Diabetes in a child with infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD)

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INTRODUCTION

IMNEPD is a mitochondrial disease caused by homozygous mutations in the *PTRH2* gene, a nuclear gene coding for a primary mitochondrial protein (peptidyl-tRNA hydrolase 2).

IMNEPD was first described in 2014. So far only 7 other case reports have been published, reporting on a total of 13 patients.

DIABETES PRESENTATION

We report on two affected siblings of whom the girl developed an antibody negative diabetes at 13 years of age with typical symptoms (polyuria, polydipsia, weight loss of 1,5 kg), and without diabetic ketoacidosis, HbA1c 10,2%, glycaemia 240 mg/dl, c-peptide 1.7 ng/ml (1.1-4.4).

As the clinical examination revealed a severe psychomotor retardation (2 word sentences, unsteady walk at 13 years of age), a sensorineural hearing loss, a peripheral neuropathy (slowed SSEP) and coordination deficits as well, we performed genetic testing for mitochondrial diseases.

GENETIC RESULT

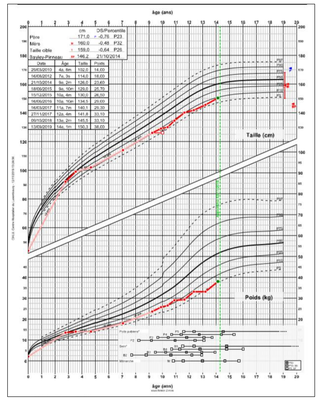
Genetic analysis showed a **new** homozygous frame shift variant (c.127dupA, p.(Ser43Lysfs*11) in the PTRH2 (NM_001015509.2) gene.

The same pathogenic variant was found in homoplasmy in her 2 years older brother, who suffered also from severe neurocognitive impairment, motor delay, sensorineural hearing loss, but has so far no diabetes. The clinically non affected parents are both heterozygous for this pathogenic variant.

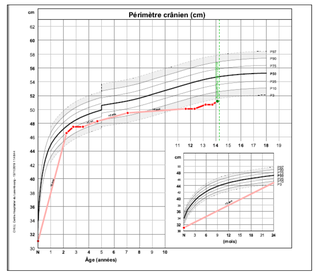
PHENOTYPE

Core clinical feature of IMNED:	Female patient	Male patient
- ***Postnatal microcephaly***	+	+
- ***Delayed speech and motor development with regression***	+	+
- ***Intellectual disability***	+	+
- ***Sensorineural hearing loss***	+	+
- ***Cerebrellar atrophy***	*MRI not possible due to cochlear transplant*	
- ***Ataxia***	+	+
- ***Peripheral sensorimotor neuropathy***	+	+
- ***Dysfuntction of pancreas (exocrine/Diabetes)***	Diabetes	exocrine
- ***Dysfunction of thyroid***	+	-
- Growth retardation	-	-
-Hand deformity	+	+

Hand deformity of the female patient with proximal placement of the thumb and ulnar deviation of the 2nd finger



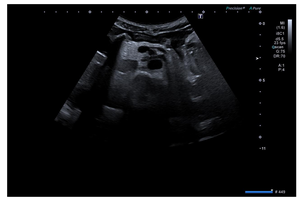
Growth and weight curve of the female patient reflecting her growth in the normal range and as well in the range of her midparental height



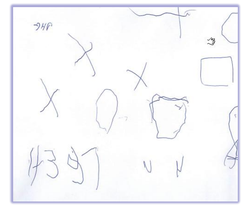
Headcircumference of the female patient showing a postnatal microcephaly

Female patient at the age of 16 years

Male patient at the age of 17 years



Ultrasound of the pancreas of the female patient showing a pancreas fibrosis



Symbols and numbers, drafted by the female patient at the age of 14 years

DIABETES TREATMENT

Basal insulin (Levemir 6 U in the morning, 4 U in the evening)

Freestyle libre 2

Last HbA1c 6,1%,

CONCLUSIONS

When auto antibody negative insulin dependent diabetes is diagnosed in an individual with neurocognitive impairment and hearing loss, patients should be tested for PTRH2 pathogenic variants, while affected IMNEPD patients should be monitored for diabetes on a regular basis.

CONTACT INFORMATION

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