Novel mutation variant in GCH1 gene - a new cause for infantile-onset severe dystonia ?

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INTRODUCTION

Dopa-responsive dystonia (DRD) encompasses a group of clinically and genetically heterogeneous disorders that typically manifest as limb-onset, diurnally fluctuating dystonia and exhibit a robust and sustained response to levodopa treatment. Autosomal dominant GTP cyclohydrolase 1 deficiency, also known as Segawa disease, is the most common and best-characterized condition that manifests as DRD. Over time, a wide spectrum of clinical features have been recognized, one of the clinical form being with cerebral palsy-like features. Thus, it may be misdiagnosed as cerebral palsy, correct and timely diagnosis being very important for initiation of levodopa therapy.

OBJECTIVES

We aimed to identify the underlying etiology of severe neonatal- onset generalized dystonia in a 12 year old patient, with non-specific cerebral MRI findings, previously diagnosed as a mixed type cerebral palsy.

MATERIALS AND METHODS

Personal history revealed he was born prematurely at 7 months, APGAR score = 6, birth weight = 1800g, remaining in the maternity ward until the age of 2 months. Two days after the birth, he suffered an episode of hypoxia which required ICU hospitalization. At the age of 2 months, the patient presented episodes of left torticollis and extended posture of the left upper limb, appeared/exacerbated in the context of crying(Fig.1). In the past, he was diagnosed with mixed type cerebral palsy.

RESULTS

The clinical neurological examination showed **generalized dystonia**, with episodes of **bilateral torticollis, retrocollis**, various dystonic postures in the left upper limb with extension and shoulder adduction, in the right upper limb with elbow flexion and abduction, in the both lower limbs with bilateral knee and hip flexion, pelvic dystonic torsion postures, episodes of facial dystonia, tongue dystonia with protrusion and laterodeviation(Fig3.). Inconsistently, in a strong emotional context or fatigue the patient has **laryngeal dystonia with stridor.** He has a **swallowing disorder for solids**, possibly in the context of oromandibular dystonia. He also has episodes of ocular dystonia with deviation to the lateral side or upwards.

The clinical picture of generalized dystonia is permanently present when the patient is awake and disappears during sleep. The dystonia shows discrete diurnal variation of the intensity, slightly improving with sleep and short naps but he has an increased intensity of the dystonic postures while being touched or in a strong emotional context.

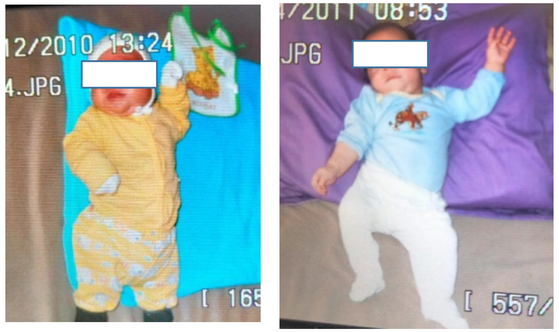

Figure 1. Dystonic posture of the patient when he was an infant.

His development is severly delayed, he does not hold his head, does not sit, does not speak, but vocalizes, communicates non-verbally with his father, does not show clinical signs of central motor neuron syndrome, has no spasticity, does not show pathological reflexes, has no acquired sphincter control.

We performed whole exome sequencing (WES) testing. Genomic DNA including mitochondrial genome was analized through WES, revealing a heterozygous GCH1 variant c.-252_-235del that was considered of unknown significance (Fig 2).

Figure 2. GCH1 gene (genecards.org)

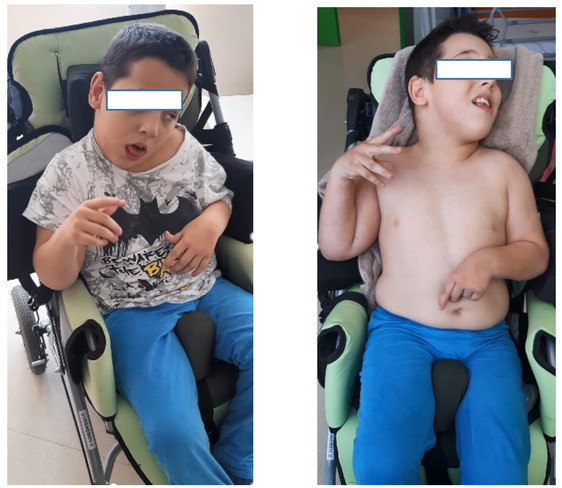

Figure 3. Dystonic posture of the patient at in the present.

He performed 2 cerebral **MRI** investigations in the last 2 years which showed minimal lesions of bilateral parietal periventricular white matter.
The patient was started on **levodopa-carbidopa treatment** and showed significant improvement on 600mg/day with a DSAP score going from 3 to 1+/2.

CONCLUSIONS

The clinical picture of generalized dystonia and available data suggests that pathogenic GCH1 mutations may cause severe dystonia.

The clinical picture in our case is not explained by structural causes, the MRI showing only minimal white matter bilateral parietal periventricular lesions, compatible with the neonatal context of hypoxia.

Even though the identified mutation has yet an unknown significance, the infantile-onset severe dystonic encephalopathy, otherwise unexplained by structural causes, diurnal variation, the marked response to levodopa-carbidopa treatment and the available data suggest that the identified GCH1 deletion is a probable cause in our patient. Further studies of a second variant in the GCH1 gene, for example a variant in a regulatory region or deep intronic region are needed to solidify/ confirm the hypothesis.

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