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Holoprosencephaly in Hungary: Birth Prevalence and Clinical Spectrum

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Abstract

A retrospective population based survey of patients born with holoprosencephaly in South-Eastern Hungary between July 1, 1992 and June 30, 2006 was performed. All live birth cases with craniofacial and non-craniofacial abnormalities were included in the study. A total of 9 patients (5 boys and 4 girls) were found with holoprosencephaly among 185 486 live births, which correspond to a birth prevalence of 0.49 per 10 000 live births (95% confidence interval [CI]: 0.17-0.80). These figures were similar to those ones found in New York State and several European regions. In our series one newborn had trisomy 13. Eight patients did not have chromosomal abnormalities on routine testing, 4 of them had craniofacial abnormalities only and another 4 showed non-craniofacial anomalies as well. Three patients died in the neonatal period and another one in childhood. Patients surviving the neonatal period had intellectual and motor handicap, and epilepsy.

Keywords

holoprosencephaly, birth prevalence, brain malformation

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Holoprosencephaly is a complex congenital brain malformation characterized by failure of the forebrain to separate into two hemispheres.[1-3] Forebrain malformations range from mild (lobar) to complete (alobar) holoprosencephaly.[1-3] Facial abnormalities are frequently associated with holoprosencephaly. Mild forms of facial dysmorphic features are hypoplasia of the nasal bridge, hypotelorism, and single central incisor; more severe forms include median cleft lip, cebocephaly, ethmocephaly, and cyclopia.[1-3]

Etiological heterogeneity has been revealed. Holoprosencephaly can be associated with chromosomal anomalies, occur as part of a syndrome, or be due to mutations in one of at least 12 known holoprosencephaly-associated genes.[4-6] Teratogenic factors, such as maternal diabetes and exposure to aspirin, alcohol, or smoking in the periconceptional period are also supposed to cause this malformation.[7,8] The etiology, however, remains unknown in a large number of patients.

Diverse data are available on the epidemiology of holoprosencephaly from various countries and regions.[9-14] Our aim was to perform a population based retrospective study in order to survey the live birth prevalence rate of this malformation and describe the associated abnormalities and clinical features as correctly as possible in a region in Hungary between 1992 and 2006.

Patients and Methods

All children in Hungary are assigned to a pediatrician and her/his clinic, therefore children born with holoprosencephaly in the South-Eastern region (Dél-Alföld – South Great Plain) in Hungary between July 1, 1992 and June 30, 2006 were ascertained by searching the databases of the pediatric clinics. All pediatricians in the region were approached by questionnaires and requested to report on patients with holoprosencephaly. They were encouraged also by telephone interviews and field trips to provide information on these patients in order to compile a register as complete as possible. As severe cases of holoprosencephaly with striking dysmorphic features were treated in the Neonatal Intensive Care Units, or Neonatal Wards in the hospitals, the survey was extended to these departments in the region as well. Demographic data were collected from the Hungarian Central Statistical Office.

The diagnosis of holoprosencephaly was always confirmed by cranial ultrasound, CT and/or MRI, performed by conventional protocols.

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Table 1. Group 1. Clinical features of patients with holoprosencephaly and craniofacial abnormalities

Patient	Sex	Age*	Associated abnormalities	Developmental delay	Intellectual disability	Neurological findings	Epilepsy	Comments
1	F	NR	Cebocephaly	+	+	Spastic quadriparesis	–	Death at the age of 5 years No autopsy
2	M	5y	Hypotelorism Midfacial dysmorphic features	+	+	Spastic quadriparesis	+	
3	M	11y	Hypotelorism Midfacial dysmorphic features	+	+	Spastic quadriparesis	+	
4	M	13y	Bilateral microphthalmos Bilateral optic nerve coloboma Cleft lip and palate	+	+	Spastic quadriparesis	+	

Abbreviations: F, female, M, male, y, years, NR, not relevant.
* age at last follow up

An attempt has been made to classify our cases into three groups according to presentation:

Group 1. Holoprosencephaly with craniofacial (eye, nose, ear, mouth and jaw) abnormalities only. These craniofacial abnormalities have been regarded as part of the holoprosencephaly sequence.[11]

Group 2. Holoprosencephaly in association with noncraniofacial abnormalities in addition to craniofacial abnormalities.

Group 3. Holoprosencephaly in association with chromosomal anomalies.

A detailed analysis of the patients with holoprosencephaly was carried out. Clinical records were retrospectively reviewed for family history, parental consanguinity and age, maternal and birth history, possible environmental factors, neonatal course, developmental milestones, and epileptic seizures. Detailed clinical and neurological examinations were carried out. Electroencephalography was performed according to the 10-20 system. Chromosomal analysis by routine G-banding technique was carried out in all patients. Molecular cytogenetic studies or mutation analysis of genes responsible for holoprosencephaly were not performed.

We calculated the birth prevalence of holoprosencephaly per 10 000 live births in the region between July 1, 1992 and June 30, 2006. The numerator was the total number of cases with holoprosencephaly in live births, and the denominator was the total number of live births during the same period of time.

Statistical analysis was performed by using the SPSS 15.0 program (SPSS Inc., an IBM Company, Chicago, Illinois, USA). We calculated 95% confidence intervals (95% CI) on the basis of approximation to the binomial distribution.

Results

There were 185.486 live births in the area between July 1, 1992 and June 30, 2006. The total number of patients born with holoprosencephaly was 9 (5 boys, 4 girls) in this period of time, which means that the prevalence at birth was 0.49 per 10 000 live births (95% CI: 0.17-0.80). Four patients (Group 1, Patients 1-4, Table 1) had only brain and craniofacial malformations, 4 children (Group 2, Patients 1-4, Table 2) had also non-craniofacial anomalies in addition to holoprosencephaly and craniofacial abnormalities and one newborn had trisomy 13 (Group 3, Patient 1, Table 3).

Cranial ultrasound was performed for all patients. Three patients (Group 2, Patients 1 and 2, and the infant in Group 3) had alobar holoprosencephaly. CT images in addition to ultrasound were available for two patients (Group 1, Patient 3 and Group 2, Patient 3) with semilobar holoprosencephaly, while MRI was carried out for 4 children (Group 1, Patients 1, 2, and 4, and Group 2, Patient 4). Patient 1 in Group 1 had alobar holoprosencephaly with a large monoventricle, fused thalami and absence of the third ventricle. The quadrigeminal plate and aqueduct were not recognizable. Patients 2 and 4 in Group 1 and Patient 4 in Group 2 had abnormal gyral configuration, absence of the anterior portion of the interhemispheric fissure, corpus callosum agenesis and a crescent-shaped monoventricle, continuous with a small third ventricle. The thalami were partially separated and the individual basal ganglia were not recognizable. The aqueduct appeared patent below the quadrigeminal plate.

The routine chromosomal analysis did not show abnormalities in 8 patients. There was no parental consanguinity or familial occurrence of the malformation. Three patients were the product of preterm delivery, while the other neonates were born at term, none of them diagnosed prenatally. There were no twins among the patients. Two patients with multiple defects (Group 2, Patients 1, 2, Table 2) and the infant with trisomy 13 (Group 3, Patient 1, Table 3) died in the neonatal period, while one patient (Group 1, Patient 1, Table 1) with holoprosencephaly and craniofacial abnormalities died in childhood. The ages of patients surviving the neonatal period ranged from 5 to 13 years at the time of the survey. Maternal diabetes was diagnosed in one patient (Group 2, Patient 4, Table 2), prenatal risk factors were not identified in the other cases. All patients

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Table 2. Group 2. Clinical features of patients with holoprosencephaly, craniofacial and non-craniofacial abnormalities

Patient	Sex	Age*	Associated abnormalities	Developmental delay	Intellectual disability	Neurological findings	Epilepsy	Comments
1	F	NR	Bilateral microphthalmos Polydactyly Thyroid hypoplasia Atrial septal defect Imperforate anus Rectovaginal fistula	NR	NR	NR	NR	Neonatal death Autopsy, no histology
2	M	NR	Cyclopia Proboscis Cryptorchism	NR	NR	NR	NR	Neonatal death Autopsy, no histology
3	M	7y	Left microphthalmos Micropenis	+	+	Generalized hypotonia Paucity of spontaneous movements	+	
4	F	8y	Cleft lip and palate Pyloric stenosis	+	+	Spastic quadriparesis	+	Maternal diabetes

Abbreviations: F, female, M, male, y, years, NR, not relevant.
* age at last follow up

Table 3. Group 3. Clinical features of a patient with holoprosencephaly in association with chromosomal anomaly

Patient	Sex	Age	Associated abnormalities	Developmental delay	Intellectual disability	Neurological findings	Epilepsy	Comments
1	F	NR	Cleft lip and palate Postaxial polydactyly (hands, bilateral), polysyndactytly (right foot) Hypoplastic left heart	NR	NR	NR	NR	Neonatal death 47, XX, trisomy 13 (Patau syndrome) Autopsy, no histology

Abbreviations: F, female, NR, not relevant

had microcephaly. Craniofacial anomalies of various severities with dysmorphic features, listed in Tables 1-3 were found in all patients. Non-craniofacial defects in Group 2 (Patients 1-4, Table 2) included limb, endocrine, genital, heart and gastrointestinal anomalies. The patient with trisomy 13 (Group 3, Table 3) had limb and heart defects in addition to craniofacial anomalies. The development of all patients who survived the neonatal period was delayed and all of them had severe intellectual disability. Spastic quadriparesis was observed in 5 children and generalized hypotonia in one child. Epileptic seizures appeared in 5 patients (Groups 1, 2, Tables 1, 2).

Discussion

Differences in the birth prevalence rate of holoprosencephaly can be explained by the survey methods employed. In a recent review Orioli and Castilla[13] compared birth prevalence rates published in several studies from various parts of the world. They suggested that the birth prevalence rate was lower than 1 per 10 000 if live births and still births were only included in the survey, while the rate was above 1 per 10 000 if terminated pregnancies were also included.

Live birth prevalence rate was surveyed in this study and the figure of 0.49 per 10 000 between 1992 and 2006 was similar to figures found in New York State[11], a region in the UK (North West Thames)[14], and three Italian regions (Emilia Romagna, North East Italy and Sicily). [14]

The range of craniofacial abnormalities in the patients in this study extended from very severe defects with cyclopia to milder forms of midfacial dysmorphic features as described in the literature.[1,2] The mesencephalic neural crest forms the membranous bones of the face in addition to ectodermal structures and impaired formation or migration of the mesencephalic neural crest due to defective genetic expression in the longitudinal axis of the neural tube may result in midfacial hypoplasia.[15] Indeed, a correlation between the degree of facial anomalies and the extent of the anatomic involvement of the midbrain has been described.[15] Non-craniofacial abnormalities can occur in more than half of the cases without chromosomal abnormalities.[9,11] The ratio was similar in our study, 4 patients out of the 8 cases without chromosomal abnormalities had non-craniofacial defects as well.

One-third of the patients with holoprosencephaly in this survey were born preterm. This finding is in agreement with

earlier studies that showed that infants with holoprosencephaly were more likely than controls to be born preterm/very preterm or with low/very low birth weight.[8] Predominance of either sex was not found in our study. Previous studies found that females had a greater risk than males for holoprosencephaly,[8,10,11] however the female predominance might have been due to a higher spontaneous abortion rate of males with holoprosencephaly.[9,13]

Maternal diabetes appears to be risk factor for holoprosencephaly.[8,9] Rasmussen and co-workers found maternal diabetes in 5 cases out of 63.[9] The only case associated with maternal diabetes in our series represents a similar ratio despite the small number of cases. Other risk factors, such as periconceptional maternal exposure to aspirin, alcohol, or tobacco were not identified in our case series.

Trisomy 13 is frequently associated with holoprosencephaly.[4] Rasmussen and co-workers found 8 cases out of 53 patients,[9] Olsen described 8 out of 78 cases,[11] while one case out of 9 in this series had trisomy 13. However, holoprosencephaly with normal karyotype on routine chromosomal studies can also have genetic etiology.[5,6] Mutation analyses of the holoprosencephaly genes or molecular cytogenetic techniques, however, were not available for our patients.

Some inaccuracy probably can not be avoided in such an epidemiological study, hence this survey also bears some limitations. Live births with holoprosencephaly were only included in this study, because data on stillbirths or terminated pregnancies were not available. Our prevalence rate might be an underestimate of the actual prevalence, since mildly affected children with holoprosencephaly might have been missed from surveillance. No etiology was found in a number of cases with multiple anomalies. The launch of a prospective study on a larger population will be considered in the near future.

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Author Contributions

Nóra Szabó has made significant contribution to acquisition of data and she wrote the first draft of the manuscript. Gyurgyinka Gergev, Jenő Kóbor and Péter Szűcs have made substantial contributions to acquisition and analysis of data, revising the manuscript critically and they approved the version to be published. Sándor Túri and László Sztriha have made substantial contribution to the design and interpretation of data. They critically revised the manuscript and approved the final version to be published.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study was approved by the Ethics Committee of the Faculty of Medicine, University of Szeged, Hungary. An informed consent was requested from the parents before participation in the study.

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