表1　患者背景と画像情報

	保存治療	手術治療	健常者
総数	133	173	44
男・女	88・45	124・49	29・15
年齢	67.1±10.1	65.8±9.7	63.9±7.9
罹病期間(年)			
しびれ発症から調査まで	7.3±5.5	10.2±7.0**	
しびれ発症から手術まで		3.2±4.4	
麻痺発症から調査まで	5.0±3.6	8.0±6.0**	
麻痺発症から手術まで		0.9±2.1	
画像			
脊柱管前後径(mm)	13.7±1.7	13.8±2.3	
MRI/T2 高輝度あり	47.3%	63.9%*	
T2 高輝度長さ(椎体)	1.8±0.8	1.6±0.8	

*：$p<0.05$
**：$p<0.01$

表2　患者報告アウトカム

	保存治療	手術治療	健常者
SF-8			
全体的健康感	42.3±7.7	45.3±8.1*1	51.1±5.6*2
身体機能	42.7±8.8	43.1±7.9	51.4±3.9*2
日常役割機能(身体)	42.6±9.3	42.7±9.4	51.8±3.6*2
体の痛み	42.4±9.0	43.6±9.4	52.3±6.8*2
活力	46.4±6.7	47.3±7.7	51.9±5.3*2
社会生活機能	43.4±9.4	43.7±9.9	53.0±4.1*2
心の健康	46.3±6.9	47.9±7.1	52.4±4.9*2
日常役割機能(精神)	44.0±10.0	45.6±10.2	52.4±3.0*2
JOACMEQ			
頚椎機能	69.5±28.6	59.2±30.8*3	90.5±17.7*4
上肢機能	83.6±20.0	80.0±19.7	99.0±2.3*4
下肢機能	72.3±27.7	67.2±27.1	97.1±8.2*4
膀胱機能	76.6±19.2	75.6±21.6	91.8±11.3*4
QOL	47.2±18.0	47.8±19.0	68.5±11.6*4

SF-8：健康関連 QOL 尺度
JOACMEQ：日本整形外科学会頚部脊髄症治療成績判定基準
*1：保存治療と比較して $p=0.04$
*2：保存治療や手術治療と比較して $p<0.01$
*3：保存治療と比較して $p=0.008$
*4：保存治療や手術治療と比較して $p<0.01$

らかさでは保存治療群で3.8±1.5，手術治療群で3.9±1.6と同等で，健常者4.7±1.5と比べると有意に体幹が硬かった($p=0.004$)．

POMSは健常者と比較すると怒り・敵意を除く5因子でストレスが高いことが示されたが，特に緊張・不安，疲労，混乱での感情ストレスが強いことが示された(表4)．

表3　旧JOA

	保存治療	手術治療
上肢運動機能	3.2±0.9	3.1±1.0
下肢運動機能	2.9±1.1	2.7±1.1*1
上肢知覚機能	1.2±0.5	1.1±0.6
下肢知覚機能	1.4±0.6	1.5±0.6
体幹知覚機能	1.7±0.5	1.6±0.6
膀胱直腸機能	2.6±0.6	2.5±0.7

*1：$p=0.029$

2. 痛みとしびれ

CPGはグレード3以上が保存治療群で約10%，手術治療群で15%を占めており，治療内容によらず活動制限を生じている割合が少なくないことを示す(表5)．疼痛強度は健常者と比べて保存治療，手術治療群ともに有意に大きかった．

身体別疼痛では頚椎疾患患者への調査にもかかわらず，腰部が保存治療群で3.7±3.1，手術治療群で3.8±2.9と最も高く，次いで頚部(保存治療3.5±2.9，手術治療3.2±2.8)と下肢(保存治療3.3±3.2，手術治療3.3±3.1)が強かった．頚部の痛みはNRS5以上の患者が36.1%であった．また頭痛が健常者と比べ両群とも強かった(保存治療1.6±2.2，手術治療1.5±1.5，健常者0.6±

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表4　Profile of Mood Status(POMS)短縮版

	保存治療	手術治療	健常者
(T得点)			
緊張・不安	48.2±9.6	47.5±10.0	43.2±8.8*3
抑うつ・落ち込み	49.4±9.6	50.1±9.5	45.3±6.8*2
怒り・敵意	47.3±9.0	48.1±9.5	44.9±6.7
活気*1：	41.2±10.1	42.1±9.2	46.2±8.8*2
疲労	48.2±8.7	47.7±9.1	44.0±6.9*3
混乱	51.9±9.3	52.1±9.9	45.8±7.6*3

*1：活気のみ高いスコアほどよい
*2：保存治療や手術治療と比較して $p<0.05$
*3：保存治療や手術治療と比較して $p<0.01$

表5　Chronic Pain Grade(CPG)のグレードと疼痛強度

	保存治療	手術治療	健常者
グレード0	7.5%	11.6%	30.6%
グレード1	45.3%	39.5%	61.1%
グレード2	36.8%	34.0%	8.3%
グレード3以上	10.4%	15.0%	0%
疼痛強度	40.0±29.0	43.4±30.0	18.7±19.0*1

*1：保存治療や手術治療と比較して $p<0.01$

1.2)．

身体別しびれでは上肢しびれ(保存治療4.4±3.1，手術治療3.9±3.2)とともに，下肢しびれ(保存治療4.1±3.2，手術治療4.2±3.2)が次に強かった．上肢しびれはNRS5以上の患者が41.4%であった．

3. 上肢しびれと関連する因子

上肢しびれと関連する因子を調べると，保存治療群では上肢機能・下肢機能・頚椎機能，さらに各ストレス因子，SF-8の各因子，SABSと相関があり，手術治療群ではさらに年齢，体重，MRIでのT2強調画像での高輝度の有無と相関があった(表6)．また満足度との関連では手術群で頚部痛みと相関があった．(Spearman相関係数0.48，$p<0.001$)

表6　上肢しびれと相関のある因子

	保存治療	手術治療
年齢	ns	.185*
体重	ns	−.195*
T2高輝度	ns	.240**
JOA 上肢運動機能	−.327**	−.477**
下肢運動機能	−.397**	−.235**
SABS*1	−.316**	−.301**
JOACMEQ 頚椎機能	−.395**	−.267**
上肢機能	−.511**	−.438**
下肢機能	−.505**	−.316**
膀胱機能	−.387**	−.212*
QOL	−.528**	−.480**
POMS 緊張・不安	.411**	.316**
抑うつ・落ち込み	.260*	.226*
怒り・敵意	.237*	.266**
活気	ns	−.257**
疲労	.475**	.327**
混乱	.299**	.279**
SF−8全体的健康感	−.593**	−.395**
身体機能	−.554**	−.324**
日常役割機能(身体)	−.556**	−.439**
活力	−.444**	−.316**
社会生活機能	−.591**	−.374**
心の健康	−.435**	−.389**
日常役割機能(精神)	−.569**	−.362**

*1：Self-Assessment Bending Scale,
*：$p<0.05$,**：$p<0.01$(Pearson　相関係数)，ns：not significant

考察・結語

たとえ早期に治療を行った場合でも感覚神経障害，すなわち痛みやしびれが改善しないことは少なくない．とくに後頚部から肩甲部にかけての痛みと上肢のしびれに対する術後の訴えは多い．今回の結果では治療の内容によらず，同程度の頚部の痛みと上肢しびれがあり，NRS5以上の強度のある患者が頚部痛みで1/3以上，上肢しびれで約4割もいた．

手術症例に関しては，後方手術という間接的除圧が多いことや，神経根への対処が不十分な可能性はある．しかし前方手術による直接除圧でもかなりの患者でしびれを訴え，QOLを悪化させるような感覚神経障害が残ることがある．これらは難治性の術後疼痛やしびれとして扱われてきたが，近年は神経障害疼痛あるいは脊髄障害性疼痛と呼ばれるようになってきた．神経障害性疼痛とは病変あるいは疾患が感覚神経への直接的影響により生じる疼痛，と定義されている[6]．その本態は

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maladaptive plasticity，すなわち障害に対する知覚神経の誤った可塑反応と考えられており[2]，障害原因がない状態や生理的な軽度の刺激でもQOL障害につながる痛みが起きている病態である．神経障害性疼痛は整形外科医が得意な侵害受容性疼痛とは異なる病態であり，非ステロイド性抗炎症薬の効果も限定的であると言われている．神経障害性疼痛には異なった治療戦略で取り組む姿勢が求められるであろう．

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CASE REPORT

Giant cell tumor of the sacrum treated with selective arterial embolization

Hitoshi Onishi · Mitsunori Kaya · Takuro Wada · Satoshi Nagoya · Mikito Sasaki · Toshihiko Yamashita

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Abstract Giant cell tumor of the sacrum is extremely difficult to manage. Standard treatments, including surgery and radiation, are associated with significant complications and recurrence rates. In this manuscript, we report an early clinical result of a case of giant cell tumor of the sacrum successfully managed with selective arterial embolization. A 56-year-old woman underwent selective embolization for management of giant cell tumor of the sacrum. Radiologically, massive shrinkage of the extraosseous mass and increased peripheral ossification were obvious. Clinically, rapid pain relief was achieved and gait disability recovered. At final follow-up 28 months after completion of treatment, she retained normal activity in daily life. We stress the effectiveness of selective arterial embolization as a less invasive and less complicated primary treatment of giant cell tumors of the sacrum.

Keywords GCT · Sacrum · Selective arterial embolization

Introduction

Giant cell tumor (GCT) of the bone is a benign neoplasm consisting of a vascularized network of spindle-shaped stromal cells surrounding multinucleated giant cells [1]. Although formally classified as benign, it sometimes behaves like a locally aggressive tumor [1]. In the sacrum, the tumor can be extremely difficult to manage [2]. Standard treatments, including surgery and radiation, are associated with significant complications and recurrence rates [3–7]. As a minimally invasive and less morbid therapeutic alternative, selective arterial embolization has been reported for treating GCTs of the sacrum [8–10]. In this manuscript, we report an early clinical result of a case with GCT of the sacrum successfully managed with selective arterial embolization. We stress the effectiveness of the procedure as being a less invasive and less complicated primary treatment for GCTs of the sacrum. The patient was informed that data concerning the case would be submitted for publication.

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Case report

A 56-year-old woman presented with severe pain in her right lower back and buttock, which severely restricted her gait. Radiographs revealed an eccentric geographic destructive osteolytic lesion in the distal part of the sacrum (Fig. 1a). Magnetic resonance images showed a massive sacral tumor arising in the sacral ala (Fig. 1b, c). A huge soft tissue mass had extended extraosseously. After these imaging studies, the patient underwent an incisional biopsy. The histological diagnosis was GCT of the bone (Fig. 2).

Intralesional embolization was performed using femoral access to selectively embolize the main arteries feeding the tumor. A catheter was advanced from the femoral artery into the internal iliac artery, and a selective angiogram was obtained to identify arteries of sufficient caliber to facilitate embolization. Injection of contrast medium showed a hypervascular, destructive tumor of the sacrum. Arteriography at the time of presentation showed markedly

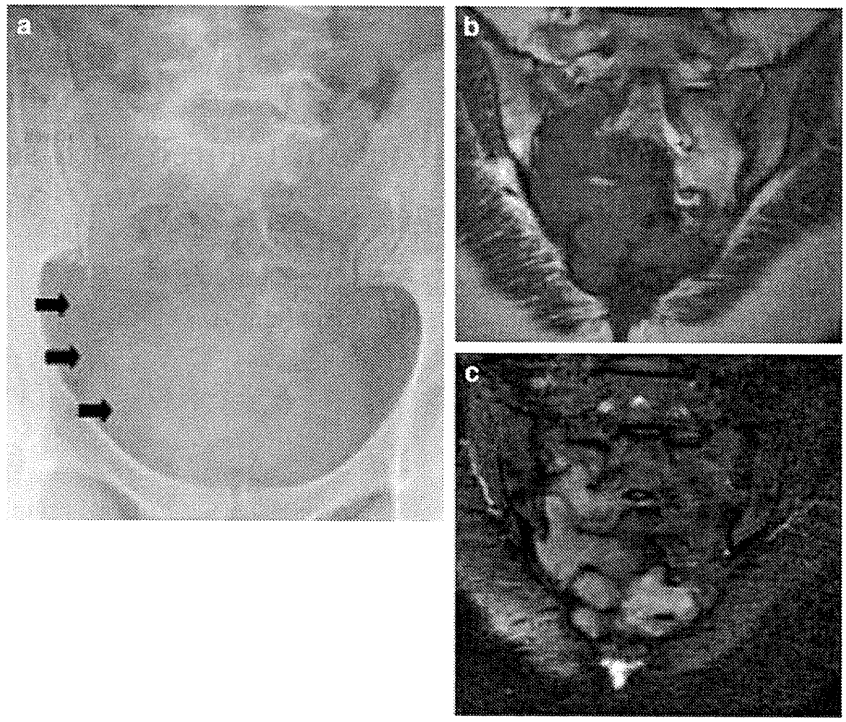

Fig. 1 **a** Radiograph of the pelvis of a 56-year-old woman with a large giant cell tumor of the sacrum (*arrow*). **b**, **c** Magnetic resonance image showing a coronal view of the tumor

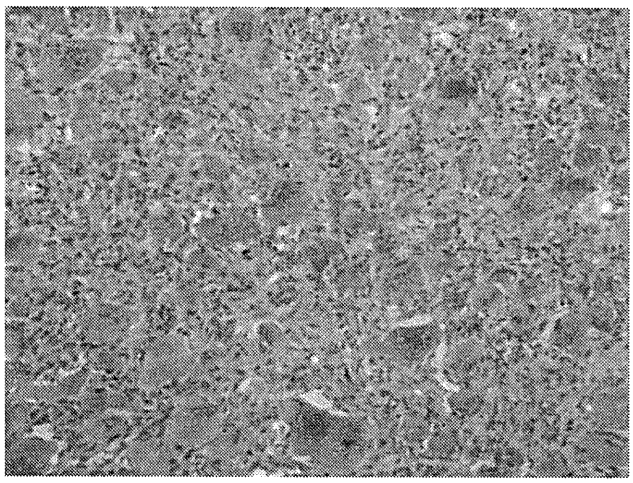

Fig. 2 Macroscopic features of pathological specimen. Typical appearance of giant cell tumor of bone with large osteoclast-like giant cells and uniform ovoid mononuclear cells

increased vascularity from the middle sacral, superior lateral sacral, inferior lateral sacral, lumbar segmental, and internal iliac arteries (Fig. 3a). These feeding branches were selectively embolized with Gelform (Astellas Pharma Inc., Tokyo, Japan). Embolization were performed every 5 weeks and the total number of the embolization were five times (Fig. 3b).

After completion of the third embolization, the patient's buttock pain improved significantly. Her gait became normal soon after completion of the fifth embolization. Computed tomography (CT) scan demonstrated massive shrinkage of the extraosseous mass and increased peripheral ossification (Fig. 4). At final follow-up 28 months after completion of the fifth embolization, radiographic and clinical signs showed stabilization and improvement (Figs. 5 and 6). The patient returned to returned to normal daily life activity.

Discussion

GCT of the sacrum is very difficult to treat. Partial and/or total sacrectomy can be an ideal therapeutic modality; however, it can result in significant morbidity, including neurological complication and infection, and mortality [3, 4]. Intralesional curettage is the most common therapeutic option for GCT of the bone, especially for lesions of the extremities [7]. However, the local recurrence rate after intralesional curettage is relatively high, and excessive intraoperative blood loss is often fatal [7]. Radiation has marginal benefit in preventing primary tumor growth and in pain control. However, it has possible deleterious local effects, including late pathologic fractures, neuritis, and radiation-induced sarcoma [7].

Because of the antiosteoclastic activity of GCT of bone, bisphosphonates were recommended for management. In vitro study has shown that bisphosphonates induce apoptosis in GCT stromal cells [11]. In addition, a recent case–control study demonstrated that bisphosphonates reduced local recurrence following surgical treatment of GCT of bone [12]. Therefore, clinical use of bisphosphonates as a conservative therapy may be warranted.

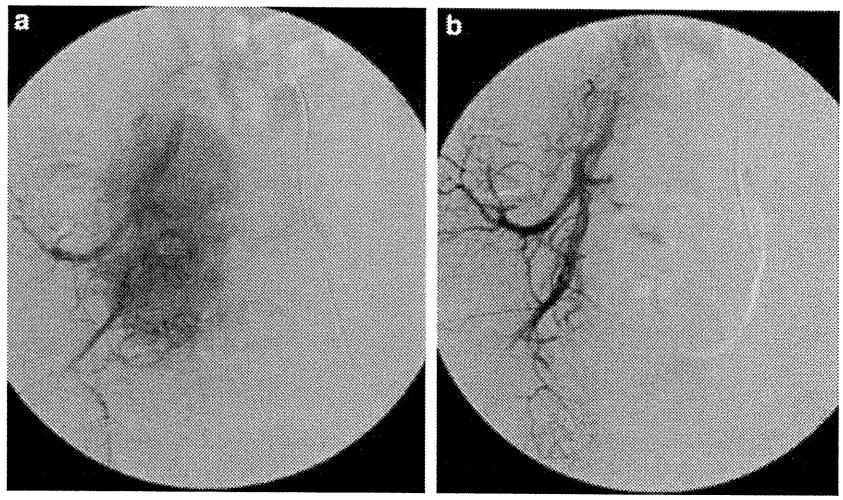

Fig. 3 **a** Arteriogram at the time of presentation shows markedly increased vascularity and uptake of contrast in the tumor. **b** Arteriogram following fifth embolization demonstrating the vascularity pattern of successful embolization

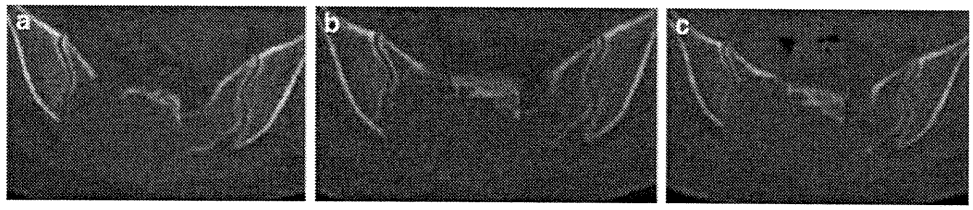

Fig. 4 Computed tomography (CT) at **a** initial presentation, **b** after third embolization, and **c** after fifth embolization. Massive tumor shrinkage and bone formation was remarkable after the third embolization, and these remodeling effects became more significant after the fifth embolization

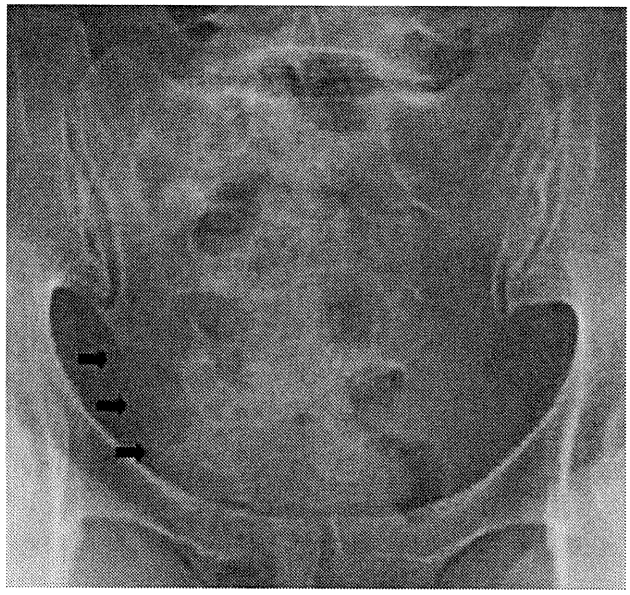

Fig. 5 Plain radiograph of sacrum 28 months after embolization shows reossification of the lower portion of the sacrum (*arrow*)

Embolization was initially used for inoperative primary or secondary bone tumors after failure of other forms of treatment [13]. Interest in arterial embolization of pelvic tumors followed its success as a palliative measure, particularly after pain resolution of pain and tumor shrinkage. As an alternative minimally invasive and effective conservative treatment for GCT of the sacrum, selective arterial embolization was introduced, and good midterm clinical results were demonstrated [6–8]. Hosalkar et al. [10] reported that seven of their nine cases had no disease progression at an average of 8.9 years of follow-up. This prompted us to employ this therapeutic modality for our patient. Although the follow-up period was short, the good outcome suggests that selective arterial embolization could be an effective, minimally invasive, and less complicated technique for this challenging disease.

Our patient exhibited a sclerotic rim of ossification and reduction in tumor size. However, it did not reossify completely, suggesting the possibility of lesion regrowth. Few published data deal with long-term follow-up of patients who undergo selective arterial embolization [8–10]. Lin et al. [8] reported the clinical results for more than 10 years of follow-up of 18 patients treated with selective intra-arterial embolization. They demonstrated that the risks of local recurrence were 31% at 10 years and 43% at 15 and 20 years and concluded that the response after embolization was durable in about one half of the patients.

Rapid pain relief is one of the greatest advantages of intra-arterial embolization for GCT of the sacrum. Typically, this GCT causes severe pain that restricts gait. Previous reports demonstrated that a large population of

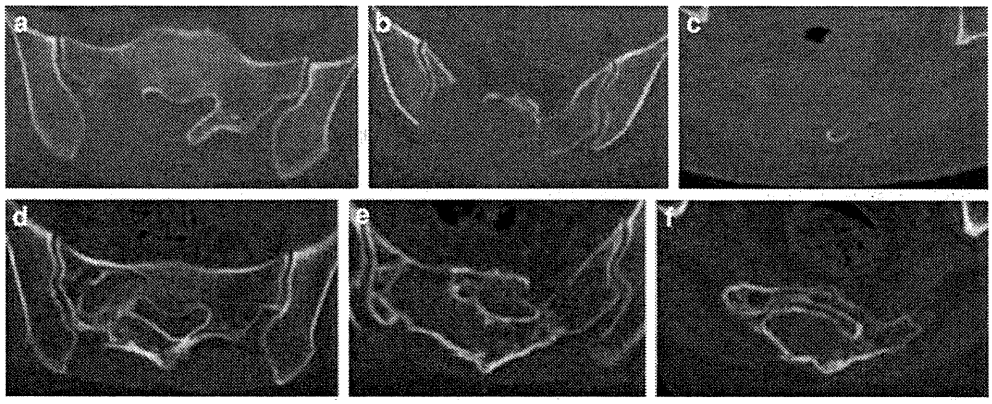

Fig. 6 Computed tomography (CT) at **a–c** initial presentation and **d–f** 28 months after five embolizations. **a**, **d** Upper part; **b**, **e** middle part; **c**, **f** lower part. Ossification is seen at the periphery. Although the mass has not completely reossified, extraosseous mass has shrunk

patients responded favorably to intra-arterial embolization, with improvement in pain [8–10]. Our patient could not walk because of severe buttock pain at first presentation. This severe pain was probably due to destruction of the weight-bearing portion of the sacrum. CT showed massive tumor shrinkage and bone formation after the third embolization, and these remodeling effects became more significant after the fifth embolization. These rapid responses to the embolization led to the rapid pain relief in this case.

Surgical treatment of sacral GCT is fraught with potential complications. Similar to previous reports, our patient had favorable clinical and radiographic response to embolization. In conclusion, selective arterial embolization can be an effective, less invasive, and less complicated primary treatment for patients with GCT of the sacrum. However, long-term follow-up is absolutely necessary because of the possibility of late disease recurrence.

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Conflict of interest statement No author has any conflict of interest.

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Subarachnoid-Pleural Fistula Treated With Noninvasive Positive Pressure Ventilation

A Two-Case Report and Literature Review

Yoshiaki Kurata, MD, Mitsunori Yoshimoto, MD, Tsuneo Takebayashi, MD, Satoshi Kawaguchi, MD, and Toshihiko Yamashita, MD

Study Design. A report on 2 cases of subarachnoid pleural fistula (SAPF) treated with noninvasive positive pressure ventilation (NPPV).

Objective. To highlight the efficacy of NPPV in patients with SAPF.

Summary of Background Data. SAPF is a rare but distressing type of cerebrospinal fluid leakage. It is known to be a complication of anterior thoracic spine surgery. The pressure gradient between the subarachnoid space and the pleural cavity maintains the cerebrospinal fluid leakage and precludes the spontaneous closure of the dura. Surgical interventions such as primary repair, patch grafts, muscle flaps, and omental flaps have been advocated. Only limited reports were found with reference to NPPV applied to SAPF.

Methods. Two patients, a 45-year-old woman and a 39-year-old woman, underwent anterior thoracic spine surgery to treat thoracic myelopathy caused by ossification of the posterior longitudinal ligament. After surgery, they developed SAPF due to perforation of the dura during surgery. Placement of thoracostomy tubes and subarachnoid drains had no effect and an NPPV device was applied.

Results. During application of the NPPV device, 14 days in the first patient and 5 days in the second patient, the raised intrapleural pressure obstructed the fluid leakage and successfully treated the fistula. No recurrence of SAPF was observed after removal of the NPPV device and the patients avoided surgical interventions.

Conclusion. SAPF is often resistant to conservative therapies and has been treated in an invasive manner. NPPV should be considered as an alternative before such interventions because it is effective, noninvasive, and safe.

Key words: subarachnoid pleural fistula, noninvasive positive pressure ventilation, anterior thoracic spine surgery, complications. **Spine 2010;35:E908–E911**

Subarachnoid-pleural fistula (SAPF) is a consequence of dural tear and cerebrospinal fluid (CSF) leakage. It develops secondary to trauma,[1–9] thoracic surgery,[10–16] or spine surgery,[17–24] and on rare occasions, spontaneously.[25] Unlike other types of CSF leakage that usually heal spontaneously or after the insertion of CSF drains, these fistulas frequently resist conservative therapies and remain open. Surgical interventions have been undertaken for such resistant fistulas. This report describes our application of noninvasive positive pressure ventilation (NPPV) in patients with SAPF that developed after anterior thoracic spine surgery.

Case Reports

Case 1

A 45-year-old woman with thoracic myelopathy was referred to our institution for surgical intervention. Ossification of the posterior longitudinal ligament (OPLL) at Th6–7 severely compressed the spinal cord (Figure 1) and caused weakness and numbness of the bilateral lower extremities.

Through the right anterior transthoracic approach, resection of the ossified lesion at Th6–7 and anterior vertebral fusion were performed. During the separation of the dura from the ossified ligament, it was punctured and leakage of the spinal fluid was observed. Direct repair of the dura could not be achieved; it was sealed with fibrin glue. A thoracostomy tube was left at the end of the surgery, and a subarachnoid drain was also placed in the lumbar spine.

Both drains were removed on postoperative day 3 when the output of each drain decreased to less than 50 mL per day. However, the patient complained of pain and discomfort in the chest, and a chest radiograph and CT revealed collection of right pleural effusion (Figure 2). Reinsertion of a lumbar subarachnoid drain was of no benefit. Thoracocentesis was performed twice, on days 9 and 23, yielding 700 mL and 1000 mL of clear, CSF-like liquid, respectively. It was diagnosed as an SAPF. On day 24, with the aim of maintaining a positive intrapleural pressure, an NPPV device with a face mask was applied to the patient. The expiratory pressure was set at 4 cm H_2O, and the inspiratory pressure at 6 cm H_2O. The patient was encouraged to wear the device for as long as she could, except during meals and bathing. The pleural effusion was absorbed and it eventually vanished during the application of the device for 14 days. After the NPPV device was removed, pleural effusion did not recur up to the 5-year follow-up (Figure 3).

Case 2

A 39-year-old woman underwent posterior decompression and spinal instrumentation of Th2–10 with pedicle

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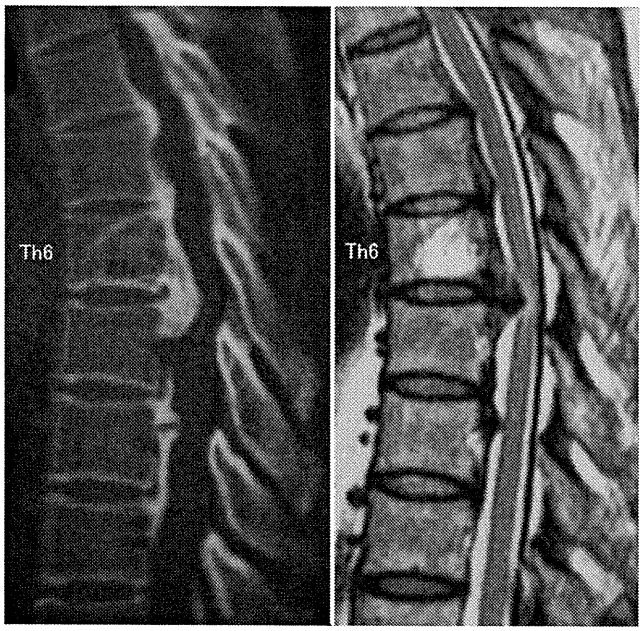

Figure 1. CT (left) and MRI (right) of case 1 demonstrating ossification of the posterior longitudinal ligament of Th4–9 and severe compression of the spinal cord at Th6–7.

screws to treat thoracic myelopathy caused by OPLL. This procedure failed to relieve the patient's symptoms; therefore, additional anterior decompression and fusion of Th5–6 were performed 6 weeks afterward.

A perforation of the dura was found during the surgery. A fat pad with fascia was put on the perforation and was augmented with fibrin glue. However, a continuous output of 150 to 200 mL per day from a thoracostomy tube was observed after the surgery. SAPF was strongly suspected. The experience of case 1 led us to use NPPV on day 10. The expiratory and inspiratory pressures were set at 4 and 6 cm H_2O, respectively. The output decreased to 50 mL per day immediately after NPPV installation; the thoracostomy tube was removed on day 14. After NPPV was discontinued on day 15, repeated chest radiographs showed no findings to suggest recurrence of SAPF.

■ Discussion

The successful outcomes of our 2 cases indicated the efficacy of NPPV in the treatment of SAPF. SAPF was first reported in 1959 by Milloy *et al*[26] and is known to be one of the complications of anterior thoracic spine surgery. There exists a mechanism to explain prolonged CSF leakage through the fistula from the subarachnoid space into the pleural cavity. The intrapleural pressure ranges from −5 to −7.5 cm H_2O, while the pressure in the subarachnoid space ranges from 10 to 15 cm H_2O. This pressure gradient not only produces a suction effect keeping CSF flow through the fistula, but consequently precludes the spontaneous closure of the dura.[22]

Massive fluid collection in the pleural cavity can cause dyspnea, chest pain, and hypoxia. Meanwhile, loss of the fluid from the subarachnoid space can lead to intracranial hypotension which distresses patients with various symptoms such as headaches, posterior neck pain and stiffness, nausea, dizziness, photophobia, and impaired hearing.[27]

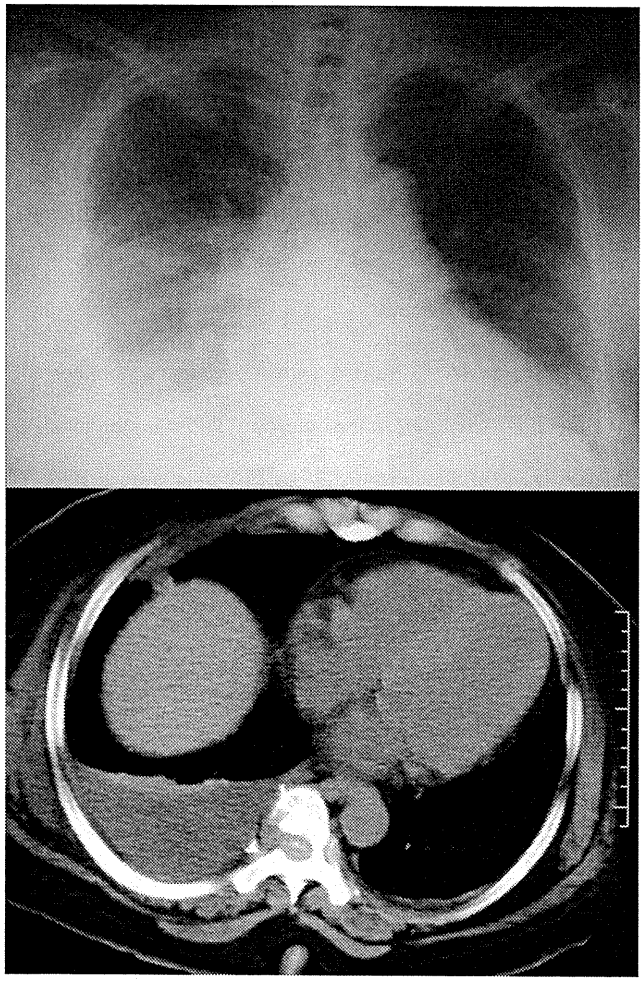

Figure 2. Postoperative plain chest radiograph (top) and CT (bottom) of case 1 on day 20 revealed massive collection of cerebrospinal fluid in the right pleural cavity.

Several authors have advocated conservative therapies for SAPF.[1,2,6,28] These include bed rest and application of a thoracostomy tube and/or a lumbar CSF drain. However, other authors have argued that early intervention in these cases is advantageous.[3–5,9,13,19] Prolonged bed rest is unsuitable for patients after spinal surgery, considering postoperative rehabilitation and also given the risk of deep venous thrombosis/pulmonary embolization. Furthermore, it is likely that a CSF drain cannot overcome the pressure gradient and a thoracostomy tube might even develop negative pressure in the pleural cavity that will prolong the patency of the fistula.

Surgical interventions such as primary repair,[19,20] patch grafts of muscle, fat, and/or fascia,[3,15,17] a cadaveric dural-pleural graft,[23] muscle flaps,[9,10,19,22] and omental flaps[18,19] have been reported with successful outcomes. Intrapleural administration of OK-432[20] is a nonsurgical but yet invasive intervention. Although most reports of SAPF cover only 1 or 2 cases, Hentschel *et al*[19]

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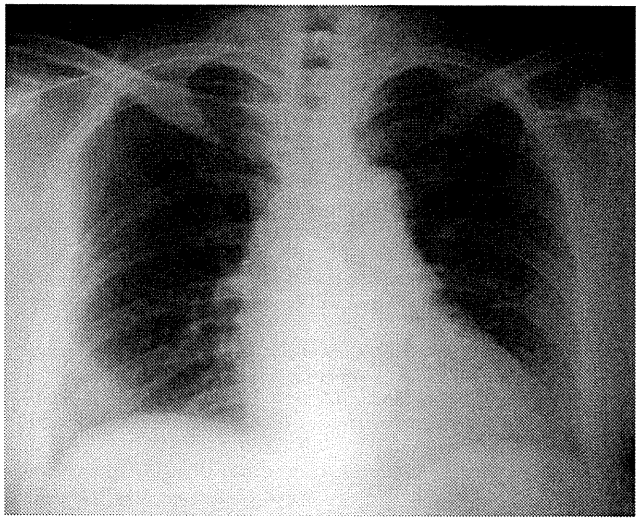

Figure 3. Plain chest radiograph of case 1 on day 50 (12 days after the removal of the noninvasive positive pressure ventilation device) demonstrating no recurrence of subarachnoid-pleural fistula.

Table 1. Patients' Characteristics and Device Settings of Noninvasive Positive Pressure Ventilation

	Age	Sex	Days Between Surgery and Device Application	Expiratory Pressure (cm H_2O)	Inspiratory Pressure (cm H_2O)	Duration (d)
Nakajima *et al*[21]	54	Female	10	N/A	N/A	7
Yoshor *et al*[24]	24	Male	9	5	10	N/A
Case 1	45	Female	24	4	6	14
Case 2	39	Female	10	4	6	5

N/A indicates not available

presented a series of 9 cases, 8 of which required open repair including 3 intercostal muscle flaps and 1 omental flap.

NPPV has been increasingly used for the treatment of acute and chronic respiratory failure, cardiogenic pulmonary edema, neuromuscular disease, and obesity-hypoventilation syndrome. Ventilatory support, including continuous positive airway pressure with or without inspiratory pressure support, is applied with the use of a full-face or nasal mask in place of an endotracheal tube.[29] NPPV was applied to our patient in expectation that the positive airway pressure would subsequently raise the intrapleural pressure and eliminate the suction effect of CSF. Cessation of CSF flow through the fistula enabled the dura to repair itself.

There have been limited reports on the application of positive pressure ventilation (PPV) to SAPF. Rena *et al*[8] reported a patient of SAPF that resulted from trauma who was intubated endotracheally and placed under PPV. Valla[16] presented an infant with SAPF after resection of a malignant tumor of the chest wall. That patient was also treated by PPV with intubation for 13 days. Samandouras *et al*[15] reported supplementary usage of mechanical ventilation for 3 days following closure of an SAPF with a pleura patch and fat pads. Although these patients recovered following the intervention, they were managed invasively with endotracheal intubation.

Only 2 reports have been found with reference to NPPV applied to SAPF (Table 1). Yoshor *et al*[24] described SAPF following thoracolumbar corpectomy and fusion for a burst fracture, which was successfully treated by NPPV with the expiratory pressure at 5 cm H_2O and the inspiratory pressure at 10 cm H_2O. Their patient underwent a similar clinical course as our patient, but the duration of NPPV application is unclear. In the other report by Nakajima *et al*,[21] a patient with thoracic OPLL underwent anterior decompression and fusion, which subsequently caused SAPF. Insertion of a lumbar drain failed to reduce the CSF leakage. NPPV was applied for 7 days with an unknown pressure setting; the authors assumed that positive intrapleural pressure obstructed the CSF leakage, successfully treating the fistula.

Appropriate length of NPPV application and pressure settings are still unknown. Although a short period causes the patient less stress, the dura needs a certain duration to repair the fistula. Fourteen days of application in case 1 was long enough, considering successful outcomes of case 2 and that of Nakajima. About 5 to 7 days of application seems to be appropriate at present, but further investigation is required. Pressure setting of NPPV is usually 3–5 cm H_2O expiratory pressure and 6 to 14 cm H_2O inspiratory pressure for patients with a respiratory dysfunction. Unlike these patients who require oxygenation and ventilation support, the aim of this therapy for SAPF patients is to maintain a positive intrapleural pressure. For this reason, the inspiratory pressure was set relatively low, while the expiratory pressure was set at the same level as that for respiratory patients. Again, further investigation is needed to determine the proper pressure setting for SAPF patients.

Some SAPFs are combined with intracranial hematomas caused by intracranial hypotension.[19,23] Conventional conservative therapies such as thoracostomy tubes and lumbar CSF drains are contraindicated in those cases because they further lower the CSF pressure and worsen the intracranial bleeding. NPPV differs from other conservative therapies considering it raises the intrapleural pressure, and can possibly be applied to such patients. But at present, SAPFs with life-threatening intracranial bleeding should be treated with surgical interventions to achieve immediate improvement without attempting NPPV, because the effect of NPPV on intracranial bleeding caused by intracranial hypotension is unknown.

NPPV has some relatively minor risks, including discomfort of a mask, skin necrosis, eye or nasal trauma, and gastric distension.[29] However, most of them can be prevented with a careful installation of the device and by a close observation of the patient. In contrast, NPPV has immense benefits. It is fully noninvasive and provides patients with a chance to avoid invasive surgical treat-

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ments. The device is small enough and can be set up by the bedside, and some devices are provided in a portable form that enables patient locomotion. When installed with a nasal mask, the patient can even talk and eat while the device is operating. The patient's daily life activity is restrained minimally by this treatment.

■ Conclusion

SAPF is an infrequent but distressing type of CSF leakage. Its unique mechanism often precludes spontaneous closure of the fistula; so far, surgical interventions have been undertaken. NPPV should be considered as an alternative before such interventions, since it is noninvasive and safe, and interferes only minimally with the patient's daily activities.

■ Key Points

- SAPF is a form of CSF leakage and one of the complications of anterior thoracic spine surgery.
- The pressure gradient between the subarachnoid space and the pleural cavity makes SAPF difficult to treat; surgical interventions have been often performed.
- NPPV successfully treated 2 cases of SAPF by raising the intrapleural pressure and blocking the fluid leakage.

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Diagnostic Features of Sciatica Without Lumbar Nerve Root Compression

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Study Design: Retrospective case series review of patients showing sciatica without radiographic evidence of nerve root compression.

Objective: To elucidate clinical features of sciatica caused by extralumbar spinal lesions.

Summary of Background Data: Sciatica caused by extralumbar spinal lesions has been reported sporadically. Given the paucity of case series studies, however, the pathology and clinical features of such sciatica remain not fully understood.

Methods: Sixty-one patients who presented with persistent sciatica were examined with lumbar magnetic resonance (MR) imaging. Of these, the records of patients showing no detectable nerve root compression in MR images were reviewed with respect to demographics, neurologic status, further diagnostic procedures, treatments, and treatment outcomes.

Results: Of 61 patients, 10 (16.4%) showed sciatica and a lack of nerve root compression in the lumbar MR imaging. In demographics, there was female sex dominance (9 patients) and right side preference (9 patients). Eight patients exhibited sensory disturbance beyond a single dermatome. Piriformis syndrome was diagnosed in 3 patients and 5 patients were considered to have sacral plexus pathologies associated with gynecologic conditions such as ectopic endometriosis, ovarian cyst, and pregnancy. A review of the literature also supported the right side preference in sciatica associated with gynecologic conditions.

Conclusions: Piriformis syndrome and gynecologic conditions account for most cases of extralumbar spinal sciatica. Female sex, right side involvement, and overlapping sensory disturbance are suggestive of extralumbar spinal sciatica associated with gynecologic conditions.

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Key Words: sciatica, gynecologic disease, piriformis syndrome

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Approximately half of all people eventually experience sciatica during their life period.[1] The majority of these sciatica cases are caused by lumbar nerve root compression secondary to discogenic disease.[2] In contrast, physicians occasionally encounter patients who present with sciatic pain, but show no radiographic evidence of lumbar nerve root compression. Such conditions have been sporadically reported in the literature as "extraspinal sciatica" where pathologies in lumbosacral plexus or peripheral nerve are suggested to be involved.[2–16] However, the paucity of case series studies has hampered our understanding of the clinical features and pathomechanisms of extraspinal sciatica. In the present study, we retrospectively reviewed 10 cases of sciatica that show no radiologic evidence of lumbar nerve root compression and discuss the characteristic features of these conditions by reviewing the literature.

MATERIALS AND METHODS

Between May 2003 and April 2004, 61 consecutive patients (30 males and 31 females) were elected for lumbar magnetic resonance (MR) imaging study due to persistent sciatica lasting for at least 2 months. The presence of sciatica was determined by pain radiating from the low back into the posterior and lateral aspect of the lower extremity[2] and positive straight leg raising (SLR) test. The result of SLR test was regarded as positive when the patients showed radiating pain extending to the lower leg by SLR of < 70 degrees.[17,18] In the lumbar MR imaging study, T1 and T2-weighted images were taken on sagittal and axial planes using a TOSHIBA 1.5T EXCELART (Pianissimo) scanner. Each intervertebral disc from L2/L3 to L5/S1 was examined with 3 consecutive slices. The MR findings were assessed by 2 orthopedic surgeons, and patients in whom nerve root compression was undetectable on lumbar MR images were enrolled into this current study. In the study, the records of patients were reviewed with respect to demographic features, associated events, neurologic

status, Freiberg sign (radiating pain extending to the lower leg by passive internal rotation of the hip joint),[19] further diagnostic procedures, treatments, and treatment outcomes.

RESULTS

Of 61 patients, 10 (16.4%) showed a lack of nerve root compression in the lumbar MR imaging despite exhibiting sciatica (Table 1). There were 9 female patients and 1 male patient with a mean age of 40 years (range: 22 to 61 y). The right side was affected in 9 patients and the left side in 1. The mean follow-up period from the initial examination was 12.5 months (range: 8 to 20 mo). There were associated events in 4 patients, including traffic accident in 1, menstruation in 2, and pregnancy (40th wk) in 1. Two patients were referred to us because their sciatica had not been relieved by lumbar surgery (medial facetectomy for lumbar spinal canal stenosis).

On physical examination, SLR test induced radicular pain at an average of 44 degrees (range: 30 to 70 degrees). Notably, in 8 patients, the area of hypesthesia included both medial and lateral side of the lower leg, meaning beyond a single dermatome. The remaining 2 patients displayed hypesthesia in only the lateral side of the lower leg. Motor weakness was found in 6 patients—both the tibialis anterior and extensor hallucis longus in 3, the tibialis anterior in 2, and the extensor hallucis longus in 1 patient. All 10 patients exhibited normal patella tendon and achilles tendon reflexes. Freiberg sign was examined in 6 patients and was positive in 3.

TABLE 1. Clinical Picture of Patients

Case	Age	Sex	Affected Side	Associated Events	Sensory Loss in the Lower Leg	Motor Loss	Freiberg Sign	Pelvic MRI Findings	Treatment	Sciatic Pain Status	Pathology
1	59	M	R	Failed lumbar surgery	Medial and lateral	—	+	Hypertrophy of the piriformis	Sciatic nerve block, piriformis excision	Disappeared	Piriformis syndrome
2	61	F	R	Failed lumbar surgery	Medial and lateral	TA, EHL	+	Retroversion of the uterus	Sciatic nerve block, piriformis excision	Disappeared	Piriformis syndrome
3	49	F	R	Traffic accident	Lateral	TA	+	Hysteromyo-ma	Sciatic nerve block	Disappeared	Piriformis syndrome
4	33	F	R	Menstrua-tion	Medial and lateral	EHL	NT	Retroversion of the uterus, fluid in Douglas pouch	Laparo-scopic resection of endome-triosis tissue	Disappeared	Ectopic endome-triosis
5	30	F	R	Menstrua-tion	Medial and lateral	TA	–	Normal	Analgesics	Decreased	Ectopic endome-triosis
6	33	F	R	Sciatica and rapid decline of muscular strength in 40th wk of pregnancy	Medial and lateral	TA, EHL	NT	Not performed	Cesarean section	Disappeared	Compression of sacral plexus by fetal head
7	54	F	R	Nothing particular	Medial and lateral	—	–	Cystic lesion in the ovary	Analgesics	Decreased	Suggestive of ovarian cyst
8	22	F	R	Nothing particular	Medial and lateral	TA, EHL	–	Retroversion of the uterus, cystic lesion in the ovary, fluid in Douglas pouch	Analgesics	Disappeared	Suggestive of ovarian cyst
9	30	F	R	Nothing particular	Lateral	—	NT	Not performed	Analgesics	Disappeared	Not determined
10	22	F	L	Nothing particular	Medial and lateral	—	NT	Not performed	Analgesics	Disappeared	Not determined

EHL indicates extensor hallucis longus; F, female; L, left; M, male; MRI, magnetic resonance imaging; NT, not tested; R, right; TA, tibialis anterior.

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MR imaging of the pelvic region was performed in 7 patients. Of these, 6 patients showed positive findings, including hypertrophy of the piriformis, retroversion of the uterus, hysteromyoma, fluid in Douglas pouch, and cystic lesion in the ovary (Table 1). All of these lesions were located in the affected side.

Upon putative diagnosis of piriformis syndrome, sciatic nerve block was performed in 3 patients who showed positive Freiberg sign (cases 1 to 3). Sciatic nerve block was effective in all these patients. However, the effect was transient in 2 patients (cases 1 and 2), for whom excision of the piriformis muscle was required for permanent pain relief. Two patients (cases 4 and 5) showed sciatica that was associated with menstrual cycle. They were suspected of having ectopic endometriosis. In the case 4 patient, there was fluid in Douglas pouch in MR imaging (Fig. 1). This patient underwent laparoscopic excision of the endometriosis tissue because of concomitant severe dysmenorrhea (Fig. 2), which resulted in relief of both sciatica and dysmenorrhea. In case 5 patient, the sciatic pain was brought under control with analgesics. Case 6 patient suffered acute onset of sciatic pain and incomplete paraplegia at the 40th week of pregnancy. Her symptoms completely disappeared after she underwent a cesarean section. Lumbar MR imaging taken after delivery showed no nerve root compression lesions. Cases 7 and 8 patients had a cystic lesion in the ovary on the affected side (Fig. 3). These lesions were potentially attributed to emergence of sciatica. Given that their symptoms were relieved with analgesics, diagnostic excision of the cystic lesion was not performed. The remaining patients, cases 9 and 10, refused to undergo pelvic MR imaging study as their symptoms gradually improved by administration of analgesics.

Example Case

Case 4

A 33-year-old woman visited the department of orthopedic surgery in our hospital with right sciatica. Neurologic examinations showed positive SLR test on the right side, motor weakness of the right extensor hallucis longus muscle, and hypesthesia in both medial and lateral side of the right lower leg. Lumbar discogenic diseases were suspected, however, lumbar MR imaging showed no evidence of nerve root compression. The patient was referred to the department of gynecology because her sciatica was associated with menstrual cycle and she had concomitant severe dysmenorrhea and pelvic MR imaging showed fluid in Douglas pouch (Fig. 1). Ectopic endometriosis was suspected and laparoscopic excision of the endometriosis tissue was performed (Fig. 2). Immediately after the operation, the leg pain completely disappeared.

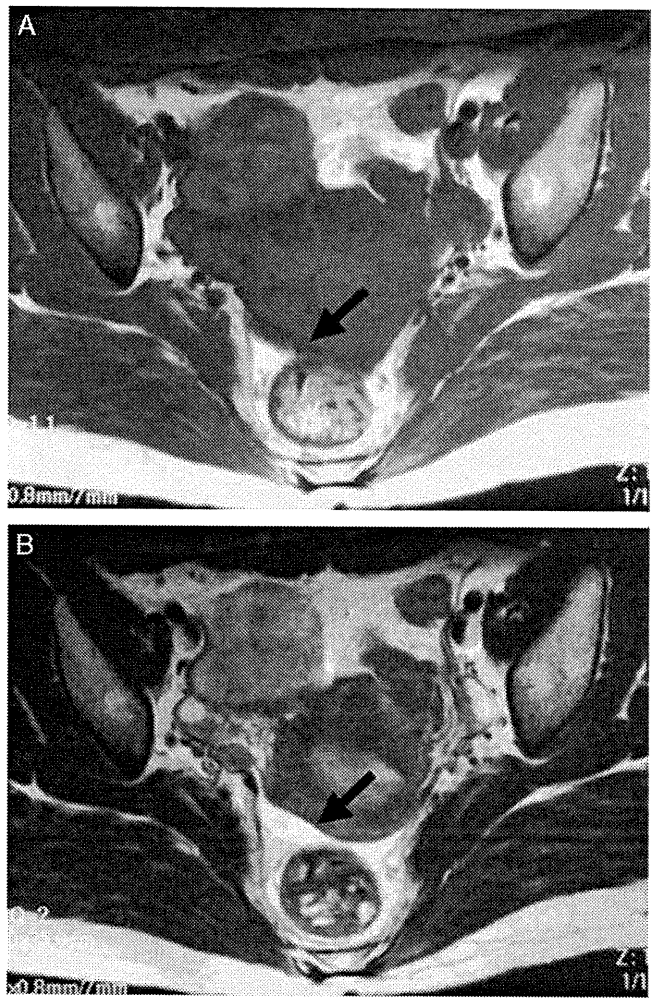

FIGURE 1. T1 (A) and T2 (B)-weighted axial magnetic resonance images of the pelvic region showing fluid in Douglas pouch (arrows).

DISCUSSION

In the present study, the authors carried out a retrospective analysis to determine the clinical features and pathology of the conditions showing sciatica and lack of nerve root compression in the lumbar MR images. Of 61 patients who showed sciatica, 10 (16.4%) were found to lack nerve root compression. These 10 patients

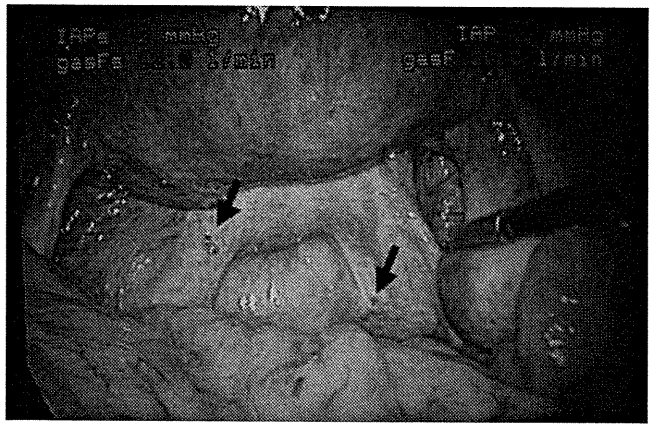

FIGURE 2. Laparoscopic findings showing endometriosis tissue (arrows).

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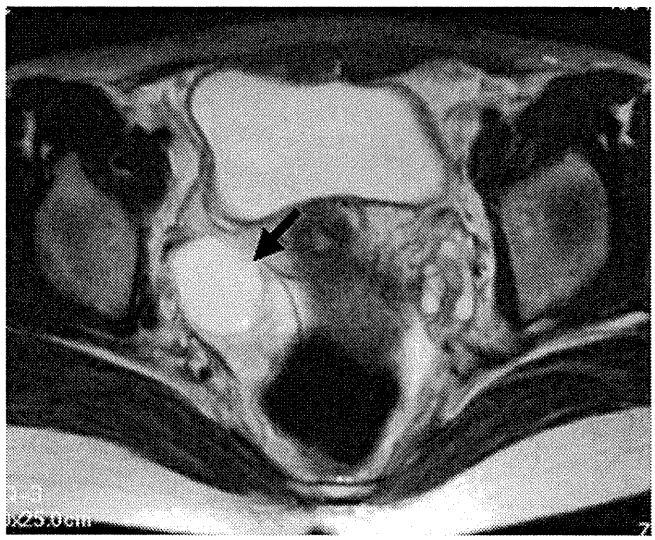

FIGURE 3. T2-weighted axial magnetic resonance images of the pelvic region showing ovarian cyst (arrow).

exhibited characteristic clinical features, including (i) dominance of female sex (9 patients), (ii) right side preference (9 patients), and (iii) sensory disturbance beyond a single dermatome (8 patients). Subsequent evaluations revealed compression of sciatic nerve by piriformis muscle (3 patients) and the sacral plexus pathologies associated with ectopic endometriosis (2), ovarian cyst (2), and pregnancy (1). The incidence of sciatica without radiographic evidence of nerve root compression was higher than expected. It is suggested that such cases have been easily forgotten because of pain relief only after administration of analgesics. Actually, pain had been relieved by analgesics in 5 cases in the current study.

Since the first description of piriformis syndrome in the year 1928,[20] additional cases have been reported in the literature.[3,19,21–23] Symptoms of piriformis syndrome and lumbar vertebra diseases are very similar. Despite the introduction of Freiberg sign and Pace test,[21,23] discrimination of piriformis syndrome from lumbar vertebra diseases is often difficult, particularly in cases with radiographic evidence of nerve root compression. In fact, 2 out of the current 3 patients with piriformis syndrome had previously been misdiagnosed and had undergone lumber surgery. These 3 patients were positive for Freiberg test. In addition, sciatic nerve block was proved to have diagnostic and therapeutic values in these patients. Of note, case 1 patient exhibited hypertrophy of piriformis muscle in MR imaging and division of piriformis muscle into 2 lobes with the sciatic nerve running between them in operative findings.[24] Involvement of such anatomic abnormality of piriformis muscle has also been reported.[25–27] Case 2 patient did not exhibit anatomic abnormality in operative findings.

With respect to the gynecologic conditions, involvement of ectopic endometriosis,[4–7,9,13,16] ovarian cysts,[10–12] and pregnancy[28,29] in development of sciatic pain has also been reported (Table 2). Concurrency of sciatica with the menstrual cycle, proposed as cyclic sciatica,[30] was a diagnostic finding in 2 of the current cases. It should be noted that in the case 4 patient, there was no direct contact between the endometriosis tissue and the sacral plexus as determined by laparoscopy (Fig. 2). Nevertheless, excision of the endometriosis tissue led to complete pain relief. Similar cases have been reported by others.[6,7] Vilos et al[6] discussed the possibility of sciatica being caused not by direct pressure on the sacral plexus, but by stimulation of the sacral plexus owing to inflammation of the retroperitoneum. Actually, there were laparoscopic findings suggesting inflammation of the retroperitoneum, such as hemorrhagic ascites, adhesion of uterine appendages, intestine, and pelvic wall in our case.

Two patients with ovarian cyst did not undergo excision of the cyst. Therefore, it remains uncertain if the ovarian cyst was the real pathology of sciatica. Nevertheless, the authors previously reported their experience in another hospital, where excision of the ovarian cyst resulted in relief of sciatica in 3 patients.[12] Also, there are 2 other similar cases in the literature.[10,11]

Sciatica caused by pressure on the lumbosacral trunk from the fetal head has been described in gynecologic text books[28,29] where the femoral nerve, obturator nerve, and very occasionally, the lateral femoral cutaneous nerve are also supposed to be

TABLE 2. Affected Side in Sciatica Caused by Gynecologic Disease

Disease	Authors	Affected Side		
		Right (cases)	Left (cases)	Bilateral (cases)
Ectopic endometriosis	Vercellini et al[16]	41	20	2
	Inaba et al[13]	1		
	Koide et al[9]	1		
Retroversion of the uterus	Murata et al[14]	1		
	Kono et al[15]	1		
Adenomyosis	Al-Khodairy et al[4]	1		
Tuboovarian abscess	Andrews et al[8]	1		
Ovarian cyst	Kanaya et al[12]	3		
	Bailly et al[11]	1		
	Le Bouedec et al[10]	1		
Total		52 (70%)	20 (27%)	2 (3%)

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compressed by the fetal head. In the case 6 patient, her symptoms completely disappeared after she underwent a cesarean section. Accordingly, the pathology was considered to be compression of the lumbosacral trunk caused by the fetal head.

The patient population in this study was biased in terms of both sex (9 females) and affected side (right side in 9 patients). Table 2 summarizes previously reported cases of sciatica caused by gynecologic diseases for which the affected side is documented.[4–16] As depicted, 52 (70%) out of these 74 cases were affected on the right side. It is suggested that the sigmoid colon plays a role in prevention of pressure on or stimulation of the sacral plexus on the left side.[16] With respect to piriformis syndrome, there was no apparent side preference according to the literature.

In the present study, MR imaging was used for screening of lumbar spinal lesions causing lumbar nerve root compression. In this regard, the negative predictive value of MR images for lumbar disc herniation and spinal stenosis has been reported to be more than 80%.[31] Therefore, for patients who show sciatica without findings of lumbar nerve root compression on MR images, it seems reasonable to assume the presence of lesions in lumbosacral plexus or sciatic nerve. In addition, attention should be paid to spinal nerve, distal to dorsal root ganglion. In the current study, extreme lateral lumber disc herniation was ruled out by axial planes of MR images. However the possibility of some spinal nerve lesions, such as far out syndrome, still remained to be ruled out.

On the basis of the present study, we propose an algorithm for the diagnosis of sciatica without radiographic evidence of nerve root compression. When there is a lack of lumbar nerve root compression, attention should be paid to pathways distal to the nerve root, including spinal nerve, lumbosacral plexus, and sciatic nerve. If neurologic examinations suggest single nerve root involvement, some spinal nerve lesions, such as extreme lateral disc herniation or far out syndrome, should be suspected first. If no spinal nerve lesion is found or neurologic examinations suggest multiple nerve root involvement, some intrapelvic or pelvic outlet lesions should be considered. Particularly in female patients affected on the right side, some gynecologic lesions should be suspected. Therefore, information about gynecologic conditions such as pregnancy, concomitant dysmenorrhea, and cyclicity of sciatica is important. If piriformis syndrome is suspected on the basis of Freiberg sign or Pace test, sciatic nerve block should be performed because of its diagnostic and therapeutic values. MR imaging of the pelvic region should be taken because of its usefulness for detection of some gynecologic abnormalities such as ovarian cyst, fluid in Douglas pouch, and retroversion of the uterus, and also abnormalities of piriformis muscle.

Given the lack of consensus regarding the pathologic linkage between gynecologic lesions and sciatica, gynecologists do not generally accept the efficacy of resection of these gynecologic lesions for relief from sciatica. It is important to accumulate evidence in this regard to better understand the significance of the gynecologic pathology of sciatica.

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脊髄損傷後の軸索再生制御機構の解明と軸索再生促進へのストラテジー

Strategy for elucidating the mechanism controlling axonal regeneration and achieving enhanced axonal regeneration after spinal cord injury

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概　要

哺乳類成体中枢神経系のニューロンの軸索は末梢神経系のニューロンの軸索に比して再生能に乏しいが，その理由の１つとして中枢神経系の損傷部においては軸索の再生を阻害する様々な因子が存在するという事が挙げられる．一方，中枢神経系においては末梢神経系に比して損傷を受けたニューロンの軸索の intrinsic な再生能自体が乏しいという側面もあり，これらの軸索再生制御機構を分子生物学的に解明する事は，脊髄損傷等の中枢神経系の損傷後に，より良い軸索の再生を得るためには極めて重要な課題の１つであり，本稿ではこれらの事項に焦点を当てて概説する．

Key Words：conditioning lesion，intrinsic growth ability，軸索再生阻害因子，ミエリン関連蛋白質，Semaphorin 3A

背　景

哺乳類の成体中枢神経系のニューロンの軸索は末梢神経系のニューロンの軸索に比して再生能に乏しい．その理由の１つとして，中枢神経系の損傷部の環境による，いわゆる extrinsic factor（外的要因）が挙げられ，大別すると，(1)ミエリン debris 中に存在する種々のいわゆるミエリン関連蛋白質と，(2)瘢痕組織中に存在する種々の細胞外基質の２つが主な軸索再生阻害因子であると考えられて来た（図１）．一方で，これらの extrinsic factor の作用は，損傷を受けたニューロンの軸索側の intrinsic な伸長能を適切な手段により促進させる事により，少なくとも部分的には相殺可能なものである事も示されて来た．したがって，中枢神経系軸索の損傷後の再生能力は，損傷を受けたニューロンの軸索側の intrinsic な再生能と損傷部環境側の extrinsic な軸索再生阻害因子の力のバランスによって決まって来るものと考えられる．

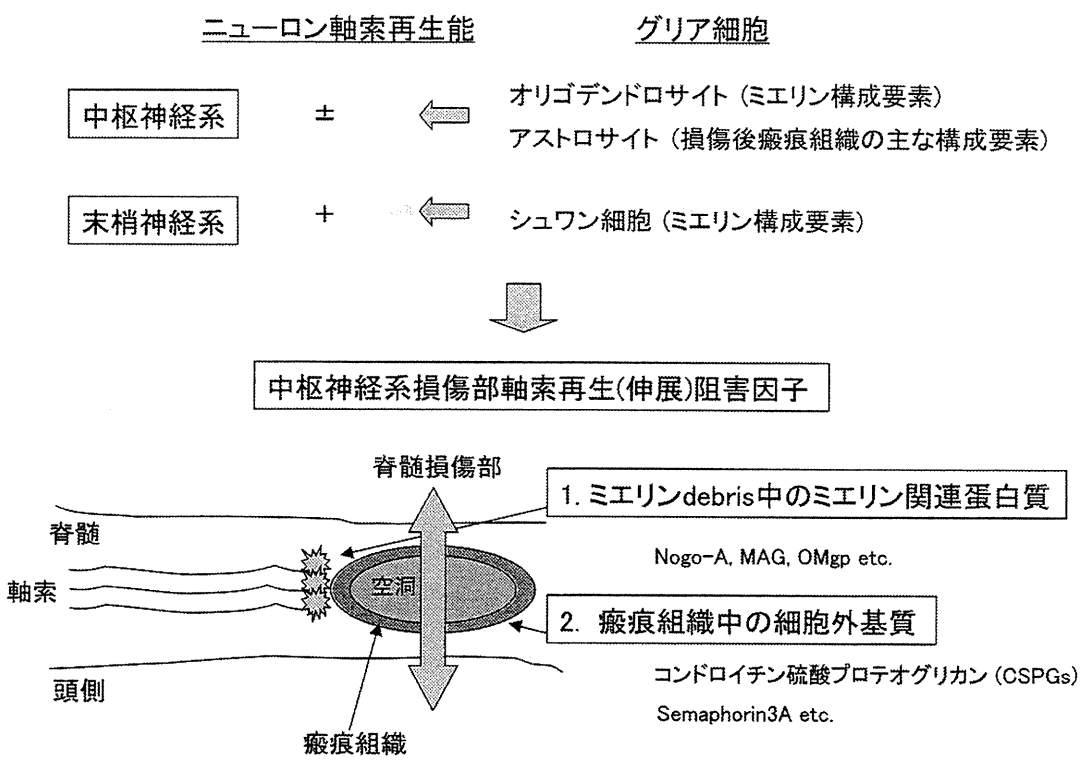

図1　末梢神経系と中枢神経系のニューロン軸索再生能の相違と構成要素の相違の関係／中枢神経系における様々な軸索再生（伸展）阻害因子
末梢神経系と中枢神経系のニューロン軸索再生能の相違は，その構成要素の相違などとも密接な関係がある．中枢神経系に存在する様々な軸索再生阻害因子は，主に，(1)損傷部ミエリン debris 中等に存在する種々のミエリン関連蛋白質と，(2)損傷部瘢痕組織中に存在する種々の細胞外基質の2つに大別される．

1．軸索再生制御機構の解明の手掛かり

これらの相互関係を解明する上で，ひいては軸索再生制御機構そのもののメカニズムに関する研究を進めていく上で非常に有用なモデルとして知られているのが，後根神経節（dorsal root ganglion；DRG）のニューロンを用いた conditioning lesion model である．DRG ニューロンの特徴として，末梢組織に innervate していく末梢側の枝と脳幹部まで脊髄内の dorsal column の中を走行していく中枢側の枝と，2本の軸索を DRG 内にある細胞体から伸ばしているという点が挙げられる（図2）．興味深い事に，末梢側の軸索（枝）は損傷後の再生能が高いのに比して，中枢側の軸索（枝）は損傷後の再生能が低く，同じ細胞体に由来する2つの軸索の再生能の違いという点が，軸索再生のメカニズムを調べる上で，非常に有用なモデルとなっている要因の1つである．さらに興味深い事に，末梢側の軸索（坐骨神経）に先に損傷を加えた後に，中枢側の脊髄の dorsal column に損傷を加えると，通常はほとんど再生しない中枢側の軸索の有意に促進された再生が認められ，これがこの系におけるいわゆる“conditioning lesion”の効果と呼ばれるものである[1]（図2）．実際，軸索再生のメカニズムを調べる上で，conditioning lesion の様に一貫して劇的な軸索再生促進効果が認められるモデルが現時点では他にほとんど知られていないため，本稿のテーマである軸索再生における分子生物学的制御機構を研究していく上で，非常に有用な貴重なモデルとなっている．

2．extrinsic factor としての軸索再生阻害因子とそのシグナル伝達のメカニズムの解明

1）ミエリン debris 中に存在する軸索再生阻害因子（ミエリン関連蛋白質）

いわゆる extrinsic factor としての軸索再生阻害因子としては，先程述べた如く，損傷部のミエリン debris 中に存在する種々のミエリン関連蛋白質と，損傷部瘢痕組織中に存在する種々の細胞外基質の2つに大別されるが，前者として，Nogo-A[2,3]，MAG[4,5]，OMgp[6] などの分子が，後者としてコンドロイチン硫酸プロテオグリ

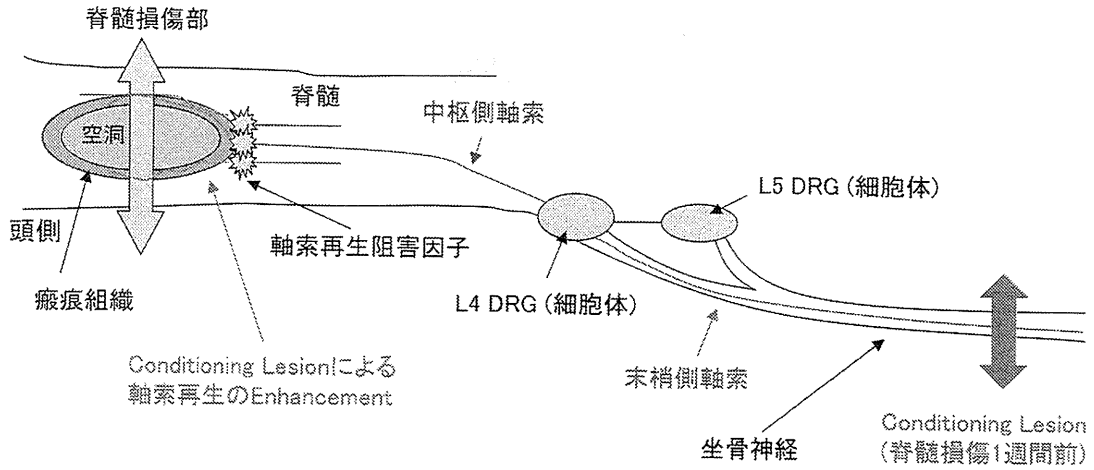

図2　後根神経節（DRG）ニューロンにおける conditioning lesion モデル
後根神経節（DRG）ニューロンは，(1)中枢側と末梢側に再生能の異なる2つの軸索（枝）を持っている，また，(2)脊髄損傷を加える約1週間前に坐骨神経（末梢側の枝）に損傷を加えておく（conditioning lesion）事により脊髄損傷後の脊髄 dorsal column（中枢側の枝）における再生が促進される，という2点において軸索再生のメカニズムを調べる上で非常に有用な系である．

カン（CSPGs）[7] や Semaphorin3A[8,9] などの分子が同定されてきた（図1）．本稿においては，これらについての詳細は紙面の制限の都合上，割愛するが，前述の Nogo-A[2,3]，MAG[4,5]，OMgp[6] の3分子は，大変興味深い事に，構造上全く異なる分子でありながら，共通のレセプター，Nogo Receptor[10] に ligand として結合する[4-6,10]事が明らかにされ，その co-receptor として同定された p75[11-13]，TROY[14,15]，LINGO-1[16] などを通じて，軸索再生（伸展）阻害のシグナルを細胞内に伝達して行くというメカニズム（図3）が解明された事から，これらの分子のノックアウトマウスを用いた脊髄損傷モデルにおける軸索の再生能を調べる研究に近年，多くの研究者達の興味が集まった．しかしながら，Nogo-A[17-19]，Nogo-Receptor[20,21]，p75 のノックアウトマウスを初めとして，これらのシグナル伝達系に関与する分子群のいずれのノックアウトマウスにおいても（研究室間でやや結果が異なるような要素も存在するものの基本的には）期待された程の劇的な軸索の再生は認められず[17-21]，これらの結果から，瘢痕組織中の細胞外基質としての軸索再生阻害因子の役割やニューロンの軸索側の intrinsic な伸長能のメカニズムの解明といった方向に，現在の研究の中心は移行しつつある．

2）　損傷部瘢痕組織中の軸索再生阻害因子

中枢神経系損傷部瘢痕組織中に存在する細胞外基質としての代表的な軸索再生阻害因子のうち，グリア瘢痕組織中に存在する CSPGs に関しては，その機能を減衰させる薬剤（chondroitinase-ABC）による軸索再生促進効果に関する報告[22]を初めとして，軸索再生を阻害する分子としての重要度に関する様々な報告がこれまでにも成されて来たが，主に fibroblast（線維芽細胞）による瘢痕組織中に存在する Semaphorin3A に関する同様の報告に関しては，これまで詳細には成されて来なかった（図3）．

すなわち，Semaphorin3A が脊髄損傷後の軸索再生を阻害する分子として重要な役割を果たしている可能性としては過去にも示唆されて来たが[8,9]，Semaphorin3A のノックアウトマウスの致死性の高さなどが原因となり，それを直接的に証明する報告は成されて来なかった．そこで我々は大規模なスクリーニングにより Semaphorin 3A に対する阻害活性および選択性の極めて高い薬剤，SM-216289 を開発し，Semaphorin3A の損傷後の脊髄内における役割に関する薬理学的なアプローチによる解明を試みた[23]．その結果，SM-216289 の投与により脊髄損傷後の，損傷部における軸索再生の促進，損傷部へのシュワン細胞の migration の促進と再生軸索に対する末梢神経型の髄鞘形成の促進，損傷部におけるアポトーシスの抑制，損傷部における血管再生の促進，さらにはこれらとの因果関係が示唆される運動機能の回復の有意な促進などを認め，Semaphorin3A 阻害薬の脊髄損傷の治療に対する有効性が示唆されるとともに，損傷後の脊髄内において，Semaphorin3A は様々な再生反応を阻害する因子として中心的役割を果たしている可能性が示唆された[23]．

以上，ここで挙げて来たそれぞれの分子の軸索再生阻害因子としての重要度（関与の度合い）に関して，それ