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HEAD AND NECK CONGENITAL MALFORMATIONS

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SUMMARY – Congenital malformations of the head and neck are a wide and extremely heterogeneous group because this region contains parts of almost all organ systems. These malformations range in their importance and severity from purely cosmetic defects and minor disturbances to lethal anomalies. They can be isolated or occur as a component of a sequence, syndrome or chromosomal disorder. Some of them are inherited, however, most of them are caused by frequently unidentified teratogens.

Key words: *Abnormalities – multiple; Head; Neck; Nervous system malformations; Musculoskeletal abnormalities; Chromosome disorders*

Introduction

When writing about congenital malformations of the head and neck, it is impossible not to mention their embryological development. The most typical feature in the development of the head and neck is formed by the pharyngeal or branchial arches. The pharyngeal arches are numbered I, II, II, IV and VI (in higher mammals, the fifth arches are transient, becoming fused with the fourth pharyngeal arch)[1,2]. They appear in the 4th and 5th weeks of development and contribute to the characteristic external appearance of the embryo. Initially, they consist of bars of mesenchymal tissue separated by deep clefts known as pharyngeal or branchial clefts. Simultaneously with the development of the arches and clefts, a number of outpocketings, the pharyngeal pouches, appear along the lateral wall of the pharyngeal gut, the most cranial part of the foregut. The puches penetrate the surrounding mesenchyma but do not establish an open communication with the external clefts. In this way, even though the development of pharyngeal arches, clefts and pouches resembles the formation of gills in fish and amphibia, in the human embryo real gills (branchia) are never formed. This is the reason why the term 'pharyngeal' is considered more appropriate than 'branchial' in the context of human embryology[3]. The arches are composed of mesoderm that originates almost entirely from two sources: the para-axial mesoderm and the neural crest. Every arch contains the following structures: (a) a core of cartilage derived from neural crest cells; (b) unsegmented mesoderm capable of forming striated muscle and bone; (c) an artery that runs from the aortic sac to the dorsal aorta on the same side; and (d) a nerve that enters it from the brain stem and carries motor fibers called special visceral (branchial) efferents, for the supply of striated muscles developing from the unsegmented mesoderm[3]. Each pharyngeal arch is covered on its lateral surface by ectodermally derived epithelium, and on its medial side by endodermally derived epithelium[1-3]. Endoderm of the pharyngeal pouches gives rise to a number of endocrine glands and a part of the middle ear. The pouches give rise to: the middle ear cavity and auditory tube (pouch 1); the stroma of the palatine tonsil (pouch 2); the inferior parathyroid glands and thymus (pouch 3); and the superior parathyroid glands and ultimobranchial body (pouches 4 and 5). Pharyngeal clefts give rise only to the external auditory meatus. The thyroid gland originates from an epithelial proliferation in the floor of the tongue and descends to its final position in the course of development. The first prominences of the facial region are paired maxillary and mandibular prominences and the frontonasal prominence. Medial and lateral nasal prominences form later around the nasal placodes on the frontonasal prominence. The importance of all these structures lies in

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the fact that they, through fusion and specialized growth, determine the size and integrity of the mandible, upper lip, palate and nose. The upper lip forms by fusion of two maxillary prominences with the two medial nasal prominences. The intermaxillary segment is formed by merging of the two medial nasal prominences in the midline. Intermaxillary segment is made of the philtrum, the upper jaw component (carrying 4 incisor teeth) and the palatal component forming triangular primary palate. The nose is derived from the frontonasal prominence, forming the bridge, the medial nasal prominences providing the crest and tip, and the lateral nasal prominences forming the alae. Fusion of the palatal shelves derived from the maxillary prominences creates the secondary (hard) palate and soft palate. The final form of the face is influenced by the development of paranasal sinuses, nasal conchae and teeth. Neural crest cells are essential for the formation of much of the craniofacial region, so that disruption of crest cell development results in severe craniofacial malformations. The skull is also a part of the head: it consists of the neurocranium (the bony part enclosing the brain), its parts being the base and the vault (calvaria). The base contains the chondrocranium (cartilaginous cranium) derived from endochondral ossification of the heavier parts of the occipital, temporal and sphenoid bones and of the entire ethmoid bone. The vault consists of membrane bones (the frontal and parietal bones, and the outermost parts of the occipital, temporal and sphenoid bones). The viscerocranium is the skeleton of the face; it consists of membrane bones including the mandible, the maxilla, the nasal and zygomatic bones, and the vomer (the frontal bone also contributes)[1-3]. The eyes begin to develop the end of the 4th week of development as a pair of outpocketings that will become the optic vesicles on each side of the forebrain. The optic vesicles contact the surface ectoderm and induce lens formation. When the optic vesicle begins to invaginate to form the pigment and neural layer of the retina, the lens placode invaginates to form the lens vesicle. Through a groove at the inferior aspect of the optic vesicle (the chorioid fissure) run the hyaloid artery and nerve fibers. The ear consists of three parts that have different origin. The external ear canal develops from the first pharyngeal cleft, whereas the eustachian tube and middle ear originate from the first pharyngeal pouch. The tympanic membrane can be considered a septum between the cleft and the pouch areas, with the epithelium on the lateral side of the membrane being derived from ectoderm and that on the medial side from endoderm. The auricle forms around the external extent of the first pharyngeal cleft from the surrounding tissue of the first and second pharyngeal arches. The ossicles are derived from tissues of the first and second arches (Meckel's and Reichert's cartilage)[1-4].

Malformations Caused by Disturbances in the Development of Pharyngeal Arches

Because glandular tissue derived from pharyngeal pouches migrates, it can remain along the pathway of its migration, forming accessory glands or remnants (for example, thymic tissue or parathyroid glands). When the 2nd pharyngeal arch fails to grow caudally over the 3rd and 4th arches, leaving remnants of the 2nd, 3rd and 4th clefts in contact with the surface by a narrow canal, branchial fistulas occur. Such fistulas usually provide drainage for cervical cysts (remnants of the cervical sinus, most often located just below the angle of the jaw). When the cervical sinus is connected to the lumen of the pharynx by a small canal, usually opening in the tonsillar region, then internal branchial fistulas develop. They result from rupture of the membrane between the 2nd pharyngeal cleft and pouch some time during development[1-4].

Congenital malformations of the thyroid gland are clinically similar to those described above, so they could be described next to each other. A thyroglossal cyst may be located at any point along the migratory pathway of the thyroid gland (from the point of appearance in the floor of the pharynx, indicated by the foramen cecum along the front of the pharyngeal gut, to the final position in front of the trachea). It is a cystic remnant of the thyroglossal duct, always located near or in the midline of the neck. It can sometimes be connected to the outside by a fistulous canal, a thyroglossal fistula. Aberrant thyroid tissue may be found at any point along the descent of the thyroid.

Some Craniofacial Defects Thought to Result from Disturbed Development of Neural Crest Cells

Treacher-Collins syndrome (mandibulofacial dysostosis, Franceschetti-Klein-Zwahlen syndrome) is a nonspecific developmental field defect, which may be inherited as an autosomal dominant condition, however, experiments suggest it can also be caused by teratogens. The main features are malar hypoplasia, downslanting palpebral fissures, defects of the lower lid, mandibular hypoplasia, and malformations of the external ear. Many other malformations such as cleft palate and pharyngeal hypoplasia may also be present[4].

Pierre Robin sequence (Robin's sequence) is characterized by micrognathia, glossoptosis (posteriorly placed tongue), and cleft soft palate. Hypoplasia of the mandibular area before the 9th week of gestation causes the tongue to be posteriorly located, presumably preventing closure of the posterior palate[1-4].

DiGeorge sequence results from disturbed development of the 3rd and 4th pharyngeal pouches, and includes hypoplasia or absence of the thymus and/or parathyroid cells with or without cardiovascular defects, abnormal external ears, micrognathia and hypertelorism. The sequence occurs sporadically and probably involves teratogens[1-4].

Goldenhar syndrome (hemifacial microstomia, oculoauriculovertebral abnormalities) includes craniofacial abnormalities that usually involve maxillary, temporal and zygomatic bones, which are reduced in size and flattened. In these patients, one can commonly observe anotia, microtia, tumors of the eyeball as well as dermoids and vertebral anomalies. Cardiac abnormalities can also be present. Causes are unknown, however, the syndrome has been more frequently observed in infants of diabetic mothers[1-5].

Other Craniofacial Defects

Cleft lip and cleft palate

Cleft lip and cleft palate are among the more common congenital malformations. Cleft lip shows an incidence of about 1:800-1000 births. It may occur as an isolated malformation (most of them are multifactorial in origin) or as part of a syndrome or as a phenotypic feature of a chromosomopathy. It is more frequent in male infants, whereas cleft palate is more common in female infants, however, its incidence is much lower (1:2500 births). The incisive foramen is considered as the dividing point between the anterior and posterior cleft deformities. Those anterior to the incisive foramen include lateral cleft lip, cleft upper jaw, and cleft between primary and secondary palates. These malformations are caused by a partial or complete lack of fusion of the maxillary prominence with the medial nasal prominence on one or both sides. Those that are situated posterior to the incisive foramen include cleft (secondary) palate and cleft uvula. Cleft palate results from the lack of fusion of the palatine shelves (because of the decreased size of the shelves, failure of the shelves to elevate, inhibition of the fusion process, or failure of the tongue to descend from between the shelves in case of micrognathia). The third category appears as a combination of clefts lying in front as well as behind the incisive foramen. Anterior clefts vary in severity from a barely visible defect to clefts extending into the nostril, and in more severe cases even into the maxilla. In these cases that frequently extend to the incisive foramen, the maxilla is split between the lateral incisor and the canine. Posterior clefts can also vary from those involving the entire secondary palate to isolated cleft of the uvula. Oblique facial clefts appear when maxillary prominence fails to merge with its corresponding lateral nasal prominence, in most cases exposing the nasolacrimal duct to the surface. Median cleft lip (a rare malformation) is caused by incomplete merging of the two medial nasal prominences in the midline. It is considered a 'midline' anomaly, usually accompanied by a deep groove between the right and the left sides of the nose, mental retardation, and holoprosencephaly[1-4].

Malformations of the Skull

In several inherited disorders (including Down syndrome and achondroplasia), growth activity of the spheno-occipital synchondrosis is deficient, so that the middle region of the face fails to protrude in the normal manner and the profile appears flat. The size of the cranial vault is determined by the volume of the brain, so that many malformations of the central nervous system result in the pathologic size and shape of the skull. In hydrocephaly, the sutures remain separate and the skull enlarges; in microcephaly, the sutures and fontanelles unite prematurely, and the skull is too small with regard to the size of the body. Similar changes can be observed with premature fusion of certain calvarial sutures – craniosynostosis when the shape of the skull depends on the suture that has closed before it was supposed to. Micrognathia is a condition in which the mandible is too small. It is attributed to faulty growth of neural crest cells contributing to the mandibular arch mesenchyma. The maxilla and zygomatic bones (also derived from the first arch) can be equally small. It is a feature of many syndromes (e.g., Treacher-Collins syndrome, Robin sequence, otocephaly) and chromosomal disorders[6,7].

Malformations of the Central Nervous System

Malformations of the central nervous system (CNS) are numerous and of diverse appearance and etiology. Structural anomalies of the brain may be due to genetic (gene mutation or chromosomal aberration) or environmental pathogenesis, however, the etiology is uncertain in most cases. The brain is affected by malformations more

Table 1. Most important periods for development of particular brain structures, and at the same time of greatest vulnerability of these structures

Developmental event	Age (postconceptual)
Neural plate	18 days
Neural tube	22 days
Anterior neuropore closure	24 days
Posterior neuropore closure	28 days
Caudal neural tube	28-32 days
Diverticulation	5-6 weeks
Neuronal proliferation	2-4 months
Neuronal migration	3-5 months
Neuronal organization and maturation	Late gestation to infancy
Myelination	Late gestation to adolescence

frequently than any other organ because its prolonged development places it at risk for a long period of time; it is one of the first systems to begin embryologic development and probably the last one to complete maturation, proceeding from a simple layer of cells to become the most complex organ of the body[8,9]. The most important periods for the development of certain brain structures, and at the same time the periods of greatest vulnerability of these structures are shown in Table 1. Many publications deal exclusively with CNS malformations, and for this reason only the most common ones will be discussed here. The selected anomalies are arranged according to the period of gestation in which they are thought to occur. Anomalies of the brain that are thought to originate in the first trimester are anencephaly, encephalocele, myelomeningocele and meningocele, Arnold-Chiari malformation, Dandy-Walker malformation, and holoprosencephaly. Some of them have already been mentioned above, because they cannot be separated from the malformations of the skull. Anencephaly is a deficit of the skin, scalp, skull and leptomeninges, resulting from defects that occur early in the embryologic development, at the time of the anterior neural tube closure. A failure of the neural tube closure produces a deformity extending from lamina terminalis to the foramen magnum. The frontal bones above the supraciliary ridge, the parietal bones and a portion of the occipital bones are usually absent. The eyes are characteristically prominent and froglike. The skin above the eyelids extends over the base of the skull and surrounds a mass of disorganized, vascularized, fibrotic tissue called area cerebrovasculosa[8]. Microscopically, an admixture of prominent blood vessels, mesenchymal tissue, neuroglial tissue and choroid plexus can be found. This tissue can be covered by a thin layer of squamous epithelium. The base of the skull is poorly formed, sella turcica is shallow, and the anterior lobe of the pituitary gland is present but the posterior lobe usually cannot be identified. This malformation is always associated with hypoplasia of the adrenals (as the result of premature involution of the fetal zone of the adrenal cortex, probably because of the failure of the fetus to take over after the production of placental chorionic gonadotropin diminishes). The spine is frequently involved, showing an open defect, craniorachischistis, or at least spina bifida (this is not the topic of the paper). As to other malformations that appear simultaneously with skull malformations (the squamous part of the occipital bone, which may be partially or totally lacking, is most commonly affected), most striking is encephalocele, a restricted disorder of the anterior neural tube closure in which cerebral tissue is herniated or displaced[10]. When no CNS tissue is present in the encephalocele, the correct term is cranial meningocele. Encephaloceles can be occipital (most common), frontal (pharyngeal), temporal or parietal. In occipital encephalocele, the protruding brain is usually connected to the underlying CNS by a narrow stalk of tissue. Encephalocele may vary in size from less than 1 cm to a mass larger than the brain. The Arnold-Chiari malformation involves displacement of the medulla, the fourth ventricle and the cerebellar vermis into the upper cervical canal, elongation and thinning of the upper medulla and lower pons, caudal distortion of the dorsal part of the brain stem, and a variety of bone defects. Most patients have an associated hydrocephalus[11]. The Dandy-Walker malformation is associated with a large posterior fossa and upward displacement of torcula and sinuses, cystic dilatation of the fourth ventricle, and aplasia or hypoplasia of the cerebellar vermis. Other abnormalities may include hydrocephalus, agenesis of the corpus callosum, and ectopia of the inferior olivary nuclei[12]. Hydrocephalus is an accumulation of excess cerebrospinal fluid (CSF) that results from an imbalance between CSF production and absorption, and produces dilatation of cerebral ventricles. The pathogenetic mechanisms underlying hydrocephalus are shown in Table 2[13,14]. Many other CNS malformations are not so obvious, such as agenesis of corpus callosum that can, in the absence of other malformations, be compatible with life, then disorders of neuronal migration, and maturation and disorders of gyrus formation. Holoprosencephaly has already been mentioned together with midline facial clefts.

It is a failure of the telencephalon to cleave into hemispheres[15,16]. The cleavage may be absent (alobar holoprosencephaly) or incomplete (semilobar or lobar holoprosencephaly). Facial abnormalities may also be present; the most severe is cyclopia, in which the orbits are fused and the eyeballs are in close proximity or fused. Above the orbit there may be a small nasal protuberance or proboscis[17]. Less severe facial abnormalities include hypotelorism, microophthalmia, cebocephaly, and cleft lip and palate. There is close correlation in severity between the cerebral and facial abnormalities. The most severe malformations are more likely to be associated with chromosomal disorders such as trisomy 13 or 15[4]. CNS anomalies originating in the second trimester of pregnancy are less dramatic morphologically. Micrencephaly and megalencephaly, gyral anomalies (agyria or lissencephaly, pachygyria – a milder variation of the former, and polymicrogyria), neuronal heterotopias, and agenesis of the corpus callosum, either partial or complete, are usually categorized in this group. Blood vessels can also show malformations (vein of Galen, arteriovenous malformation, berry aneurysms) that can show signs and symptoms very soon after birth, or may also remain undiscovered until later in life. Anomalies originating in the third trimester are rather considered encephaloclastic lesions that result from severe ischemic insult(s) than true malformations. Such anomalies are hydranencephaly and porencephaly, and multilocular cystic encephalopathy[8]. In the nervous system, cysts can sometimes be found; arachnoid cysts are usually located in the Sylvian fissure and can clinically present with symptoms of a space occupying lesion[11].

Table 2. Causes of hydrocephalus

Overproduction of CSF
Chorioid plexus papilloma
Obstruction of CSF pathways
Noncommunicating
Tumor
Aqueductal stenosis (forking, septum formation)
Arnold-Chiari malformation
Dandy-Walker malformation
Communicating
Posthemorrhage
Postinfection
Impaired CSF absorption
Abnormal arachnoid villi
Decreased venous drainage

Malformations of Sensory Organs

Malformations of the Eye

Of congenital malformations of sensory organs, those of the globe are certainly most dramatic, reflecting very early disruption of embryogenesis. When the anterior end of the notochord and surrounding mesoderm are not appropriately induced by the forebrain, a spectrum of anomalies can occur, such as the absence of an eye (anophthalmia), partial or complete fusion (cyclopia), or a small malformed globe associated with a cleft (microphthalmos with cysts and colobomas)[18]. Microphthalmia (small eye) frequently results from intrauterine infections (TORCH) as well as cataract (lens opacity) that can also be genetically determined. Aniridia is a misnomer, as there is severe hypoplasia but not absence of iridic and ciliary bodies, and dilator and sphincter muscles of the iris are not identifiable[19]. Anterior chamber anomalies further included abnormalities of the chamber angle, incomplete cleavage of the angle, and attenuation of Bowmann's membrane. Retinal dysplasia is a bilateral congenital lesion involving dysgenesis of the entire retina; a funnel shaped, white retrolental mass consists of pigmented and nonpigmented retinal epithelial cells as well as glia[20]. It can result from a variety of intrauterine insults such as trauma, drugs or infections, or it may be associated with a chromosomal disorder. Chromosomopathies that show ocular changes are listed in Table 3.

Malformations of the Ear

Auricular deformities vary from very mild alterations (supernumerary auricles, auricular tags or protruding auricles) to severe hypoplasia (microtia) or agenesis. Developmental anomalies of the first pharyngeal cleft include atresia of the external canal and first cleft cysts and sinus tracts. Atresia may be unilateral or bilateral, an isolated finding or part of a developmental syndrome. A portion of the aborted canal lining may be trapped medially to a fibrous or bony atresia, and can develop into a type of congenital cholesteatoma, which can grow inward[21]. First cleft cysts and sinuses can be thought of as partial reduplication of the external canal. The location and course around the ear vary, but many lesions have been classified into two groups. Type I lesions are usually in the postauricular region, with a cyst connected to a sinus tract running in parallel to the canal and ending in a blind pouch. Type II lesions are often below the angle of the mandible, are associated with parotid tissue, and have a tract terminating in

Table 3. Chromosomopathies with ocular anomalies

Chromosomal anomaly	Ocular anomalies
Trisomy 13	Microophthalmia – clinical anophthalmos Cyclopia Coloboma: iris and ciliary body Cataract Retinal dysplasia Dysgenesis: cornea and iris Primary hyperplastic vitreous
Trisomy 18	Microophthalmia Orbital and soft tissue changes Optic disk hypoplasia and coloboma Pupillary membrane Cornela opacity
Trisomy 21	Epicanthus Bruschfield's spots Nuclear/cortical cataracts Keratoconus
47 XYY	Subluxed lenses Coloboma: iris and cornea
Triploidy	Microophthalmia Coloboma: iris and cornea Microcornea Retinal dysplasia

the area of the cartilaginous bony junction of the canal. The tract may communicate with the canal. A rare sinus tract may go deeply toward the middle ear space. There is approximate correlation between lesion types and histologic features, but exceptions are not rare. Both types are lined with epidermoid tissue and may have prominent skin appendages, histologically resembling dermoids. Type II lesions usually have a cartilage that partially surrounds the sinus tract and mimics the structure of the external canal[22,23]. The preauricular pit is a short, superficial sinus tract that probably arises from an ectodermal inclusion between the mesenchymal auricular hillocks. Although usually superficial, the tract may extend to significant depths[24]. Developmental anomalies of the middle ear include persistent stapedial artery, abnormal carotid artery bulging into the middle ear, malformed ossicles and facial nerve dehiscence along the medial wall of the middle ear space. Ossicular anomalies and other middle ear defects causing conductive hearing loss can occur as isolated findings or can be associated with external or inner ear abnormalities. As the ossicles, except for the stapes footplate, develop from the first and second pharyngeal arches, anomalies of the ossicles are often found together with other first and second arch developmental defects. Middle ear defects can be associated with Treacher-Collins, Franceschetti-Klein, Pierre Robin, Klippel-Feil, Hanhart, Apert's Crouzon's and DiGeorge's syndromes and trisomies 13 and 18[22].

Conclusion

Congenital malformations of the face and neck are a wide and extremely heterogeneous group, because this region contains parts of almost all organ systems. These malformations range in their importance and severity from purely cosmetic defects and minor disturbances to lethal anomalies. They can be isolated or occur as a component of a sequence, syndrome or chromosomal disorder. Some of them are inherited, however, the majority are caused by mostly undetermined teratogens.

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Sažetak

PRIROĐENE NAKAZNOSTI GLAVE I VRATA

M. Kos

Prirođene nakaznosti glave i vrata su brojne i vrlo raznolike, prvenstveno stoga što se u ovom području nalaze dijelovi skoro svih organskih sustava. One se razlikuju prema važnosti i izraženosti, od estetskih poremetnja i onih koje uzrokuju lakše tegobe sve do smrtonosnih, a mogu se pojaviti kao pojedinačne ili u okviru sindroma i kromosomopatija. Neke od njih imaju nasljednu osnovu, dok je većina sporadična i, kako se vjeruje, uzrokovana teratogenim čimbenicima koji često nisu jasni.

Ključne riječi: *Nenormalnosti, višestruke; Glava; Vrat; Malformacije živčanog sustava; Mišićnokoštane nenormalnosti; Kromosomne bolesti*