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Prenatal Diagnosis, Phenotypic and Obstetric Characteristics of Holoprosencephaly

Gábor J. Joó Artúr Beke Csaba Papp Ernő Tóth-Pál Zsanett Szigeti Zoltán Bán Zoltán Papp

Semmelweis University Medical School I., Department of Obstetrics and Gynecology, Budapest, Hungary

Key Words
Holoprosencephaly · Prenataldiagnosis · Patient's history · Accompanying malformations

Abstract
The diagnosis of fetal malformations, especially those of the central nervous system, is strikingly important in the practice of genetic counseling. Early diagnosis is very significant, not only because of the prognosis, but also because of the emotional effects caused by the accompanying craniofacial malformations. The summary of the obstetrical and diagnostical characteristics should be useful in the management of holoprosencephaly. The analysis of the 50 cases we encountered between 1981 and 2000, including the anatomical, diagnostic and clinical aspects, as well as the associated craniofacial malformations, forms the essence of our publication. In one of the examined cases a familiar recurrence was verified.

Introduction

In the early weeks of embryonic development, the brain consists of three parts: prosencephalon, mesencephalon, rhombencephalon. Between the time of neural tube closure and the 5th gestational week, the prosencephalon gives origin to telencephalon (cerebral hemispheres) and diencephalon (thalamus and hypothalamus), the mesencephalon forms the midbrain and rhombencephalon develops into metencephalon (pons and cerebellum) and myelencephalon (medulla oblongata). At the time of the telencephalon/diencephalon differentiation, the prosencephalon also splits longitudinally – the hemispheres develop on the lateral aspects of the longitudinal cerebral fissure by progressive enlargement and hollowing of the cerebral vesicles. Should the prechordal mesoderm fail to migrate normally [1, 2], the prosencephalon remains undivided. As a consequence, a common cerebral ventricle develops, cortex and thalamus form a single structure, and the development of olfactory and optic bulbs is upset. There is an abnormal differentiation and development of the nasofrontal process and the midline of the face (holoprosencephaly sequence). Differing degrees of disorganization are reflected in the terms alobar, lobar and semilobar (fig. 1). Among the accompanying craniofacial mal-

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Dr. Gábor József Joó, MD
Semmelweis University Medical School Budapest
Ist Department of Obstetrics and Gynecology
HU–1088 Budapest Baross utca 27 (Hungary)
E-Mail joogabor@noi1.sote.hu

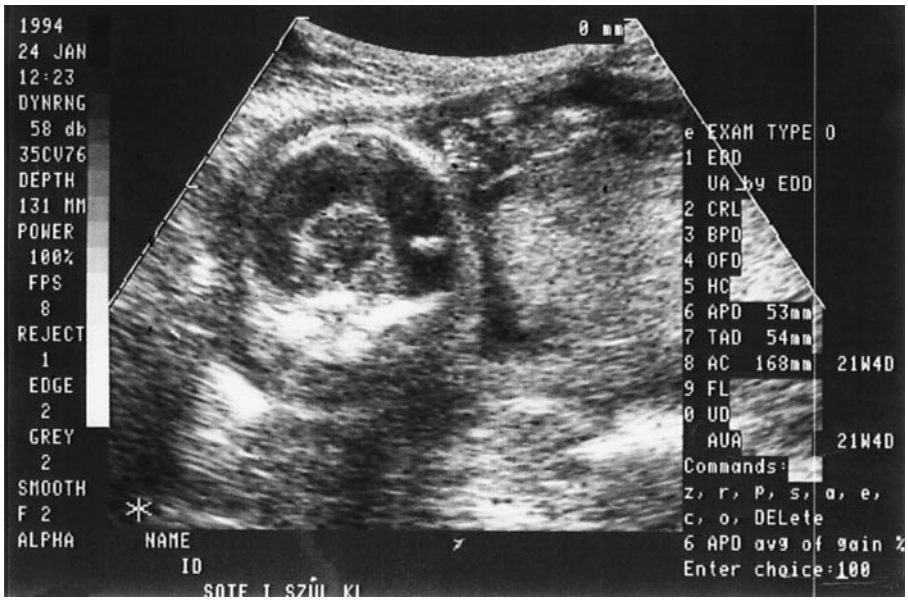

Fig. 1. Ultrasound picture of semilobar holoprosencephaly in the 32nd gestational week.

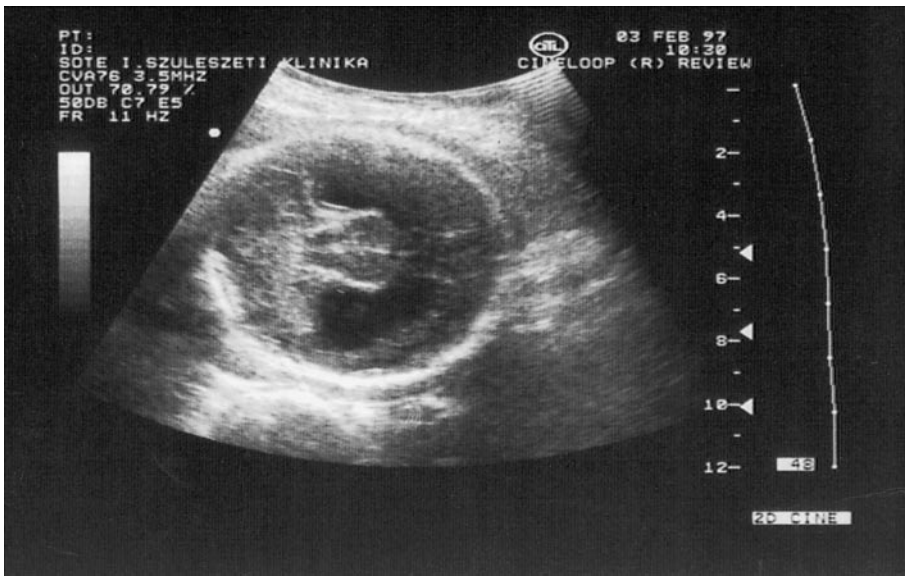

Fig. 2. Ultrasound picture of holoprosencephaly in case of trisomy 18 in the 23rd gestational week (alobar).

formations, cyclopy, cebocephaly, hypo/hypertelorism, cleft palate and nasal hypoplasia are worthy of mention. The incidence of holoprosencephaly varies between 1/1,600 [3] and 1/26,000 [4]. The etiology of the malformation is very heterogeneous. Most cases are sporadic, but holoprosencephaly can also be associated with chromosomal defects [5, 15–17, 19] (fig. 2), maternal hyperglycemia and phenylketonuria [6, 20] and intrauterine infections (cytomegalovirus) [7]. It may also constitute part of a multiple malformation syndrome (Váradi-Papp syndrome, Hall-Pallister syndrome) [2, 8].

Patients and Methods

Between 1981 and 1990 in the Department of Obstetrics and Gynecology of Debrecen University Medical School and between 1991 and 2000 in the 1st Department of Obstetrics and Gynecology of Semmelweis University Medical School, we diagnosed 50 cases of holoprosencephaly. The basic sonographic criteria of the sonographic diagnosis were: the abnormalities of the falx cerebri [9, 10] and the face [11], as well as other types of associated malformations of the central nervous system (hydrocephalus, micro/macrocephaly) or polyhydramnios [9]. In each prenatally diagnosed case the autopsy confirmed the initial ultrasound diagnosis, though the anatomic form of holoprosencephaly was uncertain in a few cases.

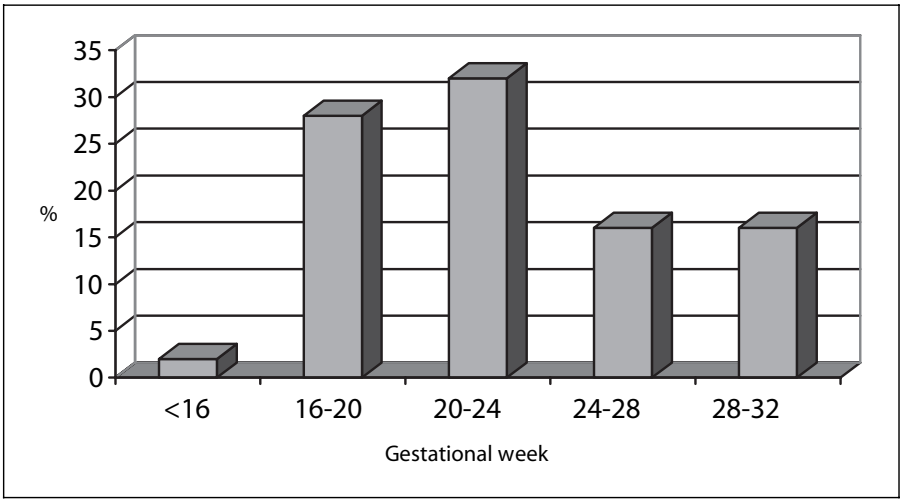

Fig. 3. The date of diagnosis.

Results

The yearly distribution of the cases (except for 1985 and 1989) seems to be regular. The distribution of sex corresponds to that of the general population (female/male: 49/51%). In 5 of the 50 cases the sex was unknown.

Regarding the maternal and paternal age, in more than 70% of all cases the pregnant patient was under 30 years of age, while 6% were of advanced maternal age (>35 years). The paternal age was generally (>70%) between 25 and 34 years.

We also examined the patients' obstetric history. Concerning maternal gravidity, we found that in 40% of the cases the examined pregnancy was the first one and in 28% the second. The incidence of multigravidity (four or more pregnancies) was 6%.

Regarding the influence of obstetric and/or genetic history on the actual pregnancy, in 15 cases a positive obstetric/genetic history was verified. In 3 cases (6%) the pregnancy was terminated because of genetic malformation (gastroschisis, spina bifida, multiple malformation syndrome), in 5 cases (10%) a spontaneous abortion occurred, while in 2 other cases (4%) a mature, live newborn was delivered with severe hydrocephalus and somatomental retardation. To summarize the data, a positive genetic history was found in 12% of the cases.

The time of diagnosis is important from a scientific and psychological point of view (fig. 3). In more than 60% of the cases, the diagnosis of holoprosencephaly was verified before the 24th gestational week. In only 6% of the cases, diagnosis was made after the 32nd gestational week.

The associated craniofacial malformations have a great diagnostic and prognostic significance. In 12% of the cases, holoprosencephaly occurred in an isolated form, while in the majority of the cases (88%) with an accompanying (mainly facial) malformation (table 1). 38 and 36% of all the associated craniofacial malformations affected the eye and the oral cavity/palate. Among ocular malformations, hypotelorism and cyclopy as well as anophthalmy showed a remarkable incidence. Regarding oral malformations, cheilognathopalatoschisis turned out to be the most frequent. The nasal malformations showed an occurrence rate of 16%.

The malformations of the central nervous system and other organs that accompany holoprosencephaly are also recapitulated (table 2). The incidence of hydrocephalus, microcephaly, and polydactyly are worth mentioning.

The incidence of twin pregnancy was 2% (1 case). In 27 cases we were able to detect the anatomic form of holoprosencephaly. Table 3 summarizes the incidence of the three anatomic types of holoprosencephaly.

In 29 of the 50 cases, intrauterine karyotyping was performed. In one case, a chromosome aberration (47,XX+18/46,XX) was detected.

In a majority of the prenatally diagnosed cases the pregnancy was terminated by abortion (72%) or induced preterm labor (24%). One patient delivered a mature newborn suffering from holoprosencephaly (she died on the 4th postnatal day). Fetus 'A' of the previously mentioned twin pregnancy was affected and died following delivery, while fetus 'B' proved to be healthy.

We also examined the outcome of subsequent pregnancies following pregnancies with holoprosencephaly. In

Table 1. Distribution of associated craniofacial malformations

Associated craniofacial malformations	n	%	Ultrasound diagnosis	Post mortem detected
Isolated brain malformation	6	12.0	6	6
Ocular malformations	19	38.0	11	19
Anophthalmy (unilateral)	5	10.0	2	5
Anophthalmy (bilateral)	0	0	0	0
Cyclopy	7	14.0	7	7
Microphthalmy	0	0	0	0
Coloboma	0	0	0	0
Hypotelorism	6	12.0	1	6
Hypertelorism	1	2.0	1	1
Nasal malformations	8	16.0	4	8
Proboscis	3	6.0	2	3
Arhinia	1	2.0	0	1
Nasal agenesis	2	4.0	2	2
Flat nose	2	4.0	0	2
Malformations of the oral cavity	18	36.0	13	18
Cheiloschisis	1	2.0	1	1
Palatoschisis	0	0	0	0
Cheilognathopalatoschisis	16	32.0	12	16
Macrostomy	0	0	0	0
Microstomy	1	2.0	0	1
Malformations of the chin	1	2.0	1	1
Agnathia	0	0	0	0
Micrognathia	1	2.0	1	1
Other craniofacial malformations	8	16.0	6	8
Facialis dysmorphism	6	12.0	5	6
Abnormal skull shape	2	4.0	1	2

half of the cases, the patient became pregnant again and in 88% of these cases, a healthy, mature newborn was delivered. No newborns with genetic malformations were delivered.

Discussion

The male/female ratio was 23/22 (52/48%) which shows a more balanced sex ratio than that found by Olsen [7] (1984–1989; male/female: 60/40%), or Croen [12] (1980–1988; male/female: 61/39%). In respect to the frequent association of holoprosencephaly and some trisomies (trisomy 13, trisomy 18), it is notable that the most common risk factor for chromosomal aberration (maternal age) was not prevalent. The results regarding maternal age coincide with those of Olsen [7] and Croen [12].

Concerning maternal gravidity, we found that in 40% of the cases the examined pregnancy was the first one and in 28% the second. The incidence of multigravidity (four or more pregnancies) was 6%. These results corresponded to the results of Croen [12].

Thirty percent of all cases had a pathological obstetric/genetic history, which emphasizes the importance of anamnesis in genetic counseling.

From an obstetric, psychological and social point of view, the date of the diagnosis has an overriding significance. According to the current Hungarian law, a pregnancy can be interrupted before the 24th gestational week because of diagnosed genetic malformation. (Before 1990, termination of pregnancy based on genetic indication was possible in Hungary until the 28th gestational week.)

Among the diagnostic criteria of holoprosencephaly, affected midface and partial or total absence of the falx cerebri are basic findings [9, 10, 13]. Our table shows a rather high incidence of the associated polyhydramnios, corresponding to Chervenak's results [9, 10].

As holoprosencephaly mainly affects the brain and the facial structures, it is really important to summarize the possible facial malformations (table 1). The ratio of isolated cases (where only the fetal brain is affected) is simi-

Table 2. Distribution of associated non-craniofacial malformations

Associated noncraniofacial malformations	n	%	Ultrasound diagnosis	Post mortem detected
Central nervous system	18	36.0	15	18
Agyria totalis	1	2.0	0	1
Hydrocephalus int./ext.	8	16.0	8	8
Microcephaly	4	8.0	4	4
Agenesis of the corpus callosum	2	4.0	1	2
Hypophyseal agenesis	1	2.0	0	1
Spina bifida	2	4.0	2	2
Cardiovascular malformations	11	22.0	8	11
Transposition of the veins	1	2.0	1	1
VSD	2	4.0	2	2
PDA	1	2.0	1	1
Stenosis ostii aortae	1	2.0	0	1
Hypoplasia of the aortic arch	1	2.0	1	1
Singular umbilical artery	5	10.0	3	5
Malformations of the urinary tract	5	10.0	4	5
Pyelectasia	1	2.0	1	1
Hydronephrosis	1	2.0	1	1
Ureter bifidus	1	2.0	0	1
Polycystic kidney disease	1	2.0	1	1
Ureteral agenesis	1	2.0	1	1
Malformations of the limbs and fingers	10	20.0	5	10
Polydactyly	6	12.0	3	6
Oligodactyly	1	2.0	0	1
Syndactyly	1	2.0	0	1
Pes varus	1	2.0	1	1
Short bones	1	2.0	1	1
Gastrointestinal malformations	6	12.0	3	6
Malrotation ventricular	1	2.0	0	1
Megalosigma	1	2.0	0	1
Omphalocele	3	6.0	3	3
Malrotation intestinorum	1	2.0	0	1
Genital malformations	2	4.0	0	2
Uterus bicollis	1	2.0	0	1
Pseudohermaphroditism	1	2.0	0	1

lar to the results of Olsen [7] (10%) and Croen [12] (8%). The ratio of ophthalmic and/or oral malformations in our study was 36–38%; according to Olsen's researches [7] in cases of holoprosencephaly sequence the incidence of ophthalmic malformations is 70%, while that of oral malformation is around 40%. In Lurie's [14] publication the incidence of oral malformations is 58%. The most frequent associated malformation of the central nervous system was hydrocephaly, although microcephaly also appeared with remarkable incidence, corresponding to the results of Chervenak [9]. Summarizing our results, the ultrasound diagnostics based on the assessment of the facial structures and the falx cerebri, seem to be a reliable method in diagnosing holoprosencephaly as well as in predicting the prognosis of the malformation.

Table 3. Distribution of the anatomic forms of holoprosencephaly

Anatomic form	n	%
Alobar	12	44.4
Semilobar	9	33.3
Lobar	6	22.2

Regarding the anatomic type of holoprosencephaly (table 3), incidence of the alobar form was 44%, the semilobar form 33% and the lobar form 22%. This trend was also observed in the publications of Croen [12], Olsen [7] and Chervenak [9]. The alobar form of holoprosencephaly

is the most severe. It is usually incompatible with postnatal life. Children with the semilobar and lobar forms are mentally and physically handicapped, and many will require long-term residential care, if they survive.

In 29 cases karyotyping was performed to exclude possible associated chromosomal aberrations. One case of pathological karyotype (47,XX+18/46,XX) was verified. Croen [12] and Olsen [7] found a higher incidence of accompanying chromosomal aberrations. According to the actual publications on holoprosencephaly, chromosomal abnormalities have been reported in 24–45% of live births with holoprosencephaly.

In a preponderant majority of the examined cases, the pregnancy was terminated by the induction of abortion or preterm delivery, certifying the effectiveness of genetic counseling.

In 25 cases, subsequent pregnancies occurred. In 22 cases (88%), the gestation as well as the delivery was without pathological finding, while in the remaining 3 cases (12%) early fetal loss occurred. Among these pregnancies no recurring genetic malformations were verified.

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