

Ossification of the ligamentum flavum: Diet and genetics

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Abstract

Ossified ligamentum flavum (OLF) is being appreciated as an important cause of thoracic myeloradiculopathy. However, despite numerous epidemiological and basic science studies, the pathogenesis of OLF has not been conclusively established. Ossification and symptom development are significantly more frequent in the Japanese population, therefore supporting a genetic predilection for the disease process. We present an unusual case of OLF in a patient from a low-risk genetic background (Chinese), exposed in youth to a lifestyle and diet from a high-risk population (Japanese). Based on our case report, we support the view that dietary habits may constitute an independent risk factor for OLF and ossification of the posterior longitudinal ligament.

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Keywords: Ossification ligamentum flavum; Pathogenesis; Diet; Genetics

1. Introduction

Ossification of the ligamentum flavum (OLF) was first reported in the 1920s by Polgar using lateral radiographs,¹ and then further described by Yamaguchi and Isuruni as thickened/ossified ligamentum flavum. It is now appreciated as an important cause of thoracic myeloradiculopathy.^{2–4} Despite numerous epidemiological and basic science studies, the pathogenesis of OLF has not been conclusively established.⁵ Case reports from Caucasian, Afro-American and Asiatic populations have been documented,^{6,7} however, ossification and symptom development are significantly more frequent in the Japanese population, therefore supporting a genetic predilection for the disease process. Of all documented cases in the literature, the large majority are Japanese subjects (88.8%), with Caucasian patients being the next most prevalent (8.2%).⁸

Recent studies have revealed that bone morphogenetic proteins and transforming growth factors play an important role in the matrix hyperplasia and ossification of the spinal ligament. Human ligamentum flavum cells have been found to be susceptible to adenovirus-mediated markers, which suggests further possible genetic modifications.⁹ In addition, based on epidemiological data, dietary habits may constitute independent risk factors for OLF and ossification of the posterior longitudinal ligament (OPLL).¹⁰

We present an unusual case of OLF in a patient from a low-risk genetic background (Chinese), exposed in youth to

a lifestyle and diet from a high-risk population (Japanese). The role of lifestyle exposure is the positive link between background and pathology.

2. Case report

A 50-year-old man presented with progressive lower limb weakness over a 24-hour period from independent mobility to loss of lower extremity movement (specifically, leg/foot-lifting). He had a background history of cervical myelopathy from OPLL of the cervical spine, treated previously with a laminoplasty. An MRI scan was performed and demonstrated multilevel thoracic ossification of the ligamentum flavum (OLF). A lesion at T10/T11 (Fig. 1) was resulting in cord signal change on T2-weighted MRI and this compression was surgically addressed.

During surgery a calcified lesion in the region of the T10/11 ligamentum flavum was exposed. The lesion was firmly adhered to the dura with no discernable plane between OLF and dura. The bony lesion was removed using a high-speed drill and curettes. The arachnoid membrane was intact at the completion of the decompression and the dural defect was reconstructed with a dural graft substitute. In the postoperative phase, his power initially worsened for 48 hours, then improved, being suitable for early rehabilitation.

On review of his family history, the patient was of Chinese extraction, both parents being born and raised in mainland China. However, the patient was born in a coastal village in Japan, then lived in Japan for a further two decades prior to moving to North America. He described his upbringing as “standard Japanese”, including diet.

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Fig. 1. Sagittal T2-weighted MRI demonstrating significant compression at the T10/11 level with cord signal change. Multilevel ossification of the ligamentum flavum can be seen.

3. Discussion

The ligamentum flavum is a yellow elastic ligament extending from C2 to S1, composed of a longitudinal network of elastic connective tissue. Thickening of this ligament may lead to various neuronal compression syndromes, notably due to fibrosis of the ligaments secondary to degenerative change or ageing. Since the initial description of thoracic myelopathy due to OLF in 1964, there have been many reports in the literature. The thickened ligament may be calcified or ossified with appropriate attenuation on CT scan or MRI. Although not well understood, the etiology of OLF also includes trauma, diffuse idiopathic skeletal hyperostosis (DISH), ankylosing spondylosis, hemochromatosis, adenocarcinomatous metastasis, fluorosis and disorders of calcium and phosphorous.^{11–13} OLF predominantly affects men younger than 50 years.

Research into OLF has been predominantly by Japanese investigators, and relates to the prevalence of this condition in the Japanese population. Higher incidences of obesity and disturbance in glucose metabolism have been reported in patients with OPLL and OLF. However, the mechanisms by which obesity and disturbance in glucose metabolism contribute to the development of OLF remains unclear, with the obvious genetic influence a major contributor. Studies have shown that numerous growth factors regulate the development, growth, and maintenance of cartilage and bone tissues and that growth factors can initiate and stimulate new cartilage and bone formation at juxtasekeletal sites. Bone morphogenetic proteins and TGF- β may have important roles in the pathogenesis of OPLL and OLF; however, the link between these biochemical and genetic findings and lifestyle factors has not been definitively documented. Animal models have revealed that OLF and secondary spinal cord compression were produced in mice via implantation of bone

morphogenic protein in comparison with controls. Elevated plasma fibronectin concentrations acting as a promoter of fibroblasts in ligaments, resulting in endochondral ossification, is another proposed etiology for the pathogenesis of OLF.¹⁴ The role of genetic background in the development of OPLL and OLF has been demonstrated by pedigree surveys, twin surveys, and a human leukocyte antigen (HLA) haplotype study,¹⁵ with initial DNA analysis studies being conducted. Initial results indicate that abnormalities in Type XI collagen gene may be associated with OPLL and OLF.¹⁶

In addition to the considerable genetic profiling of OLF, lifestyle and diet is likely to be involved in the pathogenesis of this condition, with reports that patients with OPLL and OLF have a higher prevalence of obesity, diabetes mellitus, hyperinsulinism and impaired glucose tolerance.¹⁷ Our patient represents an unusual combination of race, lifestyle and pathology. There is only a single literature report of OLF in a Chinese subject,¹⁸ despite the immense Chinese population base. Although of Chinese extraction by birth, our patient was raised in Japan and has a pathology that is very common in Japan. Although there is a possibility that the combination is purely coincidental, this scenario is highly improbable. Therefore, the question remains that an aspect of our patients' upbringing is a factor with the pathogenesis of his OLF and OPLL, most likely lifestyle- and diet-related. Our report suggests that dietary habits may constitute independent risk factors for OLF as has been previously alluded to in regional population studies based in Japan. Further work will be needed to prospectively determine the relationship between dietary habits and OLF risk.

References

1. Polgar F. Uber interakuelle wirbelvercalcung. *Fortschr Geb Rongenstr Nuklearmed Ergänzungsband* 1920;**40**:292–8.
2. Yazmaguchi M, Tamagake S, Fujita S. A case of the ossification of the ligamentum flavum with spinal cord tumour symptoms. *Seikeigeka (Orthop Surg)* 1960;**11**:951–6.
3. Omojola MF, Cardosa ER, Fox AJ, et al. Thoracic myelopathy secondary to ossified ligamentum flavum. *J Neurosurg* 1982;**56**:448–50.
4. Miyasaka K, Kiyoshi K, Ito T, et al. Ossification of spinal ligaments causing thoracic radiculomyelopathy. *Radiology* 1982;**143**:463–8.
5. Fong S, Wong H. Thoracic myelopathy secondary to ligamentum flavum ossification. *Ann Acad Med Singapore* 2004;**33**:340–6.
6. Oostenbrugge RJ, Herpers MJ, Kruijk RJ. Spinal cord compression caused by unusual location and extension of ossified ligament flava in a Caucasian male. *Spine* 1999;**24**:486–8.
7. Shiraishi T, Crock HV, Lewis P. Thoracic myelopathy due to isolated ossification of the ligamentum flavum. *J Bone Joint Surg Br* 1995;**77**:131–3.
8. Pascal-Moussellard H, Cabre P, Smadja D, et al. Symptomatic ossification of the ligamentum flavum: a clinical series from the French Antilles. *Spine* 2005;**30**:E400–5.
9. Moon S, Park S, Kim H, et al. Biologic modification of ligamentum flavum cells by marker gene transfer and recombinant human bone morphogenetic protein-2. *Spine* 2004;**29**:960–5.
10. Okamoto K, Kobashi G, Washio M, et al. Dietary habits and risk of ossification of the posterior longitudinal ligaments of the spine

- (OPLL); findings from a case-control study in Japan. *J Bone Miner Metab* 2004;**22**:612–7.
11. Resnick D, Niwayama G. Entheses and enthesopathy: Anatomic pathologic and radiologic correlation. *Radiology* 1983;**146**:1–9.
 12. Tsurumi K, Hashimoto K, Niwa G, et al. Unusual cases of ankylosing spondylitis causing myelopathy. *Jahreber Kurashiki Zentral Hosp (Tokyo)* 1964;**33**:327–40.
 13. Jayakumar PN, Devi BI, Bhat DI, et al. Thoracic cord compression due to ossified hypertrophied ligamentum flavum. *Neurol India* 2002;**50**:286–9.
 14. Miyamoto S, Yonenobu K, Ono K. Elevated plasma fibronectin concentrations in patients with ossification of the posterior longitudinal ligament and ossification of the ligamentum flavum. *Spine* 1993;**18**:2267–70.
 15. Sakou T, Matsunaga S, Koga H. Recent progress in the study of pathogenesis of ossification of the posterior longitudinal ligament. *J Orthop Sci* 2000;**5**:310–5.
 16. Maeda S, Ishidou Y, Koga H, et al. Functional impact of human collagen alpha2(XI) gene polymorphism in pathogenesis of ossification of the posterior longitudinal ligament of the spine. *J Bone Miner Res* 2001;**16**:948–57.
 17. Takeuchi Y, Matsumoto T, Takuwa Y, et al. High incidence of obesity and elevated serum immunoreactive insulin level in patients with paravertebral ligamentous ossification: a relationship to the development of ectopic ossification. *J Bone Mineral Metab* 1989;**7**:17–21.
 18. Li KK, Chung OM, Chang YP, et al. Myelopathy caused by ossification of ligamentum flavum. *Spine* 2002;**27**:E308–12.

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Mitochondrial myopathy associated with myasthenia gravis in a young man

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Abstract

An 18-year-old man presented with progressive weakness of proximal muscles with prominent diurnal variation for 3 months. He had bilateral ptosis since his childhood without diurnal variation or double vision. Neurological examination showed involvement of levator palpebrae superioris and lateral rectus muscles bilaterally. The plasma glucose after 75 gm glucose load was 302 mg/dL. The electrophysiological study revealed myopathic pattern and a decremental response in repetitive nerve stimulation. The plasma lactate was elevated and the muscle biopsy showed numerous ragged-red fibers. Serum acetylcholine receptor antibody assay was positive. We diagnosed myasthenia gravis with mitochondrial myopathy.

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Keywords: Myasthenia gravis; Mitochondrial myopathy; Chronic progressive external ophthalmoplegia (CPEO); Ragged-red fibers; Acetylcholine receptor antibody

1. Introduction

Myasthenia gravis (MG) is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscles¹ due to a decrease in the available number of acetylcholine receptors (AChR). Diplopia and ptosis are common initial presentations. Harvey and Masland in 1941 described the decremental muscle response to repeti-

tive nerve stimulation (RNS), which is the basis for the most commonly used electro-diagnostic test for this disease. Elevated serum AChR binding antibody virtually ensures the diagnosis of MG.²

Slowly progressive ptosis may also be a presenting feature of various muscle disorders. The single most common sign of mitochondrial myopathy is chronic progressive external ophthalmoplegia (CPEO), manifested as ptosis without diplopia. A number of characteristic syndromes have been documented with associated features including asymptomatic retinal pigmentation, proximal myopathy, epilepsy, encephalopathy, cardiac conduction abnormalities and diabetes.³

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