Title: Hypotonic male infant and MCT8 deficiency - a diagnosis to think about

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Hypotonic male infant and MCT8 deficiency - a diagnosis to think about

ABSTRACT:

Background: Thyroid hormone is crucial in the development of different organs, particularly the brain. MCT8 is a specific transporter of triiodothyronine (T₃) hormone and MCT8 gene mutations cause a rare X-linked disorder named MCT8 deficiency, also known as Allan-Herndon-Dudley syndrome, characterized by psychomotor retardation and hypotonia. Typically, elevation of T₃ and delayed myelination in cerebral magnetic resonance imaging are found.

Case Report: We present a 24-month-old boy, born from non-consanguineous healthy parents, with severe motor and cognitive delay and global hypotonia, being unable to hold head upright or sit without support. Deep tendon reflexes were absent on Aquilles tendon. Laboratory investigation showed the typical thyroid profile with high T₃ and slightly decreased thyroxine levels. The study of MCT8 gene confirmed the diagnosis.

Conclusion: Although being a rare disease, MCT8 mutations have been reported in about 50 families all around the world, the authors would like to show the importance of excluding Allan-Herndon-Dudley syndrome in the evaluation of floppy male infant with development delay, without history of perinatal asphyxia. The simple evaluation of thyroid status, including T₃, can guide the diagnosis, avoiding a number of useless, expensive and invasive exams and allowing an appropriate genetic counseling to the affected families.

Keywords: hypotonic infant; thyroid hormones; MCT8; Allan-Herndon-Dudley syndrome
INTRODUCTION:

Thyroid hormone (TH) plays a major role in the growth and development of multiple tissues, in particular the brain. [1,2] The effects of TH are determined by the intracellular concentration of triiodothyronine (T₃) available to bind to its nuclear receptor. [1, 3, 4, 5] Recently, monocarboxylate transporter 8 (MCT8) has been identified as an active and specific TH transporter that plays a critical role in the transport of T₃ across the blood-brain barrier and in T₃ uptake into neuronal cells. [3, 6, 7] Different mutations in MCT8 are responsible for a rare X-linked condition, Allan-Herndon-Dudley syndrome (AHDS) that is characterized by global hypotonia that progresses into spasticity with severe psychomotor delay. [8] All affected males present elevated serum levels of T₃, low to below normal serum levels of prohormone thyroxine (T₄) and thyroid stimulating hormone (TSH) in normal range. [8, 9] The authors describe a 24 month-old-boy with severe hypotonia during the first year of life which led to his inclusion in floppy infant syndrome, emphasizing the clinical, laboratory and neuroradiological findings that guided to the genetic study that confirmed the mutation in MCT8 gene.

CASE REPORT:

We present a 24th-month-old male patient, second child of non-consanguineous parents. During pregnancy thyroid hormone levels of the mother showed low free T₄ level (8.75 pmol/L; normal values 9.39 - 28.31) and normal TSH level (3.17 mUI/L, normal values 0.25 - 5.0). Delivery was uneventful. Gestational age was 38 weeks and the Apgar score in the first and fifth minutes was respectively 9 and 10. His birth
weight and length were normal and the head circumference (38 cm) was above 2SD. Neonatal period was normal. The mother’s homozygote twin sister has a 6-year-old son with the diagnosis of cerebral palsy with no reference to any risk factor (prenatal, gestational or postnatal) that supports this diagnosis. The father and paternal grandmother have a sensorineural hearing loss, which appeared around 40 years old. From the age of 3 months global hypotonia and poor head control became evident. A rehabilitation program was started without any satisfactory improvement. At the age of 12 months the severe hypotonia persisted, without any improvement in head control and there was an extreme difficulty to grab objects and to bring both hands to midline. No pyramidal tract involvement was described. At this age, the pediatrician described the child as active and reactive to stimuli, with a good visual contact and he also reported as normal the social smile and the interaction between the child and his parents. At that time, a cerebral magnetic resonance imaging (MRI) was performed and revealed an enlargement of the subarachnoid spaces, without any description of white matter disorder. Brainstem auditory evoked potential was normal. Assessment of visual evoked potentials showed evidence of a conduction delay in central optical pathways and fundus oculi examination was normal. No alterations were detected in the basic laboratory and metabolic investigations performed (serum electrolytes, urinary and hepatic function, creatine kinase, biotinidasis, uric acid, lactid and pyruvic acid, ammonia levels, urinary organic acid, plasmatic and urinary amminoacid). By the age of 21 months the patient was referred to our Neuromuscular Pediatric Unit due to the severe motor and cognitive delay. At this first visit the patient
showed global and severe hypotonia, being unable to hold the head upright and to sit without support (figure 1). On supine position, the patient presented mild dystonic movements and hypertonic posture of the limbs, of brief duration, triggered by stress conditions or sensitive stimulus. The myotatic reflex was slightly increased in triceps surae muscle and Babinski sign was observed. Deep tendon reflexes were absent on Aquilles tendon. Eye contact and visual tracking of human face were poor. He was responsive to sounds but was unable to speak.

At the age of 23 months he started myoclonic jerks characterized by flexion of the neck and upper limbs, going no longer than few seconds, showing up twice or three times per day. These epileptic seizures disappeared with the introduction of sodic valproate. Electroencephalogram revealed a slow background rhythm with brief generalized multiple spike discharges. Electromyography and neurography were normal. Electroretinogram was normal. Cerebral MRI was repeated at 24 months of age which demonstrated a delay of myelination (figure 2).

After repeating some laboratory tests alterations on thyroid function showed high free T3 level (4.84 nmol/L, normal values 0.63-3.90), low free T4 level (8.2 pmol/L, normal values 9.1 - 25.0) and normal TSH level (3.54 mUI/L, normal values 0.3 - 4.5). Towards this hormonal pattern, the existence of a deficit in T3 carrier was placed as a diagnosis to consider. To rule out this hypothesis a direct sequencing of the SLC16A2 gene revealed 26 bases duplication in exon 2. This change causes a Val254Glu substitution followed by a frame shift and a premature stop codon 24 aminoacids later (Exon 2 c.735_760dup p.Val254Glufs*24). His mother was subsequently confirmed to be a carrier for this duplication (figure 3).
The first description of this phenotype of severe X-linked psychomotor delay was made in 1944 and was named by his authors as Allan-Herndon-Dudley syndrome. [10]

Afterwards, in 2004, first mutations in MCT8 gene (SLC16A2) were discovered by two distinct investigation groups (Dumitrescu et al and Friesema et al) and neurological findings of ADHS were explained by the resistance of T3 on entering the neuronal target cells, that leads to a classical thyroid profile founded in all affected patients. [8, 9] Currently, MCT8 mutations have been reported in about 50 families worldwide. [4, 11]

Diagnosis of AHDS in our patient is supported by: the presence of an X-linked inheritance; the characteristic thyroid hormonal pattern; the marked delay of myelination of the central nervous system (CNS) found in the MRI and the presence of the pathogenic mutation in the MCT8 gene. AHDS shows a broaden and heterogeneous clinical spectrum according to the type of mutation and its repercussion to the protein synthesis. Our patient fits well with the most severe phenotype. [12]

One of the main features of AHDS, also known as MCT8 deficiency, is the markedly global hypotonia and difficulties maintaining the head up right, recognized as "limber neck" (figure 1), evident since the first months of life. [13] In the presence of a floppy infant, the evaluation of the signs of CNS involvement is essential but not always easy to recognize during the first year of life. As we could see on this case, the infant was described as having a normal eye contact and social interaction by the age of 12
months, besides the absence of deep tendon reflexes on Achilles tendon, which made
the assessment of peripheral neuromuscular involvement a hypothesis to exclude. It is
also interesting to remark that our patient, in absence of CNS involvement signs during
the first year of life, could have been submitted to a muscle biopsy in order to exclude
a congenital myopathy or other muscle disorder. However, this study wouldn’t be
considered when spasticity and abnormal movements appeared during the second
year of life.

During the evaluation of a hypotonic infant, the cerebral MRI is a helpful tool for
detecting CNS abnormalities [11]. The difficulty in interpreting a cerebral MRI during
the first year of life leads to different descriptions of the white matter abnormalities
from delayed myelination to hypomyelination, which can delay the diagnosis. [11, 12,
14, 15] Despite the static or even the clinical deterioration of these patients, several
studies confirmed that the major neuroradiological feature of this disease is the
marked delayed myelination. [14, 15] Many of these children were described as a
“Pelizaeus–Merzbacher–Like Disease” because they had a similar phenotype without
the identification of PLP1 mutation. This is a differential diagnosis that needs to be
done and the cerebral MRI is an important tool. In Pelizaeus–Merzbacher disease we
find a hypomyelination (same pattern of deficient myelination on 2 MRIs at least 6
months apart in a child older than 1 year) while in AHDS, a correct MRI interpretation
will show a progression of myelination, even if slow. [11, 14] In our case the relatively
low N-acetyl aspartic peak in the cerebral magnetic resonance spectroscopy also
supports the hypothesis of delayed myelination (figure 2). [16]
The neurological manifestations of this disease are quite complex. The axial hypotonia persists throughout adulthood, while the hypotonia of the limbs progresses to spasticity and dystonic posturing [3, 13]. The age at onset of extrapyramidal symptoms is not clear in literature and it seems essential to us to suspect of ADHS even before these signs appear. [13] Other important features are the inability to sit, stand or walk independently, the severe mental retardation with lack of speech development and rudimentary communicative skills [13, 17]. A quarter of the patients will have seizures that are usually responsive to anticonvulsant therapy. [13]

As already mentioned all affected males with MCT8 mutations exhibit a typical thyroid profile which makes crucial to request these hormones, including T₃, early in the investigation. [3, 8, 9] Mean serum T4 and free T4 are normal or slightly decreased, TSH is normal or mildly increased and serum T3 and free T3 are markedly elevated. [3, 8, 9, 14] This will allow us to avoid unnecessary tests and a specific genetic analysis of SLC16A2 can be required for a definitive diagnosis. There is another medical condition, with the same thyroid hormonal pattern, that can be found in a hypotonic infant and that is due to a mutation in the thyroid hormone receptor α gene (TRα1). We can think of this condition in the first months of life; however lately these patients present a phenotype very different form AHDS, developing the classic features of hypothyroidism (growth retardation, skeletal dysplasia, reduced muscle tone, constipation) and only a mild cognitive impairment. [18]

Some ADHS patients have been treated with TH supplementation, propylthiouracil or diiodothyropionic acid; these last two resulted in better thyroid function tests, but without any improvement of motor or cognitive skills. [19, 20, 21] Up to this
moment, we can only offer symptomatic treatment to these patients, such as rehabilitation therapies, antispasticity, antidystonic and anticonvulsant medication, nutritional and orthopedic management [13, 20, 22]. The genetic counseling should be offered to the family as soon as the diagnosis is recognized and this is similar to all other X-linked recessive conditions: if the mother has SLC16A2 mutation, boys will have a 50% risk of being affected, whereas girls will have a 50% chance of being a carrier of the mutation [13, 22].

CONCLUSION:
Through this clinical report the authors would like to show the importance of excluding AHDS in the initial laboratory evaluation of floppy male infant, without history of perinatal asphyxia, by the simple exploration of the thyroid hormone status, including T3. In spite of the absence of an effective treatment for this disease, an early diagnosis can avoid a number of useless, expensive and invasive exams and permit a correct genetic counseling to the affected families.
Consent:

Written informed consent was obtained from the parents of the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

List of abbreviations:

TH: thyroid hormone; T₃: triiodothyronine hormone; MCT8: monocarboxylate transporter 8; AHDS: Allan-Herndon-Dudley syndrome; T₄: thyroxine; TSH: thyroid stimulating hormone; MRI: magnetic resonance imaging; CNS: central nervous system; TRα1: thyroid hormone receptor α gene.

Competing interests:
The authors declare that they have no competing interests.

Authors' contributions:

FR: data analysis, literature search, manuscript preparation; JG: literature search, manuscript preparation, CO: provided medical care, manuscript review; AN: provided medical care, data analysis, manuscript review; BM: literature search, carried out the molecular genetic studies; MMB: carried out the molecular genetic studies; JA: provided medical care, data analysis; JC: provided medical care, data analysis, manuscript review, literature search. All authors read and approved the final manuscript.
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FIGURE LEGENDS:

Figure 1: Clinical features. The child at 24 months of age showing global hypotonia, hypertonic posture of the limbs and an incapacity to sit without support and to hold head upright.

Figure 2: a) Cerebral magnetic resonance image, axial, T2-fast spin echo sequence. Significant alteration in white matter substance in centrum semiovale, frontoparietal, parieto-occipital and subcortical regions, compatible with a marked delay in myelination. b) Cerebral magnetic resonance spectometry. Demonstrates a low N-acetyl aspartic peak.

Figure 3: Electropherograms. The duplication found in exon 2 of MCT8 in the patient (middle tracing), the sequence of the heterozygous mother (bottom tracing), and the corresponding normal sequence (top tracing).
Figure 3

Normal: AATCACAGCAACCGCGGGGGCTGCCG

Patient: AATCACAGCAACCGCGGGGGCTGCCG

Heterozygous mother: AATCACAGCAACCGCGGGGGCTGCCG

[Genetic sequence comparison between normal, patient, and heterozygous mother]