Citation: Murugan A, Mallick AA, Dibble L, Babiker MOE. Thin corpus callosum as a diagnostic marker for hereditary spastic paraparesis due to mutations in the *SPG11* gene: a case report. European Journal of Medical Case Reports. 2017; 1(3):122–125. https://doi.org/10.24911/ejmcr/1/29

European Journal of Medical Case Reports

CASE REPORT

Thin corpus callosum as a diagnostic marker for hereditary spastic paraparesis due to mutations in the *SPG11* gene: a case report

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ABSTRACT

Background: Hereditary spastic paraparesis (HSP) is a rare neurodegenerative condition that results in gradual deterioration of lower limb function due to spastic weakness. It can manifest at any age and predominantly presents as gait abnormalities especially tip toe walking. They are classified as simple or complicated based on additional clinical/neurological symptoms apart from lower limb involvement. These are genetically heterogeneous disorders with mutations discovered in more than 50 genes. The association of thin corpus callosum (TCC) along with clinical features of spastic paraplegia is particularly described in mutations of *SPG11* gene.

Case presentation: We describe two unrelated cases of childhood onset HSP-TCC associated with mutations in exon16 and exon 28: exon 30 respectively. Both these patients also have associated learning difficulties.

Conclusion: The constellation of clinical symptoms and MRI findings led to targeted genetic testing and subsequent identification of their diagnosis.

Key words: Corpus callosum, hereditary spastic paraparesis, *SPG11* gene, case report.

Background

The hereditary spastic paraparesises (HSPs) are clinically and genetically heterogeneous disorders. Mutations in more than 50 genes cause neurodegeneration of the distal corticospinal tracts. Various autosomal and X-linked modes of transmission are described. Genetic loci for HSP are designated SPG (for "spastic paraplegia") 1 through 56 in order of their discovery [1]. They are characterized by lower limbs spasticity and weakness occurring in variable proportions. The HSPs are classified as either pure (when lower limbs involvement is the predominant feature) or complicated when additional neurologic manifestations are present. These may include ataxia, seizures, intellectual disability, amyotrophy, extrapyramidal disturbance, or optic atrophy.

Homozygous or compound heterozygote mutations in the *SPG11* gene lead to HSP with thin corpus callosum (TCC). This rare neurodegenerative disorder is classified as a complicated form [2].

We report two unrelated cases of childhood-onset HSP in association with TCC caused by mutations in the *SPG11* gene.

Case presentation

Case 1

This 15-year-old male of an Asian origin was the 4th child born to consanguineous parents. There were

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no significant perinatal concerns. He was delayed in acquiring early motor developmental milestones. Language and fine motor milestones were also delayed. From around the age of 5 years, he needed extra support with learning. Over the years, there had been a gradual decline in his cognitive abilities. Since the age of 13 years, he developed significant gait difficulties. His legs started becoming stiffer to the extent that he was not able to cross them or bend his knees. He has had gradual worsening of these symptoms to the extent of now using a wheelchair for long distance mobilization. He has also reported symptoms of urinary urgency.

On examination, he had increased tone in both lower limbs with symmetrical hyperreflexia. He also had up going planter reflexes and was found to have some degree of impaired proprioception. He did not have any fixed joint contractures. The rest of the neurological examination was normal suggestive of a spastic paraparesis.

There was no one else in the wider family with a similar clinical presentation.

He underwent some baseline metabolic testing which included a normal acylcarnitine, white cell enzymes, biotinidase, urine organic acids and very long chain fatty acids. He also had normal Cerebro-spinal fluid (CSF) neuro-metabolites and normal CSF values for protein, lactate and glucose. All other baseline blood investigations were within normal limits.

Magentic Resonance imaging (MRI) of his head showed a thin corpus callosum with no other structural abnormality and the spinal cord was normal.

In view of his clinical presentation of spastic paraplegia and thin corpus callosum, genetic analysis for *SPG11* mutations was sent. He was found to be homozygous for c2887C>A, likely pathogenic missense mutation in exon 16 of *SPG11* gene.

Case 2

Our second patient is a 15-year-old male, who initially presented to a pediatrician for long term toe walking with significantly limited dorsiflexion needing serial ankle casting. He was noted to have delayed social and language skills. There were also concerns about him being in the autistic spectrum disorder.

He had an uncomplicated birth history and there was no one else in the family presenting with a similar clinical picture. He walked independently from the age of 18 months and his parents reported that he always disliked walking. Throughout his early childhood, he sometimes walked on tip-toes, especially when tired. By his early teenage years, he was more frequently walking on tip-toes and at the time of presentation had very limited bilateral foot dorsiflexion although he was still able to walk independently without assistance. He was found to have bilateral lower limb abnormalities with increased tone, brisk reflexes and sustained clonus. He had a mild weakness, especially in ankle dorsiflexion. He also had a detailed cognitive assessment using Wechsler Intelligence Scale for Children-UK which had shown poor verbal comprehension skills within low average of 23 % with perceptual reasoning skills in 14th percentile.

His MRI head showed thinning of the corpus callosum and bilateral periventricular flaring. Spinal cord imaging was normal. His genetic analysis showed that he is compound heterozygous for two pathogenic mutations within the *SPG11* gene: A c.4790G>A nonsense mutation in exon 28 and A c.5456_5457del frameshift mutation in exon 30, predicted to result in the p.Trp1597* and p.Glu1819fs protein change, respectively. These mutations are predicted to result in targeting of the mRNA for nonsense mediated decay or premature truncation of the protein and hence are also predicted to be pathogenic.

Discussion

The *SPG11* gene provides instructions for making the protein spatacsin. This protein is active (expressed) throughout the nervous system, although it's exact function is unknown. The Cytogenetic Location is 15q21.1, which is the long (q) arm of chromosome 15 at position 21.1.

Thinning/hypoplasia of corpus callosum can occur in various congenital or acquired conditions including neurometabolic, genetic, demyelinating or inflammatory causes [3].

The presence of HSP-TCC is the single best indicator that *SPG11* should be tested in patients with onset of symptoms in the first to third decade. The presence of one or more other signs, such as cognitive deterioration, lower motor neuron involvement and white matter lesions, increases the chance of identifying *SPG11* mutations. Additionally, evidence of white matter abnormalities in the periventricular regions increases even further the probability that *SPG11* mutation is the cause of the disease, rather than other causes of leucodystrophy [4].

In our patients, this particular clinical presentation with the MRI finding of TCC and the additional finding of periventricular flaring in the second patient led to the early genetic testing particularly for *SPG11* mutations and subsequent clinching of clinical diagnosis in a cost effective manner. We wish to highlight the constellation of findings including clinical features of spastic paraparesis and MRI finding of TCC which should prompt a targeted genetic testing for *SPG11* mutations.

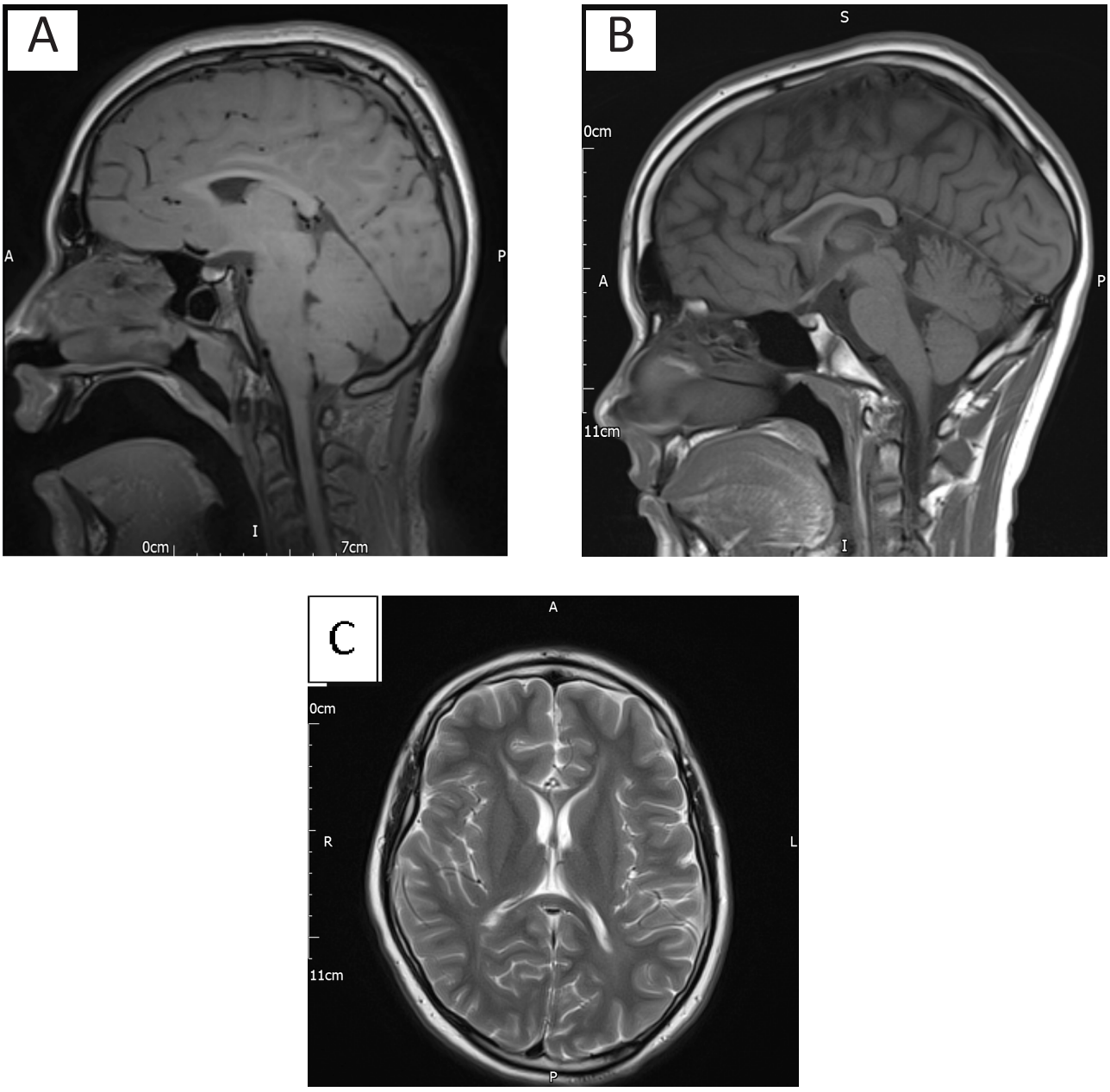

Image 1: (A) *T1 Saggital section showing thin corpus callosum in Case 1.* ***(B)*** *T1 Saggital section showing thin corpus callosum in Case 2,* ***(C)*** *T2 image showing bilateral periventricular flaring in Case 2.*

List of Abbreviations

HSP	Hereditary spastic paraparesis
TCC	Thin Corpus Callosum
CSF	Cerebro-spinal fluid
MRI	Magnetic resonance imaging

Consent for publication

Informed consent has been obtained from parents to present and publish this case.

Conflict of Interest

None

Ethical approval

Ethical approval is not required at our institution for publishing a case report in a medical journal.

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Authors' contribution

All authors contributed to the management of the patients. All have also contributed to the drafting, revising and final editing of the manuscript.

Received Date: 25 May 2017
Accepted Date: 27 June 2017
Published Online: 10 July 2017

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Summary of the case

Patient	1	Male, 15 year old
Final Diagnosis	2	*SPG11* gene mutation causing Spastic paraparesis and other associated findings
Symptoms	3	Spastic paraparesis and learning difficulties
Medications (Generic)	4	N/A
Clinical Procedure	5	Neuroimaging/Genetic testing
Specialty	6	Pediatrics, Genetics, Neurology
Objective	7	Highlight importance of genetic testing in similar cases
Background	8	The hereditary spastic paraparesises (HSPs) are clinically and genetically heterogeneous disorders. The HSPs are classified as either pure (when lower limbs involvement is the predominant feature) or complicated when additional neurologic manifestations are present. These may include ataxia, seizures, intellectual disability, amyotrophy, extrapyramidal disturbance, or optic atrophy.
Case Report	9	Two pediatric patients with findings of spastic paraparesis and thin corpus callosum in MRI with *SPG11* gene mutation
Conclusions	10	We recommend testing for *SPG11* gene mutations in any child with spastic paraparesis and thin corpus callosum in MRI
MeSH Keywords	11	Corpus callosum, hereditary spastic paraparesis, *SPG11* gene, case report