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# Spastic Paraplegias Due to Non-Traumatic Spinal Cord Disorders

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## Abstract

Spinal cord disorders are induced by diseases of various categories: infectious, inflammatory, degenerative, genetic, traumatic, and so on. These diseases involve spastic paraplegia or tetraplegia, abnormal sensation, bladder and anal dysfunction, etc. This chapter describes the medical etiologies and treatments for spastic paraplegias. I will mention diagnostic and therapeutic aspects of spastic paraplegias due to non-traumatic spinal cord disorders. I will describe my cases who suffered from amyotrophic lateral sclerosis (ALS), hereditary spastic paraplegia (HSP), HTLV-1 associated myelopathy (HAM), and multiple sclerosis (MS). I also investigate the recent therapeutic strategies for spastic paraplegias. Spastic paraplegia is an intractable condition accompanied by many spinal cord disorders. Some therapeutic methods (intrathecal baclofen and botulinum toxin injection) have symptomatic effects. Rehabilitation and some devices are also effective for spasticity.

**Keywords:** adrenoleukodystrophy (ALD), amyotrophic lateral sclerosis (ALS), hereditary spastic paraplegia (HSP), HTLV-1 associated myelopathy (HAM), multiple sclerosis (MS), intrathecal baclofen, botulinum toxin, rehabilitation

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## 1. Introduction

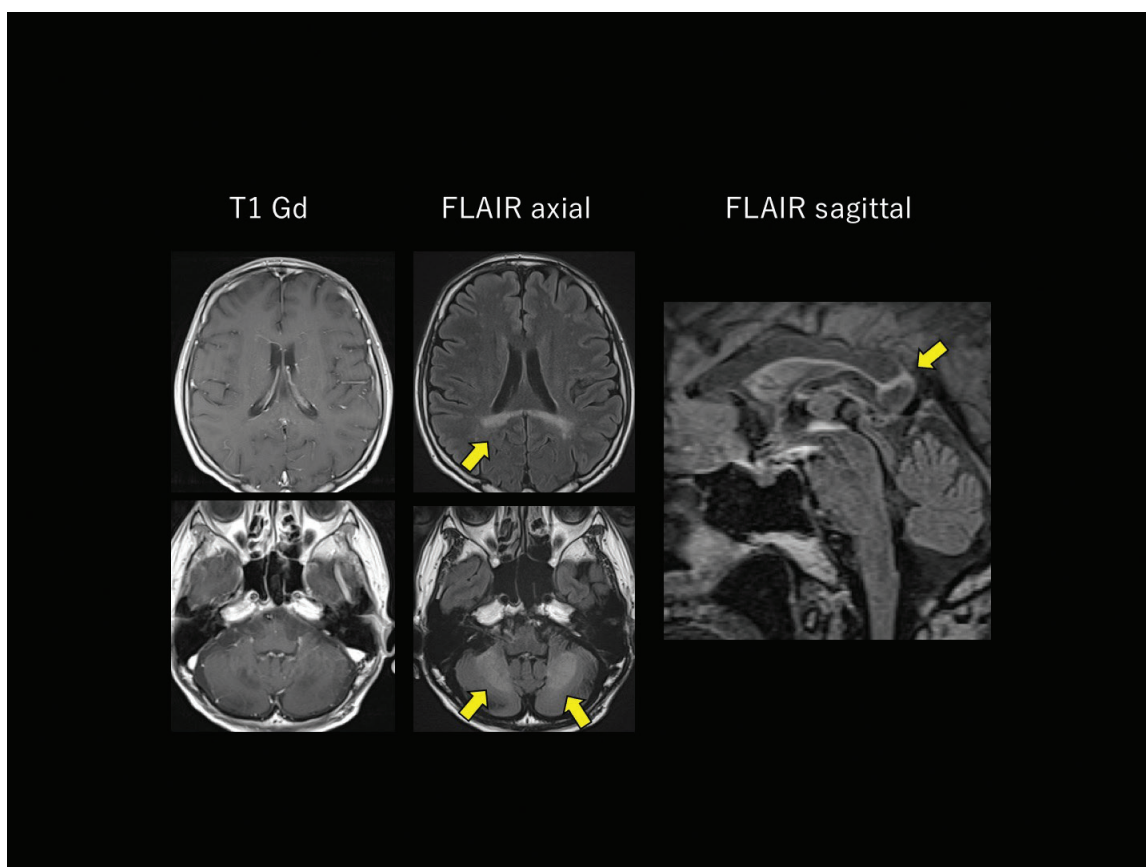
Spinal cord disorders are induced by diseases of various categories: infections [1] (e.g. herpes zoster or human T-cell lymphotropic virus type 1), inflammation (e.g. multiple sclerosis [2]), vascular diseases (e.g. spinal cord infarction [3]), degeneration (e.g. amyotrophic lateral sclerosis [4]), genetic diseases (e.g. hereditary spastic paraplegias [5]), metabolic disorders [6], trauma, etc. These diseases involve spastic paraplegia or tetraplegia, abnormal sensation, bladder and anal dysfunction, etc. This chapter describes the medical etiologies and treatments for spastic paraplegias. Diagnostic and therapeutic aspects of spastic paraplegias due to non-traumatic

spinal cord disorders will be described. In this chapter, cases with X-linked adrenoleukodystrophy (X-ALD), amyotrophic lateral sclerosis (ALS), hereditary spastic paraplegia (HSP), HTLV-1-associated myelopathy (HAM), multiple sclerosis (MS) are introduced.

## 2. Adrenoleukodystrophy (X-ALD)

Adrenoleukodystrophy is an X-linked recessive disorder that affects the central nervous system white matter and the adrenal cortex [7, 8]. It is classified into several subtypes. The most frequent type is the childhood cerebral form, which initially resembles a behavior disorder and presents adrenal insufficiency, followed by mental impairment, cortical blindness, cortical deafness, spastic tetraplegia and convulsions. This form leads to a decerebrate state for a few years after onset. Whereas the adult forms are divided into adult cerebral, adrenomyeloneuropathy, and cerebello-brainstem. Here we present adult cerebral form case with cerebellar ataxia and spastic paraplegia.

A 53-year-old man was admitted to our hospital because of mental deterioration and gait disturbance. His uncle on his mother's side suffered from gait disturbance from 40 years of age. His total IQ according to Wechsler Adult Intelligence Score (WAIS)-III was 64. He showed emotional incontinence and attention deficit. Gingival pigmentation was noted. Neurological



**Figure 1.** Brain MRI of the adrenoleukodystrophy patient. T1 gadolinium (Gd) enhance: no enhanced area in his brain. FLAIR axial: FLAIR hyperintensities in the cerebellar white matters and callosal body (arrow). FLAIR sagittal: FLAIR hyperintensities in the callosal body (arrow).

examination revealed saccadic eye movement, dysarthria, ataxia and spasticity of the bilateral feet, exaggerated deep tendon reflexes (DTRs), and bilateral positive Babinski signs. Blood examination disclosed elevation of very long chain fatty acids (C24:0/C22:0 2.09, C25:0/C22:0 0.080, and C26:0/C22:0 0.075) and ACTH (173 pg/ml). Brain MRI showed FLAIR hyperintensities in the cerebellar white matter and callosal body, whereas there was no gadolinium enhanced area (**Figure 1**). No atrophy or abnormal signals were observed on MRI of the spinal cord. Brain single photon emission computed tomography (SPECT) demonstrated cerebellar hypoperfusion. For an accurate diagnosis, gene analysis was performed by another institution, which revealed a non-synonymous missense variant of the *ABCD1* gene.

He was administered hydrocortisone and propiverine because of his adrenal insufficiency and frequent urination, and underwent physical rehabilitation (walking and balance exercise) for his leg spasticity and ataxia. We referred him to another hospital, and allogeneic hematopoietic stem cell transplantation was recommended [9, 10], but he denied this treatment.

### 3. Amyotrophic lateral sclerosis (ALS)

ALS is a fatal disorder characterized by muscle weakness and atrophy, and swallowing and respiratory disturbances [11]. The pathologic findings are upper (brain) and lower (spinal cord) motor neuron degenerations. In some ALS cases, spastic paraplegia can be a predominant symptom in the early stage of the disease. Here we present a case that showed spastic paraplegia as an initial phenotype.

A 60-year-old man was admitted to our hospital to alleviate his lower leg spasticity. Three years ago, he suffered from left leg discomfort and gait disturbance. Then the same sense of discomfort spread to his right foot. Neurological examination on admission showed marked leg spasticity with laterality and a spastic gait, exaggerated DTRs, and positive pathological reflexes. The brain and spinal cord MRI findings were normal. Motor evoked potentials suggested upper motor neuron disturbances.

We administered some muscle relaxants. He underwent gait rehabilitation and botulinum toxin injection to his lower legs. These therapies slightly improved the range of motion of knee and foot joints. But he refused intrathecal baclofen.

After 1 year, he noticed dysphagia and intrinsic hand muscle atrophy. Neurological re-evaluation revealed bulbar signs and distal muscle weakness, these findings leading to a diagnosis of ALS. Although he underwent intermittent edaravone infusion therapy [12], his muscle weakness and atrophy gradually worsened and he became bedridden.

### 4. Hereditary spastic paraplegia (HSP)

HSP is a genetic neurodegenerative disorder that involves bilateral leg spasticity with additional features: mental impairment, peripheral neuropathy, cerebellar ataxia, retinal

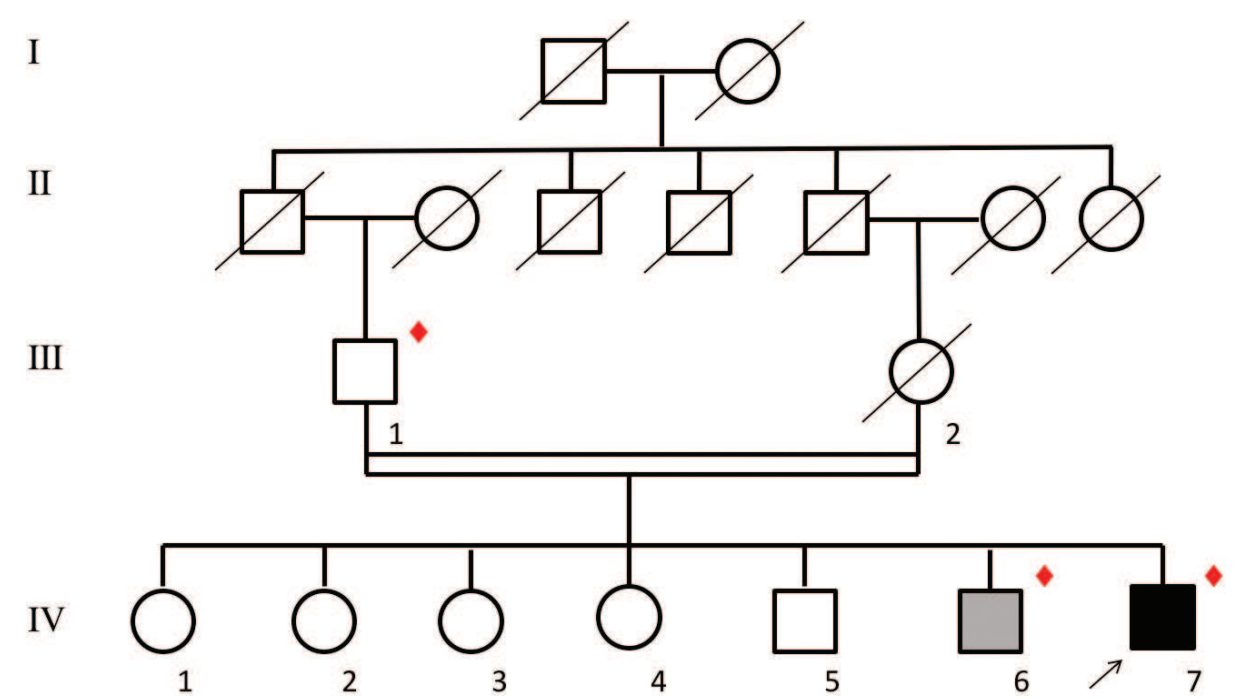
degeneration, etc. [5]. Its progression is slower than that of ALS. We have encountered and described several cases who suffered from HSPs. First, I present a SPG3A case. SPG3A is an autosomal dominant, early-onset pure spastic paraplegia caused by an *Atlastin1* (*ATL1*) gene mutation [13].

A 52-year-old man visited our clinic because of early-onset gait disturbance at age two (**Figure 2**, IV-7). He had been diagnosed as having cerebral palsy by a doctor at another hospital. He underwent bilateral Achilles tendon lengthening in his early childhood. His older brother suffered from late-onset gait disturbance (**Figure 2**, IV-6).

On examination, his gait was spastic. Muscle weakness and atrophy of his lower extremities were observed. Exaggerated DTRs except for a diminished Achilles tendon reflex and pathological reflexes of his legs were noted (**Table 1**). MRI of his brain revealed no abnormal findings, whereas his spinal cord was slightly atrophic. Serum HTLV-1 antibody was positive, but he refused a lumbar puncture. Whole-exome sequencing analysis allowed the diagnosis of SPG3A. He had a reported heterozygous missense mutation (c.1239T>C, p.F413L) of the *ATL1* gene [14] (**Figure 3**).

This mutation was not detected in DNA from his father (III-1) or older brother (IV-6). We prescribed muscle relaxants (tizanidine and dantrolene), but he could not continue to take them due to their side effects (nausea and sleepiness).

Next, I present a SPG11 case. SPG11 is an autosomal recessive, complicated SPG accompanied by mental impairment, peripheral neuropathy and a thin corpus callosum. This disease is caused by mutations of the *SPG11* gene encoding spatacsin protein [15].

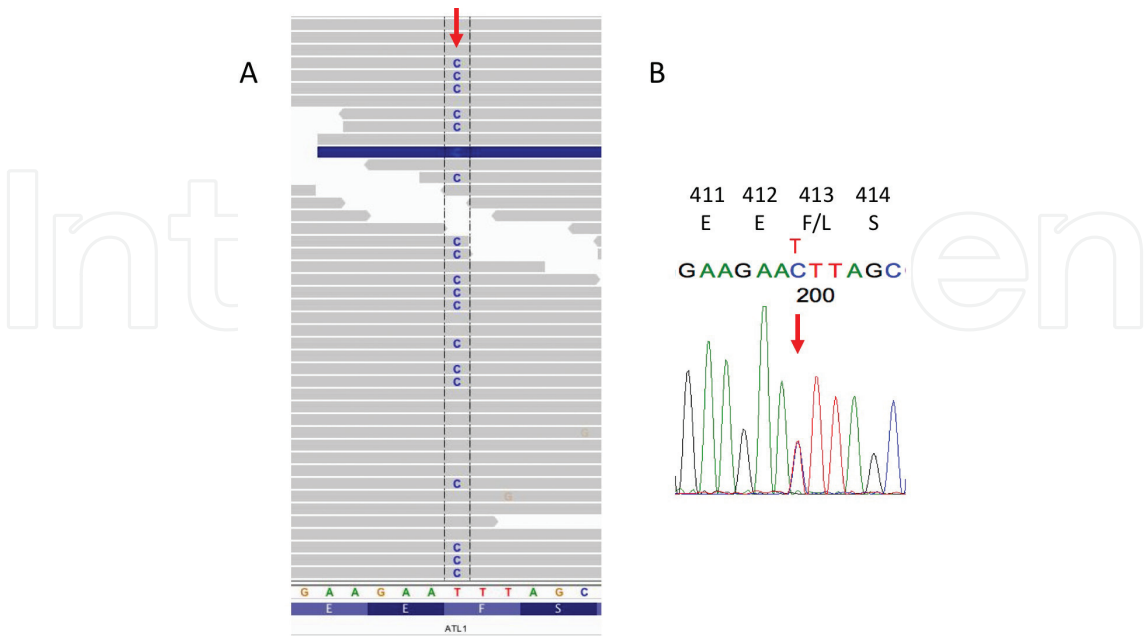


**Figure 2.** Family tree including the SPG3A/HAM cases. Proband (IV-7): SPG3A patient, HTLV-1 carrier. Older brother (IV-6): HAM patient. Father (III-1): Healthy HTLV-1 carrier. Diamonds indicate positive anti-HTLV-1 antibodies.

	IV-6 (HAM)	IV-7 (SPG3A)
Age at examination	54	52
Age at onset	42	2
DTR of legs	↑	PTR↑, ATR↓
Babinski reflex	+	+
Leg atrophy	–	+
Sensory disturbance	+	–
Spinal MRI	Normal	Mild atrophy

**Table 1.** Clinical symptoms of the HAM and SPG3A cases.

A 31-year-old man was admitted to our hospital because of standing difficulty and bilateral leg pain. He noticed gait disturbance at age 13. His gait disturbance gradually worsened and he became wheel-chair bound at age 23. He has mental impairment. On examination, exaggerated DTRs and marked spasticity with sustained clonus of both legs were observed. Brain MRI showed a thin corpus callosum. Genetic analysis disclosed compound heterozygous mutations of the *SPG11* gene [16]. We tried intrathecal low-dose baclofen administration, which dramatically alleviated his spasticity (from 4 to 2, modified Ashworth score) and pain with leg clonus. Then an intrathecal baclofen infusion pump was implanted by a neurosurgeon. He became almost free from leg clonus pain with intrathecal baclofen and the modified Ashworth score decreased to 2 or 3.



**Figure 3.** Gene analysis of the SPG3A patient. A. Whole-exome sequencing revealed the c.1239T>C (p.F413L) variant of the *Atlastin1* (*ATL1*) gene. B. Sanger sequencing confirmed the c.1239T>C (p.F413L) mutation of the *ATL1* gene.



## 5. Human T-lymphotropic virus type 1 (HTLV-1) associated myelopathy

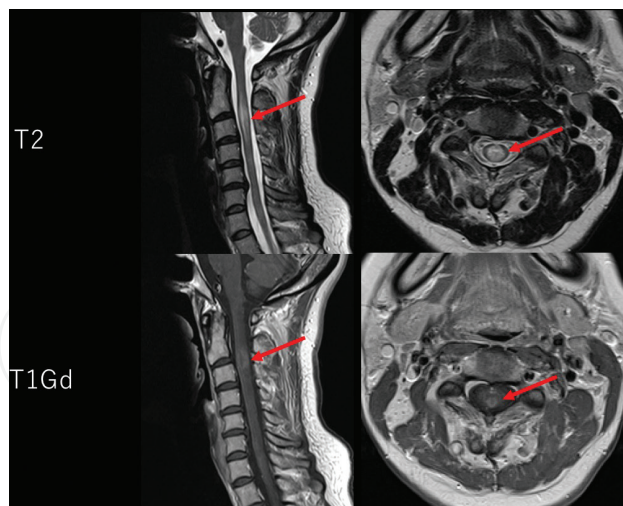
HTLV-1 associated myelopathy (HAM) is a slowly progressive thoracic myelopathy characterized by spastic paraplegia with sensory and autonomic dysfunctions [17, 18]. There are many patients in the Kyushu district, the southwest part of Japan, because the prevalence rate of HTLV-1 carriers is high in Kyushu [18]. We found a HAM patient among the family members including a case of SPG3A (**Figure 2**, IV-6).

A 54-year-old man was admitted to our hospital for the further examination of gait disturbance. He first noticed the gait disturbance about 10 years ago. He walked without a heel and had urinary incontinence for 3 years. He pointed out increased deep tendon reflexes of his legs, a positive Babinski sign, and diminished deep sensation of the legs. On examination, increased leg spasticity was observed bilaterally (**Table 1**). Anti-HTLV-1 antibody was positive in both serum and cerebrospinal fluid (CSF). Serum from his healthy 91-year-old father (III-1, **Figure 2**) was also anti-HTLV-1 antibody positive, probably due to blood transfusion. Mild pleocytosis (8/mm<sup>3</sup>), elevated neopterin (49 pmol/ml), and positive HTLV-1 proviral DNA were observed in his CSF. Whole-exome sequencing of his DNA did not identify pathogenic variants of the SPG3A and other SPG genes. We treated him with oral prednisolone [19], the symptoms did not worsen after that.

## 6. Multiple sclerosis (MS)

Multiple sclerosis (MS) is a neuroinflammatory disorder involving the spinal cord, optic nerve and brain, and is prevalent in young women. It takes relapse and remission courses. The characteristic finding is multiple lesions in the brain and spinal cord observed on MRI [20]. Neuromyelitis optica (NMO) is a similar disease to MS, but usually long cord lesions (>3 vertebral body) are observed on spinal MRI, and autoantibodies against aquaporin 4 are usually detected in patients' sera [21, 22].

A 47-year-old woman was admitted to our hospital because of gait disturbance, clumsiness and numbness of the bilateral hands. Neurological examination revealed leg spasticity, increased deep tendon reflexes of all extremities, extensor plantar responses and sensory disturbances of the bilateral upper extremities and trunk. Spinal MRI showed a central cord lesion at C2-C3 with mild enhancement (**Figure 4**). Multiple ovoid periventricular lesions were observed on brain MRI. However, clinically spasticity was presented in the clinical examination in the lower legs only. The anti-aquaporin 4 antibody was not detected in her serum. We started high-dose methylprednisolone pulse therapy and subsequently administered oral fingolimod for relapse prevention. Her symptoms gradually improved except for the leg spasticity. Then we tried to treat her with botulinum toxin injection to her legs and gait rehabilitation [2]. The modified Ashworth score for her legs improved from 3 to 2.



**Figure 4.** Spinal MRI of the multiple sclerosis patient. T2: T2 weighted image; central cord lesion in C2-C4 (arrow). T1 Gd: T1 weighted gadolinium enhancement; mild enhancement of C2-C3 lesion (arrow).

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