Case Report

Coenzyme Q10 deficiency due to a COQ4 gene defect causes childhood-onset spinocerebellar ataxia and stroke-like episodes

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ABSTRACT

Primary coenzyme Q10 deficiency-7 is caused by homozygous or compound heterozygous mutations in the COQ4 gene. Until now 12 patients have been reported, most presenting with a lethal infantile phenotype with encephalopathy, epilepsy and cardiomyopathy. We report on a new phenotype of COQ4 deficiency: a childhood onset spinocerebellar ataxia with stroke-like episodes.

List of abbreviations

CoQ10 Coenzyme Q10

1. Introduction

Coenzyme Q10 (ubiquinone; CoQ10, EC 206–147-9) is essential for mitochondrial respiratory chain electron transport [1,2]. Primary CoQ10 deficiency is caused by mutations in genes of the COQ10 biosynthetic pathway. Primary coenzyme Q10 deficiency-7 (COQ10D7, MIM 616276) is caused by homozygous or compound heterozygous mutation in the COQ4 gene (MIM 612898). Symptoms include early onset encephalomyopathy, cerebellar ataxia and nephropathy [3]. A first patient with CoQ10 deficiency due to COQ4 haploinsufficiency was published in 2012 [4]. So far a total of 12 patients with compound heterozygous or homozygous COQ4 variants have been reported, most (11/12) patients presented with a lethal infantile phenotype with encephalopathy, epilepsy and cardiomyopathy [5–7]. We report on a new phenotype of COQ4 deficiency: a childhood onset spinocerebellar ataxia with stroke-like episodes.

2. Patients and methods

The family pedigree is shown in Fig. 1: V-3 is patient 1 and V-4 is patient 2. Patient V-3 and V-4 have four healthy siblings and one younger brother with a complex constellation of congenital abnormalities not caused by mutations in the COQ4 gene.

Patient 1 is the 15 year old third child of consanguineous parents. His early psychomotor development was abnormal with delayed speech development. He developed a “tremor” at the age of four years. Physical examination was otherwise unremarkable. There were no dysmorphic features, no skin abnormalities and no hepatosplenomegaly. Brain MRI at age 5 revealed a suspected tectal glioma. He was treated with radiotherapy and the lesion has been stable since age 10. However, ambulation progressively deteriorated, and he became wheelchair dependent around age 12. On neurological examination there was dysarthria, spastic tetraparesis and prominent ataxia of upper and lower limbs. He was also wheelchair dependent for ambulation. He was treated with radiotherapy and the lesion has been stable since age 10. However, ambulation progressively deteriorated, and he became wheelchair dependent around age 12. On neurological examination there was dysarthria, spastic tetraparesis and prominent ataxia of upper and lower limbs. He was also wheelchair dependent for ambulation.


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laboratory tests were normal, specifically a normal general physical examination. MRI of the brain revealed a ca-

limbs. He developed tonic-clonic seizures treated with carbamazepine at age 12. Cognitive development was abnormal (TIQ 60), necessitating special education.

Patient 2 is the 14-year-old sister of patient 1. After a normal early development she developed tonic clonic seizures at age 9, treated with carbamazepine, and a "tremor" of the hands at age 10. Her IQ was around 55–60. Walking became difficult, with frequent falls. On examination she had a spinocerebellar syndrome like her brother, with a normal general physical examination. MRI of the brain revealed a ca-

3. Discussion

This is the first report of a childhood-onset spinocerebellar syndrome with stroke-like episodes caused by COQ4 deficiency and is different from the lethal infantile presentation described earlier [5–7]. Patient S5 reported by Brea-Calvo [5] is most comparable to our patients with progressive motor deterioration from age 10 months, spastic ataxic gait at age 3, wheelchair dependency, epilepsy and progressive deterioration. However, other primary CoQ10 deficiencies have been associated with a late-onset ataxic phenotype, like ARCA2 (due to mutations in the ACDK3 gene) [8]. Stroke-like episodes were also reported in patients with ADCK3 mutations and in patients with infantile encephalomyopathy and nephropathy with CoQ10 deficiency [8,9]. This further supports that these symptoms are related to CoQ10 deficieny.

The majority of previously reported patients with CoQ10 deficiency demonstrated cerebellar atrophy on imaging [8] but this was not seen in our patients. It is possible that this feature will develop later in life. Imaging did reveal a tectal glioma in patient 1 but this seems unrelated to the COQ4 mutation. Other primary CoQ10 deficiencies were associated with cardiac failure, but echocardiography demonstrated no cardiomyopathy in our patients. Except for the stroke-like episodes our patients did not deteriorate rapidly, it is unclear if this is due to CoQ10 supplementation. In other patients, a beneficial effect of CoQ10 supple-

mentation in a dose of 1000 mg once daily was initiated for both sib-

lings. The 6 min walk test was stable over the period of a year. Patient 2 developed a second stroke-like episode at age 14.

Fig. 1. On the right side of the figure is the family pedigree. On the left side the MRI scan from patient 2 (top row MRI at the time of the first stroke-like episode, bottom row 3 months later). There is a lesion in the left occipital lobe (indicated by the white arrow) with increased signal on FLAIR (A) and low signal on T1-weighted images (B). There is patchy enhancement after gadolinium administration (C) and is abnormal signal intensity on DWI (D) and ADC (E). There is complete normalization on a follow-up scan about 3 months later.
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References