The filum terminale (FT) is a fibrovascular band extending from the conus medullaris to the periosteum of the coccyx, and is composed of an intra- and an extradural portion.\textsuperscript{1,3,4,20,26} It is involved in the pathophysiology of tethered cord syndrome (TCS).\textsuperscript{21,26–28} This syndrome may be either primary or secondary to other congenital anomalies such as myelomeningocele, split cord malformation, and dermal sinuses.\textsuperscript{11,12,24,27,28} Although it has been reported that a filum terminale that is either fatty or thick might have a tethering effect on the spinal cord, which causes symptoms of tight spinal cord syndrome, it has been reported that a normal-thickness FT can also have a tethering effect if its natural architecture is changed due to various factors.\textsuperscript{10,21} Loss of elasticity of the FT, which begins in the early period of intrauterine life, may cause TCS during childhood and adolescence.\textsuperscript{27,28} However, first we should know the normal architecture of the FT.

Object. The structure of the filum terminale (FT) is important in the development of tethered cord syndrome (TCS) in children. Although many studies have been performed on the histological structure of the FT in adults, there has been no detailed investigation for those of fetuses. The aim of this study was to examine the histological structure of the FT in normal human fetuses and to compare the results with those of previous studies.

Methods. The histological examination of the FT was performed in 15 normal human fetuses; 11 of them were female and 4 were male. The gestational age of the fetuses ranged between 14 weeks and 35 weeks, and they weighed between 180 g and 1750 g. The FT of each fetus was cut and examined for adipose tissue, fibrous tissue, peripheral nerve, ganglion, ependymal cells, gliosis, elastic fibers, and collagen types (Types I and III).

Results. Adipose tissue was observed in 2 specimens (13%), whereas fibrous tissue was found in 8 specimens. Peripheral nerve was detected in 11 (73%), ganglion in 6, ependymal cells in 5, and glial tissue in 7 FT samples. Type III collagen was present in 12 specimens (80%) with different concentrations, whereas Type I collagen and elastic fibers were not detected.

Conclusions. The normal structure of the FT in fetuses is different from its structure in adults. The FT has no elasticity during intrauterine life because of the lack of elastic fibers. More detailed studies are needed to understand the histological basis of TCS in children.

(\text{http://thejns.org/doi/abs/10.3171/2014.1.PEDS13520})

\textbf{Key Words} \quad \text{filum terminale} \quad \text{histology} \quad \text{fetus} \quad \text{congenital} \quad \text{tethered cord syndrome}
Fetal filum terminale

search on the structure of the FT in normal human fetuses has not been reported.

The aim of our study was to reveal the architecture of the FT in normal human fetuses and to find some clues to the pathophysiology of TCS. The data from this study were compared with the previous ones, and the possible factors that play a role in the development of TCS were also emphasized.

Methods

Fifteen normal human fetuses were dissected for the histological analysis of the FT. Ethical approval for this study was obtained from the National Ethics Committee. The study was conducted in the Microsurgery Training and Research Laboratory of our institution. The fetuses were premature stillborns and were obtained from the Department of Obstetrics. Eleven of them were female and 4 were male. The gestational age of the fetuses ranged between 14 weeks and 35 weeks, and they weighed between 180 g and 1750 g. None of them had a malformation on gross anatomical examination. A wide lumbosacral laminectomy was performed. After opening the dura mater, the conus medullaris and the FT were carefully identified. One-centimeter-long segments of FT were selected and removed for histological studies. Serial longitudinal and transverse sections were obtained. First, sections were stained with H & E, and then Verhoeff van Gieson stain (Biostain) was used for histochemical analysis of the elastic fibers. For immunohistochemical examination, antigen retrieval was done by citrate. Anticollagen 1A1 (monoclonal, 1:100; Santa Cruz) and anticollagen 3 (monoclonal, 1:100; Biogenex) primary antibodies were applied using the indirect peroxidase method. The FT was examined for adipose tissue, fibrous tissue, peripheral nerve, ganglion, ependymal cells, glial tissue, and collagen types (Types I and III).

Results

High-power light microscopy findings were fairly homogeneous among all specimens. The histological data of the specimens are shown in Table 1. Hematoxylin and eosin staining of the FT confirmed findings of previous studies. The bulk of the FT is indeed composed of loose connective tissue; its collagen fibers are stained pink with H & E under light microscopy. Adipose tissue was observed in 2 fetuses (13%), which were at 25 and 15 gestational weeks. Fibrous tissue was observed in 8 fetuses (53%), with different densities. There was no meningothalial proliferation in any FT sample. Peripheral nerve was seen in 11 fetuses (73%) and ganglion in 6 fetuses. Ependymal cells were observed in 5 fetuses. Gliosis was not observed, but glial tissue was detected in 7 FT samples. Based on our histological findings, 2 different types of FT were observed and defined. The histological features of these types are documented below.

Type 1 FT

Demyelinated nerve fascicles surrounded with epi-neurium, ganglion cells in clusters (ganglions), and longitudinal collagen bundles that were tightly attached to each other were observed in this type of FT (Fig. 1). Immunohistochemical investigation showed that these collagen bundles contained Type III collagen (Fig. 2). No elastic fibers or Type I collagen was detected in Type 1 FT. There was a loose connective tissue between the collagen bundles. In addition, primitive fusiform cells and vascular structures were scattered haphazardly in this connective tissue. Adipocyte clusters accompanied these structures in only 2 samples.

Type 2 FT

The main components of this type of FT were epen-

TABLE 1: Summary of histological findings in FT specimens obtained in 15 normal, stillborn human fetuses*

<table>
<thead>
<tr>
<th>Fetus No.</th>
<th>Gestational Wk/Sex</th>
<th>Adipose Tissue</th>
<th>Fibrous Tissue</th>
<th>Peripheral Nerve</th>
<th>Ganglion</th>
<th>Ependymal Cell</th>
<th>Glial Tissue</th>
<th>Type I Collagen</th>
<th>Type III Collagen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35/M</td>
<td>−</td>
<td>−</td>
<td>+++</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>15/F</td>
<td>+</td>
<td>−</td>
<td>+++</td>
<td>++</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>25/F</td>
<td>+</td>
<td>−</td>
<td>+++</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>4</td>
<td>27/F</td>
<td>−</td>
<td>++</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>5</td>
<td>35/F</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>30/M</td>
<td>−</td>
<td>+++</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>7</td>
<td>28/F</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+++</td>
<td>++</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>34/F</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>20/F</td>
<td>−</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>−</td>
<td>++</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>24/F</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>25/F</td>
<td>−</td>
<td>+</td>
<td>+++</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>24/F</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
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<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>14</td>
<td>23/F</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+++</td>
<td>+++</td>
<td>−</td>
<td>−</td>
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<td>15</td>
<td>14/M</td>
<td>−</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>

* + = sparse; ++ = moderate; +++ = dense; − = none.
dymal cells lining the central canal and the surrounding glial tissue (Fig. 3). These components were surrounded with a thin connective tissue (probably pia mater) and transformed to a longitudinal structure with fusiform cells, which were lined up in a parallel fashion (like a balloon with rope). Type III collagen fiber was also shown in this longitudinal structure (Fig. 4). No elastic fibers or Type I collagen was detected in Type 2 FT.

Type 1 FT was observed in 5 fetuses (34%), in which the gestational age ranged between 14 and 35 weeks, whereas Type 2 FT was found in 10 fetuses (66%) ranging between 23 and 35 weeks. Type 2 FT was mainly found in older fetuses and Type 1 FT in younger. In addition, Type I collagen fibers were not observed in any sample, but Type III collagen was observed in both types of FT.

**Discussion**

In this study we tried to elucidate the histological structure of FT in normal human fetuses. Although many characteristics of fetal FT are similar to those in previous studies, the lack of Type I collagen fibers and elastic fibers in the fetus is an important finding of the present study. In addition, the location of Type III collagen was mainly in the perineurium and in perivascular spaces in the fetal FT. This is different from findings in FT studies. Presence of glial tissue, but lack of gliosis and elastic fibers, showed that the FT has no elasticity during intrauterine life.

Following neurulation, the distal neural tube undergoes canalization. The distal neural tube forms from fused vacuoles that develop from the caudal cell mass. This structure, in turn, develops into the conus medullaris, cauda equina, and FT. When a developmental defect occurs in the spinal cord or neural tube during intrauterine life, the spinal cord becomes stuck somewhere along its axis and cannot untether itself from the rapidly growing spinal column. As a result, tethering of the spinal cord occurs during fetal life. In our study, we showed that elastic fibers are not present in the fetal FT, so the elasticity of FT is low.
Since the term “tethered cord syndrome” was first used by Hoffman et al. in 1976, the normal structure of FT and its contribution to the pathophysiology of TCS have been under investigation. Knowledge about the pathophysiological features of this syndrome was advanced by Yamada and colleagues who, using an experimental model of spinal cord tethering, found evidence of cellular ischemia in the spinal cord. However, recently it was shown that the structure of the FT also plays an important role in the development of TCS. Both morphological and ultrastructural characteristics of FT in normal human bodies and in patients with TCS have been well documented and published in the literature. However, the normal structure of FT in human fetuses has only been studied by a few scientists.

The first study on the ultrastructural properties of the FT in fetuses was performed by Gamble in 1971. He worked on 18 human fetuses and found that the outer surface of the FT was contorted by indentation or deep cavitation; the surface of the cavity was often itself irregular. He concluded that transformation of the caudal part of the human fetal spinal cord into conus medullaris and FT is accompanied by a number of degenerative processes occurring simultaneously. In our study, we did not find any evidence of degenerative processes in the fetal FT.

Collagen is a group of naturally occurring proteins found in animals. It is the main component of connective tissue and is the most abundant protein in mammals, making up approximately 25%–35% of the whole-body protein content. Collagen occurs in many places throughout the body. Twenty-nine types of collagen have been identified in the human body. Type I collagen is the most abundant protein in humans, and it helps to maintain the integrity of many tissues via its interactions with cell surfaces, other extracellular matrix molecules, and growth and differentiation factors. Type I collagen is the main component of skin, tendon, vascular ligature, organs, and bones. Type III collagen is a fibril-forming collagen comprising three α(I)III chains and is expressed in early embryos and throughout embryogenesis. It is the main component of reticular fibers and is commonly found in association with Type I collagen. Fontes et al. investigated the ultrastructural properties of normal FT in 20 adult human cadavers. They proposed that the altered elasticity of the FT plays a role in the development of TCS. The changes in proportion of Type I to Type III collagen or elastic fibers are the possible causes of altered elasticity in the FT according to these investigators. If the 3D structure of FT is destroyed, it will result in low elasticity. The decrease of elastin formation or the increase of elastin degradation may be relevant to the elasticity of the FT. In our study we showed that Type I collagen and elastic fibers did not exist in the fetal filum samples. Type III collagen was observed around the perineurium of peripheral nerve and the walls of filum vessels. Therefore, the elasticity of the FT is probably low during intrauterine life.

Liu et al. recently performed a study on FT samples that were obtained in children with TCS. These investiga-
tors concluded that low elasticity resulting from the destruction of the 3D structure of the FT is involved in the development of TCS. They also suggested that cutting the FT in the early period of TCS is the treatment of choice, whether or not its appearance is normal. Selçuki et al.21 also suggested that the morphological appearance of the FT may be normal in children with TCS. In our study we showed that the structure of the FT is different in the fetus from its structure in the adult, and that it is difficult to define an FT as normal or not according to morphological or histological features. Similarly, Selden et al.22 investigated the occurrence of anatomical abnormalities of the FT in children undergoing surgical filum lysis for minimal TCS. They found that the FT samples were composed principally of neurovascular bundles with minimal fibrous tissue. No inflammation was identified in the FT of patients in either group. These investigators also suggested that loss of elasticity in the filum may be the cause of minimal TCS.

Recently, Gaddam et al.4 dissected 13 fresh stillborn cadavers. They investigated the connections between the FT and the nerve roots of the cauda equina, and sectioned these connections, when present, for histological studies. They concluded that gross anatomical connections were present between the FT and nerve roots that contain nerve fibers. In our study we could not find any connection between the FT and nerve roots of the cauda equina during the dissection of the FT in fetuses. However, we detected many peripheral nerve structures in the fetal FT. These nerves may be connected with the nerve roots of the cauda equina.

Tehli et al.26 published a study on the structure of FT obtained in patients with TCS and compared those results with 4 fetal FT samples. They found that adipose tissue, fibrosis, hyalination, and meningothelial proliferation were observed in FT samples of TCS, but that none of these findings were observed in fetal samples. They also showed that elastic fibers were present in all TCS specimens and in an adult cadaver, but were not observed in fetuses. Only peripheral nerves, ganglion cells, and ependymal cells were observed in fetal FT samples. Our results were similar to those of Tehli et al., but we investigated in detail the structure of collagen fibers and we showed the lack of Type I collagen and elastic fibers in fetal FT.

Conclusions
Fetal FT is histologically different from adult FT; fetal FT does not contain Type I collagen and elastic fibers. These structures probably develop after birth. Lack of elastic fibers and Type I collagen may affect the elasticity of the FT during intrauterine life. More histological studies with different staining techniques are required to reveal the exact pathophysiology of TCS.

Disclosure
There are no disclosures to be made regarding funding or relationships with industry for this work. There is no conflict of interest. Author contributions to the study and manuscript preparation include the following. Conception and design: İzcı, Kural, Arslan, Tehli. Acquisition of data: Kural, Arslan, Tehli. Analysis and interpretation of data: Kural, Guresci, Simsek. Drafting the article: Simsek, Tehli. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: İzcı. Administrative/technical/material support: İzcı.

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