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Original Article

Clinical manifestations in semilobar holoprosencephaly

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Holoprosencephaly (HPE) is a brain malformation caused by a primary defect in induction and patterning of the rostral neurotube (basal forebrain) during the first 4 weeks of embryogenesis. This defect results in incomplete separation of the cerebral hemispheres. Based on the degree of hemispheric nonseparation, HPE traditionally has been classified into three types: alobar, semilobar, and lobar.[1] In 1963, DeMyer *et al*. mentioned that defects in brain development may frequently coexist with abnormalities on the midfacial region. The median facio-cerebral anomalies appear in various associated gradations and combinations. When combined in patterns, these facies always predict a severe, highly characteristic brain anomaly.[2]

Advances in neuroimaging over the past decade have led to a better understanding of HPE pathogenesis and the variability of this condition. Holoprosencephaly can range from mild to severe and may presently be classified into four types.[3] Type 1 is defined as alobar holoprosencephaly. In this severe condition, brain is not separated which leads to absences of the interhemispheric fissure, third ventricle, olfactory bulbs and tracts, and optic tracts. A single primitive ventricle and fused thalami are also found in alobar holoprosencephaly. In the more moderate type 2 HPE (semilobar holoprosencephaly), the brain is partially divided, thus cerebral hemispheres are separated at the rear but still fused at the front, with only a single ventricular cavity noted. Type 3 (lobar) holoprosencephaly is established when there is well-developed interhemispheric fissure with only mild fusion/abnormalities in some structures. Type 4 is a middle interhemispheric variant of holoprosencephaly (MIHV) in which the middle part of cerebrum (posterior frontal and parietal lobes) is not fully separated.

Children with HPE have many neurological problems including mental retardation, spasticity, athetoid movements, seizure disorders, and endocrine dysfunction. The degree of neurological problems and delays generally correlate with the severity of brain malformation. Patients with the most severe type (alobar) make minimal developmental progress and have short life spans. Major cranio-facial defects add to other critical problems in the condition. In contrast, developmental outcomes and prognosis appear more favorable in milder forms of HPE (semilobar and lobar).[4]

Holoprosencephaly is an extremely heterogeneous condition, whose origin can be related

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to chromosomal, monogenic, and environmental teratogenic factors and which may be associated with other anomalies (syndromic).[5] HPE has been rarely explored and reported in developing countries due to lack of support for patient management. We present the clinical and chromosomal findings of a semilobar HPE case.

The Case

A female infant, aged 28 days, was admitted to the Pediatric Intensive Care Unit, Jogja International Hospital with a history of frequent seizures since birth and poor weight gain. She was born spontaneously at 28 weeks of gestation from a primiparous mother. This was the first pregnancy of non-consanguineous father and mother, aged 30 and 29 years, respectively. There was no history of hereditary diseases or chromosomal disorders in the family. The infant's birth weight was 1700 grams and head circumference was 33 cm. The history of pregnancy and delivery were unremarkable. History of maternal diabetes, alcohol intake or infections was not recorded. HPE was diagnosed prenatally with confirmation by abdominal ultrasound at 27 weeks of gestation. **(Figure 1)**

This patient had a specific facies of orbital hypotelorism, supercilliary depression, flat nose, and median cleft lip and palate with no median process representing philtrum-premaxillary angle. **(Figure 2)** The brain CT scan showed dilatation of the lateral ventricle, fusion of the frontal lobes, but presence of some septation posteriorly with a falx and interhemispheric fissure. The splenium of the corpus callosum was present. There were partially fused thalamus and vermis cerebelli. **(Figure 3)**

Electro encephalogram (EEG) results indicated multifocal paroxysmal epileptiform bursts. Chromosomal analysis revealed normal 46, XX. She spent most of her lifetime in the PICU as she developed many problems such as temperature dysregulation, intractable epilepsy since birth, feeding

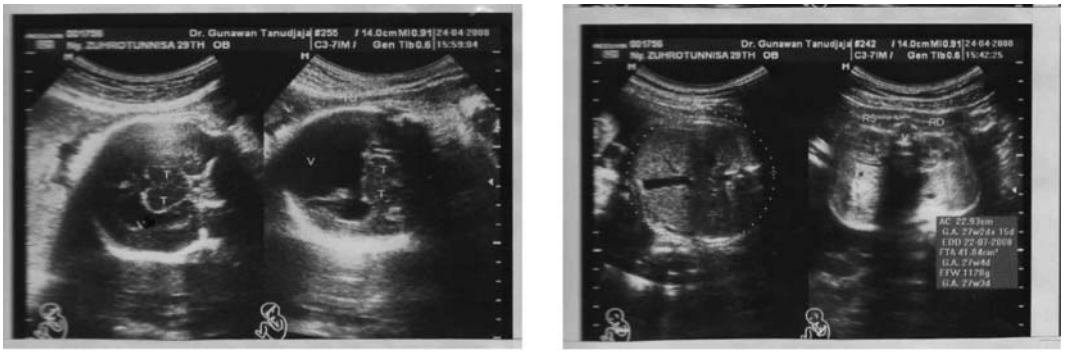

Figure 1. Prenatal diagnosis (27 week of gestational age) showing monoventricular cavity, partially fused thalami, and partial absence of falx cerebri

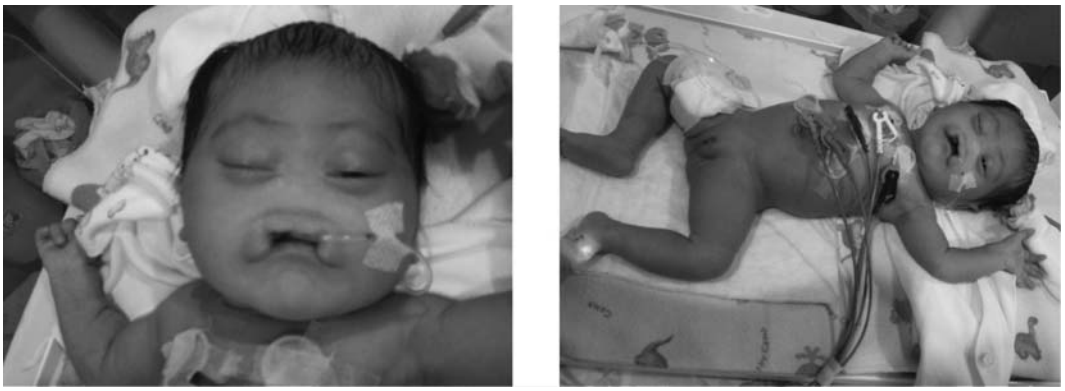

Figure 2. Anterior view of the face

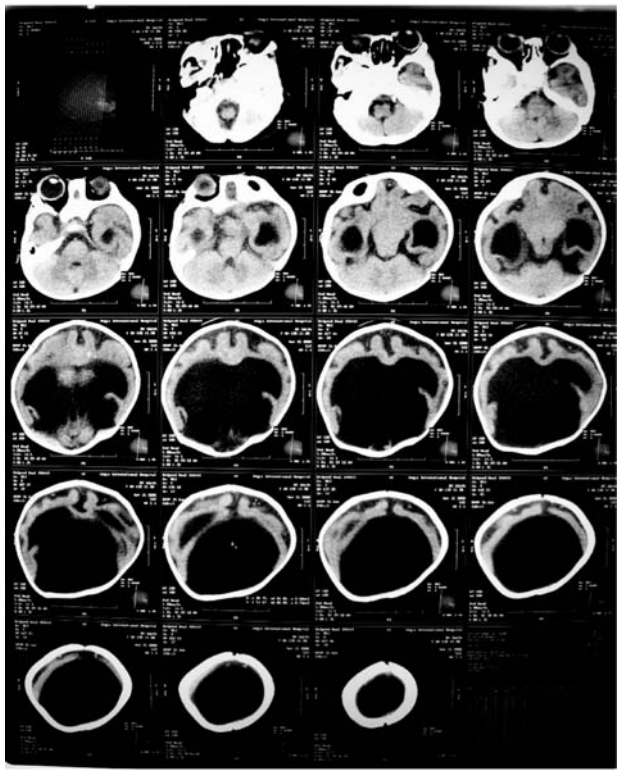

Figure 3. Brain CT scan

difficulties, and muscle tone control issues. We controlled seizures and improved muscle tone with a combination of 5 anti-convulsant medications, including intermittent parenteral midazolam. On daily follow-up, her breathing pattern and heart rate were normal, but body temperature ranged from 35.6°C to 40°C. Her extremities were tense and rigid with repetitive movement and she lacked head control. Despite the appropriate pupillary reflexes and normal retina, she could not fix and follow objects with her eyes. Minimum response to sound was observed. There was no clinical evidence of other vital organ malfunction. Levels of blood thyroid stimulating hormone (TSH), free T4, and cortisol were found to be normal. She gained only 996 grams in a 2.5 month period. The fontanelle closed at 2 months of age. Within last few days of her life, she developed central diabetes insipidus. Urine output rose tremendously to 4 mL/kg/hour, with low urine osmolality and high serum sodium concentration, despite meticulous fluid therapy as well as electrolyte stabilization. She died by the age of 6 months. Consent of post-mortem autopsy could not be obtained.

Discussion

Holoprosencephaly (HPE), the most common structural anomaly of the developing forebrain and midface in humans, is a disorder in which the cephalic neural tube fails to develop and does not divide into right and left lobes. Holoprosencephalon is the term used to describe a single, unpaired forebrain.[7] The prevalence of HPE is estimated at between 1 in 5,000-10,000 live births. Since many pregnancies with a fetal diagnosis of HPE end in miscarriage, the prevalence of HPE among all pregnancies may be as high as 1 in 200-250. Past studies have indicated that 3% of all fetuses with HPE survive to delivery, but the vast majority of these infants did not survive past the first six months of life. However, current statistics are not available.[4,5] The first population-based survey of HPE prevalence provided by Bullen *et al*. representing the total prevalence (including pregnancy termination) showed 1.2 cases per 10,000 registered births, and the birth prevalence (affected live births and stillbirths at > 24 weeks gestation) was 0.49 cases per 10,000 births.[6]

The cause of HPE is currently unknown. Often, no specific cause can be identified. Suggested risk factors include maternal diabetes, infections during pregnancy (syphilis, toxoplasmosis, rubella, herpes, and cytomegalovirus), and various drugs taken during pregnancy (alcohol, aspirin, lithium, thorazine, anticonvulsants, hormones, and retinoic acid). Women with a previous pregnancy loss and first trimester bleeding are also more likely to have a child diagnosed with HPE.[3, 5]

Although many children with HPE have normal chromosomes, specific chromosomal abnormalities have been identified in some patients. Despite its heterogeneity, there may be a common final pathway in the abnormal development of the forebrain and face. The majority of HPE cases are sporadic with cases of familial HPE reported to be autosomal dominant, autosomal recessive or X-linked in inheritance. Nearly 50% of all HPE cases have cytogenetic abnormalities, and approximately 18%-25% of them have a documented monogenic syndrome.[8] At least 12 known loci have been identified which may contain genes critical for normal brain development on 11 chromosomes. Among these, several distinct genes have been identified, including sonic hedgehog (SHH),

homolog of Drosophila odd-paired or OPA (ZIC2), TG-interacting factor (TGIF) and homolog of Drosophila So (SIX3). Sequence changes in SHH associated with HPE include insertions, deletions, missense, and nonsense mutations. All mutations reported to date in TGIF are missense. Mutations in ZIC2 are mostly frame shift or caused by alanine tract expansion and in SIX3, missense.[9] Syndromic-associated HPE may develop in Martin syndrome, Steinfeld syndrome, Meckel-Gruber syndrome, Kallmann syndrome, Hall-Pallister syndrome, Vasidi syndrome, Smith-Lemli-Opitz syndrome, and Rubinstein-Taybi syndrome.[5,8] Identification of the etiologies of such HPE cases is important for establishing the risk of recurrence. Our reported case is an isolated HPE (non-syndromic), with no chromosomal anomalies (numerical or structural). Since there was no history of hereditary or chromosomal disorders in the family, autosomal inheritance was not likely. Thus, the most probable cause of HPE in our case was spontaneous mutation in single or multiple genes, which occurred sporadically (recurrence risk was low to 50%).[10]

Many HPE cases have seizures, which may be manifested in the form of extreme stiffening and shaking spells or more subtle episodes of twitching or blanking out. The frequency of seizures may vary considerably over time.[4] Our patient had frequent generalized tonic-clonic seizures since birth, with each episode lasting up to 2 minutes. The response to a single anti-convulsive agent was not satisfactory. So we combined up to 4 oral anti-convulsant medications as well as gave continuous intravenous midazolam for the first several days to control seizures and improve muscle tone. Typically, alobar HPE cases have increased muscle tone to the point of spasticity. At the same time, they have poorly developed control of their muscles and may appear "floppy," particularly when calm. We noted increased spasticity when the patient was stimulated.

The pituitary gland may not function properly in patients with HPE. Traggiai and Stanhope[11] found that patients with HPE had a greater percentage of combined anterior and posterior pituitary hormone defects (with an more children having diabetes insipidus and less with anterior pituitary defects) than other patients with lip and palatal clefts. Despite the fact that patients with HPE had a high incidence of diabetes incipidus, they did not have a high incidence of multiple pituitary hormone deficiency. In our patient, there was strong evidence of diabetes insipidus, but no other pituitary hormonal problems. This abnormality would ideally be treated with hormonal replacement therapy, but, unfortunately, such therapy was not available in our setting.

One obvious brain stem dysfunction in our patient was erratic temperature control. Body temperature might be elevated in the absence of infection or other definable cause. At other times body temperature might be subnormal for no apparent reason. Most of the time, her fever did not respond well to antipyretics. Episodic irregular breathing pattern and heart rate were also observed in our case. Sometimes the heart rate was fast when it would be expected to be slow as the child was calming down.

The major problem in our patient was feeding difficulties. There was no anatomical separation between mouth and nose, and the nose was extremely flat. Any effort to temporarily block the palatal cleft, to promote normal feeding route, was unlikely to work, since it would totally block the airway. We fed the child through a feeding tube inserted at birth. Growth delay was apparent, despite meticulously calculated caloric food supply. Frank vomiting frequently occurred after feeding, and constipation necessitated the use of periodic rectal suppositories.

Developmental progress, although very minimum, was observed in our patient. She reacted to noises, sometimes in predictable ways to certain recognized sounds. There was no evidence that she could focus or follow objects with her eyes, despite anatomically normal eyes. No other developmental achievements were observed in this case. High-pitched cries and 'barking' sounds were the only vocal sounds she made, as there was no expressive language observed.

The data from Barr and Cohen (1999)[4] showed that more than 50% of children with isolated semilobar or lobar HPE without significant malformations of other organs may live up to 12 months of age. The outward form of the brain does not clearly show brain function, and survival correlates better to brain function than brain appearance on CT scans.

Because of the poor prognosis and ominous outcome in all patients with semilobar HPE, genetic counseling and prenatal diagnosis by ultrasound (transabdominal or transvaginal) should not be delayed. The earliest time for prenatal detection is 11-

16 weeks of gestational age.[5,10,12] For babies surviving through delivery, it is also important to provide integrated care by a medical team. This team may include a geneticist, endocrinologist, ophthalmologist, pediatrician, pediatric intensivist, neurologist, orthopedist, neurosurgeon, plastic surgeon, social worker, and nurse.

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