Unusual occurrence of cystic fibrosis and alobar holoprosencephaly

Mathew P. Cherian, MD, FRCPI, Nouriya A. Al-Sanna’a, MD, FRCP(C).

Holoprosencephaly (HPE) is the most common developmental anomaly of the forebrain and face, occurring in 1 in 250 pregnancies. The live-birth prevalence is approximately 1 in 10,000. It is caused by failure of the embryonic forebrain (prosencephalon) to sufficiently bifurcate into 2 cerebral hemispheres, a process normally complete by the fifth week of gestation, resulting in a single-lobed brain structure and associated skull and facial defects. Deep brain structures such as basal ganglia, thalamus, and hypothalamus are often profoundly affected. The facial defects can vary from severe anomalies, such as cyclopia (single central eye), ethmocephaly (a proboscis between severely hyperteloric eyes) or cebocephaly (hypotelorism with a single nostril) to mild-moderate anomalies like orbital hypotelorism, cleft lip/palate, and single maxillary incisor. Holoprosencephaly may be associated with microcephaly, macrocephaly, hydrocephalus, epilepsy and/or abnormalities of endocrine, cardiac, skeletal, and genito-urinary systems. Mildly affected children may exhibit few signs and may live normal lives. Cystic fibrosis (CF) is an autosomal recessive disease of exocrine glands associated with pulmonary disease, pancreatic exocrine insufficiency, and an increase in concentration of sweat electrolytes. It is the most common hereditary disease in Caucasian populations, with an incidence of 1 in 4100 live births and an estimated gene frequency of 3% in the United States of America. However, there is limited epidemiological data on the frequency of the disease in the Arab population. Though CF is considered rare in Arabic and African children, it is likely that many of these children remain undiagnosed due to lack of proper diagnostic facilities and public awareness of the disease. According to one study, the incidence of CF in the Kingdom of Saudi Arabia has been estimated to be 1 in 4243 live births. We report the concurrent occurrence of holoprosencephaly and CF in a girl belonging to a consanguineous Saudi family born to mother with type 1 diabetes. The objective and reason for reporting this patient is the unusual occurrence of these 2 conditions in one patient, as well as the conspicuous absence of major craniofacial defects despite the presence of the severe alobar type of brain anomaly.
Case Report. The proband was a female infant, the fifth child born to consanguineous Saudi Arab parents, by emergency Cesarian section following 39 weeks of gestation. The pregnancy was complicated by insulin-dependent diabetes mellitus and antenatal ultrasound at 26 weeks showing mild polyhydramnios and fetal brain anomalies suggestive of holoprosencephaly, characterized by a monoventricle, non-cleaved cerebral mantle, and fused thalami (Figure 1). There was no history of early deaths, pulmonary disease or gastro-intestinal disease in the family. The infant weighed 3500 grams at birth and her length and head circumference were 47 cm and 37.5 cm. The newborn presented no respiratory distress or any vital sign disturbance at birth. Examination of the head showed frontal bossing, ridged metopic suture, orbital hypotelorism, upslanting palpebral fissures, prominent eyes with supra-orbital hypoplasia, infra-orbital creases, flat nasal bridge with wide nostrils, intact palate with no midline lip defects, a right-sided pre-auricular skin tag and a short neck (Figure 2). There was no cyclopia or proboscis. Examination of the heart revealed normal heart sounds and a grade III/VI systolic murmur, maximal on the left sternal border. The abdomen and nervous system were normal. There were no deformities of the upper and lower extremities, and the spine was intact. A postnatal ultrasound confirmed the presence of alobar holoprosencephaly with complete absence of midline cleavage of cerebrum, a large dorsal cyst communicating with a monoventricle, fused thalami, lack of corpus callosum, and septum pellucidum. Skull x-ray revealed macrocephaly with closed metopic suture as well as orbital hypotelorism. Computed tomography as well as MRI of the brain confirmed the ultrasound findings (Figure 3). Further investigations were performed to delineate the spectrum of associated anomalies. Those included an echocardiogram that showed a small mid-muscular ventricular defect, renal sonogram detected absent left kidney and hypertrophied right kidney, nuclear cystourethrogram showed no vesico-ureteral reflux, spine x-rays revealed segmentation anomalies of upper thoracic spine as well as lumbo-sacral spina bifida. A chromosomal study on peripheral lymphocytes was 46XX. Her clinical features are summarized in Table 1. The family members were examined for any cranio-facial anomalies. The only abnormality was mild orbital hypotelorism in the mother, however, her brain imaging was normal. The patient’s father was found to have a right pelvic kidney, which required right nephrectomy. Starting at one month of age, the infant was hospitalized several times with recurrent airway obstruction, atelectasis, persisting pulmonary infiltrates and wheezing. Barium contrast studies showed swallowing in-coordination and gastro-esophageal reflux. As medical management failed to improve the symptoms, she underwent fundoplication.
Cystic fibrosis and holoprosencephaly ... Cherian & Al-Sanna'a

<table>
<thead>
<tr>
<th>Organs/systems involved</th>
<th>Clinical features/malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and face</td>
<td>Macrocephaly, orbital hypotelorism, upsllanting palpebral fissures, flat nose, right preauricular tag</td>
</tr>
<tr>
<td>Brain</td>
<td>Alobar holoprosencephaly, monoventricle, fused thalami, absent corpus callosum, dorsal cyst</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Left renal agenesis and hypertrophied right kidney</td>
</tr>
<tr>
<td>Spine</td>
<td>Segmentation anomalies of upper thoracic spine, lumbosacral spina bifida</td>
</tr>
<tr>
<td>Neurological</td>
<td>Spasticity, seizures, modified hypersrrhythmia in EEG, profound mental retardation and developmental delay</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>Oromotor dysfunction/severe feeding problems, gastro-esophageal reflux</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Stridor, laryngeal web</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Mid-muscular ventricular septal defect</td>
</tr>
<tr>
<td>Others</td>
<td>Cystic fibrosis, failure to thrive</td>
</tr>
</tbody>
</table>

and gastrostomy tube insertion. At one year of age, she showed severe neurodevelopmental delay and developed infantile spasms, which were well-controlled with a combination of vigabatrin and clonazepam. Her EEG showed modified hypersrrhythmia. At that time, her clinical assessment revealed hypertonia and profound psychomotor retardation. She required further hospitalizations due to repeated airway obstructions, atelecstasis, and failure to thrive and she was further investigated. Tracheal aspirate grew pseudomonas on several occasions and sweat chloride analysis using Wescor 3100 Sweat-check Analyzer showed values of >70 mEq/L on 2 occasions. Fecal fat testing on 3 consecutive days was negative. She was managed aggressively with inhalational amino glycosides, chest physiotherapy, and Pulmozyme, and albuterol inhalations. A PCR-based assay using strip technology from Innogenetics in combination with Conformation Sensitive Gel Electrophoresis (CSGE) to detect 25 mutations in Cystic Fibrosis Trans-membrane conductance Regulator (CFTR) gene specified in the American College of Medical Genetics (ACMG) standards for population based carrier screening was performed in the Mayo Molecular Genetics Laboratory, Rochester, United States of America, and none of the listed mutations were detected. From 18 months of age, she developed severe stridor and laryngoscopy revealed a posterior laryngeal web. The stridor gradually increased and at one stage, an emergency tracheostomy was carried out because of the inability to establish an airway by endotracheal intubation. The child was managed with Pancrease and vitamin supplements, Pulmozyme, and albuterol inhalations at home, but she continued to require several hospitalizations for exacerbation of respiratory symptoms. Her seizures were controlled with medications, however, she showed profound mental retardation and failure to thrive. The patient died at the age of 3 years and 9 months due to a pulmonary infection while on vacation in her home province, and no autopsy could be performed.

**Discussion.** Although holoprosencephaly is the most common developmental defect of the forebrain and mid-face, occurring in 1:250 pregnancies, there is scarcity of reports of this condition in the Arab world. Further more, the association of CF and holoprosencephaly has not been reported. The etiology of HPE is heterogeneous, and both environmental and genetic factors have been found to disrupt normal brain development, which include maternal diabetes (including gestational diabetes), intrauterine infections (cytomegalovirus), and teratogenic agents during pregnancy (alcohol, aspirin, lithium, anticonvulsants, retinoic acid, and hormones). However, only maternal diabetes has an epidemiologically established increased risk over the general population. Incidence figures from newborn surveys demonstrate a risk of HPE in infants of diabetic mothers comparable to 1% risk for caudal regression malformation sequence. The embryologic timing of cranial, cardiac, and caudal defects emphasize the need for meticulous diabetic control and pregnancy planning. A diabetic mother's risk of having a child with holoprosencephaly is approximately 1%, a greater than 100-fold increase over the general population. Teratogens are thought to act synergistically with genetic or other environmental factors to cause this disease. Ming and Muenke have hypothesized that in some conditions, specifically those that originate during early embryogenesis, alterations in modifier genes or interactions with environmental factors are required for the full expression of the disease (“multiple-hit hypothesis”).


discussion.

Approximately 24-45% of live births with HPE have chromosomal anomalies, which include trisomies, duplications, deletions, and ring arrangements. Trisomy-13 is the most frequent chromosomal abnormality and accounts for over one-half of HPE cases with cytogenetic aberrations. The genetic causes can be due to mutations in different genes and mutations have been detected in familial and sporadic cases. At present 12 loci on 11 different chromosomes have been implicated in HPE, whereas genes at 8 loci have been identified. These include sonic hedgehog gene (SHH) at 7q36, ZIC2 at 13q32, SIX3 at 2p21, TG-interacting factor at 18p11.3, PATCHED1 at 9q22.3, TDGF1, GL12, and FAST1 genes. The identification of

**Table 1 - Clinical manifestations and malformations in the proband.**
these different genes demonstrates the complexity of the genetic etiology of HPE. Of these, mutations in SHH are the most frequently identified single gene defect associated with human holoprosencephaly. Mutations in the SHH gene have been more frequently identified in familial (autosomal dominant) than sporadic cases (18% and 3.4%).

Advances in neuroimaging have led to a better understanding of the pathogenesis and neuropathology of holoprosencephaly. The brain malformations range from severe to mild and are accordingly classified to 4 major types; namely, alobar, semilobar, lobar, and the Middle Interhemispheric (MIH) variant. Based on the ultrasound and neuroimaging findings, showing hemispheral non-separation, fusion of basal ganglia and thalami and the presence of a large dorsal cyst in communication with an apparent monoventricle, our patient belongs to the severe alobar type of HPE. Simon et al observed hypothalamus, and caudate nuclei as the most commonly affected deep gray structures in 57 classic cases of HPE (99% and 96%). The thalami were least frequently involved, showing non-cleavage in 67%. A dorsal cyst is often present in HPE and is often correlated with non-separation of thalami and presence of hydrocephalus. The development of hydrocephalus is thought to be due to blockage of cerebrospinal fluid egress from the third ventricle during thalamic non-separation.

The girl in our report manifested severe gastroesophageal reflux and feeding difficulties necessitating fundoplication and gastrostomy tube placement. Oromotor dysfunction and feeding difficulties are correlated well with the grade of HPE. Approximately two-thirds of patients with alobar and semilobar HPE require a gastrostomy tube to ensure sufficient caloric intake. The most common neurological manifestations of HPE are microcephaly, macrocephaly, hydrocephalus, epilepsy, cognitive and motor delay, and mental retardation. Seizures are reported in approximately one-half of patients. Our patient developed epilepsy during infancy and EEG showed modified hypsarrhythmia. She also exhibited marked developmental delay and profound mental retardation. Endocrinopathies specifically diabetes insipidus, are frequently reported in alobar HPE owing to the midline malformation affecting the hypothalamus and pituitary fossa. However, an MRI confirmed the presence of a normal pituitary gland in our patient. Echocardiogram showed a small mid-muscular ventricular septal defect and cardiac anatomy was otherwise, normal. Congenital cardiac defects such as septal defects, or hypoplastic right ventricle are seldom reported in children with HPE. Renal anomalies are not commonly associated with HPE, however, renal ultrasound in our patient showed agenesis of left kidney and hypertrophy of right kidney. In a study of structural anomalies in 30 patients with HPE, Blaas et al identified 5 cases with hydrenephrosis, 4 with dysplastic kidneys, and a single infant with renal agenesis.

The most significant aspect in our patient is the rare presence of CF associated with holoprosencephaly. One study from Saudi Arabia on the association of CF with other inherited diseases such as sickle cell disease, insulin-dependent diabetes mellitus, congenital adrenal hyperplasia, cardiac anomalies and Ehlers-Danlos syndrome has shown that these conditions have significantly affected the course of the disease. The diagnosis of CF is made on the basis of clinical presentation of recurrent airway obstructions, pulmonary atelectasis, recurrent pneumonias, colonization of pseudomonas in respiratory passages and abnormal sweat chloride values. The DNA studies performed to detect mutations in the CF TR gene failed to detect any major mutations. Testing for genetic mutations in CF is mostly helpful in populations where most mutations are known, such as white Caucasians and Ashkenazi Jews. Since the cloning of the CF TR in 1989, more than 1500 mutations have been identified and listed in the CF TR mutation database. One in 4243 children are reported to suffer from CF in one study in Saudi Arabia, however, there is limited epidemiological data on the prevalent mutations among Arab patients with CF. Negative CF TR mutation studies in our patient do not eliminate the possibility that this patient still carries any pathogenic CF TR mutation.

Acknowledgment. The authors acknowledge the use of Saudi Aramco Medical Services Organization (SAMSO) facilities for the research data utilized in this manuscript. Opinions expressed in this article are those of the authors and not necessarily of SAMSO.

References


---

**CASE REPORTS**

Case reports will only be considered for unusual topics that add something new to the literature. All Case Reports should include at least one figure. Written informed consent for publication must accompany any photograph in which the subject can be identified. Figures should be submitted with a 300 dpi resolution when submitting electronically or printed on high-contrast glossy paper when submitting print copies. The abstract should be unstructured, and the introductory section should always include the objective and reason why the author is presenting this particular case. References should be up to date, preferably not exceeding 15.