Revue de littérature 2021
Neuropathies génétiques

CÉLINE TARD, LILLE
CENTRE DE RÉFÉRENCE DES MALADIES NEUROMUSCULAIRES NORD EST ILE DE FRANCE

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Plan

- Essais cliniques
- Cas cliniques
- Séries de cas

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CMT1A

Attarian et al. Orphanet J Rare Dis (2021) 16:433
https://doi.org/10.1186/s13023-021-02040-8

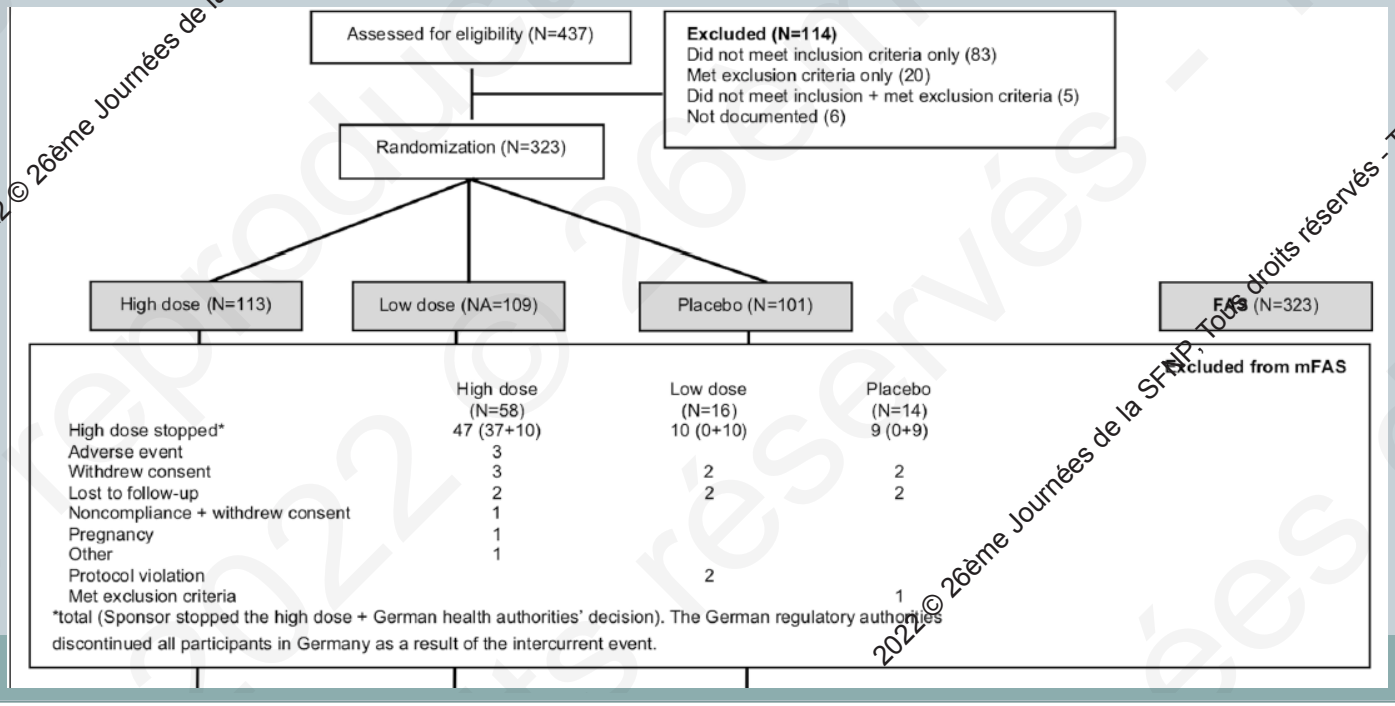
Orphanet Journal of Rare Diseases

RESEARCH Open Access

A double-blind, placebo-controlled, randomized trial of PXT3003 for the treatment of Charcot–Marie–Tooth type 1A

Shahram Attarian[1*], Peter Young[2], Thomas H. Brannagan[3], David Adams[4], Philip Van Damme[5,6], Florian P. Thomas[7,8], Carlos Casanovas[9,10], Céline Tard[11], Maggie C. Walter[12], Yann Péréon[13], David Walk[14], Amro Stino[15], Marianne de Visser[16], Camiel Verhamme[16], Anthony Amato[17], Gregory Carter[18], Laurent Magy[19], Jeffrey M. Statland[20] and Kevin Felice[21]

- Phase 3
- Placebo-faibles doses-hautes doses PXT3003 (baclofen/naltrexone/D-sorbitol [mg]: 6/0.70/210 or 3/0.35/105)



	High dose (N=58)	Low dose (N=16)	Placebo (N=14)
High dose stopped*	47 (37+10)	10 (0+10)	9 (0+9)
Adverse event	3		
Withdrew consent	3	2	2
Lost to follow-up	2	2	2
Noncompliance + withdrew consent	1		
Pregnancy	1		
Other	1		
Protocol violation		2	
Met exclusion criteria			1

*total (Sponsor stopped the high dose + German health authorities' decision). The German regulatory authorities discontinued all participants in Germany as a result of the intercurrent event.

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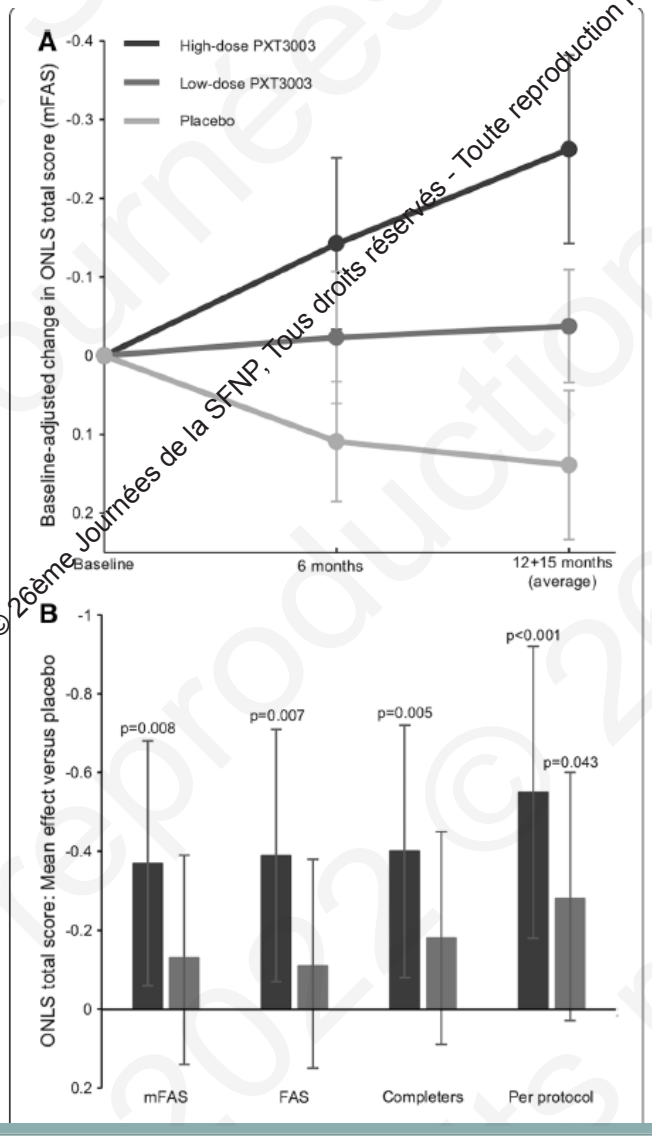

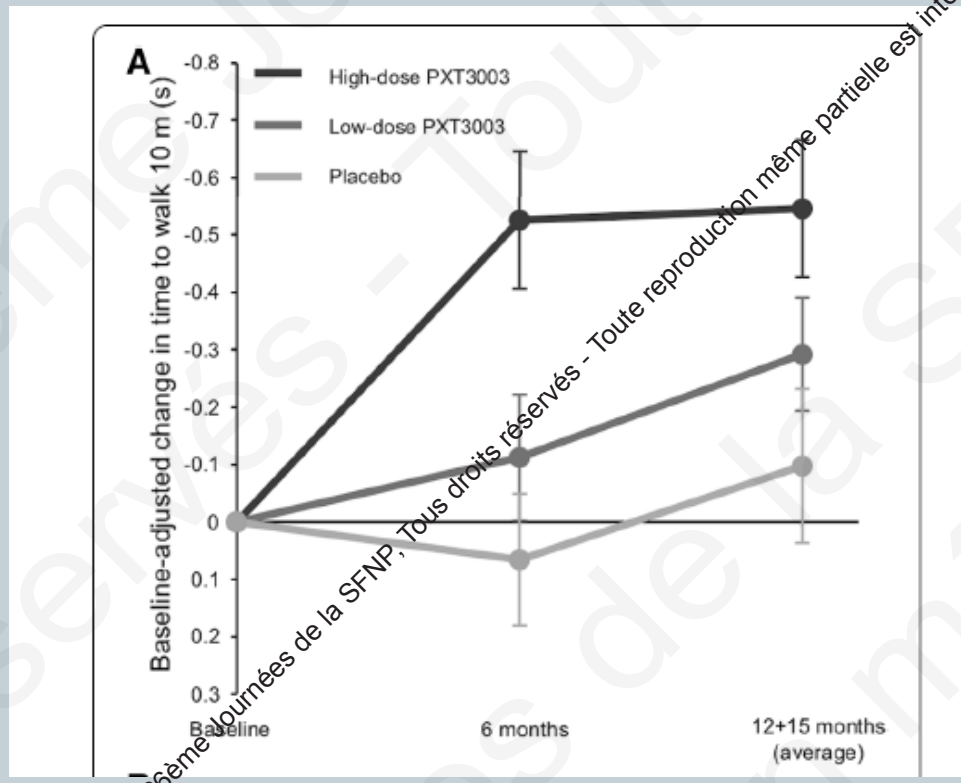

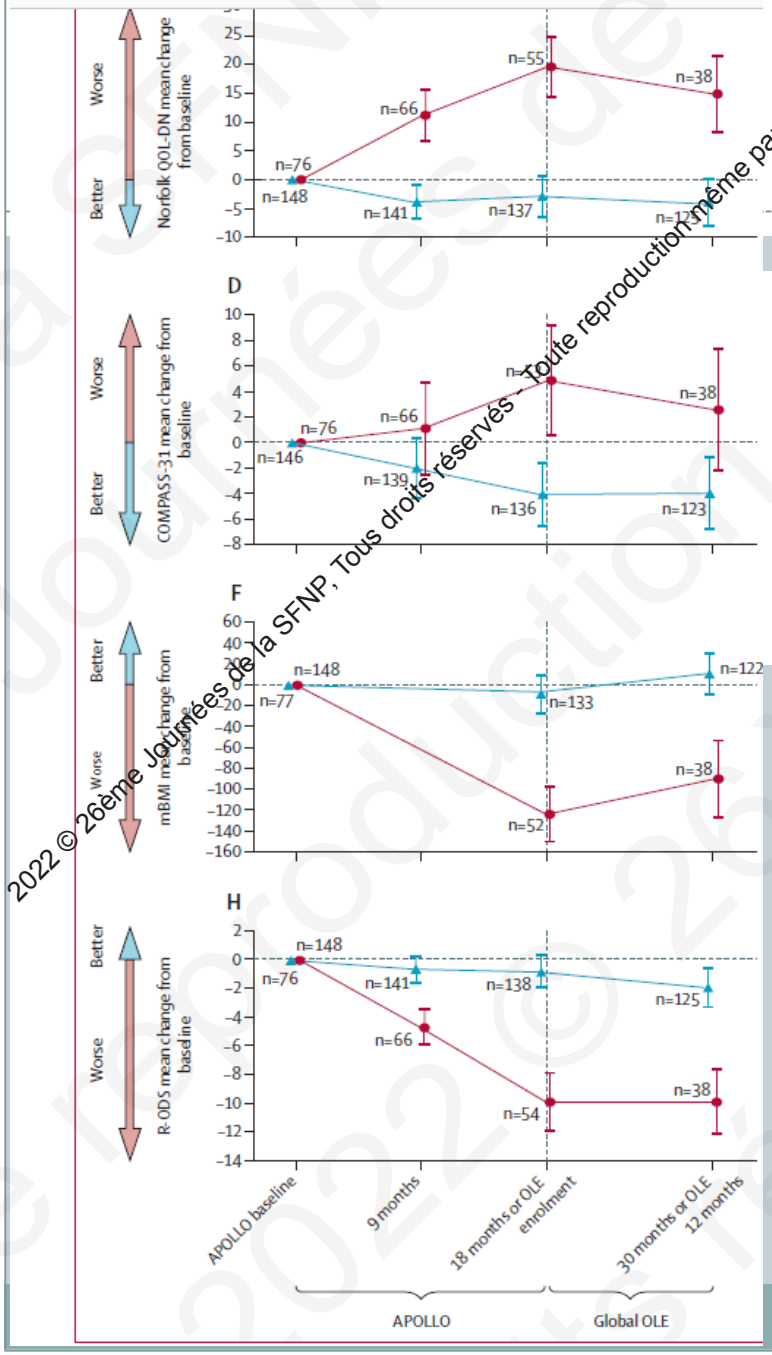

TTR

Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study

David Adams, Michael Polydefkis, Alejandra González-Duarte, Jonas Wixner, Arnt V Kristen, Hartmut H Schmidt, John L Berk, Inés Asunción Losada López, Angela Dispenzieri, Dianna Quan, Isabel M Conceição, Michel S Slama, Julian D Gillmore, Theodoros Kyriakides, Senda Ajroud-Driss, Márcia Waddington-Cruz, Michelle M Mezei, Violaine Planté-Bordeneuve, Shahram Attarian, Elizabeth Mauricio, Thomas H Brannagan III, Mitsuharu Ueda, Emre Aldinc, Jing Jing Wang, Matthew T White, John Vest, Erhan Berber, Marianne T Sweetser, Teresa Coelho, on behalf of the patisiran Global OLE study group*

Lancet Neurol 2021; 20: 49–59
Published Online

Summary

Background Hereditary transthyretin-mediated amyloidosis is a rare, inherited, progressive disease caused by mutations in the transthyretin (*TTR*) gene. We assessed the safety and efficacy of long-term treatment with patisiran,

TTR

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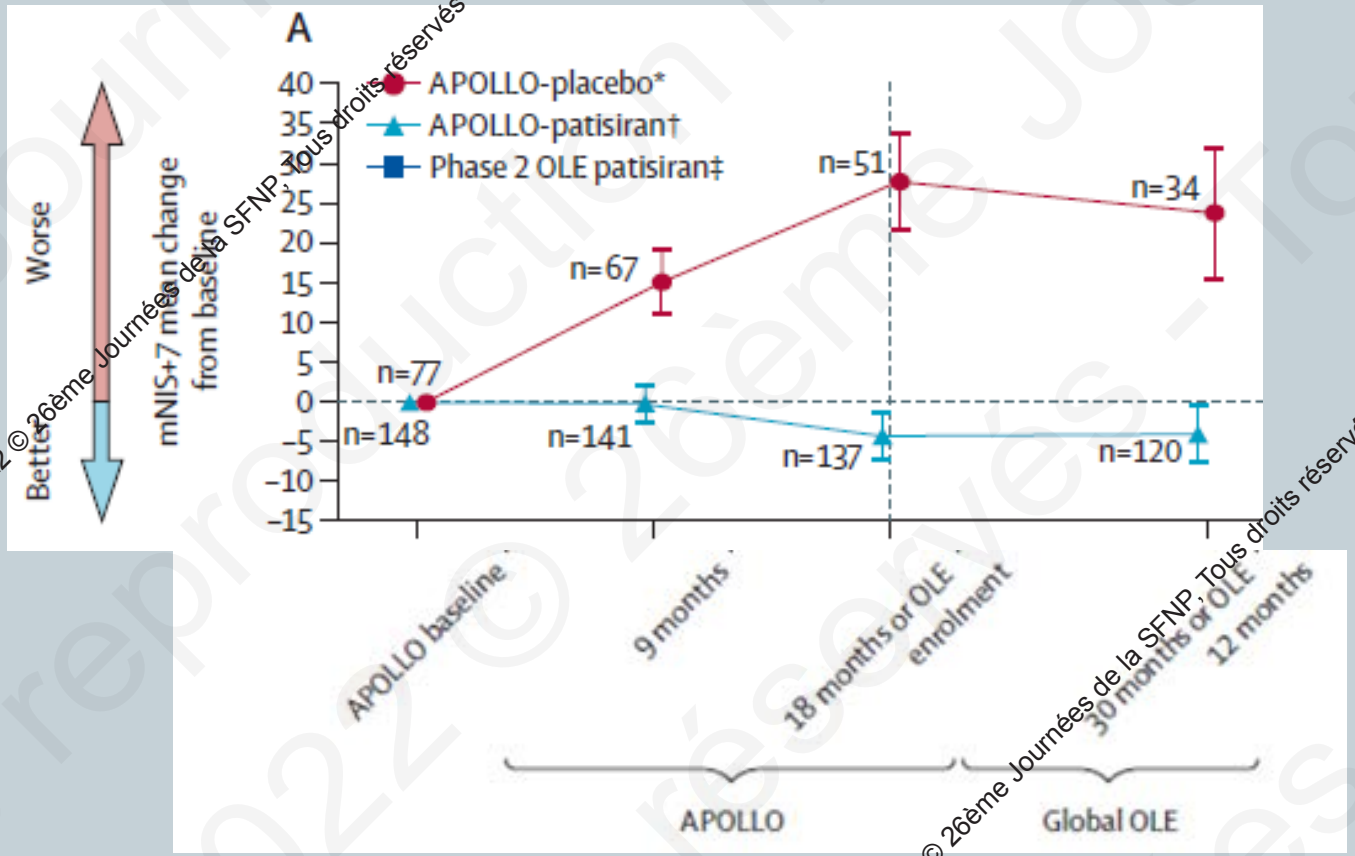

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RESEARCH SUMMARY

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Gillmore JD et al. DOI: 10.1056/NEJMoa2107454

CLINICAL PROBLEM

In transthyretin amyloidosis, misfolded transthyretin (TTR) protein accumulates, primarily in the nerves and heart, and is ultimately fatal. Current therapies reduce amyloid formation through repeated infusions that can have serious adverse effects or require infusion premedications. These treatments slow but do not stop disease progression.

CLINICAL TRIAL

Study Design: An open-label, phase 1 clinical study evaluated the safety and pharmacodynamic effects of NTLA-2001, a CRISPR-Cas9–based in vivo gene-editing therapy targeting *TTR* in human hepatocytes, in adults with hereditary transthyretin amyloidosis and polyneuropathy with or without cardiomyopathy.

Intervention: 6 patients received a single intravenous infusion of NTLA-2001 at a dose of either 0.1 or 0.3 mg per kilogram of body weight.

RESULTS

Efficacy: At 28 days after infusion, TTR levels were reduced from baseline with both doses; the reduction was greater with the larger dose.

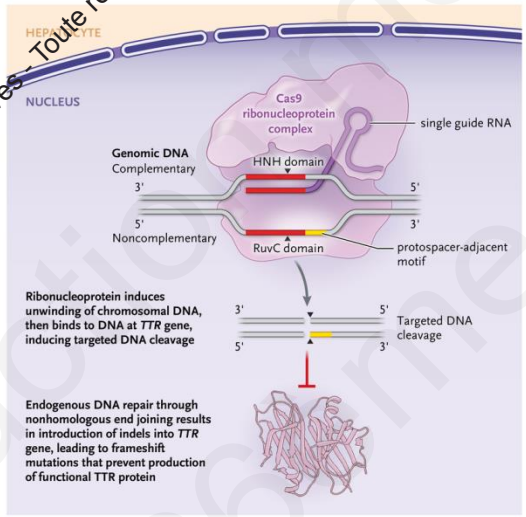
Safety: Adverse effects occurred in 3 patients and were mild.

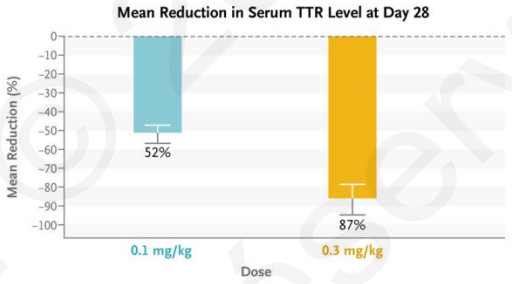
LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- The duration of TTR reduction after a single infusion of NTLA-2001 at the doses used in this study and at higher doses
- Clinical outcomes in these 6 patients and in larger trials
- Whether other adverse effects, including off-target gene editing, occur in the longer term

Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

This trial involving a small number of patients with hereditary transthyretin amyloidosis provides proof-of-concept evidence that CRISPR-Cas9–based gene editing with NTLA-2001 greatly reduces TTR levels after a single infusion with only mild adverse events.

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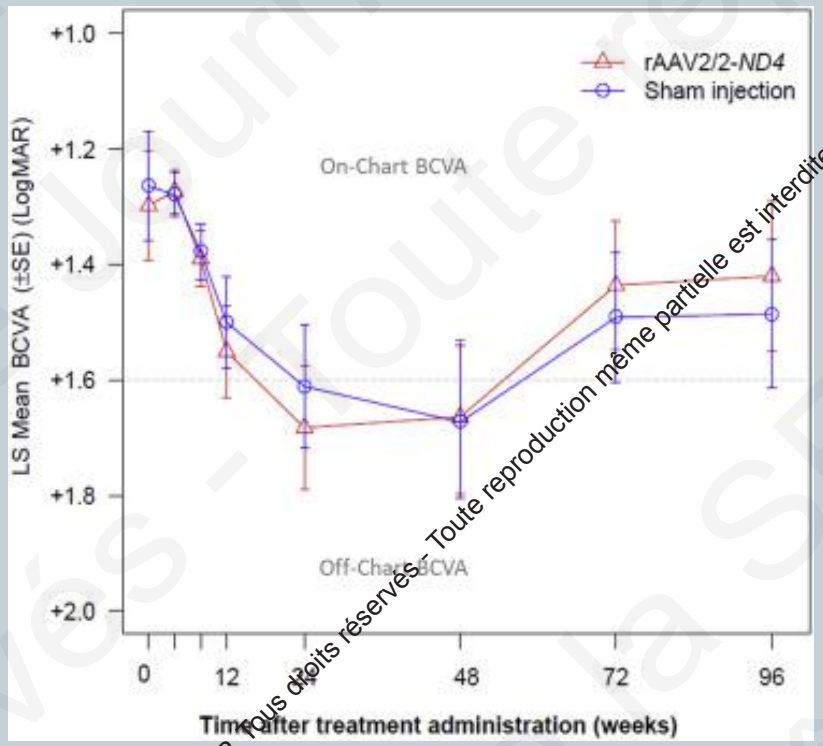
Leber

- **Efficacy and Safety of Intravitreal Gene Therapy for Leber Hereditary Optic Neuropathy Treated within 6 Months of Disease Onset**
- Newman et al., Ophtalmology, 2021
- m.11778G>A et perte de vision mono ou binoculaire ≤6 mois
- 38 patients
- Randomisation gauche/droite



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BVVL

- Atteinte auditive, tronc, neuropathie périphérqiue, atteinte respiratoire
- Anémie sévère normocytaire (3 ans d'hopsitalisation pour aplasia pure des GR)
- Répond à la supplementation en riboflavine

Contents lists available at ScienceDirect

Clinica Chimica Acta

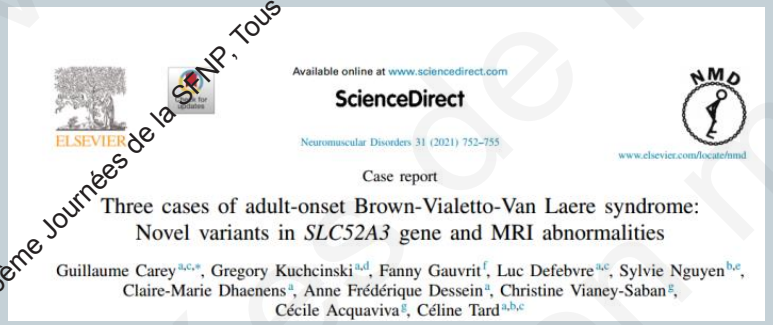
journal homepage: www.elsevier.com/locate/cca

Case report

BVVLS2 overlooked for 3 years in a pediatric patient caused by novel compound heterozygous mutations in SLC52A2 gene

Ziqiang Liu [d,1], Qi Peng [a,b,c,1], Jianwei Li [e], Chunbao Rao [a,b,c], Xiaomei Lu [a,b,c,*]

[a] Laboratory Department, Dongguan Children's Hospital, Dongguan, Guangdong, China
[b] Department of Medical and Molecular Genetics, Dongguan Institute of Pediatrics, Dongguan, Guangdong, China
[c] Key Laboratory for Children's Genetics and Infectious Diseases of Dongguan, Dongguan, Guangdong, China
[d] Child Healthcare Department, Dongguan Children's Hospital, Dongguan, Guangdong, China
[e] Department of Neurology, Dongguan Children's Hospital, Dongguan, Guangdong, China



Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 31 (2021) 752–755

www.elsevier.com/locate/nmd

Case report

Three cases of adult-onset Brown-Vialetto-Van Laere syndrome: Novel variants in *SLC52A3* gene and MRI abnormalities

Guillaume Carey [a,c,*], Gregory Kuchcinski [a,d], Fanny Gauvrit [f], Luc Defebvre [a,e], Sylvie Nguyen [b,e], Claire-Marie Dhaenens [a], Anne Frédérique Dessein [a], Christine Vianey-Saban [g], Cécile Acquaviva [g], Céline Tard [a,b,c]

Déficit de synthèse de la sérine

- Dans l'enfance : polyneuropathie, retard pyschomoteur, crises, microcéphalie
- Esotropie, strabisme
- Difficultés marche 13 ans, FR 15 ans, surdité et rétractions 20 ans
- Diagnostic 40 ans
- **Ichtyose, rétractions, neuropathie progressive**
  - HTA, aménorrhée
- Mutation récessive PSAT1
- Répond à la supplémentation en L-sérine

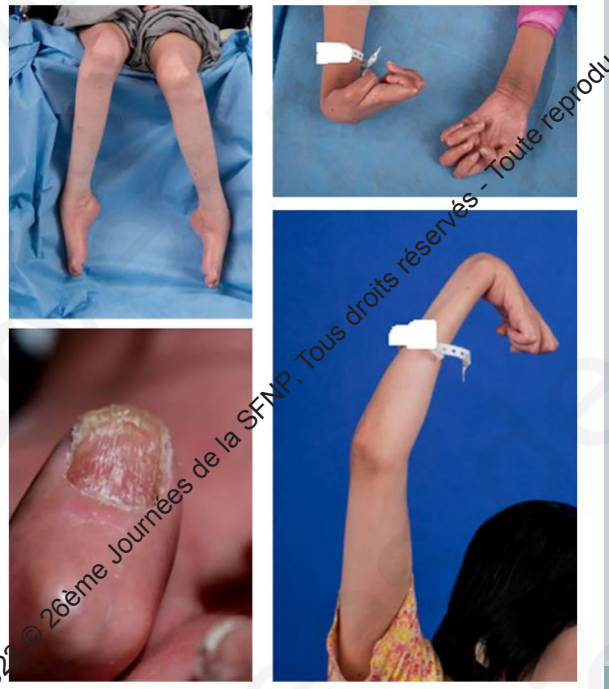
Received: 2 September 2020 | Revised: 9 November 2020 | Accepted: 14 November 2020
DOI: 10.1002/ajmg.a.62245

GENETIC SYNDROMES IN ADULTS

AMERICAN JOURNAL OF medical genetics PART A WILEY

Adult diagnosis of congenital serine biosynthesis defect: A treatable cause of progressive neuropathy

Sarah Debs[1,2] | Carlos R. Ferreira[3] | Catherine Groden[3] | H. Jeffrey Kim[4] | Kelly A. King[4] | Monique C. King[5] | Tanya Lehky[1] | Edward W. Cowen[6] | Laura H. Brown[7] | Melissa Merideth[3] | Carter M. Owen[3] | Ellen Macnamara[3] | Camilo Toro[3] | William A. Gahl[3] | Ariane Soldatos[1]



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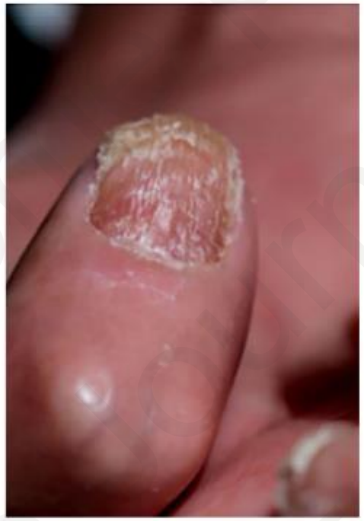

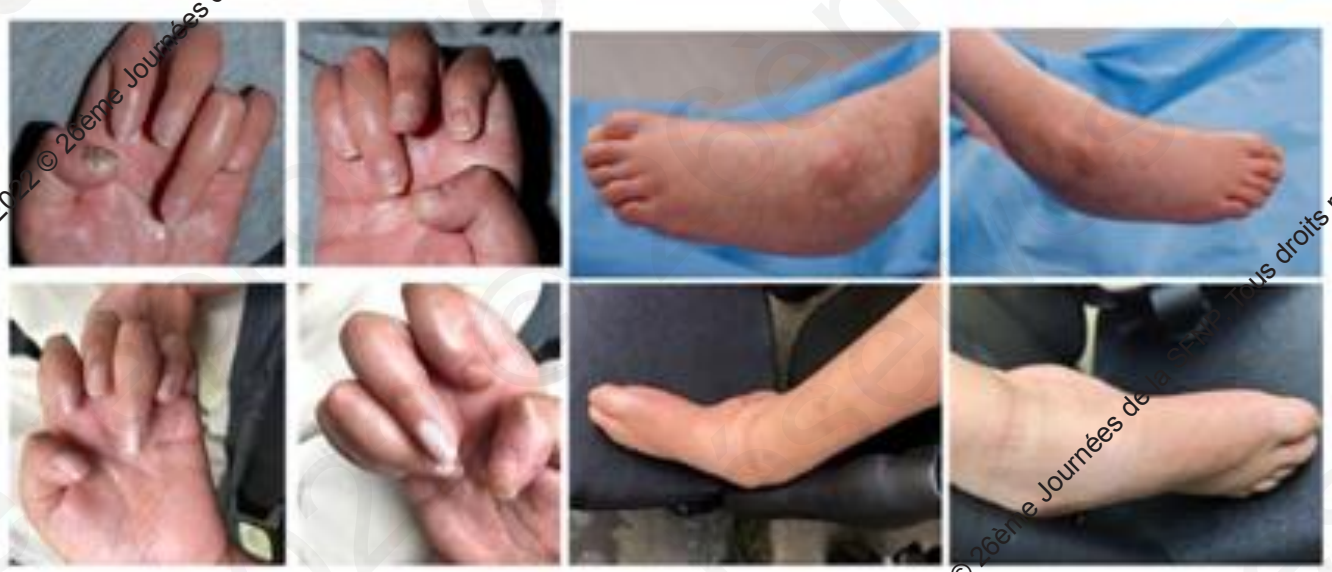

FIGURE 2 Skin and nail improvement under serine treatment. Top row: 2013 pre-treatment; bottom row: 2018 post-treatment [Color figure can be viewed at wileyonlinelibrary.com]

GM2-gangliosidose

- Sandhoff : maladie MN, SCA, tremblement (postural), dystonie, psy, neuropathie (SeMo, SNA)
- sous-unité béta hexosaminisade (HEXB)
  - Déficit hex A et hex B (≠Tay Sachs HEXA)
- Tableau de l'adulte lentement progressif, proximal proximal (scoliose)
- Neuropathie sensitive, radiculaire L5D
- Biopsie neurogène

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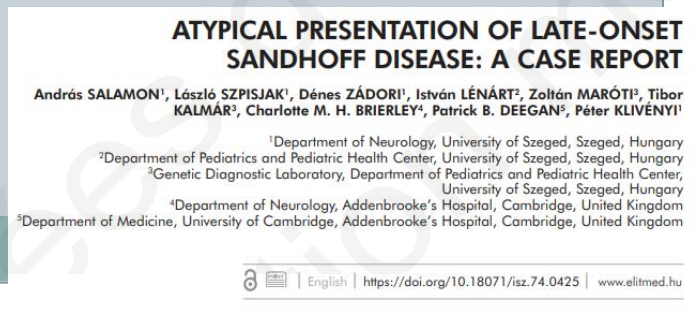

ATYPICAL PRESENTATION OF LATE-ONSET SANDHOFF DISEASE: A CASE REPORT

András SALAMON[1], László SZPISJAK[1], Dénes ZÁDORI[1], István LÉNÁRT[2], Zoltán MARÓTI[3], Tibor KALMÁR[3], Charlotte M. H. BRIERLEY[4], Patrick B. DEEGAN[5], Péter KLIVÉNYI[1]

[1]Department of Neurology, University of Szeged, Szeged, Hungary
[2]Department of Pediatrics and Pediatric Health Center, University of Szeged, Szeged, Hungary
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[4]Department of Neurology, Addenbrooke's Hospital, Cambridge, United Kingdom
[5]Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom

English | https://doi.org/10.18071/isz.74.0425 | www.elitmed.hu

CMT2

- Hypomyélinisation, hypodontie, hypogonadisme hypogonadotrope
  - Leucodystrophie
  - Sur un mode récessif
- Mutation de novo dominante

Xue et al. BMC Neurology (2021) 21:402
https://doi.org/10.1186/s12883-021-02399-y

BMC Neurology

CASE REPORT Open Access

A *de novo* variant of *POLR3B* causes demyelinating Charcot-Marie-Tooth disease in a Chinese patient: a case report

Yan-Yan Xue[1†], Hao-Ling Cheng[1,2†], Hai-Lin Dong[1], Hou-Min Yin[1], Yun Yuan[3], Ling-Chao Meng[3], Zhi-Ying Wu[1*] and Hao Yu[1*]

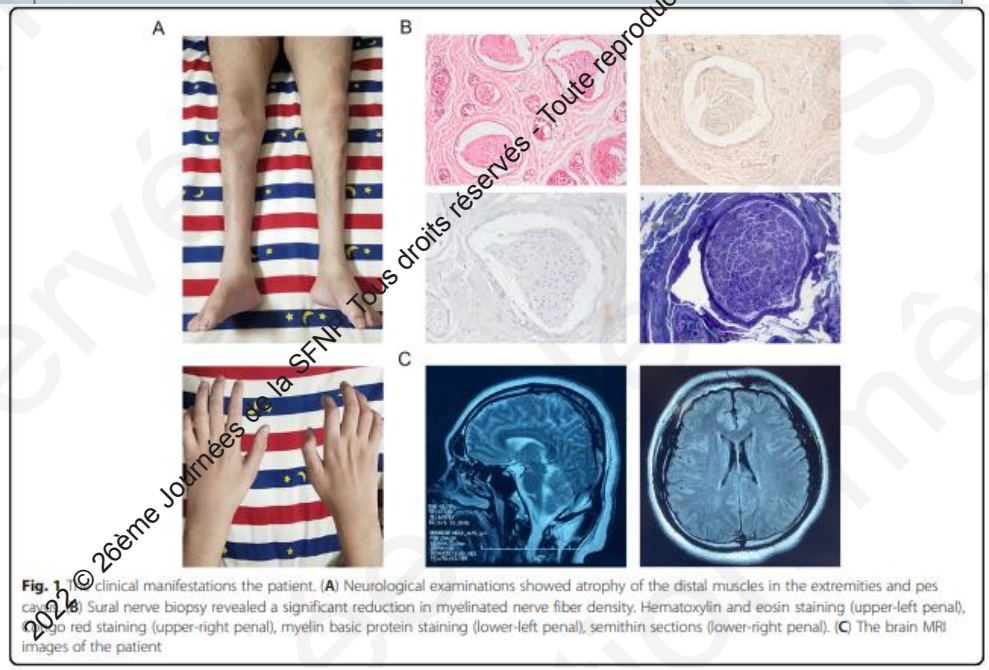

Fig. 1 The clinical manifestations the patient. (**A**) Neurological examinations showed atrophy of the distal muscles in the extremities and pes cavus. (**B**) Sural nerve biopsy revealed a significant reduction in myelinated nerve fiber density. Hematoxylin and eosin staining (upper-left penal), Congo red staining (upper-right penal), myelin basic protein staining (lower-left penal), semithin sections (lower-right penal). (**C**) The brain MRI images of the patient

CMT4H

Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7247-21
Intern Med 60: 3975-3981, 2021
http://internmed.jp

[CASE REPORT]

Sibling Cases of Charcot-Marie-Tooth Disease Type 4H with a Homozygous *FGD4* Mutation and Cauda Equina Thickening

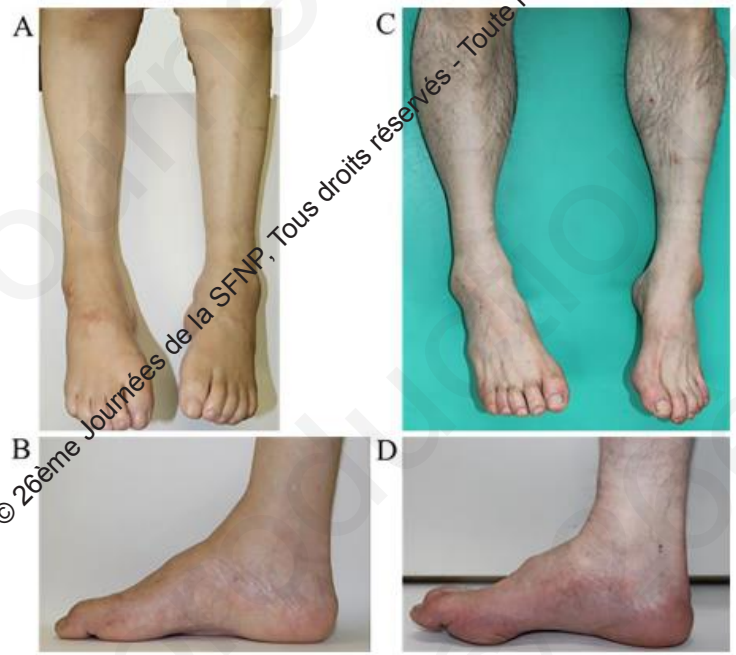

Figure 2. Photographs of characteristic foot deformities of patienst 1 and 2 are shown. Patient 1 showed pes cavus and hammer toes with distal atrophy of lower limbs (A and B). Patient 2 showed more severe foot deformities than Patient 1 (C and D).

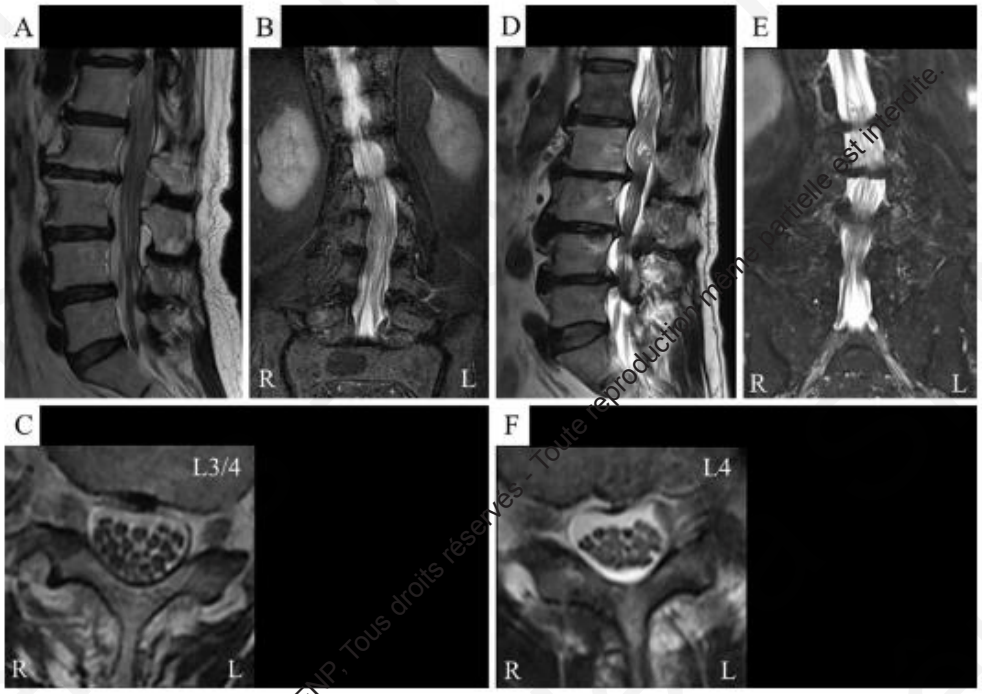

Figure 4. Lumbar spinal MRI of Patient 1 shows a prominent thickening of the cauda equina on T2-weighted sagittal (A), short tau inversion recovery (STIR) coronal (B) and T2-weighted axial (C) images. A lumbar spinal MRI of Patient 2 shows similar findings of cauda equina thickening with

PMP22

- CMT1 :
  - dup PMP22
  - Mutation ponctuelle PMP22

- CMT3 Dejerine–Sottas, plus rare et plus sévère
  - Début précoce
  - Hyperproténo rrachie
  - Vitesses très diminuées

  - mutations faux-sens
  - Petites délétions

- HNPP
  -délétion


Clinical Case Report

Medicine

OPEN

A novel PMP22 insertion mutation causing Charcot–Marie–Tooth disease type 3

A case report

Liang Han, MD[a], Yanjing Huang, MD[a], Yuan Nie, PhD[b], Jing Li, PhD[a], Gang Chen, PhD[a], Shenghao Tu, PhD[a], Pan Shen, PhD[a], Chao Chen, MD[c,*]

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PMP22

Clinical Case Report

Medicine

OPEN

A novel PMP22 insertion mutation causing Charcot–Marie–Tooth disease type 3

A case report

Liang Han, MD[a], Yanjing Huang, MD[b], Yuan Ne, PhD[b], Jing Li, PhD[a], Gang Chen, PhD[a], Shenghao Tu, PhD[a], Pan Shen, PhD[a], Chao Chen, MD[c,*]

Table 1

Motor and sensory nerves conduction in the patient's extremities.

	Latency (ms)	Amplitude (mv)	Distance (mm)	Conduction velocity (m/s)
Motor ulnar left				
Wrist-ADM	Not elicited	NA	NA	NA
Elbow-wrist	Not elicited	NA	NA	NA
Motor ulnar right				
Wrist-ADM	Not elicited	NA	NA	NA
Elbow-wrist	Not elicited	NA	NA	NA
Motor median left				
Wrist-APB	Not elicited	NA	NA	NA
Motor median right				
Wrist-APB	Not elicited	NA	NA	NA
Elbow-wrist	Not elicited	NA	NA	NA
Motor tibial left				
Ankle-AH	Not elicited	NA	NA	NA
Knee-ankle	Not elicited	NA	NA	NA
Motor tibial right				
Ankle-AH	Not elicited	NA	NA	NA
Knee-ankle	Not elicited	NA	NA	NA
Motor peroneal left				
Ankle-EDB	Not elicited	NA	NA	NA
Fibular head-ankle	Not elicited	NA	NA	NA
Motor peroneal right				
Ankle-EDB	Not elicited	NA	NA	NA
Fibular head-ankle	Not elicited	NA	NA	NA
Sensory ulnar left				
Digit V-wrist	Not elicited	NA	NA	NA
Sensory ulnar right				
Digit V-wrist	Not elicited	NA	NA	NA
Sensory median left				
Digit II-wrist	Not elicited	NA	NA	NA
Sensory median right				
Digit II-wrist	Not elicited	NA	NA	NA
Sensory superficial peroneal left				
Calf-Med. Dor. Cutan.	Not elicited	NA	NA	NA
Sensory superficial peroneal right				
Calf-Med. Dor. Cutan.	Not elicited	NA	NA	NA
Sensory sural left				
Mid calf-ankle	Not elicited	NA	NA	NA
Sensory sural right				
Mid calf-ankle	Not elicited	NA	NA	NA

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Waardenburg syndrome

- PCWH (Peripheral demyelinating neuropathy, Central dysmyelinating leukodystrophy, Waardenburg syndrome, Hirschsprung disease)

- WS : surdité, anomalies de pigmentation (cheveux, peau, yeux)

Zardadi *et al. BMC Pediatrics* (2021) 21:70
https://doi.org/10.1186/s12887-021-02521-6

BMC Pediatrics

CASE REPORT Open Access

Four mutations in *MITF*, *SOX10* and *PAX3* genes were identified as genetic causes of waardenburg syndrome in four unrelated Iranian patients: case report

Safoura Zardadi[1], Sima Rayat[1], Maryam Hassani Doabsari[2], Aliagha Alishiri[3], Mohammad Keramatipour[4], Zeynab Javanfekr Shahri[5] and Saeid Morovvati[6*]

Plan

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- Séries de cas

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CANVAS

- Atteinte motrice centrale
- Périphérique
- Signes associés ?

Motor neuron pathology in CANVAS due to RFC1 expansions

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Affiliations + expand

PMID: 34927205 DOI: 10.1093/brain/awab449

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MPZ

- CMTX
- CMT1B/CMT2I

Received: 16 February 2021 | Accepted: 19 May 2021
DOI: 10.1111/ene.14948

european journal of neurology

ORIGINAL ARTICLE

Genotype–phenotype correlation in French patients with *myelin protein zero* gene-related inherited neuropathy

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TABLE 2 Clinical and neurophysiological features in 91 patients with mutations in the *MPZ* gene, sorted by age at symptom onset

Characteristic	Group I, ≤22 y/o	Group II, 23–47 y/o	Group III, >47 y/o	*p*
Patients, *n* (%)	22 (24.2%)	32 (35.2%)	37 (40.6%)	
Age, years, mean ± SD	37.4 ± 14.3	51.9 ± 12.1	66.7 ± 10.4	
Age at onset, years, mean (range)	7.3 (2–19)	36.0 (20–47)	60.8 (50–81)	
CMTNSv2	*n* = 1	*n* = 12	*n* = 8	NA
	m = 15	m = 14.8	m = 13.5	
	SD = NA	SD = 6.7	SD = 7.4	
	Range = NA	Range = 3–24	Range = 1–22	
CMTESv2	*n* = 9	*n* = 22	*n* = 22	0.471
	m = 10.4	m = 10.0	m = 8.6	
	SD = 4.9	SD = 5.7	SD = 6.2	
	Range = 4–16	Range = 2–19	Range = 5.89–11.38	
ONLS upper limbs	*n* = 21	*n* = 27	*n* = 33	0.021[a]
	m = 1.8	m = 1.4	m = 1.0	
	SD = 0.8	SD = 1.0	SD = 1.0	
	Range = 0–3	Range = 0–3	Range = 0–3	
ONLS lower limbs	*n* = 21	*n* = 27	*n* = 33	0.585
	m = 2.2	m = 3.2	m = 2.9	
	SD = 1.3	SD = 1.8	SD = 2.2	
	Range = 1–5	Range = 0–7	Range = 0–8	
ONLS total	*n* = 21	*n* = 27	*n* = 33	0.155
	m = 4.0	m = 3.2	m = 2.9	
	SD = 1.9	SD = 1.8	SD = 2.2	
	Range = 1–8	Range = 0–7	Range = 0–8	
Median motor NCV, m/s	*n* = 12	*n* = 18	*n* = 30	<0.0001[a]
	m = 19.1	m = 31.0	m = 38.4	
	SD = 12.3	SD = 8.7	SD = 10.2	
	Range = 4.9–45	Range = 13–44.6	Range = 8.5–57	
Median motor nerve CMAP, mV	*n* = 12	*n* = 26	*n* = 35	0.001[a]
	m = 3.2	m = 5.7	m = 6.5	
	SD = 3.2	SD = 3.8	SD = 2.9	
	Range = 0.4–9.6	Range = 0.4–17.3	Range = 0.2–13.3	

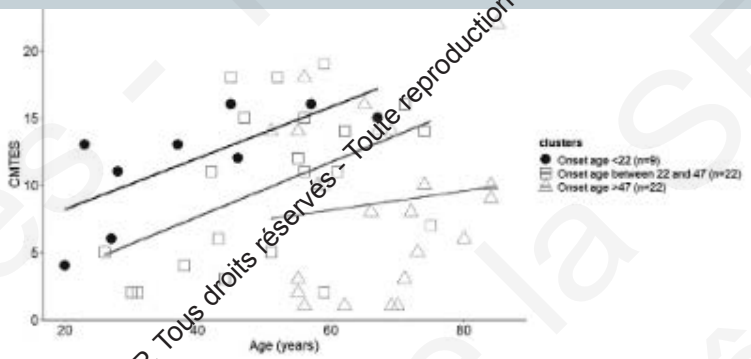

FIGURE 1 CMT Examination Score (CMTES) version 2 is correlated to the age at onset of disease (n = 53). Patients are categorized according to their age of onset. Data are statistically significant if $p < 0.05$

PIDC-like

Characteristic	CMT, *n* = 35	CIDP, *n* = 35
Male	21 (60%)	23 (66%)
Median age at disease onset, years (range)	39 (4–60)	56 (23–87)**
Childhood onset	5 (14%)	0 (0%)
Onset before age 40 years	18 (51%)	2 (6%)**
Family history	8 (23%)	0 (0%)*
Associated autoimmune disorder	8 (23%)	2 (6%)
Chronic progressive course	32 (91%)	31 (89%)
Relapsing–remitting course	3 (9%)	4 (11%)
Isolated motor symptoms at disease onset	8 (23%)	3 (9%)
Asymmetric neuropathy at onset	4 (11%)	8 (23%)
Diffuse areflexia	14 (40%)	16 (46%)
Cranial nerve involvement	6 (17%)	7 (20%)
Hearing loss	5 (14%)	0 (0%)
Pes cavus	20 (57%)	NA
Muscle atrophy at first presentation	19 (54%)	5 (14%)**
Impaired proprioception	24 (69%)	27 (77%)
Positive response to IVIg treatment	7 (20%)	20 (57%)**

Characteristic	CMT, *n* = 35	CIDP, *n* = 35
Partial motor conduction blocks observed on EDX studies, total *n* (mean per patient)[a]	20 (0.6)	76 (2.2)
SSEP analysis suggesting proximal demyelination, *n*	6/8	13/15
Abnormal plexus MRI, *n*	3/10[b]	21/25*
Nerve biopsy showing demyelination, *n*	6/9[c]	¾
Positive serum antiganglioside antibodies, *n*	3/27[d]	1/32[e]
Median CSF protein content, g/L (range)	0.5 (0.3–2.1)	0.8 (0.2–5)
CSF protein content > 0.5 g/L, *n*	15	21

Received: 6 April 2021 | Accepted: 19 May 2021
DOI: 10.1111/ene.14950

european journal of neurology

ORIGINAL ARTICLE

Charcot–Marie–Tooth disease misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy: An international multicentric retrospective study

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PMP22 et MPZ mutations : 23/35 (66%)
GJB1, BSCL2, LRSAM1, MFN2, YARS, NEFL, NEFH, PLEKHG5,SH3TC2, and AARS (34%)

TTR

- S77Y plus jeunes (58 vs 68 ans)
- Plus ataxiques

REVUE NEUROLOGIQUE 177 (2021) 1160–1167

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Revue neurologique

Original article

Electro-clinical presentation of hereditary transthyretin related amyloidosis when presenting as a polyneuropathy of unknown origin in northern France

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Table 3 – ENMG characteristics.

Characteristic	All patients ($n = 24$)	Val30Met ($n = 10$)	Ser77Tyr ($n = 14$)	P-value
Asymmetric	8/24 (33.3%)	6/10 (60.0%)	2/14 (14.3%)	0.032[a]
Non-length dependent	13/24 (54.2%)	5/10 (50.0%)	8/14 (57.1%)	1.000
Demyelination signs	17/24 (70.8%)	8/10 (80.0%)	9/14 (64.3%)	0.653
Definite CIDP criteria fulfilled	9/24 (37.5%)	5/10 (50.0%)	4/14 (28.6%)	0.403
Possible CIDP criteria fulfilled	8/24 (33.3%)	3/10 (30.0%)	5/14 (35.7%)	1.000
Abnormal spontaneous activities	16/24 (66.7%)	6/10 (60.0%)	10/14 (71.4%)	0.673
At least one nerve entrapment	6/10 (60%)	11/14 (78.6%)	17/24 (70.8%)	0.393

[a] Significant differences between the two genotypes ($P < 0.05$)

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TRPV4 : anomalies osseuses squelettiques

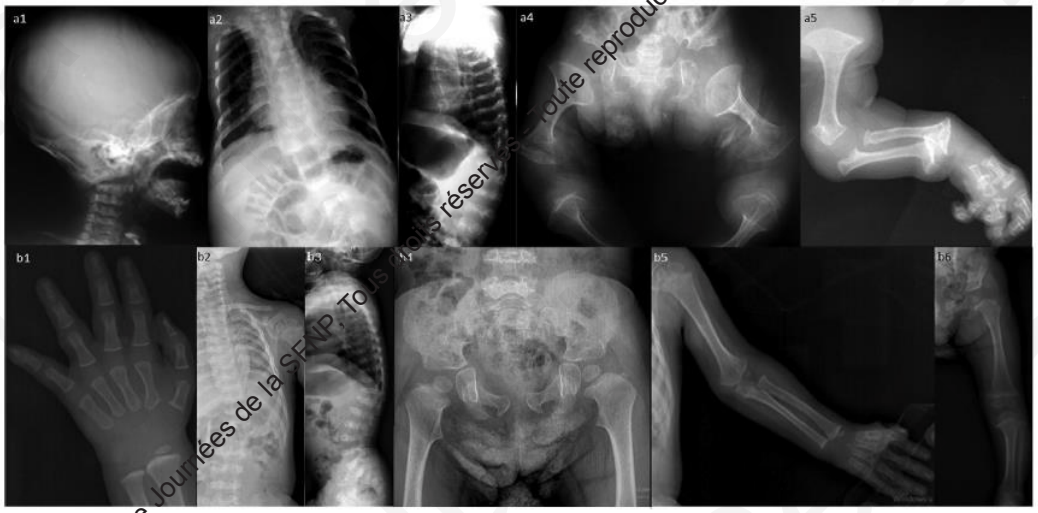

Table 2
Radiographic and electromyographic findings of patients with TRPV4-related disorders.

Clinical Diagnosis	Family 1	Family 2	Family 3	Family 4	Family 5	Family 6		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
	MD		SMDK			CDSMA	CDSMA	Scapular winging/ Segmental
Vertebral findings	Platyspondyly, increased intervertebral distance, wafer vertebra, odontoid hypoplasia	Odontoid hypoplasia, platyspondyly, increased intervertebral distance, wafer vertebra	Platyspondyly, increased intervertebral distance, odontoid hypoplasia	Platyspondyly, increased intervertebral distance, odontoid hypoplasia	Platyspondyly, increased intervertebral distance, odontoid hypoplasia	Minimal vertebral height loss	–	–
Short ribs	+	+	–	–	–	–	–	–
Abnormal long tubular bones	Dumbbell-shaped long bones, epiphyseal dysplasia, metaphyseal widening	Dumbbell-shaped long bones, epiphyseal dysplasia, metaphyseal widening	Metaphyseal irregular ossification	Metaphyseal widening, metaphyseal irregular ossification	Epiphyseal dysplasia, metaphyseal widening, metaphyseal irregular ossification	Slender long bones	–	–
Pelvic findings	Squared iliac wings with flat acetabular roofs, small sacrosciatic notches	Squared iliac wings with flat acetabular roofs, small sacrosciatic notches	Broad short basilar portions of the iliac bone, horizontal acetabular roof, short femoral neck, flattened femoral epiphyses, coxa vara	Broad short basilar portions of the iliac bone, horizontal acetabular roof	Broad short basilar portions of the iliac bone, horizontal acetabular roof, short femoral neck, flattened femoral epiphyses, coxa vara	Osteoporosis	–	–
Carpal ossification delay	+	+	–	+	+	–	–	–
Irregular contours of talus and calcaneous	+	+	–	–	–	–	–	–
MRI and EMG findings	Craniospinal MRI revealed kyphoscoliosis, vertebra plana, atlantoaxial dislocation, spinal stenosis with cord compression, myelomalacia of the spinal cord, and mild tetraventricular hydrocephalus.	–	–	–	–	EMG revealed lower motor neuron involvement	EMG revealed chronic lower motor neuron involvement	–

MD: metatropic dysplasia; SMDK: spondylometaphyseal dysplasia Kozlowski type; CDSMA: Congenital distal spinal muscular atrophy.
MRI: Magnetic resonance imaging.

European Journal of Paediatric Neurology 32 (2021) 46–55

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

Natural history of *TRPV4*-Related disorders: From skeletal dysplasia to neuromuscular phenotype

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