MODERN MEDICINE AND PRACTICE
https://inovatus.es/index.php/ejmmp

EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE
Vol. 5 No. 12 (Dec - 2025) EJMMP ISSN: 2795-921X

HEREDITARY SPASTIC PARAPLEGIAS IN CHILDREN: CLINICAL-GENETIC FEATURES AND APPROACHES TO THERAPY

Okiljonova N. A.
Tashkent State Medical University

Abstract: Based on an in-depth analysis of contemporary scientific literature, we consider it necessary to conduct a study aimed at identifying the clinical-phenotypic characteristics and molecular-genetic aspects of hereditary spastic paraplegia in children across different regions of our Republic. The findings of this research will make it possible to develop a regional system of medical-genetic counseling for families burdened with this condition. The indicators obtained as a result of the study will be used for planning and optimizing the organization of therapeutic, rehabilitative, and preventive measures for patients with these disorders.

Keywords: children, hereditary spastic paraplegias, SPG gene, diagnostics, treatment.

Relevance

Since the early days of independence, our country has continuously implemented large-scale initiatives aimed at establishing a fundamentally new and high-quality healthcare system. Systematic measures have been carried out, and effective healthcare models have been introduced. As a result, significant progress has been achieved in improving early diagnosis of hereditary diseases in children, identifying and recognizing early signs, preventing complications, and enhancing medical-genetic counseling. Despite these achievements, a number of unresolved issues remain within the healthcare system, including those related to medical-genetic counseling for hereditary neurological disorders.

The *Action Strategy for the Five Priority Areas of Development of the Republic of Uzbekistan for 2017–2021* emphasizes the need to improve the system of medical and social support for children to ensure their full participation in society. In accordance with these priorities, the study of clinical and molecular-genetic features of hereditary spastic paraplegia (HSP) in children and the optimization of medical-genetic care represent an essential and timely area of research.

Hereditary spastic paraplegia (HSP) is a hereditary disorder characterized by degeneration of the lateral columns of the pyramidal tract in the spinal cord—minimal at the cervical level and increasing caudally. The predominance of spasticity over paresis is associated with involvement of thin tonic fibers of the corticospinal tract [1,2].

In 1883, A. Strümpell described several familial cases of a progressive disorder characterized by lower-limb weakness, spasticity, mild impairment of vibratory sensation, and bladder dysfunction. M. Lorrain later continued studying these families. Today, Strümpell–Lorrain disease represents an expanding group of disorders. A search in the OMIM database using the term “spastic paraplegia” yields more than 100 genetically determined conditions [3,5].

Some are described in single families, while others may not be classified as spastic paraplegias by neurologists, even though spasticity is present but not the primary feature (e.g., in lissencephaly with cerebral and tendon xanthomatosis) [4,7]. HSP is often misdiagnosed as cerebral palsy (CP). The disease course is usually slowly progressive, with recessive forms advancing more rapidly. Several recessive HSP types demonstrate ethnic or regional clustering. In consanguineous families, HSP frequently presents with diverse and complicated recessive forms [2].

Intellectual disability is common in complicated HSP forms [3]. In addition to severe cognitive impairment and absent speech, many patients exhibit additional symptoms such as ataxia, epilepsy, microcephaly, and cataracts [4,5,6]. In some families with HSP, all affected individuals experience epilepsy. Seizure types vary widely and may include myoclonic seizures [7,8], simple or complex partial seizures [9], absence seizures [8], generalized tonic-clonic seizures, and atonic attacks [8,9]. HSP may also be accompanied by ataxia, nystagmus, and dysarthria [10].

The large number of nosological variants complicates HSP classification and makes diagnosis challenging. The high medical and social significance of these disorders arises from their severe clinical course, marked disability, and limited efficacy of symptomatic treatment.

Prevalence and Genetic Data

HSP is one of the most common degenerative conditions of childhood, exceeding the prevalence of Charcot–Marie–Tooth disease and Friedreich's ataxia [1,2]. Reported prevalence varies across studies, but overall it is estimated at 3.8 per 100,000 population (1.95 per 100,000 for dominant forms and 1.88 per 100,000 for recessive forms) [1,4]. According to the Australian HSP Research Foundation, prevalence ranges from 0.5 to 12 per 100,000 in various populations.

More than 50 genotypes of HSP have been identified to date. The most common are SPG3 and SPG4 [2,3]. Three inheritance patterns have been described: autosomal dominant, autosomal recessive, and X-linked. Autosomal-dominant forms are believed to be more frequent than recessive forms (55% vs. 45% among all HSP cases). There is no clear genotype-phenotype correlation: the same genotype may manifest as different phenotypes, and different genotypes may present with similar clinical features [4,11].

Among complicated HSP forms, recessive types predominate and are generally more severe than dominant ones [1].

Pathogenesis

The pathogenesis of HSP is not yet fully understood. Leading international medical centers have conducted studies of the clinical and neurophysiological features of HSP to elucidate the underlying mechanisms and morphological defects. Currently, four major pathogenetic mechanisms have been identified [1,12,15]:

1. **Impaired embryonic development (SPG1):**

Mutations affecting the *L1CAM* gene disrupt axonal development in the brain, cerebellum, spinal cord, and peripheral nervous system. L1CAM is essential for cell recognition, neuronal migration, cell differentiation, and axonal growth.

2. **Defects in oligodendrocyte function (SPG2):**

The *PLP* gene product is a key component of myelin and is required for oligodendrocyte maturation.

3. **Mitochondrial dysfunction (SPG7, SPG13):**

The *SPG7* gene product paraplegin is located in the inner mitochondrial membrane and participates in multiple mitochondrial processes, including protein degradation. Patients exhibit mitochondrial

abnormalities characteristic of respiratory chain defects. It remains unclear whether mitochondrial dysfunction is a primary or secondary event.

4. **Disrupted intracellular transport (SPG3, SPG4, SPG10, and others):**

Several HSP-associated genes encode proteins involved in axonal transport.

Regardless of the primary mechanism, the hallmark pathological finding in HSP is degeneration of long axons within the corticospinal tracts and posterior columns of the spinal cord, with the most pronounced degeneration in distal axonal segments. Additional morphological features include neuronal loss in layer V of the motor cortex, basal ganglia, cerebellum, and anterior horn cells of the spinal cord [1,2,3].

Overall, pathological changes are highly variable and depend on the specific type of hereditary spastic paraplegia.

Clinical Manifestations

The pronounced clinical heterogeneity of hereditary spastic paraplegias (HSP) is associated with a wide range of pathogenic processes occurring in neurons, including defects in the formation of membrane organelles, impaired molecular transport, disrupted myelination, and mitochondrial dysfunction — all caused by mutations in various genes. Currently, more than 70 genetic loci (59 identified genes) associated with different inheritance patterns have been described (Klebe et al., 2015) (http://www.neuromuscular.wustl.edu). According to international nomenclature, these loci and the corresponding genetic variants of HSP are designated chronologically using the prefix **SPG** (Spastic Paraplegia Gene).

Clinically, HSP is traditionally divided into **pure (uncomplicated)** forms and **complex ("plus")** forms, which include additional neurological or extraneurological symptoms [1,2,4,13]. Complex spastic paraplegias share clinical features with several neurodegenerative disorders, including cerebellar ataxias, amyotrophic lateral sclerosis, and sensorimotor neuropathies [7,8].

The term **Strümpell's disease** generally refers only to the pure form of hereditary spastic paraplegia [3,8].

The onset typically presents with clumsiness and difficulty with fast walking or running; some patients walk on their toes. Over time, patients develop heaviness and stiffness in the legs, and cramping appears after prolonged walking. A.E. Harding [11] proposed distinguishing two types of uncomplicated HSP:

- **Type 1** – onset before age 35;
- **Type 2** – onset after age 35.

A key feature of HSP is the predominance of **spasticity over paresis** [2,9]. Neurological examination reveals increased muscle tone of the spastic type, ankle and patellar clonus. A characteristic feature is that spasticity in the legs is more pronounced in the standing position than in the supine position. Over time, upper-limb paresis may also develop [1,6]. The disease course is slowly progressive, without exacerbations or remissions. Severity and progression rate vary significantly within families. HSP type 1 with onset before age 35 tends to have a more favorable course, often without significant subjective complaints for many years. Type 2 HSP, with onset after age 35, progresses more rapidly, leading to severe spasticity, pronounced weakness, and greater disability.

In complex HSP forms, additional neurological symptoms may occur. Intellectual disability may vary depending on the specific disorder. In some cases, cognitive impairment precedes the onset of spasticity — children may show developmental delay or learning difficulties. Intellectual disability may progress into severe dementia (often in recessive forms) or remain mild, manifesting as frontal-type personality changes. Epilepsy may occur, as well as reduced visual acuity (due to optic neuropathy and/or retinal degeneration)

and hearing loss. Additional manifestations include ataxia, dysarthria, nystagmus, and extrapyramidal symptoms [3,6,8].

Diagnosis of Hereditary Spastic Paraplegia

Diagnosis of pure Strümpell-type HSP is usually straightforward, particularly when a positive family history is present. Complex forms are rare and therefore more difficult to diagnose. Autosomal recessive HSP typically presents earlier and is more severe compared to autosomal dominant pure forms. Early-onset HSP often resembles spastic diplegic cerebral palsy (CP); thus, CP must be excluded first [2,4,7]. Unlike CP, HSP is characterized by a **progressive** increase in spasticity and is caused by **neurodegenerative processes**.

Differential diagnosis includes microcephaly with spastic tetraparesis, where microcephaly and severe intellectual disability predominate, and spasticity affects both arms and legs, unlike HSP. Diagnosis of sporadic and complex forms is complicated by the presence of numerous phenocopies. In early-onset rapidly progressive cases, diffuse involvement of both brain and spinal cord is observed. Disorders such as **Troyer syndrome**, **Sjögren–Larsson syndrome**, and **spastic paraplegia with retinal degeneration** must be considered [2,6,11].

According to the literature, recessive HSP accompanied by intellectual disability is common. Clinical and genealogical data, family history, and examination of relatives play a crucial role. Non-progressive forms with autosomal recessive inheritance must be differentiated from spastic diplegic CP. The presence of progressive spastic paraplegia and family clustering is decisive. However, when analyzing pedigrees, one must consider the possibility of very mild symptoms in relatives [1,2,6,11].

Neuroimaging and Additional Studies

- **MRI of the brain and spinal cord** is recommended.
- ✓ Brain MRI is mainly used for differential diagnosis (e.g., exclusion of leukodystrophies), though cortical atrophy may occasionally be found.
- ✓ Spinal MRI typically shows thinning and atrophy at the thoracic level [2,6].
- **Electroneuromyography (ENMG)** is not essential for diagnosis but is valuable for assessing coexisting neuropathy and its severity.
- **Somatosensory evoked potentials (SSEPs)** of the lower limbs show delayed conduction in the posterior columns.
- **Motor evoked potentials** show reduced conduction velocity along the corticospinal tract and a decrease in amplitude.
- **Molecular genetic testing** is clinically meaningful for SPG3A, SPG4, and SPG6, which together account for ~60% of autosomal dominant cases. Among recessive forms, SPG5 and SPG7 are the most common [6,11].

Disease Course

The course is **slowly progressive**, more favorable in autosomal dominant forms. However, infections, intoxications, and trauma may provoke sudden worsening of symptoms [2,14].

Treatment of Hereditary Spastic Paraplegias

Research on HSP in various populations is highly relevant for clinical neurology and medical genetics. There is **no specific treatment** capable of preventing or slowing disease progression. Management is symptomatic.

Many medications effectively reduce spasticity, improving the patient's ability to stand, sit, walk, and maintain posture [1,6,8]. By reducing spasticity in the laryngeal and lingual muscles, speech and communication may also improve.

Pharmacotherapy

Antispastic agents may be administered:

- ✓ orally,
- ✓ intramuscularly,
- ✓ intrathecally [2,6,12].

Oral medications provide short-term and partial improvement, particularly in children and adolescents. None of the oral drugs can eliminate moderate or severe spasticity, and all have significant side effects.

General principles of muscle relaxant therapy:

- ➢ start with the lowest dose;
- ➢ titrate gradually;
- ➢ avoid dose escalation if spasticity decreases adequately or adverse effects occur;
- ➢ taper doses gradually to avoid withdrawal syndromes.

Frequently used medications include **baclofen**, **tizanidine**, **midocalm (tolperisone)**, **diazepam**, and **dantrolene** [8,13].

For severe spasticity, **intrathecal baclofen pump implantation** is used abroad. The dose delivered intrathecally is ~1/100 of the oral dose. Implantation is possible in children over 3 years old but remains expensive and uncommon in many countries.

A widely accessible alternative is **botulinum toxin injections**, especially into the gastrocnemius and hamstring muscles. Botulinum toxin improves mobility and prevents tendon shortening in HSP patients [4].

Rehabilitation and Orthopedic Management

Rehabilitation measures include:

- ➢ therapeutic physical exercises to maintain motor activity and muscle strength,
- ➢ prevention of muscle atrophy and cramps,
- ➢ orthotic management,
- ➢ orthopedic surgical interventions when contractures develop [4,12,15].

Conclusion

HSP is a steadily progressive disorder with no highly effective symptomatic control methods currently available. The substantial genetic heterogeneity of HSP is compounded by population variability in disease prevalence and mutation spectra. Therefore, comprehensive epidemiological, clinical-genealogical, and molecular-genetic studies are essential for understanding disease pathogenesis and gene geography and for developing effective DNA diagnostics and medical-genetic counseling strategies tailored to specific regions.

References

1. Akhmetgaliyeva AF. Molecular-genetic study of spastic paraplegias in the Republic of Bashkortostan. Dissertation Abstract. Ufa; 2017. (In Russ).
2. Belousova ED. Hereditary spastic paraplegias. Russian Bulletin of Perinatology and Pediatrics. 2010;(1):89–95. (In Russ).
3. Gushcha AO, Kashcheyev AA, Karabanov AA, Illarioshkin SN. Chronic spinal cord stimulation in Strümpell's disease: first clinical observation. Neurological Journal. 2015;20(6):22–27. (In Russ).
4. Yevtushenko OS. Features of long-term staged medical rehabilitation of children with cerebral palsy in the Donetsk Clinical Neurorehabilitation Center. International Neurological Journal. 2014;3(65):146–148. (In Russ).
5. Zavalishin IA. Spasticity. Russian Medical Journal. 2004;5:261–265. (In Russ).
6. Illarioshkin SN, Rudenskaya GE, Ivanova-Smolenskaya IA, Klyushnikov SA. Hereditary Ataxias and Paraplegias. Moscow: Medpress; 2006. p. 286–314. (In Russ).
7. Nikiforenko AA, Buyanova GV, Maslennikova NV, Smirnov DS. Clinical cases of diagnosing hereditary diseases of the nervous system masked as cerebral palsy. Pediatric Bulletin of the South Urals. 2015;2:75–77. (In Russ).
8. Rudenskaya GE, Demina NA. Autosomal dominant hereditary spastic paraplegia with extrapyramidal disorders. Medical Genetics. 2003;9:437–441. (In Russ).
9. Carben J. X-linked spastic paraplegia. In: Brice A, Pulst S-M, editors. *Spinocerebellar Degenerations: The Ataxias and Spastic Paraplegias.* Philadelphia: Butterworth-Heinemann; 2007. p. 344–366.
10. Coutinho P, Loureiro JS. Overview on hereditary spastic paraplegias. In: Brice A, Pulst S-M, editors. *Spinocerebellar Degenerations: The Ataxias and Spastic Paraplegias.* Philadelphia: Butterworth-Heinemann; 2007. p. 320–343.
11. Depienne C, Stevanin G, Brice A, Durr A. Hereditary spastic paraplegia: an update. Curr Opin Neurol. 2007;20:674–680.
12. Fink JK. Hereditary spastic paraplegia: clinical-pathologic features and emerging molecular mechanisms. Acta Neuropathol. 2013;126(3):307–328.
13. Giudice TL, Lombardi F, Santorelli FM, Kawarai T, Orlacchio A. Hereditary spastic paraplegia: clinical-genetic characteristics and evolving molecular mechanisms. Exp Neurol. 2014;261:518–539.
14. Nance MA. Genetic testing for hereditary ataxia and hereditary spastic paraplegia. In: Brice A, Pulst S-M, editors. *Spinocerebellar Degenerations: The Ataxias and Spastic Paraplegias.* Philadelphia: Butterworth-Heinemann; 2007. p. 367–391.
15. National Institute of Health. Hereditary Spastic Paraplegia Information Page. Available from: http://www.ninds.nih.gov/disorders/hereditary_spastic_paraplegia/hereditary_spastic_paraplegia.htm