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Infantile-Onset Multisystem Neurologic, Endocrine, and Pancreatic Disease: Case and Review

Christine Le, Asuri N. Prasad, C. Anthony Rupar, Derek Deebicki, Andrea Andrade, Chitra Prasad

ABSTRACT: We report three brothers born to consanguineous parents of Syrian descent, with a homozygous novel c.324G>A (p.W108*) mutation in PTRH2 that encodes peptidyl-tRNA hydrolase 2, causing infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD). We describe the core clinical features of postnatal microcephaly, motor and language delay with regression, ataxia, and hearing loss. Additional features include epileptic seizures, pancreatic insufficiency, and peripheral neuropathy. Clinical phenotyping enabled a targeted approach to the investigation and identification of a novel homozygous nonsense mutation in PTRH2, c.324G>A (p.W108*). We compare our patients with those recently described and review the current literature for IMNEPD.


Keywords: Postnatal microcephaly, Neuroendocrinopathy, Developmental delay, Ataxia, Hearing loss and peripheral neuropathy

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Infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD) has recently been described.1,2 The index case involved two patients from a consanguineous family of Yazidian–Turkish descent with a homozygous nonsense mutation in PTRH2. The core clinical features include postnatal microcephaly, delayed speech and motor development with regression, intellectual disability, sensorineural hearing loss, progressive ataxia, cerebellar atrophy, peripheral sensorimotor neuropathy, and dys-function of the pancreas, thyroid, and liver of varying severity.1,2,3

Herein, we report three IMNEPD patients from a consanguineous family of Syrian descent. The three affected children (patient III-6, patient III-3, patient III-2; Figure 1) are from healthy parents who are first cousins. There are three unaffected children in the family who are 18 months, 23 years, and 26 years old (Figure 1).

Patient III-6 is 27 years old and is most severely affected. He had a hypoxic birth event. He first spoke at the age of 4, and regressed within 1 year to non-specific vocalizations. He lost independent ambulation at 14 months as he developed progressive truncal and limb ataxia. He has distal, more than proximal, weakness and is wheelchair-dependent. He has flexion contractures of his hands and feet, and high foot arches. At 7 years, he developed generalized tonic clonic and myoclonic seizures. He has postnatal microcephaly, mild bilateral ptosis, exotropia, mild facial dysmorphisms with hypertelorism, and a thin upper lip vermilion (Figure 2). He was diagnosed with insulin-dependent diabetes mellitus (IDDM) and microcytic anemia due to iron deficiency at age 18 and seronegative spondyloarthropathy at age 26.

Patient III-3 is 17 years old. He had an uncomplicated birth, but displayed postnatal microcephaly, motor and language regression at 1 year. He has progressive truncal and limb ataxia and a broad-based, high-steppage gait and requires a walker. He has a limited vocabulary of less than five words. He has mild bilateral ptosis, global symmetric hypotonia, hyporeflexia with distal muscle wasting that is more significant in the upper than lower extremities. He was diagnosed with IDDM at age 16 and has suspected myoclonic seizures.

Patient III-2 is 7 years old and has postnatal microcephaly with developmental regression. He acquired a limited vocabulary

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at the age of 2. He is treated with clonidine for hyperactivity. He could walk independently by the age of 3 and has a broad-based gait with mild truncal ataxia and hip girdle weakness with no muscle wasting. He is currently being investigated for nocturnal frontal lobe seizures and myoclonus. He has an undescended right testis. He does not have pancreatic dysfunction, thyroid, or liver disease.

Initial investigations for patient III-6 revealed an elevated random glucose 12 mmol/L (normal 3.4–11) but normal glycosylated hemoglobin, liver enzymes, and homocystine levels. Serum biotinidase assay, urine organic acids, plasma and urine amino acids, and serum cholesterol were all within normal limits, while X-linked adrenoleukodystrophy testing was excluded as the plasma very-long-chain fatty acids were normal. Hepatitis B and C serology was negative. A nerve conduction study was performed and revealed a sensorimotor axonal and demyelinating polyneuropathy. Electromyography was not consistent with a primary myopathy.

Cranial magnetic resonance imaging (MRI) revealed symmetrical, bilateral cerebellar atrophy in the two eldest affected patients (Figure 3). The brainstem, corpus callosum, and cerebral cortex were within normal limits. Cranial MRI in the youngest affected sibling was normal. Electroencephalograms (EEG) for patients III-2 and III-3 demonstrated background slowing with increased asynchronous delta activity consistent with diffuse encephalopathy without epileptiform activity.

The history of consanguinity suggested an autosomal recessive pattern of inheritance. In the context of middle eastern background, shared clinical features, and multisystemic involvement, a causative mutation in the mitochondrial protein PTRH2 was suspected. All exons of PTRH2 were PCR-amplified and sequenced bidirectionally. All three brothers had a homozygous nonsense mutation in PTRH2, c.324G>A (p.W108*). This G-to-A mutation results in a premature stop at codon p.108, truncating the protein by 71 amino acids and removing most of...
<table>
<thead>
<tr>
<th>Category</th>
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<tr>
<td>Age at last assessment</td>
<td>27</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Syrian</td>
<td>Syrian</td>
<td>Syrian</td>
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<tr>
<td>Birth</td>
<td>Hypoxia</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Growth</td>
<td>Postnatal growth regression (age at onset)</td>
<td>+ (14 m)</td>
<td>+ (12 m)</td>
</tr>
<tr>
<td>Head</td>
<td>Postnatal macrocephaly</td>
<td>+</td>
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<tr>
<td>Facial dysmorphism</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Hearing impairment</td>
<td>+</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Neurologic</td>
<td>Hypotonia</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Motor delay</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Distal predominant weakness</td>
<td>+</td>
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<tr>
<td>Intellectual delay</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Ataxia, limb ± truncal</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Cerebellar atrophy/hypoplasia</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Seizures (age at onset)</td>
<td>+</td>
<td>+</td>
<td>(2.5 y)</td>
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<tr>
<td>Skeletal</td>
<td>Hand deformity</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Feet deformity</td>
<td>+</td>
<td>–</td>
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</tr>
<tr>
<td>Other</td>
<td>+</td>
<td>–</td>
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<tr>
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<td>Hepatomegaly</td>
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<tr>
<td>Genitourinary</td>
<td>GU abnormality: undescended testicle*, shawl scrotum</td>
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<tr>
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<td>–</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>+</td>
<td>–</td>
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<tr>
<td>Delayed puberty</td>
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early recessive mitochondrial condition that affects the nervous system, musculoskeletal system, endocrine system, and gastrointestinal system. The inheritance pattern is autosomal recessive. Patients may have overlapping features with the Johanson–Blizzard syndrome and the mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. Mutations in the *PTRH2* gene on chromosome 17 are causative.
The authors have no conflicts of interest to declare.

All authors contributed equally to the manuscript.