Cervical Discopathy in Idiopathic Trigeminal Neuralgia: More than Coincidence?

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Research

Keywords: Trigeminal neuralgia, etiology, cervical discopathy, spinal trigeminal nucleus, pain

Posted Date: November 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1031443/v1

Abstract

Background

The most common cause of trigeminal neuralgia (TN) is neurovascular compression. However, a number of patients present with unknown etiology. This study aims to investigate the relationship between TN and cervical pathology in patients previously diagnosed with idiopathic TN.

Methods

We designed an observational case-control study. A study group consisting of patients previously diagnosed with idiopathic TN and a control group was included in the study. Cranial MRI's of TN patients were re-evaluated by a blinded neuroradiologist. Once it was confirmed that no signs of neurovascular compression or any secondary causes were present, a cervical MRI was performed to evaluate cervical pathologies.

Results

20 patients and 20 controls were investigated. The mean age of TN patients was 64.9±12.6, and the mean age of the control group was 61.3±9.1 (p=0.305). Whilst indentation on the trigeminal spinal tract above C4 spinal level was observed in 12 out of 20 patients, none of the controls had any involvement in the same region (p<0.001).

Conclusions

The results of this study suggest that extramedullary indentation on the trigeminal spinal tract caused by upper cervical discopathy may be one of the possible etiological factors in TN.

Background

Trigeminal neuralgia (TN) is an extremely debilitating condition characterized by a unilateral sudden stabbing, shock-like, and electrocution type paroxysmal pain in one or more divisions of the trigeminal nerve triggered by innocuous stimuli. Under the International Classification of Headache Disorders (ICHD-3) diagnostic criteria, TN is divided into classical, secondary and idiopathic trigeminal neuralgia [1]. New diagnostic criteria are developed based on several clinical pieces of research. [1-4] Classical trigeminal neuralgia, which is caused by neurovascular compression, is the most common form of TN. [3,5] Secondary TN, which accounts for approximately 15% of cases, results from an external cause like tumor or multiple sclerosis. [1,3,6] TN of unidentified etiology is labeled idiopathic. [1]

Anatomy of Trigeminal Nerve

The trigeminal nerve, the largest cranial nerve with three main branches, provides sensory innervations of the teeth, intracranial structures, neck, face and head. In addition, it has motor branches that innervate the

masticatory muscles including the masseter, lateral pterygoid and temporalis muscles. The sensory root, which extends from the ganglion, enters into the pons and terminates three major nuclear complexes within the brainstem. [7]

Trigeminal sensory nuclei

The trigeminal nerve has three sensory nuclei, which extend from the superior part of the midbrain to the cervical region in continuity of each other.

The mesencephalic nucleus: Lies on the upper part of the principal nucleus, processing information from all three branches of the trigeminal nerve, sending fibers to the motor nucleus, thalamus reticular formation, and the cerebellum.

Principles nucleus: Also called the pontine trigeminal nucleus, is the largest nucleus of the trigeminal nerve. Though it processes many kinds of somatosensory information, its main function is to discriminate touch and pressure.

The spinal trigeminal nucleus: Also known as the spinal trigeminal tract nucleus, the main function of this third sensory nucleus is to process nociceptive information from the trigeminal system. It extends from the principal nucleus inferiorly and connects with the substantia gelatinosa of the cervical spinal cord. It was previously assumed that the spinal trigeminal nucleus ends at the C1-C2 spinal level. However, several researchers have demonstrated in cats that the spinal trigeminal tract conveys fibers that stretch through the substantia gelatinosa of the spinal cord as far caudally as the level of T9 or even throughout the spinal cord. [7-10] Other researchers have demonstrated that the spinal trigeminal tract continues in the spinal cord as far caudally as the eighth cervical vertebra, the ninth thoracic segment, and some through the entire length of the spinal cord. [11,12] The spinal trigeminal nucleus has three subdivisions, *subnucleus oralis, subnucleus interpolaris, subnucleus caudalis.*

The subnucleus oralis, is the most superior of the three subnuclei and is divided into three subdivisions. It extends from the caudal pole of the motor nucleus of the trigeminal nerve inferiorly to the rostral or superior pole of the nucleus of the facial nerve. It receives afferents transmitting the sensations of temperature and pain from the face. [9]

The subnucleus interpolaris, is localized between the subnucleus oralis and subnucleus caudalis, extending from the rostral pole of the hypoglossal nucleus caudally to the obex. It has been postulated that this subnucleus is responsible for processing dental pain. [10]

The subnucleus caudalis, is the most inferior or caudal portion of the spinal nucleus of the trigeminal nerve and is continuous inferiorly with the substantia gelatinosa in the dorsal horn of the cervical spinal cord. The nucleus is primarily responsible for transmitting pain from the face and mouth. [8, 11-13]

Clinical Rationale for the Study

It is well-known that vascular contact has not been observed in a wide range (4%–89%) of TN patients. [5,6,14-16] Similarly, a considerable number of patients in our clinic were diagnosed with idiopathic TN due to no etiological factors being present.

A recent new hypothesis suggests that pathological changes in the upper cervical region create a change in the trigeminal spinal tract that results in TN. It has been argued that TN can be a result of pathology in the subnucleus oralis because the distribution of the trigger zone in the facial area is in line with the subnucleus oralis. [9] Additionally, a number of case reports have identified that the lesion in the upper cervical region can cause TN. [17,18]

As far as we know, there are no studies that have illustrated upper cervical discopathy resulting in TN. The aim of this study is to investigate whether there is a relationship between TN and cervical discopathy.

Methods

The study was designed as an observational case-control study. The STROBE guideline and checklist was followed. [19] It was conducted on patients admitted to the outpatient neurology clinic of a university hospital between 2018 and 2019. Patients who had a prior diagnosis of idiopathic TN and a control group consisting of patients with tension-type headache were included in the study. Both patient groups were examined by the same experienced neurologist. Radiological findings were evaluated by a blinded neuroradiologist.

Inclusion Criteria:

-A prior diagnosis of “idiopathic TN” according to ICHD-3

-18 years of age and above

-No pathological findings on cranial MRI

-Written consent given

-No systemic illnesses.

Evaluation of clinical characteristics:

All patients’ data including age, gender, duration of disease, side and involved branches of TN, pain severity (Visual Analogue Scale (VAS)), pain frequency (per day) and medical treatment were recorded.

Clinical symptoms of upper cervical discopathy such as neck pain, shoulder pain, chest pain, pain in the auricular area and occipital area were evaluated and recorded.

Patients previously diagnosed with idiopathic TN were re-examined, their cranial MRI’s were re-evaluated by a neuroradiologist. After confirming that no signs of neurovascular compression or any secondary

causes were present, a cervical MRI was performed to evaluate cervical pathologies.

Evaluation of MRI findings

MRI images were taken using a 1.5 Tesla magnet. Cervical MRI evaluation was carried out using sagittal fast spin-echo T1 and T2 and axial T2 weighted images. Section thickness was 3 mm. During cervical MRI evaluation, the spinal trigeminal tract was determined using Afshar's stereotactic atlas. [20] Assuming that the spinal trigeminal nucleus extends to the level of C4, and continues in the Lissauer's tract and the medulla spinalis, the level of the lesions were divided into two, above C4 level and below C4 level. [21] The level at which indentation was most pronounced was considered the level of the lesion.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 21.0 SPSS Inc., Chicago, IL, USA) for Windows. Frequency distribution, percentage, mean, standard deviation, median, and range were calculated where appropriate. The Chi-square test (x2) was used for categorical variables whilst the t-test was used for continuous variables under parametric conditions. Results were considered to be statistically significant at the level of $p < 0.05$.

Results

20 patients with a prior diagnosis of idiopathic trigeminal neuralgia and a control group consisting of 20 patients with tension-type headache were included in the study.

The mean age of TN patients was 64.9±12.6, and the mean age of the control group was 61.3±9.1 (p=0.305). The male/female ratio in TN patients was 2.3 and 1.8 in the control group (p=0.736).

All patients with TN had at least one of the additional following symptoms, ipsilateral neck pain, ear-auricular pain, periorbital pain, chest pain, or shoulder pain. The symptoms of the patients are illustrated in table 1.

Characteristics of Trigeminal Neuralgia

9 patients had TN on the right side, and 11 had TN on the left side. 6 patients had isolated maxillary branch involvement. 5 patients had isolated mandibular branch involvement. 2 patients had isolated ophthalmic branch involvement. 7 patients had both maxillary and mandibular branch involvement. Mean pain severity VAS was 8.6±1.7. The mean frequency of pain was found to be 124.7±113.5 per day. All patients were being treated with carbamazepine (16), pregabalin (12), gabapentin (9), and duloxetine (5).

An extramedullary, ipsilateral trigeminal spinal tract indentation above C4 level was seen in 12/20 patients whilst no indentation was seen in the control group ($p<0.001$). 5 patients had an involvement

under C4 level. No signs of changes were seen in 3 patients in the extension of the trigeminal spinal tract area.

Patients with TN on the right side,

7 of 9 patients with TN had an ipsilateral indentation on the spinal trigeminal tract and its caudal extension. 5 of 7 patients had a lesion above C4 level. 2 of the 7 patients had a lesion under C4 level. 2 patients had no involvement.

Patients with TN on the left side,

9 out of 11 patients with TN on the left side had an ipsilateral indentation on the spinal trigeminal tract and its caudal extension. 7 patients had a lesion above C4 level, whilst 2 patients had a lesion under C4 level. In addition, 1 patient had a contralateral indentation under C4 level. 1 patient had no signs of any lesions. The radiological findings are shown in table 2. MRI examples of patients are shown in figure 1,2,3,4. A comparison of the two groups is shown in table 3.

Discussion

This study illustrates that two-thirds of patients who did not have intracranial findings on MRI and had a previous diagnosis of idiopathic TN have an ipsilateral extramedullary indentation on the spinal trigeminal tract. Compression caused by upper cervical discopathy can lead to trigeminal neuralgia in two different ways, either by direct indentation of the trigeminal spinal tract or by indirect anatomical, biochemical or functional impairment of the trigeminocervical complex coming from the dorsal roots and dorsal horn. As far as we know, there is no research investigating the relationship between upper cervical discopathy and trigeminal neuralgia. However, there are some case reports which indicate that any pathology on the upper cervical region can cause TN.

One case reported that cervical discopathy on the level of C3-C4 resulted in trigeminal sensory neuropathy by affecting the spinal trigeminal tract. Surgical removal of the disk resulted in an immediate and complete resolution of TN symptoms in the patient. [22] Francois et al. demonstrated trigeminal neuralgia in 3 cases after post-traumatic cervical discopathy. Patients' symptoms of trigeminal neuralgia were reported to have disappeared after surgical decompression. It has been claimed that the cause of the pain may be due to compression of the spinal trigeminal tract. They argue that the spinal trigeminal nucleus can also extend to the lower cervical region. [23] Similarly, in our study, 25% of patients had an indentation on the Lissauer's tract which is the continuation of the trigeminal spinal tract. In another paper, Samim et al. demonstrated 6 cases that had orofacial neuralgia associated with whiplash trauma. The pain of these patients has been described as typical trigeminal neuralgia. 2 out of 6 patients had bulging between C2-C6 levels. [24]

There are many studies reporting that neuropathic pain develops as a result of spinal cord injuries. It has been reported that any pathology in the spinal cord may cause hyperexcitability in the dorsal horn. [25,26]

This might occur through dysregulation of glutamate release, uptake and receptor expression, [25,27-29] dendritic spine remodeling, [30,31] loss of local inhibitory (GABAergic) tone, [32-36] descending (particularly serotonergic) inhibitory input to spinal nociceptive circuitry, [28,39,40] or increased expression of calcium channel subunit. [39] Within a few months of spinal cord injury, NADPH-diphosphorase abnormality is seen in the nucleus cunaetus, nucleus gracilis, and spinal trigeminal tract of rats. [40] Neuropathic pain may be experienced by about 80% of individuals who sustain spinal cord injury. [41-43]

Some studies have pointed out the role of dorsal root ganglion in neuropathic pain. It is reported that chronic dorsal ganglia involvement can induce long-lasting N-methyl-D-aspartate receptor subunit 2B and neuronal nitric oxide synthase (nNOS) up-regulation in the spinal dorsal horn. This up-regulation may contribute to nociceptors activity-induced spinal plasticity and the development of central sensitization and a close correlation between nNOS and neuropathic pain has been demonstrated. [44,45] After peripheral afferent fiber injury, a cascade of events within the dorsal root ganglion and upstream within the dorsal horn of the spinal cord leads to a constitutive release of cytokines, production of abnormal ion channels, abnormal ion currents, early and late gene changes and the development of chronic neuropathic pain. [46,47] It has been observed that compression with disc herniation may cause the spread of neuropathology from the dorsal part to the ventral area of the spinal cord. [48]

It is well-known that the trigeminocervical complex plays the main role in many primary headaches. Kerr and Olafson were first to describe the trigeminocervical complex, which is formed by the association of the caudal trigeminal nucleus and the upper cervical segments. [13] The pathogenic mechanism is hypothesized to involve the convergence of the upper cervical afferents from the C1, C2, and C3 spinal nerves and trigeminal afferents in the trigeminocervical nucleus of the upper cervical cord. [49,50] Functional convergence of the upper cervical and trigeminal sensory pathways seems to allow the bidirectional referral of pain to the occipital, frontal, temporal, and/or orbital areas. [51] However, several previous studies have reported that lower cervical spine diseases (below C4) can also cause headache, to this end, it is not clear whether the middle-lower cervical roots also project into the trigeminocervical nucleus in humans. [49,51-53] The excitability of the second-order neurons within the trigeminal subnucleus caudalis has been shown to be responsible for pain perception and processing in migraine and trigeminal neuralgia. [54]

Our study shows that patients with upper cervical discopathy have a wide range of symptoms that can be mistaken for diseases such as ear, eye or heart pathologies in clinical practice. Chen et al. also reported that various symptoms including headache, perioral hyperesthesia, dizziness and tinnitus could be found in patients with upper cervical discopathy. [55]

Limitation of the study

The main limitation of this study is not being prospective. Not observing the results of surgical procedures that may have done to patients such as cervical decompression is a major limitation. Another

limitation is that the MRI device used is a low-level Tesla. Additionally, a standard rather than specialized MRI protocol is used to investigate the cranial and cervical regions. It is very difficult to locate and explore the cervical region in a routine MRI scan due to it being anatomically small in humans.

In conclusion, cervical discopathy may be more than coincidence in patients with trigeminal neuralgia. Due to its being observed in a considerable number of all TN patients, before diagnosing idiopathic trigeminal neuralgia, the cervical region must be investigated more carefully. New clinical and experimental trials that are focusing on upper cervical region are needed to shed light to this subject

Declarations

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Afyonkarahisar University of Health Sciences local ethics committee. Approval number: 2011-KAEK-2/2019/147.

Acknowledgments

We thank our all colleagues from Afyonkarahisar and Istanbul who provided insight and expertise that greatly assisted their research. We also thank Jessica Wells for editing and proofreading the manuscripts.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors have no financial conflicts of interest.

Declaration of funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

The data that supports the findings of this study is available on request from the corresponding author CB.

Statements

The manuscript has been read and approved by all the authors, the requirements for authorship have been met and each author believes that the manuscript represents honest work.

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Tables

Table 1 Additional clinical symptoms of patients with TN

	Number of the patients
Ipsilateral nape/neck pain	17 (85%)
Ipsilateral ear/auricular pain	11 (55%)
Ipsilateral periorbital pain	6 (30%)
Ipsilateral chest pain	8 (40%)
Ipsilateral shoulder pain	9 (45%)

Table 2 Radiological Findings of TN Patients

Patient number	TN side	Involved Branch	Compression level of STT	Compression side
1	Right	Maxillary+mandibular	C2	Right
2	Right	Maxillary+mandibular	C3	Bilateral
3	Right	Maxillary+mandibular	C4	Right
4	Right	Maxillary	C4	Right
5	Right	Maxillary	C4	Right
6	Right	Mandibular	C5	Bilateral
7	Right	Maxillary+mandibular	C5	Bilateral
8	Right	Mandibular	-	-
9	Right	Mandibular	-	-
10	Left	Mandibular	C3	Bilateral
11	Left	Maxillary	C3	Left
12	Left	Maxillary	C3	Bilateral
13	Left	Mandibular	C3	Left
14	Left	Opthalmic	C4	Left
15	Left	Opthalmic	C4	Left
16	Left	Maxillary+mandibular	C4	Left
17	Left	Maxillary	C5	Left
18	Left	Maxillary	C5	Left
19	Left	Maxillary+mandibular	C6	Right
20	Left	Maxillary+mandibular	-	-

TN: trigeminal neuralgia, STT: spinal trigeminal tract

Table 3 Comparison of the TN patients and controls

	Patients with TN n=20	Controls n=20	p
Age (y)	64.9±12.6	61.3±9.1	0.305
Female/Male ratio	2.3	1.8	0.736
Indentation to trigeminal spinal tractus	12	0	**<0.001**
Gliosis in medulla spinalis	9	0	**0.001**
Signal changes in nucleus	18	19	0.5
Signal changes in bone marrow	4	0	0.106

Figures

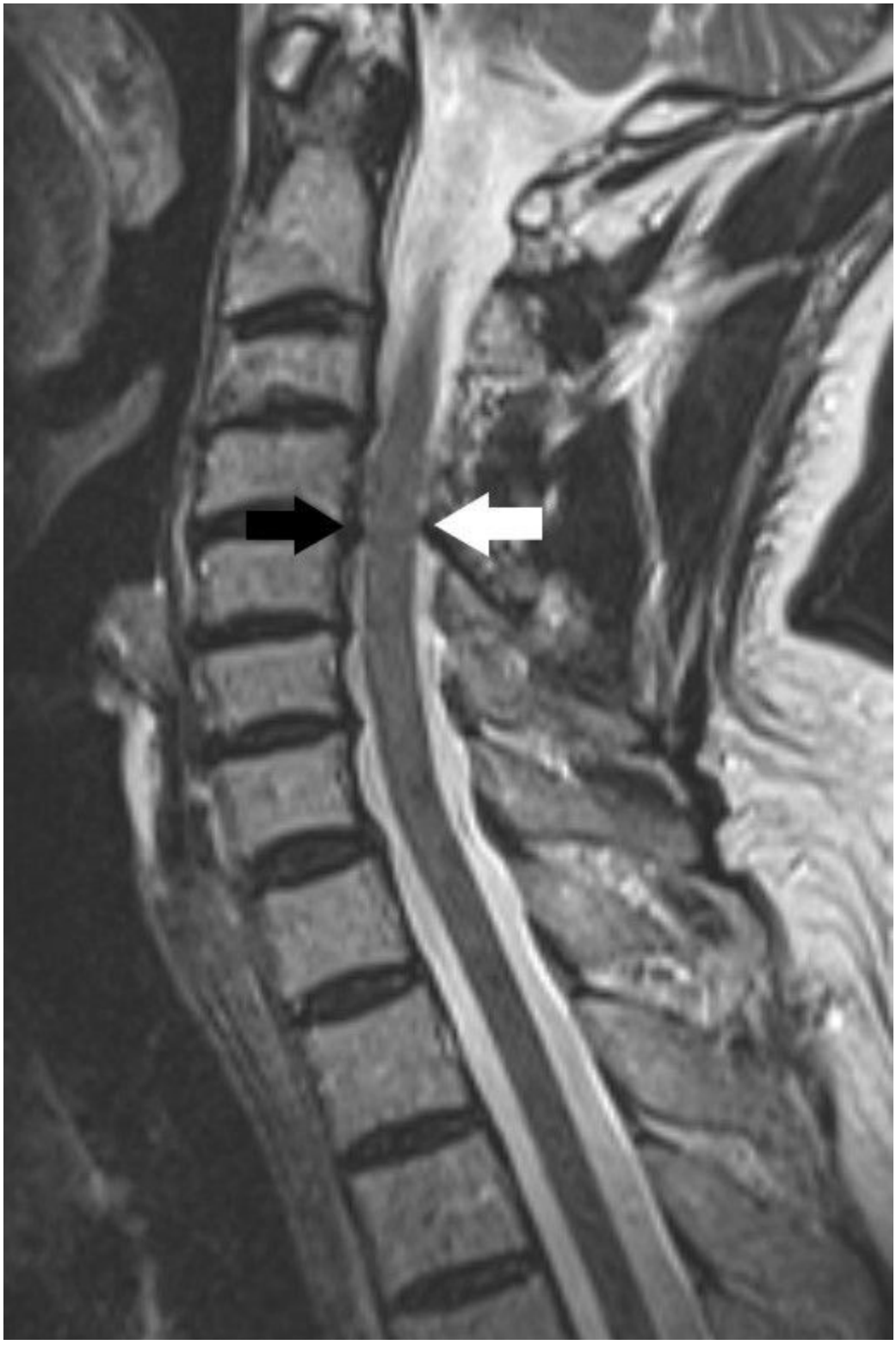

Figure 1

A 63-years-old male patient. Protruded disc at the level of C4-C5 (black arrow) and hypertrophy of ligamentum flavum (white arrow)

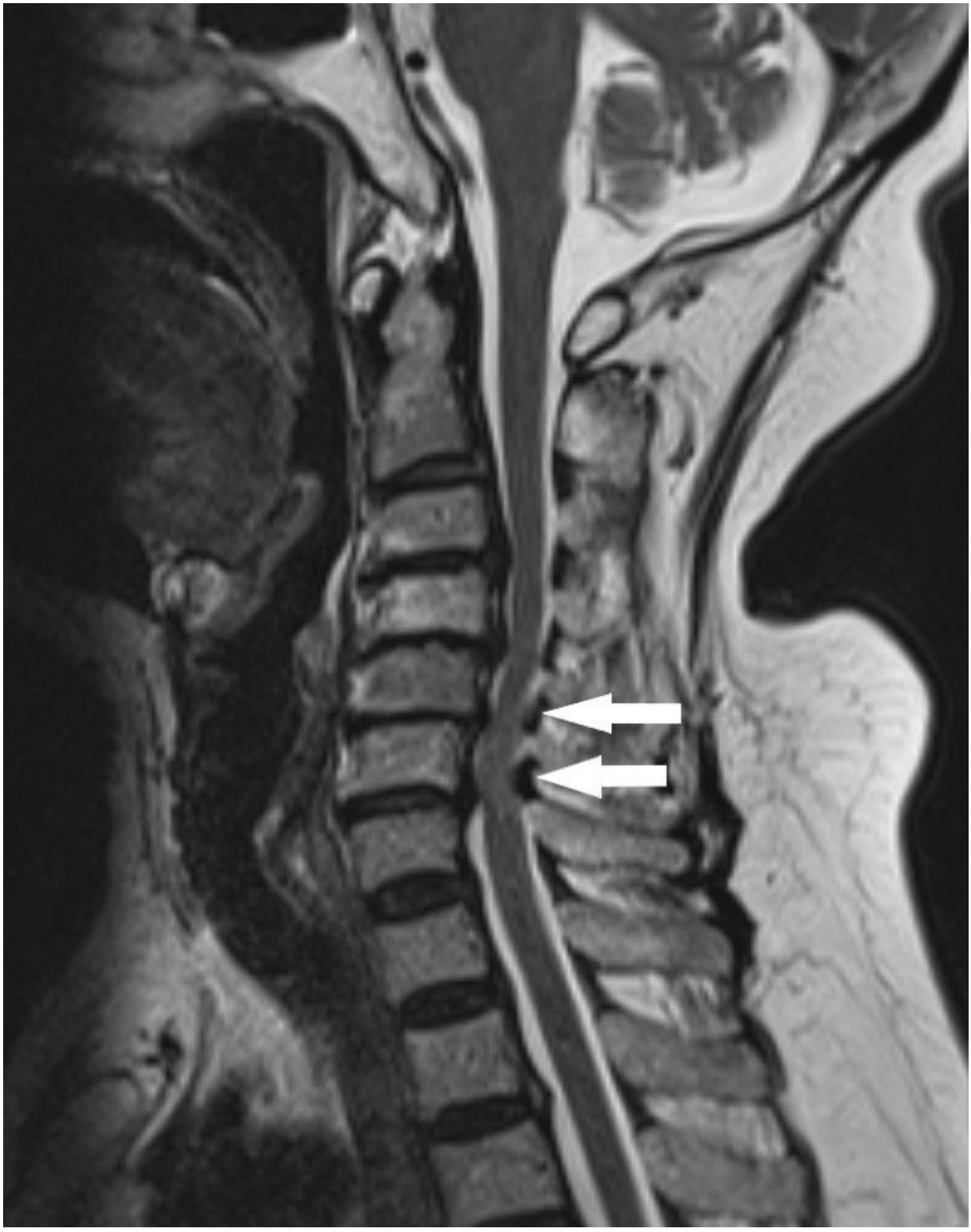

Figure 2

A 78-years-old female patient. Hypertrophy of ligamentum flavum and the compression of the medulla spinalis (white arrows).

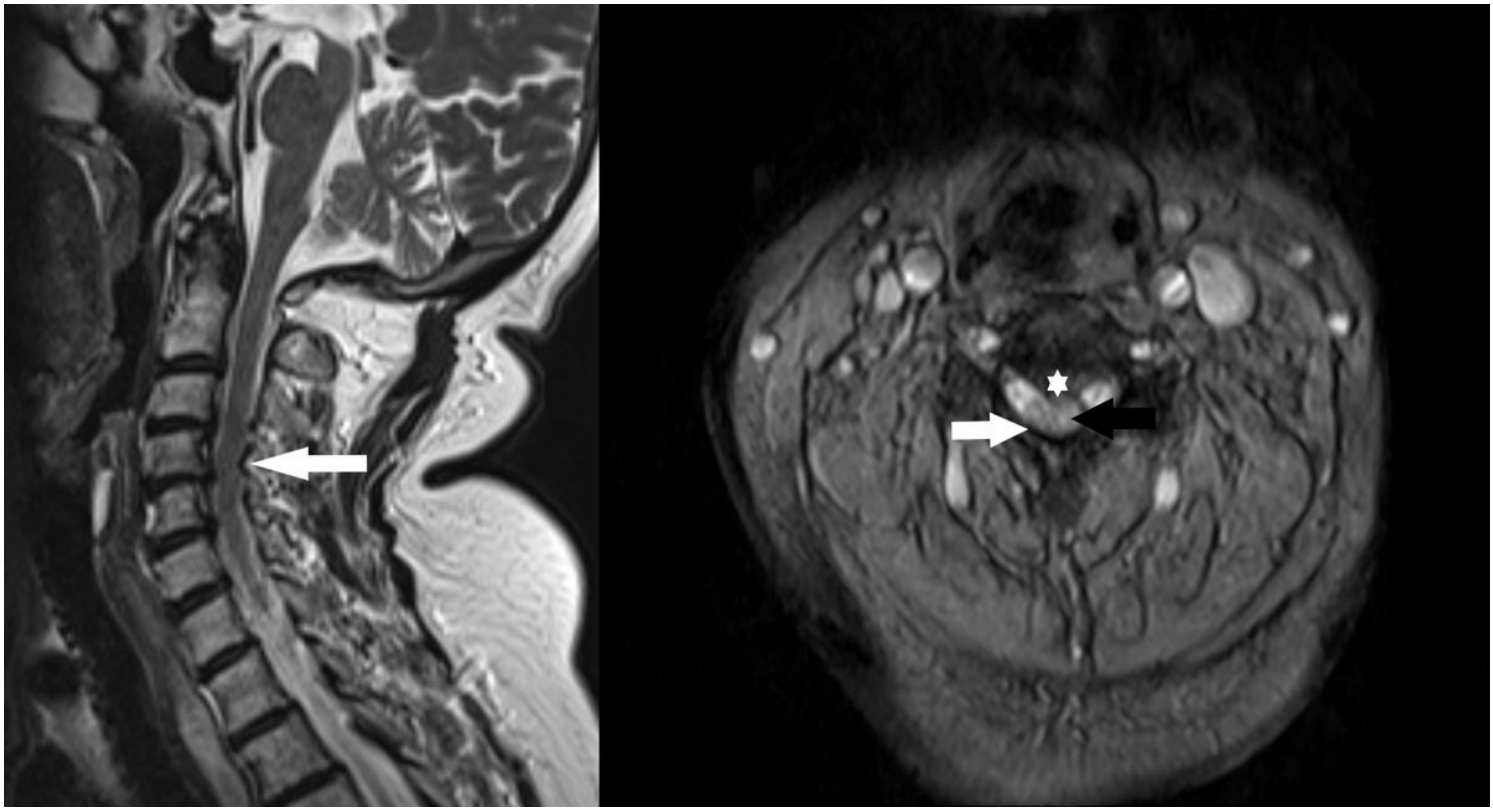

Figure 3

A 71-years-old female patient. Sagittal plane: hypertrophy of ligamentum flavum and compression of the medulla spinalis (white arrow). Axial plane: medulla spinalis (black arrow), protruded disc (*), hypertrophy of ligamentum flavum and compression of the medulla spinalis (white arrow)

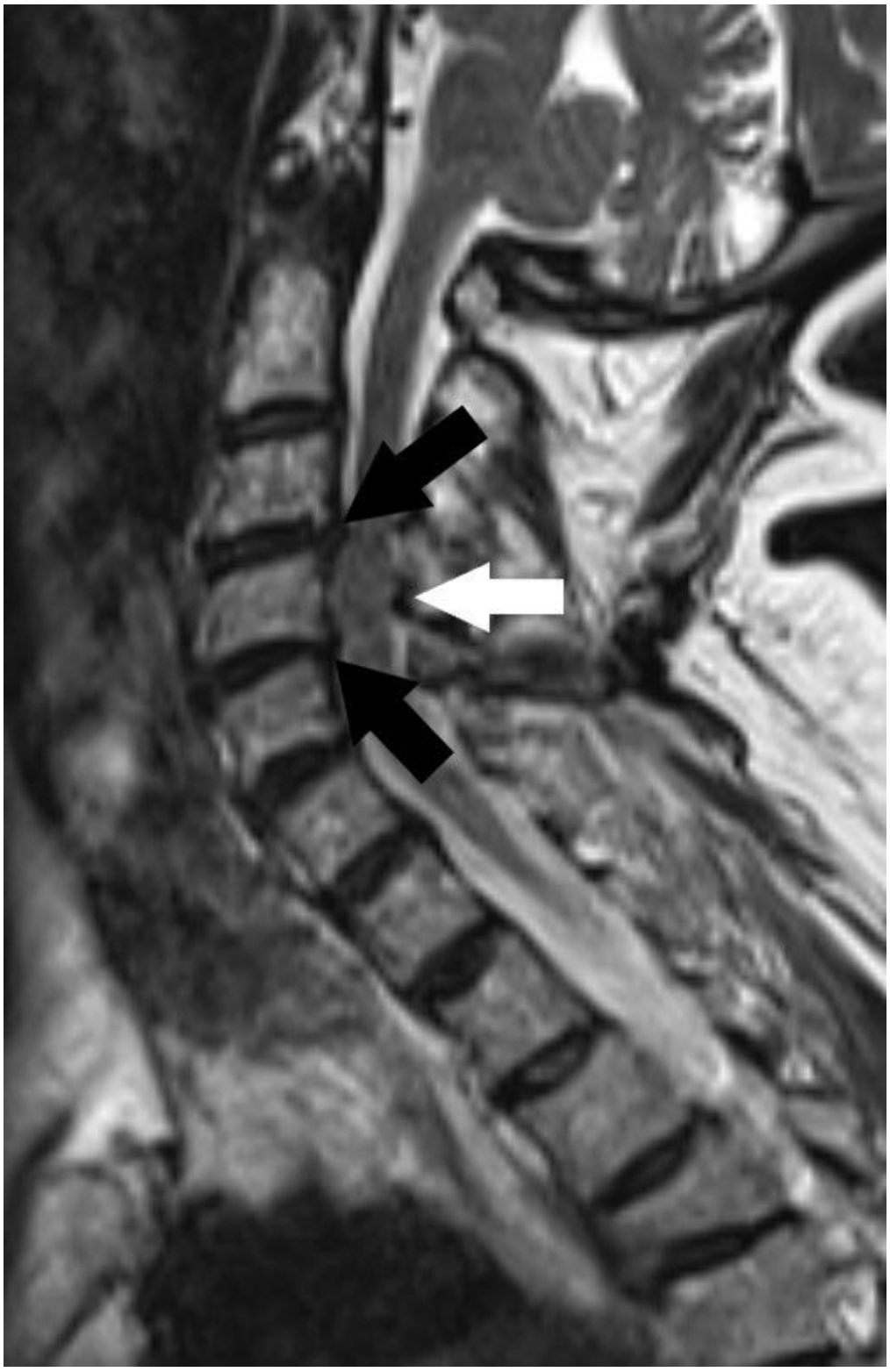

Figure 4

A 68-years-old female patient. Disc protrusions at the level of C3-C4 and C4-C5 (black arrows), hypertrophy of ligamentum flavum (white arrow)

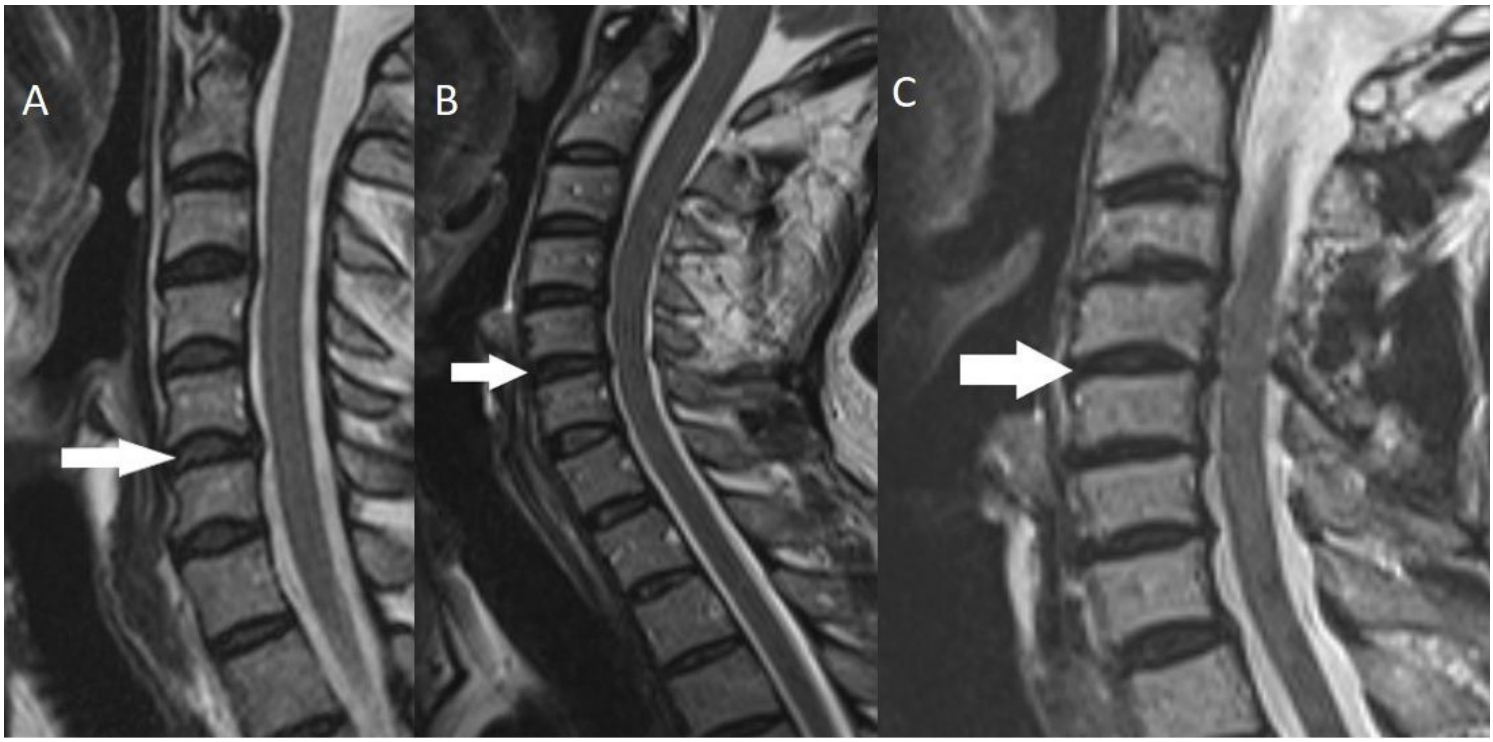

Figure 5

Legend not included with this version