

Case Report

SPG11 Presenting with Tremor

Susanne A. Schneider^{1,2}, Catherine J. Mummery³, Mohadeseh Mehrabian⁴, Henry Houlden⁴ & Peter G. Bain^{2*}

¹Schilling Section of Clinical and Molecular Neurogenetics, Department of Neurology, University Luebeck, Germany, ²Dementia Research Centre, Institute of Neurology, London, United Kingdom, ³UCL Institute of Neurology, London, United Kingdom, ⁴Department of Clinical Neuroscience, Imperial College London, Charing Cross Hospital Campus, London, United Kingdom

Abstract

Background: Hereditary spastic paraplegias (HSPs) are a clinically and genetically heterogeneous group of neurological diseases, which typically present with progressive lower extremity weakness and spasticity causing progressive walking difficulties. Complicating neurological or extraneurological features may be present.

Case Report: We describe a 19-year-old male who was referred because of an action tremor of the hands; he later developed walking difficulties. Callosal atrophy was present on his cerebral magnetic resonance imaging scan, prompting genetic testing for SPG11, which revealed homozygous mutations.

Discussion: The clinical features, differential diagnosis and management of SPG11, the most common form of autosomal recessive complicated HSP with a thin corpus callosum are discussed.

Keywords: Tremor, SPG11, hereditary spastic paraplegia, spatacsin

Citation: Schneider SA, Mummery CJ, Mehrabian M, et al. SPG11 presenting with tremor. Tremor Other Hyperkinet Mov 2012;2: http://tremorjournal.org/article/view/104

*To whom correspondence should be addressed. E-mail: p.bain@imperial.ac.uk

Editor: Elan D. Louis, Columbia University, United States of America

Received: May 4, 2012 **Accepted:** May 26, 2012 **Published:** September 14, 2012

Copyright: © 2012 Schneider et al. This is an open-access article distributed under the terms of the Creative Commons Attribution–Noncommercial–No Derivatives License, which permits the user to copy, distribute, and transmit the work provided that the original author(s) and source are credited; that no commercial use is made of the work; and that the work is not altered or transformed.

Funding: Part of this work was undertaken at University College London Hospitals/University College London, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. Dr. Schneider was supported by the Bosch Foundation.

Financial Disclosures: None.

Conflict of Interest: The authors report no conflict of interest.

Introduction

Here, we describe a case of hereditary spastic paraplegia (HSP) with tremor as the presenting feature. HSPs are a clinically and genetically heterogeneous group of diseases, which typically present with slowly progressive lower-extremity weakness and spasticity, causing progressive walking difficulties.^{1,2} Additional bladder dysfunction and mild sensory signs may be present. In contrast to these “pure” forms, “complicated” variants with additional features occur, which may include seizures, dementia, amyotrophy, or extrapyramidal dysfunction. To date, at least 48 different subtypes of HSP have been recognized. Here we present a case of SPG11 due to mutations in the *spatacsin* gene, a major cause of complex phenotypes. The presence of a thin corpus callosum is characteristic and its finding should be a red flag.

Case report

This 19-year-old right-handed male was born after an uneventful pregnancy. He reached his early milestones for standing, walking, and

speech slightly late; he was a slow learner in school but passed several exams and went on to a higher education college. He had no problems competing with his peers in sports. His problems began at age 14, when he noted a tremor of the hands, so that he required a scribe for his school exams.

His past medical history was unremarkable. He did not smoke or drink alcohol. His parents had moved to the United Kingdom from Kenya only a few years earlier. There was no history of tremor or other movement disorder in the family; however, one distant paternal cousin was said to have some form of spastic paraplegia.

When seen by a pediatric neurologist at age 16, there was an evident mild action tremor. He had increased tone in his limbs, particularly the legs, with brisk reflexes and flexor plantar responses. Power and sensory examination were normal and there were no cerebellar signs. Although he was noted to have a slightly stiff gait, initially a diagnosis of “anxiety related tremor” was made and propranolol prescribed. However, 6 months later he developed leg pain and difficulty climbing stairs. He noted problems getting on and off trains without holding a

bar for support. He also complained of leg stiffness in the mornings prompting further evaluation.

Routine bloods, thyroid function tests, and ceruloplasmin were normal. Genetic testing for Huntington's disease (HD), dentatorubral pallidoluysian atrophy, and spinocerebellar ataxias were negative. Magnetic resonance imaging (MRI) of the spine was normal; in particular, there was no spinal cord compression or lesion. An MRI scan of the brain was also reported to be normal, although on later review this was found to contain a key diagnostic clue.

When he first presented to us at age 17 his symptoms had progressed. The action tremor was intrusive, affecting both hands, right more than left, and disturbing fine manual function (e.g. writing and doing up buttons). His parents noted that he had become more anxious and prone to laughter. His appetite was normal and there were no bladder or bowel symptoms. On examination there was emotional lability. He had a moderate dysarthria, but cranial nerve examination, including fundi and eye movements, was otherwise normal. There were no abnormal signs in the upper limbs, except mild dysidiadochinesia. In particular, there was no tremor evident at rest, posture, or during intention, but mild tremor was present when trying to pick up change, open a bottle, or draw (Figure 1). In the lower limbs, there was spastic paraparesis with increased tone, very brisk reflexes, clonus at both ankles and extensor plantar responses. He wore foot splints because of bilateral upper motor neuron foot drop. There was no sensory deficit. His gait was narrow-based and there was a tendency to drag his legs.

Propranolol 80 mg/day proved unhelpful for this intermittent tremor. Baclofen 10 mg twice daily, however, relieved his muscle spasms.

His previous imaging studies were reviewed and the corpus callosum was noted to be abnormally thin (Figure 2). This prompted genetic

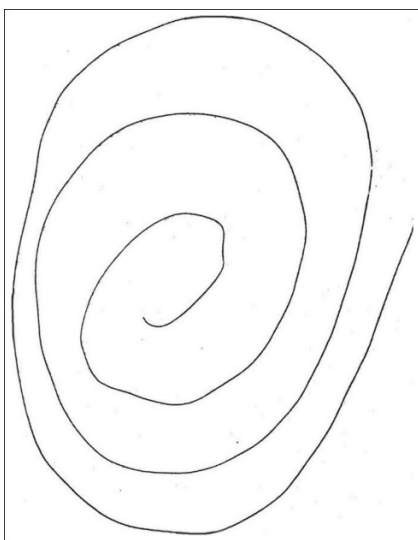


Figure 1. Ataxic-Tremor in a Spiral Drawing. A spiral drawn by the patient when aged 17 years, showing mild ataxic (wavy rather than saw-tooth) type action tremor.

testing for SPG11, which revealed a homozygous c.5769delT *spatacsin* mutation, resulting in p.S1923RfsX1950 with a premature stop at codon 1950.

Discussion

HSPs are a clinically and genetically heterogeneous group of neurological diseases. In practice “pure” manifestations are distinguished from “complicated” HSP forms, as the latter have additional neurological or extraneurological features, including mental retardation, dysarthria, ataxia, peripheral neuropathy, or muscle atrophy.¹ Extrapyramidal features as presenting or main feature are rare. Inheritance of HSPs may be autosomal dominant, autosomal recessive, or X-linked. However, most cases follow an autosomal dominant pattern with SPG4 being most frequent, accounting for ~40% of dominant HSPs. Among the autosomal recessive forms, mutations in the *spatacsin* gene on chromosome 15q (SPG11, MIM610844) are a major cause of complex phenotypes, particularly when atrophy of the corpus callosum is also present. Thus, in one study, the overall frequency of SPG11 among patients with autosomal recessive early-onset complicated HSP was 14%, but this was considerably higher in patients with a thin corpus callosum (42%).³

Onset of SPG11 is early (during infancy or adolescence; age range 1–31 years),⁴ in line with our case. Progressive leg stiffness and learning disabilities are the commonest symptoms at onset. Although our patient had slightly delayed milestones, he presented with tremor, which was followed by the development of leg stiffness and walking difficulty. Patients may develop dysarthria, cerebellar ataxia, urinary incontinence, or ophthalmological symptoms, including macular degeneration, strabismus, or cataract. Peripheral neuropathy of the axonal motor or sensorimotor type occur later in the disease course. However, with identification of the gene, unusual phenotypes are increasingly recognized and include a juvenile, slowly progressive form of motor neuron disease associated with long-term survival,⁵ but not cognitive impairment and a thin corpus callosum (TCC). A predominantly parkinsonian phenotype has also been reported recently.^{6,7} Our patient was referred to us because of tremor, which is a rare presenting sign (seen in one of 37 gene-proven cases⁸). There were no signs of parkinsonism in our patient.

However, while the clinical presentation of SPG11 can be complex and overlaps with cerebellar ataxias, leukodystrophies, and other disorders, certain features are usually not present in pure or complicated HSPs and should make the clinician suspicious of an alternative diagnosis. This includes profound involvement of the upper extremity or bulbar muscles, or diurnal fluctuations and dopa responsiveness (as seen in dopa-responsive dystonia).

Thinning of the corpus callosum and in most cases periventricular white matter alterations on MRI are characteristic of SPG11.⁹ This finding prompted us to perform molecular testing for SPG11 in our case. However, a thin corpus callosum may also occur in other subforms of HSP, including SPG15 (spastizin, 14q22), SPG21 (maspardin, 15q22), SPG32 (14q12), SPG47 (AP4B1, 1p13) and HSP-TCC with epilepsy (8p12) and occasionally in SPG4 (SPAST,

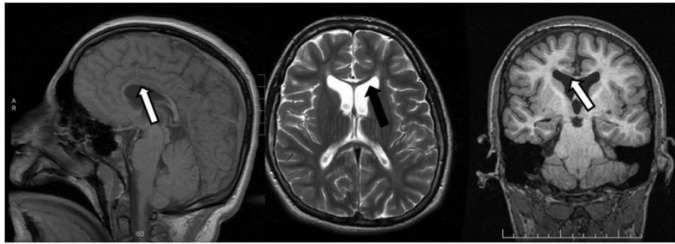


Figure 2. MR Brain Scan Showing a Thin Corpus Callosum. Sagittal brain magnetic resonance imaging of the patients with an SPG11 mutation demonstrating a thin corpus callosum (arrowed), a useful clue to this diagnosis (left, sagittal T1; center, axial T2, right, coronal T1 gradient echo).

2p22) and SPG7 (paraplegin, 16q24). Molecular testing can determine the underlying HSP form for those with known gene defects. The *spatacsin* gene (SPG11) has 40 exons and encodes a protein of 2443 amino acids of unknown function, which is widely expressed in the adult cerebellum, cerebral cortex, hippocampus, and pineal gland.¹⁰ The mutation identified in our case has previously been reported.¹¹

Neuropathologically, SPG11 is characterized by “dying-back” axonal degeneration, maximal at the distal ends of the corticospinal tracts.^{1,2} Mild loss of anterior horn cells may occur. Demyelination, if present, is consistent with the degree of axonal degeneration. Atrophy may also affect the brainstem, cerebellum, and deep gray matter, whereas the basal ganglia and spinal cord are usually spared. The pathophysiological underpinnings of tremor in SPG11 may include cerebellar dysfunction and neuropathy.

The treatment of HSPs remains symptomatic and should be tailored to the individual symptoms, for example baclofen can alleviate spasticity. Patients may benefit from a multidisciplinary approach that includes physiotherapy, speech therapy, and occupational therapy. Genetic counseling should be offered and prenatal testing may be available for families in which a disease-causing mutation has been detected.

Acknowledgment

We thank Dr Amrish Mehta, consultant neuroradiologist at Imperial College Healthcare NHS Trust, Charing Cross Hospital, London, UK, for radiological advice.

References

1. Depienne C, Stevanin G, Brice A, et al. Hereditary spastic paraplegias: an update. *Curr Opin Neurol* 2007; 20:674–680, <http://dx.doi.org/10.1097/WCO.0b013e3282f190ba>.
2. Salinas S, Poukakis C, Crosby A, et al. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. *Lancet Neurol*. 2008; 7:1127–1138.
3. Schule R, Schlipf NA, Synofzik M, et al. Frequency and phenotype of SPG11 and SPG15 in complicated hereditary spastic paraplegia. *J Neurol Neurosurg Psychiatry* 2009;80:1402–1404, <http://dx.doi.org/10.1136/jnnp.2008.167528>.
4. Stevanin G, Durr A, Brice A. Spastic Paraplegia Type 11. In: GeneReviews [Internet]. Ed. Pagon RA, Bird JD, Dolan CR, Stephens K, Adam MP. Seattle (WA): University of Washington 1993.
5. Orlicchio A, Babalini C, Borreca A, et al. SPATACSIN mutations cause autosomal recessive juvenile amyotrophic lateral sclerosis. *Brain* 2010;133:591–598, <http://dx.doi.org/10.1093/brain/awp325>.
6. Anheim M, Lagier-Tourenne C, Stevanin G, et al. SPG11 spastic paraplegia. A new cause of juvenile parkinsonism. *J Neurol* 2009;256:104–108.
7. Paisan-Ruiz C, Guevara R, Federoff M, et al. Early-onset L-dopa-responsive parkinsonism with pyramidal signs due to ATP13A2, PLA2G6, FBXO7 and spatacsin mutations. *Mov Disord* 2010;25:1791–1800, <http://dx.doi.org/10.1002/mds.23221>.
8. Stevanin G, Azzedine H, Denora P, et al. Mutations in SPG11 are frequent in autosomal recessive spastic paraplegia with thin corpus callosum, cognitive decline and lower motor neuron degeneration. *Brain* 2008;131:772–784, <http://dx.doi.org/10.1093/brain/awm293>.
9. Stevanin G, Azzedine H, Denora P, et al. Mutations in SPG11 are frequent in autosomal recessive spastic paraplegia with thin corpus callosum, cognitive decline and lower motor neuron degeneration. *Brain* 2008;131:772–784, <http://dx.doi.org/10.1093/brain/awm293>.
10. Stevanin G, Santorelli FM, Azzedine H, et al. Mutations in SPG11, encoding spatacsin, are a major cause of spastic paraplegia with thin corpus callosum. *Nat Genet* 2007;39:366–372, <http://dx.doi.org/10.1038/ng1980>.
11. Paisan-Ruiz C, Dogu O, Yilmaz A, et al. SPG11 mutations are common in familial cases of complicated hereditary spastic paraplegia. *Neurology* 2008;70:1384–1389, <http://dx.doi.org/10.1212/01.wnl.0000294327.66106.3d>.