



A Longitudinal Follow Up in a First and Second Motoneuron Involvement SLC5A7-Related Disorder

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Keywords: SLC5A7; Hereditary spastic paraplegia; Upper motor neuron; Lower motor neuron; Atypical phenotype; Longitudinal follow up.

Abstract

Objective: Mutations in SLC5A7 are associated either with a form of recessive congenital myasthenic syndrome or with autosomal dominant distal hereditary motor axonal neuropathy type VIIa. The aim of the study is to describe the twelve-year neurological and clinical follow-up of a child with a mutations in SLC5A7.

Methods: Analysis of a clinical case

Result: Here we describe the case of a female who referred to the clinician at the age of six years old with scissor gait, pyramidal signs, and mild proximal hyposthenia. Motor evoked potentials showed bilateral involvement of upper motor neuron which, together with the clinical features, could suggest a diagnosis of hereditary spastic paraparesis. However, the clinical picture slowly evolved overtime and during follow up the child presented distal hyposthenia, hollow foot, and swallowing disturbances. Electrophysiological data and muscle magnetic resonance imaging revealed a progressive lower motor neuron impairment. An NGS panel found a de novo mutation in SLC5A7.

Conclusion: The presence of peripheral signs developed at an age compatible with distal hereditary motor axonal neuropathy type VIIa and currently available genetic data on the variant found, suggest a role for SLC5A7 in the patient's clinical picture. This study therefore describes an atypical new phenotype and characterize a wider spectrum of SLC5A7 genotype.



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Introduction

Mutations in *SLC5A7* are associated with a form of recessive congenital myasthenic syndrome or with autosomal dominant distal hereditary motor axonal neuropathy type VIIa. The latter condition is characterized by the onset in the second decade of progressive distal muscle atrophy and weakness in the upper and lower limbs, resulting in difficulty in walking and grasping [1]. Significant muscle atrophy of the hands and lower limbs is often detected, combined with vocal cord paralysis, due to vagus nerve involvement [2]. The aim of this case report is to describe clinical, imaging and molecular features of a patient presenting a *de novo* variant in *SLC5A7* and an atypical phenotype.

Case report

A 6-year-old girl was born to non-consanguineous parents and first visited by us for gait disturbances. No history of other family members suffering from similar complaints was reported. She was born at term without pre-perinatal problems, and she acquired ambulation at 17 months, though with frequent falls. At age six, her clinical picture was characterized by scissor gait, pyramidal signs, and lower limb girdle hyposthenia. A first brain magnetic resonance (MRI) at age 6 documented an Arnold Chiari type 1 malformation and dysmorphic corpus callosum. Motor evoked potentials showed bilateral involvement of upper motor neuron while the electrophysiological study of sensor and motor conduction velocity was normal. No mutations in *SPAST*, *ATL1*, and *FXN* were detected at that time. She was advised to wear an ankle foot orthosis.

At age 7, the patient reported increased fatigue and at clinical follow up presented with progressive distal hyposthenia, distal lower-limb atrophy with hollow foot in combination with known symptoms and sign of pyramidal tract involvement. Spine MRI was normal and brain MRI did not show variations when compared to previous scans.

At age 13, the patient showed a respiratory restriction pattern, and an electrocardiogram showed a right intraventricular conduction delay. Her echocardiogram was unremarkable. A multigene panel encompassing over 80 known genes associated with hereditary spastic paraparesis was also normal.

When 14 years, she presented impaired hearing for high frequency sounds with normal brainstem evoked potentials. At clinical examination she was still able to walk for long distances with support. Neurophysiological studies in the limbs were normal. The following year the girl had prolonged attacks of cough with tongue fasciculations, asymmetric uvula, and difficult swallowing, though neurophysiological investigations were normal.

Muscle MRI, performed at age 17, showed a mild involvement of the right adductor muscle, and hypotrophy of the thigh posterior compartment. A mild involvement of the leg was shown at the follow up after one year with oedema of right soleus, peroneus brevis, tibialis and left gastrocnemii (**Figure 1**).

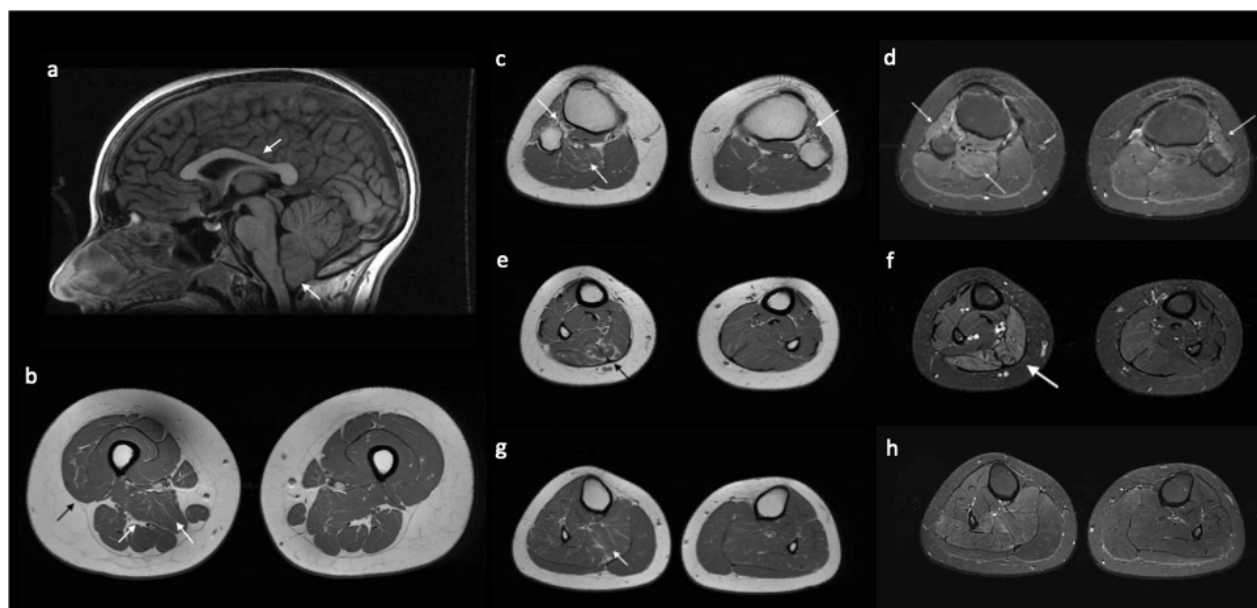


Figure 1: Sagittal T1-weighted brain Magnetic Resonance documented Arnold Chiari type 1 malformation and corpus callosum dysmorphism (a), T1-weighted muscle Magnetic Resonance axial images of the thighs (b) and legs (c,e,g), axial STIR muscle Magnetic Resonance images of the leg (d,f,h).

At age 18, the girl claimed difficulty in walking long distances and on uneven floors, fatigue and rare cramps which improved with heat, and sporadic difficulties in fine motor skills. A reduction in pyramidal signs and an increase of neuropathic features such as footdrop, hammer toes, painful hypoesthesia of the dorsal region of the left foot and facial asymmetry were recorded. However, scissors gait, increased tendon reflex, and mild retractions were still present. Due to the new clinical manifestations the patient started using a wheelchair for long distances. Neurophysiological studies showed reduced amplitude

of the motor response of the extensor digitorum brevis muscle of the right fingers and electromyography showed a chronic neurogenic damage to the distal lower limb muscles including the extensor digitorum longus muscle and the flexor digitorum longus muscle of the right lower limb. A second phoniatric examination observed an involvement of the central facial nerve with difficult swallowing and cough reflex whereas a nocturnal polysomnography showed a mild sleep apnoea syndrome with a purely central component. **Table 1** summarizes clinical evolution of symptoms overtime.

Table 1: Clinical signs development over time: + mild, ++: moderate +++: critical.

	6 yrs	7 yrs	9 yrs	13 yrs	14 yrs	15 yrs	18 yrs
Gait disturbances	+	+	+	+	+	+	+
Pyramidal signs	++	++	++	++	++	++	+
Proximal lower limb hyposthenia	+	+	+	+	+	+	+
Distal lower limb hyposthenia		+	++	++	++	++	+++
Lower limb hypotrophy		+	++	++	++	++	+++
Fatigue		+	+	+	++	++	++
Respiratory restriction				+	+	+	+
Abnormality on ECG				+	+	+	+
Hearing difficulty					+	+	+
Reduced pallesthetic sensitivity					+	+	+
Swallowing difficulties						+	+
Tongue fasciculations						+	+
Footdrop, hammer toe							+

A targeted gene panel for genes associated with peripheral nervous system disorders disclosed the heterozygous *de novo* c.872T>C (p.Ile291Thr) mutation in *SLC5A7*. The mutation, confirmed in Sanger sequencing, had a low frequency in gnomAD (0.0005) and a CADD score of 24.7. According to the ACMGG criteria the variant is classified as a “hot” VUS but its occurrence *de novo* permits its classification as likely pathogenic.

Conclusion

This clinical case reports the association of an atypical phenotype with *SLC5A7* in a patient whose clinical manifestation combined signs of upper and lower motoneuron. The presence of neurophysiological evidence of lower motor neuron impairment allowed to select the more precise diagnosis. The mutation detected in the patient has been reported in combination with a second gene variant in an individual with congenital myasthenic syndrome [3]. However, phenotypes due to autosomal dominant variants in *SLC5A7* are associated with distal hereditary motor axonal neuropathy type VIIa. In our case, the time of onset of peripheral neuropathy, the electrophysiologic studies, the muscle MRI findings which are consistent with a neurogenic muscle damage from peripheral nerve involvement, and the *de novo* variant makes it likely to assume a role for *SLC5A7* in the patient’s clinical picture. Interestingly, vocal cord involvement was not found during follow up although nerves involved in swallowing were affected, so a later involvement cannot be ruled out. Future functional investigations in model system will offer a new opportunity to corroborate predictions.

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