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Review

Common developmental abnormalities and Genetic Syndromes Affecting the Cervical Spine in Pediatric: An Update Review

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Abstract

Instability and deformity of cervical spine theoretically is a devastating issue in numerous inherited syndromes. These complications cannot be ignored amongst the further general problems that were more aware of to whom assessing these conditions. We obviously project this study with a drive of review of the existing writings on the occurrence and challenges concern in assessment and treatment of common developmental abnormalities and genetic syndromes affecting the cervical spine disorders in pediatric. The data base was basically searched for cervical spinal column subjects in 11 particular and important syndromes. The significant training and publishing in this field was very low. A total of 57 articles were involved in the pediatric evaluation. Our main discussion is about down syndrome, Larsen syndrome, Morquio syndrome, Kniest dysplasia, spondyloepiphyseal dysplasia, Goldenhar syndrome, Achondroplasia, Klippel-Feil Syndrome, Osteogenesis Imperfecta, Neurofibromatosis Type 1, Os Odontoideum and the management approach to these craniocervical specific conditions. The accurate occurrence of congenital anomalies of the cervical spine is unidentified, while the incidence is perhaps understated for the reason that many of them remain asymptomatic. Even though, some developing anomalies are remote sporadic basis, numerous ones are originated as portion of a multi-system or syndromic abnormality. There are some classic genetic syndromes affecting the craniocervical junction. So attention in the management of cervical spine abnormalities in patients with hereditary syndromes is essential.

Keywords: pediatric, Cervical Spine, developmental abnormalities, Genetic Syndromes

INTRODUCTION

Instability and deformity of cervical spine theoretically is a devastating issue in numerous inherited syndromes. These complications cannot be ignored amongst the further general problems more aware to whom assessing these conditions. It is authoritative that spine consultants comprehend the related subjects linked with these specific syndromes (Klimo et al., 2007; Laker and Concannon, 2011).

The accurate occurrence of congenital anomalies of the cervical spine is unidentified, while the incidence is perhaps understated for the reason that many of them remain asymptomatic. Some writers have described that definitive studies to approximation the occurrence of these cervical disorders remain unobtainable (Klimo et al., 2007; Schaefer-Prokop et al., 2003).

Even though limited developing anomalies are remote sporadic disorders, numerous are originated by way of portion of a multi-system or some syndromes.

Table 1. Common Genetic Syndromes Disturbing the Craniocervical Junction.
AD: autosomal dominant- AR: autosomal recessive- Chr: chromosome-*COL1A1*:collagen type 1 alpha 1-*COL2A1*:collagen type 2 alpha-1-*COL7A1*:collagen type 7 alpha 1- CVJ: craniovertebral junction- GI: gastrointestinal-*FGF3R*:fibroblast growth factor 3 receptor-*FLNB*:filamin B-*GALNS*:galactosamine-6-sulfatase.

Syndrome	Inheritance Pattern	Gene/Locus	CVJ Involvement	Systemic Findings
Achondroplasia	AD	Chr 4, *FGF3R*	Foramen magnum stenosis, cervical stenosis, kyphosis	Frontal bossing, midface hypoplasia, shortened proximal limbs (rhizomelic dwarfism),macrocephaly with ventriculomegaly, genu varum
Down	Aneuploidy	Chr 21	Atlanto-occipital instability, atlantoaxial instability, os odontoideum, C1 arch anomalies	Congenital heart anomalies, leukemia,Alzheimer'sdisease, immune dysfunction, GI abnormalities, hearing and vision problems, mental retardation, flat face, upward and slanted palpebral fissures, epicanthic folds
Goldenhar's	AD	Chr 14	Atlas assimilation, fusion of the cervical vertebrae, atlantoaxial instability	Hemifacialmicrosomia, external and middle ear anomalies,colobus's, choristomas,strabismus
Kniest's	AD	*COL2A1*	Atlantoaxial instability, odontoid hypoplasia, kyphoscoliosis	Prominent eyes and forehead, depressed midface, stiff hands and enlarged large joints, broad trunk, depressed sternum, respiratory impairment, cleft palate, tracheomalacia, retinal detachment, glaucoma
Klippel-Feil	AD/AR	*Chr 5*	CVJ segmentation, fusion of the cervical vertebrae	Short neck, low posterior hairline, limited neck movement, deafness, cardiovascular andgenitourinary anomalies
Larsen's	AD/AR	*FLNB/COL7A1*	Cervical kyphosis, anterior Posterior disconnection	Dislocation of the knees, pes cavus, hypertelorism, flattened nasal bridge, prominent forehead
Morquio's	AR	*GALNS*	Atlantoaxial instability, hypoplasia of the odontoid	Corneal clouding, aortic valve disease
Neurofibromatosis type 1	AD	Chr 17q11.2 (neurofibromin)	Cervical kyphosis, scoliosis	Café au lait spots, axillary and inguinal freckling, Lisch'snodules, neurofibromas , sphenoid dysplasia, thinning of long bones
Osteogenesis imperfecta	AD	*COL1A1*	Basilar impression, occipitocervical instability	Gray-blue sclerae, osteoporosis, bone fragility, ligament laxity, premature deafness
Spondyloepiphyseal dysplasia,congenita	AD	*COL2A1*	Atlantoaxial instability	Platyspondyly, short limbs, cleft palate, myopia, hypoplasia of the abdominal musculature,scoliosis, mental retardation, equinovarusfoot deformity

(Table1) (Klimo et al., 2007; Skórzewska et al., 2013).

Understanding of the embrio anatomy of the child cervical spinal column is vital to appropriately classify genetic anomalies, distinguish hereditary from trauma incused injuries, and assessment the area at operation (Garton et al., 2008). Since we have been exposed these abnormalities in children referred to our clinics due to various physical illness like trauma, spine diseases, hydrocephalous (Haddadi, 2016; Haddadi, 2016a; Haddadi, 2016b), we obvious to project this study with drive of review of the existence writings on the occurrence and challenging concern in assessment and treatment of Common developmental abnormalities and Genetic Syndromes Affecting the Cervical Spine Disorders in pediatric.

Table 2. Classification of Klippel-FeilSyndrome

Type	Inheritance Pattern	Characteristics
KF1	Autosomal recessive	Fusion at C1, with or without caudal fusion; associated with other anomalies
KF2	Autosomal dominant	100% penetrance of C2-3 fusion
KF3	Autosomal dominant or recessive	Congenital fusions caudal to C2-3
KF4 (Wildervanck's syndrome)	X-linked dominantly inherited pattern; hemizygous lethal	Congenital cervical fusion, hearing loss, Duane's anomaly (congenital disorder of eye movement)

Evidence Acquisition

The data base was basically searched for cervical spinal column subjects in 11 particular and important syndromes. Primary we search Medline, Google scholar, PubMed and Ovid using the following keywords: pediatric, Cervical Spine, developmental, congenital, abnormalities, Genetic, Syndromes, cervical fusion, down syndrome, Larsen syndrome, Morquio syndrome, Kniest dysplasia, spondyloepiphyseal dysplasia, Goldenhar syndrome, Achondroplasia, Klippel-Feil Syndrome, Osteogenesis Imperfecta.

Neurofibromatosis Type 1, Os Odontoideum. Criteria involved objects from journals that described an analysis about Epidemiology, Classification, Management and Outcome of congenital cervical disorders in pediatric patients (age < 18 years). The significant training and publishing in this field was very low. A total of in 57 articles were involved in the pediatric evaluation. Although we obligate to use some old primary references in this era, but based our philosophy we just include new published after 2000 for this review.

RESULTS

Particular Situations

Down syndrome

The most public hereditary chromosomal complaint is trisomy 21 or Down syndrome, by an expected occurrence of 1 in 700 living labors. The most shared cervical complications realized in these patients are Subluxation of Occipitoatlantal and atlantoaxial joints. Patients by symptomatic atlantoaxial or occipitocervical instability mighthurt from cervical aching, myelopathy, radiculopathy, spasticity, hyperreflexia, clonus or torticollis (Browd et al., 2006; Menezes and Ryken, 1992). Forty to fifty percent of kids through Down syndrome have some gradeof Occipitocervical instability (OCI). Investigation of the occipitocervical junction in these patients confirmed that the joint surface of occipital condyle and first cervical vertebra (atlas) and are compressed. Operating management is usually suggestedwhen more than ten millimeter of dislocation on the occipitoatlantal joint has seen (Brockmeyer, 1999; Lu and Sun, 2007).

Atlantoaxial subluxation (AAS) is associated to either the extreme ligamentous laxity or the osseous anomalies in patients with Down syndrome. In 10 to 30 percent of down patient's atlantoaxial instability in imaging's, as resolute by the atlantodental distance and dimensions of spinal canal measurement, is existing though only 1 percent of these patients have symptomatic C1-2 instability (Lu and Sun, 2007; Schlosser et al., 2002). Recommendations have been prepared to monitor kids with Down syndrome for instability (Schlosser et al., 2002; Cook et al., 2003). Cervical imaging's containing dynamic views must be done primarily before the age 3 of life to evaluate for extreme cervical motion. In normal imaging's, follow up might be done each five years (Menezes and Ryken, 1992; Brockmeyer, 1999). For patients with irregular consequences on screening trainings, cautious annually supplement imaging's is directed. Invasive interventions might be obligatory if neurologic deficits are existing, if spinal cord injury detected in MRI, while an os odontoideum is existing or if progression of dislocation is revealed (Menezes and Ryken, 1992).

Klippel-Feil Syndrome

In 1912, Klippel-Feil Syndrome(KFS) Primary pronounced, and today characteristic triad of a low hairline ,short neck, and restricted cervical flexibility is recognized as *KFS*, even if fewer than fifty percent of patients by inherited union of the cervical spinal column have entirely this triad. Patients reflected to take Klippel-Feil variant if they are without entirely triad (Tracy et al., 2004; Vaidyanathan et al., 2002).

A restricted range of cervical motion, chiefly by lateral bending is the most shared sign in examination of patients with these patients (Vaidyanathan et al., 2002).

Patients by widespread cervical and cranio-vertebral junction fusion are understood at an former age than persons by subaxial fusion (Vaidyanathan et al., 2002).

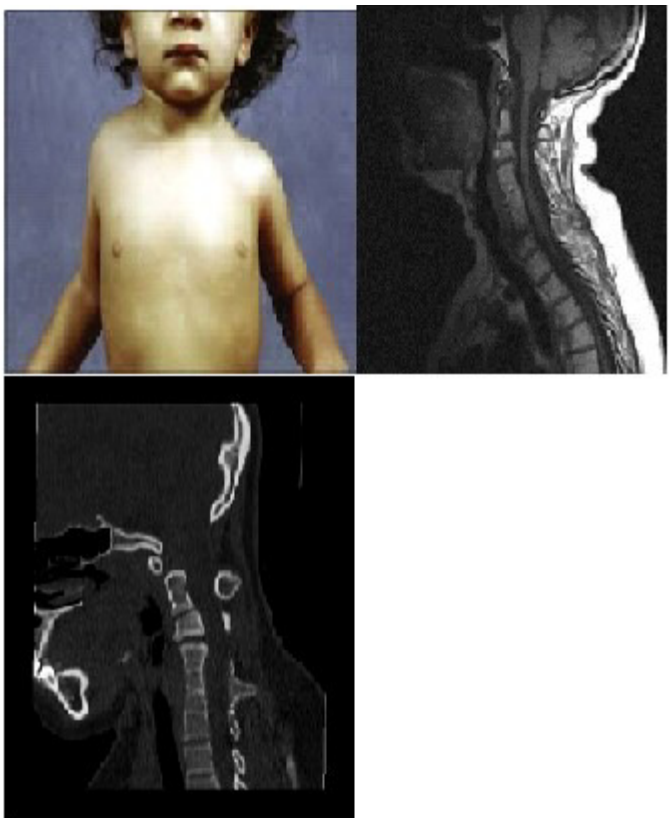

Figure 1. A three year old child with Klippel-Feil Syndrome with right shoulder is up rather than left one. Sagittal MRI and CT Scan display congenital fusion of the vertebral bodies and posterior components of C4 to C7 vertebral. There residues an unnoticeable disc space between the fused vertebrae.

twenty percent of patients with KFS have webbing in the neck or torticollis and is not definite to any specific neck abnormality. Neurological aberrations realized in these patients comprise headaches, myelopathy, radiculopathy, and brainstem dysfunction.

Amongst numerous organization systems for KFS established, currently, KFS divides into 4types and integrates the style of inheritance (Table 2) (Vaidyanathan et al., 2002; Bhat et al., 2014). X-rays must be gotten to recognize inherited fusions. Additional imaging, counting CT scan, or MRI, is completed as needed (Bhat et al., 2014; Papanastassiou et al., 2011). (Figure 1)

Achondroplasia

The most public type of dwarfism is Achondroplasia,, and described by unbalanced proximal ends shortening of the extremities relation to the other part of body. It is hereditary in autosomal dominant style, through eighty percent of patients recognized to some mutations in the fibroblast growth factor receptor 3(FGFR3) gene (Bagley et al., 2006; Brockmeyer, 2006; Dias, 2007). The basis of disease is a reduction in the degree of endochondral bone development by healthy membranous bone.

Compression is the main spinal disorder in achondroplasia, that be able to happen at the foramen magnum (FM), or other sites of spine (Bagley et al., 2006; Dias, 2007). The signs and symptoms of patients with compression of cervicomedullary (CMC) due to stenosis of the FM contain myelopathy, radiculopathy, hydrocephalus, respiratory complaints, and bulbar involvement.

Symptoms of (CMC) in infants consist of sleep orfeeding anomalies, poor head control, hypotonia, and apnea. The respiratory instabilities might have a multifactorial reason (Dias, 2007; Ryken and Menezes, 1994). A minor fraction of patients by foramen magnum stenosis have signs of CMC (Brockmeyer, 2006; Dias, 2007). Sudden deaths as a disastrous result of cervicomedullary compression have been informed in infants with achondroplasia (Ryken and Menezes, 1994; Shamji et al., 2013). Its informed a 7.5 percent sudden death risk in the initial year of lifetime and a 2.5 per-cent risk in in achondroplasia kids under 4 years (Shamji

et al., 2013).

Goldenhar's Syndrome

Goldenhar's syndrome (GS), is a categorized by hemi-facial microsomia, spinal defects and epidermoid accessories. Additional anomalies contain cardiac, ophthalmic anomalies, craniofacial, gastrointestinal, andrenal. Spinal deformities related by GS contain, failure of segmentation, failure of vertebral formation and vertebral hypoplasia (Healey et al., 2002; Erdil et al., 2003). Segmentation deficiencies are usual in the neck, while vertebral formation irregularities more often happen in the thoraco-lumbar spinal column. Studies showed, sixty percent of kids with this syndrome had vertebral abnormalities, counting unilateral thoracolumbar hemi vertebrae, spina bifida, block vertebrae, sacral agenesis, and butterfly vertebrae. Numerous patients had anomalies at several vertebral levels. Upper cervical spinal column abnormalities can too be understood in relationship by GS (up to 12 %) (Healey et al., 2002; Erdil et al., 2003).

Spondyloepiphysial Dysplasia

Spondyloepiphyseal dysplasia (SED) includes a number of complaints categorized by a typical growing of the spinal epiphysis and vertebrae. Persons by SED have short-trunk dwarfism by means of reduced proximal and middle features of the extremities nonetheless comparatively hands and feet with normal-size (Skórzewska et al., 2013; Brockmeyer, 1999).

The frequent spinal anomalies in affected kids are odontoid hypoplasia and ligamentous laxity. In about 35 percent of SED patient's compression of Spinal cord from atlantoaxial instability produce myelopathy. The myelopathy frequently progresses step by step and is demonstrated as late motor development, weakness, spasticity, respiratory abnormalities and sleep apnea. Atlantoaxial instability has been start to growth by age in SED (Brockmeyer, 1999; Dogan et al., 2006).

Morquio's Syndrome

Morquio's syndrome or Mucopolysaccharidosis (MPS) type IV, is a kind of lysosomal storage syndrome with autosomal recessive inheritance that consequences from an incapability to break down keratin sulfate, principally in cornea and the cartilage (Stevens et al., 1991). Patients frequently seem normal at natal and have favorite growing for the primary two years of life pending the fundamental skeletal anomalies converted clinically ostensible among after this 2 year. Atlantoaxial subluxation by spinal cord compression is frequent spinal anomaly is (Stevens et al., 1991). That has been recognized in up to 90 percent of patients with Morquio's syndrome (Stevens et al., 1991; Goel, 2005). Odontoid dysplasia, which might be demonstrated as aplasia, hypoplasia, or os odontoideum, is usual finding in MPS IV (Klimo et al., 2008).

Osteogenesis Imperfecta

Osteogenesis imperfecta is a genetic syndrome produced due to deficiency in collagen creation. The disorder is described by short stature, osteopenia, bones vulnerable to fracture, and advanced skeletal malformation. 56 Sillence classification is useful organization system for this disease (Brockmeyer, 1999; Janus et al., 2003).

Type I is slight with no long bone abnormalities, type II is fatal because of multiple fractures in the utero, type III is severe variety in children who stay alive the perinatal age, and type IV is an indeterminate category through modest bone abnormalities and inconstant short stature. Anomalies at the craniovertebral junction are frequently understood with type IV of disease, by an occurrence fluctuating from uncommon to 25 percent (Janus et al., 2003; Oakes et al., 2013). Upward movement of the cervical spinal column into the foramen magnum produce severe compression of the brainstem and disturbance in lower cranial nerves (Schlosser et al., 2002; Janus et al., 2003).

Larsen's Syndrome

Larsen's syndrome is an infrequent hereditary illness of connective tissue (Brockmeyer, 1999; Laville et al., 1994). The most common part of affected spine is cervical spinal column. The most typical anomalies contain dysraphism, hypoplastic vertebral bodies, wedged vertebrae, and hemi vertebrae (Laville et al., 1994; Madera et al., 2008). kyphosis has been defined in twelve percent of patients by this syndrome. By progress of the curvature and amplified instability, advanced myelopathy, segmental weakness, respiratory deficiency and even death are inevitable (Schlosser et al., 2002; Laville et al., 1994; Madera et al., 2008).

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is the frequent type of neurocutaneous syndrome, by a frequency of 1 in 3300 people (Williams et al., 2009; Brems et al., 2009). Involvement of spinal column happening in patients with this disease contain meningocele, Dural ectasia, cervical kyphosis, and paravertebral tumors (Brems et al., 2009; Crouse et al., 2011). The most shared spine tumors in kids by NF1 are Para spinal neurofibromas. These

lesions are frequently asymptomatic however can donate to the advance of instability and scoliosis (Crouse et al., 2011; Arrington et al., 2013).

Rebuilding of the cervical vertebral column to improve kyphotic deformities in these patients is characteristically done first from the anterior path, with multi-level discectomies, fusions, shadowed by rib and instrumentation if needed (Crouse et al., 2011; Arrington et al., 2013; Alwan et al., 2007).

Kniest's Syndrome

Kniest's syndrome is a type of skeletal dysplasia categorized by distinctive facial features and huge, rigid articular surface and contractures (Superti-Furga and Unger, 2007). Children with this syndrome have soft cartilage, which induce osteopenia of the spinal column and extremities (Superti-Furga and Unger, 2007; Jeanty et al., 2003).

The whole spine are exaggerated in this syndrome, but the most public complications being atlantoaxial instability, odontoid hypoplasia, cervical hypoplasia and instability, and kyphoscoliosis of the (Surgical tasks might be great because of poor bone quality and minor patient dimension (Jeanty et al., 2003; Parilla et al., 2003; Doray et al., 2000)

Os Odontoideum

Even though os odontoideum can be more of a post-traumatic than congenital complaint, its must be conversed in the setting of hereditary neck disease. Os odontoideum contains of detachment amongst the dens of C2 and the body such that a separated bone taking the place of the undamaged odontoid (Le Pape et al., 2016; Idiris and Kasim, 2017).

Kids by atlantoaxial instability from os odontoideum might be at danger for major neurological damage. If instability is supposed, flexion-extension radiographic must be gotten, amplified by CT or MRI. Stabilization and rigid instrumentation methods from posterior has been revealed to be very harmless and effective for management this complaint (Idiris and Kasim, 2017; Titelbaum and Uceda, 2015; Kemery et al., 2015).

Clinical characteristics and diagnosis

Clinical symptoms of cervical spine involvement can be different range from a simple pain and paresthesia and weakness of all four limbs or just upper limbs (lotfinia et al., 2010; Ahmad et al., 2016). Sometimes, depending on the type of conflict as atypical symptoms mimic other parts of the spine, or other diseases such as infections involving could be visible. Plain radiographs, CT scan with thin slices and MRI are the most useful tools in the diagnosis of cervical injury or other injuries in the surrounding areas (lotfinia et al., 2010; Ahmad et al., 2016; Hannah et al., 2017; Ahmad et al., 2015).

Managing of Particular anomalies by Means of Anatomic Level

Occipitoatlantoaxial Level

Instability at the cranio-cervical junction might need surgical intervention. Current trainings have revealed a strong power of rigid screw and instrumentation methods above elder bone and wire systems (Haddadi, 2016; Gluf and Brockmeyer, 2007).

For occipitoatlantal instability deprived of important cranio-cervical deformity, an infusion of occiput-to-C2 by screw insertion at C2 and occiput rod or loop instrumentation, amplified through an auto graft harvest from iliac crest or rib t, is presently the favored technique. Kids smaller than four years might be particularly puzzling, however trainings have revealed respectable long standing consequences by occipitocervical fusion in this populace (Gluf and Brockmeyer, 2007; Junichi et al., 2015) Atlantoaxial instability is characteristically treat through some kind of straight surgical approaches. Selections of direct screw instrumentation, comprise lateral mass of C1, C1 and C2 trans articular, pars of C2, and translaminar of C2 (Ahmad et al., 2016; Junichi et al., 2015). Widespread practice with these methods in children has exposed promising consequences. Distinctive circumstances rise in patents by basilar impression and basilar invagination. Basilar invagination (BI) is described via invasion of the upper cervical components inside to foramen magnum, frequently the odontoid. Management of older children by basilar invagination or basilar impression typically starts with traction and reduction of cranial component. If the impress is reducible, stabilization of occipito-cervical process via posterior approach can at that time be done to preserve the alignment. If the invagination is not reducible, trans oral odontoid resection is done, shadowed by posterior occipitocervical fusion (Ahmad et al., 2016; Ahmad et al., 2015).

Subaxial Cervical Spinal Column Abnormalities

The judgement to carry out surgical stabilization in a kidby a congenital cervical spinal column injury under C2 is centered on sign of instability of cervical spinal column, neurologic deficit, and progression of deformity (Ahmad et al., 2016; Hannah et al., 2017). Imaging data of cervical spinal column instability is not definitive, however the subsequent aid as valuable guidelines:1. Angulation of vertebral body bigger than fifteen degrees,

2. Subluxation of vertebral body bigger than five millimeters, or 3. Facets locked (Junichi et al., 2015; Gregory et al., 2015).

Classically, anterior cervical discectomy and allograft fusion by fixations from a posterior route will offer an excellent arthrodesis (Ahmad et al., 2015; Gluf and Brockmeyer, 2007; Junichi et al., 2015). Operating restoration for major cervical abnormalities might be done in staged manner, primary anterior approach through multi-level corpectomies or discectomies, shadowed by posterior approaches if needed (Junichi et al., 2015; Gregory et al., 2015). In selective patient's reductions by cervical traction could be beneficial. Exact consideration should be done to quality of bone, is vital for attaining natural cervical arrangement (Junichi et al., 2015; Gregory et al., 2015).

CONCLUSION

The accurate occurrence of congenital anomalies of the cervical spine is unidentified, while the incidence is perhaps understated for the reason that many of them remain asymptomatic. Even though some developmental anomalies are remote sporadic cases, numerous are originate as portion of a multi-system or syndromic abnormality. There are some classic Genetic Syndromes affecting the Craniocervical Junction. So, Attention in the management of cervical spine abnormalities in patients with hereditary syndromes is essential.

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