Dear Editor,

Rapid-onset dystonia-parkinsonism (DYT/PARK-ATP1A3, formerly known as DYT12) is a combined dystonia syndrome rarely encountered in clinical practice [1]. Recent reports have expanded the clinical presentation beyond the classical phenotype and there is increasing evidence that the disease has considerable overlap with other conditions also caused by ATP1A3 mutations [2–4]. We present a new family with DYT/PARK-ATP1A3, highlighting the typical presenting features of this disease and describing some unusual aspects that expand the phenotype of ATP1A3 mutations.

A 14-year-old girl was referred to our movement disorder clinic due to oromandibular dystonia. She was born after a normal pregnancy and delivery; she started walking at 14 months in a clumsy way, which motivated a Neuropediatrics consultation. At that time, myoclonus was observed affecting the upper limbs distally. She was treated with sodium valproate with improvement of the myoclonus. At age 10, she was hospitalized following a febrile illness with upper respiratory tract symptoms. Simultaneously, she developed encephalopathy, severe dysarthria, dysphagia, generalized dystonia with asymmetric upper limb involvement, bilateral myoclonus, bilateral dystymria and ataxia. There was severe functional deterioration, including the loss of walking ability. Afterwards, she had partial recovery, during several months, with subsequent stabilization. At age 14, she maintained an action predominant generalized dystonia with greater involvement of the cranial muscles (oro-linguo-palato-laringeval dystonia), a cervical tilt and an asymmetric upper limb dystonia (video 1). The lower limbs presented minor dystonic postures. A slight bradykinesia and generalized hyporeflexia were found. She had autonomous gait. There was no rigidity, tremor, motor deficits, dystymria or cognitive impairment. Myoclonus was not found.

Her father, a 49-year-old man, was hospitalized at age 6 because of measles. At that same time, he suddenly became unable to walk, to swallow and to articulate words correctly. On the following months, he slowly regained previous function. Currently, he describes some movements as clumsy, including writing and other precision manual tasks. On neurological examination, he presents a slight dysarthria and a generalized action dystonia with predominant facial and upper limb involvement (video 1). Deep tendon reflexes are weak. There is no dystymria, bradykinesia or rigidity. There are no other family members with similar history. Both patients were treated with levodopa with subjective improvement.

Work-up results of the proband included a normal brain MRI and a negative DYT-TOR1A genetic test. An EEG during the hospitalization showed generalized epileptic discharges triggered by hyperventilation and photic stimulation, compatible with a myoclonic epilepsy pattern. Genetic testing by PCR amplification and Sanger sequencing revealed a heterozygous mutation in the ATP1A3 gene [c.2267G>A; (p.Arg756His)], consistent with the diagnosis of rapid-onset dystonia-parkinsonism. The father refused genetic testing.
We present, to the best of our knowledge, the first Portuguese family with DYT/PARK-ATP1A3. In both patients, the dystonia is generalized with sudden onset in infancy or childhood and there was partial improvement followed by a static, persistent course. DYT/PARK-ATP1A3 is a rare condition, with less than 200 cases described worldwide. Transmission is autosomal dominant with reduced penetrance; some cases may be sporadic [2]. There are several classical features that allow a clinical diagnosis. First, the abrupt onset of the symptomatology is often precipitated by a stressor event, either physical (such as an infection, as in these cases) or emotional [5]. Second, there is a clear rostrocaudal gradient of the dystonia, with severe cranial and cervical involvement and milder lower limb dystonia [3]. Third, there is striking bulbar involvement, manifesting as dysarthria, hypophonia and dysphagia [2, 5]. Finally, the association of dystonia with parkinsonism can be found, as expected in combined dystonic syndromes [3]. Levodopa response is usually marginal, and significant improvement should raise the possibility of a DYT/PARK-GCH1 or DYT/PARK-TH mutations (formerly known as DYT5) [5].

A few atypical features should be noted in this family. Our proband had a previous history of gait difficulties. This could be explained by mild dystonia involving the lower limbs, delayed motor development or ataxia [3]. Additionally, contrasting with the literature, both patients had a dramatic recovery, particularly the father [3]. Finally, the identification of myoclonus in the index case with an EEG raising the possibility of concurrent myoclonic epilepsy has not been previously described in DYT/PARK-ATP1A3. To date, two other cases with the p.Arg756His mutation have been described in the literature [1, 2]. The first is a child who presented with several episodes of transient hypotonia starting at 9 months. She had partial complex seizures diagnosed at age 4 [2]. The other case is a girl from Chinese descent with sporadic onset and the classical DYT/PARK-ATP1A3 phenotype [1].

The ATP1A3 gene codes for an Na⁺/K⁺-ATPase subunit protein [2]. ATP1A3 mutations have been found in children presenting with a diverse group of neurological phenotypes, including DYT/PARK-ATP1A3, Alternating Hemiplegia of Childhood (AHC) and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome [3]. The AHC manifests as transient episodes of motor deficit with dystonia and dysautonomy, developmental delay and ocular movement disorders; up to 50% of patients have epilepsy, including myoclonic seizures [3, 4]. Although initially considered separate conditions, recent reports show the wide phenotypic variability and overlap between these syndromes, particularly in early onset cases [3–5]. In fact, the exact same mutation in ATP1A3 can cause either AHC or DYT/PARK-ATP1A3 [4]. This case may be yet another example of this interchangeability; both myoclonic jerks and hyporeflexia are not part of the classical DYT/PARK-ATP1A3 presentation but may represent this overlap between all three conditions caused by ATP1A3 mutations.

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References