Tethered cord syndrome belongs to a group of abnormalities under the term OSD. Although the incidence and prevalence of OSD and primary TCS are not well established, the advent of better neuroimaging studies and improved clinical awareness has led to an increase in the number of diagnosed cases.

Tethered cord syndrome is a clinical entity presenting with neurological symptoms, urological dysfunction, and orthopedic sequelae caused by congenital or secondary factors leading to the tethering of the distal part of the spinal cord. The presence of a thickened filum terminale with a diameter greater than 2 mm and/or conus medullaris located below the level of L1–2 (Fig. 1) are the proposed radiological diagnostic criteria in cases presenting with symptoms.1,2,9,20,30,31

Interestingly, the literature cites a significant number of cases that do not meet the proposed criteria for filum terminale thickness of the and conus medullaris level yet the patients present clinically with symptoms of TCS.13,17,24,25,20,32,33,36 The resection of the filum terminale, in these patients, leads to resolution of the clinical symptoms. These observations suggest that the radiographic criteria for TCS alone are inadequate for the diagnosis of TCS and must be combined with the clinical presentation to clinch the diagnosis. Thus, a better understanding of the pathophysiology of TCS could improve our ability to diagnose TCS in cases in which the radiographic criteria do not adequately address all presentations of the disease. (10.3171/2010.3.FOCUS1085)

Key Words: filum terminale • metabolism • pathophysiology • tethered cord • traction
A. S. Filippidis et al.

subtype of meningocele called “meningocele manqué” is also a cause of TCS. Meningocele manqué is a form of spontaneously healed meningocele resulting in the formation of dorsal bands. These dorsal bands promote spinal cord tethering. Tethered cord syndrome has also been described in association with a fatty filum terminale, imperforate anus, or a dural sinus (Figs. 1 and 2). Myelomeningocele is a form of nonoccult spinal dysraphism that is associated with tethered cord and TCS. The tethering of the cord in this case results from the attachment of the spinal cord to the dura mater or the surface ectoderm. Rare, complex, developmental syndromes presenting with anomalies in different systems like the OEIS syndrome (omphalocele, extrophy of the cloaca, an imperforate anus, spinal malformations with tethered cord) and the VATER association (vertebral anomalies, imperforate anus, tracheoesophageal fistula and renal-radial anomalies) can be associated with TCS.2,15 The Currarino triad (anorectal malformation, presacral mass, and sacral bone abnormalities) is also a syndrome that is associated with tethered cord.7 Interestingly, genetic studies suggest that TCS may be genetically transmissible.3,16,26 More recently a link between the \textit{TBX1} gene, 22q11.2 deletion, and trisomy 21 with TCS has been described.9 Other genetic abnormalities and syndromes like trisomy 13q32, trisomy 8, neurofibromatosis-1, Klippel-Feil syndrome, FG syndrome (shortness of stature, large head, congenital hypotonia, delayed motor and speech development, and a characteristic combination of minor anomalies, malformations, and functional disturbances of the CNS, and gastrointestinal system), Klippel-Trenaunay-Weber syndrome, Dandy-Walker anomaly, and Fuhrmann syndrome have also been reported in connection to TCS.3,18 The background of the presentation of TCS in conjunction with genetic abnormalities and syndromes indicates a possible genetic link that plays a key role in the development of the syndrome or its pathophysiology.3,18

\textbf{Elasticity of the Spinal Cord}

In their original series describing TCS, Hoffman et al.9 suggested that traction and elasticity of the spinal cord were fundamental factors underlying the pathophysiology of the disease. The most caudal part of the spinal cord exhibits the greatest elongation when traction forces are craniocaudally applied; thus, the conus medullaris is the region of spinal cord that is most vulnerable to traction.28 The elongation of the filum terminale follows a linear relation with the applied traction force. The spinal cord elongates in a nonlinear fashion as more weight is applied. Interestingly, the spinal cord regions above the attachment of the lowest pair of dentate ligaments do not elongate. This fits the clinical observation that neurological deficits are identified at the level of the caudal spinal cord.28,36

Spinal cord tension can also be applied transversely at the cranio-caudal axis by the flexion of the torso reminiscent of TCS.4 This clinical picture is common in patients with occult TCS involved in sporting activities like rowing or cycling.27 In cases in which a spinal mass is present in combination with a tethered cord, local compression of the spinal cord by the mass and flexion of the torso increase the intensity of the symptoms.8 Similarly in cases of spinal cord malformation in which a ventral septum is present, local pressure on the cord can exacerbate the symptomatology of TCS.10,11,19

\textbf{Filum Terminale}

The biomechanical properties of a tethered filum

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{image1.png}
\caption{Sagittal T2-weighted MR image obtained in a 9-week-old girl with a tethered cord lying at the coccyx, associated with a spinal cord lipoma and a dermal sinus.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{image2.png}
\caption{Intraoperative photograph showing the caudal spinal cord in a 9-week-old girl after untethering. A spinal nerve root can also be observed.}
\end{figure}
Pathophysiology of tethered cord syndrome

terminal exhibit a viscoelastic behavior.5,20–22,25,28,36 The addition of more traction leads to further linear extension of the filum. The connection between the conus medullaris and filum terminale permits an adaptive movement of this section of the spinal cord during spinal flexion and extension.5,20–22,25,28,36 Changes in the tissue components and anatomy of the filum terminale promoted by fibrous scarring, widening, or the coexistence of a tumor, such as a lipoma, or the presence of anorectal or other lumbosacral abnormalities, such as a myelomeningocele, alter the filum's viscoelastic property and even lead to its loss. Then, the tethered filum terminale becomes an ineffective regulator of the movement of the conus medullaris and acts as an anchor, limiting its movement and contributing to the application of traction forces that lead to neurological impairment.5,20–22,25,28,36 A key observation in TCS, a low-lying conus, is attributed to the changes that filum terminale has undergone due to developmental anomalies or acquired, secondary causes like infections, scarring, and tumors.5 Interestingly, Selçuki and Coşkun24 and Selçuki and colleagues25 have argued that TCS with a normal-lying conus can be observed in cases in which the elasticity of the filum terminale is lost due to fibrosis.24,25

Spinal Cord Tension and Blood Flow

Increase in the traction forces on the spinal cord reduces blood flow to the cord.6,36 Dolan and colleagues6 used tracers, autoradiography, and a distraction apparatus in cats to assess the spinal blood flow under various mechanical tension scenarios. Spinal evoked potentials were also used in parallel to monitor the electrophysiology of the neurons. The authors observed severe spinal cord ischemia in the group of the experiments with the longest applied distraction. Traction experiments showed that the blood flow to the gray matter was affected more and spinal evoked potentials demonstrated patterns consistent with ischemia. These results suggest that 2 factors, local distraction and vascular compromise, contribute to the pathophysiology of TCS.12,14,36,40 A decrease in the diameter of the lumen of spinal vessels, due to traction, substantially reduced the total spinal blood flow, causing local ischemic insult.5,12,14,36,40 If detethering of the cord is performed within 2–8 weeks of the initial insult, blood flow and spinal evoked potentials may return to normal. Longer delays may result in irreversible changes.12,14

The utilization of intraoperative blood flow monitoring in tethered cord surgery further strengthened the notion that ischemia is also a key contributor to the development of the disease. Schneider et al.23 used laser Doppler flowmetry and identified a significant increase in the blood flow at the caudal spinal cord after untethering operations.

Role of Traction on Hypoxia and Impaired Oxidative Metabolism

The critical observation that traction of the caudal spinal cord is the cornerstone in the TCS development led to extended studies that tried to identify the effect of spinal cord traction at the macroscopic, microscopic, and biochemical level.

Yamada and colleagues37,40 used reflection spectroscopy and traction experiments combined with anoxia to study the metabolic status of tethered spinal cord. They demonstrated that a tethered cord in humans and animal models is associated with metabolic abnormalities at the level of cytochrome αα,α in interneurons.37,40 Cytochrome αα,α is the terminal oxidase enzyme at the respiratory chain in mitochondria, and its reduction/oxygenation ratio is associated with changes in the availability of oxygen or metabolic demands in mitochondria.37,40 Increasing traction in the spinal cord is associated with increased reduction of the cytochrome αα,α. High reduction levels of cytochrome αα,α are associated with decreased metabolic demand, decreased oxygen availability, and spinal cord hypoxia and ischemia.40 Mitochondria in nerve cells with high biochemical reduction states show a decreased production of ATP (adenosine triphosphate). This change in metabolic energy storage and utilization capacity could reflect the impairment of function of nerve cells in the spinal cord.

The aforementioned results indicate that traction-induced hypoxia results in metabolic changes and energy depletion of neurons in the tethered spinal cord.40 Veins, arteries, and capillaries lose their lumen diameter as they are under mechanical forces, and thus the blood flow to the spinal cord is impaired, leading to decreased energy production and high reduction states of the cytochrome αα,α in neuronal mitochondria. The degree of the metabolic impairment is correlated with the severity of the neurological symptoms.35,36,38,39

Interestingly, the surgical untethering of the spinal cord is followed by the return of the metabolic status in the cytochrome αα,α of the mitochondria from a high reduced state to a re-oxidation state reflecting the return to normal.40 This phenomenon was observed in cases with mild or moderate metabolic redox changes while cases with severe reduction/oxygenation disruption did not yield adequate results. The return to the normal metabolic state of the spinal cord was accompanied by neurological improvement in a period ranging from 2 weeks to 2–4 months. In severe cases, only partial neurological improvement was observed, with limited metabolic shift from a predominantly high reduction state of the cytochrome to states with more oxidation. The aforementioned results were also confirmed with studies that used 2-deoxyglucose as a measure of metabolic activity.35–40

A More Functional Definition of TCS

The classic definition of the TCS involves the presence of a thickened filum terminale and/or a low-lying conus medullaris in a patient with neurological deficits. Currently, a more accepted diagnosis of TCS is defined as a pathological fixation of the spinal cord in an abnormally lying position. The data, derived from the pathophysiology of the syndrome, indicate that mechanical tension of the caudal spinal cord, vascular compromise, and hypoxia result in metabolic derangements and neurological impairment. Although the radiological evidence of a low-
lying conus are the key factors in the diagnosis of TCS, a clinical picture consistent with TCS can also be present in a group of patients—accounting for 14–18% of various published series—with a normal anatomical position of the conus. Selçuki and Coşkun found that urodynamic studies are more reliable than somatosensory evoked potentials for predicting that a tight filum terminale is the key factor that leads to the development of the syndrome. In these cases the presence of a tight, inelastic filum terminale is the key factor that should also take into account the underlying pathophysiology. An inelastic filum terminale that has lost the ability to act as a buffer to traction forces applied at the caudal spinal cord is the cause in most of these cases and it is a part of the pathophysiology of the syndrome that must be clarified to further understand when surgery should be performed in cases involving a normally positioned conus. The existence of neurological, urological, and orthopedic signs and symptoms supports an aggressive approach because about 50% of these patients improve significantly following detethering surgery.

Conclusions

The pathophysiology of TCS involves the existence of traction and the loss of the elasticity of the filum terminale as well as ischemic insult to the cord. The extension of the spinal cord, the metabolic abnormalities observed, and the decrease in spinal cord blood flow in TCS lead to neurological deficits. Further research should be conducted at the biomechanical, biochemical, and molecular levels to be able approach the specific activated pathways. The identification of the threshold level of spinal cord damage that defines the clinical picture of TCS as reversible or irreversible should also be clarified. The indications that specific genes participate in the evolution of the syndrome should be further studied to unveil the mode of inheritance in familial cases and identify key genes in the pathophysiology of the syndrome.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Filippidis, Kalani. Analysis and interpretation of data: Filippidis, Kalani. Drafting the article: Filippidis, Kalani. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Study supervision: Rekate, Theodore.

References


A. S. Filippidis et al.
Pathophysiology of tethered cord syndrome


Address correspondence to: Harold L. Rekate, M.D., Neuroscience Publications, Barrow Neurological Institute, 350 West Thomas Road, Phoenix, Arizona 85013. email: Harold.Rekate@bnaneuro.net.