CASE REPORT

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A Novel PTRH2 Gene Mutation Causing Infantile-onset Multisystem Neurologic, Endocrine, and Pancreatic Disease in a Bahraini Patient

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ABSTRACT

Infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD) is a rare autosomal recessive multisystemic disease with a prevalence of < 1/1 000 000. The wide spectrum of symptoms and associated diseases makes the diagnosis of this disease particularly challenging. Here, we report a 12-year-old Bahraini male who presented with the core clinical features of IMNEPD including intellectual disability, global developmental delay, sensorineural hearing loss, endocrine dysfunction, and exocrine pancreatic insufficiency. The diagnosis was confirmed by genetic testing using whole exome sequencing. This is the first reported case of IMNEPD from Bahrain and was found to have a novel homozygous peptidyl-tRNA hydrolase 2 (PTRH2) gene mutation (NM_001015509.2: c.370del p.(Glu124Lysfs*4)). Moreover, we conducted an extensive literature review with an emphasis on the variable clinical spectrum and genotypes of previously reported patients in comparison to our case.

Infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD) is a rare autosomal recessive mitochondrial disorder first reported in 2014.[1,2] IMNEPD is caused by various mutations in the peptidyl-tRNA hydrolase 2 (PTRH2) gene located on chromosome 17.[1] This gene encodes a protein with hydrolase activity, which contributes to protein synthesis and plays a vital role in regulating cell function, including cell survival and anoikis, stress resistance, and muscle differentiation.[3–5] Loss of PTRH2 function in human development leads to pro-survival signals loss, resulting in IMNEPD.[4,5]

IMNEPD is a multisystemic disorder with variable phenotypes. Its clinical manifestations include intellectual disability (ID), global developmental delay including motor and severe speech delay, ataxia, sensorineural hearing loss (SNHL), progressive cerebellar hypotrophy or atrophy, peripheral sensorimotor neuropathy, hypothyroidism, diabetes mellitus, exocrine pancreatic insufficiency (EPI), and liver dysfunction.[4,6] IMNEPD diagnosis is confirmed by genetic testing and the management is supportive.[6] Herein, we report a child with a novel mutation of PTRH2 born to a consanguineous Bahraini family.

CASE REPORT

A 12-year-old Bahraini male with an antenatal history of placental insufficiency, intrauterine growth retardation , and reduced fetal movements suspecting birth asphyxia was born via induced, vaginal delivery at term. His birth weight and head circumference were 2.3 kg and 31 cm, respectively (3rd percentile each). Examination revealed a right undescended testis. His parents are first-degree cousins [Figure 1].

The patient developed constipation at two months. At four months, he was investigated for cystic fibrosis due to recurrent respiratory infections, abnormal bowel habits, and family history [Figure 1]. Sweat chloride test and fecal tryptic activity were normal and stool microscopy was negative for fat globules. Cow's milk protein allergy was also suspected and managed.

At eight months, developmental delay and abnormal response to sounds were noted. Examination revealed hypotonia and a small head. His sibling's head circumference was also small (45 cm (< 1st percentile) at two years), raising the possibility of familial microcephaly. On re-evaluation at one year, the child could stand with support, sit, transfer objects, and babble, but could not crawl, or speak.

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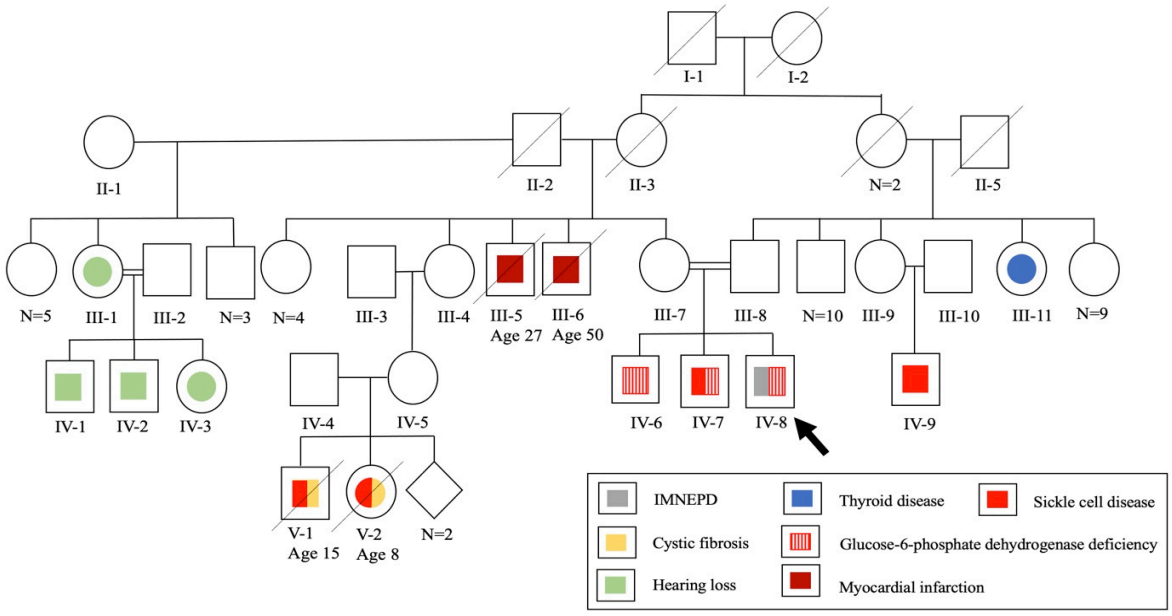

Figure 1: Family pedigree chart of a 12-year-old patient with infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD).

Brain magnetic resonance imaging was normal. The child was assessed for speech and hearing difficulties, along with a positive family history [Figure 1]. Bilateral SNHL was confirmed, predominantly on the right side. Right cochlear implant surgery was performed, yet the patient remained nonverbal.

On follow-up, weight gain remained slow, and he developed steatorrhea with abdominal distension. Repeated sweat chloride test remained normal but stool was positive for fat globules. Celiac serology showed normal tissue transglutaminase but elevated antigliadin antibodies (AGA; immunoglobulin G (IgG) 70.7 U/mL (normal < 10 U/m)). Abdominal ultrasound (US) showed fatty liver while barium meal revealed gastroesophageal reflux disease with sliding hiatal hernia. Upper gastrointestinal (GI) endoscopy and histopathology confirmed gastroesophageal reflux disease.

At three years, a targeted familial mutation analysis (c.1911delG; p.Q637HfsX26 in exon 14 of cystic fibrosis transmembrane conductance regulator gene) was negative. Genitalia re-examination revealed normally descended testis.

The patient was lost to follow-up for years. At age 11, he was diagnosed with type 1 diabetes mellitus with diabetic ketoacidosis. He was referred to a gastroenterologist due to wasting and steatorrhea. On examination, he had subtle facial features with down slanting palpebral fissure, microcephaly, finger clubbing, and abdominal distention with gases [Figure 2]. He had an unstable, broad-based gait with a high steppage. Repeated celiac serology showed normal total IgA levels and AGA IgA, but high AGA IgG (26 U/mL) and tissue transglutaminase IgA (110 U/mL, normal: < 10 U/mL for all), and equivocal anti-endomysial antibody. Repeated upper GI endoscopy showed a longitudinal esophageal ulcer and unhealthy duodenal mucosa. Histopathology was compatible with acute esophagitis, chronic gastritis, and duodenitis.

The whole exome sequencing (WES) test identified a homozygous mutation (NM_001015509.2: c.370del p.(Glu124Lysfs*4)) in the PTRH2 gene. The PTRH2 variant c.370del p.(Glu124Lysfs*4) creates a shift in the reading frame starting at codon 124. This is consistent with autosomal recessive IMNEPD type 1. According to the American College of Medical Genetics and Genomics guidelines, the identified mutation is classified as a variant of uncertain significance (VUS). In addition, WES detected a heterozygous mutation in the hemoglobin subunit alpha 1 gene (NM_000558.3:c.95+2_95+6del) which is consistent with the patient's known alpha-thalassemia carrier status. However, it did not report any genetic variants related to glucose-6-phosphate dehydrogenase (G6PD) or cystic fibrosis transmembrane conductance regulator genes, despite the patient's known G6PD deficiency. This is because not all genetic variants detected by WES will be mentioned in the final report, especially if they are

Figure 2: (**a and b**) Eleven-year-old patient showing subtle facial features with down slanting palpebral fissure and microcephaly along with (**c and d**) abdominal distension.

not relevant to the patient's clinical history. Another possibility is that the detected G6PD mutation was a VUS, and in the absence of related clinical information, it was not reported. Both parents were heterozygous carriers for PTRH2 gene mutation.

At 12 years, an orthopedics review following foot trauma revealed waddling, foot drop, and distal muscle weakness. Muscular dystrophy was suspected. The patient is currently followed by a multi-disciplinary team providing supportive care. His last weight was 21.5 kg, height was 127 cm, and head circumference was 50 cm (all < 1st percentile) indicating severe thinness, short stature, and microcephaly, respectively.

DISCUSSION

IMNEPD is a rare disease with a prevalence of < 1/1 000 000 (ORPHA:456312).[7] A total of 19 patients with IMNEPD were reported

Table 1: Clinical features and genetic variants of 20 patients with IMNEPD published worldwide.

Category	Our case	Hu et al.[1] 2014	Alazami et al.[8] 2015	Picker-Minh et al.[6] 2016	Sharkia et al.[3] 2017	Le et al.[9] 2019	Parida et al.[10] 2021	Khamirani et al.[11] 2021	Charles et al.[12] 2021	Becker et al.[13] 2021	Ando et al.[14] 2022
Patients, n	1	2	1†	5	3	3	1	1	1	2	1
Age, years	12	6, 14	10	3, 5, 7, 13, 15	13, 15, 17	7, 17, 27	12	30	19	16, 17	56
Sex	M	M, F	M	4M, 1F	3F	3M	F	M	F	M, F	M
Ethnicity	Bahraini	Turkish	Saudi	4 Saudi, 1 Tunisian	Arab	Syrian	Indian	Iranian	Indian	NR	Japanese
Consanguinity	+	+	+	+	+	+	-	NR	+	NR	-
homozygous PTRH2 variant	c.370del p.(Glu124Lysfs*4)	c.269_270delCT p.Ala90Glyfs*13	c.254A>C p.Q85P	c.254A>C p.Q85P	c.254A>C p.Q85P	c.324G>A p.W108*	c.127dupA, p.Ser43LysfsTer11	c.68 T > C, p.Val23Ala	c.328G>T; p.Glu110* (+ KIF1A c.223C > T, p.Arg75Trp, heterozygous)	c.127dupA, p.(Ser43Lysfs*11	c.280 T > A, p.Tyr94Asn,
Neurologic											
Motor/speech delay	+	+	+	+	+	+	-	+	+	+	-
SNHL	+	+	+	+	+	+ (1/3)	+	-	+	+	+
Intellectual disability	+	+	+	+ (4/5) NR (1/5)	-	+	+	-	+	+	+
Post-natal microcephaly	-	+	NR	-	+	+	-	NR	-	+	NR
Hypotonia	+	+	+	+ (1/5)	+	+ (2/3)	-	NR	+	NR	NR
Distal muscle weakness	+	+	NR	+ (3/5)	+	+ (2/3)	-	-	+	NR	+
Ataxia	+	+	+	+ (4/5)	-	+	-	NR	+	+	+
Cerebellar hypoplasia/ atrophy	-	+	NR	+ (1/5)	-	+ (2/3)	-	NR	+	NR	+
Peripheral neuropathy	+	+	NR	+ (1/5)	+	+ (1/3)	+	-	+	+	+
Facial palsy	-	+	NR	+ (2/5)	NR	NR	NR	-	-	NR	NR
Abnormal gait	+	-	NR	NR	+	+ (2/3)	NR	+	+	NR	+
Seizures	-	-	NR	NR	NR	+	-	+	+ one episode	NR	NR
EEG abnormality	Not done	+	NR	- (1/5) NR (4/5)	NR	+ (2/3)	NR	NR	-	NR	NR

Table 1: Clinical features and genetic variants of 20 patients with IMNEPD published worldwide.

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Category	Our case	Hu et al.[1] 2014	Alazami et al.[8] 2015	Picker-Minh et al.[6] 2016	Sharkia et al.[3] 2017	Le et al.[9] 2019	Parida et al.[10] 2021	Khamirani et al.[11] 2021	Charles et al.[12] 2021	Becker et al.[13] 2021	Ando et al.[14] 2022
Face											
Dysmorphic features	+	+	-	+ (3/5)	NR	+ (2/3)	-	-	-	NR	+
Myopia	-	NR	NR	NR	+	NR	NR	+	-	NR	NR
Endocrine											
Diabetes mellitus	+	+	NR	+ (1/5)	NR	+ (2/3)	+	NR	+	+ (1/2)	-
Hypothyroidism	-	+	-	-	-	-	-	NR	-	+ (1/2)	+
Delayed menarche	NA	NR	NA	NR (1/5) NA (4/5)	+	NA	-	NA	+	NR	NA
Abdomen											
Exocrine pancreatic insufficiency	+	+	NR	+ (3/5) NR (2/5)	-	+ (2/3)	-	-	+	+ (1/2)	-
Abnormal pancreas imaging	Not visualized	+ (1/2)	NR	+ (1/5)	NR	NR	-	NR	+	+ (1/2)	+
Hepatomegaly	-	+ (1/2)	NR	+ (1/5)	NR	-	-	-	NR	NR	-
Abnormal liver imaging	+	+	NR	+ (1/5)	-	NR	-	NR	+	NR	-
Genitourinary											
Undescended testes or shawl scrotum	+ undescended testes	+ (1/2) Shawl scrotum	+ Undescended testes	- Shawl scrotum (3/5) NR (2/5)	NA	+ (1/3) Undescended testes	NA	NR	NA	NR	NR
Skeletal											
Hand deformity	-	+ (2/2)	NR	+ (3/5)	-	+ (1/3)	-	-	-	+	+
Foot deformity	-	+ (1/2)	+	+ (4/5)	+ (1/3)	+ (1/3)	-	+	+	NR	+
Other	-	+ (1/2) Congenital hip dislocation	NR	NR	NR	+ (1/3) seronegative spondyloarthropathy	NR	NR	+ Scoliosis	-	-

+: present; -: not present; NR: not reported; NA: not applicable; SNHL: sensorineural hearing loss; EEG: electroencephalogram. †This child is one of the five patients reported by Picker-Minh et al.[6]

worldwide. Our patient shared most of the clinical characteristics of the previously reported patients [Table 1].[1,3,6,8–14] Of the 19 patients, 12 (63.1%) were males. The majority were children or adolescents (n = 16, 84.2%).

The proband's history revealed placental insufficiency, reduced fetal movement, and suspected birth asphyxia. Similarly, a case with birth hypoxia,[9] and another case with a history of reduced fetal movement have been reported.[1]

Figure 3 shows the clinical features reported in IMNEPD patients, including our patient.[1,3,6,8–14] Subtle facial dysmorphism was noticed in our patient but no signs of skeletal deformity except for short stature at age 13. Several features of facial dysmorphism were described, including midface hypoplasia, hypertelorism, exotropia, and thin upper lip vermilion.[1] Hands and feet are commonly affected, with features including proximal placement of thumbs, long fingers, ulnar deviation of the second and third fingers, abnormality of the hallux talipes, equinovalgus, and Achilles tendon contracture.[1,6] Other features include congenital hip dislocation, seronegative spondyloarthropathy, and scoliosis.[1,10,12] Our case was negative for postnatal microcephaly, yet microcephaly became prominent on follow-up. Microcephaly was also reported by other studies.[1,3,9,13] Hu et al,[1] found skeletal muscle fibrosis on the US in one patient, while Ando et al,[14] described another patient with nonspecific changes of left biceps muscle biopsy. These investigations were not performed in our patient.

Neurological features in our patient included speech and motor delay, SNHL, and ID. ID was variable among reported cases.[1,3,6] Ataxia, abnormal gait, distal muscle weakness, and hypotonia were frequently reported. Our patient had hypotonia and a broad-based gait with high steppage. After the foot trauma, he walked on inverted foot with waddling, foot drop, and muscle dystrophy. This indicated peripheral neuropathy. Similarly, Charles et al,[12] reported one patient with a broad-based gait.Le et al,[9] described two brothers, one with a broad-based gait with high steppage and the other with the same gait with mild truncal ataxia and hip girdle weakness. Sharkia et al,[3] described three sisters with gait instability. Ando et al,[14] reported a case with gait instability at 50 years, making him the only recorded adult-onset gait abnormality.

Progressive cerebellar hypoplasia/atrophy was identified in seven patients.[1,6,9,12,14] Moreover, sensorimotor or sensorineural demyelinating polyneuropathy and facial palsy were identified in

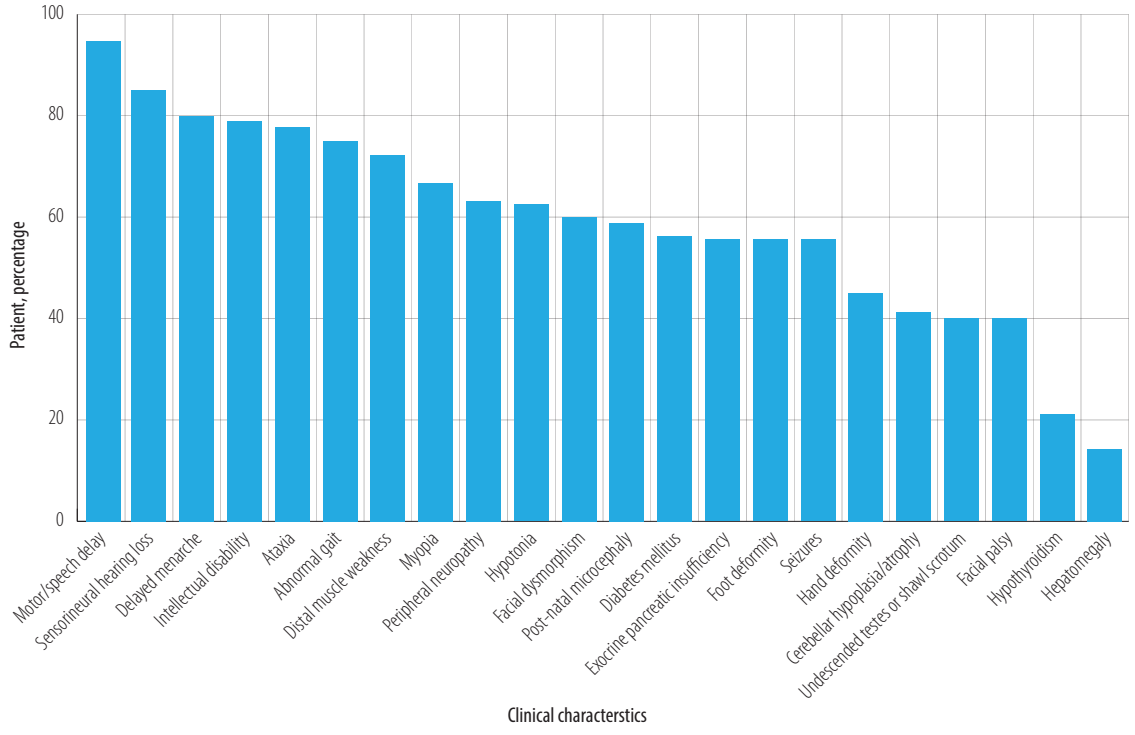

Figure 3: Clinical features in patients with infantile-onset multisystem neurologic, endocrine, and pancreatic disease.

Table 2: Differential diagnoses of infantile-onset multisystem neurologic, endocrine, and pancreatic disease and their distinguishing features.

Differential diagnoses	Distinguishing features
Johanson-Blizzard syndrome	Facial dysmorphism, urogenital defects
SSMED, Pearson syndrome, Cockayne syndrome, MELAS	Photosensitivity/dry skin
Pearson syndrome, Johanson-Blizzard syndrome	Blood count or bone marrow abnormalities
Pearson syndrome, MELAS	Metabolic acidosis
MELAS	Encephalopathy
SSMED	Thin corpus collosum and wide cerebral ventricles

SSMED: syndrome of short stature, microcephaly, and endocrine dysfunction; MELAS: mitochondrial acidosis, encephalopathy, lactate acidosis, and stroke.

10 and four patients, respectively.[6,9,10,12,14] Unlike our case, five reported patients developed seizures, and some had electroencephalogram abnormalities.[9,11,12]

EPI was the most common GI manifestation reported [Figure 3], which was demonstrated in our case. Additionally, hyperechogenic pancreas was identified on the US in four patients with EPI. Fatty liver and hepatomegaly were detected in three and two of those patients, respectively.[1,6,12] In our case, fatty liver was found at age two, yet repeated US showed normal liver echogenicity at age 11.

The proband was diagnosed with type 1 diabetes mellitus at age 11 which was an early diagnosis compared to other cases.[1,6,9–12] Delayed menarche has been reported in the majority of female patients.[3,6,10,12] Endocrine involvement can include hypothyroidism.[1,14]

Undescended testis was detected in two patients, while shawl scrotum was detected in four others.[1,6,8,9] Urolithiasis was reported in one case.[11]

Multi-organ involvement necessitates a wide range of differential diagnoses.[9] cystic fibrosis was the primary differential diagnosis in our case. Syndrome of short stature, microcephaly, and endocrine dysfunction is another.[6] It comprises of microcephaly that develops prenatally, ataxia, endocrine dysfunction, and cerebral atrophy.[6] Pearson syndrome, Cockayne syndrome, Johanson-Blizzard syndrome, and Mitochondrial acidosis, Encephalopathy, Lactate Acidosis, and Stroke (MELAS) may present with SNHL, ataxia, endocrine abnormalities, and liver and/or pancreas involvement.[6] In adolescents with type 1 and late-onset diabetes mellitus, congenital rubella syndrome can be considered.[10] Developmental delay, microcephaly, and SNHL can be also found in those patients.[10] Furthermore, IMNEPD can overlap with progressive myoclonic epilepsies, spinocerebellar ataxias, or metabolic disorders.[9] Table 2 elaborates distinguishing features of some syndromes.[6]

The diagnosis of our patient was confirmed by genetic testing via the presence of a frameshift PTRH2 mutation. PTRH2 encodes a 179-residue mitochondrial protein which comprises a mitochondrial domain (amino acids 1–61) and a catalytic hydrolase domain (amino acids 63–179).[4] Nonsense and frameshift mutations in PTRH2 produce a more severe phenotype compared to missense mutations where PTRH2 function is more preserved.[3,6,9] Additionally, the same mutation of PTRH2 can have variable phenotype, suggesting variable expressivity.[9] Our patient demonstrates a previously unreported novel nonsense mutation of PTRH2 (NM_001015509.2: c.370del p.(Glu124Lysfs*4)). This is the first IMNEPD case reported from Bahrain. Considering the high rate of consanguineous marriage in Bahrain and the surrounding region, prenatal diagnosis to detect genetic variants of such diseases is important.

CONCLUSION

IMNEPD has a wide phenotypic spectrum owing to the multi-systemic involvement, which makes the diagnosis challenging. Further research to understand the disease pathogenesis and presentations, and to explore treatment options is needed.

Disclosure

The authors declared no conflicts of interest. Informed consent was obtained from the patient's mother.

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