Hereditary Spastic Paraplegia Experience in a Tertiary Center in Taiwan

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Hereditary spastic paraplegias (HSP) are rare genetic neurodegenerative diseases. The genotypes and phenotypes are expanding as genetic test became more available.

Objectives

HSP are rare genetic diseases. Most HSP cases experienced gait problems.

For childhood-onset HSPs, many case manifest as delay walking as initial symptoms with or without mental problems for child onset HSP, which are features of “CP mimics.”

For later onset or adulthood onset HSP, gait problems progressed insidiously. Cognitive function may deteriorate in some cases.

Our work aims to know the clinical features and genotypes of HSPs population in our cohort.

Methods

The data were collected from retrospective chart review of 130 patients with diagnosis of spastic diplegia (N=25) and hereditary spastic paraplegia (N=115) with 10 patients overlapping diagnosis who visited National Taiwan University Hospital during January 2012 to December 2022.

Results

28 cases were gene confirmed, 18 males and 10 females, age 1 to 65 years old (median 36 y/o). There were 15 gene mutations, and the SPAST (8/28, 28.5%), ALT (3/28, 10.7%), CYP7B1(3/28, 10.7%), KIF1A (2/28, 7.1%), other genes were 1 case each (MYH3, AMPD2, CYP2U1, DARS2, NKXZ1, Paraplegin, REEP1, REEP2, SCN4A, Spatacsin, WASHC5, one unknown HSP gene diagnosed at other hospital.

Positive family history was found in 9 gene-confirmed patients (9/28, 32.1%, 4 are SPAST mutation) and 19 non-gene confirmed patients (19/102, 8.8%). Positive finding of whole exon sequencing or genetic panel was noted in 28/34 (82.4%) patients according to chart record. Most patients (22/28, 78.6%) among gene diagnosis group had their last follow up in 2020 to 2023.

20/26 (77%) patients remained walking ability at last follow up (2 patients without recordings). 25 patients have records of age of onset symptoms, 8 (8/25, 32%) onset before 5 y/o, 9 (9/25, 36%) childhood to adolescent, 8 (8/25, 32%) after 18 years old. In our cohort, patients with symptoms onset after 18 years old were remained walking ability till last follow up.

For those non-walkers (5 patients), information were listed in table 1. One ALT1 patient is never walker. One SCN4A with no complete data. Duration between symptoms onset to loss of walking ability varies from 6 years to around 50 years .

For young HSP patients (< 18 y/o), there were urinary problems in 1 REEP2 patient at 11 y/o. 5 patients with urination problems among elder age group, > 18 years old (1/9 (11.1%) vs 5/17 (29.4%), p= 0.3746.). Neuropathy was documented in one young KIF1A patients. In contrary, neuropathy noted in 5 adult patients either with symptoms or NCV finding (1/9 (11.1%) vs 5/17 (29.4%), p= 0.3746.)

Conclusions

HSP is a group of heterozygous diseases with a wide variety of genotypes and phenotypes. Childhood onset and later onset HSP differs not only in genotype but also clinical course and differential diagnosis.

We should consider HSP for those patients without significant preterm or perinatal insults history with “spastic diplegia” diagnosis.

Urinary symptoms and neuropathy were less mentioned in young patients (although not achieved statistic significance). This may need to further clarify if symptoms develop as disease progression so manifest at elder ages, or attributing to genetic difference or undervaluation due to less subjective symptoms.

Long term follow up cohort with genetic diagnosis may help answer this question.

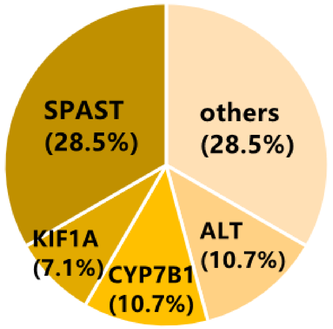

Figure 1. Genotypes of our HSP cohort. N=28. Other genes: MYH3, AMPD2, CYP2U1, DARS2, NKXZ1, Paraplegin, REEP1, REEP2, SCN4A, Spatacsin, WASHC5, one unknown HSP gene diagnosed at other hospital

Gene	Sex	Onset (age)	Motor status
ALT1	M	5m/o	3y/o, Sitter, GMFCS IV
SCN4A	F		14y/o, GCMSF V, normal intelligence
SPG7	F	8y/o	Wheelchair since 17y/o
SPG11	M	13y/o	Wheelchair since 19y/o, cognitive decline
SPG5A	M	Childhood	Wheelchair since 56y/o

Table 1. Non-sitter patients demographic data. Genotypes, age of onset and motor status.

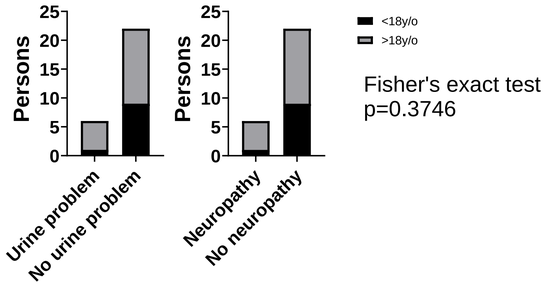

Figure 2. Urinary and neuropathy symptoms in HSP patient younger than 18 year old versus elder than 18 years old. (N=28, Fisher’s exact test)