CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Severe Respiratory and Swallowing Disorders in Infantile-Onset Multisystem Neurologic, Endocrine, and Pancreatic Disease Type 1

Two Cases

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Neurol Genet 2024;10:e200178. doi:10.1212/NXG.0000000000200178

Abstract

Objectives

The objective of this study was to expand the phenotypic spectrum of infantile-onset multisystem neurologic, endocrine, and pancreatic disease type 1 (IMNEPD1) and highlight the importance of analyzing the *PTRH2* gene in patients with neuropathy presenting with pancreatic lipomatosis.

Methods

Two sisters, aged 73 and 71 years, respectively, presented a severe, length-dependent sensorimotor axonal neuropathy, associated with deafness and intellectual deficiency.

Results

They both needed a wheelchair from the fourth decade. They developed a severe respiratory dysfunction, requiring nocturnal noninvasive ventilation from around 50 years of age. The younger sister developed severe dysphagia complicated by aspiration pneumonia. A muscle biopsy of the younger sister was suggestive of mitochondrial myopathy. The youngest presented a complete pancreatic lipomatosis. A biallelic novel likely pathogenic variant within *PTRH2*, c.254A>G (p.Gln85Arg), was evidenced in both patients.

Discussion

IMNEPD1 is a rare autosomal recessive disorder caused by sequence variant in the *PTRH2* gene and characterized by a peripheral neuropathy, cerebellar atrophy, intellectual disability, hearing loss, pancreatic insufficiency, hypothyroidism, and dysmorphic features. In addition to these classic manifestations of the disorder, severe dysphagia and respiratory insufficiency may develop over the course of the disease and should be systematically screened. *PTRH2* gene should be considered in patients with pancreatic lipomatosis and neuropathy.

Introduction

Biallelic pathogenic variants in the *PTRH2* gene cause infantile-onset multisystem neurologic, endocrine, and pancreatic disease type 1 (IMNEPD1). IMNEPD1 was first reported in 2 patients in 2014 and subsequently in several children of different families and recently in adult patients.[1-10] Peptidyl transferase RNA hydrolase 2 (PTRH2) is present in the mitochondria and

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The Article Processing Charge was funded by INSERM.

regulates cell functions, including cell survival and muscle differentiation.[11] When PTRH2 function is inhibited, the typical features encompass motor development delay, intellectual disability, hearing loss, peripheral neuropathy, ataxia, foot and facial dysmorphic features, and pancreatic insufficiency.[1-10]

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Clinical Features

We report 2 sisters of Iranian origin with a biallelic pathogenic variant in the *PTRH2* gene.

No motor milestone delay was described in either sister. They both developed severe scoliosis in childhood. Both had a moderate intellectual disability.

The elder sister (patient A) was 73 years old at the last evaluation. A progressive symmetrical weakness of the lower limbs started at the age of 6 years, leading to a steppage gait. Hand weakness appeared at the age of 10. At her last evaluation, she had complete motor weakness of hand and forearm muscles, which were severely wasted. The biceps brachialis, the triceps brachialis, and the deltoids were scored 4/5 on the MRC (Medical Research Council) scale. In the lower limbs, the leg and foot muscles were wasted and were evaluated at 0/5, whereas the quadriceps, hamstrings, and iliopsoas were scored at 4/5 on the MRC scale. She presented severe hypoesthesia in all modalities in the distal part of the 4 limbs. She developed mixed cerebellar and proprioceptive ataxia. She could walk only a few steps with 2 canes and started to use a wheelchair at 30 years of age. She presented a paretic dysarthria.

Her sister (patient B) was 71 years old at the last evaluation. She presented a similar though more severe clinical picture, characterized by a complete motor deficit in the distal muscles of the 4 limbs and severe weakness in the proximal muscles, scored 2/5 on the MRC scale. The weakness started progressively in both feet at age 8 years and spread to the hands at 22 years of age. Like her sister, she also had a severe sensory deficit and a mixed ataxia and also used wheelchair at age 30 years.

From her sixth decade, patient B presented multiple aspiration pneumonia causing acute respiratory failure requiring repeated hospitalizations for oxygen therapy and even intensive care at the age of 67. By contrast, patient A did not develop swallowing difficulties.

In both patients, bilateral sensorineural hearing loss appeared progressively in the third decade.

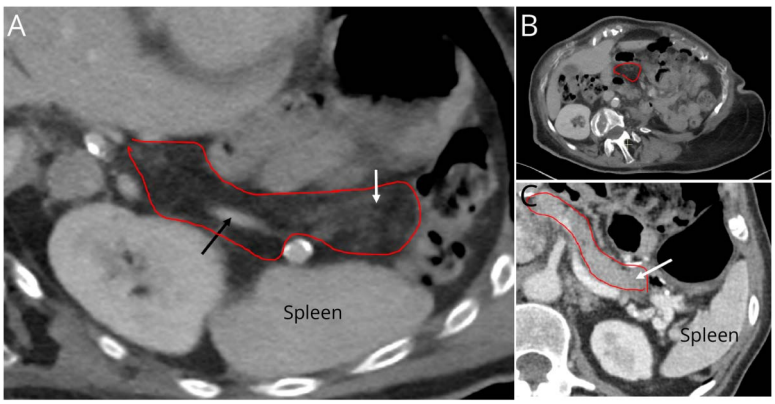
Ancillary Examinations

Respiratory insufficiency was evidenced in both patients, associated with morning hypercapnia. Vital capacity evaluated at 65 years of age was 35% and 39% of the normal value for patients A and B, respectively. The chest CT scan was normal. The patients' respiratory impairment was complicated by nocturnal hypoventilation associated with a severe sleep apnea syndrome. Nocturnal noninvasive ventilation was introduced for both patients.

Both patients developed diabetes mellitus. Patient B also developed hypothyroidism. An abdominal-pelvic CT scan of patient B revealed complete lipomatosis of the pancreas without atrophy (Figure 1). Biological work-up disclosed a low blood lipase level in both patients, 7.4 in patient A and 4 UI/L in patient B (normal value: 13–190 UI/L). The creatine kinase level was normal in both patients.

ECG and echocardiography performed in both patients were normal.

Figure 1 Pancreatic Lipomatosis



Abdominal CT scan of patient B in the axial section (A and B) and in a normal subject (C). The authors observed a complete fatty infiltration of the pancreas (outlined in red) (A and B) in comparison with a normal pancreas (C). White arrow indicates the tail of the pancreas. In contrast with the fat hypodensity, the splenic vein (black arrow) appears in hyperintense (A). The head of the pancreas in the patient (B) presents a density of −70.1 UH, corresponding to fatty tissue.

In both patients, cerebral MRI showed a diffuse cerebral atrophy predominantly in the cerebellum. Brain MRI disclosed some nonspecific hyperintensities in the subcortical white matter on the T2-weighted sequence.

Neurophysiologic studies revealed a severe length-dependent sensorimotor axonal neuropathy in both patients (eTable 1).

A biopsy of the deltoid muscle performed in patient B at age 61 years disclosed atrophic muscle fibers with fiber-type grouping. Most type I fibers were of normal size, whereas all type II fibers were atrophic. A disorganization of the myofibrillar network was present, essentially involving type II fibers. One ragged-red fiber was present along with numerous fibers with mitochondrial aggregates (Figure 2). A normal amount of mitochondrial DNA was present in the muscle. No deletion was found in the muscle and blood mitochondrial DNA.

A homozygous missense likely pathogenic variant of NM_016077.4(PTRH2): c.254A>G, p.(Gln85Arg) was evidenced in both patients, using whole-exome sequencing (WES), and then confirmed by Sanger sequencing.

The variant was absent from the gnomAD database (PM2 ACMG criteria) and was rated "deleterious" by Mutation Taster and SIFT, "probably damaging" by PolyPhen2, "damaging" by REVEL, and "likely pathogenic" by AlphaMissense. These scores enable the use of the PP3 ACMG criteria. Furthermore, the glutamine residue is conserved throughout species, and an additional substitution of this amino acid has previously been reported as pathogenic[2,10] (PM5 ACMG criteria), leading to dysfunction of the PTRH2 protein by altering hydrogen bridge bonds within the protein. This putatively affects the structure, folding, and stability of this protein (PM1 ACMG criteria).[2,3,10]

For the segregation study, we only tested the 2 affected cases in the family and confirmed the presence of this variant in both cases (PP1 ACMG criteria).

Overall, the variant has been classified as probably pathogenic according to the following ACMG criteria: PM1, PM2, PP3, PM5, and PP1.

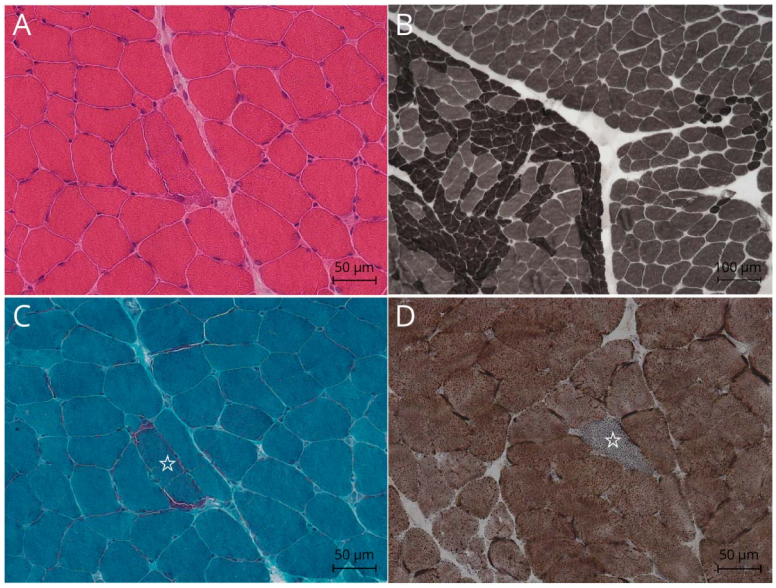
Discussion

We report 2 siblings presenting IMNEPD1, caused by a previously unreported biallelic c.254A>G variant in the *PTRH2* gene. This variant involves the same nucleotide of the known pathogenic variant, described in 6 other IMNEPD1 patients.[2,10]

In the literature, 19 IMNEPD1 patients, aged from 6 to 56 years (mean: 15.9 years), have been reported, mainly in the Middle East, in line with our 2 patients[1-10] (Table 1).

Several features presented by our patients differ from the previously published IMNEPD1 cases (Table 1). First, both of our patients presented with a severe respiratory impairment requiring nocturnal ventilation. In the absence of pulmonary parenchymal abnormality, the putative mechanism is diaphragmatic dysfunction. In addition, one of our patients had severe swallowing disorders. Respiratory and bulbar muscle involvement were not previously been reported. Since the respiratory involvement in our patients was discovered in their seventh decade, it may represent a

Figure 2 Muscle Histology



Deltoid biopsy from patient B. Transverse frozen sections stained with hematoxylin and eosin (A), ATPase 9.4 (B), modified Gomori trichrome (C), and cytochrome c oxidase/succinate dehydrogenase double staining (COX/SDH) (D). Magnification ×20 except for B (×10). Note the wide range variation in fiber size (A) and the fiber-type grouping, suggesting muscle fiber denervation (B). Some mitochondrial abnormalities are observed, a ragged-red fiber (white star, C) and fibers that are deficient in COX but retain SDH activity (white star, D).

Table Clinical and Exploration of Our Cases and Literature Review

Patient number		Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13	Pt 14	Pt 15	Pt 16	Pt 17	Pt 18	Pt 19	Pt A	Pt B
Reference		Hu et al. 2014		Picker-Minh et al. 2016							Sharkia et al. 2017	Le et al. 2019			Khamirani et al. 2021	Parida et al. 2021	Bronson CS et al. 2021	Ando et al. 2021	Bubshait et al. 2022		Our cases	
Age at examination		14	6	14	6	15	7	5	13	3	17	27	17	7	30	12	19	56	17	18	73	71
Ethnicity		Turkish	Turkish	Yazidian-Turkish	Yazidian-Turkish	Tunisian	Saudi Arabian	Saudi Arabian	Saudi Arabian	Saudi Arabian	Arab (Israel)	Syrian	Syrian	Syrian	Iranian	Indian	Southern Indian	Japanese	Saudi-Arabian	Saudi-Arabian	Iranian	Iranian
***PTRH2* variant**		c.269_270delCT				c.254A > C						c.324 G > A			c.68T > C	c.127dupA	c.328G>T	c.280T>A	c.114dup		c.254A > C	
Clinical features	Deformity of head and face	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	–	–	–
	Feet deformity	+, TEV	–	+, TEV	–	+, TEV	–	–	–	–	+, PC	–	–	+, TEV	+, PP	–	+, PC	+	+, PC	+, PC	+, PP	+, PP
	Hearing loss	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+
	Intellectual disability	+	+	+	+	NA	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
	Motor delay	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
	Ataxia	+	+	+	+	+	+	+	+	–	–	+	+	+	NA	–	+	+	+	+	+	+
	Distal weakness	+	+	+	+	+	+	+	–	–	+	+	+	–	–	–	+	+	+	+	+	+
	Swallowing difficulties	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
	Respiratory impairment	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Ancillary exams	Diabetes mellitus	+	+	+	+	+	–	–	–	–	NA	+	+	–	NA	+	+	–	+	–	+	+
	Hypothyroidism	+	+	+	+	–	–	–	–	–	–	–	–	–	NA	–	–	+	–	–	–	+
	Pancreatic abnormality	+	–	+	–	+	–	–	–	–	–	NA	NA	NA	–	–	+	+	NA	NA	NA	+
	Hepatomegaly	–	+	–	+	+	–	–	–	–	–	–	–	–	–	–	+	–	NA	NA	NA	–
	Neuropathy	+, demyelinating	+, demyelinating	+, demyelinating	+, demyelinating	+, demyelinating	NA	NA	NA	NA	+, demyelinating	+, demyelinating	+	+	–	+, demyelinating	+, axonal (biopsy)	+, axonal	+, demyelinating	+, demyelinating	+, axonal	+, axonal
	Muscle biopsy abnormality	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	+	NA	NA	NA	+
	Cerebellar atrophy	+	+	+	+	–	–	+	–	–	–	+	+	+	NA	–	+	+	+	NA	+	+

Abbreviations: – = absent; + = present; NA = not available; PC = pes cavus; PP = pes planus; Pt = patient; TEV = talipes equinovalgus.
We present the 19 patients with IMNEPD1 previously described in the literature and our 2 cases (patients A and B).

late onset complication of IMNEPD1. Indeed, the oldest patient previously reported was 56 years old.[9] It seems crucial to detect these symptoms, whose consequences can be fatal, leading to acute respiratory failure and consequently requiring adapted feeding or even gastrostomy.

The type of neuropathy is also a hallmark of the disease. Although they developed a severe sensorimotor length-dependent axonal neuropathy, no demyelinating features were present in our patients, despite their being classically described in IMNEPD1.[4,6,9] The demyelinating physiopathology of the neuropathy was retained on neurophysiologic explorations in 13 of the 14 cases in the literature and was not detailed in the other 5 cases.[1-9] Of note, the only nerve biopsy reported, a patient with the c.328G>T variant showed a chronic axonopathy without signs of demyelination.[6] Indeed, in severe forms of neuropathy, it can be difficult to differentiate between primary axonopathy and demyelination.[12] In our cases, the compound muscle action potentials of the distal motor nerves were abolished. However, normal distal motor latencies from proximal nerves were in favor of an axonal neuropathy.

Muscle biopsy performed in only 2 of the previously reported IMNEPD1 patients was reported normal in one case, whereas in the other one, the muscle biopsy revealed small numbers of ragged-red fibers and cytochrome c oxidase-deficient fibers, as observed in our patients.[6,9] Of interest, a *PTRH2* KO mouse model develops a severe myopathy and the protein encoded by *PTRH2*, PTRH2, is a mitochondrial protein.[1] However, it is not possible to classify this complex disorder as a primary multisystemic mitochondrial disease (PMD). Notably, apart from diabetes, none of the common manifestations of PMD (ptosis, external ophthalmoplegia, proximal myopathy and exercise intolerance, cardiomyopathy, optic atrophy, and pigmentary retinopathy) were found in our patients.[13] Moreover, the severe predominant motor involvement both clinically and electrophysiologically is uncommon in multisystemic mitochondrial diseases because in these latter, the neuropathy is mostly in the background and predominantly sensitive.

It must be underlined that the occurrence of pancreatic lipomatosis along with a low lipase level is a key element of diagnosis, as previously reported.[4,6] There is no other hereditary disease associating a severe neuropathy and a complete lipomatosis of the pancreas. We suggest that a low lipase level should prompt investigation for this pancreatic involvement.

We recommend systematic and repeated respiratory exploration in IMNEPD1 patients. The association of neuropathy with pancreatic lipomatosis should point toward the *PTRH2* gene.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* January 10, 2024. Accepted in final form July 16, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Antonella Spinazzola, MD.

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Klervie Loiselet, MD	Department of Pediatric Radiology, Hôpital Necker-Enfants Malades, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
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Continued

Appendix *(continued)*

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