

Pathogenesis of Cervical Myelopathy in Chronic Cervical Cord Compression Model of Rat

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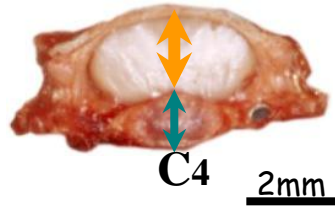
BACKGROUND

In previous studies, Various methods have been tried to induce chronic cord compression.

Compression methods	Authors	Compression course	Stenosis	Invasion in the spinal canal
Screw	Shinomiya et al., 1992 ¹⁾	More than 6 months (1 mm / week)	Almost 50%	+
	Hoshino et al., 1999 ²⁾		70%	+
Epidural tumor	Manabe et al., 1989 ³⁾	13-18 days	?	-
Expanding sheet	Kim et al., 2004 ⁴⁾	24 hours - 17 weeks	12%	+
Twy (tip-toe walking Yoshimura) mouse	Yamazaki M., et al.,1991 ⁵⁾	1-6 month	70%	-

Various methods have been undertaken to induce spinal cord compression. These include transplantation of tumor cells, placement of screws with gradual tightening, implantation of an expanding sheet, a combination of vascular ligation plus screw compression, and the tiptoe-walking Yoshimura (twy/twy) mouse. These models had various difficult problems; the time course of these tumor models was too rapid, epidural tissues were injured during the direct implantation of the sheet or screws placement, and the compression site of twy-mouse could not select without C1-C2 vertebral level.

➤ Cervical development of rat

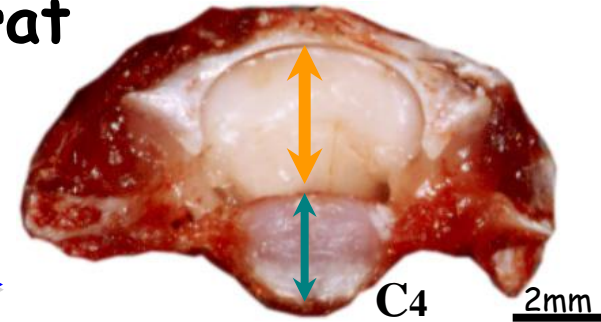


3 weeks old rat
BW.: 50g

APD of spinal canal:
1.8 times.

APD of vertebral body:
1.9 times

(APD= Anteroposterior diameter)



1 year old rat
BW.: 800g

[Hypothesis]

If surroundings of cervical spine are concluded with the string at 3 weeks old, spinal canal could not expand any more and the vertebral body could expand during development. After 1 year, the spinal canal would be locally narrowed.

PURPOSE

To produce a new model of chronic cervical cord compression satisfying following appropriate conditions*, and to evaluate motor and sensory functions, MR image and histopathological examination.

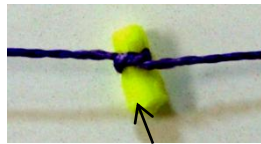
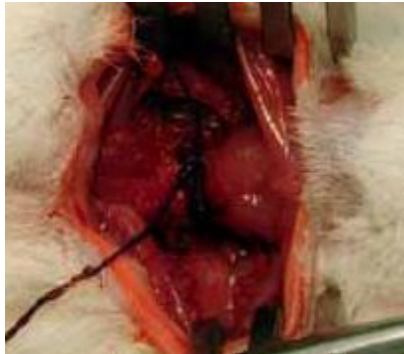
* An appropriate model for the pathophysiology of chronic cord compression should be exhibit a latency period after induction of compression with insidious onset of neurological dysfunctions, followed by a phase of progressive disturbance.

METHODS

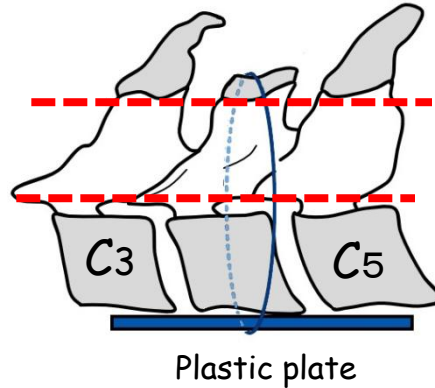
➤ Production of chronic cervical cord compression model

3 weeks old SD rat: Control rat: N=10

Model rat: N=10

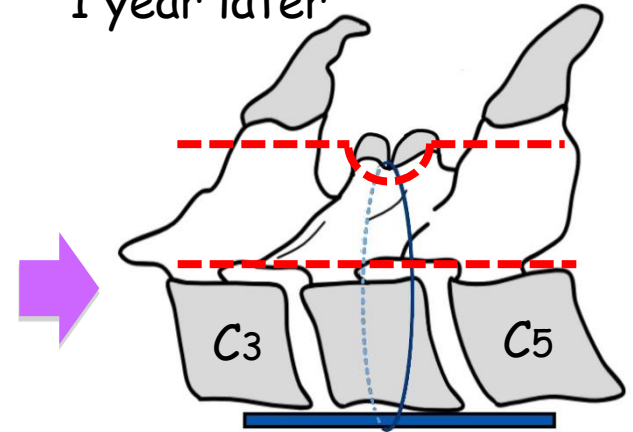


PE line + plastic plate



Fastening 3 laps around C4 using polyethylene (PE) line and plastic plate

1 year later



➤ Examination: <After 3 month, 6 month, 1 year>

◆ Behavioral assessment

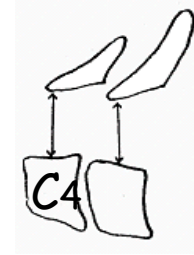
- **The Basso, Beattie, and Bresnahan (BBB) scale**
- **Treadmill test** • The maximum treadmill speed.
 - After warming-up in 5 m/min for 1 minute, the speed was increased 1m/min by 5 seconds.
- **Sensory assessment** • von Frey filaments
 - 100g hair was applied until buckling for 3 sec, 10 times.
 - Recorded the number of times of the escape response.



ICC: 0.743
(normal rat, n=5)

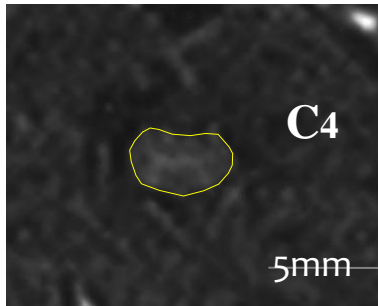
◆ Radiological assessment

- Measurement of antero-posterior distance (APD) of spinal canal
 <Burrows et al., 1963>



◆ MR imaging after 1 year

- **Transverse area of spinal cord**
 <Axial T1-w MR imaging>



Transverse area: 12.3 mm²

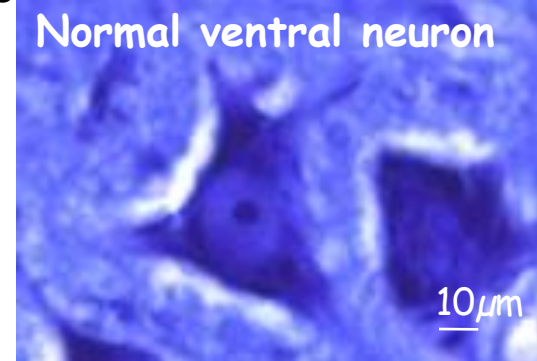
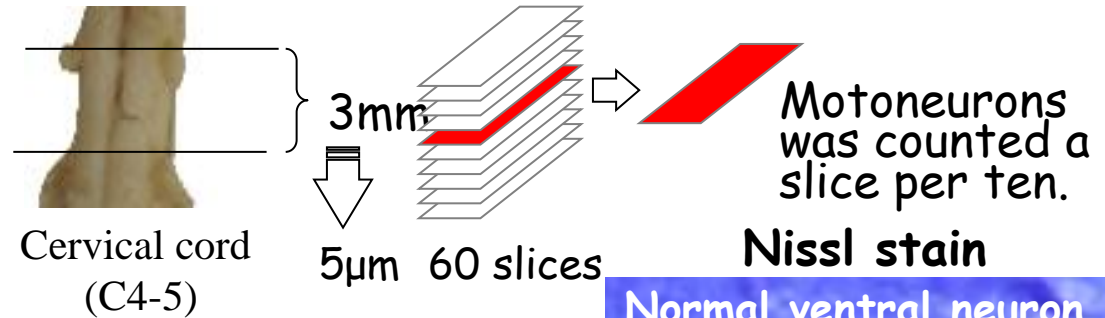
- **Signal-difference-to-noise ratios (SDNR)**
 <Sagittal T2-w MR imaging>



◆ Histological Study

(Motoneurons count after 1 year)

- Fixation: 4%-paraformaldehyde
- Decarcification: EDTA·2Na·2H₂O



SDNRs

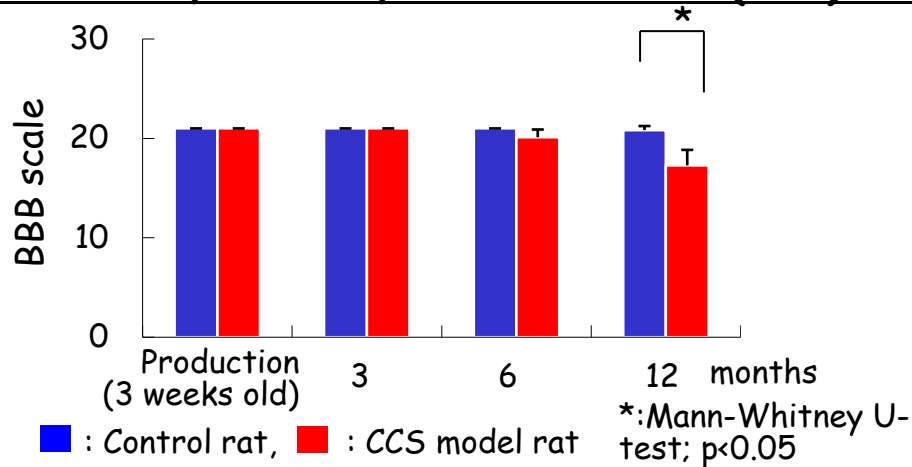
$$= \frac{SI(\text{ROI}) - SI(\text{surrounding})}{\text{Noise}(\text{background})}$$

SI = Signal Intensities

RESULTS

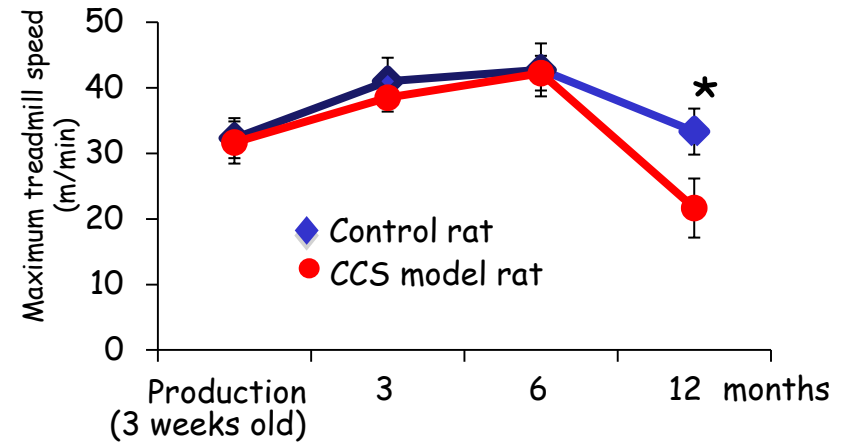
◆ Behavioral assessment

The Basso, Beattie, and Bresnahan (BBB) scale



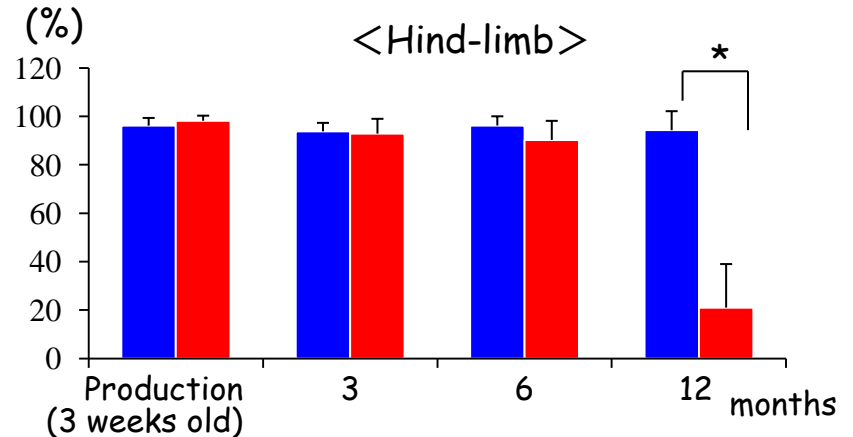
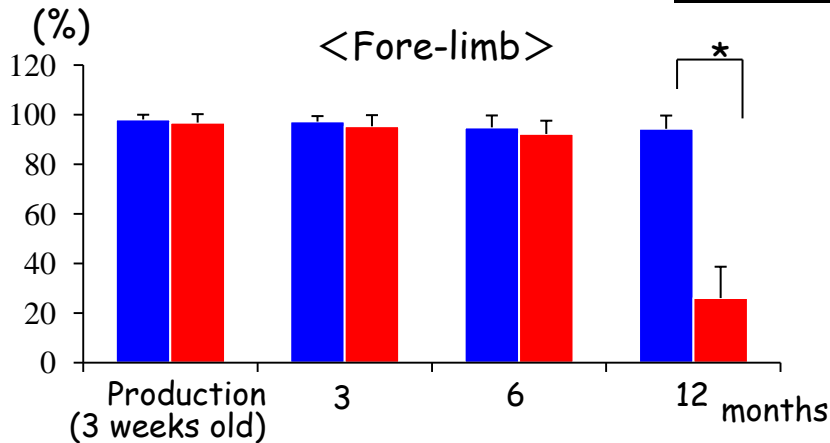
• BBB scale of CCS model (17.3 ± 1.6 points) rat was lower than control rat (20.8 ± 0.4 points) after 12 months; however there were no differences between each group until 6 months after surgery.

Treadmill test



• The maximum treadmill speed of CCS model rat was lower than control rat after 1 year.

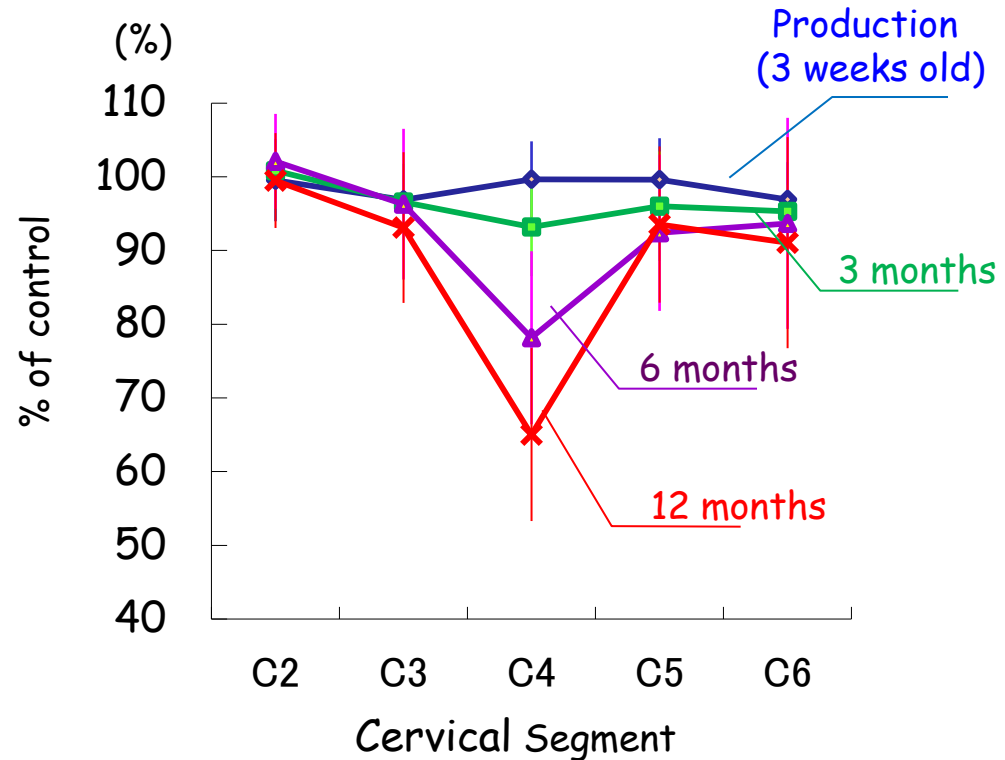
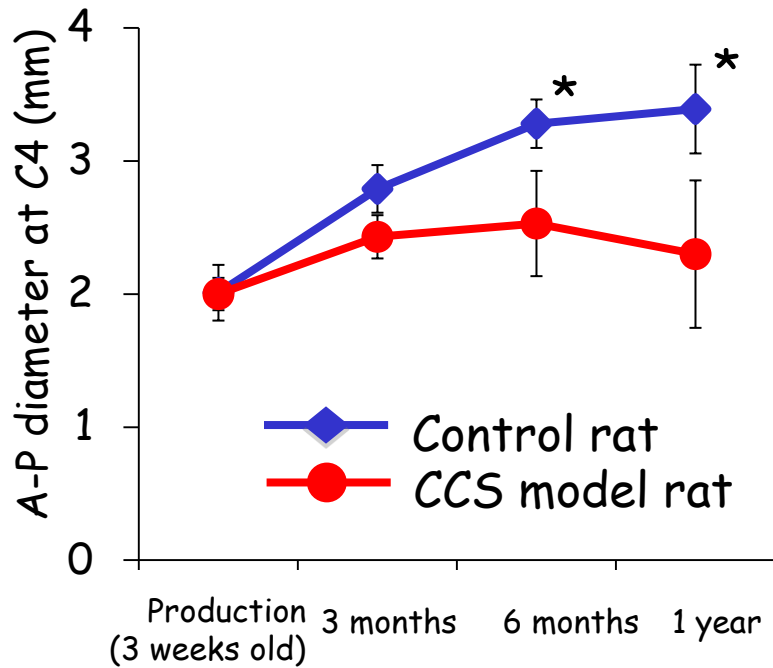
Sensory assessment



• In the von Frey filament test, the response frequency of CCS model had no differences between control rats until 6 month after surgery, but the decreasing response frequency of CCS model appeared after 12 months.

■ : Control rat, ■ : CCS model rat

◆ Radiological assessment



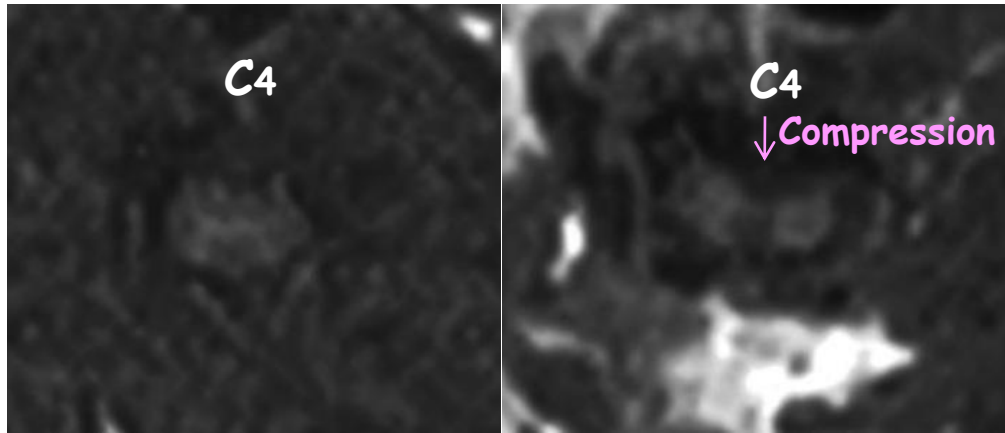
The mean A-P diameter of spinal canal at C4 compression level of CCS model was progressively narrowed, and after 12 months, which was about 65% of control rat.

◆ MR imaging study

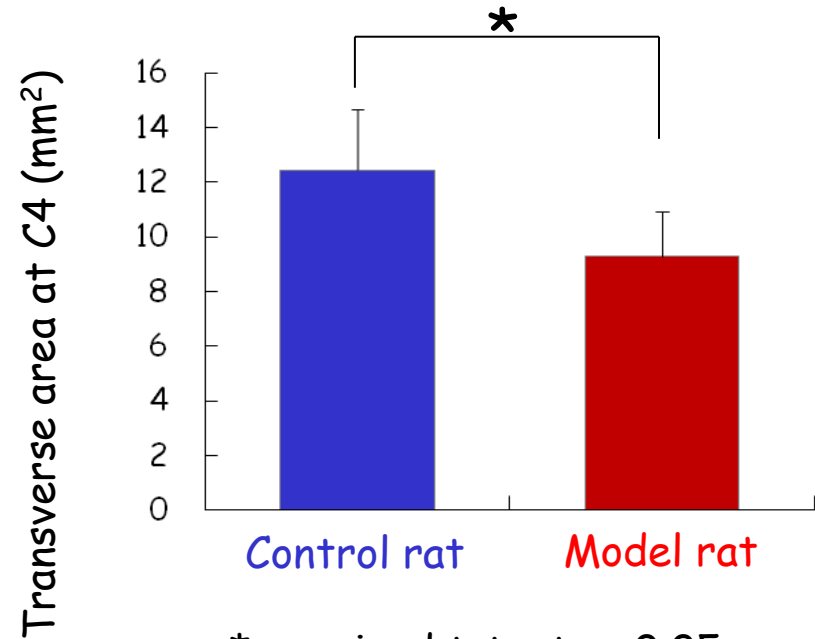
➤ Transverse area of spinal cord

Control rat

Model rat



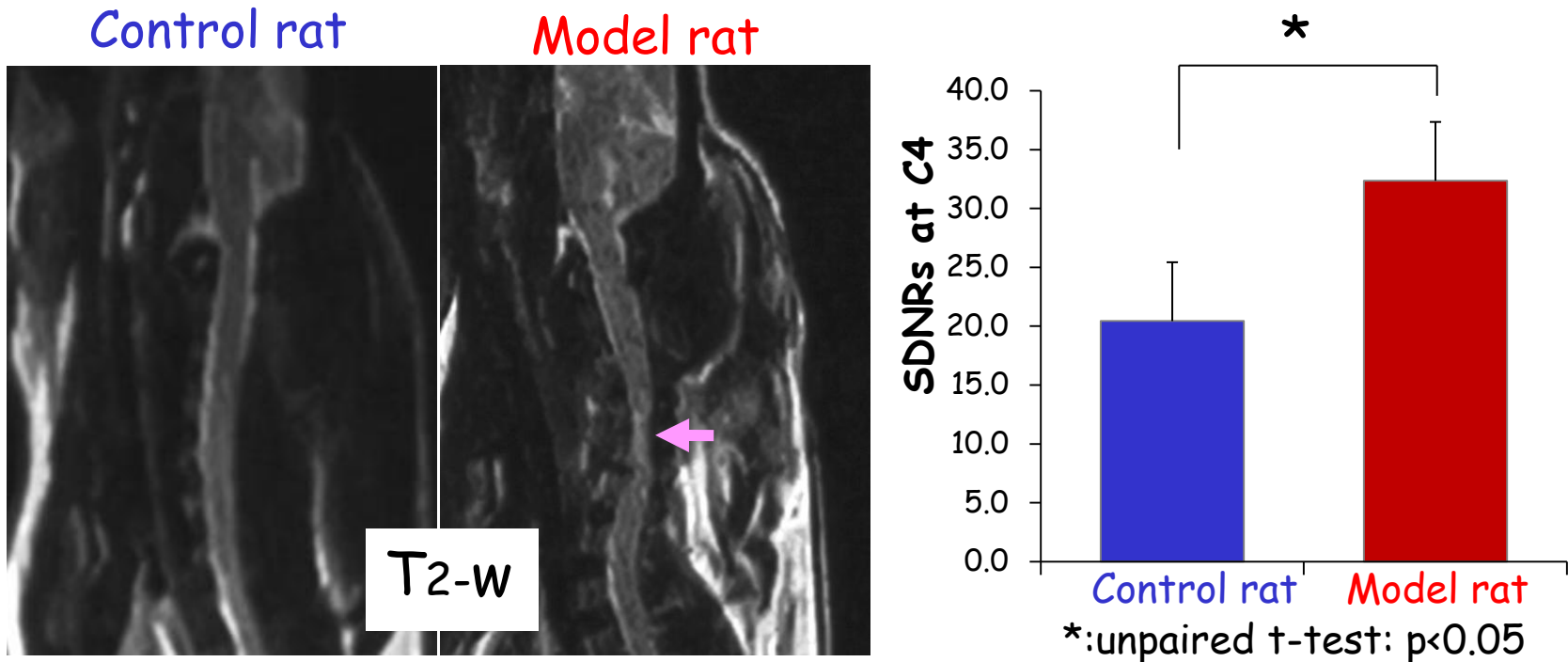
T₁-w



*:unpaired t-test: p<0.05

At 12 months after surgery, compression of the spinal cord was evident with flattening of the cross-section view in CCS model rat. The transverse area of the spinal cord was $10.57 \pm 1.9 \text{ mm}^2$ in the control rat and $7.98 \pm 1.7 \text{ mm}^2$ in CCS model rat .

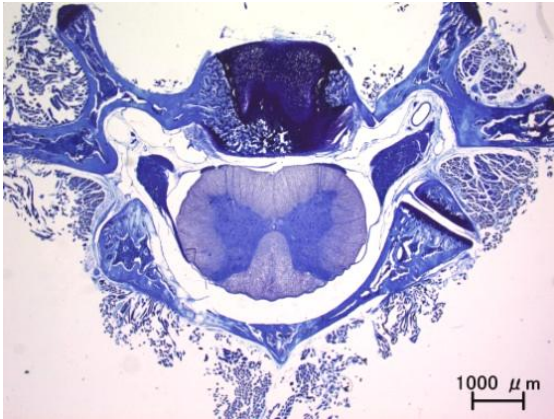
➤ High intensity area in the cervical cord
[Signal-difference-to-noise ratios (SDNR)]



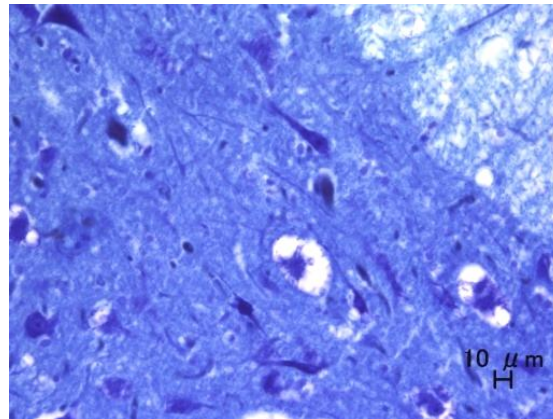
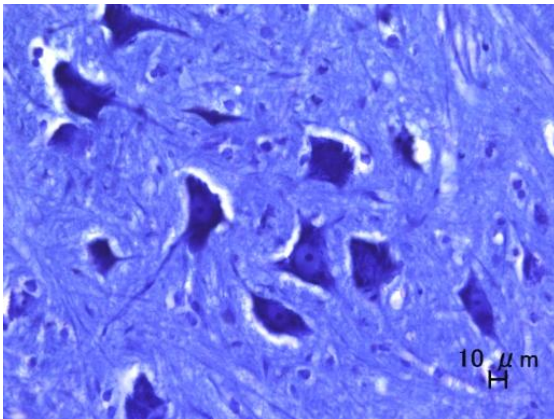
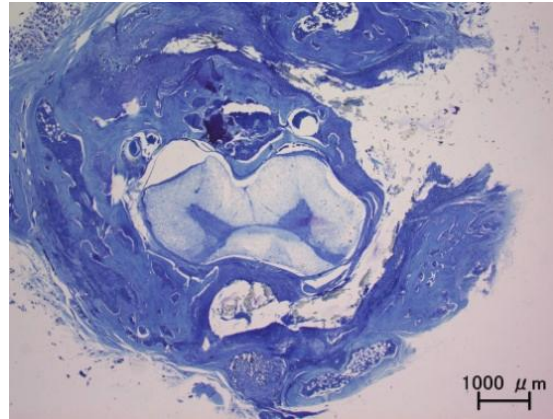
The SDNR of CCS model rat (31.4 ± 11.6) was significant higher than normal rat (20.4 ± 5.5), and a high-intensity area in T2-weighted MRI of spinal cord was observed in the CCS model rat (arrow).

◆ Histological Study

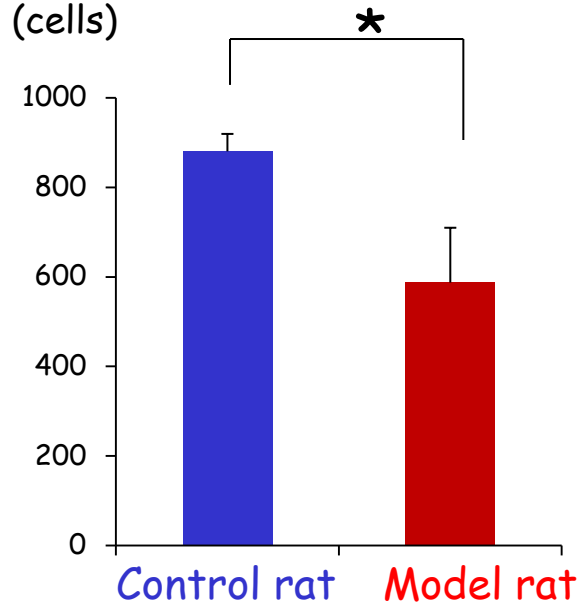
Control rat



Model rat



Number of motoneurons at C4 (Number / 60 slices) (cells)



*:unpaired t-test: $p < 0.05$

In the CCS model rat, the spinal cord was compressed along the whole circumference, and the neurons were flatter, smaller, and decreased in number of motoneurons in the gray matter.

DISCUSSION

Skeletal maturity

Rat: 2 months of age



Human: 13-16 years old

<Adler M. et al, Vet Pathol, 1983>⁶⁾

1 year old (rat)

= 80 years old (human) ?



neurological dysfunction(+)

SYMPTOMS

Production of model



Induction of compression 6 months old (rat)
= 40 years old (human)

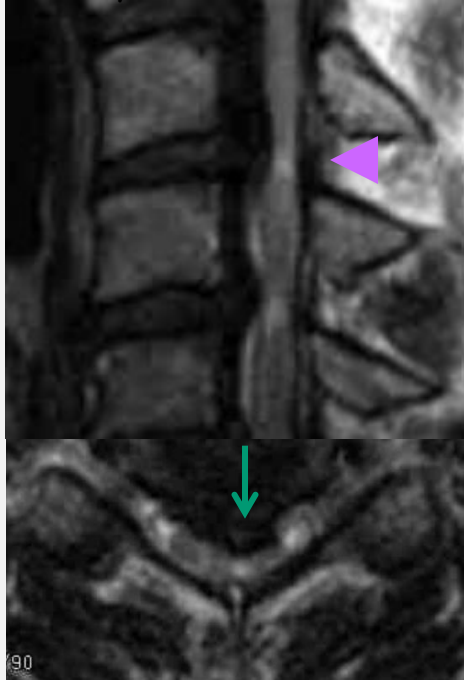
CORD COMPRESSION

time

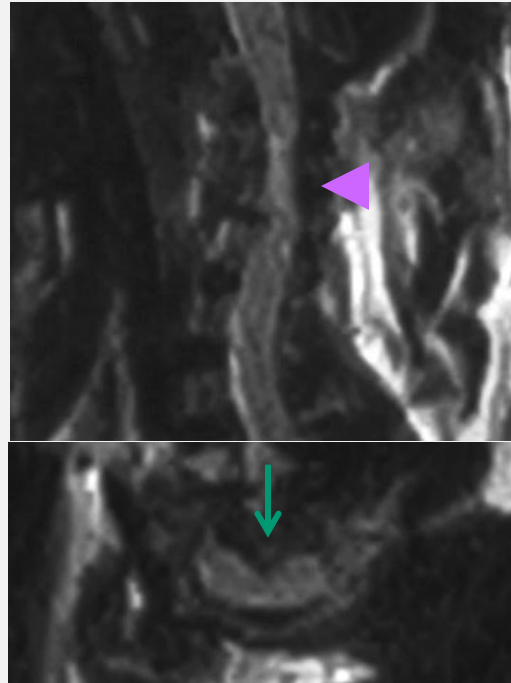
We suggested that our model might reproduce any conditions of chronic spinal cord compression in human, because induction of canal stenosis was about 40's and neurological dysfunctions were insidious onset about 80's from skeletal maturity relationships between rat and human.

Comparison of our chronic cervical compression model and cervical canal stenosis as seen human

Human
65y.o. Male OPLL

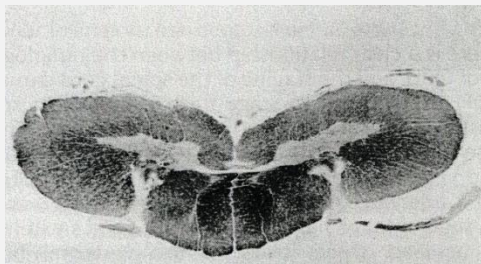


Rat model

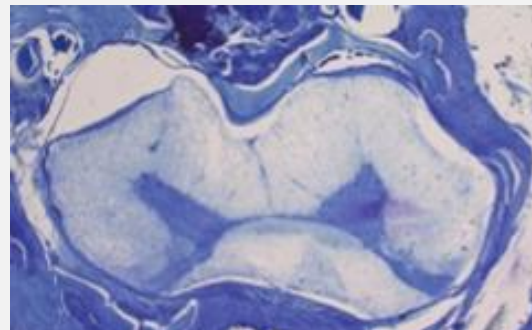


- High-intensity in the cervical cord (+)

- Decreased of transverse area



<Mizuno J. et al, Neurol Res, 1992>



- Neurons were flatted and small.
- Motoneurons were decreased
- myelin destruction
- Loss of axons

MR imaging and pathological changes in our cervical chronic compression model is almost same changes as seen human in patients with OPLL or OYL.

In this model, the polyethylene line cuts into the dorsal wall of the spinal canal following the growth of the spinal canal and vertebral body, and gradually compressed the spinal cord. After 12 months from surgery, spinal canal of CCS model rat was narrowed to 65%, and spinal cord was compressed to 74% of control rat. This model was unique because of the slow disease's course, the lack of surgical damage in spinal epidural tissues or direct damage to spinal cord. Additionally, behavioral assessment was helpful and meaningful to accurately know specific functions of spinal cord.

In our model, rats with polyethylene line presented motor deficits and sensory disturbances 12 months after surgery, however no clinical manifestation took place until 6 months after surgery. This insidious and delayed onset of symptoms is one of the most typical characteristics of chronic compression of spinal cord.

CONCLUSION

Our findings indicated that the decreased in the number of motoneurons preceded the onset of the disturbances of motor and sensory function. And our model well reproduced chronic compression of cervical cord in human.

REFERENCES: 1) Shinomiya K, et al. Spine 17, S383, 1992. 2) Hoshino Y, et al. Clin Neurophysiol 110, 305, 1999. 3) Manabe S, et al. Spine 14, 1308, 1989. 4) Kim P, et al. Ann Neurol 55, 503, 2004. 5) Yamazaki M, et al. Calcif Tissue Int 48, 182, 1991.