Hereditary Spastic Paraplegia Type 35 with a Novel Mutation in Fatty Acid 2-Hydroxylase Gene and Literature Review of the Clinical Features

Sir,

The hereditary spastic paraplegias (HSPs) are a heterogeneous group of neurodegenerative disorders. Few epidemiological studies of HSPs have been done to date. The estimated prevalence is 3–10 cases/100,000 population in Europe.[1]

The diagnostic clinical findings are spasticity and pyramidal weakness in lower limbs, with hyperreflexia and extensor plantar responses. The genetics of HSPs is complex, and all modes of inheritance (autosomal dominant [AD], autosomal recessive [AR], and X-linked [XL] recessive) have been

described.[2] AR HSPs are more frequent in consanguineous populations with a prevalence of 0.6/100,000 in Norway and up to 5.75/100,000 in Tunisia.[2,3] HSP type 35 is an AR form of HSPs caused by mutations in the fatty acid 2-hydroxylase (*FA2H*) gene at 1`q21-q23 chromosome.[2]

In the literature, a few cases have been reported with HSP type 35.[3-6] Here, we report HSP type 35 case of Turkish origin with a novel homozygous mutation in *FA2H* gene, presented with progressive gait disturbance and cognitive impairment.

A 16-years-old boy was admitted to our hospital because of progressive difficulty in walking, unsteady gait, cognitive impairment, and hand tremor. He had normal motor and intellectual development until the age of 10 years when gait disturbance and balance problems first appeared. Five years later, he began to show deterioration in academic skills. The patient was diagnosed with cerebral palsy because of these complaints in another hospital. The parents were consanguineous, and there was no family history of neurologic disease. He was born at term and had no neonatal problems. He had healthy two older sisters. Pedigree is shown in Figure 1.

Neurological examination revealed mild cognitive impairment and spasticity. The deep tendon reflexes were increased in lower limbs, with ankle clonus and bilateral Babinski signs. He had muscle weakness of Grade 4/5 distally in both lower limbs and had mild bilateral foot drop, pes cavus deformities, and muscular atrophy. Ophthalmologic examination and the other physical examination were normal.

Complete blood count, serum biochemistry, lipid profile, thyroid function tests, and serum Vitamin E and B12 levels were all normal. Brain magnetic resonance imaging (MRI) showed bilateral symmetrical hyperintense lesions in the periventricular white matter in T-weighted images [Figure 2]. Nerve conduction studies revealed demyelinating form of polyneuropathy. Based on the clinical findings and nerve conduction studies, the patient was thought as HSP.

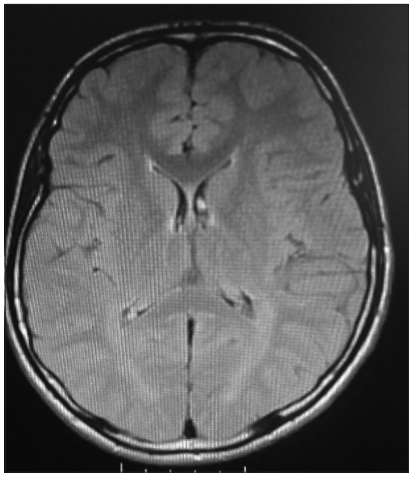

Figure 1: Pedigree of the patient

Clinical exome sequencing analysis was performed in the patient using TruSight One kits (Illumina Inc., San Diego, CA, USA). As a result of the clinical exome analysis, we identified a novel missense homozygous mutation at the *FA2H* gene (c.130C>T p. Pro44Ser p. P44S) which has not been reported previously. The mutation found was considered to be highly probable cause of disease according to in silico analysis (Sorting Tolerant From Intolerant, http://sift.jcvi.org and Mutation Taster, http://www.mutationtaster.org). Additional family screening revealed that both parents had heterozygous mutation. We confirmed that the patient was HSP type 35 due to clinical and genetically evaluation.

To date, 70 different gene loci associated with HSP were identified, involving XL, AR, AD, and maternal inheritance.[2]

AR spastic paraplegia-35 (SPG35) is a characterized by childhood onset of gait difficulties due to progressive spastic paraparesis, dysarthria, and mild cognitive decline associated with leukodystrophy on brain imaging. Other variable neurologic features, such as dystonia, optic atrophy, and seizures, may also occur.[3,4]

SPG35 is caused by mutations in the *FA2H* gene located on chromosome 16q23. *FA2H* was first described in 2008 as a rare leukodystrophy gene causing spasticity and dystonia.[7] In addition, *FA2H* gene has been shown to be associated with neurodegeneration with brain iron accumulation, thus expanding the phenotype. This phenotypic spectrum of disorders was then referred as fatty acid hydrolase-associated neurodegeneration (FAHN).[8]

FA2H gene encodes *FA2H*, a 372-amino-acid-long membrane-bound protein incorporated into the ceramide species which is necessary for the production of normal myelin. It contains two conserved domains, a cytochrome b5-like heme-binding domain, spanning residues 15–85 and responsible for the redox activity of *FA2H*, and a sterol desaturase domain at residues 210–367.[9]

To date, approximately 51 patients from 19 families have been reported in the literature.[5] Cao *et al.*[4] reported two siblings born to nonconsanguineous parents, who possess several typical clinical features of SPG35, a subtype of FAHN, owing to novel *FA2H*

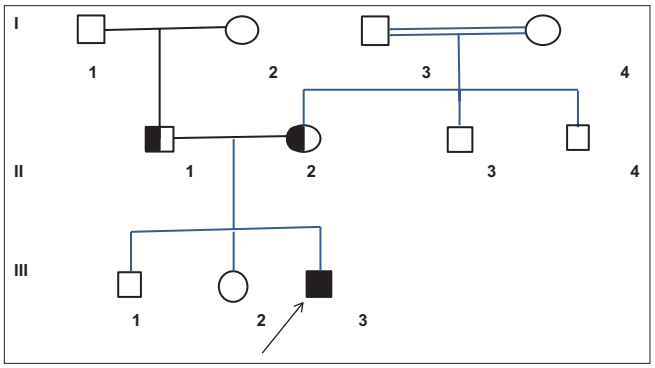

Figure 2: Cerebral magnetic resonance imaging showed bilateral symmetrical hyperintense lesions in the periventricular white matter

Table 1: The analysis of cases of hereditary spastic paraplegia type 35 from the literature and our patient

	Age at onset (y)/ Age at last physical examination	Ambulation	Speech impairment	Ocular findings	Seizures	Cognitive impairment	MRI findings	Neuropathy	Mutation
Pedroso *et al.*[10]	7/21	+	+	Strabismus	NR	NR	White matter changes, iron accumulation	NR	c.169_169dup10 c.117C>A
Garone *et al.*[11]	7/24	-	+	Optic atrophy	Rare	Severe	White matter changes, iron accumulation, cerebellar, brainstem, and cervical cord atrophy	-	c.270+3A>T
Soehn *et al.*[5]	3/12	-	NR	NR	NR	Moderate severe	NR	NR	c.527G>A
Soehn *et al.*[5]	4/9	-	NR	NR	NR	-	NR	NR	c.131C>A
Soehn *et al.*[5]	4.5/6	+	NR	NR	NR	Mild	NR	NR	c.133G>T
Soehn *et al.*[5]	4/18	-	NR	NR	NR	Mild	NR	NR	c.785A>C
Edvardson *et al.*[12]	4/12	+	-	NR	NR	-	NR	-	c.103G>T
Edvardson *et al.*[12]	4 to 6/7 to 20	-	+	NR	+/-	+	White matter changes, cerebellar atrophy	-	c.786+1G>A
Rupps *et al.*[13]	3/5	-	+	-	-	Mild	Cerebellar atrophy	-	c.209C>T c.968C>T
Liao *et al.*[3]	4/5	NR	+	Strabismus, papilledema	+	Mild	NR	-	c.230 T>G
Liao *et al.*[3]	10 to 17/26	-	+	Nystagmus	-	-/Mild	White matter changes, cerebellar atrophy	-	c.388C>T c.506+6C>G
Zaki *et al.*[14]	3 to 5/6 to 14	NR	+	Nystagmus, optic atrophy	-/+	-/Mild	White matter changes, cerebellar atrophy, iron accumulation	-/+	c.265 C>T
Kruer *et al.*[8]	4 to 5/ 15 to 20	-	+	Strabismus optic atrophy, nystagmus	+	-	White matter changes, iron accumulation, and cervical cord atrophy, thin corpus callosum	-	c.460C>T
Tonelli *et al.*[15]	38 to 40	-	+	Nystagmus, optic atrophy	-	Mild	Iron accumulation, cerebellar and cerebral atrophy	-	c.509A>G
Aguirre-Rodriguez *et al.*[16]	3/NR	NR	NR	Optic atrophy	NR	Mild	Cerebellar atrophy	NR	c.565 C>T
Dick *et al.*[7]	6/31	-	+	Optic atrophy	+	Mild	White matter changes	-	c 703 C>T c.159_176del18
Pierson *et al.*[17]	3/10	-	+	-	-	Moderate	White matter changes	+	c.707C>T
Donkervoort *et al.*[18]	3/13	-	+	NR	-	-	White matter changes, cerebellar atrophy, thin corpus callosum	NR	c.510_511delCA
Cao *et al.*[4]	4/35	-	+	Nystagmus	+	+	Cortical, cerebellar and brainstem atrophy	NR	c.968_976delCG
Bektaş *et al.*[6]	4/6	-	-	-	-	-	White matter changes	-	c.160_169dup
Our pateint	10/16	+	+	-	-	Mild	White matter changes	+	c.130C>T

missense mutation. Two affected siblings had typical clinical features of SPG35. For the two siblings, brain MRI showed progressive leukoencephalopathy with cortical, cerebellar, and brainstem atrophy. Thinning of the corpus callosum was also noted. Soehn *et al*.[5] described four novel homozygous *FA2H* mutations in four nonconsanguineous families with SPG35. All four children presented with a complicated form of HSP with tetraspasticity and additional symptoms including limb ataxia (3/4), mild cognitive deficits (3/4), and extrapyramidal involvement (3/4). In another case, Liao *et al*.[3] reported three novel *FA2H* gene mutations in two unrelated Chinese families with SPG35. Bektaş *et al*.[6] described a 5-year-old boy presenting with spastic paraplegia without seizure, neuropathy, cognitive impairment, speech disturbance, and optic atrophy in Turkey. Their patient was rapid progressive spastic paraplegia, and he was early loss of ambulation. Our case had gait difficulties due to progressive spastic paraparesis, hand tremor, mild cognitive deficits, and additional findings including demyelinating form of polyneuropathy. He had no optic atrophy and cerebellar dysfunction.

Recently, identification of the neurodegeneration with brain iron accumulation expanded the phenotypic spectrum of the disorders associated with the *FA2H* gene mutation.[8] Brain iron accumulation was not shown in the patient.

Bektaş *et al*.[6] detected a novel homozygous mutation c. 160_169 dup (p. Asp57Glyfs*48) in the gene encoding *FA2H* in their case in Turkey. We detected novel homozygous mutation c.130C>T (p. Pro44Ser) (p. P44S) in the *FA2H* gene. Furthermore, the patient had demyelinating form of polyneuropathy which has not been reported in SPG35 previously. Table 1 presents the analysis of cases of SPG35 from the literature and the patient.

In conclusion, HSPs are clinically and genetically heterogeneous disorders characterized by lower limb spasticity and weakness. SPG35 should be included in the differential diagnosis of lower limb spasticity and weakness when additional ataxia, mild cognitive deficits, and extrapyramidal involvement.

Informed consent

Informed consent was obtained from the parents of the child included in the study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. McMonagle P, Webb S, Hutchinson M. The prevalence of "pure" autosomal dominant hereditary spastic paraparesis in the island of İreland. J Neurol Neurosurg Psychiatry 2002;72:43-6.
2. Finsterer J, Löscher W, Quasthoff S, Wanschitz J, Auer-Grumbach M, Stevanin G, *et al.* Hereditary spastic paraplegias with autosomal dominant, recessive, X-linked, or maternal trait of inheritance. J Neurol Sci 2012;318:1-8.
3. Liao X, Luo Y, Zhan Z, Du J, Hu Z, Wang J, *et al.* SPG35 contributes to the second common subtype of AR-HSP in China: Frequency analysis and functional characterization of FA2H gene mutations. Clin Genet 2015;87:85-9.
4. Cao L, Huang XJ, Chen CJ, Chen SD. A rare family with hereditary spastic paraplegia type 35 due to novel FA2H mutations: A case report with literature review. J Neurol Sci 2013;329:1-5.
5. Soehn AS, Rattay TW, Beck-Wödl S, Schäferhoff K, Monk D, Döbler-Neumann M, *et al.* Uniparental disomy of chromosome 16 unmasks recessive mutations of FA2H/SPG35 in 4 families. Neurology 2016;87:186-91.
6. Bektaş G, Yeşil G, Yıldız EP, Aydınlı N, Çalışkan M, Özmen M, *et al.* Hereditary spastic paraplegia type 35 caused by a novel FA2H mutation. Turk J Pediatr 2017;59:329-34.
7. Dick KJ, Al-Mjeni R, Baskir W, Koul R, Simpson MA, Patton MA, *et al.* A novel locus for an autosomal recessive hereditary spastic paraplegia (SPG35) maps to 16q21-q23. Neurology 2008;71:248-52.
8. Kruer MC, Paisán-Ruiz C, Boddaert N, Yoon MY, Hama H, Gregory A, *et al.* Defective FA2H leads to a novel form of neurodegeneration with brain iron accumulation (NBIA). Ann Neurol 2010;68:611-8.
9. Eckhardt M, Yaghootfam A, Fewou SN, Zöller I, Gieselmann V. A mammalian fatty acid hydroxylase responsible for the formation of alpha-hydroxylated galactosylceramide in myelin. Biochem J 2005;388:245-54.
10. Pedroso JL, Handfas BW, Abrahão A, Kok F, Barsottini OG, Oliveira AS, *et al.* Fatty acid 2-hydroxylase deficiency: Clinical features and brain iron accumulation. Neurology 2015;84:960-1.
11. Garone C, Pippucci T, Cordelli DM, Zuntini R, Castegnaro G, Marconi C, *et al.* FA2H-related disorders: A novel c.270+3A>T splice-site mutation leads to a complex neurodegenerative phenotype. Dev Med Child Neurol 2011;53:958-61.
12. Edvardson S, Hama H, Shaag A, Gomori JM, Berger I, Soffer D, *et al.* Mutations in the fatty acid 2-hydroxylase gene are associated with leukodystrophy with spastic paraparesis and dystonia. Am J Hum Genet 2008;83:643-8.
13. Rupps R, Hukin J, Balicki M, Mercimek-Mahmutoglu S, Rolfs A, Dias C, *et al.* Novel mutations in FA2H-associated neurodegeneration: An underrecognized condition? J Child Neurol 2013;28:1500-4.
14. Zaki MS, Selim L, Mansour L, Mahmoud IG, Fenstermaker AG, Gabriel SB, *et al.* Mutations in FA2H in three Arab families with a clinical spectrum of neurodegeneration and hereditary spastic paraparesis. Clin Genet 2015;88:95-7.
15. Tonelli A, D'Angelo MG, Arrigoni F, Brighina E, Arnoldi A, Citterio A, *et al.* Atypical adult onset complicated spastic paraparesis with thin corpus callosum in two patients carrying a novel FA2H mutation. Eur J Neurol 2012;19:e127-9.
16. Aguirre-Rodríguez FJ, Lucenilla MI, Alvarez-Cubero MJ, Mata C, Entrala-Bernal C, Fernandez-Rosado F, *et al.* Novel FA2H mutation in a girl with familial spastic paraplegia. J Neurol Sci 2015;357:332-4.
17. Pierson TM, Simeonov DR, Sincan M, Adams DA, Markello T, Golas G, *et al.* Exome sequencing and SNP analysis detect novel compound

heterozygosity in fatty acid hydroxylase-associated neurodegeneration. Eur J Hum Genet 2012;20:476-9.
18. Donkervoort S, Dastgir J, Hu Y, Zein WM, Marks H, Blackstone C, *et al*. Phenotypic variability of a likely FA2H founder mutation in a family with complicated hereditary spastic paraplegia. Clin Genet 2014;85:393-5.

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