Strümpell-Lorrain Syndrome in Three Brothers: A Case Series

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ABSTRACT

Three brothers, aged 5, 19 and 24 years, from Tuguegarao, consulted because of walking difficulty due to stiffening of lower extremities which started at varying ages. Common findings were mild spasticity and weakness in both lower extremities, consistent with Strümpell-Lorrain Syndrome. Individualized rehabilitation medicine interventions were provided to address different functional deficits, leading to improved outcomes. This case series aims to illustrate the importance of initiating early, comprehensive rehabilitation to maximize function and minimize complications.

Key Words: Strümpell-Lorrain Syndrome, hereditary spastic paraparesis, familial spastic paraparesis, rehabilitation

Introduction

Spasticity of the lower extremities (LE) is one of the manifestations of upper motor neuron involvement. Progressive and severe spasticity may be the primary symptom. This, with similar history in other family members, is seen in a rare condition called Strümpell-Lorrain syndrome (SLS). Strümpell-Lorrain syndrome or hereditary spastic paraparesis (HSP) is a group of inherited disorders with slowly progressive spastic paraparesis as the pivotal clinical hallmark.[1] Adolf Strümpell, a German neurologist, published the first clear description of HSP in 1883, followed by Maurice Lorrain in 1888. The prevalence of HSP is reported at 2.7 to 4.3 per 100,000 in Italy, 2.0 per 100,000 in Portugal, 9.6 per 100,000 in Spain[2] and 3.0 per 100,000 in the United States.[3] Currently, there is no data available on the prevalence of HSP from the Philippine National Institutes of Health and the Philippine General Hospital Medical Records Section. No case has been reported in the Herdin database.

Strümpell-Lorrain syndrome is a genetic disorder causing axonal degeneration, most prominently in the terminal portions of the longest tracts, both crossed and uncrossed, and ascending and descending, within the spinal cord, particularly the corticospinal tracts to the limbs and the fasciculus gracilis fibers from the lower limbs. Demyelination and gliosis may accompany the axonal loss. The current hypothesis is that different mutant proteins disrupt axonal transport of macromolecule and organelles which selectively affects the distal axon.[4] The dorsal root ganglia, posterior roots, and peripheral nerves are spared. Degeneration of the anterior horn cells has been described in one patient.[2]

Presently, there is no treatment available to prevent, stop or reverse HSP.[5] Rehabilitation medicine is the mainstay in the management of these patients. This case series is presented to illustrate the importance of initiating an early and comprehensive rehabilitation program to maximize function and minimize complications.

Case Series

Patient 1. A 24-year-old male, eldest of six siblings, consulted in June 2008 because of difficulty in walking with inability to extend the knees when standing and to dorsiflex the ankles to clear the floor. His condition started at 16 years old as stiffening of both feet, progressing to involve the entire LE, leading to difficulty in walking and forcing him to stop schooling when he was in college. There were no associated numbness, urinary or bowel incontinence, and no history of infection prior to the onset of symptoms. Although he remained independent in performing activities of daily living (ADL), he stayed at home most of the time taking care of his youngest brother. Family history revealed similar symptoms in his father and two brothers (Figure 1). Pertinent physical examination showed limited range of motion (ROM) in both ankles with -30° to 0° dorsiflexion (DF) and bilateral hamstring tightness with a popliteal angle of 60°. There was full and pain-free ROM in all the other joints of the LE and in both upper extremities (UE). Muscles of both LE were graded 4/5 except for bilateral hip abductors

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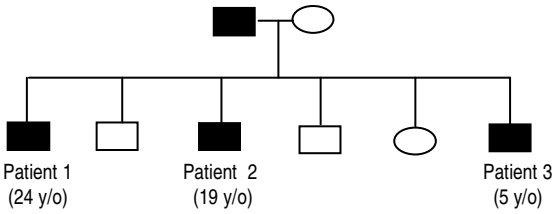

Figure 1. Family genogram

and toe extensors which were graded 3/5. There was grade 2 spasticity in both LE with hyperreflexia and clonus, extensor plantar responses, intact proprioception and vibration sense, and good standing balance. On standing, there was hip and knee flexion with forward trunk flexion. There was lateral trunk bending to the stance leg with tip-toeing, decreased hip and knee flexion with circumduction during the swing phase, and absent arm swing. Patient 1 obtained a Functional Independence Measure (FIM) score of 123/126 with difficulty in ambulation. A FIM score of 126 is complete independence. He had limited participation in vocational activities due to spasticity of the LE.

He was admitted to the Rehabilitation Medicine Ward for comprehensive rehabilitation. Physical therapy (PT) consisted of therapeutic exercises to improve ROM of LE; increase strength and motor control; and improve ambulation. Occupational therapy (OT) focused on pre-vocational training. After one month of therapy, there was an increase of 10° in ankle DF. The popliteal angle was reduced to 40° bilaterally. Muscle strength in both LE increased from 4/5 to 5/5 except for bilateral hip abductors and toe extensors which improved from 3/5 to 4/5. There was better standing posture with both hips and knees in neutral (Figure 2). There was now ankle DF during initial contact; increased hip and knee flexion during the swing phase; and increased push-off at the end of the stance phase. Vocational interests were explored, increasing the confidence and employment options of Patient 1.

Patient 2. A 19-year-old male, third of the six siblings, consulted in June 2008 because of impaired balance. His condition started at 13 years old as a sensation of falling when walking with subsequent weakness and stiffening of both LE. Patient 2 denied having numbness, urinary or bowel incontinence, or signs and symptoms of infection. Despite the difficulty in walking, he continued schooling, was independent in performing all ADL, and played basketball. Physical examination was significant for mild weakness in both LE graded 4/5 and with grade 1 spasticity, hyperreflexia, clonus, and extensor plantar responses. There was intact proprioception and vibration sense. Standing posture was normal (Figure 3). There was absent heel strike on initial contact, decreased hip and knee flexion on

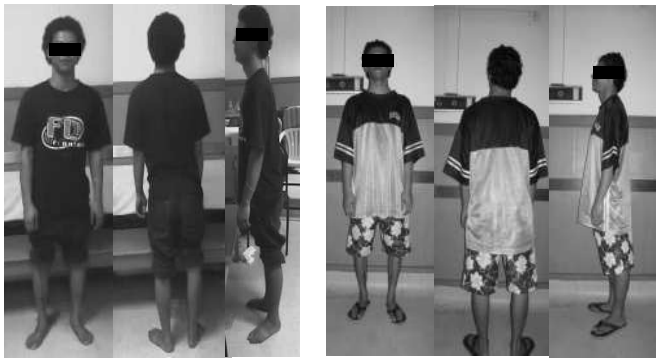

Figure 2. Standing posture of Patient 1, before and after rehabilitation

Figure 3. Baseline standing posture of Patient 2

midswing, and narrowed base of support during double support. He obtained a FIM score of 126/126.

Patient 2 was referred to a local rehabilitation center for ROM and strengthening exercises, and work simplification and energy conservation techniques. He was advised follow-up after one month but was not able to comply because of his schooling.

Patient 3. A five-year-old boy, the youngest sibling, consulted in June 2008 because of difficulty in walking described as tip-toeing and scissoring gait. He was born to a 39-year-old, G7P5 (5015) mother with unremarkable prenatal and birth history. His developmental history was at par with age until age two years when the mother noted stiffening of both LE during standing and walking, leading to foot deformities and frequent falls. There were no associated numbness, urinary or bowel incontinence, and no history of infection. On examination, there was limited ROM in both knees with extension of 135° to 30° and in both ankles with DF of -40° to 0°. The right popliteal angle was measured at 50° and the left at 60°. There was full and pain-free ROM in all the other joints of the LE and in both UE. Both hip muscles and ankle dorsiflexors were graded 3/5 and 4/5 for

the rest of the LE. There was grade 1+ spasticity in both LE with hyperreflexia, clonus, extensor plantar responses, and intact proprioception and vibration sense. Standing balance was fair. There was hip and knee flexion with forward trunk flexion in standing. Walking endurance was limited to around 15 steps without support. Patient 3 exhibited a crouched gait pattern with lateral trunk bending on the stance leg; decreased ankle DF on initial contact; and decreased hip and knee flexion with plantar flexion of the swing leg. His FIM score was 94/126 with difficulty in feeding, dressing, hygiene, and ambulation. Psychometric evaluation did not reveal any learning disorders. There were mild cognitive deficits which may be due to lack of learning opportunities as he still had no formal schooling.

Patient 3 was admitted to the Rehabilitation Medicine Ward for comprehensive rehabilitation consisting of PT to improve ROM in both LE, increase strength, and improve balance and ambulation through exercise, and OT which focused on activities to facilitate performance of age-appropriate ADL and school readiness. After one month of therapy, there was full ROM in both knees and an increase of 20° in both ankle DF. Muscle strength improved from 3/5 to 4/5 in both hip muscles and ankle dorsiflexors, and from 4/5 to 5/5 in the rest of the LE. There was now good standing balance and improved standing posture with both hips and knees in neutral (Figure 4). He ambulated independently with improved endurance, and achieved modified independence in feeding and dressing. He was provided with school-readiness activities in preparation for formal schooling.

Discussion

Individuals with Strumpell-Lorrain Syndrome or hereditary spastic paraparesis (HSP) usually present with a history of normal gestation, delivery, and early childhood development followed by slow, progressive stiffness of the LE leading to gait difficulty. These findings were evident in this case series with onset of symptoms observed at 16-, 13- and 2-years of age, respectively.

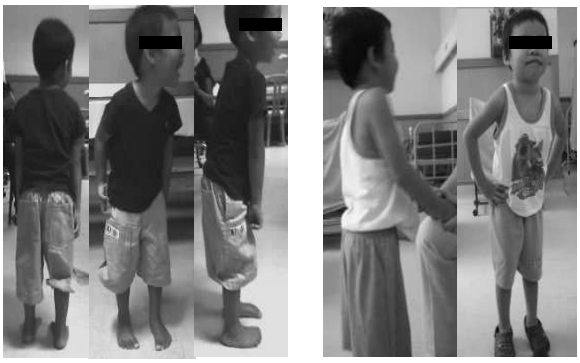

Figure 4. Standing posture of Patient 3, before and after rehabilitation

Hereditary spastic paraparesis may be classified as uncomplicated (pure) or complicated.[6] The cardinal abnormalities of pure HSP include spasticity, hyperreflexia, and extensor plantar reflexes with weakness in the LE as manifested in these siblings. Spasticity in the hamstrings, quadriceps and ankles results in the classic gait described as circumduction and toe-walking. There is muscle weakness in the iliopsoas, anterior tibialis and, to a lesser extent, hamstrings. There is marked discrepancy between the often severe spasticity and only mild or absent muscle weakness exemplified by a patient who is non-ambulatory due to spasticity but on manual muscle testing has normal strength.[2] These siblings manifested dynamic spasticity of the LE making ambulation difficult despite muscle strengths of 3/5 to 4/5.

An important negative finding is normal cranial nerve function as observed in these siblings. All three brothers presented with normal function of the UE. In contrast, complicated HSP is associated with optic atrophy, retinopathy, dementia, mental retardation, deafness, peripheral neuropathy, and epilepsy.

Hereditary spastic paraparesis is a diagnosis of exclusion in the absence of a positive family history. Neuroradiological studies and biochemical tests are important. Disorders clinically resembling HSP include vitamin B12 deficiency, dopa-responsive dystonia, structural brain or spinal cord abnormalities, multiple sclerosis, and amyotrophic lateral sclerosis. The primary differential diagnosis for this case series is structural brain and spinal cord abnormalities which were ruled out since these disorders do not usually present with a familial pattern. In addition, there were no bowel and bladder incontinence, sensory and motor level involvement, or spinal or referred pain pointing to a spinal cord lesion. Brain abnormalities may present with involvement of the UE, weakness greater than spasticity, flaccidity, and cognitive impairments which were not evident in these patients. Cerebral palsy was ruled out in the youngest brother in the absence of neonatal difficulties and in light of a seemingly progressive disease with a familial pattern of involvement. Metabolic disorders should also be ruled out in childhood onset HSP.

Based on clinical criteria, HSP may be classified as: obligatory, common, uncommon and diagnostic alerts.[2] "Obligatory" features include family history, progressive gait disturbance, spasticity and hyperreflexia of the LE, and extensor plantar responses, all of which were present in the three brothers. "Common" features are paresis of the LE, sphincter disturbances, dorsal column disturbances, pes cavus, and hyperreflexia of the UE. Paresis of the UE and distal amyotrophy fall under the "uncommon" category while the "diagnostic alerts" are described as paresis greater than spasticity, prominent ataxia and involvement of the UE, peripheral neuropathy, and retinal pigmentation.

In families in which several members have the typical features, diagnosis presents with few difficulties. In this series, three out of the six siblings manifested with symptoms at varying ages compatible with the syndrome. The other siblings (two boys, one girl) are apparently asymptomatic. There is reported history of bilateral weakness of the LE in the father but he remains ambulatory without assistive device. However, a clinical diagnosis of HSP could not be ascertained since the father was not available for evaluation.

When the symptoms of HSP appear in early childhood, magnetic resonance imaging (MRI) of the brain and spinal cord is essential to exclude structural abnormalities. One study suggests that thinning of cervical and thoracic spinal cord, and volume loss of corpus callosum may be seen.[4] Electrophysiologic studies can assess peripheral nerve, muscle, dorsal column, and corticospinal tract involvement. Nerve conduction tests and electromyography are normal in HSP.[2] Central motor conduction latencies may be delayed or not detectable from the LE while somatosensory evoked potentials from the LE tend to be small.[4] Cerebrospinal fluid analysis is unremarkable.[2]

It is possible to determine the exact loci of gene mutation through genetic analysis for precise and definitive diagnosis. Ten HSP genes and various loci responsible for the modes of inheritance of HSP—10 autosomal dominant (AD), 8 autosomal recessive (AR) and 3 x-linked types—have been identified.[3] A recent review revealed that at least 34 HSP genes, specific spastic gait genes or loci have been localized with 17 of these identified, paving the way for an emerging classification of HSP based on clinical and molecular data.[6] Autosomal dominant HSP (ADHSP) is the most common form, representing approximately 70 to 80% of cases.[6,7] There are more males than females (60% to 40%) in both AD and AR types of HSP.[8] Screening for the two most common HSP-related genes, SPAST (formerly SPG4) and SPG3A can provide a molecular genetic diagnosis in more than 50% of ADHSP cases.[7] Clinically, all brothers seem to have ADHSP. Salinas et al. reported that "a family history compatible with autosomal dominant transmission in the context of adult-onset spastic paraplegia is almost always indicative of HSP."[7] As up to 25% of affected individuals with ADHSP are asymptomatic, it is crucial to conduct a clinical examination of other family members to help establish the diagnosis and to improve prognosis.[2] Due to financial constraints, appropriate diagnostic tests such as MRI for the youngest brother with the earliest disease onset, and genetic studies for the three brothers and the asymptomatic siblings were not done.

The primary neuropathological finding in HSP is axonal degeneration of the terminal portions of the long descending (corticospinal) and ascending (dorsal columns) tracts in the spinal cord. This is the proposed mechanism for the uncomplicated form of HSP. This abnormality is hypothesized to be mediated by the SPG4 gene or spastin which plays a key role in the dynamics of microtubule turnover, an important component of the intracellular cytoskeleton where axonal transport occurs.[4] Other mutant proteins, paraplegin (SPG7) and proteolipoprotein (SPG1), also disrupt axonal transport of macromolecules and organelles, selectively affecting the distal axon.[4] Abnormality in membrane trafficking is another potential mechanism.[7]

There is no disease modifying treatment available that can prevent, retard, or reverse the progressive course of HSP. Management is currently limited to symptomatic treatment of spasticity, urinary urgency, and improvement of strength and gait.[9] Lambrecq et al. reported functional improvement with chronic intrathecal delivery of baclofen in patients with HSP[10] while Hecht et al. reported that there is some evidence that botulinum neurotoxin A injection can reduce spasticity in individuals with HSP with mild to moderate spasticity effectively and safely.[11] However, spasticity is not always harmful.[12] Some patients with upper motor neuron weakness rely on increased tone to maintain the ability to stand and walk.

Rehabilitation medicine intervention is important in maximizing function and preventing complications in patients with HSP. Physical therapy improves ROM, muscle strength, gait, and endurance through therapeutic exercises. Use of therapeutic electrical stimulation has been reported to improve the gait in one patient with HSP by strengthening the stimulated spastic muscle and inhibition of the antagonist muscle.[13] Occupational therapy focuses on energy conservation, work simplification, and facilitation of ADL skills and pre-vocational or vocational training. Assistive devices such as a cane, walker or wheelchair are vital to facilitate ambulation and mobility in patients with more progressive disease. Psychological intervention reduces stress, facilitates acceptance of the condition, and promotes confidence and well-being.

Careful positioning of the affected extremity to maintain adequate muscle length can be achieved with the use of orthoses. With established contractures and spastic deformities, surgery may correct deformity and allow better positioning and function, including gait. In the case series of Dennis et al., the most common procedures performed on children with HSP were hamstring and heel cord lengthenings, and adductor longus release with improvement in gait.[8] Despite the presence of significant dynamic spasticity, anti-spasticity medications were not prescribed to any of the three brothers since spasticity provided positive effects during standing and walking. Systemic anti-spasticity medications may unmask an underlying weakness of the LE and may lead to more gait deviations and increase difficulty in ambulation. An individualized rehabilitation program was prescribed for each patient, targeting the most significant functional goal for each brother—ambulation for Patient 1, maintenance of

independent functional status for Patient 2, and ambulation and acquisition of age-appropriate ADL skills for Patient 3.

Severity and prognosis of HSP vary between and within families but life expectancy is normal. However, complications from HSP can shorten lifespan. Patients with ADHSP generally function well before age 50 years and may become wheelchair-bound at an average of 60 years.[8] Since all three brothers apparently have the pure type of HSP, they may not manifest other neurologic signs and symptoms (other than weakness, hyperreflexia, spasticity) and extra-neurologic complications. Diagnostic evaluation and management for Patient 1 was relatively delayed with progression of symptoms noted in the past eight years. Although his FIM score upon discharge improved from 123/126 to 125/126, he may continue to benefit from intensive rehabilitation to become a community ambulator and to seek future employment as a clerk. Patient 2, although he had an earlier onset of symptoms compared with Patient 1, presented with the least severe impairments. He may need a shorter period of out-patient or home therapy to maintain his functional gains. He plans to finish college to obtain his degree. Patient 3, despite presenting with the earliest disease onset, has the benefit of early recognition and diagnosis, and initiation of habilitation intervention with positive outcome. His FIM score improved from 96/126 to 110/126 on discharge. With continuing intensive habilitation, he should be able to acquire more age-appropriate skills and attend school. Regular follow-up with a local rehabilitation medicine specialist (physiatrist) in the community for monitoring and continuing rehabilitation was emphasized to further enhance or maintain their level of functioning and to prevent or delay the onset of complications. The availability of an increasing number of HSP genetic analyses can facilitate genetic counseling to include asymptomatic individuals[1] and provide prenatal genetic testing.[8] Limited genetic counseling in the absence of the definitive diagnosis was included in the multidisciplinary rehabilitation management of the three brothers. Issues on the hereditary nature of HSP, personal relationship, marriage, and potential risk of recurrence of the condition in future offspring were addressed. It has been observed that HSP tends to be non-progressive in individuals with childhood onset compared with those with adult onset who tend to have a slowly progressive course. The question of whether HSP represents a neurodevelopmental disorder in the former group and/or neurodegenerative disorder in the latter group remains to be answered.[9]

Conclusion and Recommendations

Strümpell-Lorrain syndrome comprises a clinically and genetically heterogeneous group of disorders with progressive spasticity as its clinical hallmark. Prompt recognition of the condition is important to allow early, comprehensive, and holistic rehabilitation intervention. Rehabilitation medicine can improve function hampered by abnormal tone evident in HSP by improving the joint ROM, motor strength, gait and endurance; facilitating ADL skills through modification; providing educational, vocational, and avocational (recreational) opportunities; and addressing relevant psychosocial issues. The lack of a definitive treatment, and, in this case series, lack of precise diagnosis, should not delay the initiation of rehabilitation interventions to maximize function and minimize complications in individuals with HSP. However, this should not undermine the importance of conducting a complete diagnostic investigation.

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