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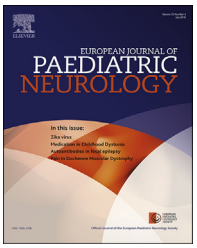

Case study

SLC19A3 related disorder: Treatment implication and clinical outcome of 2 new patients

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ABSTRACT

Encephalopathies with neostriatal involvement constitute a heterogeneous group of acquired and genetically inherited conditions that include Bilateral Striatal Necrosis (BSN) and other Striatal Lesions (SL) (Tonduti et al). We describe two new patients suffering from BSN due to biallelic *SLC19A3* mutations. In the first patient vitamin supplementation was started early on, resulting in the remission of the clinical picture, and an almost complete normalization of the neuroradiological findings. In the second one treatment was started late, compliance was irregular and the resulting clinical outcome was poor. The clinical outcome of our two patients confirms and further stresses the importance of the early administration of vitamin supplementation in all patients presenting with neostriatal lesions, or clear bilateral striatal necrosis. Patient 2 didn't present any additional episode of acute decompensation after the age of 20 years despite having completely stopped treatment. This suggests the existence of an age dependency of thiamin requirement in humans.

1. Introduction

Encephalopathies with neostriatal involvement constitute a heterogeneous group of acquired and genetically inherited conditions that includes Bilateral Striatal Necrosis (BSN) and other Striatal Lesions (SL).[1]

Thiamin metabolism disorders represent one of the causes of inherited BSN. They are a group of conditions due to

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abnormal transport or activation of thiamin into the cells and mitochondria. Thiamine is normally introduced with the diet in the form of thiamine monophosphate (TMP). TMP enters the cell through a facilitated transport mediated by SLC19A3 and SLC19A2, and is then converted into its active form, thiamine pyrophosphate (TPP), by thiamine pyrophosphokinase 1 (TPK1). Subsequently, the carrier SLC25A19 transports TPP into the mitochondria where it acts as a cofactor necessary for the correct proceeding of multiple enzymes, particularly pyruvate dehydrogenase complex, alpha ketoglutarate dehydrogenase and branched chain ketoacids dehydrogenase.[2]

Mutations of *SLC19A3* cause the so-called "thiamin-biotin responsive basal ganglia disease", a condition clinically characterized by recurrent encephalopathic episodes triggered by metabolic challenges such as acute infections. Patients presenting with a chronic progressive course have rarely been reported. In pediatric onset patients neostriatal involvement is invariably present on MRI; involvement of extra-striatal structures (mainly cerebral cortex and thalami) is also common. High doses of thiamin and biotin have demonstrated to result in a rapid resolution of the clinical picture.[2]

We report on two new patients affected by an *SLC19A3*-related BSN and describe their clinical and radiological features as well as treatment implications.

2. Case studies

2.1. *Patient 1*

She is a 2-year old girl, first child of related (cousins) healthy parents. She was born after an uneventful pregnancy and delivery. Psychomotor development proceeded regularly. At 11 months of age, 1 week after a viral illness and 3 days after a mild head trauma, the girl presented with irritability, progressive loss of postural control, generalized choreo-dystonic movements. MRI showed bilateral signal abnormalities involving neostriata, multiple cortico-subcortical areas and medial thalamic nuclei. Signs of cytotoxic edema involving the peripheral parts of neostriata and extra-striatal regions were evident on diffusion sequences. The central part of neostriatal nuclei was necrotic. Proton-MR Spectroscopy showed a high lactate peak and mild reduction of NAA, while the other metabolites were normal (Fig. 1). Routine blood analysis and first line metabolic screening[1] documented high level of plasma lactate (3.9–8.2 mmol/L). The girl was referred to our Institute to explore the possibility of a mitochondrial encephalopathy. When she was admitted vitamin treatment was started (thiamin 100 mg, Riboflavin 50 mg, CoenzymeQ10 50 mg) resulting in a rapid amelioration and normalization of the clinical picture. On the suspicion of thiamin metabolism disorder *SLC19A3* gene was sequenced revealing the known homozygous mutation c.68G > T (p.Gly23Val).[3] Parents were both found to be healthy heterozygous carriers of the mutation.

At the last follow up, at 2 years of age, the girl was still on thiamin and biotin supplementation. The neurological examination and psychomotor development were normal. Control MRI showed only mild T2 hyperintense signals of the internal rim of the putamen and of the head of the caudate nuclei; mild basal ganglia atrophy was also present. Proton-MR spectroscopy was normal (Fig. 1).

2.2. *Patient 2*

He is a 36-year old man born after normal pregnancy and delivery from healthy unrelated parents. Psychomotor development before disease onset proceeded regularly.

At the age of 2 years and 6 months, without any apparent triggering factor, he acutely presented with abnormal gait, frequent falls, and convergent strabismus. CT demonstrated bilateral hypodensity of the neostriata. Over the subsequent 15 days he spontaneously recovered.

One year later (3 years 4 months of age) he presented a second acute episode, similar to the previous one. Suspecting a mitochondrial disease, muscle biopsy was performed (showing normal mitochondrial chain respiratory complexes and pyruvate dehydrogenase activities). Vitamin supplementation, including thiamin, was started. Not seeing any clear beneficial effect, compliance to treatment was irregular. In the subsequent years the boy presented 4 additional milder acute episodes without clear triggering factors, characterized by gait instability and global clumsiness followed by spontaneous partial resolution over 3–4 days. The clinical picture slowly progressed towards a generalized dystonia predominant in the lower limbs without significant functional disability, mild dysarthria and intellectual disability. At 14 years of age, after vitamin treatment interruption, the boy suffered from a new severe acute deterioration with confusion, generalized epileptic seizures, paroxysmal exacerbation of upper limbs and oro-mandibular dystonia. MRI showed bilateral T2-hyperintense signal of swollen neostriata associated with multiple areas of signal abnormality in fronto-parietal and cerebellar cortex. The episode lasted 3 weeks and spontaneously improved. After the resolution of the acute symptoms, the neurological picture stabilized towards a hypokinetic-rigid syndrome associated with generalized dystonia and moderate intellectual disability. Thiamin treatment was started again and the clinical picture remained stable. Follow-up MRI (performed at 16, 18, 22 years of age, Fig. 2) showed a regression of the cortical abnormalities and an evolution of neostriata abnormalities towards a global atrophy with multiple small areas of necrosis. Different therapeutic attempts to control extrapyramidal symptoms including L-Dopa/carbidopa, trihexyphenidyl, oral baclofen, and bilateral deep brain stimulation of subthalamic nuclei failed to produce positive results. At 20 years of age thiamin supplementation was stopped but the clinical picture remained stable; the patient never suffered from other episodes of acute deterioration. At the last follow-up visit, at 36 years of age, the clinical picture was unmodified, but an etiological diagnosis was not yet achieved. At this time a customized gene panel in use at our Institution, which included genes for primary and symptomatic movement disorders, revealed the presence of compound heterozygous *SLC19A3* mutations (c.487T > C; p.Ser163Pro/c.658A > C; p.Thr200Pro) both located in exon 3.

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