Brain & Development 36 (2014) 716–720

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case report

Delayed myelination is not a constant feature of Allan–Herndon–Dudley syndrome: Report of a new case and review of the literature

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Received 5 August 2013; received in revised form 20 October 2013; accepted 21 October 2013

Abstract

Introduction: Allan–Herndon–Dudley syndrome is an X-linked condition caused by mutations of the monocarboxylate transporter 8 gene. This syndrome is characterized by axial hypotonia, severe mental retardation, dysarthria, athetoid movements, spastic paraplegia, and a typical thyroid hormone profile. In most of the cases reported so far, brain magnetic resonance imaging showed delayed myelination of the central white matter and this finding greatly affects the diagnosis of the syndrome. *Case report*: We present a new case studied with magnetic resonance imaging and spectroscopy and we reviewed all the articles published between 2004 and 2012 containing information on brain neuroimaging in this syndrome. An Italian boy, showing a classical phenotype of the syndrome, was diagnosed at 17 months of age. Genetic analysis revealed a new frameshift mutation of the monocarboxylate transporter 8 gene. His brain magnetic resonance imaging and spectroscopy, performed at the age of 14 months, were normal. *Discussion*: Among the 33 cases reported in the literature, 3 cases had normal neuroimaging and in 7 of 14 cases, having a longitudinal follow-up, the initial finding of delayed myelination gradually improved. Our case and the review of the pertinent literature suggest that Allan–Herndon–Dudley syndrome should be suspected in males with the typical neurological and thyroid profile, even in cases with normal brain myelination.

Keywords: Allan–Herndon–Dudley syndrome; Monocarboxylate transporter 8; SLC16A2 gene; Brain magnetic resonance imaging; Thyroid hormone; Central hypotonia

1. Introduction

Allan–Herndon–Dudley syndrome (AHDS) (OMIM 300523) is an X-linked condition characterized by severe mental retardation, dysarthria, athetoid movements, initial peripheral hypotonia evolving into spastic quadriplegia, inability to sit, stand or walk independently, severe mental retardation and absence of speech [1,2]. This syndrome is caused by mutations in the monocarboxylate transporter 8 (MCT8) gene, also known as SLC16A2 [1–3]; though it is ubiquitously expressed, the brain is considered to be especially dependent on this transporter for thyroid hormone [1,2]. Insufficient thyroid hormone uptake into cells, and particularly in neurons, causes typical biochemical abnormalities:

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http://dx.doi.org/10.1016/j.braindev.2013.10.009

elevated serum T3, low or low-normal T4 and FT4, decreased rT3 levels, with thyroid-stimulating hormone (TSH) levels mostly within the reference range [1,2].

In most of the cases reported so far, brain magnetic resonance imaging (MRI) showed delayed myelination of the central white matter [1–17].

The purpose of the present article is to describe a new case of AHDS and to review all the articles published between 2004 and 2012 containing information on brain MRI.

2. Case report

Our patient is an only child, born from healthy non-consanguineous parents, with family history positive for thyroid disorders in the maternal line: the grandfather had hypothyroidism and one aunt had hyperthyroidism.

The proband was born at the 37th week of gestation and the delivery was uneventful; during pregnancy an intrauterine growth retardation (abdominal circumference at 10th percentile) was detected since the 29th week of gestation. At birth weight was 2.4 kg (3rd percentile), length was 47 cm (3–10th percentile), and head circumference was 33 cm (25th percentile). Apgar score was normal. In the first month he had poor sucking and, then, he showed a poor head control. In the following months, a severe psychomotor retardation was evident, with no achievement of rolling, sitting, crawling, walking and absence of speech. Between 6 and 12 months of age, he presented a height curve deflection (from −1.02 to −1.47 standard deviation, World Health Organization Growth chart 0–5 years).

At 14 months of age he was admitted to our Department; at admission, his growth parameters were as follows: weight 2.090 kg (<3rd percentile), length 74 cm (10th percentile), and cranial circumference 45.5 cm (10th percentile). The physical examination revealed severe muscular hypotrophy, elongated face, bilateral convergent strabismus, and hypotonic tetraparesis with bilateral piramydal signs (Babinski sign and brisk tendon reflexes).

During hospitalization the following investigations were performed, and all revealed normal values: white and red cells count, platelets count, inflammation indexes, electrolytes, vitamin D, renal and liver function, lactate, ammonium, and anti-transglutaminase antibodies. The coagulation profile was consistent with vitamin K deficiency. The thyroid function showed low fT4 values in 3 consecutive blood samples (7.66, 6.87, and 7.6 pmol/L respectively; normal values 9–20 pmol/L) with normal TSH (6.66, 5.61, and 5.57 mIU/L; normal values 0.4–6 mIU/L), and high fT3 (12.34 pmol/L; normal values 3.9–6.8 pmol/L). Anti-thyroid antibodies could not be detected in the serum, and thyroid ultrasonography was normal. Basal levels of the other pituitary hormones were normal. Bone age was consistent with chronological age. Plasmatic aminoacids, urinary organic acids, audiometry, and high resolution karyotype were normal. Brain MRI (at age 14 months) showed normal myelination of the central white matter (Fig. 1); brain spectroscopy was also normal.

In our case clinical and laboratory findings were suggestive for AHDS. Mutation analysis of the MCT8 gene revealed the presence of a new frameshift mutation (c.1251e1252insG in exon 4). This nucleotide insertion creates a stop codon at aminoacid position 452, resulting in a truncated protein lacking of the last four transmembrane domains as well as the carboxyl cytoplasmic end that is predicted to be non-functional [3]. DNA sequencing in both directions confirmed the mutation. The genetic analysis, conducted on the parents, revealed that the mother, asymptomatic with a normal thyroid function, was heterozygous for this mutation, while the father was negative.

3. Discussion

We describe a new Italian patient with a clinical and molecular diagnosis of AHDS, carrying a new frameshift mutation (that creates a stop codon at aminoacid position 452) never reported so far. Interestingly in our case, despite a severe clinical phenotype and a severe truncating mutation, brain myelination on MRI was normal at an early stage (14 months of age) (Fig. 1).

This finding significantly differs from the majority of the previously reported cases (Table 1), in which a delayed myelination of central white matter was documented on brain MRI [1–17].

Among the 33 cases reported so far, 3 patients with the classical phenotype and mutation on the MCT8 gene had normal cerebral myelination (at 3 months, at 2 and 13 years of age respectively) [1,2] (Table 1). In other 2 cases, brain MRI was normal at 3 and 4 months of

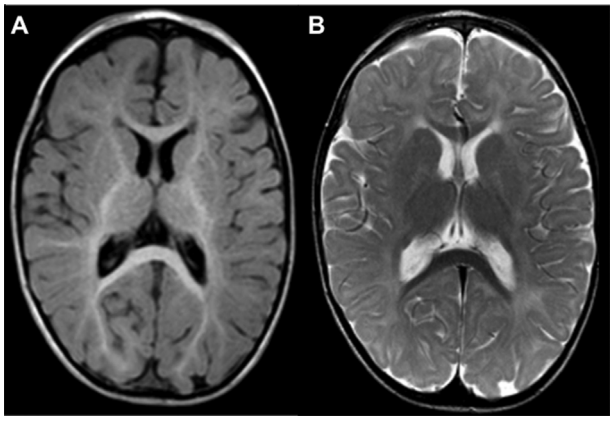

Fig. 1. Brain MRI on T1-weighted (A) and T2-weighted (B) images in our patient at 14 months of age: myelination of the corpus callosum, the internal capsules and the subcortical white matter is normal for age.