“The face predicts the brain”: rare facial anomalies associated with forebrain malformations

A. IANNIRUBERTO, P. ROSSI, F. VOLPE, L. FALASCA, A. FALASCA, M. IANNIRUBERTO

SUMMARY: “The face predicts the brain”: rare facial anomalies associated with forebrain malformations.

Malformations of the forebrain are frequently associated with a wide spectrum of craniofacial anomalies, which, depending on the severity, are cyclopia, proboscis, otoccephaly, cleft lip/palate, hypotelorism and other alterations of the central midline structures.

The parallelism between the abnormal facial phenotype and malformations of the forebrain is probably the result of a common cause of a lack of embryological induction of the prechordal mesenchyme.

Molecular studies have shown, in some cases, chromosomal disorders, but in many other cases, the etiology is unknown with the possibility of the existence of environmental or metabolic teratogenic factors.

In this paper, after a thorough discussion on the more frequently seen brain malformation, the holoprosencephaly, some rare craniofacial malformations such cyclopia, proboscis, otoccephaly, craniosynostosis and epignathus have been described, whose conditions have been easily diagnosed in recent years with the use of high resolution ultrasound.

KEY WORDS: Holoprosencephaly - Proboscis - Cyclopia - Otocephaly - Craniosynostosis - Epignathus - Sonographic prenatal diagnosis.

Introduction

In recent years, with the use of real-time high-resolution ultrasound, it has become easier to acquire detailed images of normal fetal anatomy and morphological abnormalities, especially in the early stages of pregnancy.

In this study, we intend to focus attention on some fetal facial malformations, because very often they are associated with severe brain malformations. The statement “the face often predicts the brain” is confirmed by many scientific publications and comments, that have been reported recently on a possible common cause of the origin of the anomalies of the embryological development of the facial structures and brain.

It is interesting that in the literature of Greek mythology, characters such as Thersites in Homer’s Iliad were described as having an unpleasant and disfigured face, which reflected their cruelty. Likewise “kalokagathia” poses the principle that juxtaposes beauty and good against ugly and bad (Figure 1).
The most severe brain malformation that has been found is the holoprosencephaly, therefore, after a thorough discussion on its etiopathogenesis, we will briefly examine some of the most frequent associated facial malformations (proboscis, cyclopia, otocephaly). Moreover a case of craniostenosis and a case of epignathus have been described, because the craniofacial dysmorphism could be associated occasionally to the central nervous system anomaly.

The cases that we are presenting have been diagnosed prenatally by echography, using axial, sagittal, coronary and oblique scans in various planes. In more recent years, the diagnosis has become easier, especially in early phases of gestation, with the use of ultrasound through its various three-dimensional mode which can make multiplanar and surface (rendering) evaluations.

For detailed information of normal fetal anatomy, craniofacial anomalies and diagnostic ultrasound methods in the prenatal period, we refer to the most recent available literature publications (1, 2).

**Holoprosencephaly**

Holoprosencephaly is a complex brain malformation due to the failed differentiation of the embryonic prosencephalon in both cerebral hemispheres and diencephalon (neurohypophysis, thalamus, third ventricle and olfactory bulbs). The prosencephalon is the most rostral of the three primitive brain vesicles and its failed differentiation, which occurs between the 18th and 28th day of pregnancy, may be due to the absent or deficient induction of the prechordal mesenchyme located anteriorly to the embryonic notochord; this is also responsible for the development of the facial midline structures (forehead, nose, interorbital structures, upper lip, premaxilla).

Holoprosencephaly has been observed in 1 out of 16,000 births, but because it is frequently associated with fetal death, its incidence is much higher; a study of first and second trimester abortions showed 1 in 250 cases (3).

The etiology is very heterogeneous. In some cases there was a familial tendency with autosomal recessive or autosomal dominant inheritance with incomplete penetrance and variable expression, with an inheritance risk of 25 and 50% respectively (4).

In about 70% of cases trisomy 13 was present, but other chromosomal abnormalities, such as trisomy 18, triploidy, 5p+, 13q-, 18p-, have been found in the alobar and semilobar forms.

Thus far the known genes associated with holoprosencephaly are: Sonic hedgehog (SHH), ZIC2, SIX3, TGF1, PTCH, GLI2, TMEM1, FAST1 (5). The protein Sonic hedgehog (SHH), isolated on chromosome 7q36, plays a critical role in the prosencephalon and in the development of the central nervous system. This is expressed in the notochord of the human embryo and is the principal gene implicated in many cases of holoprosencephaly. Other causes of holoprosencephaly (6) are metabolic and environmental factors, such as insulin-dependent diabetes mellitus (7), alcoholism especially if associated with smoking (8), the administration of retinoid acid in pregnancy, and inhibitors of the biosynthesis of cholesterol (9), or infections (toxoplasmosis, rubella, cytomegalovirus) (10, 11). These malformations can be induced in animals with x-radiation, veratrum alkaloid, salicylates.

There are three main varieties of holoprosencephaly: alobar, semilobar and lobar. A very rare form is the median interhemispheric, which at the middle of the lateral ventricles has extensive communication at cell-level. The most common form is alobar which is characterized by the absence of falx cerebri and an interhemispheric fissure, but includes the formation of a single ventricle. Furthermore, the thalami are fused and the third ventricle, the neurohypophysis, the olfactory bulbs, the septum pellucidum are absent; there is dysgenesis of the corpus callosum. The tela choroidea, the roof of the ventricular cavity between the cerebral convexity...
and the cranial vault, forms a cystic structure, with varying dimensions, called the dorsal sac.

In the semilobar variety the two cerebral hemispheres are partially separated posteriorly, with a single ventricular cavity, partial fusion of the thalami, the absence of the septum pellucidum and dysgenesis of the corpus callosum. In the lobar form the brain is almost completely divided in two distinct hemispheres, with varying degrees of fusion at the level of the cingulate gyrus and the frontal horns of the lateral ventricles, with extensive communication between the frontal horns and the third ventricle. The *septum pellucidum* is absent. The olfactory tracts and bulbs and the corpus callosum may be absent, hypoplastic or normal. Investigations with MRI have showed the fusion of the fornix, which appears as a solid beam on the center line in the upper portion of the third ventricle or, with the ultrasound technique, it appears as a small round structure in the middle portion of the third ventricle (2).

Especially in alobar and semilobar holoprosencephaly, anomalies are frequent, such as microcephaly, macrocephaly, encephalocele, obstructive hydrocephalus, hypotelorism, hypertelorism, median or lateral cleft lip and/or cleft palate, flat nose, central single incisors, cyclopia, etmocephaly, anophthalmia, cebocephaly, arhinia or proboscis.

The severity of facial dysmorphism is correlated with brain abnormalities in about 80% of cases (*the face predicts the brain*) (5).

Morphological facial abnormalities of the holoprosencephaly have been subdivided by DeMyer et al. (12) in 5 categories:

1) *cyclopia*, characterized by a single eye or partially split eyes in a single orbit and the absence of the nose (*arhinia*) with proboscis which usually emerges above the orbit (Figure 2);

2) *ethmocephaly*, characterized by marked hypotelorism, arhinia and a proboscis emerging above the orbits (Figure 3);

3) *cebocephaly*, characterized by extreme hypotelorism and a small nose-like proboscis with one nostril, without a cleft lip and/or median cleft palate;

4) face with a median cleft lip, hypotelorism and an absent or very flat nose;

5) face with a bilateral cleft lip and palate, hypotelorism and a flat nose.

Cyclopia and etmocephaly are invariably associated with alobar holoprosencephaly. Cebocephaly and median cleft lip can be found in the alobar or semilobar variety. The malformation also influences the development of the hypothalamus and pituitary gland, therefore there are frequent endocrine disorders such as diabetes insipidus, growth hormone deficiency, adrenal and thyroid hypoplasia, hypogonadism.
Proboscis

The proboscis is a trunk-like appendix usually associated with the absence of nose. The proboscis, which is located above a single orbit (cyclopia) or between the orbits (cerebephaly), is characterized by a single central aperture and rarely by two openings not connected with the nasal choanae (Figures 4, 5). The ethmoid, the nasal choanae, the nasal and lacrimal bones are absent. A bilateral proboscis is very rare. Cyclopia and cebocephaly, conditions in which there is the proboscis, were found respectively in 1:40,000 and 1:16,000 births. The presence of a proboscis is frequently associated with holoprosencephaly, particularly of alobar type. It is assumed that a primary prechordal mesenchyme disorder could cause facial structures abnormalities. An abnormal development of the nasal prominences may cause a fusion of the olfactory placodes and subsequent formation of a proboscis (13, 14).

Cyclopia

It is a common opinion that every legend derives from a true fact. But conversely could also be said that reality has a foundation in legend. In fact, the description in the Greek mythology of the Cyclops, Polyphemus in particular, suggests that the ancient Greeks probably had knowledge of cyclopia. Most likely, the legend of the Cyclops could have its origin in some fossils of dwarf elephants which were less than a meter tall, from the Paleolithic era. These animals are characterized by the presence of a large hole in the center of the skull. This hole, which connects the nasal proboscis, could have been mistaken for a single eye in an enormous centrally positioned orbit (Figure 6). Their fossil remains could be considered to be that of gigantic men with a single eye in the middle of their forehead. In fact Empedocles says that “in many Sicilian caves, fossils of a race of gigantic men, which up until now had disappeared, have been found”. Another possibility is that
“The face predicts the brain”: rare facial anomalies associated with forebrain malformations

Figure 4 - A) Profile of a fetus with a proboscis that is emerging above an orbit with a single eye. Arhinia. B) Sagittal sonogram scan showing the proboscis (black arrow) over one eye (white arrow).

Figure 5 - A) Face profile of a fetus with proboscis and arhinia. B) Sagittal sonogram scan showing the proboscis (arrow).
The Cyclops were ancient Greeks blacksmiths who had emigrated to Sicily, namely in the Aeolian Islands, where traces of metal processing have been found. The presence of these people with one eye may be due to the custom of covering the left eye with a bandage to protect it from sparks emitted from the hot metal. Finally, it has also been suggested that these ancient blacksmiths, of considerable size, had a tattoo on their forehead representing the Sun god to whom they were devoted (15).

Cyclopia is characterized by the presence of a median eye or an equal ocular structure (sinoftalmia) in a single orbital cavity. The defect of lateralization (which is not a fusion) could be caused by the lack of the normal inhibition of the middle portion of the individual single optical field. At a very early stage, the prechordal dish in the embryo normally induces equal optical primordiums (16-18). Cyclopia is frequently associated with holoprosencephaly and occasionally chromosomal abnormalities have been noted. In one case duplication of segment 3p21-3pter has been reported (19). The association with the proboscis is frequent and after the first description in 1708 by Jean Palfyn (Traitè des Monstres) (Figure 6B) the prenatal echographic diagnosis in early pregnancy has been easier with the use of three-dimensional ultrasound.

Otocephaly

Otocephaly (also called agnathia-otocephaly or agnathia-microstomia-synothia) is a very rare lethal malformation and is characterized by a hypoplastic (micrognathia) or an absent (agnathia) mandible, a small or absent mouth (microstomia), with the temporal bones coming closer together and the displacement of the ears in a horizontal plane and in the midline, where the auricular lobes are very close (melotia) or fused (synotia) (Figures 7, 8).

Otocephaly is considered to be the most severe form of malformation of the first branchial arch.

The embryological facial structures, such as the neck, sinuses, mouth, larynx and pharynx are derived from the branchial arches. In particular, the facial structure is derived largely from the first branchial arch, which consists of 4 components: 1) bar cartilage, 2) nervous branch, 3) muscle tissue, 4) artery of the aortic arch.

The malformation, which occurs between the 4th and 8th week of pregnancy, results from failure of migration of the mesenchimal cells to the neural crest in the first branchial arch, with subsequent underdevelopment or absence of the mandibular prominences. Under normal conditions the two mandibular prominences, which delimit the stomodaeum (a depression of the cephalic ectoderm predetermined to form the primitive
"The face predicts the brain": rare facial anomalies associated with forebrain malformations

Figure 7 - A) Otocephaly. Hypotelorism. A proboscis with double opening that emerges above the orbit. Fusion of the ears located on the midline. Absence of the mouth. B) Coronal oblique scan showing a proboscis (big arrow) above the orbits. Hypotelorism. Ears are fused and located anteriorly (small arrows).

Figure 8 - A) Otocephaly. Facial profile that shows a proboscis between the orbits. Sinotheria. B) Sagittal sonogram scan shows a proboscis next to the eye. Absence of the mouth.
oral cavity) are fused to form the embryonic mandible (20, 21).

The etiology is unknown. Otocephaly can be attributed to genetic or teratogenic causes, but other factors may be involved. The administration of theophylline, beclomethasone dipropionate and salicylates during pregnancy may be the cause of the malformation (22). Experimentally otocephaly has been induced in mice through the administration of streptonigrina or with x-irradiation (23-25). Recent molecular genetic studies have highlighted a mutation in the homeobox gene-1 (PRX-1), which is associated with the gene PRX-2, and is responsible for the function of the craniofacial mesenchyme (26-28). The PRX1 and PRX2 regulate the production of an unknown factor that stimulates the expression of Sonic hedgehog (SHH) in the oral epithelium, which interacts with the mesenchyme and stimulates cellular proliferation (29). Experimentally it has been shown that genihomeobox PRX1 and PRX2 are important for a correct scheletrogenesis in many cases and the lack of which causes a reduction or absence of skeletal elements in the skull and in the face of the mice (30). Otocephaly may be associated with holoprosencephaly, cerebellar hypoplasia, cephalocele, proboscis, absence of olfactory bulbs, microstomia, hypoplastic tongue, tracheoesophageal fistula, cardiac abnormalities, adrenal hypoplasia, hypotelorism, choanal atresia, ectopic kidneys, absence of the pituitary gland, situs inversus (31). The absence of cerebral anomalies is very rare, and in the literature only two cases have been reported (31, 32). Moreover one of our presented cases of otocephaly is characterized by a normal ventricular system (Figure 9).

The incidence of the otocephaly is estimated to be about 1 in 70,000 births. Described for the first time by Kerckring in 1717 (33) and subsequently by Ahfeld in 1882 (34), otocephaly has been classified anatomically in 1988 by Leech into 4 categories (35): 1) isolated agnathia, 2) agnathia with holoprosencephaly, 3) agnathia with situs inversus and visceral anomalies and 4)
Craniostenosis

Craniostenosis (or craniosynostosis) is an anomaly of the shape and size of the skull caused by the premature closure of one or more cranial sutures, which causes an inhibition of the growth of the adjacent bones in a direction perpendicular to the closed suture. Therefore, it causes a compensatory growth of the skull in the direction where there is no resistance, that is towards open sutures and fontanels, causing a deformity of the skull and an asymmetric face. Depending on the affected sutures, craniosynostosis can be classified as scaphocephaly, turricephaly, trigonocephaly, plagiocephaly, oxicephaly and cloverleaf skull.

The incidence is about 1 in 2200 live births and it occurs in isolate form or, more rarely, associated with very complex polymalformative syndromes (Apert, Crouzon, Pfeiffer, Seathre-Chotzen, Carpenter) and many other syndromes with autosomal dominant or recessive inheritance. Craniosynostosis can be classified as idiopathic, not resulting from any alterations, or secondary to pathologies such as metabolic diseases (rickets, hyperthyroidism, mucopolysaccharidosis), hemolytic anemia, polycythemia, sickle cell anemia, congenital hemolytic jaundice, malformations (microcephaly, encephalocele, oloprosencephaly, agenesis of the corpus callosum, ventriculomegalgy), teratogenic (retinoids, hydantoin, aminopterin), infectious (37).

The craniostenosis can prevent normal growth of the brain with intracranial hypertension, brain dysfunction, visual disturbances due to the traction or distortion of the optic nerve.

During the intrauterine life, the cranial bones are separated by fibrous tissue and the physiological mechanism responsible for the closure of the cranial sutures is not known, therefore also the pathogenesis of craniosynostosis has not yet been identified. However some conditions have been hypothesized: 1) hypoplasia of fibrous tissue which is normally interposed between the bones, 2) decreased primary intracranial pressure or hyperdrainage syndrome in case of CSF derivation, 3) abnormal ossification, 4) primary anomaly of the basis of the skull that interferes with blood circulation.

In some cases of craniostenosis there is a mutation of one of the genes encloing for one of the three fibrolast growth factors (FGFR1, FGFR2, FGFR3) (38). Almost all mutations are placed on FGFR2. One mutation on FGFR1 is associated with Pfeiffer syndrome and two mutations in FGFR3. A mutation on Ser252Trp noted in many cases of the Apert syndrome could be responsible of a greater frequency of cleft palate. Cerebral anomalies could be founded in the Apert and Pfeiffer syndromes.

Among the various forms of craniosynostosis, the most characteristic is the cloverleaf skull or Kleeblattschädel syndrome due to premature closure of the coronal, sagittal and lambdoid sutures with hydrocephalus (usually of a communicating type or stenosis of the aqueduct). The result is the prominence of the temporal, occipital and frontal bones with a cloverleaf skull shape (Figure 10). Transmission is autosomal dominant and in one reported case in the literature a gene mutation MSX2 has been discovered (39, 40). It can be isolated or associated with chromosomal abnormalities and dysplastic skeletal forms.

Prenatal ultrasound diagnosis of cloverleaf skull is easy due to the typically featured frontal and two posterior-lateral protrusions.

Epignathus

Epignathus is a rare form of teratoma located in the oropharynx. It can be of various sizes, protrudes from the mouth and has a high mortality rate caused by severe airway obstruction in the neonatal period. This hideous abnormality was given the name of epignathus by St Hilaire (41). After the publication in 1875 of the first cases of epignathus by Ahlfeld (42), other cases have been reported in literature, especially those diagnosed prenatally with ultrasonography (43) (Figure 11).

Epignathus consists of at least one type of tissue of each of the germinal lines, with a prevalence of nervous tissue in 68% of cases (44) and includes the absence of malignant degeneration, except in very rare cases of incomplete surgical resection (45).

The etiology is unknown and several theories have been proposed: a) origin in pluripotent cells adjacent to Rathke’s pouch (46), b) derived from the pluripotent primordial germ cells that, from the yolk sac, near to the allantois, migrate to the genital crest between the 4th and the 5th week of gestation. Some cells can lose their purpose and give rise to teratomas in each part of the body, from the brain down to the coccyx, usually in paramedian and median line c) remains of a parasitic conjoined twin (47), d) remains of the primitive node or primitive notochord (48).
The epignathus can be attached to the hard palate in 39% of cases, to the nasopharynx in 34%, to the sphenoid in 15%, to the oropharynx in 10%, to the maxilla and ethmoide septum in 5% (49).

In some very rare cases it has been described an intracranial extension with destruction of the nervous tissue. Cytogenetic studies have shown that the tumour is identical to the fetal karyotype. Chromosomal abnormal-
“The face predicts the brain”: rare facial anomalies associated with forebrain malformations

...
2005;70:173.