Needle EMG: (EDB TA) Neurogenic

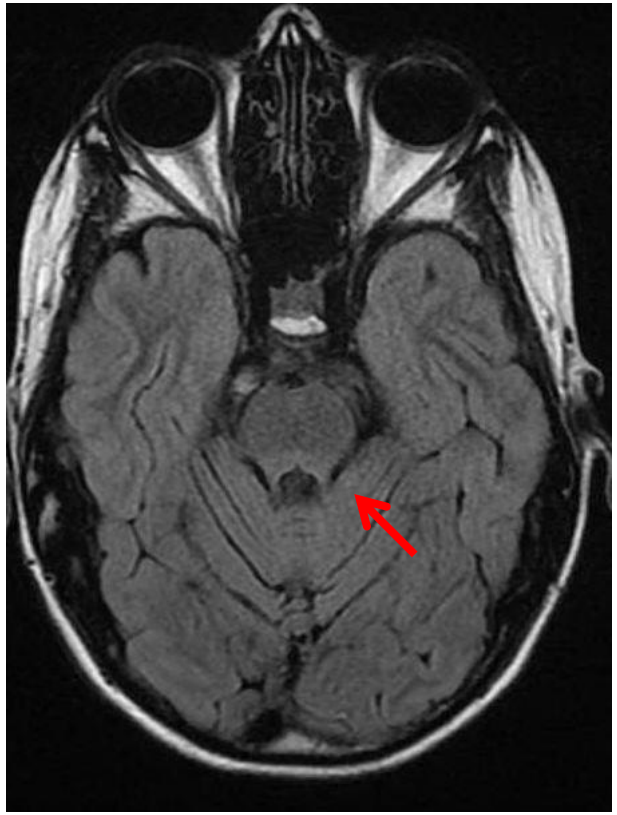
sensory neuropathy

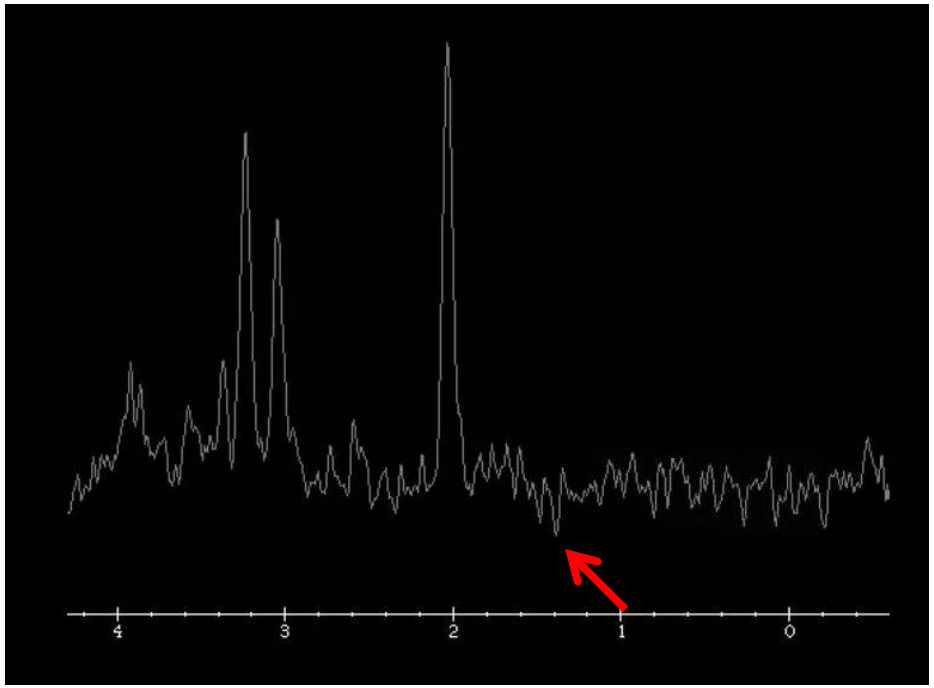
CASE 5

- ENMG: neuropathie axonale sensitive
- Bilan biologique : α-FT, vit E, cholesterol…
- Acidose lactique (3-4 mmol/L)
- Cerebral MRI: cerebellar atrophy, lactatoracchia
- Épilepsie myoclonique, ataxie

CASE 5

12 ans





CASE 5

- ENMG: neuropathie axonale sensitive
- Bilan biologique : α-FT, vit E, cholesterol…
- Acidose lactique (3-4 mmol/L)
- Cerebral MRI: cerebellar atrophy, lactatoracchia
- Épilepsie myoclonique, ataxie

MERFF syndrome: Myoclonic Epilepsy with Ragged Red Fibers, (m.8344 A>G)

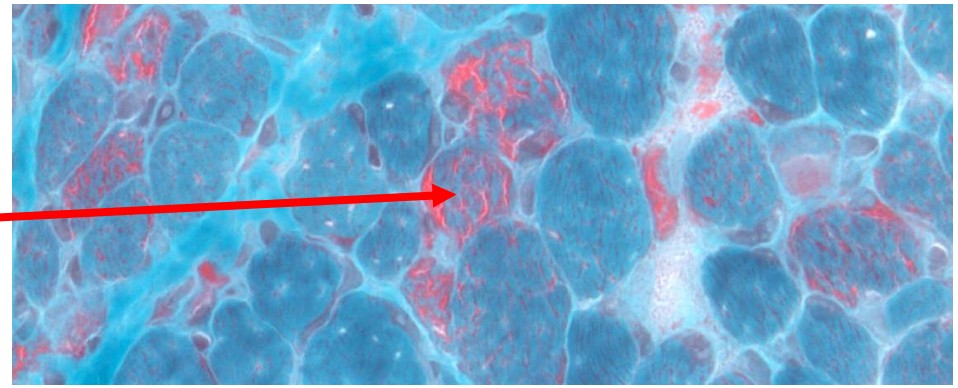
Myoclonic Epilepsy with Ragged Red Fibers (MERRF)

- **Encephalomyopathie mitochondriale** (& MELAS, MNGIE…)

Mutation la plus fréquente : (m8344 A>G)du gene MT-TK (mitochondrial transfer RNA gene for lysine)

- **Caractéristiques cliniques** :

- **Epilepsie myoclonique**
- Ataxie sensitive et cerebelleuse
- Autres : surdité, atrophie optique, petite taille
- Atteinte musculaire : **Ragged Red Fibers**



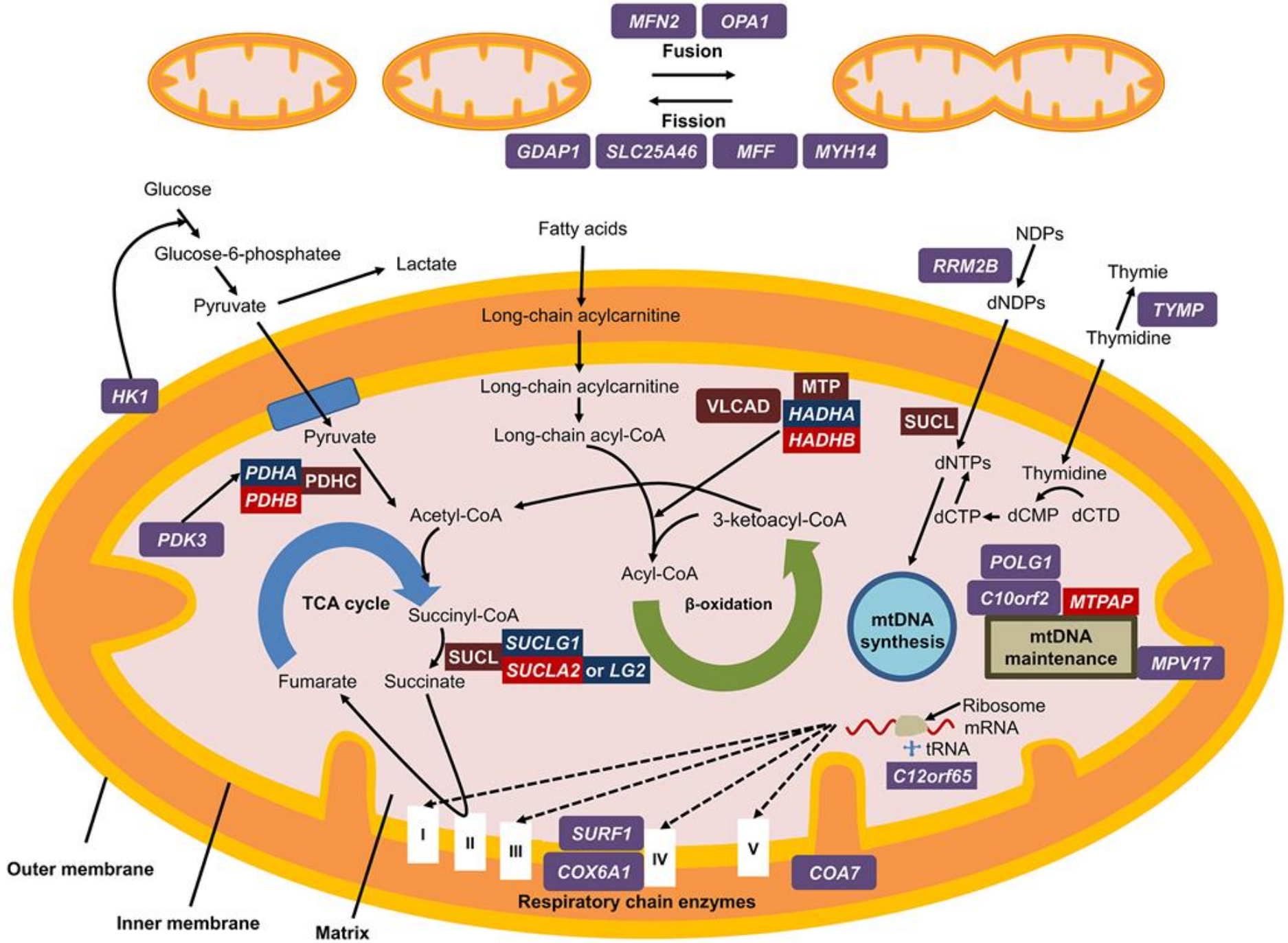

MFN2
OPA1
Fusion
Fission
GDAP1
SLC25A46
MFF
MYH14
Glucose
Glucose-6-phosphatee
Lactate
Pyruvate
HK1
Pyruvate
PDHA
PDHB
PDHC
PDK3
Acetyl-CoA
TCA cycle
Succinyl-CoA
SUCL
SUCLG1
SUCLA2 or LG2
Fumarate
Succinate
Fatty acids
Long-chain acylcarnitine
Long-chain acylcarnitine
Long-chain acyl-CoA
VLCAD
MTP
HADHA
HADHB
3-ketoacyl-CoA
Acyl-CoA
β-oxidation
NDPs
RRM2B
dNDPs
Thymie
TYMP
Thymidine
SUCL
dNTPs
Thymidine
dCTP
dCMP
dCTD
mtDNA synthesis
POLG1
C10orf2
MTPAP
mtDNA maintenance
MPV17
Ribosome
mRNA
tRNA
C12orf65
I
II
III
IV
V
SURF1
COX6A1
COA7
Respiratory chain enzymes
Outer membrane
Inner membrane
Matrix

Table 2 Genetic pathophysiology, phenotype, inheritance pattern, and neuropathy type of the mitochondrial-related nuclear genes described in this report (upper table) and previously reported genes (lower table)

Gene	Pathophysiology	Phenotype	Inheritance	Neuropathy type
PDHB	Pyruvate dehydrogenase complex	Pyruvate dehydrogenase E1-beta deficiency	AR	Sensory-motor axonal
MTPAP	mtDNA maintenance and repair	SPAX4 Cellular radiosensitivity	AR	Sensory-motor axonal
HADHB	Mitochondrial energy production (beta-oxidation)	Trifunctional protein deficiency	AR	Sensory-motor axonal
SUCLA2	Mitochondrial energy production (tricarboxylic acid cycle), mtDNA synthesis	Mitochondrial DNA depletion syndrome 5	AR	Sensory-motor axonal
MFN2	Mitochondrial dynamics (fusion)	CMT2A2, HMSN6 (CMT6A)	AR and AD	Sensory-motor axonal
OPA1	Mitochondrial dynamics (fusion)	Optic Atrophy I, Mitochondrial DNA depletion syndrome	AD	Sensory-motor axonal
GDAP1	Mitochondrial dynamics (fission)	CMT4A, CMT2K, CMTRIA, CMT with vocal cord paresis	AR and AD	Sensory-motor axonal (with or without secondary demyelinating changes)
SLC25A46	Mitochondrial dynamics (fission)	HMSN6B (CMT6B)	AR	Motor or sensory-motor axonal
MYH14	Mitochondrial dynamics (fission)	Peripheral neuropathy, myopathy, hoarseness, and hearing loss Deafness, autosomal dominant 4A	AD	Motor axonal (with or without sensory demyelinating changes)
MFF	Mitochondrial dynamics (fission)	Encephalopathy due to defective mitochondrial and peroxisomal fission 2	AR	Motor demyelinating or mixed
DHTKD1	Mitochondrial energy production (tricarboxylic acid cycle)	CMT2Q	AD	Sensory-motor axonal
HK1	Mitochondrial energy production (glycolytic system)	CMT4G	AR	Sensory-motor demyelinating
COX6A1	Mitochondrial respiratory chain (complex IV)	CMTRID	AR	Sensory-motor axonal or mixed
SURF1	Mitochondrial respiratory chain (complex IV)	CMT4K, Leigh syndrome	AR	Sensory-motor demyelinating
AIFM1	Oxidative phosphorylation and redox control in healthy cells	CMTX4 (Cowchock syndrome) Combined oxidative phosphorylation deficiency	XLR	Sensory-motor axonal
PDK3	Pyruvate dehydrogenase complex	CMTX6	XLD	Sensory-motor axonal (with or without secondary demyelinating changes)
C12orf65	Mitochondrial energy production (oxidative phosphorylation), Mitochondrial translation	Combined oxidative phosphorylation deficiency 7 SPG55, CMT6	AR	Sensory-motor axonal
POLG1	mtDNA replication and maintenance	Childhood MCHS, Alpers syndrome ANS disorders, MEMSA, MNGIE-like, SANDO autosomal recessive and dominant PEO	AR and AD	Sensory axonal; hypomyelinating when early onset
C10orf2 (Twinkle)	mtDNA replication and maintenance	ANS disorders Mitochondrial DNA Depletion Syndrome, PEO	AR and AD	Usually sensory axonal
TYMP	mtDNA replication and maintenance	Mitochondrial DNA Depletion Syndrome, MNGIE	AR	Sensory-motor demyelinating
RRM2B	mtDNA replication and maintenance	Mitochondrial DNA Depletion Syndrome, MNGIE-like, PEO	AR and AD	Sensory-motor demyelinating
MPV17	mtDNA maintenance	Mitochondrial DNA Depletion Syndrome Navajo neurohepatopathy	AR	Sensory-motor axonal or demyelinating
SLC25A19	mtDNA replication and maintenance	Bilateral striatal degeneration and progressive polyneuropathy	AR	Motor or sensory-motor axonal
COA7	Assembling mitochondrial respiratory chain complexes	Spinocerebellar ataxia, autosomal recessive, with axonal neuropathy	AR	Sensory-motor axonal

Neuropathie sensitive chez l'enfant

Aigu ? / Chronique ?

aigu / Subaigu

- **Variant atypique de SGB**(PCB, MFS etc)
- **Déficit vit B12:** chirurgie gastrique, intestinale, NO intoxication…
- **héréditaire**: PDH deficiency

> **Antiganglioside autoantibodies and vitamins level +/- metabolic screening**

Chronique

- **Déficit vitamine E**
- **Ataxie de Friedreich si ataxie** et +/- **signes associés** : Cardiomyopathie, scoliose …
- **Mito (MERRF, POLG) / PDH**
- **Examens complémentaires**

- *IRM cérébrale : atrophie cerebelleuse ? Spectro ?*
- *OPH :* apraxie, telangiectasies, FO (atrophie, rétinite…)
- *Biologie*: Alpha fetoprotein, Vitamin E, Albuminemia, Ig G/A/M, Cholesterol, apolipoprotein…
- **Muscle biopsy** > mito
- **Genetic tests**

Neuropathie douloureuse et traitements topic

- Essai chez 205 patients avec douleurs neuropathiques : Créme ketamine (10%), baclofen (2%), gabapentin (6%), amitriptyline (4%), bupivacaine (2%), and clonidine (0.2%) :
  - diminution du score de douleurs de 2.4 pts
  - Bénéfices ressentis chez 82% des patients
  - Réduction des traitements oraux 35 %

  (*Somberg, Am J therap 2015*)

- Effet de la Crème amytriptyline 10% x 2/ jour sur neuropathies chimio-induites
  - 25 patients : score douleur DN4 6/10 > 3/10 à 1 mois
  - (*AL Genevois, C Greco, J Pain 2021*)
  - Chez la souris : amitriptyline creme inhibe reponses nociceptives, via Nav1.8, Nav1.7, and Nav1.9. Amitriptyline > TRPA1 activation > mobilisation ions calcium