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Congenital fusion of cervical vertebrae: a review on embryological etiology

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ABSTRACT

Congenital fusion of cervical vertebrae is a rare anomaly. In this condition, two fused vertebrae appear structurally and functionally as one. This anomaly may be symptomatic or asymptomatic. Myelopathy, limitation in neck movement, muscular atrophy and regional sensory loss are examples of probable morbidity associated with this anomaly. Combination of genetic and environmental factors are involved in pathogenesis of this anomaly. Malformation of notochord, poor performance of retinoids, decreased local blood supply of spine and alteration in genes expression, especially members of Hox and Pax family genes are some of the proposed reasons of congenital fusion of cervical vertebrae. Diagnosis of this congenital anomaly in childhood seems to have an important role in prevention of probable secondary disorders in adulthood. We offer to clinicians that after performing careful physical tests and noticing the presence of signs and symptoms that mentioned in this paper, if a patient suspected to have congenital fusion of cervical vertebrae, genetic tests ought to be performed.

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Introduction

Small size and foramen transversarium are characteristics features of seven cervical vertebrae. Each cervical vertebra has the following features: the superior surface of centrum is concave and that's inferior surface is convex, each transverse process perforated by a foramen transversarium, the spinous process is bifid (except 7th vertebrae), and the shape of vertebral foramen is three-sided (1-3).

For many years, cervical region abnormalities were of attention mainly to clinicians. Congenital fusion of cervical vertebrae (CFCV) is an uncommon but well-known disorder. Some clinicians consider CFCV as an accidental finding of radiological survey, independent to any disease, whilst others estimate that CFCV might be a reason for secondary changes and mobility trouble of adjacent vertebrae (4-7). Most common fusions are between the facet joints of the second and third cervical vertebrae (C2 and C3) (8). Some clinical signs and symptoms such as shortening of cervical spine, webbing of the neck, malformations of osseous tissue, trouble of neck movement, hemi-vertebrae, kyphosis and lowered line of hair can occur following CFCV (9,10). One of the secondary effects of CFCV on the adjacent level is formation of osteophyte (11).

A complex sequence of events occurs through

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development of vertebral column. Changes in the pattern of development in each phase can result in malformation of vertebral column. Diagnosis of these congenital abnormalities with help of basic embryological knowledge, physical tests and radiological assessments seems to have an important role in prevention of secondary disorders and in reducing the side effects of surgery (12). Somites are derived from paraxial mesoderm, and sclerotomal portion of somites contributes to the developing of vertebrae(13). One of the proposed reason of CFCV is disturbance in normal spinal segmentation during embryological development, following decrease in local blood supply between 3th to 8th week of embryonic period (14). Alterations of Hox genes expression play an important role in pathogenesis of CFCV (15-17). This paper deals first with normal development of cervical vertebrae, followed by description and embryological etiology of congenital fusion of cervical vertebrae.

Literature review

1. Normal development of cervical vertebrae

At the 8th week of embryonic life, organogenesis is usually complete (18). During this phase, formation of cervical vertebrae occurs following migration, segmentation and chondrification process. At the 6th week, chondrification centers are recognized and ossification of the centrum and lamina occurs at the 8th week of gestational age (19). In humans, formation of somites initiates along the dorsal side of developing embryo in the 20th day of embryonic life (20). They comprise the precursors of vertebral skeleton, trunk muscles and spinal cord meninges (21). In a short time after formation, each somite separates into two subdivisions, the sclerotome or ventromedial portion and dermomyotome or dorsolateral portion of the somite. Vertebrae and ribs originate from the sclerotome. Following the migration of ventral sclerotomal cell to surround the notochord, centrum is forms. Vertebral arch and spinous process are formed from dorsal sclerotomal cell surrounding the neural tube and more laterally located sclerotomal cell forms the transvers process and ribs (22-25).

With progression of development, resegmentation procedure occurs, this term refer to normally fusion between the caudal half of each sclerotome and cranial half of the adjacent sclerotome. The space between cranial and caudal portions of original sclerotome segment filled with mesenchymal cells. These cells do not proliferate and contribute to formation of annulus fibrosus portion of intervertebral disc. Another portion of intervertebral disc is nucleus pulposus that is surrounded with annulus fibrosus and is the remnant of embryonic notochord (26-28).

1.2.Genes and regulation of vertebral development

Precise survey of vertebral development presents valuable information about the main roles of genes in all phase of development. Regulatory functions of genes were proven in differentiation, migration and ossification of vertebral precursor cells. In addition to the roles of many genes in vertebral development, Hox and Pax genes are considered more than other genes.

Vertebra Hox genes play a key role in patterning of vertebrae (17,29). Controlling the body plan during establishment of cranial-caudal axis is one of the important functions of Hox genes (30,31). In mammals, determining the type of segment structure (vertebrae in human) is mediated with Hox genes (30). Hox genes contain a specific DNA sequence that is known as homeobox (30,32,33).

Pax genes encode a family of nine proteins (Pax1 to Pax9), and based on difference in structural domain, divided into four groups (Pax family group I to IV)(34,35). During organogenesis, Pax proteins have a critical functions (36) and any alteration in Pax genes expression cause significant abnormalities in embryo(37-41). Among the Pax proteins, Pax1 and Pax9 are expressed during skeletal development (42-45). During vertebral evolution, both pax1 and pax9 activate the expression of Bapx1, an expressed protein in the sclerotome(43,46).

1.3. Development of 1st and 2nd cervical vertebrae

Unusual morphology and distinctive origin of 1st and 2nd cervical vertebrae (atlas and axis respectively) is the reason of being called atypical cervical vertebrae. The main unique feature of atlas is the absence of vertebral body. The atlas consists of two lateral masses connected by anterior and posterior arch. In the rotational movement of the atlas and head around the cranially projection of axis (called odontoid process) (47,48).

Proatlas (not found in human) is formed from fusion between lowest occipital somite and the 1st cervical somite. In normal development, proatlas cells contribute to the formation of superior portion of the axis dense. The 1st, 2nd and 3rd cervical somites contribute to the formation of C1 and C2 vertebral primordia. C1 and C2 vertebral primordia are involved in the formation of inferior portion of dense, axis body, lateral masses and anterior/posterior arch of atlas (49,50).

2. Congenital fusion of cervical vertebrae

Congenital anomalies of the vertebral column do not have a low incidence (51). When two

vertebrae fused together, two vertebrae appear structurally and functionally as one (10). In referred condition, the fusion of vertebrae results in more biomechanical pressure in relating segments leading to premature deteriorating changes at relating motion segments (52). During blastemal stage, combination of genetic and environmental factors are involved in pathogenesis of CFCV(1). CFCV may be symptomatic or asymptomatic; myelopathy is one of the serious clinical features of CFCV in some patients. CFCV may be associated with klippel- feil syndrome and limited neck movement; muscular atrophy and sensory loss may also be observed (10, 53-56). In this portion, we surveyed the molecular embryology of CFCV etiology.

Malformations of notochord (chorda dorsalis) is one of the primary proposed reason of CFCV (1,10,57,58). Retinoids are one of the main factors that are involved in pathogenesis of skeletal anomalies such as abnormal axial skeleton, disordered segmentation of notochord, oversized vertebrae and CFCV (27,59,60). Retinoids may have a key role in establishment of somites (61,62). The retinoids have effects on evolution of the vertebrae via regulation of Hox genes, which are important in vertebral development (63-66). Some studies suggest that decrease in local blood supply of spine in embryonic life is the leading cause of CFCV (1,10).

Common site of CFCV is between facet joint of C2 and C3 (8,67-70). Many studies have found association between cervical anomalies, especially fusion of C2 and C3, and dental malocclusion, fetal alcohol syndrome, cleft lip and plate(71-75).

2.1. Occipitalization of the atlas

Because of juxtaposition to the spinomedullary region, atlanto-occipital fusion or atlas occipitalization is considered as important congenital malformations in skull base (76). As regards, both Arnold-chiari malformation and atlas occipitalization cause obstruction of foramen magnum , not all atlas occipitalization can be distinguished from Arnold-chiari (77,78). In Arnold-chiari malformation, portions of cerebellum are located below the foramen magnum (79,80). Some surveys reported that the occurrence of atlas occipitalization differs from 0.5 to 1.0% in Caucasians (76,81).

A wide range of signs and symptoms can be produced with atlas occipitalization, which differ from headache to full blown neurological syndrome (82,83). During embryonic development, failure of segmentation between lowest occipital sclerotome and the 1st cervical sclerotome is the main cause of atlas occipitalization (47,83). Fusion between the 2nd and 3rd cervical vertebrae with instability of the atlanto-axial articulation is observed in almost 70% of patients with atlas occipitalization (52).

2.2. Atlanto-axial subluxation

Atlanto-axial subluxation (AAS) is a disorder of atlas (C1) and axis (C2) and is characterized with abnormal fusion between anterior facet of atlas and facet of axis. AAS causes impairment in rotational movement of the neck. It may be associated with dislocation of the lateral mass of C1 on C2 (84-86). In other words, AAS may occur with or without C1-C2 dislocation (87). AAS may be acquired (as result of trauma) or inherited (87).Congenitally, AAS may be associated with some conditions such as klippel-feil syndrome (56,88,89), Down syndrome (90,91), Marfan syndrome (92), Morquio syndrome (93,94) and Grisel syndrome(95,96).

2.3. Genetically etiology of CFCV

So far, many genes in the evolution and pathogenesis of cervical vertebrae have been studied.; The chromosomal address of Human Pax1 gene is 20p11.2 (97,98). Alterations in expression of this gene have been associated with some vertebral anomalies (99-101). Hox genes encode transcriptional regulatory proteins that play a key role in control of axial skeletal formation. (102). HoxPG3, HoxPG4 and HoxPG5 are examples of Hox family genes involved in establishing morphologies in the cervical skeleton (17). Mutations in some members of Hox genes family have been associated with cervical vertebrae anomalies (103-106).

Conclusion

Clinical embryology is one of the most important parts of medical sciences, and detailed scrutiny of embryological etiology of anomalies plays an important role in reducing the incidence of this anomalies. Early diagnosis of these anomalies will be helpful in recording the change due to an injury, aging, or progressive degenerative process. We offer to clinicians, after performing careful physical tests and noticing the presence of signs and symptoms that mentioned in this paper, if a patient suspected to have CFCV, genetic tests ought to be performed.

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Conflict of Interest

The authors declare no conflict of interest.

Table 1. Summary of the genes involved in pathogenesis of CFCV.

Involved gene	Anatomical characterization	Reference
Pax1 (usually associated with pax9)	Fusion between 1st and 2nd cervical vertebrae	(99)
	Fusion between 4th and 5th cervical vertebrae	(99)
	Fusion between atlas and dense of axis	(43)
	Fusion between vertebral bodies	(43)
	Fusion between 1st , 2nd and 3rd cervical vertebrae arches	(107)
HoxB/HoxD	Fusion between 1st and 2nd cervical vertebrae	(108)
Hoxd3	Partial occipitalization of 1st cervical vertebra	(104)
Meox1	Cranio-vertebral fusion	(109)
	Fused cervical vertebrae	(110)
Cyp26b1	Abnormally fused cervical vertebrae	(65, 111-113)
	Fusion between atlas and axis	(112)
GDF6	Intervertebral joint fusion	(114, 115)
	Fusion of vertebral bodies of 2nd and 3rd cervical vertebra	(116)

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