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CERVICAL RIBS: ASSOCIATION WITH CHILDHOOD NEOPLASMS AND IMPLICATION IN THORACIC OUTLET SYNDROME

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ABSTRACT

Importance: To describe the association between cervical rib (CR) and different types of pediatric neoplasms focusing on their embryological origin.
Objective: The purpose of this study is to review the association between the development of CR and childhood cancers. Also, we are describing the wide range of clinical manifestations of CR and their causality of Thoracic Outlet Syndrome (TOS) among paediatrics and adults.
Evidence Review: A thorough search through Medline and ScienceDirect databases was conducted to identify any relevant studies. The eligible extracted manuscripts were of CR and its association with childhood cancers or thoracic outlet syndrome. The resultant 87 studies were filtered down to 43.
Findings: Prevalence of CR was reported from 15.2% in Oceania to 0.8% in Africa in a recent meta-analysis. CR was reported in 2 out of 4 case-control studies in 26.8% of Acute Lymphoblastic Leukemia (ALL) cases in the first study and in 12.1% in the second study. Also, 27.4% of patients with a brain tumour had a CR anomaly in the first study compared with 18.2% of astrocytoma patients in the other research. However, there was no significant association between CR and any malignancies in the other studies.
Conclusion and Relevance: CR may co-occur with pediatric neoplasms such as ALL, neuroblastoma and astrocytoma due to the similarity in their abnormal genetic abnormalities. It is believed that over-expression or down-expression of specific HOX genes is associated with both pediatric neoplasms and CR. Thus, CR may be an accompanying sign for particular malignancies. Also, CR is an essential etiology for non-traumatic TOS giving rise to acute limb ischemia or cerebrovascular accidents.

Key words: Cervical Rib, Embryology, Thoracic Outlet Syndrome, Rib anomalies, Neoplasm.

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INTRODUCTION

The prevalence of cervical rib (CR) differs among the different populations, and it is estimated to be between 0.8% and 15.2% with female predominance. Stillborn fetuses have a higher incidence of CR compared with full-term fetuses. It is hypothesized that a CR occurs because of an abnormal HOX gene expression that is crucial for the normal spatiotemporal limb and organ development along the anterior-posterior axis.[1] The CR appears to be associated with multiple childhood neoplasms like ALL, neuroblastoma and astrocytoma. Although almost 90% of the cases are asymptomatic, CR may cause TOS, either the neurological or the vascular type, depending on its size and the patient's other accompanying risk factors such as age and routine overhead exercises. In this article, we review the association between CR specifically and childhood cancers on the spot of the available studies addressing this topic. Also, we discuss the clinical implications of the CR in the pediatric and adult population focusing on arterial TOS.

LITERATURE SEARCH

Primarily literature was searched through Medline and ScienceDirect databases. Relevant studies were identified using the keywords such as "Cervical Rib", "thoracic outlet syndrome", "neoplasm", "Rib anomalies", and "Embryology". Extracted manuscripts were further filtered, addressing pediatric neoplasms, thoracic outlet syndromes, and their association with CR. Preference was given to those manuscripts which were addressing the population of Saudi Arabia. Most of the citations were of 10 to 15 years old. However, a couple of manuscripts of the year 1992 were added for the need base purpose. Eventually, the resulting studies were filtered down to 43 relevant studies from 87 studies. Furthermore, four studies were the capstone of this review.

RESULTS AND DISCUSSION

The manifestations of CRs are of broad perspective, and we tried to give an account of various viewpoints of the CRs categorically. We discussed the various aspects including, the occurrence in a diverse population, the modalities used for its diagnosis, the morphology and embryology, the predisposing factors, and the clinical implications of CR on thoracic outlet syndrome (TOS).

Epidemiology

There is a considerable variation regarding the prevalence of CR among the different examined populations suggesting an ethnic predisposition for the development of CR.[2] Most studies have been using plain X-Ray or CT scan to evaluate the presence of CR (Figure 1).

A very recent meta-analysis showed that the lower prevalence of CR internationally was in Africa with Pooled Prevalence Estimate

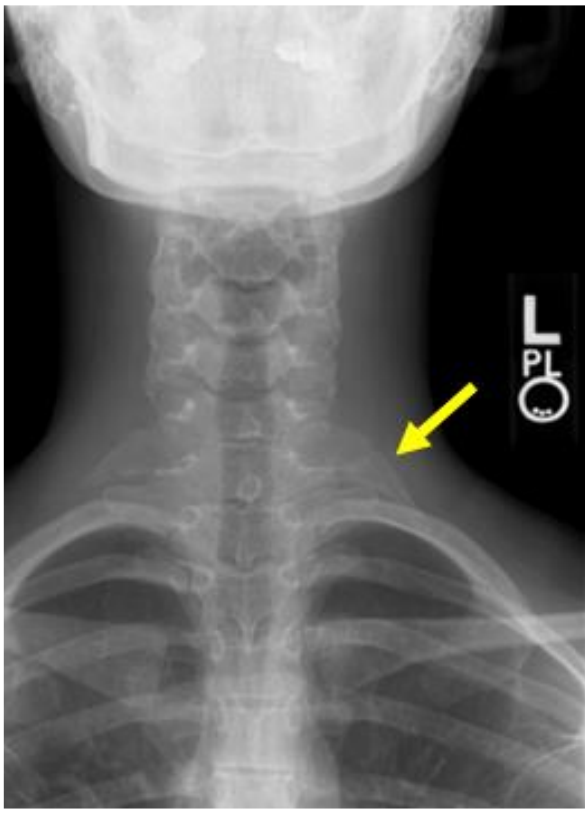

Figure 1: A-P plain cervical X-ray is showing a left-sided CR extending toward the 1st rib; arrow. Used with generous permission from (Henry BM, Cervical Rib Prevalence and its Association with Thoracic Outlet Syndrome: A Meta-Analysis of 141 Studies with Surgical Considerations. World Neurosurgery).

(PPE) of 0.8%.[2] Brewing et el. found the prevalence of CRs to be 0.74% in London.[3] In 2010, A cross-sectional study showed that CRs is present in 3.4% of the Saudi population with a female to male ratio of 2:1. They were bilateral in 41% of those individuals.[4] This indicates a higher prevalence of CR among the Saudi population compared with PPE internationally, which is 1.1%.[2] The highest PPE reported was 15.2% in Oceania. However, only two studies were performed there, and more are required to support this finding. Both Europe and North America had almost the same prevalence of 1.1%. CR is more prevalent in females than males, with a ratio of 1.3:0.7.[2] The incidence of CR is much higher in fetuses compared with adults. One postulated hypothesis to explain this gap is the "fusion" of CR during the postnatal growth with other structures such as the adjacent ribs or the transverse processes, in the case of a small rudimentary CR. Another finding is that CR is associated with significant congenital abnormalities, increasing the risk of intrauterine death and linked to early childhood cancers, thus leading to an increase in early mortality rate. So, fetuses with CR die much earlier and do not live till adulthood to be counted and reported in the epidemiological studies, which mostly have reported CR prevalence in adults rather than in newborns and children. Galis *et al.* reported that at least 78% of the fetuses with a CR anomaly die even before birth, and 83 % die before the age of one.[5]

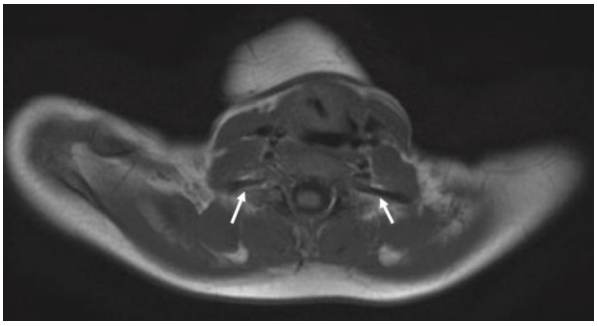

Figure 2: Axial T1-weighted MRI image showing bilateral CR in a 16-month-old female patient; arrows. Copyright (2021) Wiley. Used with permission from (Desurkar A, Mills K, Pitt M, et al. Congenital lower brachial plexus palsy due to Cervical Ribs. Developmental Medicine & Child Neurology. John Wiley and Sons). ©The Authors. Journal compilation © Mac Keith Press 2011.

These findings point out that the CR is likely a representative of disturbances in a specific genetic pathway during embryonic development.[6,7] Per our search, only one study has evaluated the prevalence of CR using MRI instead of X-ray and CT scan. Walden *et al.* evaluated 2083 MRI examinations at John Hopkins institution and reported the prevalence as 1.2 %, with 40 % of the cases being bilateral and 68 % female (Figure 2).[8] Because CRs is still fibrous or cartilaginous in children and not yet ossified, MRI may be used in future studies to determine the prevalence of CR in children.

Morphology

The length of the CR varies considerably among individuals from just slight elongations of the transverse rib of C7 to a complete CR fused with the 1st rib.[9] Only 25 % of CR anomalies are complete.[10] The mean length of CR was 3.8cm according to Walden et al. MRI study.[8] Gruber first described CR in 1869. CRs are categorized into four types depending on the extent of the CR and its fusion or articulation with the first thoracic rib. These types are: [11]

Type I: A CR extending just beyond the transverse process of C7 but does not reach the first rib.
Type II: A CR that elongates beyond the transverse process of C7 with a free tip almost touching the first rib.
Type III: A CR that elongates beyond the transverse process with a fibrous band attaching cartilage to the first rib.
Type IV: A CR that is completely fused to the first rib.

Rarely, a CR may pseudo-articulates with the scalene tubercle of the first rib as reported by Balakrishnan et al.[10] Furthermore, even rarer is the fusion of the CR with the 2nd rib as reported by Hines et al.[12] Complete CRs has the capability of causing either neurological or arterial TOS, or both. However, incomplete CRs can only cause neurological TOS.[13]

Cervical ribs and childhood cancers

Stillborn fetuses have a higher frequency of CR compared with healthy, full-term babies.[7] Bots J *et al.* reported that 40 % of the electively studied 199 aborted fetuses had these anomalies (Figure 3).[6]
Furtado *et al.* reported that 13 out of 17 stillbirths examined in his study sample for aneuploidy by karyotyping had CR; this indicates a strong association between the CRs and fetal aneuploidy. Out of those 13 studied, 4 had monosomy X, 4 had trisomy 21, 2 had trisomy 13, and one had trisomy 18.[7] It has been hypothesized that the association between CR and cancer is caused by a common underlying genetic defect causing abnormal HOX genes expression. HOX proteins are transcriptional factors that enhance or suppress the expression of specific other genes. HOX genes are crucial for the normal temporospatial limb and organ development along the anterior-posterior axis. Aside from this function, HOX genes play a role as tumour-suppressing genes in specific tissues and as proto-oncogenes in others. Over-expression or abnormally temporospatial - in wrong tissues or wrong timing of its expression of HOX genes in a specific tissue are two proposed mechanisms for the oncogenic effect of these genes.

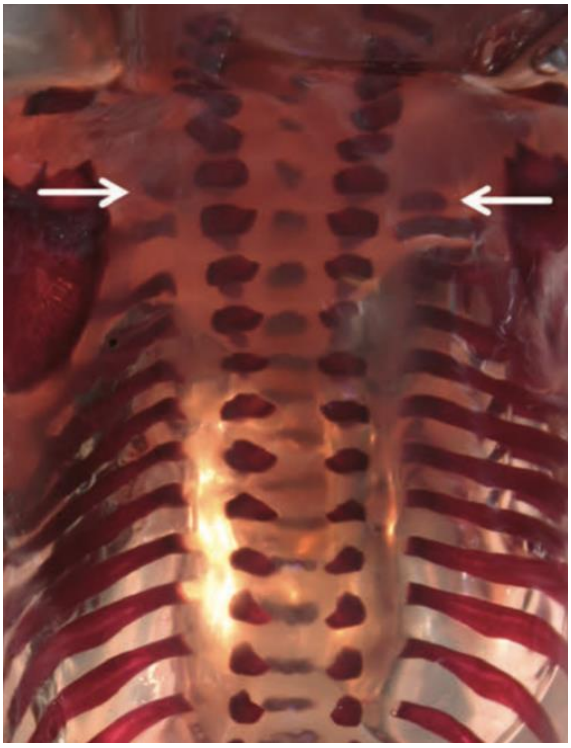

Figure 3: Alizarin red (which stains calcium-containing structures with red) is used to stain bones. This gives high contrast against other tissues making detection of CRs easier. Copyright (2021) Wiley. Used with permission from (Bots J, Wijnaendts LCD, Delen S et al. Analysis of Cervical Ribs in a series of human fetuses, Journal of Anatomy. John Wiley and Sons) © 2011 Anatomical Society of Great Britain and Ireland.

Silencing or down-regulating specific HOX genes epigenetically in other tissues is a third proposed mechanism of how HOX genes could contribute to the development of cancers due to loss of their function as tumour suppressor genes.[1] For example, HOX-2A and HOX-2E genes are expressed in a normal kidney but not in renal carcinoma biopsies suggesting their importance as tumour suppressor genes. On the other hand, the HOX-3H gene is expressed in renal carcinoma and not in a normal kidney suggesting its role as an oncogene.[14] So, by abnormal gene expression, both the CR and cancer may co-occur because of a defective background of HOX genes expression.[1] Merks *et al.* have found a significant positive association between CR anomalies and astrocytoma, germ cell tumor and acute lymphoblastic leukaemia.[15] Schumacher *et al.* have found a strong significant association between CR and neuroblastoma, brain tumor, acute lymphoblastic leukemia, soft tissue sarcoma, Wilms tumor and Ewing sarcoma.[16] However, Zierhut *et al.* have found no significant association between the CR and pediatric cancers in their case-control study.[17] Numerous systemic reviews have confirmed the association between minor anomalies and childhood cancers;[18] and much fewer have pointed outFfigure 1 the association between rib anomalies (numerical abnormalities, increased or decreased the number of ribs or morphological abnormalities) and childhood cancers. However, most of these studies do not point specifically to the CRs, aside from other rib anomalies and their association with malignancies. As per our literature review, these studies have explored the CR association specifically. Table 1 summarizes the result of these studies.

The presence of a CR and its fusion with the first thoracic rib may narrow the thoracic outlet and increase the risk of developing TOS. This risk is increased even more if the patient usually performs sports or tasks that require hyper-abduction of the arm.[21] Arterial compression and its sequels require the presence of a complete CR to occur (type III and type IV).[11] CRs is well known to be

Table 1. Results of the studies that examined the association between CR and Childhood Cancers. (Arranged in chronological order)

Name	Year	Study type	Population	CRs frequency	Neoplasm type
Schumacher et al. [16]	1992	Case-control	1000 patients vs 200 control	20.4% of cases vs 4.5 % of controls	•33.0% of neuroblastoma patients had a CR anomaly (either unilateral or bilateral); • 27.4% of brain tumor patients had a CR anomaly; •26.8% of ALL patients had a CR anomaly; •24.5% of sarcoma patients had a CR anomaly; •23.5%of Wilms tumor patients had a CR anomaly; •17.1% of Ewing sarcoma patients had a CR anomaly.
Kimonis et al. [20]	2004	Comparative	82 patients vs 38 unaffected siblings	-	•No significant difference between the frequency of CRs in patients with nevoid basal cell carcinoma syndrome and in unaffected siblings (4% vs 6%; *P*=0.65).
Merks et al. [15]	2005	Case-control	906 patients vs 881 control	8.6% of cases vs 6.1 % of controls	• 12.1% of patients with ALL had a CR anomaly; • 18.2% of patients with astrocytoma had a CR anomaly; • 14.7% of patients with germ cell tumors had a CR anomaly.
Loder et al. [19]	2007	Case-control	218 patients vs 200 control	CR was not found in any of the cases examined	• CR risk is not reported.
Zierhut et al [17]	2011	Case-control	455 patients vs 1133 control	1.3 % of cases vs 0.79 % of controls	• The adjusted models showed no association between CRs and the studied pediatrics cancers.

CR= cervical rib; ALL= acute lymphoblastic leukemia.

associated with non-traumatic TOS. This syndrome arises because of several conditions such as CR, scapular ptosis or scalene muscle abnormalities. The CR may compress the subclavian artery, vein, or the lower brachial plexus giving rise to the vascular TOS, neurogenic TOS or both. The majority of patients - 90 % of the cases - with CR are asymptomatic and thus do not require a surgical intervention.[10] A retrospective

cohort study between 1994 and 2011 - conducted by Weber *et al.* assessing 400 patients with TOS- divided the subjects into two groups based on TOS etiology. A group with TOS due to bone anomaly and a group with TOS due to non-bone anomaly. In this study, 29 % of the cases were associated with a bone anomalies, and 69 % of these cases were due to CR; other causes included first rib aberrations and clavicular anomalies. 64% of TOS-CR cases were neurological, 34% were arterial, and 2 % were due to subclavian/axillary vein compression.[22] Chances of developing TOS increase with age (especially after 30 years) as a consequence of shoulder sagging which puts more traction on the neurovascular bundles and increases their angulation risk as they pass to the upper limb.[23] No correlation has been established between the size of the CR and the severity of the symptoms.[24]

Clinical significance of CR and its implication in TOS:

1. Neurological TOS

Paresthesia, pain and numbness are the most common sensory, neurological manifestations seen in descending order of frequency with paresthesia being present in 90 % of bone anomaly associated TOS cases.[22] These symptoms distribute along C8 and T1 dermatomes because the nerve roots of these two segments are most affected by compression of the underneath CR. Weakness and wasting of the ulnar nerve-innervated hand muscles are also seen.[11]

2. Vascular symptoms

Less than 10% of TOS cases in adults are vascular. However, the incidence of vascular TOS is relatively higher in the pediatric population.[25] Vascular TOS is divided into Venous TOS and Arterial TOS as the following:

2.1. Venous TOS (VTOS): The clinical manifestations which suggest obstruction of venous return and thus VTOS - are swelling, cyanosis of an upper extremity, venous thrombosis and distention of the superficial veins of the shoulder and chest.[11,13] Collin *et al.* reported a case of a 25-year old female with bilateral CR complaining of pain, numbness and purple discolouration in the left fourth digit. After MRI venography (MRV) and MRI angiography (MRA), left and right subclavian veins (among others) were found to be compressed with diminished venous return.[26]

2.2. Arterial TOS (ATOS): The most common cause of ATOS is CR. However, ATOS is rare, and it is the least common form of TOS making out only 1% of total TOS cases.[27] The CR leads to both compression of the subclavian artery (resulting in stenosis or even complete occlusion upon arm abduction) and ischemic intimal wall damage distal to the site of compression. This favours the aneurysm formation. Turbulent blood flow in the post-stenotic aneurysm may lead to endothelial injury and thrombus formation (Figure 4).[28,29]

Ante-grade thromboembolism propagation may occlude the small vessels distally and lead to infarction and gangrene of finger-tips. Common clinical presentations of this

antegrade propagation are pain, weakness, and discolouration of the affected arm. [11] Also, retrograde thromboembolism travelling to the brain may lead to stroke, especially in young individuals. Kataria *et al.* have reported a recurrent right cerebellar and subacute brainstem infarction in a 14-year old unconscious girl with absent right radial pulsation. Although those cases are rare, they raise the importance of early diagnosis of CR anomalies to prevent such catastrophic consequences.[30] Palmer *et al.* have proposed a theory for this retrograde embolism propagation. The theory states that the relative proximal higher blood flow to the vertebral and carotid artery may drag small thromboembolism from the occluded subclavian artery-especially when the arm is abducted-causing a stroke.[28] Lee *et al.* reported a 15-year old female patient diagnosed with both cerebrovascular accident (an example of the retrograde embolic event) and acute upper limb ischemia (an example of an ante-grade embolic event).[11] Repetitive overhead exercises in young athletes can lead to acute upper limb or acute on chronic limb ischemia. This is associated with increased morbidity in this group and may even force them to quit their sports.[31] Radiographic investigations of the chest and cervical spine are advised as part of the diagnostic workout of ATOS as CR is the most common cause of it.[32]

3. Pediatric population

According to a retrospective study, non-inflammatory neck mass and neck pain are the most common manifestations seen in the pediatric population.[33] Vu *et al.* reported

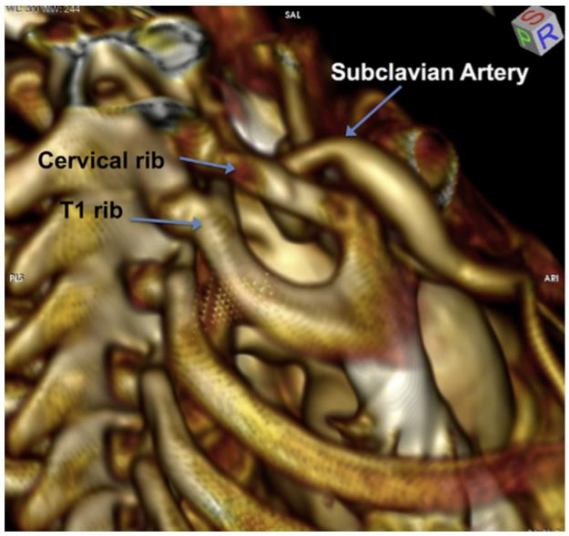

Figure 4. A Reconstructed 3-D CT angiogram of a 56-year-old patient shows subclavian artery compression as it passes above the CR. Also, note the post-stenotic aneurysm. Used with generous permission from (Weaver FA. Bilateral Cervical Ribs Causing Cerebellar Stroke and Arterial Thoracic Outlet Syndrome: A Case Report and Review of the Literature. Annals of Vascular Surgery).

taking a biopsy from a suspected cervical lymph node. However, bone and cartilage were seen under the microscope and the biopsy appeared to be of a CR presented as a neck mass.[25] The traditional neurological and vascular symptoms are seen in adults are also reported in children. Desurkar *et al.* reported two cases of Congenital lower Brachial Plexus Palsy (CBPP) without intrapartum trauma, and both had an unassisted normal vaginal delivery. The only abnormal finding was the presence of CRs bilaterally suggesting the CR as a cause or at least a contributory factor in the development of CBPP. The presence of neurological symptoms from birth indicates that the compression by the CR might occur early in-utero and even before birth.[34] Tzou *et al.*

support prenatal ultrasonography screening to assess the brachial plexus integrity. So, extra precautions are taken during delivery to lower the incidence of CBPP secondary to CR if it is suspected.[35] Also, a fractured CR has been reported as an infrequent cause of TOS in children, and same is the case with adults.[36]

4. Miscellaneous

A hard supraclavicular mass due to the hypertrophied joint formed between the CR and the first rib [37] and a pulsatile supraclavicular mass due to post-stenotic aneurysm formation[10, 38] have both been reported as local symptoms for CR. Thus, a CR should be kept in mind as a differential diagnosis of supraclavicular mass. Ang *et al.* reported a case undergoing FNA of a supraclavicular mass which appeared after the examination to be from a CR.[39] Isolated fracture of a CR causing TOS is extremely rare, as reported in the literature.[40] Rongioletti reported two patients with type I and type III CR presenting with localized pruritus as a clinical presentation of CR. This itching is probably a result of peripheral nerve compression. One of these two patients underwent CR surgical resection which resulted in resolving pruritus.[41] Erken *et al.* reported a positive association between CR and sacralization.[42] However, sacralization was not found to be significantly associated or predictive for the presence of CR as concluded by another studies with only 2.9% co-occurrence between the two phenomena.[43]

CONCLUSION

Although CRs is widely asymptomatic and is usually found incidentally in plain X-ray, they may co-occur in patients with childhood neoplasms because they may share the same abnormal genetic background. The CR appears to be associated significantly with ALL, neuroblastoma and astrocytoma. More studies are required to support these results and to examine the other CR neoplasms associations. Aside from pediatric oncology, CR is an important aetiology for non-traumatic TOS. It may compress the lower brachial plexus, the subclavian artery or/and the subclavian vein. Thus, it gives rise to a broad spectrum of clinical presentations ranging from a palpable neck mass and pain to acute limb ischemia and stroke.

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