

Thoracic Outlet Syndrome: A Significant Family Genetic Phenotypic Presentation

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Abstract: We report on a very rare case of diagnosis and successful surgical treatment of three young family members with a four-fold presentation of thoracic outlet syndrome. In the relevant family case, we are considering and discussing the population incidence, a possible HOX genes disorder, and a significant phenotypic presentation.

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Introduction

Thoracic outlet syndrome (TOS) is a clinical syndrome characterised by a series of symptoms brought about by the compression of the neurovascular bundle by bony or/and muscular obstacles in the area of the superior aperture. In 1927 Adson and Coffey first described the compression of the subclavian artery using the anterior scalene muscle with arterial symptomatology. The term “thoracic outlet” was first introduced by Peet et al. in 1956. Galen and Vesalius were the first to describe the presence of a cervical and abnormal first rib (Borchardt, 1901). In 1861 Coote performed the first cervical rib resection, which was described in the literature. The term TOS is non-specific. The clinical presentation can vary from light symptoms, to even vein thrombosis and upper extremity muscle atrophy. By the character of the compression and a compressed structure, we can specify TOS and divide it into arterial (ATOS), venous (VTOS), and neurogenic (NTOS). The symptoms of ATOS include ischemia of the fingers, limb claudication, pallor, coldness, and paraesthesia. Pain, paraesthesia and weakness in the hand, arm and shoulder, plus neck pain and occipital headaches, are the classical symptoms of NTOS. VTOS involves arm swelling, finger paraesthesia, plus cyanosis. TOS is often misdiagnosed and significantly underdiagnosed in the population. Hereditary TOS is not exactly defined in the literature. A significant part of patients is diagnosed between the ages of 20 and 50 (Köknel Talu, 2005). Teenagers are rarely diagnosed with TOS and pediatric patients are very rarely diagnosed (Arthur et al., 2008; Rigberg and Gelabert, 2009). The incidence of TOS in the population is, at least, 1–2%. The incidence of NTOS in the population is, roughly, 94–97%, whereas the incidence of ATOS is, roughly, 1% (Jusufovic et al., 2012). Cervical rib anomalies in the population are extremely rare, and the frequency of detection of this anomaly in the general population constitutes approx. 1–2% (Walden et al., 2013). Approximately 70% of all cases are in women. Most cases of cervical rib are demonstrated as NTOS. The incidence of bone abnormalities resulting in TOS is estimated to be 30%. The most frequent bone anomalies leading to TOS included cervical ribs (70%), clavicular anomalies (20%), and isolated first rib aberrations (10%) (Weber and Criado, 2014). Cervical ribs can develop with a unilateral or bilateral distribution. The frequent occurrence of cervical ribs is described in the Klippel-Trenaunay syndrome (Glass et al., 2002), which is associated with other vascular pathologies. Rib anomalies are the most frequent causes of the compression of cervical plexus. The personal history of a significant part of NTOS patients includes a neck trauma or a car accident. VTOS can be presented in the case of excessive unilateral load of arms. Symptoms of ATOS usually develop spontaneously, and in most cases it is associated with a cervical rib and with isolated first rib aberrations. A golden diagnostic standard is a clinical examination, provocative tests (Adson's, Wright's test), X-ray scanning, ultrasound, and magnetic resonance imaging.

Case report

We admitted two female patients to our Department of Cardiovascular Surgery with incidentally diagnosed TOS for resection of the first rib; a 14-years-old female patient, and her 35-years-old aunt on the mother's side; both patients had manifested TOS of the right upper extremity. The 37-years-old mother of the 14-years-old female patient and, at the same time, the sister of the 35-years-old female patient had transaxillary first rib resection six years ago, due to a manifested VTOS on the right side, at another hospital. The mother had manifested VTOS in the form of Paget-Schroetter syndrome, with repeated thromboses of the subclavian vein; a stent was implanted into the subclavian vein after the first rib resection.

Case 1

The 14-years-old female patient suffers with asthma, atopic dermatitis, S/P adenoidectomy at the age of two, with polyvalent allergy a year ago due to manifested VTOS after the first rib resection on the left side with a good effect; now admitted due to oedema of the right upper extremity, receives a Dabigatran therapy, a ultrasound examination carried out with maximum provocative

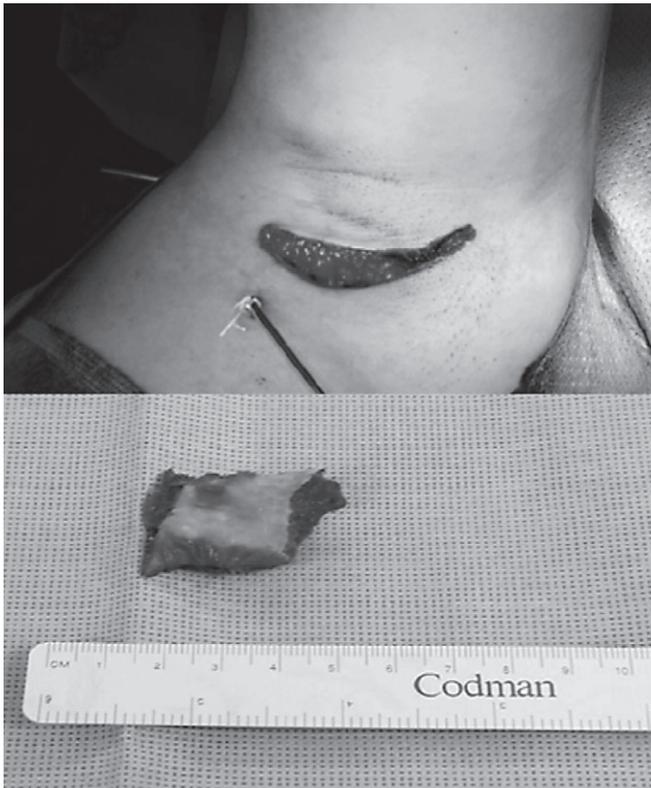


Figure 1 – The 14-years-old female patient – surgical wound – the resected first rib.

manoeuvres (limb elevation while she was breathing in), with alterations of Doppler signal on the subclavian artery, approximately 40% of artery compression, and flow alterations in the subclavian vein with roughly 50% of vein flow. Transaxillary first rib resection was performed on the patient (Figure 1). The procedure was without any complications. Following the operation, small apical pneumothorax was in regression. The patient was discharged from the hospital for home treatment on the sixth post-operative day. After the 21 days the post-operative ultrasound examination revealed no flow alterations in the subclavian artery and vein, the surgical wound was healed; the patient remained without oedema of the right upper extremity and without clinical problems.

Case 2

The 35-years-old female patient suffers with asthma, thyroid gland hypofunction, with polyvalent allergy, now with oedema of the right upper extremity mainly during the elevation of the extremity, and with finger paresthesia. The patient was examined with an X-ray photograph which shows a significant lateral fragment of vertebra C7 the character of which is even an incipient cervical rib on the right; according to the control ultrasound examination with maximum augmentation

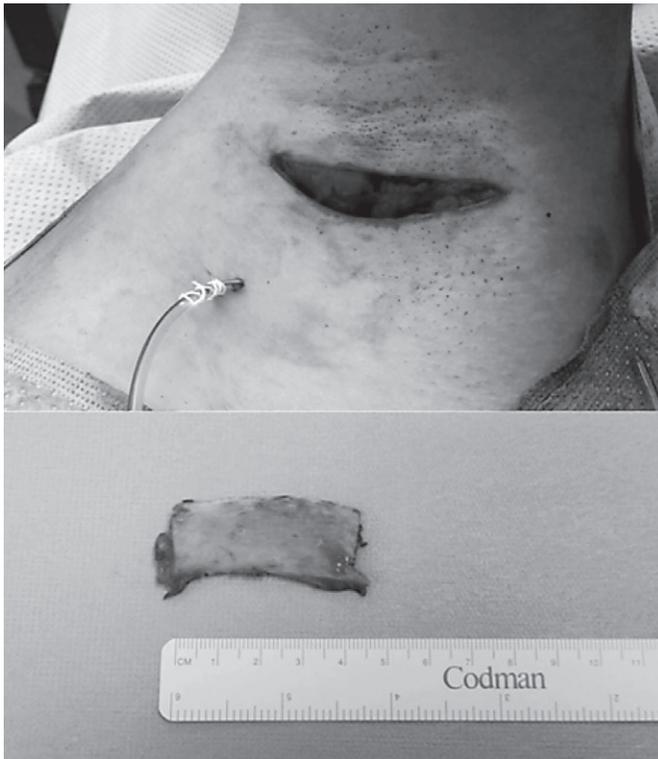


Figure 2 – The 35-years-old female patient – surgical wound – the resected first rib.

manoeuvres (limb elevation while she was breathing in), significant flow alterations in the subclavian vein colliding with the abnormal first rib, without any alteration of flow in the subclavian artery. Transaxillary first rib resection was performed on the patient (Figure 2). The procedure was without any complications. The patient was discharged from hospital for home treatment on the sixth post-operative day. After the 21 days the post-operative ultrasound examination with provocative manoeuvres revealed no flow alterations in the subclavian vein and artery, the surgical wound was healed; the patient's condition were clinically improved, without subjective problems.

Discussion

We presented a very rare case of four-fold TOS syndromes manifested in three members of the same family. We have performed transaxillary first rib resections with optimum clinical results. In addition to standard clinical examinations using elevation and traction tests, also ultrasound and standard imaging methods of anteroposterior X-ray photographs and CT scans were used to diagnose TOS. Based on the studies dealing with this diagnosis, there is very frequent underreporting and an incorrect and poor detection of the presence of bone anomalies including the cervical rib and structural anomalies of the ribs resulting in the clinical symptoms of TOS (Viertel et al., 2012). Transaxillary or supraclavicular decompression can be used for vascular bundles or for the removal of bone anomalies. We selected the universal transaxillary approach in which we are experienced in our Department of Cardiovascular Surgery and which is normally applied. In our department, we have operated on patients with TOS syndrome for more than 30 years. We operate on a full range of patients with different symptomatology. We have not yet encountered such a strong family-related presentation of TOS syndrome. In a detailed clinical examination, no significantly genetically determined syndrome was identified in this family. Female patients were without other obvious abnormalities. No specific abnormality associated with the known and also molecularly genetically detectable mutation of HOX genes, was identified in the patients. No molecular genetic techniques have been developed yet for undefined nonspecific mutations of HOX genes. As a result, at the moment it is impossible to objectify these mutations in detail. The occurrence of this pathology fully falls within the category of polygenic inheritance, but with a very strong polygenically determined phenotypic penetrance. Following available anatomical-embryological studies, the axial skeleton, to which the paraxial mesoderm gives rise, is determined by the so-called HOX genes (Kmita and Duboule, 2003; Mallo et al., 2009; Wellik, 2009). These genes present an evolutionary conserved group. This group of genes is extremely important, among other things, for the differentiation and structuring of the vertebral column, and today 39 HOX genes are described for the development of the vertebral column, which are divided into four different clusters. The four clusters described as HOXA, HOXB, HOXC and HOXD, are

located on four different chromosomes 7p14, 17q21, 12q13 and 2q31, respectively, and contain 9–11 genes (Quinonez and Innis, 2014). Up to now, 10 mutations of HOX genes were described with a clear mechanism of inheritance, expressivity and mechanism of pathogenesis, and phenotypic manifestation (e.g. HOXA1 mutation reported as Bosley-Salih-Alorainy syndrome, HOXA13 as Guttmacher syndrome, HOXC13 ectodermal dysplasia 9, HOXD13 syndactyly type 5). Non-specified mutations in HOX genes are described, too. They are associated with anomalies and abnormalities of the vertebral column, the quantity and anomalies of ribs, and include the occurrence of a cervical rib (Kmita and Duboule, 2003). It is described that aberrations in HOX gene expression have a role in tumour suppression and in oncogenesis (Merks et al., 2005; Shah and Sukumar, 2010). The literature emphasizes, that for complete phenotypic penetrance (complete homeotic transformation), an alteration of expression in several homologous or paralogous HOX genes, is required (Deschamps and van Nes, 2005; Bots et al., 2011). Mutagenic agents of HOX genes leading to the occurrence of bone abnormalities represented mainly by cervical ribs and structural abnormalities of costal arch, which can be represented by TOS syndrome, are not yet known, and they require further analysis. However, within the population incidence their acceleration and higher line phenotypic presentation in the relevant family line, is possible. In the case reported by us concerning the family presence of TOS, we can take into account the acceleration of agents leading to alterations of HOX gene expression. However, in the relevant family, potential risk factors are not known. It is advisable to examine the family members of patients with TOS syndrome caused by bone abnormalities in relation to suspected cases of clinical TOS symptomatology, and also to bear in mind the possible association between family history of TOS and incidence. In addition, for in patients with bone abnormalities with clinical TOS presentation, it is necessary to consider possible higher cancer incidence, mainly in patients with higher genetic family burden, and to bear in mind this potential risk. The aim of our report is to demonstrate HOX gene mutations associated with the occurrence of TOS syndrome, which have not been genetically specified yet. The literature available in fact does not describe this correlation. Many variations of mutations in this area can be represented by a wide phenotype diversity. It is necessary to take into consideration the relevant mutations of HOX genes, and in certain cases, also their strong family transmission between individuals; a significant clinical presentation, and the possibility of the prevalence of other cancer types with increasing age.

Conclusion

Future studies concerning the frequency of cervical ribs and structural bone anomalies of the first cervical rib presented with clinical TOS syndrome will have to address the relevant issue as an indicator of potentially higher medical risks for the relevant affected population, and its possible inheritance.

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