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REVIEW ARTICLE

Risk factors for development of myelopathy in patients with cervical spondylotic cord compression

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Yoshiaki Toyama

Abstract

Purpose To clarify risk factors for the development of myelopathy in patients with cervical spondylotic cord compression.

Method The authors reviewed articles in which risk factors for the development of myelopathy in patients with cervical spondylotic cord compression were discussed. Ossification of the posterior longitudinal ligament (OPLL) was also reviewed as a disease which causes cervical cord compression to clarify pathomechanism of the development of myelopathy.

Results Cervical motion segment disorders are considered to be multifactorial, and developmental size of the canal and foramina, pathological encroachment, biomechanical effects, and circulatory deficiencies are always present to some degree. Static and dynamic factors should be considered for the development of myelopathy. To clarify the pathomechanism of the development of myelopathy in patients with cervical spondylotic spinal cord compression, the exact natural history of CSM should be understood.

Conclusion Several predictable risk factors for the development of myelopathy have been proposed in CSM or OPLL studies, but they were not definitive. Further prospective population-based study is needed to clarify the mechanism.

Keywords Natural history · Dynamic factor · Developmental canal stenosis · Ossification of the posterior longitudinal ligament (OPLL)

Introduction

Cervical spondylotic myelopathy (CSM) is universally the most common cause of spinal cord impairment. Brain et al. [6] first suggested that symptomatology, whether radiculopathy or myelopathy, resulted from disk protrusion and associated soft tissue abnormalities. Law et al. [31] summarized the pathomechanism of the development of canal compromise. Spondylosis with the development of disk space narrowing and elongation, osteophyte production, and ligamentous hypertrophy results in acircumferential compromise to the spinal cord. However, the precise pathophysiologic mechanism of myelopathy in patients with cervical spondylotic cord compression remains unclear. Ehni [12] proposed that the development of myelopathy of cervical motion segment disorders should be viewed as multifactorial, and he chose four major factors for the development of myelopathy: (1) developmental size of the canal and foramina, (2) pathological encroachments, (3) biomechanical effects, and (4) circulatory deficiencies. The elements of stenosis are both dynamic and static. The static components of deformation of the canal by ligament and bone changes are magnified by the dynamic elements. This idea of the development of myelopathy on cervical motion segment disorders is generally accepted, and the static and dynamic factors should be

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considered when viewing risk factors for the development of myelopathy of CSM.

Ossification of the posterior longitudinal ligament (OPLL) is a hyperostotic condition of the spine associated with severe neurologic deficit [66], and is a different entity from CSM. Ehni [12] included OPLL as a cause of pathological encroachments on CSM. It is very valuable to know the pathomechanism of the development of myelopathy in OPLL for reviewing the risk factors of CSM. Therefore, the risk factors for the development of myelopathy in patients with cervical spondylotic cord compression in addition to OPLL are reviewed in this article.

Natural history of CSM

Accurate knowledge of the natural history of a disease is always essential to clarify the pathomechanism of the disease. The natural history of the mild form CSM is a controversial. Several authors have described the clinical course of patients with symptomatic cervical spondylosis. Clark and Robinson [11] showed that approximately 75 % of patients showed episodic progression of symptoms with intervening stability, although approximately two-thirds of patients showed subtle clinical decline during periods of stability. Lees and Turner [32] showed that myelopathy rarely developed in patients with spondylosis if it was not present at the first visit. Kadanka et al. [26] suggested that 80 % of patients with mild myelopathy improve with or without surgery. In contrast to the studies cited above, several authors have suggested that CSM has a largely progressive course over time [35, 55]. A high-quality evidence-based study is necessary to clarify the exact natural history of CSM. Shimomura et al. [59] conducted a prospective study involving 56 patients with mild forms of CSM. They reported that 80 % of patients showed clinically stable myelopathy over a 3-year period. Sampath et al. [57] have found similar results with conservative management. Recently, Sumi et al. [61] performed a further prospective cohort study involving the same cases that had been studied by Shimomura et al. They showed the prognosis of 55 mild CSM patients without surgical intervention by a cohort study. They reported that deterioration of myelopathy was observed in 25.5 % and the remaining 74.5 % of patients maintained a mild extent of myelopathy without deterioration through the average 94.3 months of follow-up.

Little is known about the spontaneous course and prognosis of clinically "silent" presymptomatic spondylotic cervical cord compression. Bendarik et al. [4] performed a large cohort study of presymptomatic magnetic resonance signs of spondylotic cervical cord compression. They followed 199 patients with this condition for at least a 2-year (range 2–12 years) period. Clinical evidence of the first signs and symptoms of CSM within the follow-up periods was found in 45 patients (22.6 %). As for OPLL, a total of 323 patients without myelopathy at the first visit were reviewed to discern the natural history of disease progression [38]. The development of myelopathy in these patients was found in 55 (17 %) with follow-up for an average of 17.6 years. Therefore, the rate of deterioration of myelopathy in OPLL resembles that in CSM.

This review gives a general presentation of the clinical course and prognosis of CSM; the prognostic risk factors for the development of myelopathy in asymptomatic patients with cervical spondylotic compression must be examined. Knowledge about the risk factor is extremely important to properly manage patients with cervical spondylosis and very subtle signs of myelopathy. The authors review risk factors for the development of myelopathy in patients with cervical spondylotic cord compression chiefly from the aspect of static and dynamic compromise.

Static risk factors

Cross-sectional area of the spinal cord has been found to be an independent prognostic factor for severity of myelopathy, but not for the presence of clinical myelopathy [20]. Kadanka et al. [27] found that the critical degree of spinal cord compression that is required to induce a clinically significant sign was 50 and 60 mm^2 of the cross-sectional transverse area at the level of maximum compression in association with MRI hyperintensities. Okada et al. [46] showed that the ratio of the spinal canal to the spinal cord was significantly higher in CSM patients than in age-matched normal adults, and concluded that the narrow area and high ratio of the spinal canal to the spinal cord are responsible for a static factor in CSM.

Several authors reported the static cord compression in OPLL as a predictable factor for the development of myelopathy. On the basis of postmortem examinations, Kameyama et al. [28] reported that irreversible cord damage occurred in patients with 40 % or greater maximum stenosis of the spinal canal. The static compression factor of the spinal cord seems to be a radiographic predictor of the development of myelopathy. The authors designed as a nationwide multicenter prospective study based on definite inclusion criteria. They revealed that spinal canal stenosis due to OPLL (Fig. 1) greater than 60 % in a plain roentgenogram was a risk factor for the development of myelopathy [39].
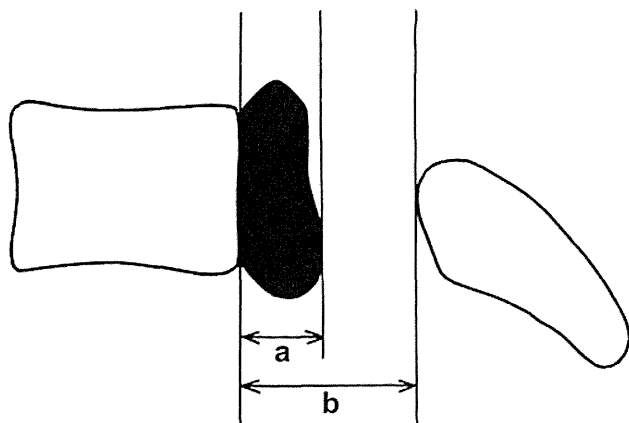
Fig. 1 Diagram showing measurement of maximum percentage of spinal canal stenosis due to OPLL (% = a/b ×100). *Black area* represents OPLL. (modified, reprinted with permission from the publisher. Sakou (56)

Developmental canal stenosis

Premorbid shallowness of the anteroposterior canal diameter represents a predisposing factor for the development of cervical myelopathy [14]. Other authors also reported the importance of the development of canal stenosis in the pathomechanism of CSM [1, 51]. The cervical spine is not always sufficiently well made in early life in to provide spinal canals and foramina with enough capacity to comfortably contain and protect the spinal cord and roots from ordinary degenerative encroachments throughout a long life. Achondroplasia, long recognized as a condition featuring paucity of room for neural elements and vulnerability to minimum trauma and small arthrotic encroachments even in early life [16, 53], is not unique, for non-achondroplastics also show evidence of similar developmental fallibility [13]. Degenerative changes in the various components of cervical motion segments must be evaluated not only for their severity but also in relation to the premorbid or developmental size of the spinal canal. Understanding of the physiological spinal canal size of the cervical spine in healthy adults is necessary to determine the pathological canal stenosis. Boijsen [8] first defined the proper measurement of canal diameter as the distance from the midpoint of the back of the vertebra to the nearest point of the same vertebral lamina as projected on lateral radiographs. On the bases of studies in Caucasians, Boijsen [8] reported that the average sagittal canal size ranged from 14.2 to 23 mm (average 18.5 mm) at the level of C4–C6. Wolf et al. [69] reported the average size of 17.5 mm at the level of C3–C7. Pallis et al. [48] noted that spondylotic myelopathy occurred in patients with a canal diameter averaging 14 mm, which was believed at that time to be less than the normal average of 18.5 mm as determined by Boijsen's method. Morishita et al. [42] suggested that

cervical spinal canal diameter of less than 13 mm may be associated with an increased risk for the development of CSM.

Possible errors related to magnification and a problem with the determination of spinal canal stenosis from direct measurements of plain cervical spine radiographs exist. The actual ratio of the canal-to-body diameter (Fig. 2) rather than volume was first introduced by Ehni [13], who noted that myelopathy was usually present when the Boijsen measurement of the canal diameter to the adjacent midbody vertebral width was 80 to 85 % or less. Pavlov et al. [50] confirmed these findings and established a 92 % accuracy for the diagnosis of canal stenosis when the ratios were lower than 0.82. Lohnert and Latal [33] suggested that the development of CSM can be determined by the finding of the spinal canal to 11 mm, or the decrease in the Torg-Pavlov ratio (canal-to-body ratio) below 0.8. Chen et al. [10] assessed the sagittal diameters of the cervical canal in 200 Chinese males with CSM and compared them with those of the general Chinese population. They determined that the cut-off value of the Torg-Pavlov ratio for the critical development of myelopathy was 0.81 at the C5 level. Iizuka et al. [24] examined the presence of CSM in 237 patients with lumbar spinal stenosis (LSS). They concluded that the Torg-Pavlov ratio was the most important predictive factor of CSM in patients with LSS.

Pathological encroachments

The accumulation of degenerative changes affects both the canal diameter and sagittal mobility of the cervical spine
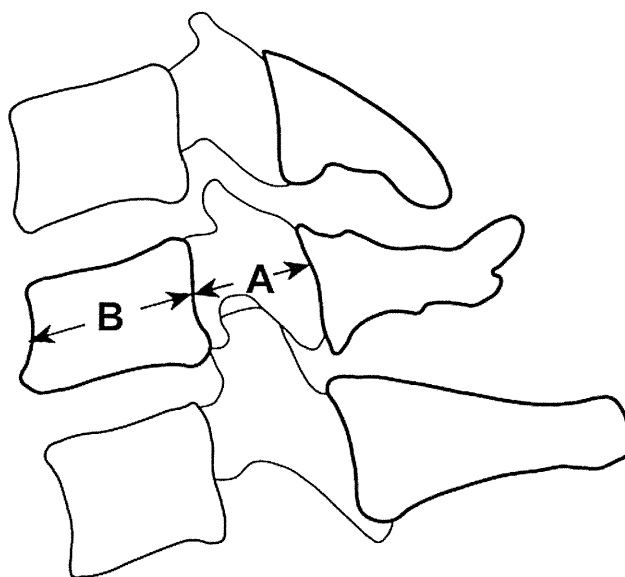

Fig. 2 Diagram showing canal-to-body ratio (A:B) (modified, reprinted with permission from Law et al. [31])

[43]. When room needed by the neural elements is reduced to a critical degree, motion-related, biomechanical, or dynamic factors that transiently reduce the neural space, now compressing the roots and spinal cord and their capillaries, begin to have acute neurophysiological and chronic neuropathological effects that culminate in clinical neurological disease. Shinomiya et al. [60] studied the critical level of cord compression by using experimental CSM model. In this study, Spinal cord compression was applied anteriorly using one screw through the C5 vertebral body or three screws through the C4, C5, and C6 vertebral bodies. They showed that myelopathy did not develop up to 50 % of spinal canal decrease on single level compression but, rather, on multi-level compression.

Imaging and electrophysiological parameters as risk factors

The most useful indicators for poor prognosis for CSM are a ratio of the canal-to-body diameter of less than 0.8 and a spinal cord compression ratio (Fig. 3). This last measure is obtained easily from axial slices on contrast computed tomography or magnetic resonance imaging and is derived by measuring the smallest anteroposterior diameter of the outlined cord by its maximum transverse diameter [18]. Conventional MRI may provide confusion findings because of a frequent disproportion between the degree of the spinal

cord compression and clinical symptoms. Bednarik et al. [4] suggested intramedullar MRI hyperintensity as a significant predictor of later development of myelopathy. Intramedullar hyperintensity chiefly indicates lesion in the gray matter, which has an influence predominantly on disability of the upper extremities and less impact on the overall disability of CSM patients. Wada et al. [67] reported that patients with multisegmental area of high signal intensity on T2-weighted MR images tend to have poorer surgical results. However, in most studies, these imaging parameters were not sensitive indicators for the development of myelopathy [19, 40, 70]. Shimomura et al. [59] showed that the risk factor for mild forms of CSM was circumferential spinal cord compression in the maximum compression segment on axial MRI. Ten (30.3 %) of 33 CSM patients with circumferential spinal cord compression deteriorated during follow-up, compared with only one (4.3 %) of 23 CSM patients without circumferential spinal cord compression. Sumi et al. [61] suggested that myelopathy is more likely to develop from angular-edge deformity of the spinal cord detected in an axial MRI than from an ovoid deformity of the spinal cord. They showed that angular-edge deformity was shown in 13 (92.9 %) of 14 cases with myelopathy deterioration and in 23 (56.1 %) of 41 cases without deterioration. Matsunaga et al. [39] proposed that myelopathy developed significantly more highly in lateral-deviated type OPLL than in central type OPLL on computer tomography (Fig. 4). Angular-edge

Fig. 3 Diagram showing cord compression ratio (a/b):
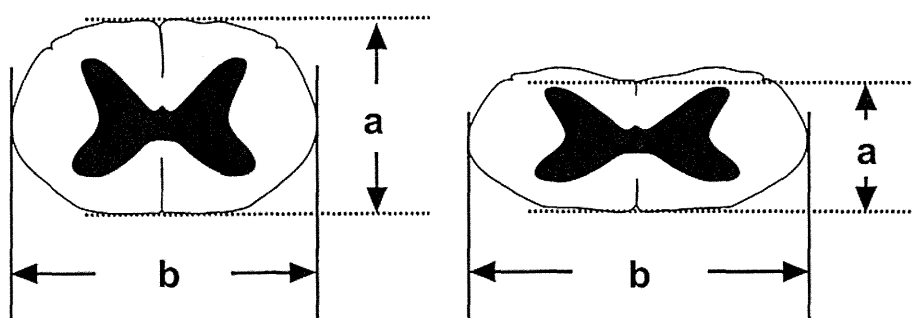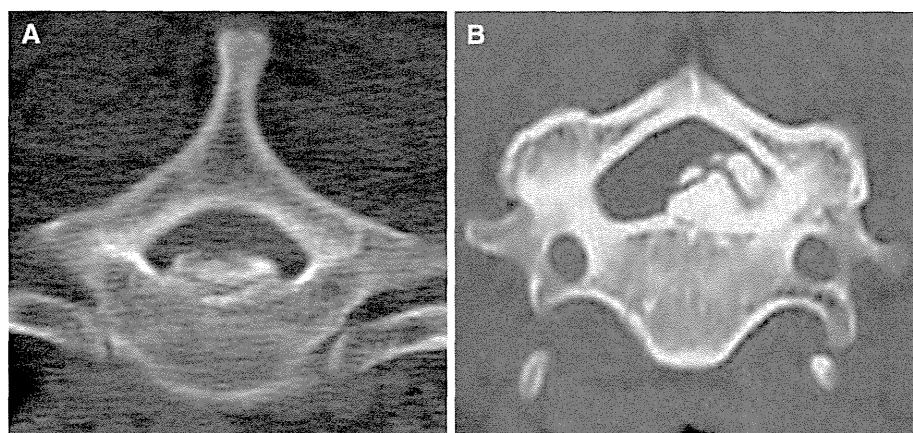a sagittal diameter, b transverse diameter (modified, reprinted with permission from Law et al. [31])

Fig. 4 OPLL pattern on CT examination. a central type, b lateral deviated type (reprinted with permission from Matsunaga et al. [39])

deformity and lateral-deviated type OPLL might indicate the same cord compression pattern in an axial view. The recent magnetic resonance diffusion tensor imaging (DTI) is known to be more sensitive to subtle pathological changes of the spinal cord than conventional MRI. Kerkovský et al. [29] reported that the DTI parameters reflect the presence of symptomatic myelopathy and show considerable potential for discriminating between symptomatic and asymptomatic patients with cervical spondylosis.

Soo et al. [62] evaluated the clinical and imaging features with computed tomographic myelography (CTM) of patients with CSM. They analyzed the following parameters obtained from axial CTM images at the level of maximum compression: surface area and ratio of antero-posterior to the transverse diameter of the spinal cord; subarachoid space and vertebral areas. The only predictable parameter for myelopathy was a narrow spinal cord area. Hukuda et al. [23] assessed CTM to measure the size of the vertebral body, spinal canal, and spinal cord in the cervical spine. They suggested that a large vertebral body is a risk factor for the development of myelopathy, along with a narrow spinal canal.

Bednarik et al. [3] reported that electromyographic signs of anterior horn lesion and abnormal somatosensory evoked potentials together with clinical signs of cervical radiculopathy and MRI hyperintensity are useful predictors of early progression into symptomatic CSM in patients with presymptomatic spondylotic cervical cord compression. Asymptomatic spondylotic patients with abnormal somatosensory evoked potentials and radiculopathy have shown increased propensity to progress towards clinical myelopathy [2, 25].

Dynamic risk factors

Biomechanical effects

So important are the dynamic effects that neural consequences of spondylotic encroachments at a cervical motion segment are almost unknown in the absence of motion. Several authors noted that repetitive flexion–extension movements of the cervical spine for long-term periods cause irreversible change of the spinal cord and that dynamic factors should be considered in pathomechanism of CSM [7, 54]. The pincer mechanism explained by bulging ligamentum flava in the extension of cervical spine and anterior bone spur formation or intervertebral disk bulging has been considered for dynamic canal stenosis (Fig. 5) in CSM [64]. Flexion and extension kinematic MR imaging demonstrated additional information concerning the dynamic factors in the pathogenesis of CSM [44]. In OPLL patients with less than 60 % spinal canal stenosis,
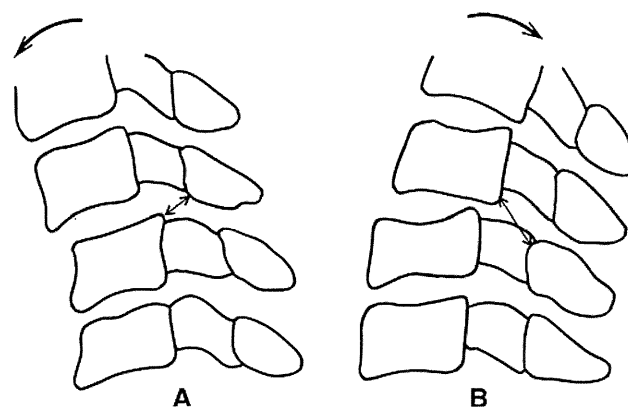

Fig. 5 Dynamic canal stenosis. Flexion–extension movements of the cervical spine cause dynamic canal stenosis by a pincer mechanism. a flexion, b extension (modified, reprinted with permission from the publisher. Sakou (56)

dynamic factors should be considered for the occurrence of myelopathy [39]. A large range of motion of the cervical spine was a risk factor for the development of myelopathy. Similarly, Morio et al. [41] also previously noted the existence of dynamic factors related to the development of myelopathy in patients with OPLL.

There is insufficient evidence that individuals with spondylotic spinal cord encroachment without myelopathy are at increased risk of spinal cord injury from minor trauma in cervical spine. There is no evidence that prophylactic decompression surgery is helpful in asymptomatic individuals who have cervical spondylotic cord compression [5, 45]. As for OPLL, trauma in the cervical spine may have precipitated the onset of symptoms, which, in some cases, included quadriparesis. However, the prevalence of trauma that caused symptoms was only 15 % in the retrospective study. In the prospective investigation for 368 OPLL patients without myelopathy at the time of initial consultation, only 6 patients (2 %) subsequently developed trauma-induced myelopathy [37]. Prophylactic decompression surgery for patients who had potential spinal cord compression due to OPLL needs further study to provide scientific data.

Dynamic factors in an athetoid-dystonic condition

The dynamic factors are mainly related to the development of myelopathy in some athetoid-dystonic conditions [21, 52]. Dystonic-athetoid neck movement may cause excessive axial neck rotation as well as flexion and extension movements of the spine. These repetitive exaggerated movements may result in early degenerative changes of the vertebrae which may enhance myelopathy.

Circulatory factors

The importance of circulatory deficiencies in clinical myelopathy lacks universal recognition. The state of the cord's circulation (whether already critical and vulnerable to the slightest additional interference) is of obvious importance. Blood supplied to the roots and cord is highly variable and perhaps barely adequate for perfusion in seemingly normal individuals. Age-related atherosclerosis must increase vulnerability to the effects of acquired spondylotic encroachments. Recent improved understanding of the biomolecular mechanism has yielded new evidence on the circulatory factors for CSM. Chronic compressive lesion to the cervical area resulting in lack of perfusion has yielded considerable evidence to support ischemia as an important pathogenesis in patients with CSM. In the hypoxic condition, up-regulation of the vascular endothelial growth factor (VEGF) is consistent with increasing hypoxia induced factor-1α (HIF-1α) [34].

Other factors

Genetic factors

There is no literature supporting a genetic factor for the development of myelopathy in patients with cervical spondylotic cord compression. Several reports indicate a genetic predisposition for cervical spondylosis. In 1969, Bull et al. [9] first described the possibility of a genetic contribution to the development of CSM. They evaluated several hundred cervical radiographs in an attempt to understand cervical spondylosis, noting a higher prevalence of monozygotic and dizygotic twins. Unfortunately, the quality of the evidence provided in their study discussing a genetic predisposition for cervical spondylosis was not adequate. Patel et al. [49] performed a very rigorous study using the Utah Population Database of over 2 million Utah residents to determine a genetic predisposition among patients diagnosed with CSM. The genealogical index of familiarity analysis for patients with CSM showed a significant relationship for individuals with this disease, supporting an inherited predisposition to CSM. However, the candidate gene for CSM has not been determined. It is difficult to clarify the pathogenic gene for a common disease because the common disease generally develops with a multifactorial complex nature.

Genetic predisposition to OPLL is expected to be more important. A nationwide survey in Japan of 347 families of OPLL revealed that OPLL was radiographically detected in 24 % of the second-degree or closer blood relatives and in 30 % of OPLL patients' siblings [65]. In a nationwide twin study in Japan, ten sets of twins (eight monozygotic pairs and two dizygotic pairs) who exhibited OPLL were enrolled. Six of the eight monozygotic twins had OPLL [36]. A human leukocyte antigen (HLA) haplotype analysis provided further evidence of a genetic predisposition to OPLL. A sibling who had the same haplotypes as the proband showed high prevalence of OPLL [36]. Some candidate genes (collagen α2 (XI) [30], collagen 6A [63], human NPPS gene [47], and TGF 3 [22]) for OPLL were reported. Now a nationwide DNA analysis of candidate genes for the sibpair of OPLL is proceeding by the Investigation Committee on Ossification of the Spinal Ligaments of the Japanese Ministry of Public Health and Welfare.

Cellular and molecular markers

Improved understanding of the pathophysiology of CSM, particularly at the cellular and molecular level, may enable the application of a biochemical marker to predict the development of myelopathy in future. Free radical- and cation-mediated cell injury, glutamatergic toxicity, and apoptosis may be of relevance to the pathophysiology of CSM [15]. Frank [17] provided new evidence that arachnoid cells with HLA-DR expression may initiate or sustain the intradural inflammatory reaction found in CSM. Wang et al. [68] investigated a possible association of collagen IX tryptophan (Trp) alleles (Trp2 and Trp3) and smoking with CSM. They could find a significant association between the Trp2 alleles and CSM risk and a risk that increased by smoking. Setzer et al. [58] presented a noteworthy study supporting the hypothesis that the apolipoprotein (APOE) epsilon four allele increases the risk of myelopathy in patients with chronic cervical spinal cord compression. Recent improvements in molecular biology might provide a biomarker for prediction of the development of myelopathy.

Conclusion

The clinicians who are treating patients with spondylotic cervical cord compression or OPLL should manage the patients with consideration of the natural history of each disease. To clarify the pathomechanism of the development of myelopathy in patients with cervical spondylotic spinal cord compression, the exact natural history of CSM should be understood. It is important to know the risk factors for the development of myelopathy in patients with spondylotic cervical compression, and more careful follow-up is necessary for patients with the risk factors. Cervical motion segment disorders are considered to be multifactorial, and developmental size of the canal and foramina, pathological

encroachments, biomechanical effects, and circulatory deficiencies are always present to some degree. Several predictable risk factors for the development of myelopathy have been proposed in CSM or OPLL studies.

Conflict of interest None.

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Hindawi

Case Report

A Newly Developed Robot Suit Hybrid Assistive Limb Facilitated Walking Rehabilitation after Spinal Surgery for Thoracic Ossification of the Posterior Longitudinal Ligament: A Case Report

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Most patients with thoracic ossification of the posterior longitudinal ligament (OPLL) exhibit delayed recovery of gait dysfunction after spinal injury. The hybrid assistive limb (HAL) is a new robot suit controlling knee and hip joint motion by detecting very weak bioelectric signals on the surface of the skin. This study is to report the feasibility and benefits of patient-assistive HAL walking rehabilitation for facilitating locomotor function after spinal surgery. The patient was a 60-year-old woman with thoracic OPLL, and her motor and sensory paralyses did not improve after spinal surgery, indicating severe impairment in the paretic legs. The subject underwent 6 HAL sessions per week for 8 weeks, consisting of a standing and sitting exercise and walking on the ground with HAL. Clinical outcomes were evaluated before and after HAL training and 1 year after surgery. The subject improved considerably as a result of HAL training. Subsequently, her walking ability recovered rapidly, and she was able to walk unaided six months after surgery. This case study suggests that HAL training is a feasible and effective option to facilitating locomotor function and the early HAL training with physiotherapy may enhance motor recovery of patients with residual paralysis after surgery.

1. Introduction

Decompression is the primary treatment for patients with compressive myelopathy due to thoracic ossification of the posterior longitudinal ligament (OPLL) and ossification of the ligamentum flavum (OLF), but surgical outcomes vary. Studies of postoperative clinical outcomes of thoracic OPLL indicate that most patients exhibit delayed recovery of motor weakness in the lower limbs and gait dysfunction after surgery [1, 2]. Gait dysfunction is the most important negative surgical outcome, being a clinical deficit of spinal myelopathy [3].

Robotic therapy is becoming increasingly common for gait rehabilitation after stroke or spinal cord injury, using an exoskeleton robotic device (e.g., Lokomat, LOPES exoskeleton robot) or a robotic device with foot-driven plates (e.g., Gait Trainer GT I, Haptic Walker) [4–6]. The robot suit hybrid assistive limb (HAL) is a new robot suit to assist voluntary control of knee and hip joint motion by detecting very weak bioelectric signals on the surface of the skin [7]. The HAL suit is a hybrid control system comprising cybernic voluntary control (CVC) and cybernic autonomous control (CAC) subsystems and has power units and force-pressure sensors in the shoes [8, 9]. The power units consist of angular