Children with genetically confirmed Hereditary Spastic Paraplegia (HSP): A case series from Eastern Mediterranean Region of Turkey

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INTRODUCTION

Hereditary spastic paraplegias (HSP) are genetically classified according to the mode of inheritance, chromosomal locus and causative mutation. The inheritance patterns of the cases are defined as autosomal dominant (AD), autosomal recessive (AR), X-linked dominant or mitochondrial inheritance. They are named SPG according to genetic loci and numbered as SPG 1, SPG 2, SPG3, and so on, respectively. The number of genetic loci continues to increase with new genetic descriptions. In contrast, correlation of clinical classification (pure or complex) with genetic classification (SPGtype) is not possible as some genetic HSP strains are associated with both pure and complex phenotypes. Beside this sometimes, a specific form of spastic paraparesis may be caused by both dominant and recessive variants in the same gene.

OBJECTIVES

We retrospectively evaluated 7 consecutive children with genetically confirmed HSP at the pediatric neurology division of Baskent University, Adana Hospital between february 2019 and June 2022.

MATERIALS & METHODS

The age of onset ranged from 2 months to 7 years and 4 patients were less than 2 years old at the time of onset. The follow-up period of the patients was 4-10 years. All of the patients admitted with lower extremity spasticity,weakness,brisk reflexes and motor delay accept one patient. One patient each had seizure, ataxia and three of them had neurogenic bladder. Third patients had corpus callosum hypoplasia. Genetic analyzes were revealed pathogenic mutations in the SPG genes. Demographic, clinical and genetic characteristics of the patients are shown in table1.

DISCUSSION

The HSP associated with **SPG11** is one of the most common types of AR complicated form HSP. Up-to-date all reported cases with SPG11 gene mutations related with HSP are always seen as a homozygous or compound heterozygous mutations. Our case 1 was diagnosed as a possible pure HSP associated with the heterozygous SPG11 mutations since no other cause could be found in her analysis. However the mother has also the same heterozygous variant, there has been still an unclarified genetic situations such as incomplete penetrance or variable expression patterns. **SPG46,** one of autosomal recessive complicated HSP. The second presented case was accepted as AD inherited **GBA2-associated HSP**. Heterozygous mutation with **GBA2-associated HSP** are reported for the first time and expand the inheritance pattern of GBA2-associated HSP. Heterozygous or homozygous variants in **KIF1A** underlie a wide spectrum of neurodegenerative disorders that range from pure to complex forms of **SPG30** as well as ataxic phenotype and other 'atypical' phenotypes. Age of onset in both AR and AD SPG30 is highly variable from congenital to adult-onset cases. The third case in this study has previously reported **KIF1A** mutation related with pure HSP with cerebellar and corpus collasum hypoplasia on brain MRI.**(Figure 1)** Although **C19orf12** homozygous mutations are often related with **MPAN**. C19orf12 mutation can present with or without typical features of NBIA, i.e., that it can cause spastic **SPG43** without vision loss and brain iron accumulation, or with vision loss and evidence of brain iron accumulation but without extrapyramidal features. To the best of our knowledge, only three article was reported with **SPG43** in literature. The fourth case in present study had **a novel homozygous C19orf12** mutation with iron accumulation in the brain which expands the genetic variants and clinical findings **C19orf12-associated HSP**. **(Figüre 2) SPG73** has been reported a pure form of AD-HSP characterized by adult-onset slowly progressive form in an Italian family in 2015. However Hong et al reported a Chinese family with the relatively benign clinical course with congenital onset. Our case five diagnosed as first Turkish patient with **CPT1C** mutation related pure HSP and third family in literature. He is also the youngest patient diagnosed as **SPG73.** His father also had some mutation without any neurologic symptoms. The mother of Chinese cases reported by Hong et al also had CPT1C mutation with only hyperreflexia and mild extensor plantar response without any other symptoms. Therefore incomplete penetrance or variable expression patterns are present for CPT1C mutation of our case and Hong et al cases. The **TFG gene** has been linked to diverse hereditary neurodegenerative disorders, including AR inherited complicated **SPG57.** Until now, nine families affected with **SPG57** and fifth pathogenic variants of **TFG** have been reported. The clinical variation of **SPG57** explained as mutations in TFG gene different domains of the TFG gene. Our case six has two different homozygous mutation in **TGF** gene. These mutations were novel mutations and the patient's parents were also heterozygous for the same two different mutations. So that, these mutations were considered as causative mutations. She was the first Turkish patient with **TFG** gene mutation in literature. She is diagnosed as pure form of HSP which form did not reported previously. However new neurologic or extraneurologic findings can be added in the following years since the age of patients is only four. This case also expands the genetic variants and clinical findings of **TFG mutation related HSP**. **SPG4** is the most common form of AD pure HSP and associated with SPAST gene (Spastin). SPG4 is usualy adult onset but age of onset varies with a range that extends from birth to the eighth decade due to incomplete penetrance. Our case 7 year old girl with pure HSP.

Patient no.	Age(y) /Sex	Brain MRG	Spinal MRG	Genetic mutation
1	7Y6mo/Female	Cerebellary, CC hypoplasia, vermis dysplasia	N	SPG11 c.6730C>T heterozygote (p.L2244F)
2	4y7mo/Male	CC hypoplasia,	N	GBA2 NM_020944.3 c.1688-2A>C heterozygote
3	9y10mo/Female	Vermis, CC hypoplasia	N	KIF1A c.773C>T heterozygote (p.V391M)
4	16y11mo/Female	Bilateral globus pallidus T2 hypointensity, iron accumaltion	-	C19orf12 c.385C>T (p.Q1239*) (p.Gln129Ter) Homozygote
5	5y6/Male	N	N	CPT1C c.109C>T (p.R37C) heterozygote
6	5y8mo/female	N	N	TFG NM_001195478.1 c.269-8_269-4dup Homozygote TFG NM_001195478.1 c.288_297 delCCTTGAATCAinsTGACTTG Homozygote
7	7y2mo/Female	N	N	SPAST NM_014946.4 c.1496G>A heterozygote p.R499H

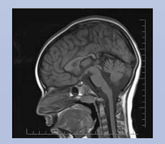

Figure 1. cerebellar and corpus collasum hypoplasia

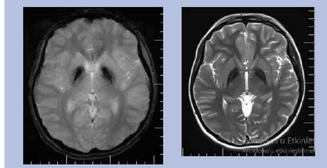

Figure 2. Bilateral hypointensity of globus pallidus and substantia nigra in T2-weighted images

CONCLUSION

Herein we report the first case of HSP associated with the heterozygous SPG11 mutation in literature. Although SPG11 mutation usually related with complicated form of HSP, this case is pure form. Heterozygous mutation with GBA2-associated HSP are also reported for the first time which expand the inheritance pattern. We also report a novel homozygous C19orf12 mutation associated HSP with iron accumulation in the brain which expands the genetic variants. We also determine the first Turkish patients with CPT1C and TFG gene mutation related pure HSP. In addition TFG gene mutation related pure form of HSP identified first time in literature.

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