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Bone marrow-derived osteoblast progenitor cells in circulating blood contribute to ectopic bone formation in mice

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Abstract

Recent studies have suggested the existence of osteoblastic cells in the circulation, but the origin and role of these cells *in vivo* are not clear. Here, we examined how these cells contribute to osteogenesis in a bone morphogenetic protein (BMP)-induced model of ectopic bone formation. Following lethal dose-irradiation and subsequent green fluorescent protein-transgenic bone marrow cell-transplantation (GFP-BMT) in mice, a BMP-2-containing collagen pellet was implanted into muscle. Three weeks later, a significant number of GFP-positive osteoblastic cells were present in the newly generated ectopic bone. Moreover, peripheral blood mononuclear cells (PBMNCs) from the BMP-2-implanted mouse were then shown to include osteoblast progenitor cells (OPCs) in culture. Passive transfer of the PBMNCs isolated from the BMP-2-implanted GFP-mouse to the BMP-2-implanted nude mouse led to GFP-positive osteoblast accumulation in the ectopic bone. These data provide new insight into the mechanism of ectopic bone formation involving bone marrow-derived OPCs in circulating blood.

Keywords: Bone morphogenetic protein; Ectopic bone; Circulating osteoblast progenitor cells; Bone marrow transplantation

BMP-2 and other members of the BMP family are well-known inducers of bone formation *in vitro* and *in vivo* [1]. During healing of bone fractures, stimulation from BMPs recruits OPCs to the fracture sites and induces their differentiation to become osteoblasts. An experimental model of ectopic bone formation in mice has also indicated that BMP-2 stimulation is essential for the recruitment of OPCs to the osteogenic sites [2]. The source and the route for the recruitment of the OPCs in this model, however, have not been fully elucidated. Notably, the surrounding soft tissues, the periosteum and the bone marrow all constitute potential origins for the OPCs involved in osteogenesis, but it is unclear how these OPCs target the region expressing BMPs [3].

Recent studies have shown the existence of OPCs (or indeed osteoblasts) in the circulating blood of various mammals, including humans [4–6]. These reports indicate an ability of circulating cells to function as osteoblasts in culture and to form osseous tissues after transplantation, suggesting that OPCs and/or osteoblasts may be supplied via the circulation to regenerating bone *in vivo*. This hypothesis is potentially an attractive one for the field of bone-regenerative medicine, especially if an adequate number of circulating OPCs can be isolated from peripheral blood, expanded in culture, and delivered to sites requiring bone regeneration. However, the origins of circulating OPCs and evidence of endogenously circulating cells with the potential to migrate and contribute to bone regeneration *in vivo* have not yet been fully demonstrated.

Abbreviations: OPCs, osteoblast progenitor cells; BMPs, bone morphogenetic proteins; MOPCs, marrow-derived OPCs; GFP, green fluorescent protein; BMT, bone marrow transplantation; PBMNCs, peripheral blood mononuclear cells; DAPI, 6-diamidino-2-phenylindole; FITC, fluorescein isothiocyanate; H&E, hematoxylin and eosin; TRAP, tartrate-resistant acid phosphatise.

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Here, we report for the first time that marrow-derived OPCs (MOPCs) can migrate to a BMP-2 pellet implanted into mouse muscle and differentiate to become osteoblasts within the BMP-2-induced ectopic bone. We have also succeeded in culturing circulating OPCs from PBMNCs isolated from BMP-2-implanted mice. Furthermore, intravenous transfer of the GFP-transgenic PBMNCs containing OPCs to nude mice implanted with BMP-2 pellet generates a significant number of GFP-osteoblasts in the BMP-2-induced ectopic bone. We believe that these new findings will accelerate further understanding of the role of circulating OPCs, not only in ectopic osteogenesis, but also in the healing of bone fractures *in vivo*.

Materials and methods

Bone marrow cell transplantation (BMT). Under sterile conditions, bone marrow cells were isolated from 8- to 10-week-old male C57BL/6 transgenic mice that ubiquitously expressed enhanced GFP [7]. Eight- to 10-week-old female C57BL/6 mice were lethally irradiated with 10 Gy. For BMT, each irradiated mouse received 5×10^6 bone marrow cells from GFP transgenic mice. Experiments on BMT mice were performed at least 6 weeks after BMT. All animals were handled according to approved protocols and the guidelines of the Animal Committee of Osaka University.

Preparation and implantation of BMP-2-containing collagen pellets. Recombinant human BMP-2 was provided by Astellas Pharma Inc. (Tokyo, Japan). The BMP-2 was suspended in buffer solution (5 mmol/L glutamic acid, 2.5% glycine, 0.5% sucrose, and 0.01% Tween 80) at a concentration of 1 μg/μL. Next, 3 μL (3 μg of BMP-2) of the BMP-2 solution was diluted in 22 μL PBS and blotted onto a porous collagen disc (6 mm diameter, 1 mm thickness), freeze-dried, and stored at −20 °C. All procedures were carried out under sterile conditions. BMP-2-containing or control PBS-containing collagen pellets were implanted onto the backs (below muscle fascia) of BMT mice, C57BL/6 mice, or nude mice. Three weeks later, fluorescent photos of ectopic bone formation were taken using a digital microscope (Multiviewer system VB-S20 KEYENCE, Osaka, Japan).

Morphological and immunofluorescent analysis of the ectopic bone. Ectopic bone was removed and fixed with 4% paraformaldehyde at 4 °C for 48 h. After taking soft X-ray photos, the bones were decalcified at 4 °C for 6 days with the EDTA solution replaced every other day. After decalcification, the pellets were equilibrated in PBS containing 15% sucrose for 12 h and then in PBS containing 30% sucrose for 12 h, embedded in Tissue-Tec OCT Compound (Sakura Finetek Japan, Tokyo, Japan), and frozen on dry ice and stored at −20 °C. For immunofluorescence staining, 6-μm-thick sections were cut with a Cryostat (Leica Microsystems AG, Wetzlar, Germany). After washing, the sections were treated with 0.1% trypsin (Difco Laboratories, Detroit, MI) in PBS for 30 min at 37 °C to activate antigens. Then the sections were blocked with normal goat serum for 1 h before incubation with polyclonal anti-mouse osteocalcin antibody (1:250, Takara Bio Inc., Shiga, Japan). Subsequently, sections were stained with Alexa Fluor 546 goat anti-rabbit secondary antibody (Molecular Probes, Eugene, OR) for 2 h. Then, sections were stained with 4′,6-diamidino-2-phenylindole (DAPI) for 10 min at room temperature and mounted with anti-fade solution VECTOR Shield (Vector Laboratories, Inc., Burlingame, CA).

GFP and tartrate-resistant acid phosphatase (TRAP) double staining of the ectopic bone. For GFP immunohistochemistry, 6-μm-thick sections of BMP-2-induced ectopic bone were treated with 0.6% hydrogen peroxide in 80% methanol for 30 min and then 3% hydrogen peroxide in PBS for 15 min to inhibit endogenous peroxidase. Then the sections were blocked with normal goat serum for 1 h before incubation with polyclonal anti-GFP antibody (1:250, MBL, Nagoya, Japan). Signals were detected using diaminobenzidine. Subsequently, to detect osteoclasts, TRAP staining was carried out using a staining kit (Cell Garage, Tokyo, Japan) according to the manufacturer's protocol. Counterstaining was performed with hematoxylin.

Culture of MOPCs in PBMNCs. Peripheral blood was taken from the heart of BMP-2-implanted mice with a 24-gauge needle and 1-ml syringe containing heparin and enriched for light-density mononuclear cells (PBMNCs) by Ficoll-Paque (Amersham Biosciences AB, Uppsala, Sweden) centrifugation. Red blood cells were removed by resuspending in 0.125% Tris–NH_4Cl buffer and sieving through a nylon mesh. To culture MOPCs, were then inoculated in basal medium consisting of DMEM supplemented with 10% FCS, 100 U/mL streptomycin/penicillin, and 50% conditioned culture medium (DMEM with 10% FCS) of mouse bone marrow-mesenchymal cells as a growth factor supplement (Otsuru and Tamai, unpublished data). To induce osteoblast differentiation, those cells were cultured in the osteogenic medium consisting of IMDM supplemented with 0.1 μM dexamethasone (Nacalai Tesque, Kyoto, Japan), 10 mM β-glycerol phosphate (Sigma, Saint Louis, MO), and 0.05 mM ascorbic acid 2-phosphate (Sigma) for 3–4 weeks. Cells were then fixed with 4% paraformaldehyde for 10 min and treated with 0.2% Triton X in phosphate-buffered saline (PBS) for 10 min.

Immunostaining of cultured MOPCs. Cultured MOPCs were pretreated with 3% skim milk (Nacalai Tesque) in PBS for 1 h before incubation with polyclonal anti-mouse osteocalcin antibody (1:250, Takara Bio Inc.), monoclonal anti-mouse alkaline phosphatase antibody (1:250, R&D Systems, Minneapolis, MN) or polyclonal anti-mouse osteopontin antibody (1:250, LSL, Tokyo, Japan). Subsequently, sections were stained with Alexa Fluor 546 goat anti-rabbit or anti-rat IgG secondary antibody (Molecular Probes) for 2 h. Those cells were stained with 4′,6-diamidino-2-phenylindole (DAPI) for 10 min at room temperature and mounted with the anti-fade solution VECTOR Shield (Vector Laboratories, Inc.).

Passive transfer of PBMNCs from BMP-2-implanted GFP-mouse to BMP-2-implanted nude mouse. For passive transfer of PBMNCs containing MOPCs, nude mice implanted with BMP-2-containing collagen pellets were injected with PBMNCs from the GFP-transgenic BMP-2-implanted mice via a tail vein. Injections were carried out everyday for one week.

Results

Bone marrow-derived cells contribute to BMP-2-induced ectopic bone formation

We first evaluated whether bone marrow-derived cells are involved in the process of BMP-2-induced ectopic bone formation. We implanted BMP-2 pellets under the muscular fascia in the backs of GFP-BMT mice that had been transplanted with GFP-transgenic bone marrow cells after lethal dose irradiation (Fig. 1A). Three weeks after the implantation of BMP-2 collagen pellets, intense GFP fluorescence had accumulated in the region of the BMP-2-induced ectopic bone (Fig. 1B). Immunohistological analysis revealed that a significant number of GFP-positive cells expressing osteocalcin (OC) were seen lining the newly generated bone (Fig. 1C). Tartrate-resistant acid phosphatase (TRAP) and GFP double staining revealed that some of the GFP-positive lining cells were TRAP-positive osteoclasts, which were clearly distinguishable from GFP-positive/TRAP-negative positive cells (Fig. 1D).

Successful culture of OPCs in PBMNCs from a BMP-2-implanted mouse

To determine if a BMP-2-implanted mouse contained OPCs in circulating blood, we isolated PBMNCs from a BMP-2-implanted mouse and cultured those cells in the con-

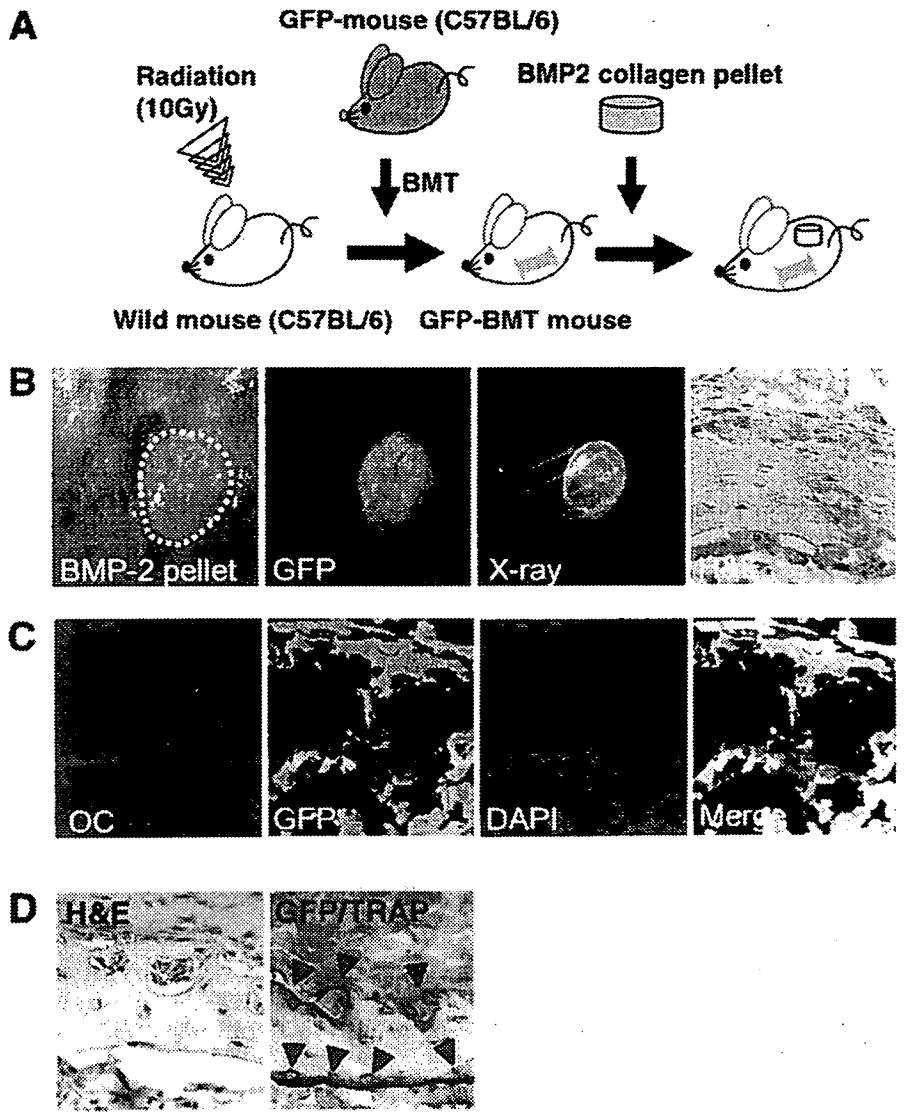

Fig. 1. Bone marrow-derived osteoblast progenitor cells contribute to BMP-2-induced ectopic bone formation in GFP-BMT mice. (A) A BMP-2 pellet is shown implanted under the muscular fascia of a GFP-BMT mouse. (B) A BMP-2 pellet shows accumulation of GFP fluorescence three weeks after implantation. Soft X-ray photo of the BMP-2 pellet demonstrates that ectopic bone has formed in the BMP-2 pellet. Histologic section stained with hematoxylin and eosin (H&E) of the BMP-2 pellet also reveals bone formation in the BMP-2 pellet. Magnification, 400×. (C) Immunofluorescence staining shows that cells lining the newly generated ectopic bone are osteoblasts expressing osteocalcin (OC), and that some of those cells show GFP fluorescence (GFP), revealed as yellow-colored cells in merged picture (Merge) of OC, GFP and DAPI staining (DAPI). Magnification, 400×. (D) GFP and TRAP double staining reveals that the bone marrow-derived osteoclasts (red arrow-head) as well as bone marrow-derived non-osteoclastic cells (brown arrow-head) line the newly formed ectopic bone. Magnification, 400×.

ditioned culture medium, as described in the methods section (Fig. 2A). As we expected, adhesive stromal type cells successfully expanded in culture. Then we looked at the expression of osteoblast-specific proteins before and after induction of osteogenic differentiation. OP, a marker of undifferentiated osteoblasts, was shown to be expressed in the cultures without induction of differentiation (Fig. 2B). Under these culture conditions, however, the differentiation-specific makers ALP and OC were not expressed (Fig. 2B). After change of culture medium to the osteogenic medium, however, these cells then expressed and secreted abundant ALP and OC as well as OP in the culture medium (Fig. 2C).

Intravenous transplantation of GFP-PBMNCs provides GFP-osteoblasts in the ectopic bone in the BMP-2-implanted nude mouse

To confirm further that significant numbers of MOPCs mobilize from bone marrow to peripheral blood and contribute to ectopic bone formation, we isolated PBMNCs

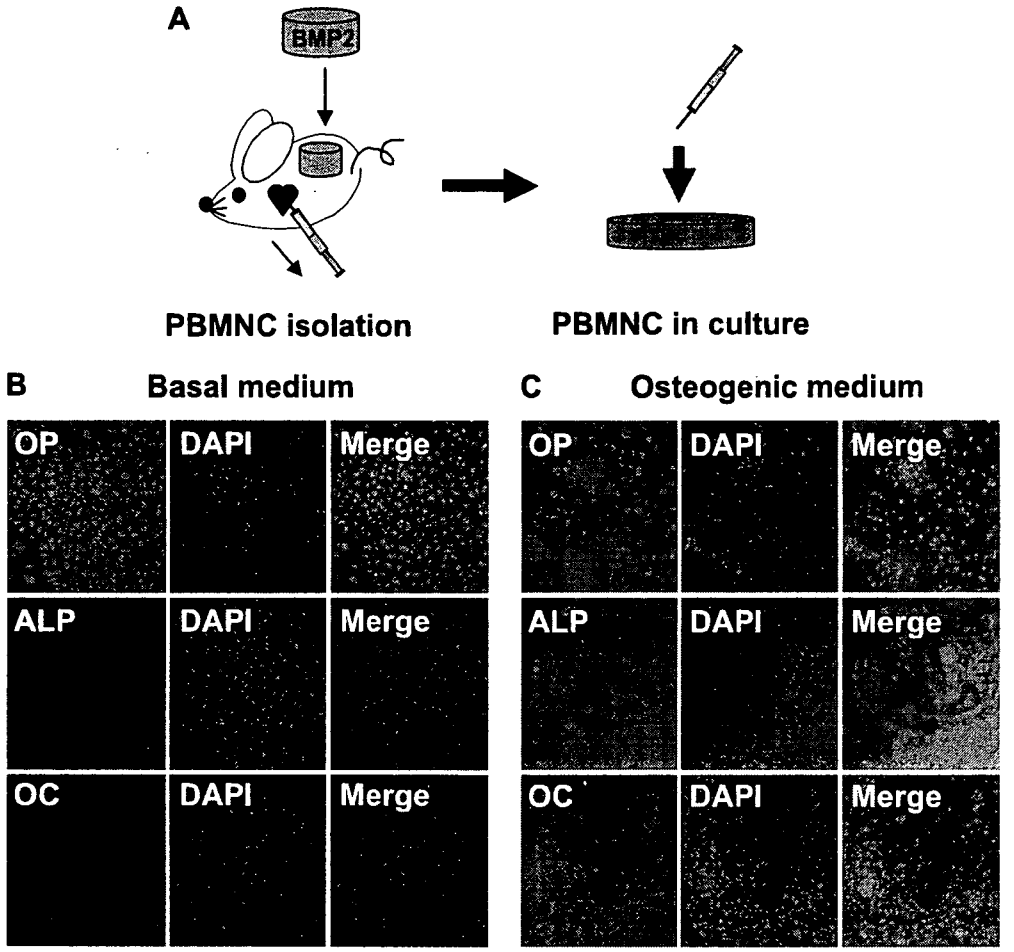

Fig. 2. OPCs in PBMNCs from a BMP-2-implanted mouse express bone matrix proteins in culture. (A) Cultured PBMNCs isolated from peripheral blood of a BMP-2-implanted mouse. (B) Immunofluorescence staining of the cultured cells from isolated PBMNCs shows only osteopontin (OP) expression in normal medium. (C) When those cells were cultured in osteogenic medium, however, there is positive immunoreactivity for alkaline phosphatase (ALP) and osteocalcin (OC) as well as OP. The staining patterns and DAPI staining (DAPI) are shown in the merged image (Merge). Magnification, 200×.

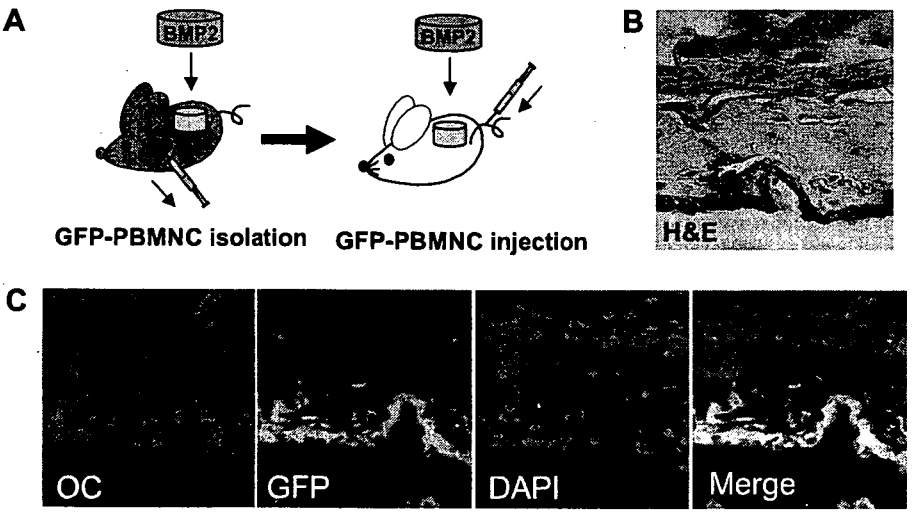

Fig. 3. OPCs in PBMNCs can contribute to ectopic bone formation in a BMP-2 pellet. (A) A nude mouse implanted with a BMP-2 pellet is injected daily for 7 days with PBMNCs taken from BMP-2-implanted GFP transgenic mice. (B) A histologic H&E-stained section shows ectopic bone formation in the BMP-2 pellet. Magnification, 400×. (C) Immunofluorescence staining of the newly generated ectopic bone shows that osteocalcin-expressing osteoblasts (OC) and GFP-positive cells derived from the injected PBMNCs (GFP) co-localize with yellow-colored cells in the merged picture (Merge) with DAPI staining (DAPI). Magnification, 400×.

everyday from BMP-2 pellet-implanted GFP-transgenic mice and injected the isolated PBMNCs (1×10^6) through the tail veins of BMP-2 pellet-implanted nude mice daily for 7 days (Fig. 3A). Two weeks later, the implanted pellets were recovered and examined histologically. We observed that GFP-positive osteoblasts originating from the injected PBMNCs contributed significantly to ectopic bone formation in the mice (Fig. 3B).

Discussion

Circulating mesenchymal precursor/stem cells or osteoblast lineage cells have been shown to exist in various mammals, including humans and mice [4–6,8,9]. Moreover, those circulating mesenchymal/osteoblast lineage cells have been isolated from peripheral blood, expanded in culture, and inoculated to show their potency to become osteoblasts both *in vitro* and *in vivo*. Nevertheless, a number of important questions have been raised following those observations, including as to where those circulating cells came from and where they went *in vivo*? In this study, we have shown, for the first time, clear evidence that marrow cells in intact bone are the major, if not the exclusive, source of circulating OPCs in an *in vivo* model of ectopic bone formation using BMP-2-stimulation in mouse muscle. Of note, our GFP-BMT mouse model showed that ~40% of osteocalcin-producing cells in the ectopic bone were derived from MOPCs, suggesting that endogenous circulating MOPCs may contribute to ectopic bone formation observed in various pathological conditions, and possibly, to fracture healing. Other findings that showed the need for adequate blood flow to obtain mature bone regeneration also add credence to the importance of MOPCs in the circulation [10].

Currently, little is known about the signals that trigger the migration of OPCs from the bone marrow into the circulation and this was not addressed in detail in the current study. Vascular endothelial growth factor (VEGF) previously has been shown to have the capacity to recruit marrow-derived vascular endothelial progenitor cells [11] and we also observed elevation of VEGF levels in the muscle around the implanted BMP-2 pellets (data not shown). This observation may suggest that VEGF contributes to angiogenesis in the area of bone regeneration, although further evidence is needed to support this hypothesis.

The importance of providing additional OPCs to sites of new bone formation has been shown in a number of previous studies [12–17]. From a clinical perspective, identification of signals that induce migration of MOPCs into the circulation could have potential future clinical applications, since increasing MOPCs in the circulation may help patients with delayed or non-union of bone fractures by increasing the number of MOPCs at the bone repair site. The ability to induce circulating MOPCs to enter the peripheral blood circulation may also enable us to easily isolate these cells by simple venous blood sampling, thus providing an opportunity to develop novel cell-based regenerative therapies for bone fractures and possibly for other damaged tissues. Because current procedures to isolate mesenchymal cells directly from the bone marrow are invasive and carry a possible risk of bone marrow infection, the easier approach of isolating MOPCs from peripheral blood has advantages in terms of safety, repeatability, and acceptability. In addition, this method may also be helpful in developing new therapies for genetic disorders such as osteogenesis imperfecta through genetic manipulation of isolated MOPCs [18,19]. Thus, further investigation of circulating MOPCs is warranted to more precisely characterize their cell biology and the mechanisms that lead to their induction. Such work may have very exciting implications for novel therapeutic strategies in bone regenerative medicine.

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Surgical Outcome of Drop Foot Caused by Degenerative Lumbar Diseases

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Study Design. A total of 46 patients undergoing lumbar spine surgery for degenerative lumbar disease and presenting with drop foot were included in this retrospective study.

Objective. To determine which preoperative patients' symptoms were of statistical significance in their effect on surgical outcome.

Summary of Background Data. Drop foot is a neuromuscular condition that results in palsy of the ankle dorsiflexion and is a major problem in Japanese daily life. Few studies have described the effect of a surgical intervention on drop foot associated with degenerative lumbar disorders and the factors that affect the surgical outcome. The manual muscle test can be used to determine the muscular strength of the tibialis anterior. Drop foot is then defined as a score below 3 out of 5.

Methods. Patient medical history, preoperative tibialis anterior strength, presence of leg pain, and duration of palsy were recorded and compared with surgical outcome.

Results. Of patients, 61% recovered from drop foot after surgery. Patients with a tibialis anterior score of 2–3– and those suffering from palsy for a shorter duration of time showed better surgical results. Cases without leg pain were also shown to be treated effectively with surgery.

Conclusions. Palsy duration and preoperative strength were factors that most affected drop foot recovery following surgical intervention for spinal degeneration.

Key words: drop foot, degenerative lumbar disease, manual muscle test, tibialis anterior. **Spine 2007;32: E262–E266**

Drop foot, or palsy of ankle dorsiflexion, is a neuromuscular condition in which patients suffer pain, weakness, and sometimes loss of function. The etiology of drop foot includes peroneal nerve palsy, sciatic nerve palsy, Charcot-Marie-Tooth disease, polyneuropathy, epiconus syndrome due to disorders in the thoracolumbar junction, and palsy of the lower lumbar root due to degenerative disorders.

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Due to the resulting "steppage gait," patients with a drop foot have considerable difficulty in ambulating with standard shoes, sandals, or slippers. The addition of an ankle-foot orthosis or the use of calf high boots greatly improves both their gait and risk of tripping and/or falling, as they provide support and prevent the foot from plantar flexing. Among certain cultural groups, such as the Japanese, this neurologic deficit can be that much worse an impairment as it is customary to remove footwear indoors.

Although there have been case reports of drop foot with unusual etiology such as brain tumors,[1] pelvic hydatid disease,[2] or iatrogenic drop foot after spinal anesthesia,[3,4] lateral meniscus repair,[5,6] and lumbar operations,[7–9] there have been few studies describing its onset and recovery from motor deficits following degenerative lumbar diseases, and no definite conclusion has been reached regarding factors that influence surgical outcome. In the current study, we retrospectively examined motor recovery after surgery in patients suffering from drop foot caused by degenerative lumbar diseases and who underwent decompression with or without fusion surgery. We also studied the factors that influenced recovery from drop foot.

Patients and Methods

Forty-six patients (27 men and 19 women) who underwent lumbar spine surgery for degenerative lumbar disorders between June 1993 and September 2001, and who presented with drop foot were included in the study. The mean age at surgery was 56.6 years (range 23–86), and the mean follow-up period was 3.7 years (range 2–9). Drop foot was unilateral in 41 patients and bilateral in 5 patients.

Drop foot was assessed by determining muscle strength of the tibialis anterior using a manual muscle test and by characterizing it according to the Medical Research Council scale (Table 1).[10] A score below 3 (out of 5) was used as a cutoff since we reasoned that muscle strength grade ≥3 enabled the patient to achieve a degree of dorsiflexion in a sitting position. Tibialis anterior strength was estimated as grade 3 when patients could dorsiflex and invert their ankle in a sitting position through a full range of motion. Tibialis anterior strength was estimated as grade 3– when patients could dorsiflex and invert their ankle in a sitting position but could not achieve a full range of motion.

Patients scoring ≤3 were seen to stumble while walking in sandals or slippers. When the patient had drop foot bilaterally, the side of the weaker ankle dorsiflexor muscle was used for grading. A detailed preoperative diagnosis revealed a herniated disc in 24 patients, spinal canal stenosis in 16, degenerative spondylolisthesis in 3, isthmic spondylolisthesis in 2, and spondylolysis in 1 (Table 2). The duration of drop foot symptoms before surgery ranged from 4 to 720 days (mean 97). Most lumbar disc herniations occurred at the L4/5 level (Figure 1). Extraforaminal lesions were seen only in L5/S single herniation.

Table 1. Manual Muscle Test of Tibialis Anterior According to The Medical Research Council Scale of Muscle Strength

0	No contraction of tibialis anterior
1	Slight contraction of tibialis anterior is observed, but no joint motion of ankle
2	Patient can invert and dorsiflex ankle with gravity eliminated through full range of motion
3	Patient can dorsiflex and invert ankle against gravity through partial range of motion
3	Patient can dorsiflex and invert ankle against gravity through full range of motion
4	Patient can dorsiflex and invert ankle against gravity and moderate resistance
5	Patient can dorsiflex and invert ankle against gravity and full resistance

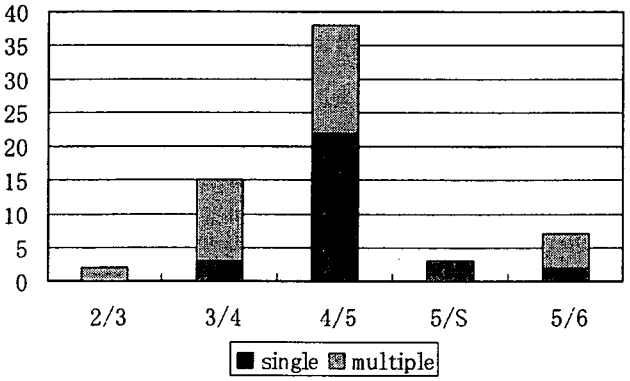

Figure 1. Compromised levels affected in drop foot. Most lumbar herniation occurred at the L4/5 level. Extraforaminal lesions were seen in only L5/S single herniation.

Lumbar surgery involved a standard discectomy in 24 patients, bilateral fenestration (laminectomy with or without discectomy) in 16, posterior lumbar interbody fusion in 5, and repair of spondylolysis in 1. Preoperative strength of the tibialis anterior was graded as 0 or 1 in 17 patients and 2 or 3− in 29. Eight patients did not complain of leg pain. Radicular symptoms were seen in 34 patients and cauda equina syndrome (defined as perineal numbness and/or bowel and bladder dysfunction) in 12. Combined radicular and cauda equina symptoms were included within the cauda equina syndrome category. The number of involved segments was multilevel in 16 cases and single level in 30.

Patients stayed in the hospital for approximately 2–4 weeks after surgery, and we examined motor recovery 4–6 weeks, 3 months, 6 months, 1 year, 1.5 years, 2 years, and every 1 year after surgery. Follow-up of the patients with complete recovery was stopped at the time of the 2-year follow-up as muscle strength would not be worsened once motor had recovered completely. Experienced orthopedic spine surgeons evaluated preoperative and postoperative muscle strength.

Surgical outcome was evaluated by recovery from tibialis anterior weakness, and ranked "excellent" when muscular strength recovered to a manual muscle test score of 4 or 5, "good" when it scored 3, "fair" when muscular strength recovered but it remained below 3, and "poor" when there was no improvement in muscular strength at the final (or latest) follow-up. We also evaluated the recovery rate of tibialis anterior strength:

postoperative tibialis anterior strength

$$-\text{preoperative tibialis anterior strength}/5$$

$$-\text{preoperative tibialis anterior strength} \times 100(\%)$$

Grade 3 minus tibialis anterior strength was calculated as 2.5.

Statistical analyses were performed to assess factors that influenced the surgical outcome (tibialis anterior strength at the final follow-up). The tests included a Mann-Whitney *U* test and multivariate logistic regression analysis using JMP 5.0 (SAS Institute Inc., Cary, NC). *P* values below 0.05 were regarded as statistically significant. Multivariate logistic regression analysis was performed with factors that were thought to be significant ($P \leq 0.2$) in the results of Mann-Whitney *U* test to gain better sensitivity. Multivariate logistic regression analysis of final diagnosis (herniated soft disc *vs.* canal stenosis) excluded 3 patients that were diagnosed as isthmic spondylolisthesis and spondylolysis. Three patients with degenerative spondylolisthesis were included in the canal stenosis group. The correlated factors studied were: final diagnosis (herniated soft disc *vs.* spinal canal stenosis); the number of involved segments (multiple *vs.* single); neurologic involvement (nerve root impairment *vs.* cauda equina syndrome); age at surgery; gender; preoperative severity of palsy (tibialis anterior 0–1 *vs.* 2–3−); leg pain; and duration of palsy before surgery.

Table 2. Diagnosis (n = 46)

Diagnosis	No. Patients
Disc herniation	24
Canal stenosis	16
Degenerative spondylolisthesis	3
Isthmic spondylolisthesis	2
Spondylolysis	1

■ Results

According to the functional motor recovery from drop foot, overall outcome was "excellent" in 19 patients (41%), "good" in 9 (20%), "fair" in 5 (11%), and "poor" in 13 (28%). Thus, at least some degree of tibialis anterior functional recovery was observed in 61% of the cases with drop foot (Figure 2). Complete restoration of

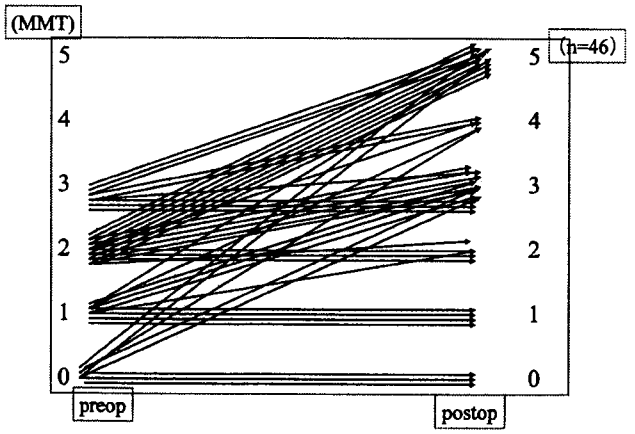

Figure 2. Tibialis anterior strength of all 46 patients. Fourteen patients had complete recovery, and 13 had no improvement after operation. MMT indicates manual muscle test; postop, postoperatively; preop, preoperatively.

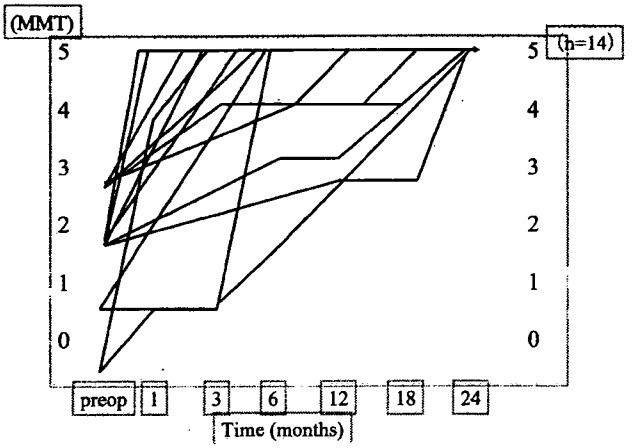

Figure 3. Progress toward recovery for each of the 14 patients who completely recovered (manual muscle test score of 5). The longest duration to recover fully was 2 years. MMT indicates manual muscle test; preop, preoperatively.

tibialis anterior strength (manual muscle test score of 5) was observed in 14 patients (30%), 4 of whom had originally presented with severe palsy and a preoperative tibialis anterior strength of 0–1. Looking into the duration to reach complete recovery of tibialis anterior, 10/14 (71%) patients recovered completely within 1 year, but 4 had progress of recovery 1 year after operation (Figure 3). The average recovery rate of tibialis anterior strength was 48.7% ± 40.8% (range 0% to 100%).

Excluding the 3 cases of ischemic spondylolisthesis and spondylolysis, we compared the surgical results of patients separated into 2 groups by diagnosis: herniated disc and spinal canal stenosis. We found no significant difference between the 2 groups ($P = 0.317$; Tables 3, 4). No significant difference was also found between the groups of single-level and multilevel compression ($P = 0.416$; Tables 3, 4) or between radicular and cauda equina symptoms ($P = 1.000$). However, when comparing age at surgery, better surgical results were achieved in younger patients, and it means that if patients would be 10 years older, surgical outcome would be poorer (relative risk: 1.48; $P = 0.027$; Table 4). In addition, postoperative tibialis anterior strength at the final follow-up had a significant correlation with preoperative tibialis anterior strength; patients scoring a preoperative tibialis anterior strength of 2–3– showing greater improvement than those scoring a strength of 0–1 ($P = 0.047$; Tables 3, 4). Eight patients in the study did not complain of leg pain. When the surgical outcomes of these patients were compared with those of patients suffering from leg pain, no significant difference was found ($P = 1.000$; Tables 3, 4). However, a significant difference was observed in surgical outcome between groups of patients suffering varying durations of palsy before surgery; the shorter duration group achieving better surgical results and odds ratio was 1.81 when duration period of drop foot doubled ($P = 0.001$; Table 4).

Multivariate logistic regression analysis was performed with these 4 factors (age, gender, preoperative tibialis anterior strength, and duration), which were thought to be significant in the results of the Mann-Whitney U test, and it revealed that duration of palsy before surgery ($P = 0.004$; Table 5) and preoperative tibialis anterior strength ($P = 0.049$) were the factors that most affected "postoperative" tibialis anterior strength.

Table 4. Statistical Analysis No. 1

	Mann-Whitney U Test		
	P	Odds Ratio	95% CI
Age: 10 yr	0.027 (n = 46)	1.48	1.04–2.16
Gender: male-female	0.167 (n = 46)	2.22	0.75–6.88
Diagnosis: lumbar canal stenosis-lumbar disc herniation	0.317 (n = 43)	0.74	0.42–1.31
Preoperative tibialis anterior: 2–3– and 0–1	0.047 (n = 46)	0.34	0.11–1.02
Segment: multiple-single	0.416 (n = 46)	1.63	0.53–5.09
Pain: present-absent	1.000 (n = 46)	0.98	0.25–3.98
Involvement: cauda equina syndrome-root	1.000 (n = 46)	1.00	0.53–1.91
Duration: 2 times	0.001 (n = 46)	1.83	1.29–2.69

CI indicates confidence interval.

Table 3. Surgical Results in Each Factor

Causal Factors	No.	Excellent	Good	Fair	Poor	P (Mann-Whitney U test)
Herniated disc	25	13	5	2	5	
Spinal canal stenosis	18	7	3	1	7	0.317
Single-level compression	30	13	7	3	7	
Multilevel compression	16	6	2	2	6	0.416
Radicular symptom	34	13	9	3	9	
Cauda equina syndrome	12	6	0	2	4	1.000
Preoperative tibialis anterior						
0–1	17	5	1	4	7	
2–3–	29	14	8	1	6	0.047
Leg pain						
Present	38	16	7	4	11	
Absent	8	3	2	1	2	1.000
Gender						
Male	27	9	5	4	9	
Female	19	10	4	1	4	0.167

Table 5. Statistical Analysis No. 2

	Multivariate Logistic Regression (R^2 = 0.17, n = 46)		
	P	Odds Ratio	95% CI
Duration: 2 times*	0.004	1.81	1.20–2.97
Preoperative tibialis anterior: 2–3− and 0–1	0.049	0.29	0.08–1.00
Gender: male-female	0.091	3.12	0.83–12.67
Age: 10 yr	0.289	1.25	0.83–1.93

*Preoperative duration of palsy.
CI indicates confidence interval.

■ Discussion

In spinal anatomy, the L4 and L5 nerve roots are distributed throughout the tibialis anterior,[11,12] and it is mainly the L4 nerve root that controls tibialis anterior movement. So, impairment of the L4 nerve root was thought to commonly cause drop foot. But in this study, the main lesion occurred in the L4/5 segment, with only 3 patients presenting with a L3/4 single lesion, and there was no extraforaminal lesion in the L4/5 segment. None of these 3 patients with L3/4 single lesion complained of radicular symptoms. In addition, if tibialis anterior would be ruled by L4 nerve root, there would be cases with drop foot due to L4 radiculopathy, but, actually, we have never experienced drop foot with L4 radiculopathy so far. From the results of the current study, we could conclude that drop foot would be mainly caused by an impairment of the L5 nerve root and that this root mainly rules the tibialis anterior.

In an investigation of cases with drop foot caused by degenerative lumbar diseases, Girardi *et al*[13] reported that no statistically significant relationship was found between the extent of recovery and age, diagnosis (herniated nucleus pulposus or lumbar spinal stenosis), duration of symptoms, or severity of preoperative weakness. In their investigation, however, the authors defined drop foot as a muscle weakness of the tibialis anterior, scoring less than 4 out of 5. The weakest tibialis anterior strength observed in a patient was 2 out of 5, while no patients presented with a preoperative tibialis anterior strength of 0–1. In our clinical experiences, patients with tibialis anterior strength of 4 out of 5 do not show drop foot at all. By contrast, we defined drop foot as a muscle weakness of the tibialis anterior scoring less than 3 out of 5, in compliance with the Medical Research Council guidelines. Moreover, 17 patients (37%) in our study presented with a preoperative tibialis anterior strength of 0–1. Focusing exclusively on those patients with a preoperative tibialis anterior strength of 2–3−, we demonstrate recovery from drop foot in 76% (22/29, 14 excellent and 8 good cases) of cases.

In a previous study on recovery from motor deficits, there are some reports concerning postoperative motor deficits as neurologic complications,[7–9] however, there are few reports concerning preoperative motor deficits. Postacchini *et al*[14] reported an inverse relationship between the severity of the preoperative motor deficit and ability to recover complete motor function in contrast to the findings of Girardi *et al*.[13] In the current study, we have found improved surgical outcome in the patients with shorter duration of palsy and higher strength of tibialis anterior, which supports the results of Postacchini *et al*,[14] and all patients who had completely recovered had palsy for 3 months or less, but there was a patient who had a 4-day duration of drop foot who did not recover at all.

Concerning the recovery process, Jonsson and Stromqvist[15] reported that most recovery occurred during the first 4 months following surgery. In the current study, we describe 14 patients who made a full recovery. Of these, the shortest duration to reach full tibialis anterior strength was 6 weeks, while the longest duration was 2 years (Figure 3). Taking these results into consideration, progress of recovery could be prospected 2 years after surgery.

A clinical question that might arise is whether to operate on a patient suffering from drop foot but without any leg pain. In the current study, 8 patients presented in this manner, 5 of which (63%) made a full recovery. There was no significant difference in neurologic recovery (P = 1.000) between these patients and those suffering from leg pain, suggesting that drop foot without radicular pain due to degenerative lumbar diseases can be treated effectively with surgery.

In the current study, age at surgery significantly affected postoperative tibialis anterior strength, and the risk increased by 1.45 times with each 10-year rise in age, as shown by a Mann-Whitney *U* test. However, the multiple regression analysis failed to show a relationship between age at surgery and postoperative tibialis anterior strength. We speculate that the significant Mann-Whitney *U* test resulted from the tendency for older age patients to have suffered a longer duration of symptoms.

■ Conclusion

Severity of palsy before surgery and duration of symptoms are considered to be key prognostic factors for successful surgery for drop foot, while compression pathology (herniated or canal stenosis), age at surgery, neurologic involvement, leg pain, and number of compressed segments have little effect on surgical outcome.

■ Key Points

- Of patients, 61% recovered from drop foot after surgery.
- Preoperative strength of the tibialis anterior and duration of palsy were factors that most affected the surgical outcome.
- Cases with painless palsy can be successfully treated with operation.

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Persistent Local Pain After Posterior Spine Surgery for Thoracic Lesions

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Abstract: Many surgeons have investigated local pain associated with posterior spine surgery for cervical or lumbar lesions. However, little information is available concerning local pain after posterior thoracic spine surgery. This prospective study was, thus, performed to investigate the frequency and clinical features of local pain after posterior spine surgery for thoracic lesions. In 29 consecutive patients undergoing posterior spine surgery for various thoracic spinal disorders, local pain was investigated before and after surgery. In all 19 patients with preoperative back pain presumably due to thoracic lesions, pain was well alleviated after surgery. In contrast, 6 patients (21%) newly developed persistent shoulder angle pain after surgery, which resembled axial pain after cervical laminoplasty. In 5 of these 6 patients surgical exposure was extended to the cervicothoracic junction, whereas persistent shoulder angle pain was independent of disease etiologies and surgical procedure, and all of the 5 patients had no other etiologies of local pain such as surgical site infections, hardware failures, pseudoarthrosis, other metastasis, and vertebral fractures. These results suggest that dissection of muscle attachments to the cervicothoracic junction would play some part in the development of persistent local pain after posterior spine surgery for thoracic lesions, although surgical exposure of the zygapophysial joints at the cervicothoracic junction might be a possible source of postoperative shoulder pain. Therefore, to minimize such surgical complications, muscle insertions into the cervicothoracic junction should be preserved as far as possible.

Key Words: thoracic spine/surgery, postoperative complication, local pain

(*J Spinal Disord Tech* 2007;20:226–228)

Local pain associated with posterior spine surgery for cervical or lumbar lesions have been investigated by many surgeons. Persistent low back pain has been one of the longstanding problems after posterior lumbar spine surgery.[1–7] Since the first report of intractable neck and shoulder pain as a noticeable complication after cervical laminoplasty by Hosono et al,[8] postlaminoplasty axial pain has come to be recognized as one of the most notorious complications.[9–13] However, to our knowledge, little information is available concerning local pain associated with posterior thoracic spine surgery. We therefore prospectively investigated the frequency and clinical features of local pain in patients undergoing posterior spine surgery for thoracic lesions and discuss herein the possible pathogenesis of persistent local pain after surgery.

MATERIALS AND METHODS

Patient Data

Between February 2001 and July 2004, 29 consecutive patients (12 men, 17 women) underwent posterior surgery for various disorders of thoracic spine in our institute. Mean age at time of surgery was 54 years (range, 31 to 81 y). Thoracic spine lesions included metastatic spinal tumor (n = 11), spinal cord tumor (n = 7), ossification of the spinal ligament (n = 5), primary spine tumor (n = 2), osteoporotic vertebral fracture (n = 2), vertebral necrosis (n = 1), and spinal pseudoarthrosis of ankylosing spondylitis (n = 1).

Surgical Procedure

Surgical procedures such as decompression and fusion were limited to within the thoracic spine in all 29 patients, whereas dissection of the paraspinal muscles was extended to the cervicothoracic junction to obtain sufficient surgical exposure in 7 patients. Details of surgical procedures were as follows: decompression and fusion with instrumentation in 16 patients; laminectomy in 4; extirpation of spinal cord tumor with instrumented fusion in 4; extirpation of cord tumor in 3; and open biopsy in 2.

Evaluation of Local Pain

Local pain such as back pain was investigated before surgery and for 6 months postoperatively. Radiating pain displaying the distinctive features of radiculopathy was excluded from this study. According to a previous report of axial pain after cervical laminoplasty, local pain was graded as severe (painkillers

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or local injection regularly needed), moderate (physiotherapy or compress regularly needed), or mild (no treatment needed).[5] Severe or moderate pain continuing for > 3 months after surgery was considered as constituting persistent postoperative local pain.

Statistical Analysis

Fisher exact probability test was used for statistical analysis (JMP 5.0.1, SAS Institute, Cary, NC). Values of $P < 0.05$ were considered statistically significant.

RESULTS

Local Pain Before Surgery

As for local pain before surgery, 19 of the 29 patients had suffered from severe or moderate back pain presumably due to thoracic spine lesions, and no patient had complained of local pain other than backache before surgery. All 19 patients with preoperative back pain experienced good alleviation by a few months after surgery at the latest.

New Persistent Local Pain Developed After Surgery

New and persistent local pain developed in 6 of the 29 patients (21%) after surgery. In all 6 patients, painful areas exclusively involved the angle of the shoulder and pain intensity increased in the sitting position and decreased in the supine position. Physical examination of them demonstrated severe tenderness around the superior angle of the scapula and active elevation of their arms increased pain intensity. Among these 6 patients, 5 patients complained of intractable shoulder angle pain persisting for 6 months after surgery. Development of persistent shoulder angle pain was independent of disease etiologies and surgical procedures. Within the study

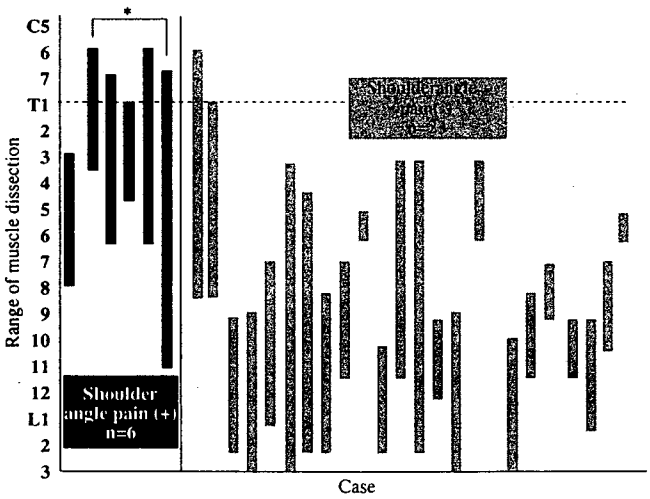

FIGURE 1. Development of persistent local pain after surgery. In 5 patients* with intractable local pain persisting for ≥ 6 months after surgery, the most cranial level of the muscle dissection was between C6 and T1.

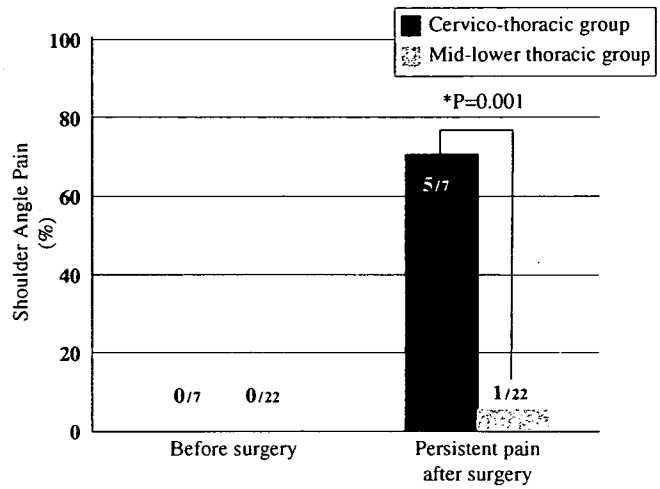

FIGURE 2. The frequency of persistent local pain after surgery. The frequency of persistent local pain after surgery was significantly higher in the cervicothoracic group than that in the midlower thoracic group (*Fisher exact probability test).

duration (6 mo after surgery), all of the 5 patients had no other etiologies of local pain such as surgical site infections, hardware failures, pseudoarthrosis, other metastasis, and vertebral fractures. These 5 patients were found to have a common factor in that surgical exposure had been extended to the cervicothoracic junction. The most cranial level of paraspinal muscle dissection was C6 in 2 patients, C7 in 2, or T1 in 1 (Fig. 1). According to the most cranial level of muscle dissection, all 29 patients were divided into 2 groups: the cervicothoracic group (most cranial level of dissection between C6 and T1; n = 7); and the mid-lower thoracic group (most cranial level of dissection below T2; n = 22). Postoperative persistent local pain developed in 5 of the 7 patients in the cervicothoracic group, but only 1 of the 22 patients in the mid-lower thoracic group ($P = 0.001$, Fisher exact probability test) (Fig. 2).

DISCUSSION

Low back pain after posterior lumbar spine surgery has long been one of the most important interests among spine surgeons.[1–7] Approximately 15% of the patients undergoing excision of a lumbar disc have suffered from persistent disabling low back pain after surgery.[1,2,5] Although the pathogenesis of low back pain associated with posterior lumbar spine surgery may be multifactorial, the frequency of persistent low back pain is significantly correlated with intraoperative back muscle injury.[3] Conversely, neck and shoulder pain, as so-called axial pain, has come to be recognized as a key complication after cervical laminoplasty.[8–13] For 25% of patients undergoing cervical laminoplasty, axial pain was sufficiently severe as to represent a continuous chief complaint after surgery.[8] Recently, many surgeons have indicated that nuchal muscles may be directly involved in

this complication.[10–13] However, few studies have examined local pain after posterior thoracic spine surgery. The outcomes of spine surgery should be evaluated using both neurologic recovery and axial symptoms.[8] The present study was thus conducted to investigate the frequency and clinical features of local pain associated with posterior thoracic spine surgery.

In the current study, preoperative back pain presumably due to thoracic lesions was well alleviated in all affected patients after posterior thoracic spine surgery. In contrast, 6 patients (21%) newly developed intractable shoulder angle pain after surgery and 5 of them complained of the pain persisting for 6 months postoperatively. Persistent shoulder angle pain was independent of disease etiologies and surgical procedures. All of the 5 patients had no other etiologies of local pain such as surgical site infections, hardware failures, pseudoarthrosis, other metastasis, and vertebral fractures within the study duration. However, development of shoulder angle pain was closely correlated with surgical exposure of the cervicothoracic junction. Even more interestingly, pain displayed clinical characteristics quite similar to axial pain after cervical laminoplasty, in that the painful area was somewhat separate from the surgical wound (the shoulder angles) and pain intensity increased in the sitting position and decreased in the supine position.[14] We recently reported a significant result in our prospective study that the detachment of muscle insertions into the C7 spinous process significantly increases the frequency of persistent axial pain after cervical laminoplasty.[15] These results suggest that dissection of the muscles attaching to the cervicothoracic junction would play some part in the development of persistent local pain after posterior spine surgery for cervical or thoracic lesions, although surgical exposure of the zygapophysial joints at the cervicothoracic junction might be a possible source of postoperative shoulder pain.[8] That is, the spinous processes of the cervicothoracic junction would play a critical role as fulcrums for shoulder suspensory muscles. The transverse portion of the trapezius muscle arises from C7 and the first 5 thoracic spinous processes, and the rhomboid minor muscle attaches to the spinous processes of C7 and T1.[16–19] Clinical characteristics of stress fracture of the spinous process also represent supporting evidence for this critical role. Stress fracture of the spinous process, as so-called Clay-shoveler fracture, is well known to usually occur between C7 and T1.[6,20–22] This is because C7 and T1 spinous processes are subject to considerable mechanical stress by the over-use of shoulder suspensory muscles. Based on these results, we speculate that postoperative persistent shoulder angle pain might be caused by shoulder suspensory muscle injury after surgical exposure of the cervicothoracic junction.

In conclusion, the present study demonstrated that persistent shoulder angle pain developed after posterior thoracic spine surgery exclusively in patients for whom muscle attachments to the cervicothoracic junction had been dissected during surgery. Such intractable local pain should be mentioned when obtaining informed consent as a possible surgical complication. Dissection of shoulder suspensory muscles would play some role in the development of persistent shoulder angle pain after posterior spine surgery, although a possible source of the pain might be surgical exposure of the zygapophysial joints. To minimize such surgical complications, muscle insertions into the cervicothoracic junction should be preserved as far as possible when the situation allows.

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Intra-Extradural Plexiform Schwannoma of the Cervical Spine

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Study Design. Case report.

Objective. To describe the clinical and radiographic features of an extremely rare case with intra-extradural plexiform schwannoma of the cervical spine.

Summary of Background Data. Plexiform schwannoma is a rare neurogenic tumor that predominantly occurs in the dermis and subcutis. Noncutaneous deep-seated lesions have rarely been described. No cases of intra-extradural plexiform schwannoma of the cervical spine have previously been reported.

Methods. A 16-year-old boy presented with a 3-month history of left neck and shoulder angle pain, motor weakness of the left upper extremity, clumsiness of bilateral hands, and mild gait disturbance. Preoperative magnetic resonance imaging showed a multinodular inhomogeneous dumbbell-shaped tumor encroaching on the cord at C3–C4. T1-weighted imaging showed the tumor as inhomogeneous with slightly higher intensity than muscle. T2-weighted imaging demonstrated a multinodular inhomogeneous tumor with much higher intensity than muscle, and each nodule of the tumor displayed a peripheral rim of higher intensity and central relatively lower intensity.

Results. Through hemi-laminectomy from C3–C4 and facetectomy of the left side of C3–C4, the intradural parts of the multinodular tumor were completely extirpated and extradural parts of the multinodular tumor were enucleated as much as possible. Gross examination of the tumor showed yellowish-white soft contents that were encapsulated and multilobulated. Histologic examination revealed benign schwannoma. After surgery, preoperative neurologic symptoms completely resolved.

Conclusion. To the best of our knowledge, this is the first reported case of intra-extradural plexiform schwannoma. Careful magnetic resonance imaging might be helpful in suggesting this rare plexiform schwannoma before surgery.

Key words: plexiform schwannoma, spinal cord tumor, magnetic resonance imaging. **Spine 2007;32: E611–E614**

Plexiform schwannoma is a rare variant of schwannoma. This tumor predominantly occurs as a slowly growing asymptomatic solitary nodular lesion in the dermis and subcutis, and noncutaneous deep-seated lesions have rarely been described.[1–11] To the best of our knowledge, no cases with intra-extradural plexiform schwannoma arising from the cervical nerve rootlet have been reported. The present report describes clinical and radiographic features of a patient with intra-extradural plexiform schwannoma of the cervical spine.

Case Report

A previously healthy 16-year-old boy presented with a 3-month history of intolerable left neck and shoulder angle pain, motor weakness of the left upper extremity, clumsiness of both hands, and mild gait disturbance. Physical examination revealed mild hypalgesia and hypesthesia of the right side of the body and right extremities. Left upper extremity muscles displayed Grade 4/5 power, and grip strength of the left hand was decreased to 12 kg. Grasp and release of the fingers within 10 seconds (10-second test) was 18 times bilaterally. All deep tendon reflexes displayed left-dominant exaggeration, and positive results were seen for Hoffmann reflex bilaterally and Babinski reflex on the left side. Gait was mildly spastic. Three small café-au lait spots were identified, but no familial history of neurofibromatosis was evident.

Preoperative radiography of the cervical spine showed a left expanding C3–C4 intervertebral foramen displaying scalloping with clear sclerotic margins (Figure 1). Magnetic resonance imaging (MRI) before surgery showed an inhomogeneous multinodular dumbbell-shaped tumor encroaching on the cord at the C3–C4 levels (Figure 2). T1-weighted MRI showed an inhomogeneous intra-extradural tumor with slightly higher intensity than muscle (Figure 2a). T2-weighted MRI demonstrated multinodular tumor with inhomogeneous and much higher intensity than muscle. Each nodule of the tumor displayed a peripheral rim of higher intensity and central relatively lower intensity (Figure 2b). The tumor displayed inhomogeneous enhancement on contrast-enhanced MRI (Figure 2c). Preoperative computed tomography after myelography (CTM) showed an intra-extradural tumor with homogeneously lower density than muscle (Figure 3a). Coronal reconstruction imaging of CTM demonstrated intradural portion of the multinodular tumor (Figure 3b).

At operation, using hemi-laminectomy from C3–C4 and facetectomy of the left side of C3–C4, an intra-extradural tumor was found arising from one of the left

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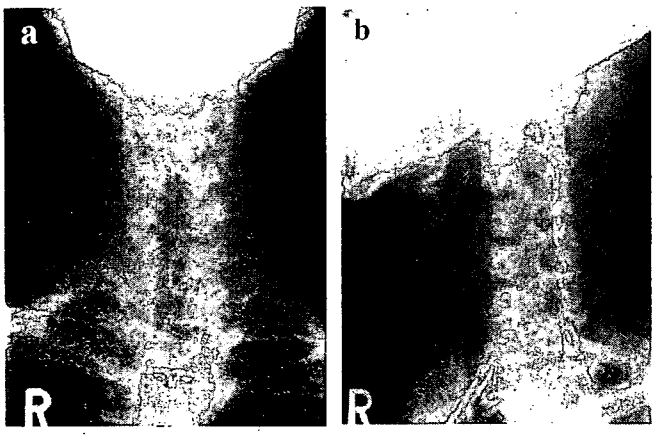

Figure 1. **a, b,** Preoperative radiography of the cervical spine shows left expanding C3–C4 intervertebral foramen with scalloping and clear sclerotic margins.

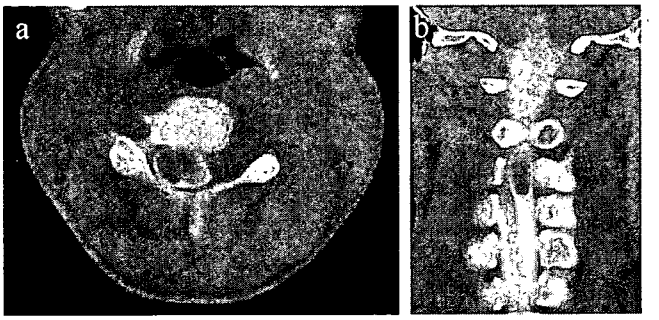

Figure 3. Preoperative computed tomography after myelography (CTM). **a,** CTM shows an intra-extradural tumor with homogeneously lower density than muscle. **b,** Coronal reconstruction image of CTM demonstrates intradural portion of the multinodular tumor.

C4 dorsal nerve rootlets. The intradural part of the tumor (2 nodules) was completely extirpated, and the extradural part of the tumor was enucleated as much as possible. Gross findings of the tumor showed yellowish-white, soft contents that were encapsulated and multilobulated. After subtotal extirpation of the tumor, C3–C4 posterior spinal fusion was performed using a unilateral lateral mass screw system (Figure 4).

Histopathologic examination revealed spindle-shaped cells arranged in short bundles with foci of nuclear palisading (Antoni A element) and relatively hypocellular lesions with a myxoid background (Antoni B element) (Figure 5). The tumor showed diffuse, uniform staining for S-100 protein. These findings were compatible with benign schwannoma.

After surgery, all preoperative symptoms completely resolved. At 1 year after surgery, the patient is doing well with no evidence of local recurrence or new lesions at any other site.

■ Discussion

Plexiform schwannoma is a rare benign neurogenic tumor. So far, close to 100 cases have been reported since Harkin *et al* described the first case in 1978.[1] Rongioletti *et al* reported that approximately 5% of schwannoma develop into plexiform schwannoma.[7] Plexiform schwannoma predominantly arises in children and young adults, and usually occurs as a slowly growing, asymptomatic, solitary nodular lesion in the dermis and subcutis.[1–9] Conversely, noncutaneous deep-seated lesions are occasionally described.[10,11] Agaram *et al* reported that about 90% of plexiform schwannomas are located superficially (dermis and subcutis), with deep-seated lesions accounting for only about 10%. In their experience, 50% of deep-seated plexiform schwannomas were located in the extremities, 12% in the pelvis, and the residual 38% in various other sites, such as the esophagus.[10] To the best of our knowledge, no cases of intra-extradural plexiform schwannoma arising from the cervical nerve rootlet have been reported. This case represents the first description of intra-extradural plexiform schwannoma of the cervical spine.

It is important to differentiate between plexiform schwannoma and plexiform neurofibroma, one of the more common plexiform neurogenic tumors and pathognomonic of neurofibromatosis Type 1, as plexiform neurofibroma is predisposed to malignant transformation but plexiform schwannoma has never been reported to develop into malignancy.[10] Histopathologic features of plexiform schwannoma are similar to those of a conventional schwannoma, but more Antoni A than Antoni B in pattern. All schwannomas are uniformly S-100 protein-positive, unlike neurofibroma, which shows patchy positivity for S-100 protein.[10,12] Although the present patient displayed 3 small café-au lait spots, neither other

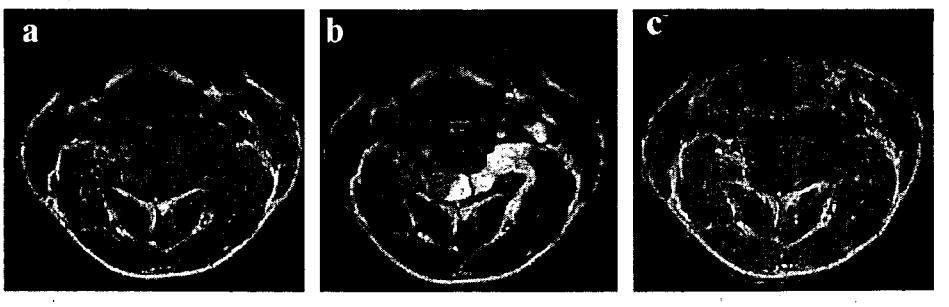

Figure 2. Preoperative magnetic resonance imaging (MRI). **a,** T1-weighted MRI shows an intra-extradural tumor with inhomogeneous and slightly higher intensity than muscle. **b,** T2-weighted MRI demonstrates a multinodular tumor with inhomogeneous and much higher intensity than muscle. Each nodule of the tumor displays a peripheral rim of higher intensity and central relatively lower intensity. **c,** The tumor displays inhomogeneous enhancement on contrast-enhanced MRI.

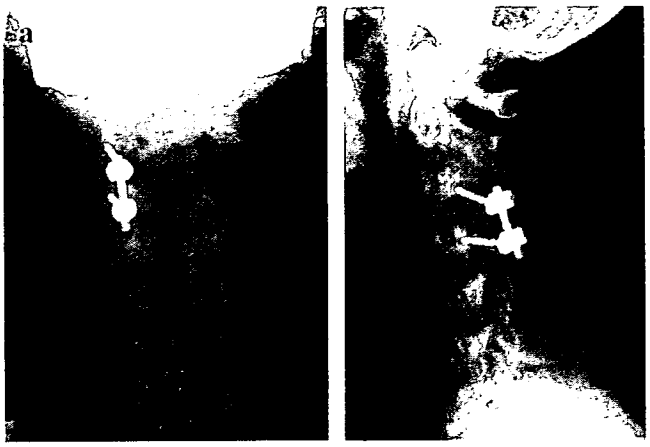

Figure 4. a, b, Postoperative radiography of the cervical spine. C3–C4 posterior spinal fusion was performed using unilateral lateral mass screw system after subtotal extirpation of the tumor.

neurogenic tumors nor evident familial history of neurofibromatosis were present. Histopathologic examination of the tumor revealed both Antoni A and B elements. The tumor showed diffuse and uniform staining for S-100 protein. These findings confirmed a diagnosis of plexiform schwannoma in the present case.

Diagnostic imaging for plexiform schwannoma has been detailed in only a few reports.[9,11] Ikushima *et al* reported that computed tomography showed a mass with homogeneously lower density than muscle and scalloping of adjacent bone with a clear sclerotic margin.[9] In that case, T1-weighted MRI demonstrated the tumor with inhomogeneous slightly higher intensity than muscle and T2-weighted MRI showed an inhomogeneous, very high intensity mass. They speculated that the ambiguous curvilinear strands of low signal intensity within the tumor on both T1- and T2-weighted MRI could be due to thin fibrous septa between individual nodules of the multinodular tumor, and could represent a valuable imaging sign of plexiform schwannoma.[9] In the case reported by Katsumi *et al*,[11] MRI revealed a multinodular irregular inhomogeneous mass, with T1-weighted MRI showing a multinodular tumor isointense to muscle. T2-weighted MRI demonstrated very high intensity and, in some nodules, a highly intense peripheral rim and central low intensity.[11] In the present case, CTM showed an intra-extradural tumor with homogeneously slightly lower density than muscle (Figure 3). T1-weighted MRI showed the tumor with an inhomogeneous and slightly higher intensity than muscle (Figure 2a) and T2-weighted MRI demonstrated the multinodular tumor with inhomogeneous and much higher intensity than muscle. Each nodule of the tumor displayed a peripheral rim of higher intensity and central relatively lower intensity (Figure 2b). These distinctive findings in the present case suggested plexiform schwannoma before surgery. Careful MRI examination might thus help to suggest rare plexiform schwannoma before surgery, although limited information has been available concerning diagnostic imaging for plexiform schwannoma.

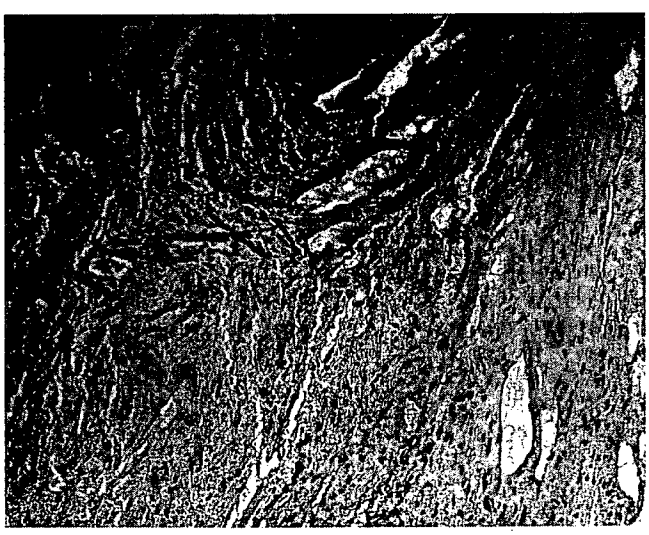

Figure 5. Histopathologic manifestations. Photomicrograph of the specimen shows spindle-shaped cells arranged in short bundles with foci of nuclear palisading (Antoni A element) and relatively hypocellular lesions with a myxoid background (Antoni B element), compatible with a diagnosis of benign schwannoma (hematoxylin-eosin, original magnification ×100).

■ Key Points

- This report describes an extremely rare case with intra-extradural plexiform schwannoma of the cervical spine.
- T1-weighted magnetic resonance imaging showed an inhomogeneous intra-extradural tumor with slightly higher intensity than muscle. T2-weighted imaging demonstrated a multinodular inhomogeneous tumor with much higher intensity than muscle, and each nodule of the tumor displayed a peripheral rim of higher intensity and central relatively lower intensity.
- Careful magnetic resonance imaging might be helpful in suggesting this rare plexiform schwannoma before surgery.

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Surgical Treatment of Cervical Kyphosis in Larsen Syndrome

Report of 3 Cases and Review of the Literature

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Study Design. A retrospective case series.

Objective. To review the surgical results for midcervical kyphosis in 3 cases with Larsen syndrome, and to discuss the choice of surgical treatments.

Summary of Background Data. Cervical kyphosis is the most hazardous and serious manifestation of Larsen syndrome due to the risk of life-threatening paralysis, and thus usually requires surgical treatment. However, little information has been reported concerning surgical treatments for this challenging condition.

Methods. Three patients with Larsen syndrome were surgically treated for midcervical kyphosis at our institution.

Results. An infant with mild cervical kyphosis was successfully treated with posterior arthrodesis using a halo immobilization, and anterior vertebral growth with a mature posterior fusion mass resulted in spontaneous correction of the kyphosis. In the remaining 2 infants with myelopathic symptoms due to severe and structural kyphosis, anterior decompression and fusion *via* a lateral approach followed by posterior fusion with segmental spinal instrumentation and halo immobilization resulted in improved neurologic symptoms and solid fusion.

Conclusions. Posterior spinal fusion is only indicated for patients with mild and flexible cervical kyphosis, and anterior decompression and circumferential arthrodesis is required for patients with severe kyphotic deformity, who usually develop myelopathic symptoms. Anterior surgery for such a small patient with severe kyphosis involves much higher risk of spinal cord injury during decompression maneuvers and difficulty in stabilization of the reconstructed cervical spine. Therefore, all patients with Larsen syndrome should be screened with radiographs at the first visit to detect cervical kyphosis early so that posterior alone fusion is possible.

Key words: cervical vertebrae/surgery, kyphosis/surgery, quadriplegia/surgery, postoperative complications, infant. **Spine 2007;32:E39–E44**

Cervical kyphosis is potentially the most serious manifestation of Larsen syndrome due to the risk of life-threatening paralysis,[1,2] and thus surgical treatment is usually indicated. However, surgical treatment for this challenging condition has only been described in a few reports.[1,3–7] The present report reviews the surgical results for midcervical kyphosis in 3 cases with Larsen syndrome, and the choice of surgical treatments is discussed.

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Case Reports

Surgery for cervical kyphosis was performed at our institution for 3 patients with Larsen syndrome between 1992 and 1999. All surgeries were performed by one of the senior authors (K.Y). A summary of data for the 3 patients is shown in Table 1.

Case 1. A male infant was noted at birth to have bilateral dislocations of the hips and knees, equinovarus deformities of the feet and typical face of Larsen syndrome. Radiography at birth revealed 64° cervical kyphosis from C3–C6, with hypoplasia of C4 and C5 vertebrae. At 9 months of age, conservative treatment using a Minerva-type brace for left-dominant quadriparesis was implemented due to progression of kyphosis to 90°. However, he gradually became seriously quadriparetic with sleep apnea and numerous recurrent respiratory infections by 2 years and 10 months. At that time, progressive kyphosis measured 110° (Figure 1a). Magnetic resonance imaging (MRI) of the cervical spine showed severe impingement on the cord at the apex of the kyphosis (Figure 1b). Because preoperative halo traction failed to reduce the magnitude of the severe kyphosis, anterior decompression with corpectomies of C4 and C5, and arthrodesis from C3–C6 using tibial strut bone grafts was performed *via* a lateral approach.

Operative Technique for Lateral Approach to the Cervical Spine. The patient was placed in the right decubitus position and a skin incision was made along the posterior margin of the sternocleidomastoid muscle (Figure 2). Fascia of the posterior triangle of the neck was bluntly dissected to identify the levator scapulas muscle. With retraction of the carotid sheath and sternocleidomastoid muscle ventrally and the levator scapulas muscle dorsally, the scalene muscles were exposed. The phrenic nerve was identified, and then the insertions of the anterior scalene muscle were carefully dissected from the anterior tubercles of the transverse processes from C3–C6 vertebrae. The longus colli and capitis muscles were also dissected from the anterior tubercles to identify anterior aspect of the cervical spine. The insertions of the medial and posterior scalene muscles were dissected from the posterior tubercles to expose the transverse processes from C3–C6. The vertebral artery and the C4–C6 nerve roots lying posterior to the vertebral artery were identified (Figure 2b). The vertebral artery was anteriorly dislocated by resecting the transverse processes from C3–C6 (Figure 2c). After exposure of lateral aspect of the cervical spine, the tight cartilaginous tissue and anterior longitudinal ligaments attaching to the cervical vertebrae were released ventrally and cut. Under surgical microscope, the lateral aspect of the dura from C4–C5 was exposed by removing left lateral masses and pedicles of the C4 and C5 vertebrae with a rongeur

Table 1. Summary of Data on the 3 Patients Surgically Treated at Our Institution

Case No.	Sex/Age (mo)	Surgical Procedure (instrumentation + immobilization)	Follow-up (yr)	Cervical Kyphosis			
				Preoperative (level) (°)	Preoperative Correction (manipulation) (°)	Postoperative (°)	Latest Follow-up (°)
1	M/34	1st: ASF (no instrumentation + halo) 2nd: ASF + PSF (SSI + halo)	13.8	110 (C3–C6)	110 (halo traction)	70	70
2	F/58	PSF (no instrumentation + halo)	8.3	60 (C3–C5)	27 (passive extension)	32	16
3	M/10	1st: PSF (no instrumentation + orthosis)*	1.6	93 (C3–C6)	—	60	146
	29	2nd: ASF + PSF (SSI + halo)	6.4	146	146 (halo traction)	117	110

Age indicates age at the operation; ASF, anterior spinal fusion; PSF, posterior spinal fusion; SSI, segmental spinal instrumentation; halo, halo vest.
*The first PSF was performed in the other institute.

and a diamond-headed airtome. This allows us to remove vertebral bodies of the C4 and C5 vertebrae including discs between C3–C4 and C5–C6 in clear visualization of the dura and nerve roots. Removal of the vertebral bodies and discs started at the middle of bodies and discs and then using with a diamond burr, the dorsal cortices of the bodies were made very thin to the width of spinal canal. Even after subtotal removal of the bodies, kyphosis was not correctable manually (push his neck at the middle). Then, inserting a thin spatula between the posterior longitudinal ligament (PLL) and the dura to avoid dural injury, the PLL was cut at the middle of the exposed area (Figure 2d). With this procedure, the vertebrae became mobile slightly, and the dura shifted ventrally. Under manual correction, a proper size of strut from tibia was inserted.

After anterior spinal fusion (ASF), kyphosis was corrected to 70° using halo immobilization. Posterior dislodgement of bone grafts occurred on postoperative day 4. Anterior revision surgery was therefore combined with posterior spinal fusion (PSF). On an urgent basis, repeated ASF was performed using morselized bone chips glued together with tissue adhesive. Posterior arthrodesis from C2–C7 with segmental spinal instrumentation (SSI) followed the anterior revision. After posterior surgery, the kyphosis remained at 70° on postoperative radiography (Figure 1c). Quadriparesis and respiratory dysfunction improved, with motor strength of the extremities recovering to Grade 3 or 4 on manual muscle testing. At 5 months after posterior surgery, fusion appeared solid and the halo vest was removed. As of 16 years of age (13 years after surgery), radiography revealed that surgical correction of the kyphosis was well maintained (Figure 1d).

Case 2. A female infant displayed dislocations of both knees, equinovarus deformities of the feet, thoracolumbar kyphoscoliosis, and a "Dish face" at birth. At the age of 1 year and 5 months, 51° cervical kyphosis from C3–C5 with hypoplastic C4 vertebra was identified. Radiography at 4 years 10 months revealed progression of the kyphosis to 60° (Figure 3a), reduced to 27° in a passive extended position (Figure 3b). Preoperative MRI of the cervical spine showed impingement on the spinal cord at the apex of the kyphosis (Figure 3c). Motor weakness was not present at that time, but hyperreflexia of the lower extremities was identified. On the basis of these manifestations, PSF from C3–C5 was performed using tibial bone grafts. Postoperative radiography in halo immobilization demonstrated kyphosis correction to 32° (Figure 3d). At 4 months after surgery, posterior fusion appeared well incorporated and the halo vest was removed. As of 8 years after surgery, the kyphosis had been further corrected to 16° due to anterior growth with solid posterior fusion (Figure 3e).

Case 3. A male infant with typical face of Larsen syndrome was noted at birth to display bilateral dislocations of the elbows, hips and knees, equinovarus deformities of the feet, and cervical kyphosis. Radiography of the cervical spine at birth showed 40° kyphosis from C3–C6, with hypoplasia of C4 and C5 vertebrae. At 10 months of age, posterior arthrodesis from C2–C7 was performed at another institute for progressive kyphosis measuring 93° (Figure 4a). Postoperative radiography in an orthosis demonstrated kyphosis correction to 60° (Figure 4b). Despite immobilization with an orthosis, the patient had gradually become seriously quadriparetic with sleep apnea. When referred to our clinic for the first time at the age of 2 years and 5 months, reconstructed sagittal images from computed tomography showed failed PSF and progression of the kyphosis to 146° (Figure 4c). MRI demonstrated severe impingement at the apex of the kyphosis (Figure 4d). Degree of the kyphosis could not be decreased by preoperative halo traction. Anterior decompression was thus performed with corpectomies of C4 and C5 and release of tight cartilaginous tissue ventral to the cervical vertebrae *via* a lateral approach, in the same way as Case 1. Anterior arthrodesis was performed from C3–C6 using glued tibial bone chips. After ASF, the cervical spine was immobilized in a halo. Posterior arthrodesis with SSI from the occiput to T4 followed ASF. Postoperative radiography showed kyphosis correction to 117° (Figure 4e). After surgery, quadriparesis and respiratory dysfunction were improved. At 6 months after surgery, solid fusion was confirmed and the halo vest was removed. As of the latest follow-up, 6 years after surgery, surgical correction of the kyphosis was well maintained (Figure 4f).

■ Discussion

In 1950, Larsen *et al* first described a clinical syndrome with a characteristic group of congenital anomalies, including anterior dislocation of the knees, dislocations of the elbows and hips, equinovarus or equinovalgus deformities of the feet, abnormalities in the hands, and so-called "Dish face."[8] Other than these anomalies, patients with Larsen syndrome frequently develop various spinal deformities, such as kyphotic deformity of the cervical spine and thoracolumbar scoliosis.[1,2,9,10] Among the various anomalies, cervical kyphosis is the most hazardous and serious manifestation of Larsen syndrome because kyphosis can progress to the point where life-threatening paralysis results.[1,2] Indeed, Micheli *et al* reported that 1 patient died at the age of 26 months because of the impingement on the spinal cord at the apex of the kyphosis. They called careful attention to