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An Editorial on Hereditary Spastic Paraplegias

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Editorial

Hereditary Spastic Paraplegias are a set of neurodegenerative illnesses that affect the corticospinal pathways and cause stiffness and paralysis in the lower limbs. For both autosomal dominant and autosomal recessive forms, the estimated frequency of HSP is roughly 1.8/100,000 patients. The inheritance pattern is used to classify HSP. Clinical phenomenology and pathophysiological processes at the molecular level. Axonal degeneration affecting the lateral corticospinal pathways in both the cervical and thoracic spinal cords is the most prevalent neuropathological symptom. The goal of this review paper is to give a thorough understanding of the HSP classification, neuropathology, and differential diagnosis.

The Hereditary Spastic Paraplegias (HSPs) are a diverse collection of neurological illnesses characterised by severe lower-extremity spasticity caused by a length-dependent axonopathy of corticospinal upper motor neurons. HSPs can in "pure" and "complex" versions, with additional neurologic and extraneurologic characteristics. HSPs are one of the most genetically varied neurologic illnesses, with over 70 different genetic loci and over 60 mutant genes previously identified. Many studies describing the molecular pathophysiology of HSPs have emphasised the relevance of fundamental cellular activities in axon growth and maintenance, including membrane trafficking, mitochondrial function, organelle shape and biogenesis, axon transport, and lipid/cholesterol metabolism. For the most prevalent HSPs, a surprisingly limited number of converging cellular pathogenic motifs have been found, and some of these pathways suggest promising targets for future therapeutics.

Hereditary Spastic Paraplegia (HSP) refers to a diverse collection of inherited neurodegenerative illnesses characterised by increasing lower-limb stiffness. Differentiating HSP from other genetic illnesses linked with spasticity can be difficult since the pathogenic mechanism, related clinical symptoms, and imaging abnormalities vary significantly depending on the afflicted gene. Although next-generation sequencing-based gene panels are now commonly accessible, they have limitations, and most suspected cases do not receive a molecular diagnosis. Symptomatic care is still evolving, but with a better knowledge of the pathophysiological underpinnings of specific HSP subtypes, targeted molecular therapeutics and tailored therapy are becoming more feasible. Hereditary spastic paraplegia is a broad and diverse set of hereditary neurodegenerative and neurodevelopmental illnesses caused by primary retrograde malfunction of the corticospinal tract's long descending fibres.

Although spastic paraparesis and urinary dysfunction are the most prevalent clinical manifestations, a complex set of neurological and systemic compromises has lately been identified, and an increasing number of novel genetic subtypes have been reported in the previous decade. The key phase in the diagnostic process is to characterise an individual's and family's medical history; yet, in many cases, there are few and unspecific data, resulting in a low rate of conclusive diagnosis based simply on clinical and neuroimaging findings. Similarly, a wide range of neurological acquired and hereditary illnesses should be considered in the differential diagnosis and correctly ruled out following a thorough lab, neuroimaging, and genetic examination. The goal of this review paper is to give a comprehensive summary of the primary clinical and genetic characteristics of the traditional and newly identified subtypes of hereditary spastic paraplegia (HSP). Hereditary spastic paraplegia (HSP) is a condition that describes genetic illnesses that are characterised by lower limb weakness and stiffness.

There are around 50 different genetic forms of HSP. HSP affects people from all walks of life, with prevalence rates ranging from 1.2 to 9.6 per 100,000. The signs and symptoms might appear at any age. After childhood, gait disability normally progresses slowly over several years. Beginning in infancy or early childhood, gait disability may not progress considerably. Degeneration of corticospinal tract axons (maximal in the thoracic spinal cord) and fasciculus gracilis fibres are regularly seen in postmortem investigations (maximal in the cervico-medullary region). HSP syndromes appear to be characterised by motor-sensory axon degeneration affecting mostly (but not solely) the distal ends of long CNS axons.

Proteins encoded by HSP genes have a wide range of activities, including:

- Axonal transport (for example, SPG30/KIF1A, SPG10/KIF5A, and potentially SPG4/Spastin)
- Morphology of the endoplasmic reticulum (e.g., SPG3A/Atlastin, SPG4/Spastin, SPG12/reticulon 2, and SPG31/REEP1, all of which interact)
- Mitochondrial function (e.g. SPG13/chaperonin 60/heat-shock protein 60; and mitochondrial ATP6)
- SPG2/Proteolipid protein and SPG42/Connexin 47, for example, are involved in myelin production.
- Protein folding and the ER-stress response (SPG6/NIPA1, SPG8/K1AA0196 (Strumpellin), SGP17/BSCL2 (Seipin), "mutilating sensory neuropathy with spastic paraplegia" caused by the CcT5 mutation, and likely SPG18/ERLIN2)
- Neurodevelopment of the corticospinal tract (e.g. SPG1/L1 cell adhesion molecule and SPG22/thyroid transporter MCT8)
- SPG28/DDHD1, SPG35/FA2H, SPG39/NTE, SPG54/DDHD2, and SPG56/CYP2U1) are all involved in fatty acid and phospholipid metabolism.
- SPG47/AP4B1, SPG48/KIAA0415, SPG50/AP4M1, SPG51/AP4E, SPG52/AP4S1, and VSPG53/VPS37A are examples of endosome membrane trafficking and vesicle production.

For several forms of HSP, animal models (including bovine, murine, zebrafish, Drosophila, and C. elegans) are available, allowing researchers to investigate illness causes and potential therapies. This review focuses on new ideas around this vast group of clinically related illnesses [1-5].

Conflict of Interest

The author declares that there is no conflict of interest associated with this paper.

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