FETOPATHOLOGICAL ASPECTS OF HOLOPROSENCEPHALY

Tanya T. Kitova, Masmoudi Aida1, Zghall Dorra1, Chelli Dalenda1, Soumeya Siala Gaigi1
Department of Anatomy, Histology and Embryology, Medical University, Plovdiv;1Service d’embryo-foeto-pathologie Centre de Maternité et de Néonatologie de Tunis

ABSTRACT
Holoprosencephaly (HPE) is a congenital central nervous system malformation estimated to occur in 1/250 conceptuses and 1/10,000 live births. While the severe forms, which are incompatible with life, are easier to detect in the prenatal period, the milder forms can remain unrecognised. As this can have serious consequences for the pregnancy and malformation carriers it is of crucial importance to find ways of timely detection of this pathological condition.

The present study aimed at finding an association of holoprosencephaly with facial dysmorphia and anomalies of visceral organs that would alert the physician to be very careful in making the prenatal diagnosis, which may require termination of pregnancy by medical indications.

MATERIAL AND METHODS: The study included 15 fetuses diagnosed with holoprosencephaly out of 2095 cases analysed post-mortem in the Fetopathology Clinic at the Centre for Maternity and Neonatology in the town of Tunisia over a period of 3 years (Oct. 2006 – Oct. 2009). The fetuses were analysed macro- and microscopically.

RESULTS: All forms of holoprosencephaly include elements of facial dysmorphia with the facial phenotypes of cyclopia, cebocephaly and ethmocephaly. It can be associated with specific internal organs anomalies, the hydrocephaly being the most common anomaly of the central nervous system. Our study suggested that holoprosencephaly can be correlated with craniofacial anomalies affecting the midfacial and medium craniovisceral structures.

CONCLUSION: The anatomical variations of HPE and the phenotypic facial correlations require a systematic and targeted study of central nervous system.

Key words: holoprosencephaly, facial dysmorphism, facial phenotype, cyclopia, agenesis nasalis, trisomy 13

INTRODUCTION
Holoprosencephaly (HPE) is a congenital anomaly of the central nervous system occurring at the stage of separation of prosencephalon into diencephalon and telencephalon. HPE belongs to the group of midline anomalies and was first described by Yakovlev in 19591 as a case of cyclopia, and the name was given by DeMyer2. Holoprosencephaly can be differentiated from, as well as associated with other anomalies. It has a prevalence of 1 in 250 fetuses and 1 in 10 000 to 1 in 20 000 in newborns.3 The anomaly is usually incompatible with life, but in its mild forms4 the search for additional references is necessary, given the demand for early termination of pregnancy by medical indications.

AIM
The aim of the study was to search for association of holoprosencephaly with facial dysmorphism and anomalies of visceral organs, requiring adequate consideration in making the prenatal diagnosis, concerned eventually with pregnancy termination by medical indications.

MATERIAL AND METHODS
Cases with diagnosis holoprosencephaly were selected out of 2095 autopsies carried out in the Fetopathology Clinic at the Centre for Maternity and Neonatology in the town of Tunisia over a period of 3 years (Oct. 2006 – Oct. 2009). Data including maternal age, prenatal diagnosis, previous pregnancies and childbirths, medication received by the mother, blood group, incest, term, method and place of pregnancy termination, fetal weight at autopsy were collected. Each case was radiographically examined for skull characterization and comparison...
of the metric indices, and in 2 cases the diagnosis was confirmed by MRI. The karyotype of three fetuses was studied.

The form and size of the head, forehead, direction of palpebral fissures, root and line of the nose and nostrils and their passage, philtrum, position of the lips and mouth angle, tongue and tongue frenulum, palate and uvula, morphology and attachment of the ear auricles were described and measured at baseline. The following biometric data were recorded: vortex-talon and vortex-coccyx length, cranial, thoracic, and umbilical circumference, foot and palpebral fissure length, distance between eyes, shape, length, and formations in the neck, arm and foot (number and position of the fingers, shape, form and color of the nail, middle palm crease). The examination of the visceral organs was done using standard technique for fetus autopsy.

Cranial cavity and brain were examined after fixation with 40% formalin for one to six months. Brain weight, bitemporal and fronto-occipital distance of the skull were measured and subcutaneous structures and fonticuli, skull base, brain gyration, ventricular system, brainstem and cerebellum, meninges and spinal cord were examined.

The data were analyzed statistically with variation and non-parametric correlation analysis using statistical program SPSS-13.

RESULTS

Holoprosencephaly was diagnosed in 15 fetuses out of 2095 autopsies.

The results are presented according to maternal characteristics and main findings of the fetal CNS.

According to the indications for pregnancy termination: 14 cases were abortions by medical indications and one was spontaneous.

According to prenatal diagnosis data: holoprosencephaly was diagnosed sonographically in 13 cases and in 7 of them additional anomalies were found. One fetus was with trisomy 13, and the other two cases studied were with normal karyotype.

According to CNS findings:

Eight cases of alobar holoprosencephaly (HPEA) (Fig. 1). This is the variant of total absence of interhemispheric fissure, with globular cerebral mass (pancake or ball-shaped), missing corpus callosum and septum pellucidum. Monoventricle is located centrally. Olfactory structures on the basal brain surface are missing.

One case of alobar holoprosencephaly (HPEA) (Fig. 1) with missing prosencephalic structures, but developed
DeMyer et Zeman classification. Interhemispheric fissure separates the two hemispheres, the cavity of the ventricle is paired with normal configuration, but olfactory structures are not present on the basal brain surface. The only case of spontaneous abortion, with HPE not diagnosed prenatally falls into this group.

**Analysis of facial dysmorphia:**

Three cases of cyclopia: severe facial dysmorphia presented with cyclopia, nasal agenesis and cleft lip.

Seven cases of cebocephaly: severe facial dysmorphia presented with hypotelorism, one nostril, high-arched palate and microcephaly.

Four cases of minor facial anomalies: facial dysmorphia presented with hypotelorism, high-arched palate and microcephaly.

One case of ethmocephaly: facial dysmorphia presented with exophthalmos, proboscis, nasal agenesis and labiopalatine cleft.

Midfacial anomalies were found in all 15 cases; they are presented according to the phenotype spectrum of HPE (Table 2).

Table 1. Type of holoprosencephaly, maternal age, number of pregnancy and incest

<table>
<thead>
<tr>
<th>Type of anomaly</th>
<th>Maternal age</th>
<th>Number of pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n yrs</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>Alobar</td>
<td>8 &lt; 30</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>&lt; 35</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>&gt; 35</td>
<td>x</td>
</tr>
<tr>
<td>Aprosencephaly</td>
<td>1 &lt; 30</td>
<td>x</td>
</tr>
<tr>
<td>Semilobar</td>
<td>1 &lt; 30</td>
<td>x</td>
</tr>
<tr>
<td>Minor form of lobar (arhinencephaly) in 2 case</td>
<td>3 &lt; 30</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>&lt; 35</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>&gt; 35</td>
<td>x</td>
</tr>
</tbody>
</table>

Table 2. Facial dysmorphia and gender by types of holoprosencephaly

<table>
<thead>
<tr>
<th>HPE (n = 15)</th>
<th>n %</th>
<th>Cyclopia</th>
<th>Cebocephaly</th>
<th>Minor facial anomalies</th>
<th>Ethmocephaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alobar</td>
<td>8</td>
<td>53.3</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Aprosencephaly</td>
<td>1</td>
<td>6.6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semilobar</td>
<td>1</td>
<td>6.6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>3</td>
<td>20</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Arhinencephaly</td>
<td>2</td>
<td>13.3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Distribution by maternal blood group and HPE of the fetuses.
Table 3. Distribution by age of the fetuses and type of holoprosencephaly

<table>
<thead>
<tr>
<th>Week of gestation</th>
<th>HPE 14-18</th>
<th>20</th>
<th>21</th>
<th>23</th>
<th>25</th>
<th>27</th>
<th>30</th>
<th>35</th>
<th>39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alobar</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aprosencephaly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semilobar</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arhinencephaly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Correlation between holoprosencephaly, facial dysmorphia, number of pregnancy, incest and maternal age. (Spearman coefficient, n = 15)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Holoprosencephaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial dysmorphia</td>
<td>0.506</td>
</tr>
<tr>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>Number of pregnancy</td>
<td>-0.465</td>
</tr>
<tr>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Incest</td>
<td>-0.368</td>
</tr>
<tr>
<td></td>
<td>0.178</td>
</tr>
<tr>
<td>Maternal age</td>
<td>-0.203</td>
</tr>
<tr>
<td></td>
<td>0.468</td>
</tr>
</tbody>
</table>

DISCUSSION

Holoprosencephaly belongs to the group of major malformations occurring during the early stages of embryogenesis. It results from disrupted early development of the prosencephalon.6-8

This anomaly occurs in a wide variation range - from aprosencephaly to arhinencephaly isolated, but always involves medfacial anomalies. According to De-Myer: “the face predicts the brain”. The more severe facial anomalies are, the more severe the brain anomalies are, but not vice versa.9

In our study the alobar NPE presents with severe facial dysmorphia in 87% of cases. It affects more often females. No statistically significant correlation was found between age, incest, number pregnancy and holoprosencephaly.

Cases of alobar holoprosencephaly without facial anomalies are very rare and are referred to as autosomal recessive (Mason10).

Figure 4. Associated anomalies.
Lobar HPE correlates with the phenotype of minor facial anomalies and affects predominantly males.

Whatever the type of holoprosencephaly it is always accompanied with medfacial dysmorphia.11,12

Arhinenencephaly with cebocephaly phenotype is the only case sonographically misdiagnosed prenatally in a miscarriage in third pregnancy of a 36-year-old female. The fetus has a right foot hexadactyly with septal heart defects, additional spleen and bilateral ptosis of the kidney.

Facial dysmorphies affect the sphenethmoidal complex13 and nose as craniofacial architecture medium14. Our study confirms that the underdevelopment of the nose can evolve to hypo- and agenesis, some nasal anomalies are combined with eye anomalies, others with palatal and some others with oral defects.15

It also shows that cebocephaly is the more frequent facial phenotype and represents 47% of the cases discussed, and minor facial anomalies are three times rarer in alobar compared with lobar HPE.

Minor facial anomalies are associated with lobar, a milder form of HPE sometimes compatible with life, as well as with alobar HPE that is always not compatible with life. Therefore their detection is particularly important in the prenatal diagnosis of HPE.

The karyotype study in three of the cases reveals trisomy 13 for aprosencephaly.

In our study in all cases holoprosencephaly is associated with neurological (45%) and with other anomalies. Among the neurological abnormalities hydrocephalus is the most frequent anomaly present in 30% of cases, followed by microcephaly found in 15% of the cases.

CONCLUSIONS

1. HPE can be associated both with severe facial dysmorphies – cyclopia, cebo - and ethmocephalia, and minor facial anomalies.
2. When HPE is associated with anomalies of the visceral organs it is diagnosed earlier – at 20 weeks of gestation, but when accompanied with minor facial anomalies, its diagnosis is delayed - after 23 weeks of gestation.
3. Carriers of HPE are more often multiparous females - 67% of the mothers in our study.
4. HPE can develop in cases without parental incest, but also in fetuses from incestuous marriage.
5. The anatomical variations of HPE and phenotype changes make the prenatal diagnosis difficult. Detection of only minor facial anomalies requires systematic and targeted study of central nervous system.

REFERENCES

ФЕТОПАТОЛОГИЧЕСКИЕ АСПЕКТЫ ГО-ЛЮПРОЗЕНЦЕФАЛИИ (HPE)
Т. Китова, М. Аида, З. Дорра, С. Даленда, С. Гайги
РЕЗЮМЕ
ВВЕДЕНИЕ: Голопрозенцефалия (HPE) представляет собой аномалию центральной нервной системы, варьирующую в границах 1 – 250 для фетусов и 1 - 10 000 для новорожденных. Тяжелые формы несовместимы с жизнью. Их легко можно диагностировать во время пренатального периода, а что касается легких форм, они могут остаться нераспознанными. Внимание авторов привлечено важностью этой аномалии; ее следует распознать и вовремя диагностировать, так как она может отразиться на беременности и несущих ее новорожденных.
ЦЕЛЬ: Настоящее исследование ставит себе цель найти ассоциацию HPE с лицевыми дисморфиями и аномалиями внутренних органов, что требует адекватно повышенного внимания при постановке пренатального диагноза с целью эвентуального прекращения беременности по медицинским показаниям.
МАТЕРИАЛ И МЕТОД: В исследование включено 15 фетусов с диагностированной голопрозенцефалией (сделано всего 2095 аутопсий в Centre de Maternité et Néonatalogie de Tunis в течение трех лет: октябрь 2006 – октябрь 2009 г.). Применен метод аутопсии фетусов (макроскопический и микроскопический анализ).
РЕЗУЛЬТАТЫ: Все типы HPE содержат элементы фациальной дисморфии с лицевыми фенотипами циклопии, цебо- и этмоцефалии. HPE можно ассоциировать с аномалиями внутренних органов. Гидроцефалия является самой часто встречаемой ассоциированной аномалией центральной нервной системы. Настоящее исследование показывает, что HPE представляет краино-фациальную аномалию с затрагиванием срединных мягколицевых и срединных костных краино-висцеральных структур.
ЗАКЛЮЧЕНИЕ: Анатомические вариации HPE и фенотипные лицевые корреляции требуют систематического и целенаправленного исследования центральной нервной системы.