

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

Hasan M. Isa^{1*}, Sara D. Khalaf¹, Sara Janahi², Mohammed M. Nasser³, Noor AlHamad², Hasan
Alhaddar¹, Maryam Busehail⁴

¹Pediatric Department, Salmaniya Medical Complex, Arabian Gulf University, Manama, Bahrain

²Arabian Gulf University, Manama, Bahrain

³Cairo university, Cairo, Egypt

⁴Genetic specialist, Salmaniya medical complex, Manama, Bahrain

Received: 17 October 2022

Accepted: 29 December 2022

**Corresponding author: halfaraj@hotmail.com*

DOI 10.5001/omj.2024.08

Abstract

Infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD) is an exceedingly 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 are reporting 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 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.

Keywords: child; intellectual disability; sensorineural hearing loss; diabetes; exocrine pancreatic insufficiency; novel mutation

Infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD) is a rare autosomal recessive mitochondrial disorder which was 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 regulation of cell function, including cell survival and anoikis, stress resistance, and muscle differentiation^{3,4,5} Loss of PTRH2 function in human development leads to loss of pro-survival signals, resulting in IMNEPD.^{4,5}

IMNEPD is a multisystemic disorder with variable phenotypes. The clinical manifestations of this disorder include intellectual disability, global developmental delay (GDD) including motor and severe speech delay, ataxia, sensorineural hearing loss, progressive cerebellar hypotrophy or

atrophy, peripheral sensorimotor neuropathy, hypothyroidism, diabetes mellitus, exocrine pancreatic insufficiency, and liver dysfunction.^{4,6}

Multiple laboratory investigations are required to investigate a case suspected of IMNEPD, but confirmation of diagnosis is by genetic testing.⁶ Management of this condition is mainly supportive as there is no definitive treatment until now.⁶

Herein, we report a child with a novel mutation of PTRH2 born to a consanguineous Bahraini family. The core clinical features of the disorder are well-represented in this patient, which will be elaborated on in this report.

Case report

This is a 12-year-old Bahraini male with a significant antenatal history of placental insufficiency, intrauterine growth restriction (IUGR), and reduced fetal movements which resulted in an induced, vacuum-assisted vaginal delivery at term. Birth asphyxia was suspected during his birth. His APGAR score was 8, 9, and 10 at 1, 5, and 10 minutes, respectively. His birth weight was 2.3 kg (3rd centile) and head circumference was 31 cm (3rd centile). The family history was positive for consanguinity, as the parents are first-degree cousins (Figure 1). Neonatal screening was positive for glucose-6-phosphate dehydrogenase deficiency and alpha thalassemia trait. The proband was admitted to the neonatal intensive care unit (NICU) for one week as he had transient tachypnea of newborn. He was also found to have stridor due to laryngomalacia and right undescended testis.

Three weeks later, the proband was readmitted with acute bronchiolitis and subclinical hypothyroidism for 15 days including two days in the pediatric intensive care unit (PICU). Re-examination of his genitalia confirmed that the right testis was still at the neck of scrotum. Neurological and cardiac examinations performed at that time were unremarkable.

At two months of age, the patient developed constipation which became chronic. His stool was described as smelly, yellowish, full of mucus, and hard in consistency. At four months of age, he was admitted again to PICU with difficulty breathing, wheezing and intermittent productive cough. Additionally, he had a two-week history of recurrent non-bloody, and non-bilious vomiting. His feeding was normal, and his weight was 5.5 kg. Cystic fibrosis (CF) was suspected due to his recurrent respiratory infections, abnormal bowel habitus, and a family history of CF (Figure 1). Sweat chloride test was done which was normal (28 mmol/L, normal range: 5-35). Stool microscopy was negative for fat globules and tryptic activity was normal. Consequently, the patient was managed as acute bronchiolitis/acute exacerbation of bronchial asthma. Barium meal study for his recurrent vomiting showed a moderate spontaneous gastroesophageal reflux (GER), but no structural abnormality of the esophagus or hiatal hernia. On discharge, the patient was prescribed domperidone, cimetidine and lactulose for reflux and constipation as well as regular budesonide twice daily and salbutamol when needed as treatment for bronchial asthma. Cow's milk protein allergy was also suspected. Thus, amino acid-based hypoallergenic formula (EleCare) was started for the child along with dietary advice to the mother to avoid dairy products while breastfeeding. The patient's constipation improved, and his weight increased by 1.2 kg over a period of two months. However, he was still vomiting up to two times daily and he had excessive salivation.

At eight months of age, the child was referred to pediatric neurologist for developmental delay. He was also not responding normally to sounds and commands. Neurological examination was positive for hypotonia and suspicion of familial small head as his brother had a head circumference of 45 centimeters at two years of age. The patient's thyroid stimulating hormone was high (11 μ IU/mL, normal range: 0.25-5.0). On re-evaluation at one year of age, the child could stand only with support and sitting was recent. He could reach for and transfer objects as well as babble, but still could not crawl, cruise, or speak. Magnetic resonance imaging (MRI) of the brain was normal. The child was referred to a hearing clinic for speech and hearing difficulties, along with a positive family history of hearing loss (Figure 1). On follow-up, bilateral sensorineural hearing loss was confirmed by pediatric otorhinolaryngologist, predominantly on the right side. The patient was also diagnosed with adenoid hypertrophy and bilateral otitis media with effusion, for which he underwent adenoidectomy and bilateral myringotomy at around two years of age. Right cochlear implant surgery was done later in the same year and hearing aids were provided. Despite this, the patient remained nonverbal.

The proband also developed oily, offensive smelling stool, which was copious in amount. His vomiting was controlled but his weight gain remained slow (9.2 kg) and his abdomen became distended. He had started taking family diet, and dairy products were re-introduced. Repeated sweat chloride test increased to 46 mmol/L but his stool was positive for fat globules. Celiac serology showed normal tissue transglutaminase (tTG) and high antigliadin (AGA) IgA 10.7 U/ml and IgG 70.7 U/ml (normal: <10). Upper gastrointestinal (GI) endoscopy showed severe ulcerative esophagitis. There was a narrow segment between the first and second part of the duodenum and unhealthy duodenal mucosa. Histopathology revealed severe chronic esophagitis and normal duodenal mucosa. Gastroesophageal reflux disease (GERD) was confirmed, and omeprazole 10

mg daily was started. Additionally, abdominal ultrasound showed fatty liver while barium meal revealed moderate GER again but with sliding hiatal hernia. Sweat chloride test decreased to 35 mmol/L.

At three years of age, a targeted familial mutation analysis based on positive family history in the cousin for cystic fibrosis transmembrane conductance regulator (CFTR) gene was done but the specific deletion mutation (c.1911delG; p.Q637HfsX26, in exon 14 of CFTR gene) was not detected. The child was still having steatorrhea and on-off vomiting, so a trial of pancreatic enzymes supplementation along with aqueous fat-soluble vitamins (A, D, E and K) was given. In the same year, both testes were descended with normal cords. The child had poor adherence to his asthma medication. Budesonide dose was reduced to once daily and eventually stopped by his mother at around the age of four years.

The patient lost follow up for several years after that. During that time, he was managed in primary care for a cut wound injury and recurrent upper respiratory tract infections (URTIs). At the age of seven years, he had a visit to a dentist for recurrent dental carries. At eight years of age, he was admitted to the hospital for an unwitnessed fall from a height. Abdominal and pelvic ultrasound was performed to rule out any intraabdominal injury, but it was unremarkable.

At 11 years of age, the child presented to the emergency room with polyuria, polydipsia, weight loss and abdominal pain of one month duration. Random glucose test was high (35.4 mmol/L, normal: 3.6-8.9). On examination, he was thin, afebrile, but dehydrated. Abdomen was soft and non-tender. The patient was diagnosed with type 1 diabetes mellitus with diabetic ketoacidosis which was managed with rehydration and insulin infusion. Following this episode, he was started on regular insulin (0.6 IU/kg). Repeated sweat chloride test was 53 mmol/L and stool fat globules

were not seen. The patient also had low vitamin D level (25 nmol/L, normal: >50) and iron deficiency anemia. Repeated thyroid function tests were normal.

Following this episode, the child was referred back to the pediatric gastroenterologist due to persistent wasting, stunting, and chronic steatorrhea. On examination, he was pale, with subtle facial features with down slanting palpebral fissure, microcephaly, finger clubbing, and his abdomen was massively distended with gases (Figure 2.). He had an unstable, broad-based gait with a high steppage. Pancreatic enzymes supplementation along with fat soluble vitamins were restarted. Repeated celiac serology showed AGA IgA 7 U/ml and IgG 26 U/mL, tTG IgA 110 U/ml (normal: <10 for all), equivocal anti-endomysial antibody (EMA), and normal IgA levels. Repeated upper GI endoscopy showed longitudinal esophageal ulcer and shiny, unhealthy-looking duodenal mucosa. There was no evidence of duodenal stenosis. Histopathology showed a maintained villous architecture, mild to moderate chronic inflammation in lamina propria and submucosal Brunner's glands which was compatible with mild acute esophagitis, mild chronic non-specific gastritis (antrum) and mild chronic duodenitis. Whole exome sequencing (WES) test identified a homozygous mutation (NM_001015509.2: c.370del p.(Glu124Lysfs*4)) in PTRH2 gene. The PTRH2 variant c.370del p.(Glu124Lysfs*4) creates a shift in the reading frame starting at codon 124. This consistent with autosomal recessive infantile-onset multisystem neurologic, endocrine, and pancreatic disease type 1. According to American college of medical genetics and genomics (ACMG) guidelines, the identified mutation is classified as variant of uncertain significance (VUS). In addition, WES detected a heterozygous mutation in HBA1 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 G6PD or CFTR 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 not relevant to the patient's provided 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 parented were counselled and tested to confirm the carrier status especially that both were lacking any clinical symptoms and signs indicating the disease (the results are still pending).

At 12 years of age, he developed an oral abscess that was managed with Augmentin for five days. Later that year, he presented with right foot pain of one-month duration, which was preceded by trauma to the foot by hitting a table accidentally. There was no swelling, but the patient was observed walking with inverted foot. Fracture of the metatarsal bone was suspected. Two days later, he developed hip pain that was exacerbated by flexion following a recent history of URTI. Right hip was warm but there was no effusion, and the range of motion was normal. Follow up with orthopedic team revealed waddling, foot drop, distal muscle weakness, and normal joints. Muscular dystrophy was suspected, and the patient was managed with physiotherapy. The patient is currently followed by a multi-disciplinary team along with supportive care. His last weight is 21.5 kg, height is 127 cm, and head circumference is 50 cm (all <1st centile) indicating the presence of sever thinness, short stature and microcephaly.

Table 1: Clinical features and genetic variants of 20 patients with infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD) published worldwide including the present case.

Category	The present 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 2020	Khamira ni et al. ¹¹ 2021	Bronson 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 (y)	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	c.370del	c.269_270del	c.254A>C	c.254A>C	c.254A>C	c.324G>A	c.127dupA,	c.68 T >	c.328G>T;	c.127dupA,	c.280 T >
PTRH2 variant	p.(Glu124Lysfs s*4)	CT p.Ala90Glyfs *13	p.Q85P	p.Q85P	p.Q85P	p.W108*	p.Ser43LysfsTe r11	C, p.Val23Ala	p.Glu110* (+ KIF1A c.223C > T, p.Arg75Trp, heterozygous)	p.(Ser43Lysfs*11	A, p.Tyr94Asn
Neurologic											
Motor/speech delay	+	+	+	+	+	+	-	+	+	+	-
SNHL	+	+	+	+	+	+	+	-	+	+	+
Intellectual disability	+	+	+	+	+	+	+	-	+	+	+
				(4/5) NR (1/5)	-	+					
Post-natal microcephaly	-	+	NR	-	+	+	-	NR	-	+	NR

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	+	- Shawl Undescended testes	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)	NR	NR	NR	+ (1/3)	NR	NR	+ Scoliosis	-	-
		Congenital hip dislocation				seronegative spondyloarthropathy					

+: present; -: not present; NR: not reported; NA: not applicable; SNHL: sensorineural hearing loss.

†This child is one of the five patients reported by Picker-Minh et al.

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.

Discussion

IMNEPD is a very rare disease with a prevalence of $<1/1,000,000$ (ORPHA:456312).⁷ On an extensive literature search, hardly a total of 19 patients with IMNEPD were reported worldwide. In terms of clinical presentation, our patient shared most of the clinical characteristics of the previously reported patients such as the presence of motor and speech delay, sensorineural hearing loss, hypotonia, distal muscle weakness, diabetes mellitus and exocrine pancreatic insufficiency. Despite that our patient did not have postnatal microcephaly or any skeletal deformities, microcephaly became more prominent on follow up. Moreover, hypothyroidism was not found in most of the reported case including the proband case. A summary of the previously reported cases is shown in Table 1.^{1,3,6,8-14} Reported cases of IMNEPD were mainly of Middle eastern, West Asian, and South Asian origin, with only a single case from East Asia (Japan). Despite the autosomal recessive inheritance of IMNEPD, our review revealed male predominance and our patient is a male.² Out of the 19 patients, 11 (57.9%) were males while only eight (42.1%) were females. This might indicate an alternative mode of inheritance. As for the age distribution of patients, majority were children or adolescents (n= 15, 79%), while adults comprised 21% (n= 4) of the cases.

In this report, the proband's prenatal and birth history revealed placental insufficiency, IUGR, reduced fetal movement and suspected birth asphyxia. Similarly, Le et al. reported a single case with history of birth hypoxia.⁹ Hu et al. likewise reported another case with a prenatal history of reduced fetal movement.¹ However, there is no established connection between IMNEPD and any of these events in terms of causation.

Clinical features reported in patients with IMNEPD, including our patient, are detailed in Figure 3.^{1,3,6,8-14} Subtle facial dysmorphism was noticed in our patient. Several features of facial dysmorphism have been described, including midface hypoplasia, hypertelorism, exotropia, and thin upper lip vermilion.¹ Signs of skeletal deformity were not apparent in our patient, but their association with IMNEPD is well-documented. Short stature was observed in our patient at 13 years of age (130 cm, <3rd centile). Hands and feet are most commonly affected, with features including proximal placement of thumbs, long fingers, ulnar deviation of the 2nd and 3rd fingers, abnormality of the hallux talipes, equinovalgus, and achilles tendon contracture.^{1,6} Less common types of skeletal involvement are congenital bilateral hip dislocation, seronegative spondyloarthropathy and scoliosis of the vertebral column, each of which was only reported once.^{1,10,12} Muscular changes were also described in some reports. Hu et al. found skeletal muscle fibrosis on ultrasound in one patient, while Ando et al. described another patient whose left biceps muscle biopsy showed nonspecific changes, including small number of ragged red fibers and cytochrome c oxidase-deficient fibers.^{1,14} These investigations were not performed in our patient.

Delayed speech and motor development, sensorineural hearing impairment and intellectual disability were the most prominent neurological features present in our patient. This is supported by the literature, as these were the most common clinical features associated IMNEPD (Figure 3). Intellectual disability in IMNEPD is variable. For instance, three patients reported by Sharkia et al. had normal intelligence, while five patients reported by Picker-Minh et al. and two patients reported by Hu et al. had moderate to severe intellectual disabilities, with intelligence quotients ranging from 39 to 70.^{1,3,6} Ataxia, abnormal gait, distal muscle weakness and hypotonia were also frequently reported. Ataxia has been described both with and without cerebellar atrophy and could therefore also be attributed to the demyelinating peripheral neuropathy.⁶ Our patient had hypotonia

and an unstable, broad based gait with a high steppage. After the trauma sustained to his foot, he was observed walking on inverted foot with waddling and foot drop. Distal muscle weakness was also noted. The term peripheral neuropathy was not documented, but the examination findings could indicate its presence in our patient. Similarly, Bronson et al. reported one patient with a broad-based gait.¹² Le et al. likewise described two brothers, one with a broad-based gait with high steppage, and the other also with a broad-based gait with mild truncal ataxia and hip girdle weakness.⁹ Sharkia et al. described three sisters with gait instability.³ Interestingly, Ando et al. reported a 56-year-old male whose gait instability first presented when he was 50 years of age, making him the only recorded IMNEPD case with an adult-onset gait abnormality.¹⁴

Although our patient had no brain anomalies at one year of age, progressive cerebellar hypoplasia/atrophy was identified in seven previously reported patients.^{1,6,9,12,14} Moreover, sensorimotor or sensorineural demyelinating polyneuropathy and facial palsy were identified in ten and four patients, respectively.^{6,9,10,12,14} Unlike our case, five reported patients developed seizures and some had electroencephalography (EEG) abnormalities.^{9,11,12} Hu et al. reported two patients with alpha-beta-waves detected on their EEGs, even in sleep.¹ Two more patients reported by Le et al. demonstrated background slowing and increased asynchronous delta activity on EEG, which is consistent with diffuse encephalopathy without epileptiform activity.⁹

Exocrine pancreatic insufficiency (EPI) is the most common gastrointestinal manifestation reported in patients with IMNEPD (Figure 3). This is also demonstrated in our case, as EPI became evident when the proband presented with steatorrhea. Additionally, hyperechogenic pancreas was identified in abdominal ultrasound of four reported patients with EPI. Hu et al, Picker-minh et al., and Bronson et al. attributed this finding to pancreatic lipomatosis, which later progressed to pancreatic atrophy in a single patient.^{1,6,12} Fatty liver and hepatomegaly were also detected in three

and two of those patients, respectively.^{1,6,12} In our case, fatty liver was found on abdominal ultrasound at two years of age. However, repeated imaging at 11 years of age showed normal liver echogenicity.

The proband was diagnosed with type 1 diabetes at 11 years of age, after he presented with features of diabetes ketoacidosis. This is an unusually early diagnosis compared to other diabetic patients with IMNEPD, who are usually diagnosed either during adolescence or in early adulthood.^{1,6,9,10-12} Delayed menarche has also been reported in majority of female patients with IMNEPD.^{3,6,10,12} Least commonly, endocrine involvement of IMNEPD can include hypothyroidism.^{1,14}

Urogenital involvement in IMNEPD is minimal and mostly restricted to abnormality of the male genitalia. Undescended testis was detected in two patients, like our patient, while small scrotum was detected in four others.^{1,6,8,9} Urolithiasis was additionally reported in a single case.¹¹

The multi-organ involvement and variable manifestations of IMNEPD necessitate a wide range of differential diagnoses.⁹ As demonstrated in our case; CF was the primary differential diagnosis. This is due to the signs and symptoms that he portrayed, which included recurrent respiratory infections, abdominal distention with persistent steatorrhea, intellectual disability, developmental delay, hearing impairment, and a diagnosis of type 1 diabetes. Sweat chloride test, stool tryptic activity and genetic testing were used to definitively exclude CF as a possibility. Another differential diagnosis which closely resembles IMNEPD is the Syndrome of short stature, microcephaly, and endocrine dysfunction (SSMED).⁶ The features of this syndrome comprise of microcephaly, ataxia, endocrine dysfunction, and sporadically cerebral atrophy. In contrast to IMNEPD, the microcephaly in SSMED develops prenatally.⁶ Similar to IMNEPD, Pearson syndrome, Cockayne syndrome, Johanson-Blizzard syndrome, and Mitochondrial acidosis,

encephalopathy, lactate acidosis, and stroke (MELAS) may present with sensorineural hearing loss, ataxia, endocrine abnormalities and liver and/or pancreas involvement in variable combinations.⁶ In adolescents with intellectual disability and late-onset diabetes mellitus, congenital rubella syndrome should also be considered.¹⁰ Developmental delay, microcephaly, and sensorineural hearing loss can be found in those patients as well.¹⁰ Furthermore, IMNEPD's neurological manifestations can overlap with progressive myoclonic epilepsies, spinocerebellar ataxias, or specific metabolic disorders.⁹ Additional distinguishing features of some of these syndromes are elaborated on in Table 2.⁶

The diagnosis of our patient was confirmed by genetic testing via the presence of a frameshift PTRH2 mutation. PTRH2 encodes a 179-residues 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 also the first IMNEPD case reported from Bahrain. Considering the well-known high rate of culturally preferred consanguineous marriage in Bahrain and the other Arabian Gulf countries, prenatal diagnosis to detect genetic variants of such multisystemic disease is particularly important. It can help in making decisions about pregnancy continuation or abortion and can facilitate proper planning for future pregnancies on solid basis.

Conclusion

This study showed that IMNEPD is an exceedingly rare disorder with a wide phenotypic spectrum owing to the multi-systemic involvement. This makes the diagnosis of patients with this disorder challenging and late diagnosis is also expected. As no definitive treatment exists, multi-disciplinary care is necessary for the management of such patients. Further clinical and genetic research is needed to better understand the disease pathogenesis, clinical presentations, and outcome, and to explore innovative treatment options.

References

1. Hu H, Matter ML, Issa-Jahns L, Jijiwa M, Kraemer N, Musante L, et al. Mutations in PTRH2 cause novel infantile-onset multisystem disease with intellectual disability, microcephaly, progressive ataxia, and muscle weakness. *Ann Clin Transl Neurol*. 2014;1(12):1024-35. doi: 10.1002/acn3.149.
2. Kniffin CL, Vernon HJ., 2022. Entry - #616263 - Neurologic, endocrine, and pancreatic disease, multisystem, infantile-onset 1; IMNEPD1- OMIM. [online] OmiKHAMm.org. Available at: <<https://omim.org/entry/616263>> [Accessed 30 September 2022].
3. Sharkia R, Shalev SA, Zalan A, Marom-David M, Watemberg N, Urquhart JE, et al. Homozygous mutation in PTRH2 gene causes progressive sensorineural deafness and peripheral neuropathy. *Am J Med Genet A*. 2017;173(4):1051-5. doi: 10.1002/ajmg.a.38140.
4. Corpuz AD, Ramos JW, Matter ML. PTRH2: an adhesion regulated molecular switch at the nexus of life, death, and differentiation. *Cell Death Discov*. 2020;6(1):1-1. doi: [10.1038/s41420-020-00357-0](https://doi.org/10.1038/s41420-020-00357-0).
5. Doe J, Kaindl AM, Jijiwa M, de la Vega M, Hu H, Griffiths GS, et al. PTRH2 gene mutation causes progressive congenital skeletal muscle pathology. *Hum Mol Genet*. 2017;26(8):1458-64. doi: [10.1093/hmg/ddx048](https://doi.org/10.1093/hmg/ddx048).
6. Picker-Minh S, Mignot C, Doummar D, Hashem M, Fageih E, Josset P, et al. Phenotype variability of infantile-onset multisystem neurologic, endocrine, and pancreatic disease IMNEPD. *Orphanet J Rare Dis*. 2016;11(1):1-7. doi: [10.1038/s41439-021-00147-9](https://doi.org/10.1038/s41439-021-00147-9).
7. Orphanet: Infantile multisystem neurologic endocrine pancreatic disease (2022). [online] Orpha.net. Available at: <https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=456312> [Accessed 29 September 2022].

8. Alazami AM, Patel N, Shamseldin HE, Anazi S, Al-Dosari MS, Alzahrani F, et al. Accelerating novel candidate gene discovery in neurogenetic disorders via whole-exome sequencing of prescreened multiplex consanguineous families. *Cell Rep.* 2015;10(2):148-61. doi: 10.1016/j.celrep.2014.12.015.
9. Le C, Prasad AN, Rupar CA, Debicki D, Andrade A, Prasad C. Infantile-onset multisystem neurologic, endocrine, and pancreatic disease: case and review. *Canadian J Neurol Sci.* 2019;46(4):459-63. doi: 10.1017/cjn.2019.35.
10. Parida P, Dubbudu A, Biswal SR, Sharawat IK, Panda PK. Diabetes mellitus in an adolescent girl with intellectual disability caused by novel single base pair duplication in the PTRH2 gene: expanding the clinical spectrum of IMNEPD. *Brain Dev.* 2021;43(2):314-9. doi: 10.1016/j.braindev.2020.09.009
11. Khamirani HJ, Zoghi S, Dianatpour M, Jankhah A, Tabei SS, Mohammadi S, et al. A novel PTRH2 missense mutation causing IMNEPD: a case report. *Hum Genome Var.* 2021;8(1):1-4. doi:10.1038/s41439-021-00147-9.
12. Bronson SC, Suresh E, Kumar SS, Mythili C, Shanmugam A. A novel synergistic association of variants in PTRH2 and KIF1A relates to a syndrome of hereditary axonopathy, outer hair cell dysfunction, intellectual disability, pancreatic lipomatosis, diabetes, cerebellar atrophy, and vertebral artery hypoplasia. *Cureus.* 2021;13(2):e13174. doi: 10.7759/cureus.13174.
13. Becker M, Seneca S, Schierloh U, Witsch M, De Beaufort C, Scalais E. Diabetes in a child with infantile onset multisystem neurological, endocrine and pancreatic disease (IMNEPD). *Horm Res Paediatr.* 2021;6:94.

14. Ando M, Higuchi Y, Takeuchi M, Hashiguchi A, Takashima H. The first case of infantile-onset multisystem neurologic, endocrine, and pancreatic disease caused by novel PTRH2 mutation in Japan. *Neurol Sci.* 2022;43(3):2133-6. doi: 10.1007/s10072-021-05817-8.

Figure legend

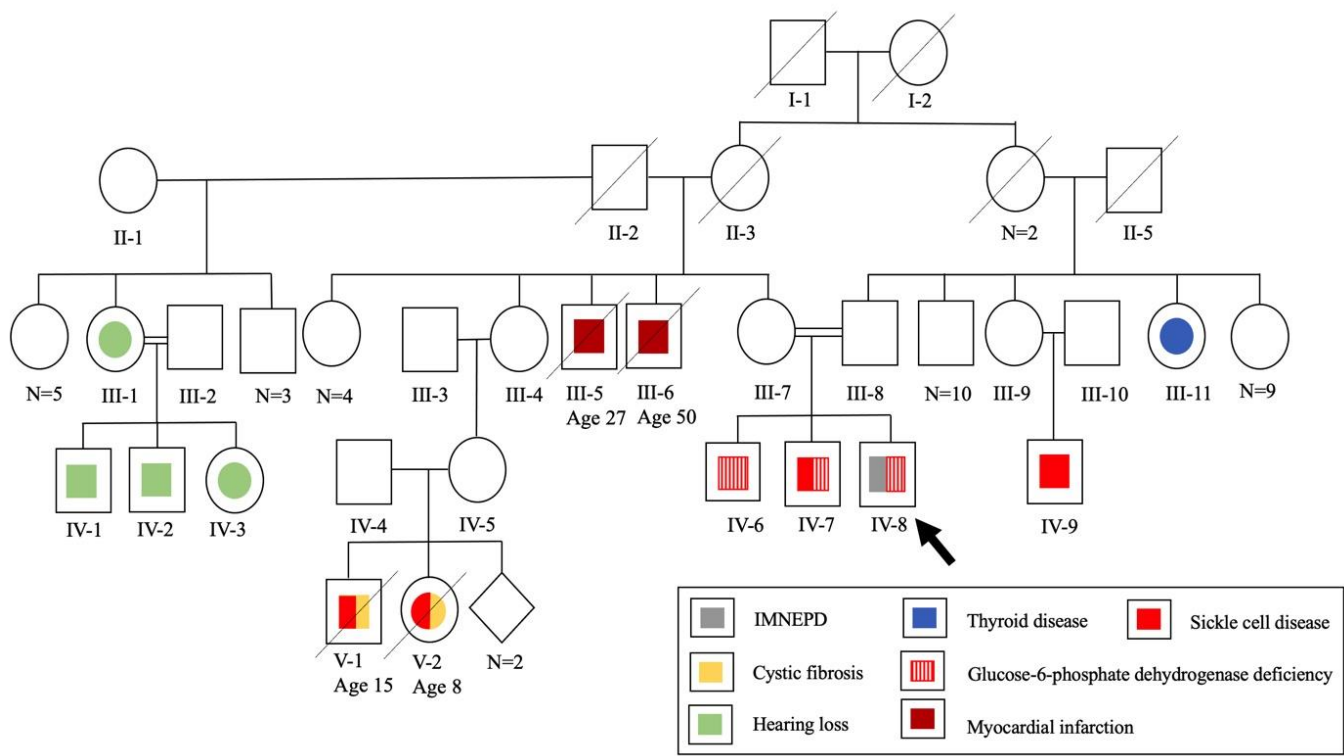


Figure 1. Family pedigree chart of patient with Infantile-onset multisystem neurologic, endocrine, and pancreatic disease.



Figure 2. Patient's photos showing (A and B) subtle facial features with down slanting palpebral fissure and microcephaly along with (C and D) abdominal distension.

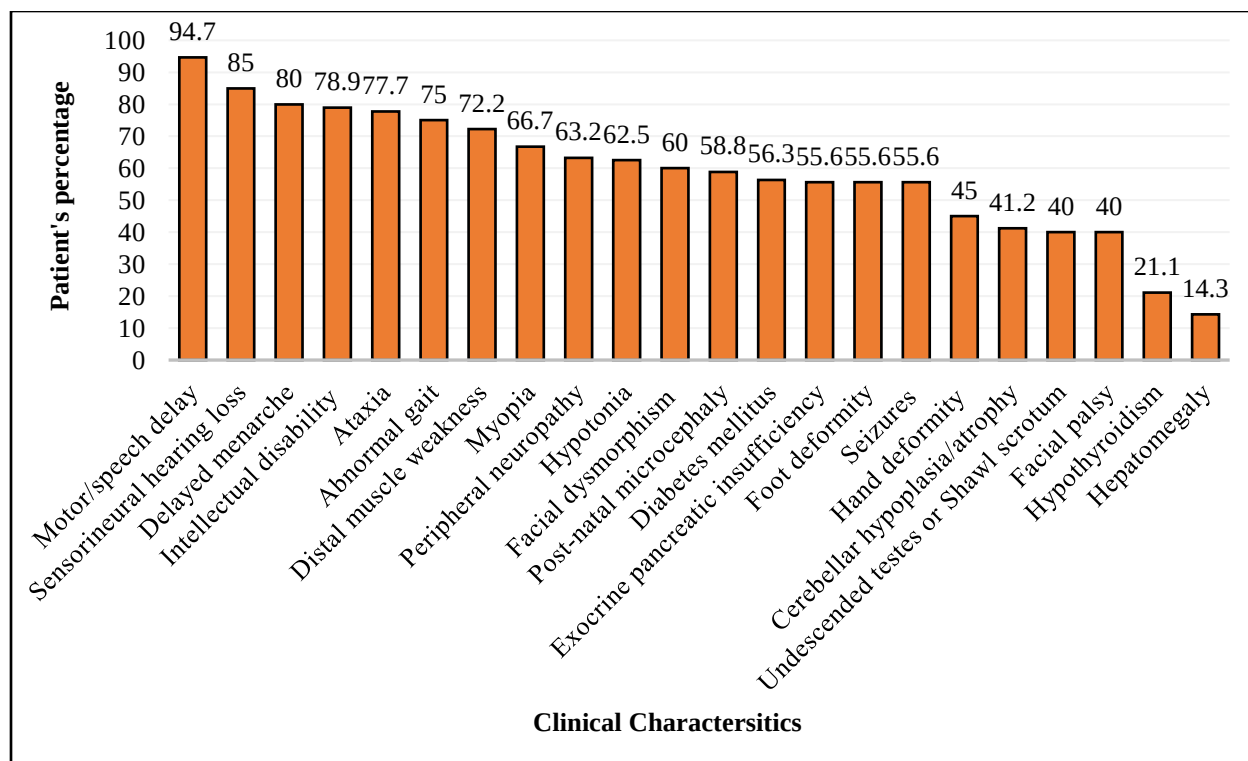


Figure 3. Clinical features in patients with infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD)