Case Report

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Late diagnosis of the X-linked MCT8 deficiency (Allan–Herndon–Dudley syndrome) in a teenage girl with primary ovarian insufficiency

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Abstract

Objectives: To report an unusual case of MCT8 deficiency (Allan–Herndon–Dudley syndrome), an X-linked condition caused by pathogenic variants in the SLC16A2 gene. Defective transport of thyroid hormones (THs) in this condition leads to severe neurodevelopmental impairment in males, while heterozygous females are usually asymptomatic or have mild TH abnormalities.

Case presentation: A girl with profound developmental delay, epilepsy, primary amenorrhea, elevated T3, low T4 and free T4 levels was diagnosed with MCT8-deficiency at age 17 years, during evaluation for primary ovarian insufficiency (POI). Cytogenetic analysis demonstrated balanced t(X;16)(q13.2;q12.1) translocation with a breakpoint disrupting SLC16A2. X-chromosome inactivation studies revealed a skewed inactivation of the normal X chromosome.

Conclusions: MCT8-deficiency can manifest clinically and phenotypically in women with SLC16A2 aberrations when nonrandom X inactivation occurs, while lack of X chromosome integrity due to translocation can cause POI.

Keywords: Allan–Herndon–Dudley syndrome; MCT8 deficiency; SLC16A2 gene; X chromosome translocation

Introduction

MCT8 deficiency (formerly referred to as the Allan–Herndon–Dudley syndrome, OMIM#300095) is an X-linked disorder, characterized by profound infantile hypotonia, muscular hypoplasia, and severe intellectual disability [1]. It is caused by defects in the SLC16A2 (OMIM#300095) gene, mapped at Xq13.2, which encodes a monocarboxylate transporter 8 (MCT8) belonging to the Solute carrier 16 (SLC16) family of transporters. MCT8 is widely expressed in tissues such as the brain, choroid plexus, adrenal glands, kidney, heart, uterus, placenta, and thyroid [2]. As MCT8 is crucial for thyroid hormone transport across the blood–brain barrier and into the neurons during fetal and postnatal development, its deficiency or impaired function leads to intellectual disability and thyroid function abnormalities. MCT8-deficiency manifests fully in boys with SLC16A2 hemizygous pathogenic variants; however, affected girls with complete MCT8-deficiency phenotype with heterozygous single nucleotide variant (SNV) or gene deletions have been reported [3, 4]. Clinical manifestations in girls can vary depending on the inactivation status of the X chromosome containing a pathogenic variant relative to the X chromosome with a normal allele [5]. Affected females with skewed X inactivation, leading to a predominant or complete inactivation of the normal X chromosome, would be expected to manifest the full MCT8-deficiency phenotype, similar to male patients. We report a case of MCT8-deficiency in a girl with SLC16A2 gene disruption due to a balanced translocation t(X;16)(q13;q12.1), whose diagnosis was delayed to late adolescence. In addition to characteristic neurological abnormalities of the disease, she was also affected by POI, which has not been previously reported in female patients with MCT8 deficiency.

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Case report

We evaluated a 17-year-old Caucasian young woman with profound psychomotor retardation, cortical visual impairment, truncal hypotonia, spastic quadriplegia, mixed intractable epilepsy since 2 years of age, dystonia, scoliosis, and Magnetic Resonance Imaging (MRI) findings of delayed myelination. She presented with primary amenorrhea, delayed pubertal development, an elevated FSH of 54 IU/L (reference range [RR]: 0.64–11), high-normal LH of 10.2 IU/L (RR: 0.9–14.7), and low estradiol level of 13 pg/mL (48 pmol/L) (RR>34 pg/mL, >125 pmol/L), consistent with POI. Additional laboratory evaluations revealed low-normal serum concentrations of TSH (0.4 mIU/L, RR: 0.4–5.70) and free T4 (0.82 ng/dL/10.5 pmol/L; RR: 0.89–1.78 or 11.5–23 pmol/L).

Upon initial endocrine evaluation, the possibility of central hypothyroidism (given her brain abnormalities) or hypothryoxinemia (given her chronically ill status and a concurrent acute illness at the time of the blood draw) were considered. However, serial thyroid function tests over time confirmed persistently mildly low free T4, low-normal total T4, a substantially elevated T3 and undetectable reverse T3 concentrations, with low-normal TSH (Table 1).

Thyroglobulin, thyroid peroxidase, and TSH receptor antibodies were negative. Physical examination revealed a body mass index below the 3rd percentile for age, mild tachycardia, Tanner II–III breast and pubic hair development. The patient had profound intellectual disability, was nonverbal and wheelchair bound with truncal hypotonia, peripheral spasticity, and contractures of all four extremities. She had some vocalizations and smiled responsively. A pelvic sonogram showed the uterus to measure 6 × 2 cm in AP diameter, with a postpubertal configuration (fundus: corpus ratio 1.3), small ovaries (right ovary volume 2.2 mL, left ovary 1.3 mL) with few 1–3 mm follicles. The abnormal thyroid hormone pattern coupled with severe neurodevelopmental manifestations raised the possibility of MCT8 deficiency. Concurrent metaphase chromosome and FISH analyses were obtained from phytohemagglutinin stimulated lymphocyte cultures of a peripheral blood sample. Classical G-banding karyotype was performed at the 500–650 band resolution and showed a female karyotype with a balanced translocation 46,X,t(X;16)(q13.2;q12.1) between chromosomes X and 16 with breakpoints at Xq13 and 16q12.1 (Figure 1A). A subsequent FISH analysis using two RPCI-11 bacterial artificial chromosome (BAC) clones (Invitrogen, Carlsbad California, USA) RP11-248015 (chrX:73,445,725–73,589,974; hg 19) and RP11-34806 (chrX:73,758,112–73,935,340; hg 19), flanking the SLC16A2 gene, confirmed that the translocation breakpoint has disrupted the SLC16A2 gene at Xq13.2 (Figure 1B). The X chromosome inactivation study was performed at a clinical reference laboratory as previously described [6] and revealed a complete (100 %) inactivation of a normal X chromosome.

Table 1: Thyroid hormone profile of the patient during 6 months of observation.

<table>
<thead>
<tr>
<th></th>
<th>At initial evaluation</th>
<th>2 months later</th>
<th>3 months later</th>
<th>6 months later</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4, µg/dL</td>
<td>–</td>
<td>6.5</td>
<td>6.2</td>
<td>6.4</td>
</tr>
<tr>
<td>[reference range 5–12]</td>
<td>82.6</td>
<td>79.8</td>
<td>82.4</td>
<td></td>
</tr>
<tr>
<td>T4, nmol/L</td>
<td>0.82</td>
<td>0.82</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>[ref range 64–154]</td>
<td>10.5</td>
<td>10.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT4, ng/dL</td>
<td>0.89–1.78</td>
<td>5.1</td>
<td>5.5</td>
<td>5.0</td>
</tr>
<tr>
<td>[ref range 11.5–23]</td>
<td>335</td>
<td>356</td>
<td>327</td>
<td></td>
</tr>
<tr>
<td>T3, ng/dL</td>
<td>–</td>
<td>5.1</td>
<td>5.5</td>
<td>5.0</td>
</tr>
<tr>
<td>[ref range 86–192]</td>
<td>&lt;5</td>
<td></td>
<td></td>
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<tr>
<td>T3, nmol/L</td>
<td>1.3–2.9</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>[ref range 5–12]</td>
<td>10–25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reverse T3, ng/dL</td>
<td>0.15–0.38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH, mIU/L</td>
<td>0.4</td>
<td>0.6</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>[ref range 0.4–5.7]</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Hormonal values in SI units are shown in italics.

Discussion

MCT8-deficiency is an X-linked disorder characterized by severe psychomotor retardation and abnormalities of thyroid function, the clinical phenotype of which was first described in 1944 by American geneticists Allan and Nash, and their social worker, Florence Dudley in a 6-generation family, in males only. In 2004, MCT8 was discovered as a crucial thyroid hormone transporter, inactivating mutations in which were found to determine the phenotype of MCT8-deficiency [7]. Loss-of-function pathogenic variants in SLC16A2 can result not only in impaired protein synthesis but also in disturbed protein folding, defective trafficking, rapid protein degradation, and/or loss of thyroid hormone binding and transport [8]. The abnormal thyroid profile seen in individuals with MCT8-deficiency is characterized by high total and free T3, low reverse T3, low or low normal T4, and normal or mildly high TSH. The pattern may show some variation, as different genotypes may affect MCT8-thyroid transport, type 1 deiodinase activity, and the completeness of T3 transport into the cells differently [8, 9]. The explanation for the low T4 and high T3 serum concentrations observed in MCT8 deficiency remains incompletely understood [9].
Regardless of the mechanisms, the peripheral tissues predominantly rely on transporters other than MCT8 for the transport across the cell membrane of thyroid hormone; hence, the increased peripheral T3 concentration leading to hyperthyroidism resulting in tachycardia, increased metabolic rate, and sleep disturbances [9].

Most affected individuals (boys) with MCT8 deficiency are diagnosed during infancy or early childhood, when they are evaluated for hypotonia and other neurodevelopmental abnormalities, but the diagnosis can be missed if serum T3 concentrations are not measured. Feeding problems due to hypotonia are identified early in life, followed by motor and speech delays with spastic quadriplegia and joint contractures, which progress later in life [1, 10]. Dystonia, dyskinesias, and true seizures, as noted in our patient, may also occur. Delayed puberty has been reported in about 30% of boys with MCT8 deficiency [10], while hypergonadotropic hypogonadism has not been described. A possible cause of POI observed in our patient might be a translocation involving the X chromosome. One of the X chromosomes is inactivated in somatic cells; however, both X chromosomes are active in developing oocytes [11]. Previous studies on patients with POI and balanced and unbalanced X-autosome translocations showed that integrity of the X chromosome is essential to maintain fertility [12]. The breakpoint Xq13 identified in our patient is one among multiple critical regions for POI on the X chromosome [12]. Multiple hypotheses have been suggested to explain POI in women with X chromosome structural rearrangements, including disruption of an ovary-expressed gene by a translocation breakpoint, aneuploidy attributable to meiotic errors or difficulties to complete meiosis, aberrant expression of other X-linked genes due to a position effect of translocated DNA segments. Although other possible genetic causes of POI cannot be excluded, broken integrity of the X chromosome is a likely explanation in our, and most, patients. It is unclear if lack of functional SLC16A2 per se could cause POI, as SLC16A2 mRNA expression has been found in the apical membrane of ovarian cells [2].

Since MCT8 deficiency is an X-linked condition, most females with a heterozygous pathogenic SNV are unlikely to present with the full phenotype but may have minor thyroid dysfunction [5]. In fact, most female carriers (mothers of affected boys) reported so far have shown normal growth and psychomotor development without neurological symptoms [13]. This could be explained by random X-inactivation; however, the penetrance of certain clinical manifestations of
the peripheral phenotype of MCT8 deficiency in female carriers may also vary reflecting the level of X-chromosome inactivation in specific tissues [14]. Our patient had complete phenotypic manifestations of MCT8-deficiency as seen in males, and as previously described [3, 4]. A previously reported case similar in a woman [3] showed a de novo translocation t(X;9)(q13.2;p24), disrupting the SLC16A2 gene. A complete loss of MCT8 expression was observed in that patient due to skewed X-inactivation of a normal X chromosome. Likewise, the patient in the current report showed a balanced translocation t(X;16)(q13.2;q12.1) with 100% inactivation of a normal X chromosome, resulting in the MCT8-deficiency phenotype. In women with balanced X-autosome translocations, complete inactivation of a normal X chromosome is well-known phenomenon, resulting from a natural selection of cells with optimal genetic and functional balance as shown in the Figure 1A. Inactivation of a translocated X chromosome will lead to a functional disomy for the Xq13.2-qter segment and a functional monosomy for 16q12-qter segment, imbalance that is likely associated with a nonviable condition at the cellular level.

What is new?

- MCT8-deficiency can present in women as severely as in men.
- In addition to profound developmental delay, primary ovarian insufficiency can also be observed.
- Clinical and genetic evaluation for MCT8 deficiency and X chromosome inactivation should be considered in girls with features suggestive of MCT8-deficiency.

References