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

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.

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