Pathophysiology of tethered cord syndrome: correlation with symptomatology

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Tethered cord syndrome (TCS) is a stretch-induced functional disorder of the spinal cord. The mechanical cause of TCS is an inelastic structure anchoring the caudal end of the spinal cord that prevents cephalad movement of the lumbosacral cord. Stretching of the spinal cord occurs in patients either when the spinal column grows faster than the spinal cord or when the spinal cord undergoes forcible flexion and extension.

Research in patients and experimental animals suggests that there is a link between the clinical dysfunctions that characterize TCS and putative pathophysiological changes that accompany this syndrome. Among these changes are depression of electrophysiological activity and shifts in the reduction/oxidation ratio of cytochrome oxidase. The latter suggests that there is impairment of oxidative metabolism. These putative pathophysiological changes in TCS occur mainly within the lumbosacral cord under excessive tension.

The authors discuss the pathophysiology of TCS and examine related symptoms.

KEY WORDS • tethered cord syndrome • pathophysiology • oxidative metabolism • cytochrome oxidase • hypoxemia ischemia

GENERAL CONCEPTS OF TETHERED CORD SYNDROME

The symptomatology of TCS includes lower-limb motor and sensory deficits, incontinence, and musculoskeletal deformities. It is believed that the lesions causing TCS symptoms are located in the lumbosacral cord and that signs and symptoms of TCS can be reversed in many patients. Mechanical causes of cord tethering include a thickening of the terminal filum attached to the elongated spinal cord⁸ or any inelastic structures, such as fibrous or fibroadipose filum,^{32,37} tumors, lipoma, epidermoid tumor, myelomeningoceles, lipomyelomeningoceles, or scar formations that are fastened to the caudal spinal cord³⁸ or osseous or dural septum. These structures lack viscoelasticity, and thus their quality is the determining factor for tight fixation of the spinal cord.

Although the following findings in patients with TCS are recognized by clinicians, their correlation to the TCS pathophysiology may not have been well explained. First, TCS lesions are predominantly restricted to the lumbosacral cord. Second, the associated sensory deficits are often distributed in a patchy pattern. Third, TCS-induced

incontinence becomes irreversible earlier than motor and sensory dysfunction. Fourth, scoliosis and exaggerated lumbosacral lordosis are common findings. Fifth, what appear to be adequate untethering procedures in patients with myelomeningoceles are often not followed by neurological improvement, which is different from those with “tethered spinal cord.”⁸

Defining the mechanism of cord tethering-induced pathophysiology may provide a key step in addressing these issues and in explaining the patient's clinical signs and symptoms. Such definition may also provide a useful means to formulate a rationale for diagnostic and surgical approaches to this disorder. Insights into the pathophysiology of TCS have been derived from correlations among research data and clinical findings such as symptomatology, diagnosis, and surgery-related outcome. In our research on spinal cord tethering, emphasis has been on oxidative metabolism and electrical activities in spinal cords of humans and of experimental animals, because links are proposed between impairments of these factors and the pathophysiology of TCS.^{26,38} This research has suggested that the pathophysiological effects of spinal cord tethering are analogous to those that occur in animal models of hypoxemia^{2,16,33} and brain¹⁷ and spinal cord ischemia.³⁸

Abbreviation used in this paper: TCS = tethered cord syndrome.

OXIDATIVE METABOLIC CHANGES IN TCS

The studies reviewed in this report of the tethering-induced changes in cord tissue oxidative metabolism are based on the following principles. One is that because of its high requirement for energy in the form of adenosine 5'-triphosphate, the cells of the central nervous system must rely absolutely on oxidative metabolism for all of their functions such as the maintenance of transmembrane ionic gradients, the transmission of electrical signals, and also for cell survival.^{16,17} In fact, brief periods of anoxia or ischemia are well known to produce pathophysiological changes or cell death; and even minor impairments of oxidative metabolism underlie neurological dysfunction and produce the changes associated with many neurological disorders.

A second principle is that changes in oxidative metabolism may be signaled by recording shifts in the reduction/oxidation ratios of the components of the mitochondrial electron transport chain. This is because O_2 consumption and adenosine 5'-triphosphate production are tightly coupled to mitochondrial electron transport.³ Of advantage to studies involving assessment of spinal cords in animal models and humans is that these redox shifts can be recorded noninvasively by reflection spectrophotometry.^{11,16,38} When O_2 is decreased, for example, cytochrome a, a_3 is known to become increasingly reduced (that is, the reduction/oxidation ratio is increased) and energy production is decreased. In contrast, when the O_2 supply is increased or the substrate supply is decreased, the redox ratio of this cytochrome is decreased.

As expected from studies in isolated mitochondria,³ cytochrome a, a_3 in animal and human spinal cords became further reduced when arterial O_2 tension was reduced.^{16,33} We also found in our studies that when the oxygenation of spinal cord was decreased, cytochrome a, a_3 was further reduced. These changes were reversible on restoration of O_2 supply or blood pressure to the levels before hypoxia.³⁸

These events were defined in more detail in animal models. For example, such studies showed that when mean arterial blood pressure was decreased to less than 60 mm Hg during hypoxemia (PaO_2 20 mm Hg), interneuron potentials quickly disappeared; additionally, a combination of extreme hypoxemia (20 mm Hg) and hypotension (5–10 mm Hg) resulted in maximum reduction of cytochrome a, a_3 and complete loss of all electrical activities, including long tract potentials.³³ These changes were only reversible if adequate O_2 supply was quickly restored and blood pressure was elevated to a normal level.

Similar changes were noted in response to ischemia in animal spinal cords.³⁴ Immediately after occlusion of the aorta, for example, tissue O_2 tension declined to zero, interneuron potentials were diminished and then absent, and cytochrome a, a_3 became maximally reduced. If blood flow was reestablished by removal of the aortic occlusion within a short time, cytochrome a, a_3 returned to its baseline redox state (sometimes this cytochrome became transiently hyperoxidized before recovering to its baseline state) and there was recovery of interneuron potentials. If ischemia was prolonged beyond 10 minutes, however, normal recovery was usually not observed despite removal of the aortic clamp.

Metabolic and electrical changes in animal models during and after spinal cord tethering were predictable based on the aforementioned findings.^{29,38} For example, the shift toward reduction of cytochrome a, a_3 increased with the weight causing spinal traction in cat models of cord tethering. Additionally, the increase in cytochrome a, a_3 reduction caused by cord tethering was greater in the caudal segment than in the cephalic segment, whereas spinal cord segments above the attachment of the lowest pair of dentate ligaments did not show changes in redox level of the cytochrome. There were three patterns of metabolic effects that occurred with experimental traction of the spinal cord. 1) With low-grade traction (2-g), there was only a small shift toward reduction of cytochrome a, a_3 (this was called the Type 1 pattern). When the traction weight was removed, cytochrome a, a_3 quickly underwent an oxidative shift back to its pretraction redox ratio. 2) With medium-grade traction (3- to 4-g), cytochrome a, a_3 became moderately reduced (Type 2). Removal of the traction was also followed by rapid recovery of this cytochrome to its pretraction redox state. 3) High-grade traction (5-g) produced marked reduction of cytochrome a, a_3 . When this level of traction was removed, recovery of the pretraction redox state of cytochrome a, a_3 was typically incomplete.

In addition to the correlation between cytochrome a, a_3 redox shifts and traction weight, the following observations were also derived from these studies. 1) The greater the traction weight, the greater was the elongation of the spinal cord. 2) The lower the cord segment, the greater was the elongation after imposition of traction; and elongation of the terminal filum was far greater than that of any cord segment. 3) Traction produced no elongation in the spinal cord cephalic to the attachment of the lowest pair of dentate ligaments.²¹ The results of a 2-deoxyglucose metabolism study also support cytochrome redox findings because mild metabolic changes were noted in the spinal cords with mild-medium traction, and severe impairment in those with high-grade traction.²⁸

Based on the correlation between the clinical conditions and spinal cord redox, patients with TCS were divided into three groups. During surgery in the patients with mild-to-moderate TCS (Groups 1 and 2), untethering produced shifts toward oxidation of this cytochrome, which we suggest confirms the clinical diagnosis of TCS.³⁸ These patients recovered from mild or moderate neurological deficits within 2 weeks and 2 to 4 months, respectively, after surgery. In contrast, surgery in patients with the moderate-to-severe TCS-related neurological deficits provoked only mild oxidative shift of cytochrome a, a_3 from markedly reduced state of the spinal cord before untethering. These patients (Group 3) recovered only partially after untethering surgery.

DISCUSSION

Physiological Correlation Between TCS and Hypoxemia/Ischemia

In experimental conditions, tethering of the spinal cord resulted in changes similar to those expected from studies of hypoxemia.^{2,33} For example, hypoxemia induced shifts toward reduction of cytochrome a, a_3 and diminished interneuron potentials. When hypoxemia was sufficiently

severe, cytochrome a, a₃ reached a peak level of reduction and there was loss of interneuron potentials. Similar effects of ischemia have been observed in brain and spinal cord tissue. In low- and medium-grade experimental traction, we have found that spinal cord blood flow decreased in proportion to the traction stress until traction reached a threshold beyond which blood flow did not further decrease. Electron microscopic examination of the spinal cord specimen after the release of high-grade traction showed wrinkling of the neuronal membranes.^{26,28} We postulate that this wrinkling was the result of neuronal membrane stretching causing the loss of transmembrane ion homeostasis and depression of electrical activity. Whether stretching itself directly causes the impairment of oxidative metabolism signaled by shifts toward reduction of cytochrome a, a₃ or whether these are caused by traction-induced hypoxemia remains unknown.

Correlation Between the Oxidative Metabolism and Clinical Findings

There are parallels between the experimental study findings of cord tethering and those obtained in surgically treated patients with TCS. In both, for example, the TCS insult and resultant effects could be found in three groups (mild, medium, and severe) (Table 1).

The results reported in Table 1 show that cytochrome a, a₃ was shifted toward reduction under mild and medium spinal cord–tethering insults. In these patients (Groups 1 and 2), shifts toward oxidation of cytochrome a, a₃ occurred after untethering and recovery from the TCS symptoms followed. In patients with severe traction (Group 3), however, reduction of the cytochrome during tethering was more severe and not fully reversible after surgery. Similar results were obtained in experimental animals (Types 1, 2, and 3). In these studies, high-grade tethering (Type 3) caused neurological deficits characteristic of human TCS symptoms and was accompanied by an increased reduction level of cytochrome a, a₃ and electrical depression. In these animals, recovery after untethering was incomplete.^{19,38} Schneider, et al.,¹⁹ reported finding decreased blood flow in patients with TCS and its normal recovery after untethering, and they correlated this finding with symptomatic postoperative improvement. Their results seem to correspond to the improvement in oxidative metabolism and neurological findings that were observed in our patients in Groups 1 and 2 after untethering surgery. Blood flow study alone, however, cannot be relied on to determine the functional improvement in patients with TCS.

TABLE 1
Summary of effects in three TCS groups

Group	Neurological Status		Redox Ratio of Cytochrome a, a ₃	
	Tethered	Untethered	Tethered	Untethered
1	mild deficit	normal (2 wks)	mildly reduced	normally oxidized
2	mod deficit	normal (2 mos)	mod reduced	normally oxidized
3	severe deficit	partially improved	highly reduced	partially oxidized

Localization of Physiological Changes to Clinical Status

Several questions remain related to the clinical findings in TCS.

Why are the Lesions Restricted to the Lumbosacral Cord? Clinically, the signs and symptoms in patients with TCS indicate that lesions are located in the lumbosacral cord. The impairment of oxidative metabolism and the elongation of the spinal cord in the animal traction model were found only below the attachment of the lowest pair of dentate ligaments. In humans, therefore, the lesions occur below the T-12 and L-1 cord segments unless different types of lesions coexist in higher spinal cord segments.

Why Does Incontinence Become Irreversible Earlier Than Motor/Sensory Dysfunction? The conus medullaris is most vulnerable to traction because of its proximity to the caudal fixation and its smallest diameter is often found in the spinal cord. Results of oxidative metabolic changes, interneuron deterioration, and elongation studies support this conclusion. After repeated stretching of the conus medullaris, histological damage can occur early, resulting in permanent incontinence.

Why are Sensory Deficits Often Distributed in a Patchy Pattern? Tethered cord syndrome lesions are mainly located in the gray matter, where 90% of mitochondria are found in the spinal cord. The authors of other functional studies in experimental cats with horseradish transport⁵ and those with 2-deoxyglucose metabolism^{26,28} have demonstrated the intact function of the white matter. Therefore, these findings correlate with lack of a clear-cut sensory level pattern typically observed in patients with TCS. Despite the previously described elongation rates in the cat model, various segments of the human lumbosacral cord may elongate slightly at different rates. This view is based on the finding that peripheral nerve elongation is caused by traction. When an excised nerve segment is suspended and pulled down with a weight, for example, earlier elongation is greatest in the lowest one third, less in the highest one third, and least in the middle one third. The elongation gradually extends to the middle one third, and the other two thirds contract accordingly.^{28,35} A similar phenomenon has also been noted in the cat spinal cord during traction. Such differential elongations may be influenced by the duration of the traction effect, presence of arachnoid adhesion, and spinal curvature.

Why do Symptoms Vary in Intensity as They Progress? There are two factors that cause temporary accentuation of signs and symptoms of TCS. The first is sustained reduction of cytochrome a, a₃ associated with repeated mild stretching of the spinal cord during daily activity that requires spinal flexion and extension. More prolonged or stepwise worsening of TCS may be related to sudden forcible spinal flexion and extension. In our recent study involving simulation of human spinal dynamics, the cord was suddenly stretched by dropping the weight from a 1-cm height above the suspended level in the described traction model and histological changes were investigated.³⁶ It became clear that this form of insult caused neuronal damages and axonal degeneration in the central area of the lumbosacral cord, including interneurons and the distal end of the long tracts. Also noted were simultaneous regeneration processes in the same area mixed with de-

generating neurons. These experimental results are likely to correspond to the sudden worsening of signs and symptoms in patients with TCS. Recovery from these deficits by regeneration of short-circuit axons, however, can occur if the patient remains at rest without stressful spinal movements.

Why are Scoliosis and Exaggerated Lumbosacral Lordosis Common in TCS? Musculoskeletal deformities include scoliosis, exaggerated lumbosacral lordosis, high-arched feet, and hammer toes. Development of scoliosis and lordosis is the functional adjustment of paravertebral muscles to alter the spinal column curvature, so that the spinal cord takes the shortest course in the concave side of the spinal canal to minimize the intramedullary tension. High-arched feet and hammer toes are apparently caused by weakness of some muscles (due to intramedullary lesions), which lose balance against unopposed muscle groups in the feet and toes. This imbalance of muscular strength is similar to that in claw hand in ulnar nerve palsy.

Are There Differences Between the Underlying Mechanism of Deficits in Patients With Myelomeningoceles and Those With TCS?⁸ The answer to this question requires the criteria for diagnosing TCS, and the problems associated with myelomeningoceles are discussed in a later section.

The diagnosis of the TCS is primarily established based on neurological signs and symptoms and musculoskeletal deformities in children^{8,13,18,20} and adults.^{9,15,31} Typical neuroimaging features, such as an elongated cord continuous to a thick filum or a tumor, support the diagnosis. In a number of cases in which these neuroimaging abnormalities were documented, however, the patients were asymptomatic at the time of prophylactic sectioning of the thick terminal filum in infancy²² or were asymptomatic until adulthood, even after 70 years of age.³⁷

It has been proposed that an elongated cord is not an essential factor for establishing the diagnosis of TCS. The caudal end of the spinal cord, for example, was located above the L1–2 interspace in 18% of patients with TCS (including children and adults) in one study²⁴ and above L2–3 in 50% on neuroimaging studies in adults in several other studies.^{28,31,37} Despite the suggested abnormal thickness of the terminal filum ($\geq 2 \text{ mm}^4$), these figures are only of relative importance. When the terminal filum is less than 2 mm thick in diameter a diagnosis of TCS is not precluded (for example, the thickness of 1 mm has been included in TCS diagnosis,⁷ especially for adolescent and adult patients^{25,27,31,37}). The consistent neuroimaging feature and intraoperative finding is the posterior displacement of the conus medullaris and terminal filum.^{31,37} Testing of inelastic filum intraoperatively and histological demonstration of fibrous filum replacing ependymal tissue prove the presence of a tight filum as a mechanical source of high tension within the spinal cord.^{31,37} Furthermore, two methods of physiological investigation provide evidence of intramedullary dysfunction before untethering and functional postoperative improvement: 1) intraoperative redox studies of cytochrome *a*, *a*₃ (for oxidative metabolism),^{28,29,35,38} and 2) somatosensory evoked potential monitoring that demonstrates interneuron-originated long tract potentials.⁶ The latter corresponds to the

interneuron potential study in animal experiments.^{29,38} Another effective means of detecting intramedullary dysfunction would be to stimulate a sensory nerve (preferably nerve root) and record potentials from the corresponding motor nerve root.

Cases Involving Myelomeningoceles

Can the Complexity of Symptoms in Patients With Myelomeningocele be Explained by our Experimental Studies? This question is linked to the following comment. “The tethered cord syndrome as it presents to the pediatric neurosurgeons is a progressive disorder the symptoms of which may wax and wane but the course of which is relentlessly downhill. How could ‘tethered cord associated with myelomeningocele’ be explained by experimental model of cord tethering?”²³

This question implicates various clinical situations. In 1981, Yamada, et al.,³⁸ included TCS-related myelomeningoceles and lipomyelomeningoceles as stretch-induced spinal cord disorders, namely, under the condition that oxidative metabolism of the spinal cord is impaired. The statement may have caused such misunderstanding because some physicians believe that all the patients with these anomalies have TCS.

Pathological conditions range from a strict sense of TCS to the most devastating neurological status. The former condition corresponds to oxidative metabolic impairment Types 1 and 2 in the animal model, and Groups 1 and 2 in human TCS. The latter refers to patients with myelomeningocele who present with total paraplegia, incontinence, and patulous anus. In these infants, the surgeon may relieve the spinal cord tension by dissecting fibrous tissue, but no neurological improvement follows. We found that there was no redox baseline change of cytochrome *a*, *a*₃ in response to “test” stress (hypoxic or stimulation).³⁰ This extreme condition is attributed to failure of neuronal development in the lumbosacral cord or total neuronal damage caused by severe cord tethering, infection, or possibly abnormal osmosis or toxic components in the amnion during the fetal stage. Naturally the diagnosis of TCS is not applicable to the patients in whom the aforementioned redox responses are absent.

Another trait of the spinal cord associated with myelomeningocele is that it is often surrounded by densely adhesive arachnoid membrane, fibrous tissue, or epithelium. This environment excludes pure TCS; instead, it indicates the following: 1) a preexisting circulatory impairment; and 2) congenital intramedullary disease associated with myelomeningocele.

One key question is why does surgical untethering not always produce neurological improvement? We believe the answer is twofold. First, the diagnosis was inaccurate—that is, the absence of TCS, as previously mentioned. Second, TCS may have been present before surgery. The procedure to dissect severe scar tissue may have caused damage to nerve tissue or denuded the nerve tissue (spinal cord or nerve roots) from the vascular supply after meticulous dissection of scar tissue. The latter complication can be associated with formation of scar tissue that often shares its circulation with the adjacent nerve structure. Resection of fibroadipose tissue surrounding the spinal cord and nerve roots in cases of lipomyelomeningocele can also cause similar complications.³² For prevention

of such complications, nerve root stimulation studies have been advocated to confirm nerve tissue during dissection.^{1,10,12,14}

CONCLUSIONS

Completely reversible signs and symptoms of TCS after untethering procedures are likely related to the metabolic derangement of spinal cord neurons, specifically to changes in oxidative metabolism without associated histological damage. In cases in which only partially reversible signs and symptoms are demonstrated after untethering, a combination of impaired oxidative metabolism and neuronal damage is suspected. Accordingly, complete recovery of neurological functions is not expected.

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References

- Albright AL, Pollack IF, Adelson PD, et al: Outcome data and analysis in pediatric neurosurgery. **Neurosurgery** 45:101-106, 1999
- Austin GM, McCouch GP: Presynaptic component of intermediary cord potential. **J Neurophysiol** 18:441-451, 1955
- Chance B, Williams GR: The respiratory chain and oxidative phosphorylation. **Adv Enzymol Relat Subj Biochem** 17: 65-134, 1956
- Fitz CR, Harwood-Nash DC: The tethered conus. **AJR** 125: 515-523, 1975
- Fuse T, Patrickson JW, Yamada S: Axonal transport of horseradish peroxidase in the experimental tethered spinal cord. **Pediatr Neurosci** 15:296-301, 1989
- Gilmore RL, Walsh J: The clinical neurophysiology of tethered cord syndrome and other dysraphic syndromes, in Yamada S (ed): **Tethered Cord Syndrome**. Park Ridge, IL: AANS, 1996, pp 167-182
- Hochhauser L, Caung S, Harwood-Nash DS, et al: The tethered cord syndrome revisited. **AJNR** 7:543, 1986 (Abstract)
- Hoffman HJ, Hendrick EB, Humphreys RP: The tethered spinal cord: its protean manifestations, diagnosis and surgical correction. **Childs Brain** 2:145-155, 1976
- Iskandar BJ, Fulmer BB, Hadley MN, et al: Congenital tethered spinal cord syndrome in adults. **J Neurosurg** 88:958-961, 1998
- James HE, Mulcahy JJ, Walsh JW, et al: Use of anal sphincter electromyography during operations on the conus medullaris and sacral nerve roots. **Neurosurgery** 4:521-523, 1979
- Jobsis FF, O'Connor M, Vitale A, et al: Intracellular redox changes in functioning cerebral cortex. I. Metabolic effects of epileptiform activity. **J Neurophysiol** 34:735-749, 1971
- Kothbauer K, Schmid UD, Seiler RW, et al: Intraoperative motor and sensory monitoring of the cauda equina. **Neurosurgery** 34:702-707, 1994
- McLone DG, Naidich TP: The tethered spinal cord, in McLaurin RL, Schut L, Venes JL, et al (eds): **Pediatric Neurosurgery, ed 2**. Philadelphia: WB Saunders, 1989, pp 71-96
- Pang D: Intraoperative neurophysiological monitoring of the lower sacral nerve roots and spinal cord, in Yamada S (ed): **Tethered Cord Syndrome**. Park Ridge, IL: AANS, 1996, pp 135-147
- Pang D, Wilberger JE Jr: Tethered cord syndrome in adults. **J Neurosurg** 57:32-47, 1982
- Rosenthal M, LaManna J, Yamada S, et al: Oxidative metabolism, extracellular potassium and sustained potential shift in cat spinal cord in situ. **Brain Res** 162:113-127, 1979
- Rosenthal M, Martel D, LaManna JC, et al: In situ studies of oxidative energy metabolism during transient cortical ischemia in cats. **Exp Neurol** 50:477-494, 1976
- Schneider S: Tethered cord syndrome: the neurological examination, in Yamada S (ed): **Tethered Cord Syndrome**. Park Ridge, IL: AANS, 1996, pp 49-54
- Schneider SJ, Rosenthal AD, Greenberg BM, et al: A preliminary report on the use of laser-Doppler flowmetry during tethered spinal cord release. **Neurosurgery** 32:214-218, 1993
- Sutton LN, Duhaime AC, Schut L: Lipomyelomeningocele, in Park TS (ed): **Contemporary Issues in Neurological Surgery: Spinal Dysraphism**. Boston: Blackwell, 1992, pp 59-73
- Tani S, Yamada S, Knighton RS: Extensibility of the lumbar and sacral cord. Pathophysiology of the tethered spinal cord in cats. **J Neurosurg** 66:116-223, 1987
- Till K: Occult spinal dysraphism. The value of prophylactic surgical treatment, in Sano K, Ishii S, Le Vay D (eds): **Recent Progress in Neurological Surgery. Proceedings of the Symposia of the Fifth International Congress of Neurological Surgery, Tokyo, October 7-13, 1973**. New York: Elsevier, 1974, pp 61-66
- Venes J: Comment on Fuse T, Patrickson JW, Yamada S: Axonal transport of horseradish peroxidase in the experimental tethered spinal cord. **Pediatr Neurosci** 15:296-301, 1989
- Warder DE, Oakes WJ: Tethered cord syndrome and the conus in a normal position. **Neurosurgery** 33:374-378, 1993
- Yamada S, Iacono R, Morgese V, et al: Tethered cord syndrome in adults, in Menezes A, Sonntag VK (eds): **Principles in Spinal Surgery**. New York: McGraw-Hill, 1996, pp 433-445
- Yamada S, Iacono RP, Andrade T, et al: Pathophysiology of tethered cord syndrome. **Neurosurg Clin N Am** 6:311-323, 1995
- Yamada S, Iacono RP, Douglas CD, et al: Tethered cord syndrome in adults, in Yamada S (ed): **Tethered Cord Syndrome**. Park Ridge, IL: AANS, 1996, pp 149-165
- Yamada S, Iacono RP, Yamada BS: Pathophysiology of the tethered spinal cord, in Yamada S (ed): **Tethered Cord Syndrome**. Park Ridge, IL: AANS, 1996, pp 29-48
- Yamada S, Knierim D, Yonekura M, et al: Tethered cord syndrome. **J Am Paraplegia Soc** 6:58-61, 1983
- Yamada S, Knierim DS, Won DJ, et al: Are lipomyelomeningoceles always associated with tethered cord syndrome? **J Neurosurg** 96:414, 2002 (Abstract)
- Yamada S, Lonser RR: Adult tethered cord syndrome. **J Spinal Disord** 13:319-323, 2000
- Yamada S, Lonser RR, Yamada SM, et al: Tethered cord syndrome associated with myelomeningoceles and lipomyelomeningoceles, in Yamada S (ed): **Tethered Cord Syndrome**. Park Ridge, IL: AANS, 1996, pp 103-123
- Yamada S, Sanders D, Haugen G: Functional and metabolic responses of the spinal cord to anoxia and asphyxia, in Austin GM (ed): **Contemporary Aspects of Cerebrovascular Disease**. Dallas: Professional Information Library, 1976, pp 239-246
- Yamada S, Sanders DC, Maeda G: Oxidative metabolism during and following ischemia of cat spinal cord. **Neurol Res** 3: 1-16, 1981
- Yamada S, Schreider S, Ashwal S, et al: Pathophysiological mechanisms in the tethered spinal cord syndrome, in Holtzman RNN, Stein BM (eds): **The Tethered Spinal Cord**. New York: Thieme-Stratton, 1985, pp 29-40
- Yamada S, Schultz RL, Mandybur GT, et al: Axonal degeneration after sudden forceful traction of the spinal cord: is it the cause of permanent neurological deficit? **J Neurosurg** 98:681, 2003 (Abstract)
- Yamada S, Won D, Kido DK: Adult tethered cord syndrome: new classification correlated with symptomatology, imaging and pathophysiology. **Neurosurg Q** 11:260-275, 2001
- Yamada S, Zinke DE, Sanders D: Pathophysiology of "tethered cord syndrome." **J Neurosurg** 54:494-503, 1981

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