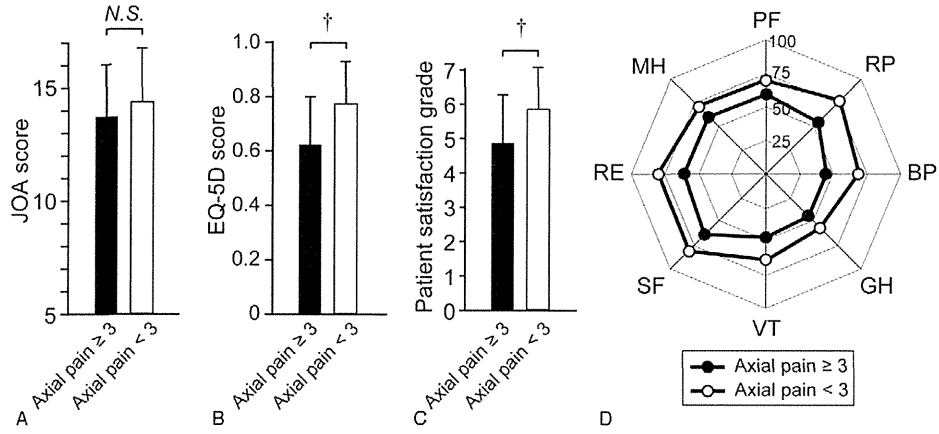

Figure 4. Impact of axial pain on clinical outcomes at the 2-year follow-up. Patients with axial pain intensity ≥3 showed significantly worse clinical outcomes than patients with a pain intensity <3 in the EQ-5D index (B) as well as worse patient satisfaction grades (C), but no difference in the JOA score (A). †$P < 0.01$, Mann–Whitney U test. Patients with axial pain intensity ≥3 also had lower mean SF-36 subscale scores than patients with pain intensity <3 (D).

unchanged axial pain intensity after surgery. An alternative explanation is that chronic pain interferes with a broad spectrum of HRQOL domains, including physical, emotional, and social functioning.[11] Therefore, when axial pain is persistent, its impact on HRQOL might increase over time.

In contrast to HRQOL measures, the JOA score showed no significant correlation with axial pain intensity at any time point. The JOA score is a widely accepted tool for grading objective functional status, such as ambulation, sensation, and sphincter control in patients with cervical myelopathy. However, because the JOA score is focused on measuring the severity of myelopathy symptoms, it may not directly reflect the severity of bodily pain, including axial neck pain. This is supported by a recent study that demonstrated a poor correlation between the modified JOA score and the SF-36 body pain domain.[12] These results are in accordance with the growing awareness that traditional outcome measures do not adequately represent patients' experience of disease or perceptions of treatment.[3] Outcome measures for cervical spine surgery need to be multimodal, incorporating patient-reported outcome measures, to reflect patients' perceptions of treatment.

Generic HRQOL instruments, including the SF-36 and EQ-5D, allow for comparisons of outcomes across various treatments and disease conditions. A recent multicenter study in North America prospectively analyzed the efficacy of decompression surgery for cervical spondylotic myelopathy and showed significantly improved SF-36 scores in every HRQOL domain except GH. Although the study included anterior surgery, this trend is similar to that shown in the present results. The EQ-5D is a preference-based instrument that is readily adaptable for cost-effectiveness analysis. The mean EQ-5D score gain in the current cohort (0.15) is comparable to those of anterior decompression and fusion (0.14)[13] and posterior cervical fusion (0.10),[14] but lower than that of cervical total disc arthroplasty (0.41).[15] The difference is attributed to a younger mean age of 47 years and localized disc degeneration in patients who underwent total disc arthroplasty.

The exact etiology of persistent axial pain following laminoplasty is still unclear. Possible sources of postoperative axial pain include surgical damage to the zygapophysial joints, nerve roots, and extensor muscles, especially those that attach to C2 and C7.[16,17] Preserving C2 and/or C7 muscle attachments is theoretically beneficial because the C2 spinous process is the major insertion of semispinalis muscle and the C7 spinous process provides a long lever arm to the extensor muscle complex, including semispinalis, rhomboid, and trapezius muscles. Indeed, the present patients with C2 laminoplasty had significantly decreased cervical lordosis than those without C2 laminoplasty, although neither C2 nor C7 laminoplasty significantly increased postoperative axial pain intensity. Nevertheless, the present results may underestimate the importance of C2 preservation due to the limited number of patients with C2 laminoplasty. The efficacy of C2 and/or C7 preservation in reducing axial pain is controversial, but surgeons should attempt it as long as the neurologic decompression is not compromised.[17]

The high impact of axial pain on postoperative HRQOL suggests that the optimal surgical procedure for multilevel compressive cervical myelopathy should be determined not only to improve neurological outcomes but also to reduce postoperative axial pain. Anterior decompression and fusion generally yields a lower rate of persistent axial pain than laminoplasty.[18] However, when 3 or more segments are involved, increased complication rates associated with anterior surgery, particularly fusion-related problems, make posterior options more attractive.[19] Laminectomy with instrumented fusion is another option, especially when a patient has segmental instability, which is commonly associated with severe disc degeneration.[20] Several retrospective studies demonstrated that laminectomy with fusion was

associated with less axial neck pain postoperatively than laminoplasty.[21] However, there is no apparent superiority over the other regarding postoperative axial pain because of the lack of high-quality evidence.[22] Future prospective studies are needed to determine whether posterior fusion reduces axial pain in patients with multilevel cervical myelopathy.

One of the limitations of this study is the lack of a condition-specific scale for neck pain disability. The neck disability index (NDI) is one of the most widely used self-administered questionnaires for neck pain.[23] The NDI has been translated and validated in a number of languages; however, the Japanese version of the NDI was not available when we started this study.[24] Time-dependent changes in the NDI and their relationships with axial pain intensity following laminoplasty remain to be evaluated in future studies.

The present results highlight the importance of reducing axial pain to improve the efficacy of cervical laminoplasty. Because the impact of axial pain on HRQOL is significant, there seems to be plenty of room for improvement. Several modifications using less invasive and reconstructive techniques have been proposed as preventive measures against axial pain following laminoplasty.[25] Future prospective research is needed to confirm the effectiveness of the modifications not only in reducing axial pain but also in improving HRQOL with the use of patient-reported outcome measures.

CONCLUSION

The intensity of axial neck pain remained at preoperative levels until the 2-year follow-up after conventional double-door cervical laminoplasty. This pain had a significant impact on clinical outcomes, including a wide range of HRQOL measures and patient satisfaction with outcome, in patients undergoing laminoplasty.

➢ Key Points

- ❑ The intensity of axial neck pain remained at preoperative levels until the 2-year follow-up after conventional double-door cervical laminoplasty.
- ❑ The EQ-5D score and all SF-36 domains, excluding general health perceptions, improved significantly compared with baseline levels at the 6-month follow-up or later.
- ❑ Baseline axial pain intensity showed a significant negative correlation with baseline HRQOL only in the SF-36 bodily pain domain. In contrast, axial pain intensity showed significant negative correlations with all HRQOL measures at the 6-month follow-up.
- ❑ At the 2-year follow-up, patients with axial pain intensity ≥ 3 showed significantly worse outcomes than patients with pain intensity <3 in the EQ-5D score, SF-36 score, and patient satisfaction grades, but not in the JOA score.
- ❑ Axial pain had a substantial negative impact on clinical outcomes, including a wide range of HRQOL measures and patient satisfaction with outcome, after cervical laminoplasty.

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Variety of the Wave Change in Compound Muscle Action Potential in an Animal Model

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Study Design: Animal study.
Purpose: To review the present warning point criteria of the compound muscle action potential (CMAP) and investigate new criteria for spinal surgery safety using an animal model.
Overview of Literature: Little is known about correlation palesis and amplitude of spinal cord monitoring.
Methods: After laminectomy of the tenth thoracic spinal lamina, 2–140 g force was delivered to the spinal cord with a tension gage to create a bilateral contusion injury. The study morphology change of the CMAP wave and locomotor scale were evaluated for one month.
Results: Four different types of wave morphology changes were observed: no change, amplitude decrease only, morphology change only, and amplitude and morphology change. Amplitude and morphology changed simultaneously and significantly as the injury force increased ($p<0.05$) Locomotor scale in the amplitude and morphology group worsened more than the other groups.
Conclusions: Amplitude and morphology change of the CMAP wave exists and could be the key of the alarm point in CMAP.

Keywords: Compound muscle action potential; Morphology change; Amplitude

Introduction

Presently, non-compound muscle action potential specific criteria, such as somatosensory evoked potential (SSEP) criteria (an amplitude decrease ≥50% and ≥10% latency), are often used as the criteria for the warning point of compound muscle action potential (CMAP) [1,2]. Several studies have addressed the definition of alarms, with no consensus reached. We have reviewed conventional CMAP alarm points and classified CMAP waveform changes into four grades as novel criteria. Grade 0 is defined as a normal waveform, grade 1 as an amplitude decrease ≥50% and ≥10% latency, grade 2 as multi-phasing of waveform, and grade 3 as loss of amplitude [3]. The waveform changes from grade 1 to grade 3 in proportion to the severity of injury. The following reports our basic review of the waveform changes using Sprague-Dawley rats.

Materials and Methods

1. Modeling of spinal injuries

Forty-one 8-week-old Sprague-Dawley rats (200–230 g)

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were used. After anesthesia from ether inhalation and intraperitoneal administration of ketamine (100 mg/kg) and xylazine (10 mg/kg), T10 of the spine of each rat was laminectomized to expose the dura mater, which was pressed with a tension gage (Fig. 1). To create single crush and sustained crush models, stepwise compressions were performed at intensities of 2–140 g for 1–150 seconds. The bladders of the rats were manually voided twice a day for a week after the injury. To prevent infection, 1.0 mL of Bactramin (Roche, Basel, Switzerland) was mixed in 500 mL of bottled water provided for hydration for 2 weeks following spinal cord injury. Food was provided on the cage floor, and the rats had no difficulty reaching their water bottles. All animals were treated and cared for in accordance with the Nagoya University School of Medicine Guidelines pertaining to the treatment of experimental animals.

2. Measurement of control waveform

The cranial bones were exposed and bores were drilled 3 mm lateral and 2 mm posterior to the bregma where bipolar stimulating needles were inserted. A Nihon Koden Neuropack 8 (Nihon Koden Corp., Tokyo, Japan) was used as the stimulator. Except for the stimulus intensity, the stimulus conditions were approximately the same as actual spinal surgery (a train of four pulses at 2-ms intervals, stimulus intensities of 10–60 mA, and 20 additions with a phase switch after 10 additions). A Nihon Koden Neuropack (MEB-2200, ver. 04.02) used in spinal surgery was used to derive the control waveform by inserting bipolar needles in both perifemoral muscles (Fig. 1). The ground electrode was placed subcutaneously between the coil and the recording electrodes.

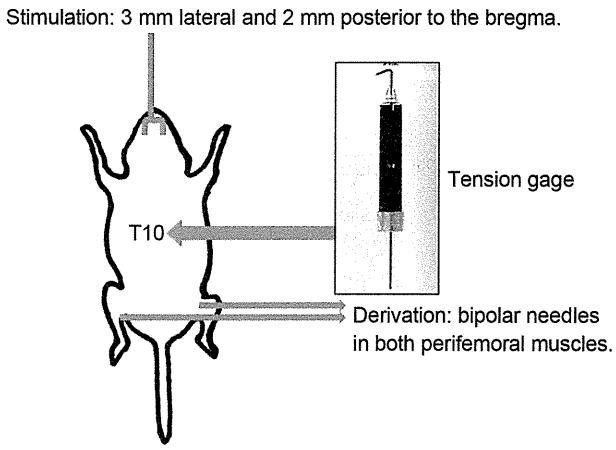

Fig. 1. Spinal cord injury and protocol of compound muscle action potential.

3. Derivation and review of CMAP waveform

Derivation was started immediately after the infliction of injury at every 30 seconds for up to 15 minutes under the same conditions as the foregoing waveform measurement. We reviewed amplitude decrease and morphology change. Morphology change was having occurred in the event of any of the following: change in the number of waves in the waveform, prolonged duration, and shift in the location of the peak latency. For convenience, integrated intensity was defined as compression time multiplied by compression intensity.

4. Evaluation of the motor function of the lower limbs

The locomotor performance of 16 animals was analyzed using the Basso, Beattie and Bresnahan (BBB, 0–21 pts) open-field score for 4 weeks (1 day, 3 days, 5 days, 1 week, 2 weeks, 3 weeks, and 4 weeks) [4]. The evaluations were made by two blind observers for all analyzed rats.

5. Statistical analyses

Statistical analyses were performed with an unpaired two-tailed Student's *t*-test for single comparisons and one-way analysis of variance (ANOVA) for multiple comparisons. For the locomotor performance scores, repeated measures ANOVA and the Mann-Whitney *U*-test were used. In all statistical analyses, values of $p<0.05$ were considered to indicate significance. To obtain the data for statistical analyses, the investigators were blinded to the genotypes in all procedures.

Results

1. Types of waveform change

Four different types of waveforms were obtained: no change, amplitude decrease only, morphology change only, and amplitude and morphology change. In the 50 limbs of 25 animals, type 1 accounted for 14% (7/50 limbs), type 2 for 36% (18/50 limbs), type 3 for 18% (9/50 limbs), and type 4 for 32% (16/50 limbs) (Fig. 2). No

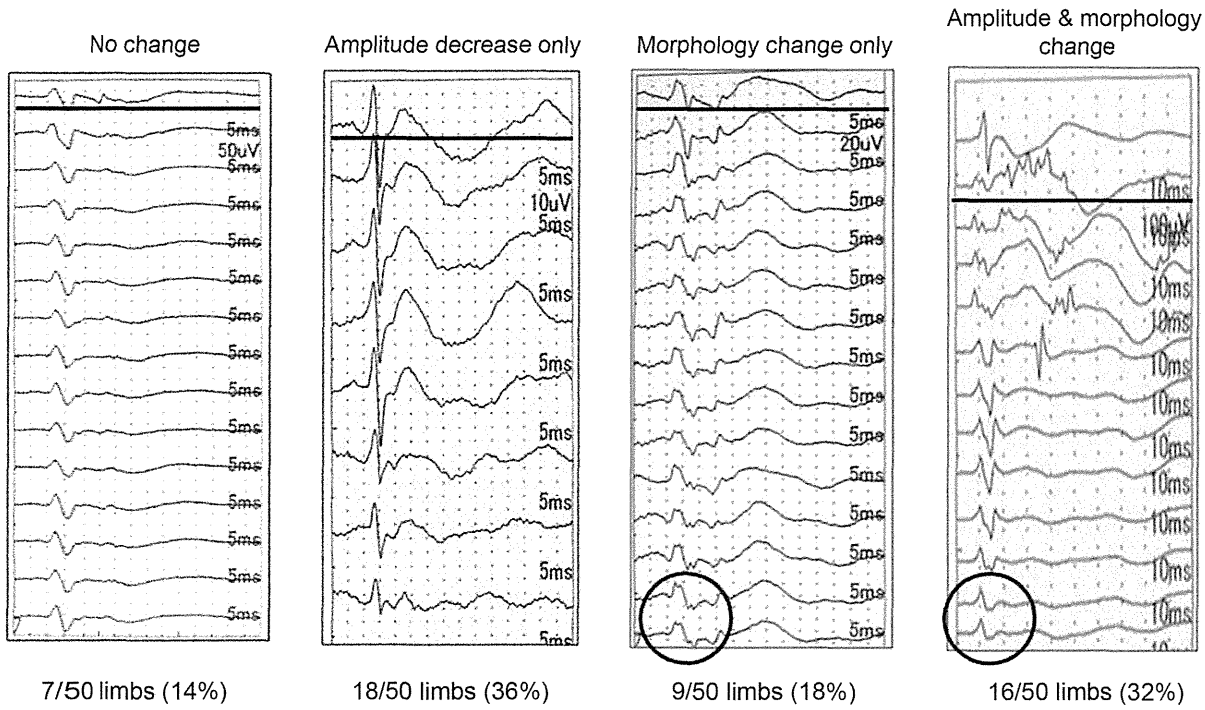

Fig. 2. The results of wave type.

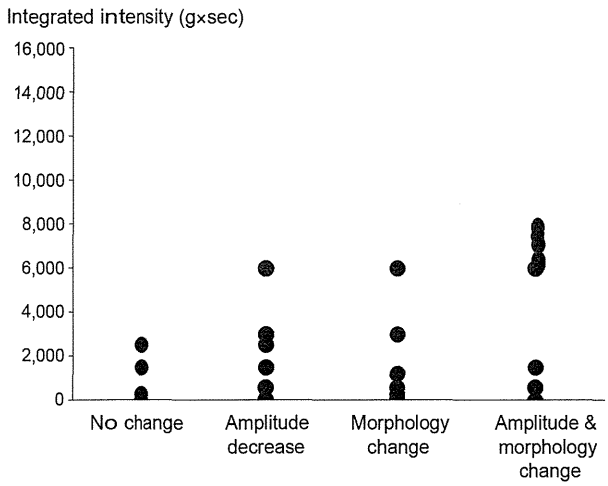

Fig. 3. Relationship between the wave type and the injury force.

change of latency was seen in any rat.

2. Stimulus intensity and waveform change

While the integrated intensity was naturally low in the group with no change, the amplitude group and the morphology group produced their respective waveforms at approximately the same level of intensity. At high intensities, numerous waveforms were derived that exhibited amplitude decrease and morphology change (Fig. 3). In a box plot, the amplitude group and the morphology group were significantly correlated with high intensities ($p<0.05$) (Fig. 4).

1) Evaluation of lower limb motor function

At 4 weeks after spinal cord injury, the best result was found in the no change group according to the BBB score (20). While the amplitude and morphology group (BBB, 13.5) exhibited the strongest degree of paralysis due to its highest integral intensity, there was no significant difference between that group and the amplitude group (BBB, 16.1) or the morphology group (BBB, 16.5) using repeated measure ANOVA ($p=0.07$). However, the amplitude and morphology group exhibited a significantly higher degree of paralysis up to the third day (Fig. 5).

Discussion

The CMAP alarm point for stopping surgery remains equivocal [5-8]. Luk et al. [2] applied the same criteria as those for SSEP (amplitude decrease ≥50% and ≥10% latency), Langeloo et al. [9] defined an amplitude decrease ≥50% or more in any muscle as an alarm point, and Sala et al. [10,11] defined waveform loss as an alarm point. Quinones-Hinojosa et al. [12] discussed morphologi-

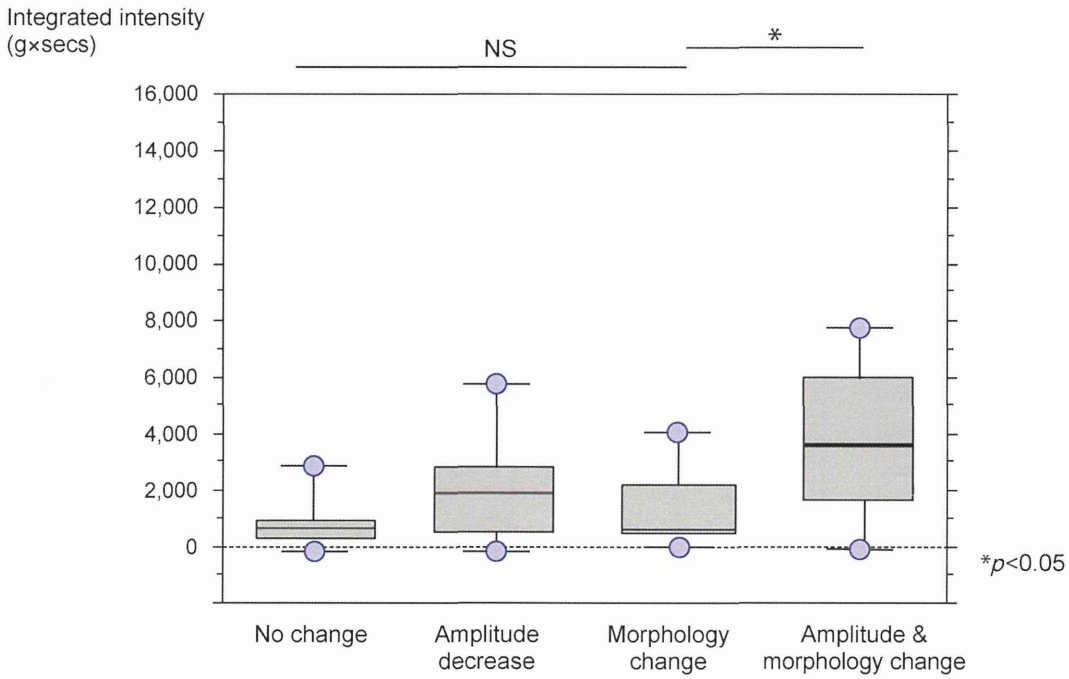

Fig. 4. Relationship between the wave type and the injury force in a box plot. NS, not significant.

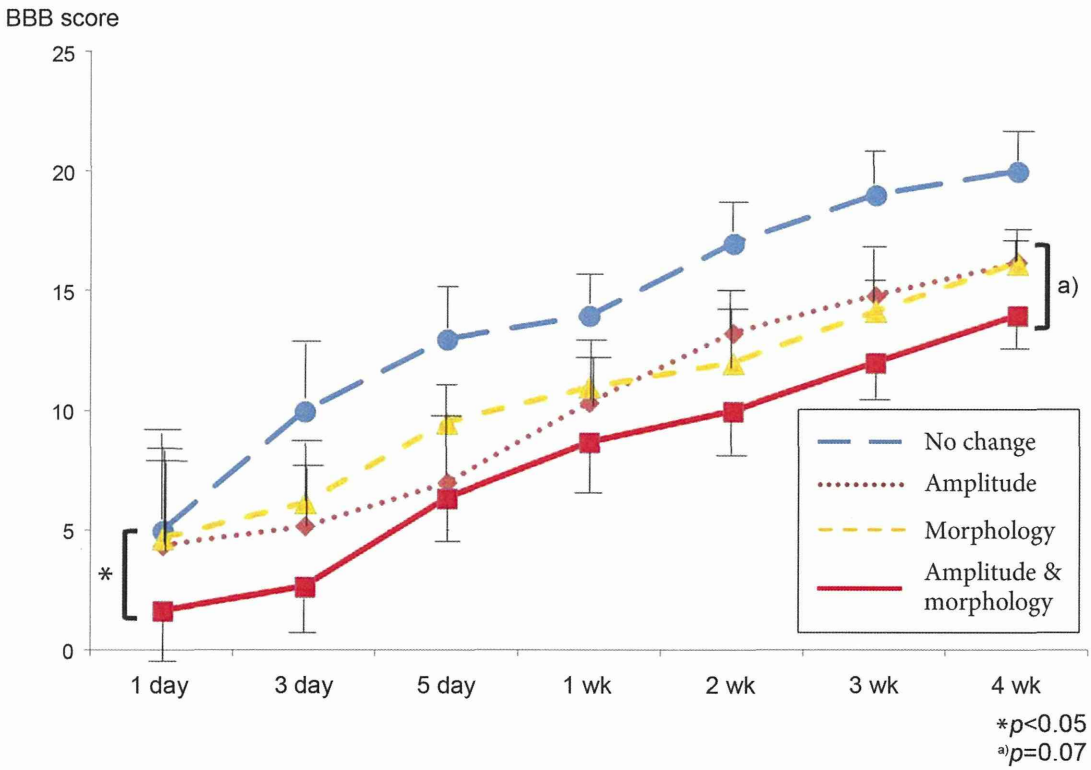

Fig. 5. Relationship between the wave type and Basso, Beattie and Bresnahan (BBB) score.

cal change, defining waveform change from a biphase to a monophase as an alarm point. We proposed defining morphology change as an alarm point [3]. Some authors also reported on a basic study of electrophysiology. How-

ever, the data only concerned the stimulation method, SSEP alarm point, and electromyography potential [13-15]. So, it is clinically unclear and difficult to demonstrate what degree of injury and paralysis of the spinal cord causes morphology change or amplitude decrease. In this study, we used an animal testing model to demonstrate the foregoing.

We were able to classify the waveform into four types. Eighteen percent of the animals exhibited morphology change only without amplitude change. These waveforms were caused by approximately the same force causing the amplitude decrease. This is a novel observation and we believe morphology change should be considered when discussing CMAP alarm points. Additionally, relatively severe injuries tend to be accompanied by amplitude decrease and also morphology change, indicating more critical conditions. Presently, particularly severe paralysis was evident immediately after the injury in the amplitude and morphology groups. This indicates that the concurrence of morphology change and amplitude decrease should be interpreted as a higher level of alarm.

A limitation of this study is the difficulty to explain the mechanism of each waveform. More electrophysiological experiments are needed before clinical applications can be contemplated.

Conclusions

Change in the morphology and amplitude was accompanied by significant aggravation of paralysis immediately after the injury. It is suggested that morphology change can potentially be one of the alarm points.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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ARTICLE

Phenotypic differences of patients with fibrodysplasia ossificans progressive due to p.Arg258Ser variants of *ACVR1*

Yasuo Nakahara[1], Ryuyo Suzuki[2], Takenobu Katagiri[3,4], Junya Toguchida[5,6,7] and Nobuhiko Haga[1]

Fibrodysplasia ossificans progressiva (FOP) is a rare, congenital disorder caused by heterozygous mutation of the bone morphogenetic protein type I receptor *ACVR1*. Various forms of atypical FOP have recently been identified, and a recurrent mutation, *ACVR1* (p.Arg258Ser) was reported. We encountered a 17-year-old Japanese female patient with sporadic occurrence of FOP. At the age of 7 years, radiological examination revealed progressive heterotopic ossification and cervical spine malformations. Although great toe malformation was not observed, we diagnosed her as having FOP. Then, *ACVR1* was analyzed and a recurrent mutation of p.Arg258Ser was identified. We noticed that there may be phenotypic differences between c.774G>T and c.774G>C, which lead to the same amino-acid change, p.Arg258Ser. Genotype–phenotype correlation was discussed with the review of the previous reports.

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INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP, MIM#135100, http://www.omim.org/) is a rare hereditary disease caused by a heterozygous mutation in the type I activin receptor (*ACVR1*) gene that encodes a bone morphogenetic protein receptor. This disease leads to heterotopic ossification in the muscle tissue and the surrounding fascia, tendons and ligaments throughout the body.[1] The allele exhibits variable expressivity and has complete penetrance. However, most patients have low reproductive fitness, and most cases are identified in spontaneous mutations of a gamete from either one of the healthy parents. There is no racial, geographic or gender predisposition; the worldwide prevalence is approximately one in every two million people.[1,2] FOP is diagnosed when clinical symptoms and mutational analysis is confirmed. Ninety-seven percent of patients worldwide have classic FOP, which is defined by the presence of two classic clinical features: characteristic malformations of the great toes and onset of soft tissue flare-ups leading to progressive heterotopic ossification.

Because of the systemic heterotopic ossification, the pathological progression is associated with a restricted range of motion (ROM) affecting most joints. The ossification progression varies among individuals. Heterotopic ossification around the joints of the extremities causes extra-articular ankylosis, resulting in restricted activities of daily living, particularly difficulty in walking. Furthermore, some patients present with respiratory difficulties caused by heterotopic ossification in the spinal column and thorax. Progression of this condition reduces life expectancy.

As previously mentioned, although many reports have documented sporadic cases of FOP, familial cases due to autosomal dominant inheritance have also been reported. Linkage analysis of 32 sporadic and five familial FOP patients revealed a mutation (p.Arg206His) in the *ACVR1* gene that was common to both sporadic and familial cases (classic FOP). To date, 11 point mutations have been identified in the *ACVR1* gene.[1–15] Among them, a recurrent mutation, NM_001105.4: p.Arg258Ser, was reported in the same kinase domain as the mutation reported in 2010 (p.Gly356Asp).[14,15] Herein we report the results and analysis of the third patient with *ACVR1* (p.Arg258Ser) caused by c.774G>T mutation.

MATERIALS AND METHODS

The patient was a 17-year old female. No other individuals in her family, including siblings, had FOP symptoms. The patient exhibited normal development and no notable restriction of ROM of her joints or trunk from birth until 7 years of age. At the age of 7 years, the patient fell from a swing and was examined by her local physician. X-ray imaging indicated fusion in her cervical vertebrae. Thereafter, the patient's ROM in the shoulders and elbows gradually worsened. Biopsy of the cervical lesion was performed; however, no ossification was found. At the age of 14 years, the patient was examined by her local physician because of obvious body movement difficulties. Computed tomography scans revealed heterotopic ossification around the paraspinal muscles and bilateral shoulder and hip joints. The patient was referred to our institution at the age of 15 years and 2 months. At 17 years of age, the most recent findings were oral restriction (22 mm) and no evidence of scoliosis. In the upper extremities, restricted shoulder flexion (20/5°) and external rotation (40/5°) and ankyloses of the elbow joints were observed. Joint movements distal to the wrists were not affected. In the lower extremities, contracture of the right hip in external rotation and of the left hip in internal rotation resulted in a so-called 'windblown deformity'. Restriction of ROM was also evident in the knees (85–110/70–110°) and ankle joint dorsiflexion (20/5°). The toes were generally short, without obvious great toe malformation. X-rays revealed no spinal deformity; however, there was heterotopic ossification of the bilateral paraspinal muscles (Figure 1a); morphological changes in the cervical vertebrae (bony fusion of the posterior elements (Figure 1b)); shortening of the first metacarpal bone (Figure 1c); overall shortening of the second to fifth toes (Figure 1d); and heterotopic ossification of the bilateral shoulder, elbow and hip joints (Figure 1e).

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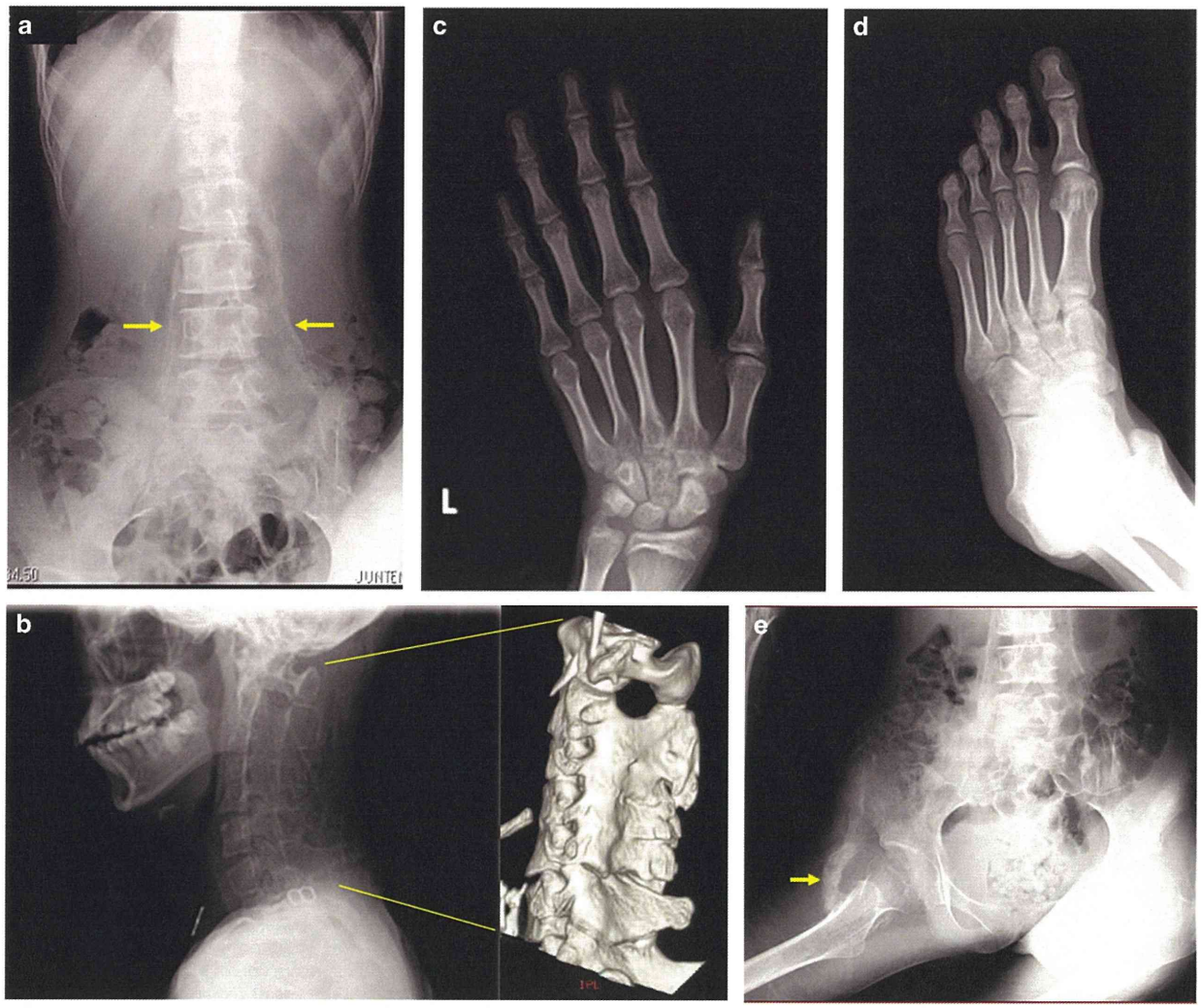

Figure 1. (**a**): Bilateral heterotopic ossification in the paraspinal muscles (arrow). No scoliosis is observed. (**b**): Bony fusion of the posterior elements of the cervical vertebrae (left image: X-ray, right image: 3D-CT). (**c**): Slight shortening of the first metacarpal bones. (**d**): Overall shortening of toes. No malformation of the great toes was observed. (**e**): Heterotopic ossification of the right hip joint (arrow), windblown deformity and diffuse osteopenia. 3D-CT, three-dimensional computed tomography.

Written informed consent was obtained from the patient and her family for gene analysis and preparation of this report. The Ethical Committee of The University of Tokyo approved this study. Genetic diagnosis was performed at the Project of Clinical and Basic Research for FOP at Saitama Medical University. All exons of *ACVR1* were amplified by a standard PCR method using Pfx platinum DNA polymerase (Invitrogen, Carlsbad, CA, USA). The PCR product that was purified by a Microcon-100 column (Takara Bio Shiga, Japan) was directly sequenced using an ABI3500 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

RESULTS

Analysis was performed to verify the *ACVR1* (p.Arg206His) mutation; however, it was not identified. All exons of *ACVR1* were then examined, leading to the identification of the *ACVR1* (c.774G>T; p.Arg258Ser) mutation in exon 5 of *ACVR1* (Figure 2), which is the same mutation reported by Ratbi *et al.* and Eresen-Yazıcıoğlu *et al.*

DISCUSSION

We report the clinical and radiological findings of the patient with FOP due to a recurrent mutations of *ACVR1*, c774G>T

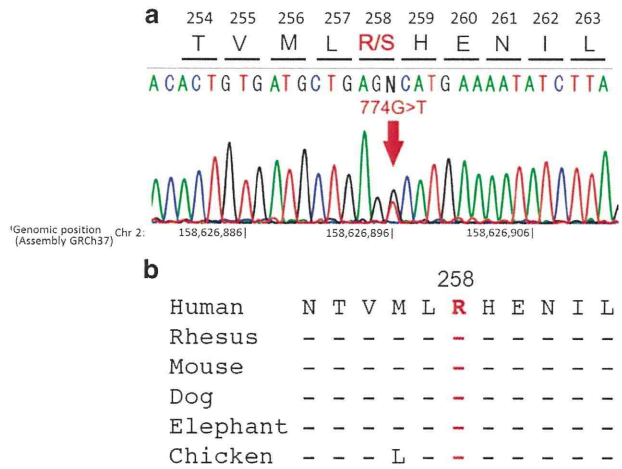

Figure 2. (**a**) The c.774G>T mutation of *ACVR1*. Analysis by direct sequence identified the *ACVR1* (c.774G>T) heterozygous mutation in exon 5 of *ACVR1*. (**b**) Genomic conservation among species.

(p.Arg258Ser). Characteristic findings of the classic FOP include great toe malformation from the time of birth and progressive heterotopic ossification of the muscle and the surrounding tissue until ~ 10 years of age. However, reports of an FOP variant without great toe malformation have recently appeared.[6,9,12,16]

There have been two previous reports of patients with p.Arg258Ser caused by c.774G>T, but neither had great toe malformation. Ratbi *et al.*[14] reported a patient due to c.774G>T (p.Arg258Ser), whose onset of heterotopic ossification at 8 years of age, and other signs included short first metatarsals and exostosis of different sizes involving the dorsal and lumbar vertebrae, distal segment of the left femur and proximal segment of the left tibia that were observed in the X-rays. Eresen-Yazıcıoğlu *et al.*[15] reported the same mutation, c.774G>T (p.Arg258Ser), in a patient with FOP, whose onset of heterotopic ossification occurred at 10 years of age, and ROM was restricted in the temporomandibular, shoulder, elbow and knee joints. X-rays revealed kyphosis of the thoracic vertebrae and lumbar lordosis, and thinning of the scalp hair was also observed. Both two patients did not have great toe malformation.

Bocciardi *et al.*[9] reported additional two unrelated patients with FOP, who had a same amino-acid alteration (p.Arg258Ser) but a different nucleotide alteration of c.774G>C.[9] Phynotypic difference between c.774G>T and c.774G>C is the presence of great toe malformation. Great toe malformation was not observed in any patients with c.774G>T while it was not a common factor in patients with c.774G>C as one of two patients in fact had malformation of the great toes. The patient (FOP12) had no great toe deformity, and onset of ectopic ossification was observed at the age of 4 years because of painful swelling in the vertebral region, and the patient (FOP12) did not experience another flare-up until the age of 18 years. On the other hand, the patient (FOP17) had great toe malformation, and the onset of heterotopic ossification was at 14 years of age.

Clinical manifestations of the patients with FOP due to p.Arg258Ser of *ACVR1* were summarized in Table 1 together with those of the patients due to the common *ACVR1* mutation (p.Arg206His). The clinical features of the present patient resemble those reported by Ratbi *et al.* and Eresen-Yazıcıoğlu *et al.* in that there was no great toe malformation, and the clinical course demonstrated a somewhat delayed onset compared with classic FOP. The difference included no obvious spinal deformity and overall shortening of the toes, and no ossification was observed in the biopsy that was performed at the site of swelling. We believe that the lack of obvious spinal deformity was due to the late onset of heterotopic ossification and because the ossification was relatively symmetrical. The observation that ossification did not occur after the biopsy is an important difference between this variant and classic FOP. However, the progression of decreased activities of daily living after onset was comparatively faster than those in previous reports.

Patients with c.774G>T and c.774G>C lead to the same amino-acid change p.Arg258Ser. It has been known that the mutation which result in same amino-acid change is insignificant to phenotypic differences because such changes in DNA would not alter the composition of the proteins encoded by genes. But recently, there have been reports that in some cases it can still result in altered function because synonymous mutations can alter protein folding.[17,18]

Meanwhile, comparison of phenotypic difference among five patients is too few to support the hypothesis of the genotype–phenotype correlation. Therefore, possibility of other factors including environmental factors and other genomic modifiers must also be taken into consideration.

In FOP, the clinical symptoms, mutations and mechanism of onset are gradually being discovered. Moreover, it has become evident that the location of mutation differentiates the clinical symptoms from typical to atypical FOP features. This report is extremely significant in terms of providing new evidence of symptoms experienced by patients with c.774G>T who present with clinical findings that are different from those of c.774G>C but in whom mutation occurs in the same amino acid. Accumulating data on novel mutations is important for evaluating pathology, establishing treatments, and contributing to clarify *in vivo* mechanisms of p.Arg258Ser and its relationship with other mutation types in future studies.

Table 1. Comparison of the six patients diagnosed with an *ACVR1* (c.617G>A) mutation at our institution and the patients diagnosed with the *ACVR1* (c.774G>T) or *ACVR1* (c.774G>C) mutation

	Classic FOP	*This patient*	*Ratbi et al.*	*Eresen-Yazıcıoğlu et al.*	*Bocciardi et al.*
ACVR1 mutation	c.617G>A	c.774G>T	c.774G>T	c.774G>T	c.774G>C
Codon change	p.Arg206His	p.Arg258Ser	p.ArgR258Ser	p.Arg258Ser	p.Arg258Ser
Gender	4 males, 2 females	female	male	male	2 females
Age of onset (year)	0–11	7	8	10	4, 14
Classic FOP feature					
Malformations of great toe	6/6	–	–	–	1/2
Progressive HO	6/6	+	+	+	2/2
Common features in classic FOP					
Proximal medial tibial exostoses	5/6	–	+	*	*
Cervical spine malformations	6/6	+	*	*	*
Short broad femoral necks	6/6	–	*	*	*
Thumb malformations (short first metacarpal)	5/6	+	+	*	*
Conductive hearing impairment	1/6	–	–	*	*
Additional features					
Little finger camptodactyly	–	–	–	*	*
Short toes	–	+	–	*	*
Absent DIP joints in toes	–	–	–	*	*
Thin scalp hair	1/6	–	–	+	*
Reference	Patients at our institution		Ratbi *et al.*[14]	Eresen-Yazıcıoğlu *et al.*[15]	Bocciardi *et al.*[9]

Abbreviations: ACVR1, activin receptor 1; DIP, distal interphalangeal; FOP, fibrodysplasia ossificans progressiva; HO, heterotopic ossification; –, absent; +, present; *, no description.

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COMPETING INTERESTS

The authors declare no conflict of interest.

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CASE REPORT

Cervical myelopathy due to calcification of the posterior atlantoaxial membrane associated with generalized articular deposition of calcium pyrophosphate dihydrate: a case report and review of the literature

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Introduction

The ligamentum flavum can undergo either calcification or ossification that can lead to radiculomyelopathy [1, 2]. Calcification of the ligamentum flavum (CLF) characteristically occurs in the cervical spine in elderly women [1]. Theoretically speaking, calcification of the spinal ligament can affect any level of the cervical spine; however, we seldom encounter calcification of the posterior atlantoaxial membrane.

In the present report, we illustrate a unique case of cervical myelopathy due to calcification of the posterior atlantoaxial membrane that occurred concomitantly with generalized deposition of calcium pyrophosphate dihydrate (CPPD) as well as cervical ossification of the longitudinal ligament of the spine (OPLL).

Report of case

An 83-year-old woman visited our institution due to spastic gait, clumsiness, and numbness of bilateral hands progressing over the course of 2 months without preceding craniocervical trauma. Neurological examination revealed hyperreflexia of all four extremities, disturbance of discrete movement of bilateral hands, and bilateral positive Babinski signs. There was no bowel or bladder dysfunction. She had a history of surgical treatment of bilateral carpal tunnel release and right total knee arthroplasty. Routine blood tests were unremarkable except for a mildly increased blood sugar level (mild diabetes mellitus).

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On X-ray examination, mixed-type OPLL extending from C2 to C5, retro-odontoid calcification, as well as a round calcified mass between the posterior arch of C1 and the lamina of C2 were noted (Fig. 1a). Calcified lesions were also found in the left knee, shoulders, and fingers (Fig. 1b–d). Joint fluid analyses of the left knee joint by polarization microscopy revealed CPPD crystals. Computed tomography (CT) clearly demonstrated oval calcification of the posterior atlantoaxial membrane, retro-odontoid calcification, as well as OPLL extending from C2 to C5. A calcified lesion was visualized as vague spotty images on CT (Fig. 2a, b). Subsequent magnetic resonance (MR) imaging demonstrated overt compression of the spinal cord due to calcification of the posterior atlantoaxial membrane, which was low intensity on both T1- and T2-weighted images (Fig. 3a–c). In turn, subaxial spinal cord compression due to OPLL was not evident (Fig. 3a–c). A change in the intensity of the spinal cord on T2-weighted images was also identified at the level of C1/2 (Fig. 3b).

Taking all of these findings into account, we attributed cervical myelopathy to the calcification of the posterior atlantoaxial membrane and posterior decompression surgery was performed. After bilateral exposure of C1/2, en-block extirpation of the posterior atlantoaxial membrane including the left calcified lesion was performed with partial laminectomy of C2, whereas we were able to preserve the posterior arch of C1. At the surgery, the lesion was carefully dissected from the dura matter. Chalky white deposits within the degenerated posterior atlantoaxial membrane were confirmed (Fig. 4a). Extensor muscles dissected from C2 were reconstructed after the decompression as much as possible. Histopathological examination revealed that calcified granules within degenerated fibrous tissue were surrounded by macrophages (Fig. 4b). The calcified granules were Alizarin red S positive (Fig. 4c). Furthermore, Raman

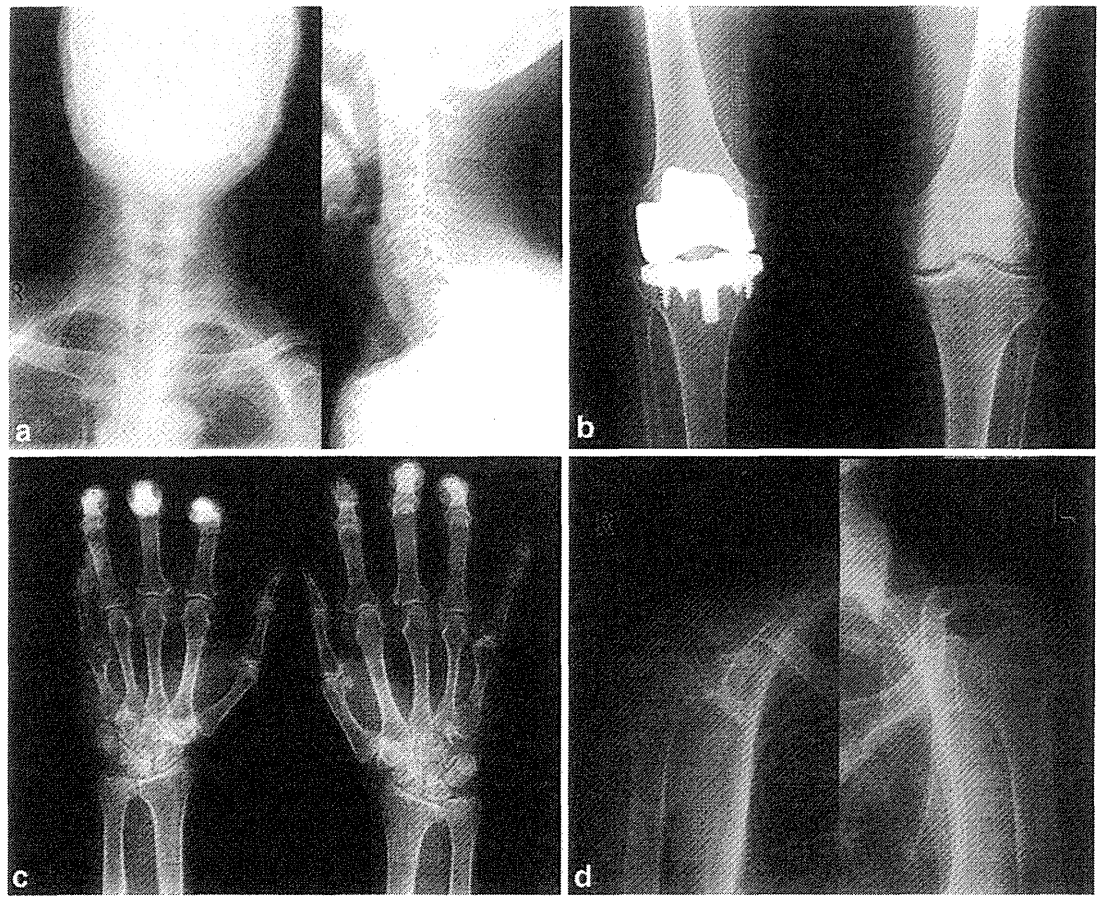

Fig. 1 Standard X-rays. **a** Ossification of the posterior longitudinal ligament of the cervical spine and an oval mass between the posterior arch of C1 and the lamina of C2 were confirmed. **b–d** Generalized articular calcifications were also seen

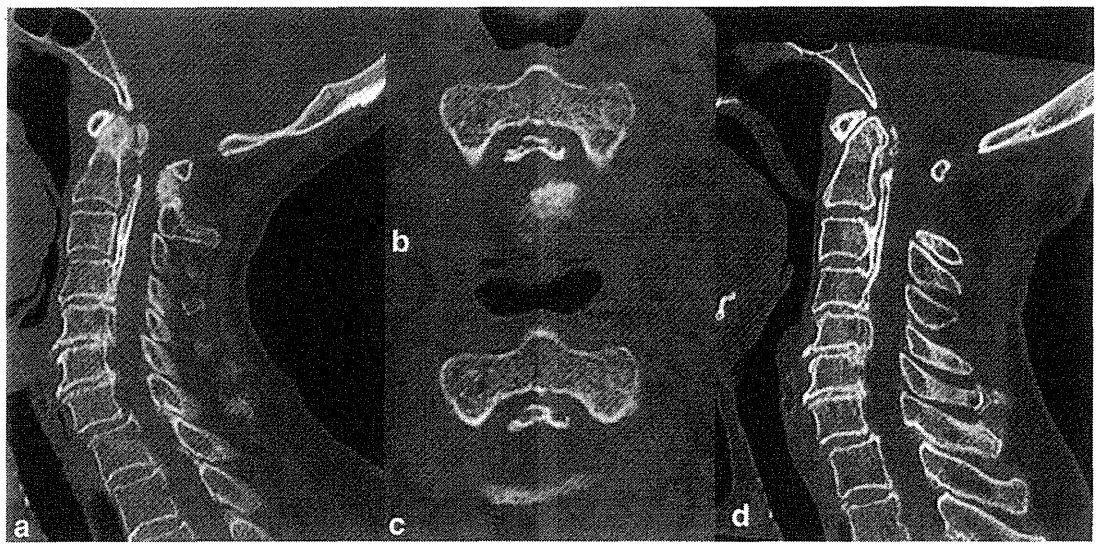

Fig. 2 **a, b** Pre-operative computed tomography (CT) revealed ossification of the longitudinal ligament of the spine extending from C2 to C5 and calcification at the posterior atlantoaxial membrane and retro-odontoid space. **c, d** Post-operative CT revealed extirpation of the calcification of the posterior atlantoaxial membrane

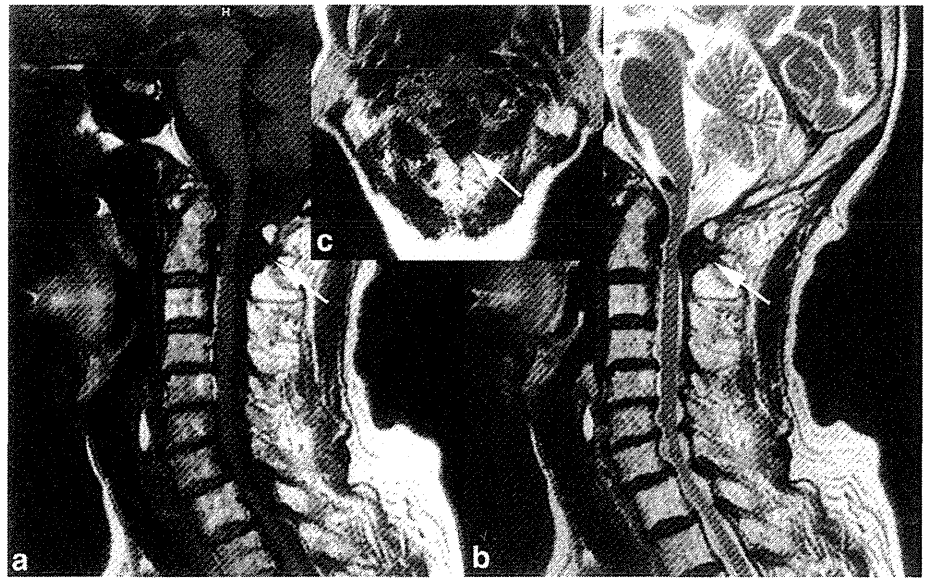

Fig. 3 Pre-operative magnetic resonance imaging demonstrated overt compression of the spinal cord due to calcification of the posterior atlantoaxial membrane (**c**), which was low intensity on both T1- (**a**) and T2-weighted (**b**) images (*arrows*), as well as a change in the intensity of the spinal cord on the T2-weighted image

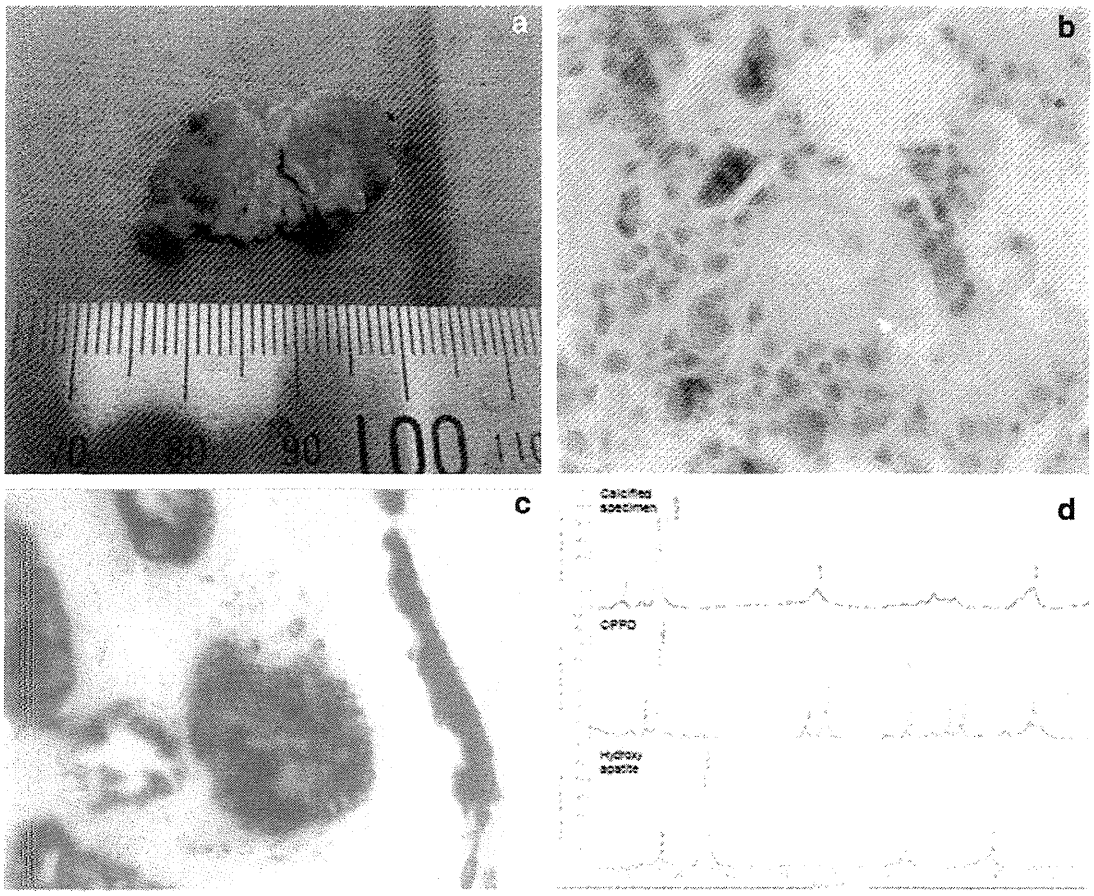

Fig. 4 **a** The presence of marked chalky white matter in the posterior atlantoaxial membrane was confirmed. **b** Histopathological examination revealed calcium pyrophosphate dihydrate (CPPD) crystals surrounded by macrophages (*arrow*, Original maginification ×400, H&E). **c** The calcified granules were positive for Alizarin red S staining (Original maginification×400). **d** Raman spectroscopy analysis revealed that the calcified lesion consisted only of CPPD, not hydroxy apatite

spectroscopy analysis revealed that the calcified lesion consisted only of CPPD, not hydroxyapatite (Fig. 4d).

After the surgical treatment, the patient quickly recovered from neurological deterioration. At the latest follow-up, 2 years after the surgery, the patient was doing well and had no neurological deterioration. Postoperative CT revealed complete resection of the calcification of the posterior atlantoaxial membrane (Fig. 2c, d). No obvious instability and progression of OPLL were observed in dynamic X-rays of the cervical spine.

Written informed consent was obtained from the patient to publish this case report and any accompanying images.

Discussion

The first case of myelopathy due to CLF at the cervical spine was described in the late 1970s [3, 4]. Since those reports, to the best of our knowledge, more than 100 cases of symptomatic cervical CLF have been reported. The overwhelming majority of these cases have been reported from Japan. We have summarized the data available from previously reported cases in Table 1. This entity is more prevalent in elderly females [1, 5].

Theoretically speaking, CLFs can arise from any level of the cervical spine; but they predominantly arise from the lower cervical spine, with the two most commonly affected levels being C4/5 and C5/6 (Table 1). To the best of the authors' knowledge, Inoue et al. [6] briefly reported the first case of calcification of the posterior atlantoaxial membrane. The case was a 42-year-old man without any systemic background for ectopic ossification, yet he displayed multiple-level cervical ossification of the ligamentum flavum (OLF), thoracic OPLL, cervical CLF, and calcification of the posterior atlantoaxial membrane. However, the authors did not perform a detailed crystallographic analysis of the calcification of the posterior atlantoaxial membrane. Although the present case is the second report of calcification of the posterior atlantoaxial membrane, this is the first to include a crystallographic analysis.

The precise pathophysiology of CLF remains unknown; however, elastic fibers undergoing breakdown (i.e., degenerative changes in the ligamentum flavum) have been reported to exhibit increased affinity for calcium [7, 8]. It is commonly recognized that degenerative changes in the ligamentum flavum are induced by a combination of various factors, including the aging process, the decrease in estrogen in elderly women, mechanical stress of the lower cervical spine [7, 8], and chondrocytic metaplasia [9].

There have been no previous reports on calcification of the posterior atlantoaxial membrane. Functionally speaking, the ligamentum flavum provides a static, elastic force to support the spinal column in its return to a neutral position after flexion and extension movements. In turn, the posterior atlantoaxial membrane predominantly consists of a collagenous tissue, while elastic fibers comprise a minor counterpart [10]. Macroscopically, Ramsey [10] reported a definite lack of yellow color in these two upper cervical ligaments attached to the laminae of C1 and C2. On microscopic examination of the posterior atlantoaxial membrane

Table 1 Age distribution and topographic and crystallographic characterization of the 33 previously reported papers on the calcification of ligamentum flavum, along with a list of those papers

	Cervical segment						
	C1/2	C2/3	C3/4	C4/5	C5/6	C6/7	C7/T1
Distribution of calcium deposits	1	5	37	62	71	36	8
	Crystal type						
	CAP		CPPD	CPPD + HAP		HAP	Others
Number of identified calcium deposits	2		63	15		22	2
	Patient's age group						
	40s		50s		60s		Over 70
Female/total number	2/2		4/9		29/35		43/57

(1) Nanko et al. [14][a], (2) Kamakura et al. [4], (3) Jyotoku and Harada [16][a], (4) Kawano et al. [17], (5) Kida and Tabata [18][a], (6) Nagashima et al. [19][a], (7) Fujiwara et al. [20][a], (8) Akino et al. [15][a], (9) Iwasaki et al. [11], (10) Nakajima et al. [7], (11) Nagashima et al. [37], (12) Ogata et al. [12], (13) Hirano et al. [21][a], (14) Berghausen et al. [22], (15) Kubota et al. [23], (16) Kawano et al. [24], (17) Koyama et al. [38][a], (18) Hankey et al. [25], (19) Gomez and Chou [26], (20) Sato et al. [27], (21) Ohnishi et al. [28][a], (22) Okada et al. [8], (23) Takayama et al. [29][a], (24) Baba et al. [5], (25) Haraguchi et al. [30][a], (26) Higashi et al. [31][a], (27) Yamagami et al. [32], (28) Cabre et al. [13], (29) Ugarriza et al. [33], (30) Guesmi et al. [34], (31) Muthukumar and Karuppaswamy [35], (32) Yabuki and Kikuchi [36], (33) Mwaka et al. [9]

CAP carbonate apatite, *CPPD* calcium pyrophosphate dihydrate, *HAP* hydroxy apatite

[a] Articles in Japanese

in adults, the concentration of elastic fibers is approximately half that seen in true ligamentum flavum. These differences may contribute to the discrepant prevalence of CLF and calcification of the posterior atlantoaxial membrane.

Some authors have assumed a possible association between CLF and articular chondrocalcinosis (pseudogout) [5]. The generalized articular chondrocalcinosis seen in the present case led us to hypothesize that, at least in part,chondrocalcinosis played a role in the calcification of the posterior atlantoaxial membrane. The unusual mechanical stress that converged on C1/2 due to the mixed-type OPLL extending from C2 to C5 in the present case may also have played a significant role in this condition.

The etiology of CLF is likely to be different from that of OLF [1]; however, Inoue et al. [6] suggested the possibility that the same factor may have initiated ossification and calcification in spinal ligaments. Further studies are needed to elucidate the pathophysiology of calcification and ossification of the spinal ligaments.

Standard X-rays can show abnormal shadows of calcification on the posterior wall of the spinal canal [11]. However, these sometimes fail to demonstrate any abnormality other than mild spondylosis [12]. MR imaging is useful for identifying spinal cord and/or nerve root involvement; however, it cannot distinguish between calcification and hypertrophied (uncalcified) spinal ligaments since these two conditions both yield low intensity on the T1- and T2-weighted images. On the other hand, CT can clearly differentiate between these two conditions and is the best modality for detecting calcification of the spinal ligaments [13].

The natural history of cervical myelopathy due to CLF is not fully understood, since most of the previously reported cases were treated surgically. However, Cabre et al. [13] reported conservative treatment of two cases; i.e., one declined surgery and the other one had cardiorespiratory disease contraindicating surgery. These two cases uniformly worsened neurologically, whereas surgical treatment has achieved good results in most previous reports [5, 13]. Taking all of these findings into account, surgical treatment was advocated in symptomatic patients with cervical CLF [13]. One can perhaps extend this surgical indication to include calcification of the posterior atlantoaxial membrane.

In conclusion, calcification of the posterior atlantoaxial membrane is an extremely rare disease. We must to keep in mind the possibility of latent calcification of the cervical spinal ligaments in patients with generalized articular calcification. When symptomatic, surgical treatment is advocated to prevent further neurological compromise.

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Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) of the whole spine and its association with lumbar spondylosis and knee osteoarthritis: the ROAD study

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Abstract We aimed to assess the prevalence of diffuse idiopathic skeletal hyperostosis (DISH) and its association with lumbar spondylosis (LS) and knee osteoarthritis (KOA) using a population-based cohort study entitled Research on Osteoarthritis/osteoporosis Against Disability (ROAD). In the baseline ROAD study, which was performed between 2005 and 2007, 1,690 participants in mountainous and coastal areas underwent anthropometric measurements and radiographic examinations of the whole spine (cervical, thoracic, and lumbar) and both knees. They also completed an interviewer-administered questionnaire. Presence of DISH was diagnosed according to Resnick criteria, and LS and KOA were defined as Kellgren-Lawrence (KL) grade ≥3. Among the 1,690 participants, whole-spine radiographs of 1,647 individuals (97.5 %; 573 men, 1,074 women; mean age, 65.3 years) were evaluated. Prevalence of DISH was 10.8 % (men 22.0 %, women 4.8 %), and was significantly higher in older participants (presence of DISH 72.3 years, absence of DISH 64.4 years) and mainly distributed at the thoracic spine (88.7 %). Logistic regression analysis revealed that presence of DISH was significantly associated with older age [+1 year, odds ratio (OR): 1.06, 95 % confidence interval (CI): 1.03–1.14], male sex (OR: 5.55, 95 % CI: 3.57–8.63), higher body mass index (+1 kg/m^2, OR: 1.08, 95 % CI: 1.02–1.14), presence of LS (KL2 vs KL0: 1, OR: 5.50, 95 % CI: 2.81–10.8) (KL ≥3 vs KL0: 1, OR: 4.09, 95 % CI: 2.08–8.03), and presence of KOA (KL ≥3 vs KL0: 1, OR: 1.89, 95 % CI: 1.14–3.10) after adjusting for smoking, alcohol consumption, and residential area (mountainous vs coastal). This cross-sectional population-based study clarified the prevalence of DISH in general inhabitants and its significant association with LS and severe KOA.

Keywords Prevalence · Diffuse idiopathic skeletal hyperostosis · Knee osteoarthritis · Lumbar spondylosis · ROAD study

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Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is characterised by calcification and ossification of soft tissue such as entheses and joint capsules [1]. Resnick and Niwayama specifically defined DISH as the radiographic finding of calcification or ossification along the anterolateral aspects of at least 4 contiguous vertebral levels (across 3 disc spaces), with relative preservation of disc height in the involved vertebral segments and without degenerative disc disease [2]. In 1998, Mata and co-workers [3] developed a

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