**RESEARCH PAPER**

# A Case of Late-Onset Hereditary Spastic Paraplegia (HSP)

Dr. N. N. Anand [1], Dr Manasvi P [2], Dr. Aswathy T Menon[3], Dr. Karthikeya T M [4], Dr. Divya Sriramulu [5]
Dr. Arun Kumar K[6], Dr. Suhas Goud[7], Dr. Snega R Laxmi[8]

[1]*Professor, Head of Department, Department of General Medicine, Sree Balaji Medical College and Hospital*
*Email: drnaganand1971@gmail.com*
[2]*Junior resident, Department of General Medicine, Sree Balaji Medical College and Hospital*
[3] *Assistant Professor, Department of General Medicine, Sree Balaji Medical College and Hospital*
[4]*Assistant Professor, Department of General Medicine, Sree Balaji Medical College and Hospital*
[5] *Assistant Professor, Department of General Medicine, Sree Balaji Medical College and Hospital*
[6] *Senior Resident, Department of General Medicine, Sree Balaji Medical College and Hospital*
[7]*Junior resident, Department of General Medicine, Sree Balaji Medical College and Hospital*
[8]*Junior resident, Department of General Medicine, Sree Balaji Medical College and Hospital*

***Received: 28th Aug, 2025; Revised: 20th Nov, 2025; Accepted: 21th Dec, 2025; Available Online: 17th Jan, 2026***

**ABSTRACT**

**Overview**:Hereditary spastic paraplegia (HSP) represents a heterogeneous group of genetic disorders of the nervous system, which is identified by "progressive lower-limb" spasticity and weakness. Autosomal dominant HSP due to ATL1 (SPG3A) mutations typically presents in childhood, while late-onset cases remain exceedingly rare and often difficult to diagnose due to overlap with acquired spastic paraparesis and age-related neurological conditions.

**Case Presentation:**We report about a 61 year old male with progressively worsening gait difficulty and lower-limb stiffness. Although he recalled mild walking difficulty since childhood, rapid worsening over one year prompted evaluation. Neurological examination revealed lower-limb spasticity, clonus, hyperreflexia and bilateral extensor plantar responses without sensory, cerebellar, cognitive, or bladder involvement. Significant autosomal dominant family history was noted, with two affected siblings.

**Investigations & Diagnosis:**Routine metabolic, nutritional, autoimmune, and infectious profiles were normal. Electrophysiology demonstrated intact peripheral nerve function. MRI spine showed advanced multilevel degenerative disk and facet changes, while MRI brain demonstrated frontal periventricular hyperintensities suggestive of the "ears of the lynx" sign. Whole-exome approaches pointed out a likely pathogenic ATL1 missense version (c.1376A>G; p.Tyr459Cys), confirming late-onset ATL1-HSP. Differential diagnoses including primary lateral sclerosis, spinocerebellar ataxia, and chronic myelopathy were excluded.

**Management & Outcome:**The patient received oral baclofen and structured physiotherapy. At six-month follow-up, gait stability and spasticity demonstrated modest improvement, with stable upper-limb strength and no new neurological deficits.

**Conclusion:**This case highlights an uncommon late-onset presentation of ATL1-associated HSP, emphasizing the need to consider genetic etiologies in adult-onset spastic paraparesis, particularly with subtle lifelong symptoms and positive family history. Genetic testing remains essential for timely diagnosis, counseling, and management**.**

**Keywords**: N\A.

**How to cite this article:** Anand NN, Manasvi P, Menon AT, Karthikeya TM, Sriramulu D, Kumar AK, Goud S, Laxmi SR, A Case of Late-Onset Hereditary Spastic Paraplegia (HSP).. Int J Drug Deliv Technol. 2026;16(1): 516-518: DOI: 10.25258/ijddt.16.1.56

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Hereditary spastic paraplegia (HSP) is a rare, heterogeneous group of familial neurodegenerative disorders characterized by slowly progressive spasticity and weakness of the lower extremities. Prevalence estimates for HSP range from 1.2 to 9.6 per 100,000.

Pure HSP involves isolated lower limb pyramidal symptoms, though it may also include mild urinary disturbances or impaired distal vibration sensation. Complicated HSP includes additional major features such as cognitive impairment, ataxia, peripheral neuropathy, seizures, or muscle atrophy. The disease exhibits varied inheritance patterns: "autosomal recessive or AR", "autosomal dominant or AD" and X-based.

Autosomal dominant forms are the most common type of HSP. While many recessive forms (e.g., SPG11, SPG15) typically present in childhood or early adolescence, AD forms such as SPG4 (*SPAST*) are frequently associated with late onset (sometimes presenting above 30 years of age). This case highlights the critical difficulty in diagnosing late-onset HSP (SPG3A, *ATL1*) in the adult patient, where its subtle, gradual presentation can be easily misattributed

**Author for Correspondence: drnaganand1971@gmail.com*

to common geriatric or incidental structural disorders.

## CASE PRESENTATION

A 61 year old gentleman presented to the out patient department with progressive difficulty in walking. He reported mild walking difficulty starting in childhood, characterised by tripping on uneven surfaces, but experienced progressive worsening of lower limb stiffness over the last year.

There were no difficulties in moving the upper limbs or stiffness in the upper limbs, cranio-bulbar symptoms, seizures, or cognitive decline. Also, there was no involvement of bladder or bowel. His medical history included controlled diabetes and hypertension for the past four years.

Neurological Examination:

Cognition: Normal.

Motor: bilateral Lower limb power was 4/5, while upper limbs were normal Spasticity was present, with patellar and ankle clonus, and bilateral extensor plantar responses.

Sensory/Cerebellar: Normal sensory and cerebellar examinations; Romberg test was negative.

Family History: Strong positive family history, consistent with AD inheritance: His father and his brother were affected; his father faced difficulty during walking, along with the visual and hearing disability in his older age. His brother had toe walking and hearing impairment.

**Investigations**:

Routine and Metabolic Exclusion: Complete hemogram, renal, hepatic, and thyroid function tests were normal. Levels of Vitamin B12 and homocysteine were within normal limits, ruling out key nutritional deficiencies that mimic myelopathy. Serology (HIV, syphilis) was negative.

Electrophysiology: Nerve conduction studies (NCS) were normal, helping to differentiate from peripheral neuropathy or slowly progressive axonal motor neuropathy (a feature sometimes seen in complex SPG3A). Cerebrospinal fluid analysis was normal.

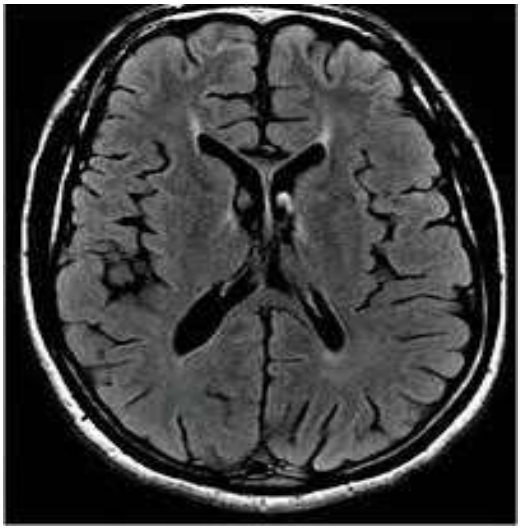
Imaging: MRI spine showed multilevel “degenerative disk and changes in facet, along with canal stenosis at C5-6 and C6-7. Also, the report showcased “T4 and T5 vertebral body fusion” and a “posterior disk osteophyte complex at T7-8”.

MRI Brain: "Ears of the Lynx Sign": hyperintense signals at the tips of the frontal horns of the lateral ventricles on T2/FLAIR axial MRI

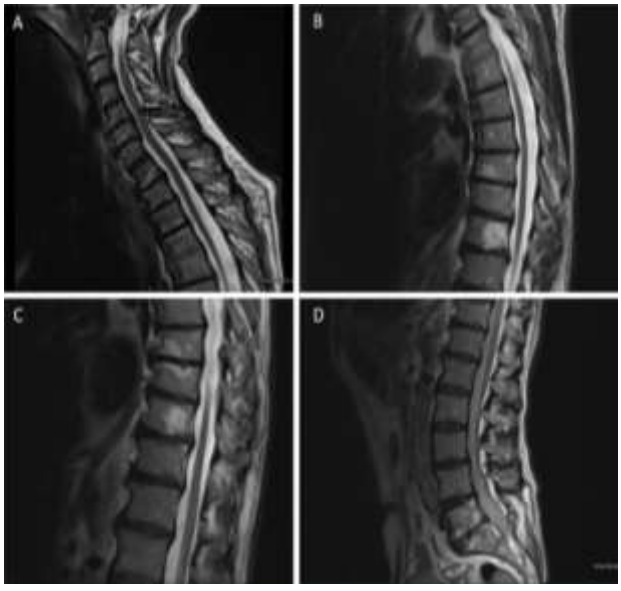
Genetic Confirmation: Based on the clinical phenotype of slowly progressive, pure spasticity, late onset, and strong family history suggesting AD inheritance, genetic testing was pursued. WES (“Whole exome sequencing”) identified a missense variation in exon 12 of the *ATL1* gene [c.1376A>G; p.(Tyr459Cys)]. This variant was classified as likely pathogenic based on ACMG categorisation (according to criteria of PM1, PP2, PM2, PP3, PP5).

The differential diagnoses considered included spinocerebellar ataxia, primary lateral sclerosis, and chronic demyelinating myelopathy. However, the absence of cerebellar atrophy, normal electrophysiology, and slow, symmetric progression favored a diagnosis of probable late-onset hereditary spastic paraplegia with complex features.

The patient was treated with oral baclofen (10 mg three times daily), targeted physiotherapy, and rehabilitative gait training. At six-month follow-up, spasticity and gait improved modestly, and upper-limb weakness remained stable.



Ears of the lynx sign on MRI brain: Axial image across the anterior forceps of the corpus callosum shows an abnormality in the region of the forceps minor of the corpus callosum, corresponding to the genu fibers, which appear dark on T1-weighted and bright on FLAIR image




MRI spine showed multilevel “degenerative disk and changes in facet, along with canal stenosis at C5-6 and C6-7. Also, the report showcased “T4 and T5 vertebral body fusion” and a “posterior disk osteophyte complex at T7-8”.

**DISCUSSION**:

Hereditary spastic paraplegia encompasses a broad group of neurodegenerative disorders which is associated with progressive spastic paraparesis due to involvement of corticospinal tracts and dorsal columns. ATL1-associated HSP (SPG3A) consisted approximately 10% of autosomal dominant cases and classically presents in childhood or adolescence, with >80% manifesting before age 10. Thus, presentation in the seventh decade, as observed here, represents an exceptionally rare phenotype and expands the known clinical spectrum of ATL1-related disease.

Late-onset HSP frequently poses diagnostic uncertainty due to phenotypic overlap with primary lateral sclerosis (PLS), adult-onset leukodystrophies, cervical spondylotic myelopathy, and metabolic myelopathies. The diagnostic process in older adults requires careful exclusion of structural and inflammatory etiologies, as age-related spinal changes and cerebrovascular changes may mimic or coexist with HSP, leading to misattribution of symptoms. In this case, absence of sensory deficits, preserved cognition, normal NCS, and lack of cerebellar atrophy reduced suspicion for other mimics such as multiple sclerosis, neuromyelitis optica, and spinocerebellar ataxias.

Neuroimaging plays a supportive but not definitive role. The “ears-of-the-lynx” sign, typically associated with SPG11, has occasionally been described in other forms of upper motor neuron neurodegeneration and may reflect nonspecific corticospinal tract degeneration. Spinal cord atrophy, particularly at thoracic levels, further supports pyramidal tract involvement in HSP. Importantly, early subtle symptoms in adolescence—such as tripping—highlight the need to revisit childhood motor milestones during adult evaluation.

Genetic analysis remains the cornerstone of diagnosis in atypical HSP. The pathogenic ATL1 variant identified (c.1376A>G; p.Tyr459Cys) has been described in association with variable penetrance and incomplete expressivity, supporting emerging evidence that ATL1 mutations may produce late-onset or complex phenotypes. Current literature suggests that missense ATL1 variants disrupt atlastin-1 GTPase activity, affecting axonal maintenance and ER network formation.

Management remains supportive, focused on reducing spasticity and improving gait through medications (baclofen, tizanidine) and physiotherapy. Disease-modifying therapies remain under investigation. Early genetic confirmation facilitates prognostication, family counseling, and patient inclusion in emerging clinical research initiatives.

**CONCLUSION**

This case underscores the importance of maintaining high clinical suspicion for hereditary spastic paraplegia in adults presenting with progressive spastic paraparesis, especially when subtle lifelong motor symptoms accompany a positive family history. Although ATL1-associated HSP typically manifests in childhood, this rare late-onset presentation demonstrates the expanding phenotypic spectrum and highlights the diagnostic challenges in older patients where degenerative, structural, and vascular causes may confound evaluation. Comprehensive assessment, including neuroimaging and genetic testing, remains essential for accurate diagnosis, prognostication, and counseling. Early recognition facilitates targeted symptomatic management, optimizes functional outcomes, and enables at-risk family screening.

**REFERENCE**

1. Fink JK. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. N Engl J Med. 2013;368:1356–1366.
2. Ruano L, Melo C, Silva MC, Coutinho P. The global epidemiology of hereditary spastic paraplegia: a systematic review. Neuroepidemiology. 2014;42(3):174–183.
3. Lo Giudice T, Lombardi F, Santorelli FM, Kawarai T, Orlacchio A. Hereditary spastic paraplegia: clinical-genetic characteristics and evolving molecular mechanisms. Exp Neurol. 2014;261:518–539.
4. Harding AE. Classification of the hereditary ataxias and paraplegias. Lancet. 1983;1:1151–1155.
5. Fink JK. Hereditary spastic paraplegia: clinical principles and genetic advances. Lancet Neurol. 2013;12(12):1161-1172.
6. Hazan J et al. Spastin, a new AAA protein, is altered in the most frequent form of autosomal dominant spastic paraplegia. Nat Genet. 1999;23:296-303.
7. Gordon PH, et al. Primary lateral sclerosis: diagnosis and management. Neurology. 2006;66(5):646-652.
8. Harding AE. Hereditary spastic paraplegias. Semin Neurol. 1993;13:333-336.
9. Floeter MK. Spastic Paraparesis Differential Diagnosis. Continuum (Minneap Minn). 2019;25(1):151-171.
10. Stevanin G, et al. The “ears of the lynx” sign. Brain. 2008;131:1380-1391.
11. Hedera P. Hereditary spastic paraplegia overview. GeneReviews. University of Washington; Updated 2022.
12. Namekawa M, et al. Late-onset ATL1 mutation causing hereditary spastic paraplegia. J Neurol Sci. 2008;272:171-174.
13. Dorboz I, et al. Phenotypic variability of ATL1 mutations. Neurology. 2014;83:117-125.
14. Park SH, Blackstone C. Further evidence that Hereditary Spastic Paraplegia genes are essential for ER network integrity. Hum Mol Genet. 2010;19:2774-2786.