Centre National de référence
des maladies neurogénétiques

Central ou périphérique ?

Central **et** périphérique !

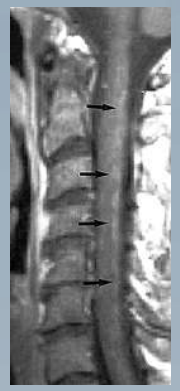
Christophe Verny
Service de neurologie
CHU Angers

Centre National de référence
des maladies neurogénétiques

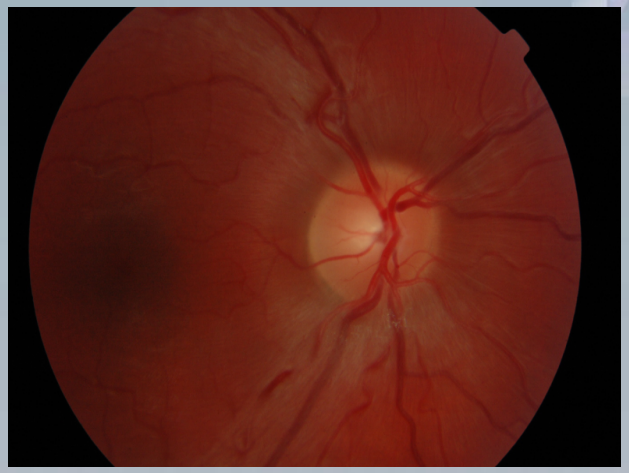
Alcool
Diabète

N Périphérique + médullaire

Quelques rares toxiques:
(organophosphoré,
protoxyde d'azote...)



Charlevoix-Saguenay (ARSACS)
Neuro-ophtalmologie+++



Adrenomyeloneuropathie
Liée à l'X
Forme « light » de l'ALD
Hétérozygotes
VLCFA

L'hypermyélinisation des fibres nerveuses rétiniennes

Paraparésies spastiques…

- SPG 2 , 3A, 7, 10, 11, 21, 23, 25, 26, 27, 30, 36, 55, 56, 57, 60, 61, 66, 68…
- Maladie à dépots de polyglucosans:
  - Myélopathie, polyneuropathie (sensitive), démence, leucopathie…
- MtATP6

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Contents lists available at ScienceDirect

Mitochondrion

journal homepage: www.elsevier.com/locate/mito

Hereditary spastic paraplegia-like disorder due to a mitochondrial ATP6 gene point mutation

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ABSTRACT

Hereditary spastic paraplegia refers to a genetically heterogeneous syndrome. We identified five members of a family suffering from a late-onset spastic paraplegia-like disorder, carrying the homoplasmic m.9176 T>C mutation in the mitochondrial ATP6 gene. The clinical severity of the disease observed in the family was correlated with the biochemical and assembly defects of the ATP synthase. The m.9176 T>C mutation has been previously associated to Leigh syndrome or familial bilateral striatal necrosis. Other factors such as modifying genes may be involved in the phenotypic expression of the disease. The family belongs to the mitochondrial haplogroup J, previously shown to play a role in modulating the phenotype of mitochondrial diseases and be associated with longevity. Moreover other nuclear modifying genes or environmental factors may contribute to the disease phenotype. This finding extends the genetic heterogeneity of the hereditary spastic paraplegia together with the clinical spectrum of mutations of the ATP6 gene.

N Périphérique + cervelet

- **Paranéoplasique:**
  - Anti-HU: neuronopathie douloureuse et proprioceptive (ataxiante+++)
    - +/- atteinte cérebelleuse
    - +/- épilepsie/encéphalite limbique, signes oculomoteurs, dysautonomie...
  - Anti CV2: neuropathie sensitivo-motrice
    - +/- atteinte cérebelleuse, encéphalitique, nervite optique, myélopathie, myasthénie...
  - Anti Yo (Pour P Labauge)

N Périphérique + cervelet

- **Creutzfeldt-Jakob:**
  - Sporadique: neuropathie motrice et sensitive, clinique dans 20%, électrique dans > 80%
  - Génétique :idem
    - Mutation Y163X: dysautonomique + sensitive
    - Evolution lente+++

N Périphérique + cervelet

- **Friedreich +++**
  - Syndrome cérebelleux + pyramidal + neuropathie (sensitive) + cardiomyopathie + atrophie optique + diabète...
- Vitamine E (exceptionnel mais ttt...)
- **SCA 1, 2, 3**, 4, 18, 25
- **Ataxie avec apraxie oculomotrice.**
- **Marinesco-Sjögren:** ataxie cérébelleuse, retard mental, neuropathie, cataracte…

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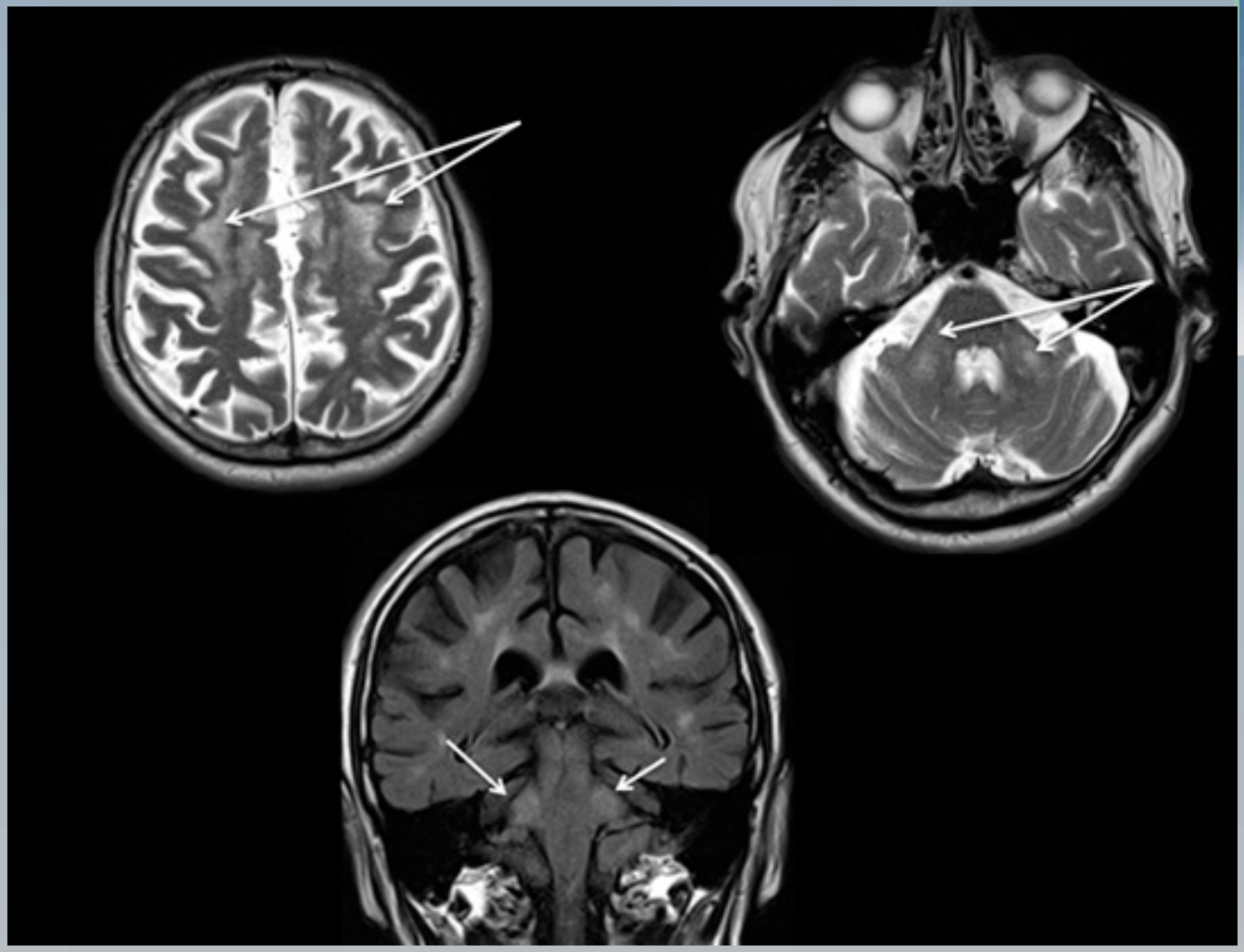
68 ans: Tremblement d'intention, un peu figé, neuropathie surtout sensitive… Diagnostic?



N Périphérique + cervelet

- **FXTAS:pré-mutation X-Fragile:**
  - **Polyneuropathie sensitive et dysautonomique > moteur**
    - **Cervelet: ataxie, dysmétrie, nystagmus**
    - **Parkinsionisme**

N Périphérique + cervelet

- **Ataxie télangiectasie (AR):**
  - Ataxie cérebelleuse, apraxie oculomotrice, choreo-athétose, dystonie, neuropathie sensitive, amyotrophie spinale...: α FP
- **Xanthomatose cérébrotendineuse (AR):**
  - Neuropathie sensitivomotrice axonale et/ou démyélinisante + Atteinte cérébelleuse + 1er motoneurone + Myoclonie, démence, cataracte+++
  - Xanthome tendineux
  - Cholestanol : Traitement (Chenodeoxycholic Acid)
- **Refsum, acide phytanique (AR):**
  - Neuropathie démyélinisante, cataracte, rétinite pigmentaire...
  - Régime+++

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Mémoire

Étude rétrospective multicentrique de 15 cas adultes de xanthomatose cérébrotendineuse : aspects cliniques et paracliniques typiques et atypiques

Cerebrotendinous xanthomatosis: A multicentric retrospective study of 15 adults, clinical and paraclinical typical and atypical aspects

C. Lionnet [a], C. Carra [a], X. Ayrignac [a], T. Levade [b], D. Gayraud [c], G. Castelnovo [d], G. Besson [e], G. Androdias [f], S. Vukusic [f], C. Confavreux [f], C. Zaenker [g], J. De Seze [h], N. Collongues [h], F. Blanc [h], C. Tranchant [h], D. Wallon [i], D. Hannequin [i], A. Gerdelat-Mas [j], D. Brassat [j], M. Clanet [j], H. Zephir [k], O. Outteryck [k], P. Vermersch [k], P. Labauge [a,*]

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PERGAMON

Neuromuscular Disorders 16 (2006) 805–808

www.elsevier.com/locate/nmd

Case report

Refsum's disease may mimic familial Guillain Barre syndrome

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Abstract

Refsum's disease is a rare autosomal recessive disorder with clinical features including retinitis pigmentosa, anosmia, deafness, chronic sensory-motor neuropathy, ataxia and the accumulation of phytanic acid in blood plasma and body tissues. We report the occurrence of Refsum's disease in two sisters, both presenting with acute demyelinating polyneuropathy mimicking the familial Guillain Barre syndrome. Thus, when GBS is suspected, particularly in cases of familial recurrence as well as in atypical cases of acute polyneuropathy, the diagnosis of Refsum's disease should be considered, looking for other features of the disease and, if appropriate, testing plasma phytanic acid levels.

Keywords: Refsum; Guillain Barre; Hereditary neuropathy; Phytanic acid

N Périphérique + supra-tentoriel

- **Infectieux:** VIH, Syphilis, Herpès, VZV, CMV, hépatites, Lyme, Brucellose, ...
- **Toxique:** chimiothérapie, anti-viraux, radiothérapie, métaux lourds,...
- **Tumoral:** Neurofibromatoses, envahissement métastatique, lymphome...
- **Paranéoplasique:** Anti-Hu, Anti-CV2, Anti-amphiphysine, GB et lymphome...

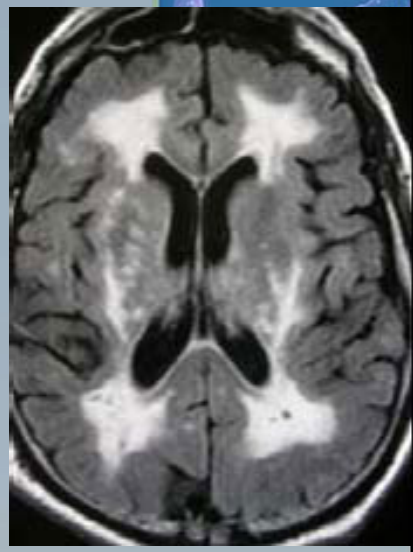
N Périphérique + supra-tentoriel

- **Inflammatoire:** Gougerot, maladie caeliaque, Sarcoïdose, Whipple, Behcet, Lupus, PAN, Wegener, Churg et Strauss, Horton...
- **Carentiel:** Vit B1, B6, B12, Folates,...
- **Endocrinien:** Dysthyroïdie...

N Périphérique + supra-tentoriel

- SLA...DFT-SLA...
- Neuroacanthocytose: HD + neuropathie
- Fabry, α-Galactosidase (lié à l'X):
  - neuropathie sensitive (douloureuse) + AVC + cornée + rein + peau ... Enzymothérapie...
- Tay-Sachs, Hexosaminidase A (AR):
  - Neuropathie sensitivo-motrice axonale + cervelet + démence + MAI ...
- Krabbe, β-galactosidase (AR):
  - Retard mental (démence si début tardif), spasticité, atrophie optique, neuropathie...
- Porphyries...

N Périphérique + supra-tentoriel



- **CADASIL**
  - Accidents lacunaires, migraines, psy,
  - Neuropathie sensitive 40%
  - Motrice 30%!!!
- **CMT « plus »: PMP22, Cx32**
- **Leucodystrophie métachromatique (AR) :**
  Déficit en Aryl-sulfatase A: troubles psy, Sd sous cortico-frontal, paraparésie spastique, ataxie, épilepsie, atrophie optique, polyneuropathie démyélinisante...

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N Périphérique + supra-tentoriel

- **Adrenoleucodystrophie (liée à l'X):** plus de la moitié des adrénomyéloneuropathies ont des atteintes de la SB, associés à des troubles cognitifs, psychiatriques, hémi ou tértra-parésie, épilepsie, insuffisance surrénale.

  Dosage des AGTLC puis bio mol. Greffe?

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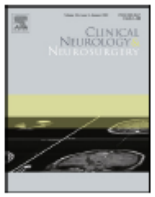

Case report

Adult-onset cerebral X-linked adrenoleukodystrophy with major contrast-enhancement mimicking acquired disease

Clarisse Carra-Dalliere[a,*], Clarisse Scherer[b], Xavier Ayrignac[a], Nicolas Menjot de Champfleur[c], Celine Bellesme[d], Pierre Labauge[a], Christophe Verny[b]

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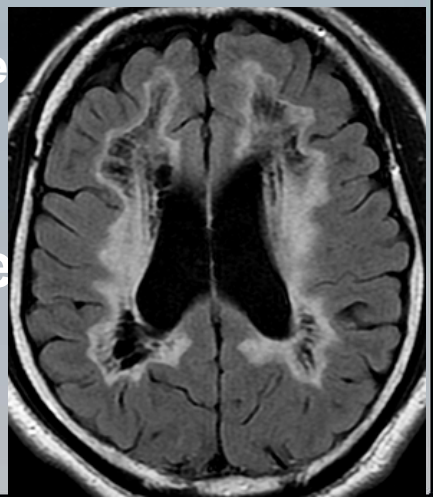
Autres Leucodystrophies + Neuropathies

- Pelizaeus-Merzbacher (SPG2 lié à l'X)
  - Paraparésie spastique, neuropathie, leucodystrophie, retard mental, dysarthrie...
- Pelizaeus-Merzbacher « like » (AR)
  - Sd cérébelleux, pyramidal, dysautonomique
- Adult-onset Leukodystrophy (Lamin B1, AD)
- Cockayne Syndrome (A ou B) (AR)
  - Retard mental ,ataxie, atrophie optique, leucodystrophie hydrocéphalie, neuropathie démyélinisantes, calcifications...
- Leukoencephalopathies with vanishing white matter



Mitochondrie (mt DNA)

- **MELAS** (Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke): Céphalées, pseudo-stroke, myopathie, polyneuropathie (Se-Mo Ax), RP, cardipathie, diabète... Traitement: Arginine
- **NARP** (Neurogenic Weakness, Ataxia, Retinis Pigmentosa): PN Se ou Se-Mo Ax
- **MILS** (Maternally Inherited Leigh Syndrome) : retard Imental, épilepsie, MAI, ataxie, ophtalmoplégie, encéphalite nécrosante... PN Se-Mo Démyélinisante
- **CMT 2 (ATP-6)** NP Mo Ax, retard apprentissage, surdité...
- **MERFF** (Myoclonic Epilepsy with RRF): Epilepsie, myopathie, ataxie, retard mental, atrophie optique, NP Se.

Acta Neurol Belg (2012) 112:417–418
DOI 10.1007/s13760-012-0081-6

NEURO-IMAGES

Posterior leukoencephalopathy in NARP syndrome

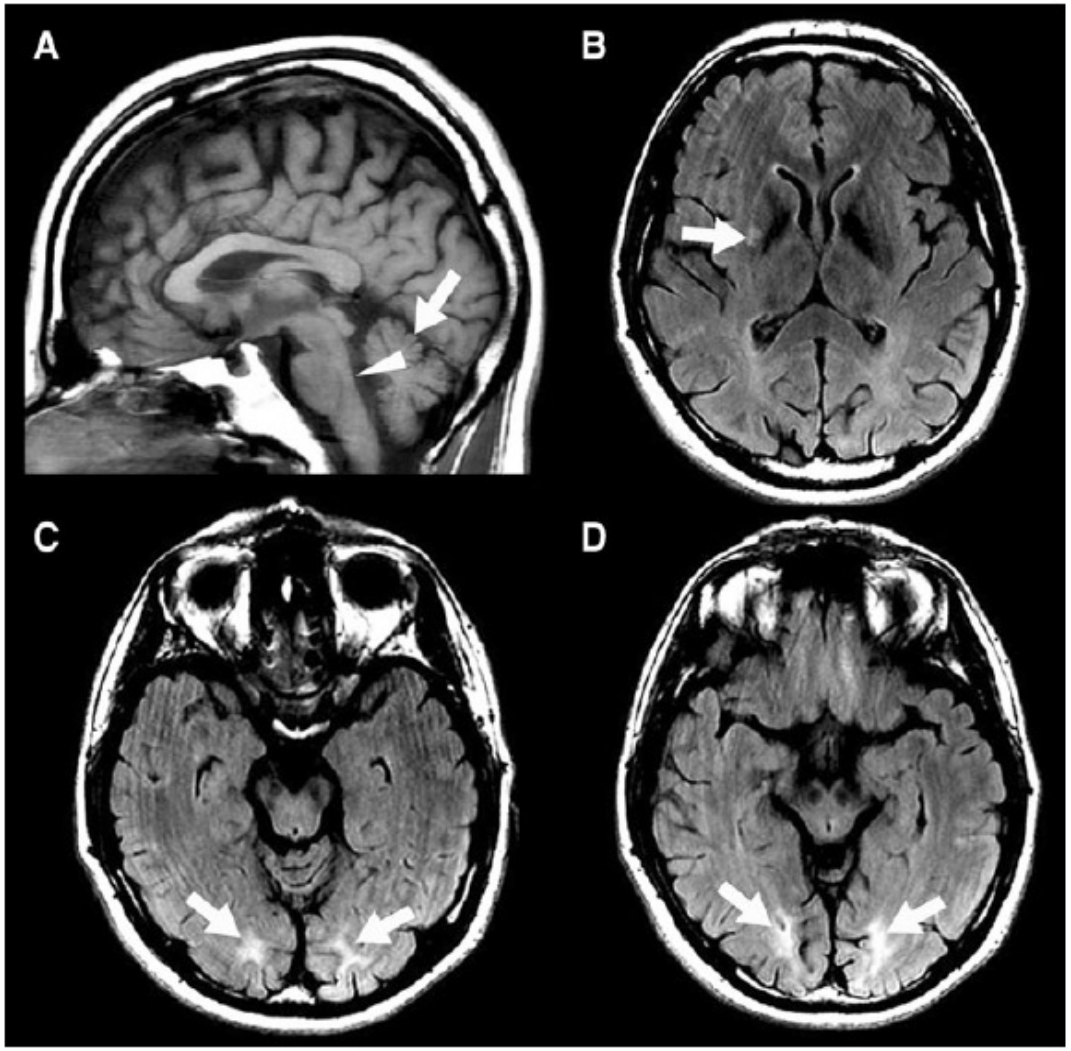
Dimitri Renard · Pierre Labauge

Received: 3 January 2012 / Accepted: 2 May 2012 / Published online: 12 May 2012

Keywords Neuropathy · Ataxia · Retinitis pigmentosa · NARP · Mitochondriopathy · Leukoencephalopathy

We present a 49-year-old man with mild cognitive deficit since childhood and adult-onset retinitis pigmentosa, seizures, ataxia, distal weakness/amyotrophy, spasticity, and areflexia. MRI showed pontocerebellar atrophy, putaminal signal changes, and bilateral occipital leukoencephalopathy (Fig. 1). EMG showed sensory predominant neuropathy. Genetic analysis revealed an mtDNA T8993G point mutation. A diagnosis of NARP (neuropathy, ataxia, retinitis pigmentosa) was made.

Leukoencephalopathy, most often widespread, can be seen in mitochondrial diseases [1, 2]. Posterior predominant signal changes are seen especially in MELAS. Leukoencephalopathy may be related to impaired microcirculatory autocontrol due to endothelial/myocytic mitochondrial dysfunction. Less dense sympathetic adrenergic innervation, important in cerebral blood flow autoregulation, of the vertebro-basilar arteries possibly explain posterior-predominant signal changes in mitochondrial disorders.



Mitochondrie (n DNA)

- **POLG** (polymerase Gamma) : Ptosis, ophtalmoplégie, neuropathie (Se++), myopathie, **(Mendelian PEO)** ... Mais également épilepsie, migraine, rétinite, surdité, ataxie, parkinsonisme, ... Et la neuropathie peut être Se-Mo! Et AD ou AR!

- **MNGIE** (Mitochondrial Neuro-gastro-intestinal Encephalopathy): troubles digestifs, PEO, rétinite, myopathie, leucoencéphalopathie, NP Se-Mo démyélinisante.

Mitochondrie (n DNA)

- **Wolfram** (AR): Surdité, diabète, neuropathie, épilepsie, trouble psy, démence, atrophie optique...

- **MFN2** :CMT2A2 (AD): neuropathie Se-Mo axonale, atrophie optique possible ainsi qu'une encéphalopathie, syndrome pyramidal, atteinte cognitive, myopathie. Grande variabilité phénotypique même intra-familiale.

ORIGINAL ARTICLE

Neurologic Features and Genotype-Phenotype Correlation in Wolfram Syndrome

Annabelle Chaussenot, MD,[1] Sylvie Bannwarth, PhD,[1,2] Cecile Rouzier, MD,[1,2] Bernard Vialettes, MD,[3] Samira Ait El Mkadem, PhD,[1,2] Brigitte Chabrol, MD,[4] Aline Cano, MD,[4] Pierre Labauge, MD, PhD,[5] and Véronique Paquis-Flucklinger, MD, PhD[1,2]

Objective: Wolfram syndrome (WS) is a rare neurodegenerative disorder characterized by juvenile-onset diabetes mellitus and optic atrophy. Our aim was to describe the nature and the frequency of the neurologic manifestations, which had been poorly studied until now.

Methods: We performed a detailed clinical study with genotype-phenotype correlation in a series of 59 patients with WS.

Results: The onset of neurologic symptoms, with a median age of 15 years, was much earlier than previously reported. Cognitive impairment, which was not frequent in previous reports, was observed in 32% of patients with neurologic signs. Like epilepsy, it was mainly found in patients who developed neurologic signs before 15 years of age. In contrast to previous series, we also found malformations of cortical development on magnetic resonance imaging in epileptic children and white matter involvement, including diffuse leukoencephalopathy, in adult patients. We identified 109 mutated alleles corresponding to 56 different mutations of the *WFS1* gene, among which 10 were novel. Homozygosity or compound heterozygosity for missense mutation does not seem to influence the age of onset and the occurrence of neurologic complications. However, an interesting point concerns a possible correlation between the location of the mutations and the development of the neurologic manifestations.

Interpretation: This series concerns the largest cohort of WS patients reported to date. It illustrates the wide variety of neurologic signs in this syndrome and the necessity of rapid therapeutic coverage to improve the prognosis.

ANN NEUROL 2011;69:501–508

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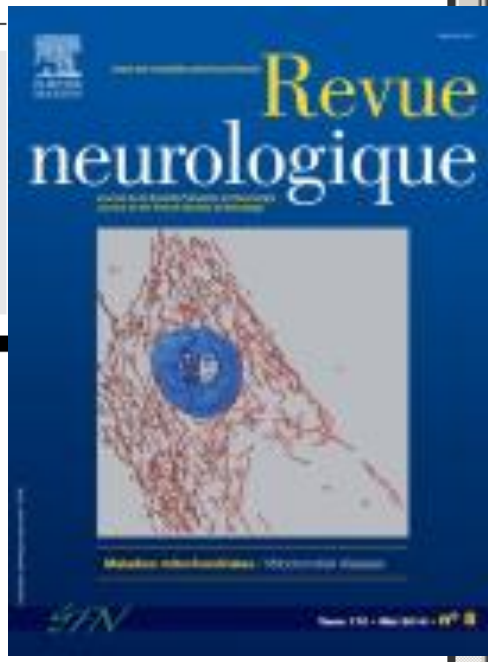

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Mitochondrial diseases

Inherited peripheral neuropathies due to mitochondrial disorders

Dysfonctions mitochondriales à l'origine de neuropathies périphériques héréditaires

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INFO ARTICLE

ABSTRACT