ABSTRACT

Introduction: Spinocerebellar ataxia type 13 is a rare autosomal dominant disease caused by point mutations in the KCNC3 gene coding for the Kv3.3 voltage-gated potassium channel. This disease can present different neurodevelopmental and neurodegenerative forms. Case report: We present a case of a child who had a trunk and appendicular ataxia, exuberant gait ataxia, tremor, dysarthria, and dysrhythmic and scanning speech. She presented a delay and difficulty in acquiring fine motor skills. Cerebral magnetic resonance imaging showed moderate hypoplasia of the cerebellum. A pathogenic variant c1268 G>A p.(Arg423His) in heterozygosity in the KCNC3 gene was detected, allowing the diagnosis of Spinocerebellar Ataxia type 13. Later, the same diagnosis was established in the patient’s father. However, he gradually improved his ataxia and motor function throughout his life. Discussion: Unlike most spinocerebellar ataxias, including the other spinocerebellar ataxia type 13 phenotypes, this one does not lead to progressive ataxia. Children with this disease should be follow-up by a multidisciplinary team and referred to an early intervention program. A regular neurologic examination is recommended to evaluate disease progression.

KEYWORDS Cerebellar Ataxia, Cerebellum Hypoplasia, Genetic Disease, Hereditary Ataxia, Spinocerebellar Ataxia type 13

Introduction

The Spinocerebellar ataxias (SCA) are a clinically and genetically heterogeneous group of disorders with an autosomal dominant inheritance. Several known mutations cause SCA, and over forty SCA have been described. SCA3 is the most prevalent subtype globally and in Portugal [1,2]. Spinocerebellar Ataxia type 13 (SCA13) is a rare disease caused by point mutations in the KCNC3 gene, located on chromosome 19q13, coding for the Kv3.3 voltage-gated potassium channel. This channel is expressed in cerebellar neurons, but other neuronal circuits can be severely impacted [3,4]. The Kv3.3 channel subunit is one of the four members of the Kv3 family of voltage-dependent K+ channels. Like the other family members, the Kv3.3 channels activate at positive membrane potentials. Their principal function is to drive the repolarization phase of action potentials [5,6]. While mutations in the human genes for ion channels are well known to produce disorders of excitability as well as movement disorders, it is uncommon for channelopathies to lead to neurodegeneration. An apparent exception is SCA13, a disease caused by mutations in Kv3.3, resulting in cerebellum degeneration [5].

Clinically, it is a phenotypic spectrum that includes non-progressive infantile-onset ataxia, progressive childhood-onset and adult-onset cerebellar ataxia [7]. In addition, the SCA13 exists in different neurodevelopmental and neurodegenerative forms, and the age of onset is correlated with the causative mutation [8].

A regular neurologic examination is recommended to evaluate disease progression, and a multidisciplinary approach is essential to manage ataxia and related neurologic manifestations.
A 4-year-old girl was referred to a pediatric appointment due to an unbalanced gait. According to the parents, the patient acquired autonomous walking at 18 months, described as peculiar, with imbalance and frequent falls. She always had a generalized tremor without progressive worsening. However, the tremor of the upper limbs affected her daily activities, namely handling cutlery and pencils. The patient attended preschool with good adaptation, but the teacher reported difficulty in fine motor skills, poor agility, and frequent falls.

Her personal history reveals a gestation of 39 weeks, supervised and without complications, birth by unassisted vaginal delivery, and an eventful neonatal period. A delay and difficulty in acquiring fine motor skills should be highlighted. Still, according to the parents, the remaining stages of psychomotor development were reached within the expected times. Relevant pathological antecedents, dysphagia, or eating difficulties were denied.

Regarding family history: the patient’s father, currently 32 years old, was adopted at age 4 (unknown biological family history). He presented generalized tremor, ataxic gait, and frequent falls at that time, but with marked improvement throughout his life. The aetiology was not identified. In adolescence, he also developed epilepsy and performed brain magnetic resonance imaging (MRI) that showed cerebellum atrophy (figure 1).

On physical examination, she presented head titubation and ataxic movements of the limbs, characterized by intention and action tremor, dysmetria, and dysdiadochokinesia. In addition, she manifested trunk ataxia, an exuberant ataxic gait, and could not perform a tandem gait test. She also had dysarthria and dysrhythmic and scanning speech. She had no nystagmus or abnormal eye movements and no atrophies or spasticity. Superficial and deep sensitivity were preserved and normal. A scale for assessing and rating ataxia (SARA) was applied with a score of 16.5.

The following investigation was carried out: complete blood count, urea, creatinine, ionogram, aspartate and alanine transaminase, total bilirubin, creatine phosphokinase, albumin, total protein, total thyroxine, and thyroid-stimulating hormone levels were normal; normal metabolic study (serum ammonia, pyruvate, lactate, urinary organic acids, plasma and urinary amino acids levels). Cerebral MRI showed moderate hypoplasia of the cerebellum (hemispherical and vermian) (figure 1). Because of the suspicion of hereditary cerebellar ataxia, a 214-gene next-generation sequencing (NGS) panel was performed and detected a pathogenic variant c1268G>A p.(Arg423His) in heterozygosity in the KCNC3 gene, allowing the diagnosis of Spinocerebellar Ataxia type 13 to be established. The patient underwent a cognitive assessment (Weschler Intelligence Scale for Children - WISC III) that revealed a total intelligence quotient of 72. She was integrated into a National Early Childhood Intervention System and started physical, speech, and occupational therapy. Two years after the diagnosis, she maintains an overlapping neurological exam, with no aggravation or appearance of new deficits.

After diagnosis, the father was re-evaluated in a neurology appointment. He presented irregular bilateral postural tremor, mild bilateral dysmetria, and unstable tandem gait without worsening the ataxic condition. Later, he performed a genetic study that identified the same pathogenic variant. His cognitive assessment revealed an intellectual level on what was expected for his age and educational level. Currently, he has no treatment and no seizures. The patient’s parents did not intend to have a genetic counseling consultation. However, in the future, this may be appropriate for the girl with SCA13.

**Discussion**

The diagnosis of SCA13 is established by identifying a heterozygous KCNC3 pathogenic variant through molecular genetic tests in patients with suggestive symptoms and brain imaging findings [7]. Considering the family history, it was decided to carry out a multigene panel for hereditary ataxia in the child. Subsequently, the analysis of the father’s KCNC3 gene was performed. The p.Arg423His (R423H) variant, identified in the patient and her father, was described in cases of congenital-onset cerebellar hypoplasia with non-progressive cerebellar ataxia [7,9]. The R423H mutation has been found in the S4 transmembrane domain of the channel, and it is a loss-of-function mutation. The Kv3.3 channel in most SCA13 patients is likely to be a tetramer containing both wild-type and mutant channels. R423H mutates the fourth arginine in the Kv3.3 S4 segment to histidine [5].

This phenotype can present with appendicular, truncal and/or gait ataxia, dysarthria, tremor, delay in acquiring speech/language and motor milestones, and cognitive impairment. Some patients may also manifest psychiatric disorders, nystagmus, hyperreflexia, and seizures. In addition, the brain MRI demonstrates congenital-onset non-progressive cerebellar hypoplasia [7]. Unlike other phenotypes, this one does not lead to progressive ataxia and can be associated with a gradual improvement in motor function throughout life, as observed in the patient’s father [7,9]. During childhood, he had gait ataxia that led to frequent falls. However, currently, he has a postural tremor and mild bilateral dysmetria, which do not affect his daily and professional activities. His gait has improved, keeping only an unstable tandem gait. His epilepsy has been under control without medication for several years. There was no information about his psychomotor development in the first years of life. Still, cognitive assessment performed in adulthood is normal. Therefore, his clinical evolution was favourable over the years, with improvements being noted.

The approach and follow-up by a multidisciplinary team are recommended for children with SCA13. They should be referred to an early intervention program and undergo physical, occupational, and speech therapy according to their needs and clinical manifestations. The neurodevelopmental assessment is essential and determines which therapies to perform and allows the development of an individualized education plan when necessary [7]. In this case, the girl started speech therapy because of dysarthria.
In addition, she performed physical and occupational therapy to promote motor skills development and improve her daily activities such as eating, dressing, and writing. SCA13 is inherited in an autosomal dominant way. Thus, many of the patients have a parent with the same disease. However, in rare cases, this disease may result from a de novo pathogenic variant. Therefore, it is recommended to provide genetic counseling to young adults affected by the disease or at risk [7].

Conclusion

The report of this family is relevant because it demonstrates a rare phenotype of an autosomal dominant hereditary ataxia, which does not course with progressive ataxia, and even some motor skills improvements can be achieved.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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