ELSEVIER

Brain & Development xxx (2009) xxx–xxx

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case report

Hereditary spastic paraplegia and axonal motor neuropathy caused by a novel SPG3A de novo mutation

Carlo Fusco [a,*], Daniele Frattini [a], Enrico Farnetti [b], Davide Nicoli [b], Bruno Casali [b], Francesco Fiorentino [c], Andrea Nuccitelli [c], Elvio Della Giustina [a]

[a] *Child Neurology Unit, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy*
[b] *Molecular Biology Unit, Santa Maria Nuova, Reggio Emilia, Italy*
[c] *Molecular Biology & Cytogenetics, Genoma Laboratories, Rome, Italy*

Received 24 April 2009; received in revised form 13 July 2009; accepted 16 August 2009

Abstract

Mutations in the SPG3A gene (atlastin protein) cause approximately 10% of autosomal-dominant hereditary spastic paraplegia. Most patients with an SPG3A mutation present with a pure phenotype and early-onset disease, although complicated forms with peripheral neuropathy are also reported. We report a new heterozygous S398F mutation in exon 12 of the SPG3A gene causing a very early-onset spastic paraplegia in association with motor axonal neuropathy in a 4-year-old girl resembling diplegic cerebral palsy.

Keywords: Hereditary spastic paraplegia; SPG3A; Axonal neuropathy

1. Introduction

Hereditary spastic paraplegia (HSP) comprises a group of inherited neurodegenerative disorders with the shared characteristics of progressive weakness and spasticity predominantly affecting the lower limb due a length-dependent, retrograde axonopathy of corticospinal motor neurons [1,2]. Traditionally, HSP are divided into pure (uncomplicated) and complicated, depending on the presence of other neurological features in addition to spastic paraparesis. Moreover, HSP can be inherited as an autosomal dominant, recessive, or X-linked recessive trait, and at least 41 spastic paraplegia gene loci have been mapped [3]. Early-onset HSP SPG3A (OMIM 182600) is caused by mutations in the gene encoding the large oligomeric GTPase atlastin-1 protein [4]. Mutations in SPG3A (also known as atlastin GTPase 1 [ATL1]) cause both pure and uncomplicated phenotypes with early onset and slow progression [5]. We report a 4-year-old girl carrying a new SPG3A mutation with early onset and severe phenotype, complicated by axonal motor neuropathy.

2. Case report

This patient was born to healthy nonconsanguineous parents after an uncomplicated pregnancy and delivery. Neonatal period was normal. At 6 months of life, neurological examination found signs of spasticity in the lower limbs resembling diplegic cerebral palsy. Routine laboratory studies and vitamin B12, apolipoprotein and lipid profile, plasma amino acids, biotinidase and

* Corresponding author. Address: Child Neurology Unit, Arcispedale Santa Maria Nuova, Viale Risorgimento 80, 42100 Reggio Emilia, Italy. Tel.: +39 0522295968; fax: +39 0522295046.
E-mail address: fusco.carlo@asmn.re.it (C. Fusco).

0387-7604/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.braindev.2009.08.003

vitamin E levels were normal. Brain and spinal magnetic resonance was normal. Ophthalmologic examinations yielded normal results. Nerve conduction velocities (NCV) and electromyography (EMG) were normal at 6 months old. Molecular analysis excluded mutations in MPZ, PMP22, SPAST, SPG7, KIF5A, and BSCL2. Genomic DNA was extracted from peripheral blood using a rapid extraction kit (Puregene Gentra System). SPG3A was amplified by PCR and both strands sequenced. Molecular analysis revealed a novel heterozygous S398F mutation in exon 12. To confirm the result and exclude the presence of a polymorphism, we tested samples from the patient and her parents by RFLP-PCR and subsequently from 200 unrelated healthy controls. The S398F mutation was found in the DNA of the patient only. NCV and EMG at 1 and 2 years of life showed progressive reduction of the compound muscle action potential of the peroneal and posterior tibial nerves with normal motor and sensory NCV in lower and upper limbs (Table 1). Sensory nerve conduction velocity, distal latency and amplitude potential of sural, superficial peroneal and median nerves were normal. Electromyography of the bilateral anterior tibial and gastrocnemius muscles showed chronic neurogenic changes. Brainstem evoked potentials showed reduced IV and V wave amplitude. The somatosensory evoked potential from the lower limbs showed very small cortical potentials. The last neurologic examination, performed at 4 years old, showed markedly increased tone, brisk tendon reflex, bilateral Babinski signs, distal atrophy, pes cavus, and weakness in lower limbs. The upper limbs were spared and there was no evidence of language or cognitive impairment (coefficient of 94 was found for total IQ on Wechsler Preschool and Primary Scale of Intelligence). No sphincter disturbance was reported.

Table 1
Motor nerve conduction findings.

Age	1 year	2 years
Right peroneal		
Conduction velocity	38 m/s (>36)	44 m/s (>40)
Response amplitude	0.8 mV (>2)	0.5 mV (>3)
Distal latency	2.1 ms (<3.2)	2 ms (<3.5)
Left peroneal		
Conduction velocity	38 m/s (>36)	45 m/s (>40)
Response amplitude	0.9 mV (>2)	0.5 mV (>3)
Distal latency	2 ms (<3.2)	2 ms (<3.5)
Right posterior tibial		
Conduction velocity	38 m/s (>35)	44 m/s (>40)
Response amplitude	1 mV (>3.5)	0.8 mV (>4)
Distal latency	2.6 ms (<3.5)	2.4 ms (<4)
Left posterior tibial		
Conduction velocity	38 m/s (>35)	44 m/s (>40)
Response amplitude	0.9 mV (>3.5)	0.7 mV (>4)
Distal latency	2.6 ms (<3.5)	2.5 ms (<4)

() = normal values.

3. Discussion

The diagnosis of HSP in sporadic case presents several difficulties and further investigation is often required. The onset of HSP may be subtle, with development of leg stiffness, brisk reflex, clonus and mild distal hypertonia in the lower limb mimicking spastic diplegic cerebral palsy. Thereby, we first excluded cerebral palsy because of normality of perinatal history and cerebral magnetic resonance imaging study. Moreover, metabolic conditions clinically resembling complicated HSP including amino acids disorders, biotinidase, vitamin B12 and vitamin E deficiency, and inherited neuropathy were ruled out. Numerous studies have documented that HSP syndromes are heterogeneous, but the most striking feature reported for most affected members showing a mutation in SPG3A is the young age at onset [6]. In fact, SPG3A mutations cause approximately 10% of dominantly inherited, uncomplicated HSP and approximately 25% of early childhood onset of dominant HSP [7]. The clinical features that we describe here, associated with an S398F mutation in exon 12 of SPG3A, are a very early onset (before or at age of 6 months) and a progressive form of spastic paraplegia of the lower limbs associated with axonal motor neuropathy. Up to now, SPG3A was associated with an early onset of symptoms, mainly in the first decade [7], while our patient developed a spastic paraplegia before or at age of 6 months. Moreover, although SPG3A-HSP was first considered pure and almost indistinguishable from SPG4 HSP, except that it begins earlier, SPG3A mutations associated with axonal neuropathy are reported, usually with sensory-motor axonal neuropathy [5–9]. Ivanova et al. described SPG3A patients with axonal predominantly motor polyneuropathy, but reduction of sensory action potential or velocity conduction of sural nerve was also present. In our case, the neurophysiological studies revealed a pure motor axonal polyneuropathy in the lower limb without sensory nerve involvement (Table 1). All of the neurophysiological examinations performed on our patient showed reductions in potential amplitude, with normal conduction velocities, reflecting the main axonal involvement often observed in HSP SPG3A patients. Besides, this neurophysiological pattern in part differs from other reports where an increased central conduction times were often found for auditory and motor symptoms, but not for somatosensory evoked potentials [7]. The clinical and neurophysiological findings that we have described might find an possible explanation in view of experimental literature data and in light of the localization and the functions of human atlastin protein. In fact, atlastin

Please cite this article in press as: Fusco C et al. Hereditary spastic paraplegia and axonal motor neuropathy caused by a novel SPG3A de novo mutation. Brain Dev (2009), doi:10.1016/j.braindev.2009.08.003

GTPase 1 is predominantly localized to the central nervous system, but it is also expressed at low levels in peripheral tissue [4]. This protein has been implicated in intracellular membrane trafficking, particularly at the endoplasmatic reticulum-to-Golgi interface; atlastin GTPase 1 is also present in growth cones and is required for axon formation and elongation during development [4]. In our patient, the axonal motor neuropathy and the chronic neurogenic changes in the lower limbs could reflect axonal loss in motor nerves, involvement of the lower motor neurons, or both. Alternatively, axonal loss in both motor and sensory tracts in HSP supportive of a "dying back" process has been reported [10]. Thus, the associated axonal peripheral motor neuropathy might suggest an important role for atlastin GTPase 1 also in peripheral nervous system development. Finally, very early-onset spasticity with associated axonal motor neuropathy as the earliest sign of disease is of practical importance, as it directly points to the right diagnosis and allows genetic counseling of this form of HSP for any further gestation. The interindividual variability of the genotype–phenotype correlation probably reflects the limitations of our understanding of the relationship between the biologic functions of the affected protein, postulated modulator genes and environmental factors. In conclusion, although SPG3A mutations are frequent in young-onset spastic paraplegia we were able to show that an S398F mutation in exon 12 of SPG3A causes a very early onset (before or at 6 month of life) of spastic paraplegia with associated motor axonal neuropathy. This report further on expands the clinical spectrum of SPG3A mutations. We finally remark that HSP with SPG3A de novo mutations should be considered in patients with symptoms resembling spastic diplegic cerebral palsy with normal neuroimaging and perinatal and familiar history.

Acknowledgements

Thanks go to Mrs. Elena Bonini and Mrs. Giuliana Soncini for their technical assistance.

References

[1] Loureiro JL, Miller-Fleming L, Thieleke-Matos C, Magalhães P, Cruz VT, Coutinho P, et al. Novel SPG3A and SPG4 mutations in dominant spastic paraplegia families. Acta Neurol Scand 2009;119:113–8.
[2] Dalpozzo F, Rossetto MG, Boaretto F, Sartori E, Mostacciuolo ML, Daga A, et al. Infancy onset hereditary spastic paraplegia associated with a novel atlastin mutation. Neurology 2003;61:580–1.
[3] Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. Lancet Neurol 2008;7:1127–38.
[4] Rismanchi N, Soderblom C, Stadler J, Zhu PP, Blackstone C. Atlastin GTPases are required for Golgi apparatus and ER morphogenesis. Hum Mol Genet 2008;17:1591–604.
[5] Haberlová J, Claeys KG, Zámečník J, De Jonghe P, Seeman P. Extending the clinical spectrum of SPG3A mutations to a very severe and very early complicated phenotype. J Neurol 2008;255:927–8.
[6] Abel A, Fonknechten N, Hofer A, Dürr A, Cruaud C, Voit T, et al. Early onset autosomal dominant spastic paraplegia caused by novel mutations in SPG3A. Neurogenetics 2004;5:239–43.
[7] Dürr A, Camuzat A, Colin E, Tallaksen C, Hannequin D, Coutinho P, et al. Atlastin1 mutations are frequent in young-onset autosomal dominant spastic paraplegia. Arch Neurol 2004;61:1867–72.
[8] Scarano V, Mancini P, Criscuolo C, De Michele G, Rinaldi C, Tucci T, et al. The R495W mutation in SPG3A causes spastic paraplegia associated with axonal neuropathy. J Neurol 2005;252:901–3.
[9] Ivanova N, Claeys KG, Deconinck T, Litvinenko I, Jordanova A, Auer-Grumbach M, et al. Hereditary spastic paraplegia 3A associated with axonal neuropathy. Arch Neurol 2007;64:706–13.
[10] DeLuca GC, Ebers GC, Esiri MM. The extent of axonal loss in the long tracts in hereditary spastic paraplegia. Neurophatol Appl Neurobiol 2004;30:576–84.

Please cite this article in press as: Fusco C et al. Hereditary spastic paraplegia and axonal motor neuropathy caused by a novel SPG3A de novo mutation. Brain Dev (2009), doi:10.1016/j.braindev.2009.08.003