MÜHAZİRƏ - ЛЕКЦИЯ - LECTURE

HEREDITARY SPASTIC PARAPLEGIA

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Historical note and nomenclature.

Hereditary spastic paraplegia is the name given to a group of diseases that are heterogenous and inherited, in which the main clinical feature is progressive spasticity of the lower limbs. The original description of hereditary spastic paraplegia was made by Strümpell in 1880. He described “a pure spastic movement disorder of the legs” in 2 brothers who developed a spastic gait at the ages of 37 and 56 years. Their father was said to be “a little lame,” suggesting that the mode of inheritance might be autosomal dominant (Strümpell 1880). He later defined additional cases and described the pathological changes of the spinal cord, especially the degeneration of the pyramidal tracts. At the end of 19th century, Lorrain published 3 cases with similar clinical features (Lorrain 1898). The disease was also called Strümpell-Lorrain syndrome. Many cases with additional neurologic features were added to the literature, and many case reports seem to have given different names to possibly the same disease.

In 1981, Harding reviewed a clinical and genetic study of 22 families with pure hereditary spastic paraplegias, and she devised the “type I” and “type II” clinical classifications of pure autosomal dominant spastic paraplegia. Type I autosomal dominant spastic paraplegia was defined as having early onset (younger than 35 years) with slow, progressive symptoms and spasticity that was more marked than muscle weakness. Type II was defined as having late onset (older than 35 years), with rapidly developing symptoms and muscle weakness that was more prominent than spasticity. She also noted that

autosomal recessive pure forms were almost always early onset, and the severity of the dominant and recessive forms did not differ. In 1983, Harding published a classification of hereditary ataxias and paraplegias, and she classified hereditary spastic paraplegias into pure and complicated forms (Harding 1983). Pure hereditary spastic paraplegia (Strümpell disease) was then divided into 3 forms according to the mode of inheritance: autosomal dominant, autosomal recessive, or X-linked recessive.

In 1996, Fink and colleagues offered a useful subclassification based on the mode of inheritance and the chromosomes patients showed linkages to (eg, autosomal dominant chromosome 2p-linked, uncomplicated hereditary spastic paraplegia) (Fink et al 1996). They also suggested an alternative classification of the Genome Database designation for X-linked and autosomal hereditary spastic paraplegia loci, like *SPG1*, *SPG2* (X-linked), and *SPG3* (chromosome 14q). They are generally designated in the order of their discovery, but some designations have been reserved for unpublished loci (Fink 2004).

Generally, the last classification has been preferred because it is up-to-date, and more than 40 loci and many genes have been discovered.

Epidemiology. Prevalence of hereditary spastic paraplegias varies in different countries. In 1991, Polo and colleagues reported the point prevalence of pure hereditary spastic paraplegias as 9.6 per 100,000 in Cantabria in 1986. They used the hospital records to reach patients, and they included the secondary cases in their study. They compared their results with those of Chen, which was 18.4 per

100,000 in Guam; Skre, which was 11.9 in Western Norway; and Lucci, which was 1 per 100,000 in Emilia-Italy (Polo et al 1991).

In Portugal, Silva and colleagues reported that the prevalence of hereditary ataxias and familial spastic paraplegia in the district of Viana do Castelo was found to be 6.4 per 100,000 (Silva et al 1997). They also compared prevalences in different countries. In Libya in 1984, Sridharan found prevalence of familial spastic paraplegia to be 2.1 per 100,000 and overall prevalence of hereditary ataxias and familial spastic paraplegia 4.8 per 100,000. In Japan, it was reported as 0.1 and 1.5 per 100,000 respectively. In Italy's Valle d'Aosta region in 1991, prevalence of familial spastic paraplegia was reported as 4.3 per 100,000, and overall prevalence of hereditary ataxias and familial spastic paraplegia was 14 per 100,000. The methodology and classification of patients and diagnostic criteria were significantly different than the study done in Spain. In 2002, McMonagle and colleagues reported the estimated prevalence of pure autosomal dominant spastic paraplegia as 1.27 per 100,000 on the island of Ireland (McMonagle et al 2002). In South Tunisia, minimal prevalence was demonstrated (5.75/100,000), but in contrast to Western countries, the major types were recessively inherited, and SPG11 and SPG15 were the most common types (Boukhris et al 2009). In Norway, prevalence of hereditary spastic paraplegia was 7.4/100,000. Autosomal dominant hereditary spastic paraplegia was estimated at 5.5/100,000, and autosomal recessive hereditary spastic paraplegia was 0.6/100,000 (Erichsen et al 2009).

The primary reason for such differing prevalence rates is the variability of methodology in each study. Perhaps geographical and sociocultural factors also contribute to the variability of the results.

Clinical manifestations.

Pure hereditary spastic paraplegia. Pure (or uncomplicated) hereditary spastic paraplegia is characterized by progressive spasticity of the lower limbs, hyperreflexia, and extensor plantar responses in isolation without any other neurologic

abnormalities. The age of onset can vary from infancy to the eighth decade (Harding 1981), and a majority of the patients give history of first symptoms in the period between the second and fourth decades. Initial presentation of the disease begins with difficulty in walking and gait problems. Motor milestones, especially the time of walking, may be delayed in childhood onset forms. Stiffness of the legs, easily worn-out shoes, toe-walking, and paresthesia below the knees are the other complaints of these patients. There also may be urinary disturbances, such as urgency, frequency, and hesitancy.

Obligatory criteria suggested for the diagnosis of pure hereditary spastic paraplegia include positive family history, progressive gait disturbance, spasticity of the lower limbs, and hyperreflexia of the lower limbs (McDermott et al 2000). Gait disturbance progresses slowly without exacerbations, remissions, or worsenings (Fink 1996). In addition to hypertonicity causing spastic circumduction and toe walking, there is mild or absent muscle weakness. If muscle weakness is present, it usually involves iliopsoas, tibialis anterior, and, to a lesser extent, the hamstring muscles. Muscle wasting can occur, but it is uncommon; when present, it is found in distal muscles of the lower limbs, small muscles of the foot, and tibialis anterior, usually in patients who have had the disease for more than 10 years (Harding 1981; Durr et al 1994).

Sensory impairment is seen in 10% to 65% of cases and is common in long-standing disease; incidence increases with disease duration (Harding 1981; McDermott et al 2000). Vibration sense is often affected in the lower extremities. Joint position sense also may be impaired, but cutaneous sensory loss is uncommon (Harding 1981; Durr et al 1994; Fink et al 1996). Deep tendon reflexes may be brisk in the upper extremities but are pathologically increased in the lower extremities. Sometimes ankle jerk may be absent (Harding 1981). Ankle clonus and extensor plantar responses occur in all patients. Pes cavus is also a common finding of the disease. Fink and colleagues describe pes cavus as usually occurring in older affected patients, whereas Harding found pes cavus in one third of patients (Harding 1981; Fink et

al 1996). Flat foot, rather than pes cavus, has been identified in a Chinese family with pure type of autosomal dominant hereditary spastic paraplegia and *SPG3A* mutation (Li et al 2007).

Urinary sphincter disturbances occur in most patients. Although rare, anal sphincter involvement and sexual dysfunction can also be seen. Scheltens and colleagues describe a Dutch family with urinary and anal sphincter disturbances (Scheltens et al 1990).

Restless leg syndrome with a moderate and severe grade is also associated with hereditary spastic paraplegia. It has been found more frequently (20.5%) than the general population (11%) (Sperfeld et al 2007).

Upper limb involvement is not common. In addition to mild hyperreflexia, there may be terminal dysmetria or clumsiness without other cerebellar signs due to pyramidal tract involvement. Muscle strength and tone is normal in the upper extremities. Corticobulbar tract and cranial nerves are also preserved.

If paresis is more marked than spasticity, ataxia, prominent amyotrophy or early onset amyotrophy during the course of the disease, prominent involvement of upper limbs, asymmetry, retinal pigmentation, cranial nerve involvement, or extrapyramidal signs, diagnosis of hereditary spastic paraplegia should be cautious, and other causes within the differential diagnosis should be reconsidered (McDermott et al 2000).

Complicated hereditary spastic paraplegia.

In addition to spastic paraparesis, patients with complicated hereditary spastic paraplegia also have associated neurologic abnormalities. These associated clinical findings include optic atrophy, retinopathy, extrapyramidal signs, amyotrophy, dementia, mental retardation, ataxia, nystagmus, dysarthria, deafness, epilepsy, ichthyosis, peripheral neuropathy, and neuropsychiatric symptoms (McMonagle et al 2006). Syndromic forms are also included in the complicated hereditary spastic paraplegia (Harding 1983; McDermott et al 2000).

Differential diagnosis.

hereditary spastic paraplegia is considered when family history points out a progressive spastic paraparesis. In fact, diagnosis of hereditary spastic paraplegia is a diagnosis of exclusion; the other disorders that cause similar symptoms should be excluded by detailed investigation. Structural spinal cord abnormalities such as Arnold-Chiari malformation, cervical or lumbar spondylolysis, arteriovenous malformation, tethered cord syndrome, and syringomyelia should be excluded. Granulomas like tuberculosis and neoplasms involving the spinal cord also should be considered in the differential diagnosis. Degenerative diseases such as multiple sclerosis, amyotrophic lateral sclerosis, or spinocerebellar ataxias should be distinguished. The most important type of spinocerebellar ataxias that mimics hereditary spastic paraplegia is SCA3 (Machado-Joseph disease), and definite diagnosis requires genetic testing to differentiate SCA3 from hereditary spastic paraplegias (Wang et al 2009).

Adrenoleukodystrophy and adrenomyeloneuropathy, Krabbe leukodystrophy, metachromatic leukodystrophy, and metabolic causes such as subacute combined degeneration, vitamin E deficiency, abetalipoproteinemia, arginase deficiency, and mitochondrial encephalopathies should also be considered before hereditary spastic paraplegia is diagnosed.

Infectious causes like tertiary syphilis, AIDS, and HTLV-1 infections are the other causes that should be excluded. Spastic diplegias or dopa-responsive dystonias may present in a similar manner as hereditary spastic paraplegia.

Diagnostic workup. Diagnostic workup can help exclude some of the diseases in the differential diagnosis. For the structural malformations of spinal cord and degenerative diseases, MRI of spine and brain are helpful. Lysosomal enzymes and plasma long-chain fatty acid levels should be screened. Lipoprotein electrophoresis for abetalipoproteinemia, serum vitamin B12, folate and vitamin E levels, and antibodies for HIV and HTLV-1 are important. CSF analysis may help to diagnose mitochondrial encephalopathies or multiple sclerosis because CSF

analysis is usually normal in hereditary spastic paraplegia. EMG and nerve conduction velocities are normal in most of the pure cases, but they are helpful in diagnosing amyotrophic lateral sclerosis. Perinatal history is important for cerebral palsy, and diurnal fluctuation history can indicate dopa-responsive dystonias.

Cranial and spinal MRI is generally normal, but incidence of spinal atrophy, especially in the cervical and upper thoracic regions, is higher than normal population. Spinal cord atrophy may be seen in SPG6 and SPG8 more severely than other types

of hereditary spastic paraplegia (Hedera et al 2005; Sperfeld et al 2005). Sometimes cortical atrophy and hypoplasia of corpus callosum may be detected in cranial MRI (Harding 1993; McDermott et al 2000). If a marked atrophy or marked changes in cerebral white matter are seen, other diseases should be investigated and excluded before a definite diagnosis of hereditary spastic paraplegia can be made.

Table 1. Differential Diagnosis and Diagnostic Workup

Differential diagnosis	Laboratory investigations	
<u>Structural malformations</u>		
	<ul style="list-style-type: none"> • Chiari malformation • Syringomyelia • Tethered cord syndrome • Tumors of posterior fossa and spinal cord • Granulomas (tuberculosis) 	- Cranial and spinal cord MRI
<u>Bone and ligament dysplasias</u>		
	<ul style="list-style-type: none"> • Cervical or lumbar spondylolysis • Ossification of posterior ligament 	- Cranial and spinal cord MRI
<u>Infections</u>		
	<ul style="list-style-type: none"> • Tertiary syphilis • HTLV-1 infections • HIV 	- Antibodies for syphilis, HIV and HTLV-1
<u>Degenerative diseases</u>		
	<ul style="list-style-type: none"> • Multiple sclerosis • Amyotrophic lateral sclerosis • Spinocerebellar ataxias 	<ul style="list-style-type: none"> - CSF analysis - EMG
<u>Leukodystrophies</u>		
	<ul style="list-style-type: none"> • Krabbe leukodystrophy • Metachromatic leukodystrophy • Adrenoleukodystrophy • Adrenomyeloneuropathy 	- Lysosomal enzymes (aryl sulphatase, galactoceramidase), very long chain fatty acids
<u>Mitochondrial diseases</u>		
		<ul style="list-style-type: none"> - CSF and blood lactate and pyruvate levels - Associated clinical signs

Prognosis and complications. Type I early onset hereditary spastic paraplegia is slowly progressive, whereas type II has late onset with more rapid progression. Severity of disease does not differ in type I and type II patients. Autosomal recessive forms of pure hereditary spastic paraplegia do not differ from the autosomal dominant ones (Harding 1981; 1983). Sixteen percent of patients may be symptomless.

These diseases do not limit life expectancy. In her discussion, Harding cites the findings of Bell and Carmichael, who found the mean age of death to be 57.5 ± 3.02 years, with the mean duration of the disease as 27.21 ± 13.69 years; also, they reported 1 patient who had the disease for more than 80 years (Harding 1981).

In complicated hereditary spastic paraplegia, exact and certain knowledge about prognosis is really absent because there is a great variability in forms of the disease, in and among families. Complications are usually orthopedic.

Management. Currently, treatment of hereditary spastic paraplegia is based on symptoms (Fink et al 1996). Treatment modality for spasticity is the main point of the treatment. Antispastic drugs such as baclofen and dantrolene sodium can be used. For severe cases, intrathecal baclofen treatment can be considered. In 1990, Vanneste and Augustijn reported 2 patients who had no benefit from intrathecal baclofen (Vanneste and Augustijn 1990), but in 1992, continuous intrathecal baclofen was found effective in relieving spasticity (Meythaler et al 1992) but not in sleep and respiratory functions (Bensmail et al 2006). Although not much literature is found specifically for hereditary spastic paraplegia, botulinum toxin is being used for spasticity in spastic paraparesis, and it has been found effective in reduction of muscle tone and improvement of gait. In a series of 19 patients, botulinum toxin was effective in reduction of spasticity, especially in mild and

moderate degrees of spasticity, without many side effects. Its effect was thought to be higher when combined with physical therapy (Hecht et al 2008). In a clinical trial of 12 children with hereditary spastic paraplegia, botulinum toxin improved motor function and muscle tone, even in a very severe patient with infantile onset ascending hereditary spastic paraplegia. The effect lasted for a mean of 6 months, and botulinum toxin was suggested for a prolonged functional improvement (Geva-Dayana et al 2010). No difference was found between placebo group and hereditary spastic paraplegia patients in a double-blind control trial of gabapentin (Scheuer et al 2007).

Baclofen dosage generally starts with low doses and gradually increases to a maximum of 12 mg/kg per day (3 to 4 divided doses). But this dosage may not be sufficient; to be effective, the dose must be large enough to cross the blood-brain barrier and reach the spinal cord.

Dantrolene sodium dosage is 1 to 3 mg/kg per day.

An early and regular physical rehabilitation program may be beneficial for patients to help maintain flexibility, strength, range of motion, and ambulation.

Myocardial involvement may occur as cardiomyopathy in hereditary spastic paraplegia. A routine cardiological evaluation like the other neuromuscular disorders in the follow up of patients is suggested (Gdynia et al 2006).

Although no efficient treatment exists, experimental studies like paraplegin synthesis after an adenoassociated virus vector injection into skeletal muscle of mice that leads to an improvement by reducing abnormal mitochondria and vinblastine, a vinca alkaloid treatment in drosophila with spastin mutations, provide novel insights and hope into both molecular mechanisms and future therapeutic modalities (Orso et al 2005; Pirozzi et al 2006).

НАСЛЕДСТВЕННАЯ СПАСТИЧЕСКАЯ ПАРАПЛЕГИЯ

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