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Review

Hereditary spastic paraplegia: Clinical-genetic characteristics and evolving molecular mechanisms

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ABSTRACT

Hereditary spastic paraplegia (HSP) is a group of clinically and genetically heterogeneous neurological disorders characterized by pathophysiologic hallmark of length-dependent distal axonal degeneration of the corticospinal tracts. The prominent features of this pathological condition are progressive spasticity and weakness of the lower limbs. To date, 72 spastic gait disease-loci and 55 spastic paraplegia genes (*SPGs*) have been identified. All modes of inheritance (autosomal dominant, autosomal recessive, and X-linked) have been described. Recently, a late onset spastic gait disorder with maternal trait of inheritance has been reported, as well as mutations in genes not yet classified as spastic gait disease. Several cellular processes are involved in its pathogenesis, such as membrane and axonal transport, endoplasmic reticulum membrane modeling and shaping, mitochondrial function, DNA repair, autophagy, and abnormalities in lipid metabolism and myelination processes. Moreover, recent evidences have been found about the impairment of endosome membrane trafficking in vesicle formation and about the involvement of oxidative stress and mtDNA polymorphisms in the onset of the disease. Interactome networks have been postulated by bioinformatics and biological analyses of spastic paraplegia genes, which would contribute to the development of new therapeutic approaches.

Contents

Abbreviations: AAA, ATPases associated with diverse cellular activities; AD, autosomal dominant; AEPs, auditory evoked potentials; AP, adaptor protein complex; AR, autosomal recessive; BiP, binding immunoglobulin protein; BMP, bone morphogenetic protein; CMT, Charcot–Marie–Tooth disease; DCVs, dense core vesicles; DTI, diffusion tensor imaging; ER, endoplasmic reticulum; EGFR, epidermal growth factor receptor; ERAD, ER-associated degradation; ESCRT, endosomal sorting complex required for transport; HSP, hereditary spastic paraplegia; JALS, juvenile amyotrophic lateral sclerosis; MEPs, motor evoked potentials; MIT, microtubule interacting and transport (domain); NBIA, neurodegeneration with brain iron accumulation; RHD, reticulon homology domain; UPR, unfolded protein response; SCA, spinocerebellar ataxias; SEPs, sensory evoked potentials; SMA, spinal muscolar atrophy; SPG, spastic paraplegia gene; TCC, thin *corpus callosum*; VEPs, visual evoked potentials; WASH, Wiskott-Aldrich syndrome protein and scar homolog (complex); WMLs, white matter lesions; XL, X-linked.

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Introduction

Hereditary spastic paraplegias (HSPs) constitute a heterogeneous group of neurodegenerative diseases characterized by genetic mutations that cause distal neuropathy of the longest corticospinal tract axons (Harding, 1993) ; ascending fibers (column of Goll and spinocerebellar tracts) are also often involved (reviewed in Blackstone, 2012; Deluca et al., 2004; reviewed in Orlacchio et al., 2006). As a result of corticospinal dysfunction, progressive weakness and spasticity, extensor plantar responses, and hyperreflexia of deep tendon reflexes in lower limbs are common clinical features in pure forms. *Iliopsoas*, *quadriceps femoris,* and *tibialis anterior* are the muscles most affected by spasticity and weakness. Hypertonic bladder and lower limb sensory disturbances (generally mild, regarding vibration and joint position sense) may be present in pure forms too.

Other manifestations may occur in complicated forms, including above all cognitive impairment, cerebellar atrophy, polyneuropathy, thin *corpus callosum* (TCC), epilepsy, skeletal abnormalities, amyotrophy, and optic atrophy.