CASE REPORT

Semilobar holoprosencephaly with 21q22 deletion: an autopsy report

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SUMMARY

Holoprosencephaly (HPE) is the most common forebrain developmental anomaly with a prevalence of 1:16 000 live-births. Possible aetiological agents include environmental factors and genetic defects such as trisomies (13, 18) and deletions (18p, 7q, 2p and 21q). This complex malformation is due to incomplete division of the cerebral hemisphere. The phenotypes of HPE include alobar, semilobar, lobar and midline interhemispheric fusion variants. Craniofacial anomalies occur in 80% of cases. Severely affected babies die in the neonatal period. Here we report an autopsied case of semilobar HPE with pituitary and adrenal agenesis with 21q22 deletion. Additional findings are noted that would help expand the spectrum of 21q22 deletion.

BACKGROUND

Holoprosencephaly (HPE) is a congenital manifestation of developmental malformation manifesting with defective forebrain development and separation into two hemispheres.^{1–2} The aetiology is complex, and besides the genetic factors, many other factors have been implicated in the causation, for example, pre-pregnancy diabetes, gestational diabetes mellitus, infections during pregnancy, alcohol exposure, smoking, low socioeconomic status and substance abuse.² It is considered as one of the commonest developmental defects of cerebral development, and is estimated to occur in 1/16 000 live-births and 1/250 conceptuses.^{3–4} According to the ranges of severity, three types have been described: lobar, semilobar and alobar. Another milder subtype, called the middle interhemispheric variant or syntelencephaly, is also reported.⁴ Children with HPE have many medical problems that include developmental delay and feeding difficulties, epilepsy, instability of temperature, heart rate and respiration. There can be a myriad of associated endocrine disorders.⁴ In the present case we describe an autopsied case of semilobar HPE with pituitary and adrenal agenesis with 21q22 deletion.

CASE PRESENTATION

A female neonate was born to a primigravida mother at 39+5 weeks of gestation by spontaneous vaginal delivery following a consanguineous marriage. Antenatal ultrasonography showed severe polyhydramnios, microcephaly, alobar HPE, absent nose, cyclopia and mild scalp oedema. There was no history of radiation exposure, smoking, alcohol or any drug intake during

pregnancy. Blood sugar and lipid profile were normal. TORCH profile was negative. The family history was unremarkable. The baby did not cry immediately after birth and the APGAR scores were 4/10 and 4/10 at 1 and 5 min, respectively. She was hypotonic and showed features of respiratory distress immediately after birth. There were multiple congenital anomalies in the form of microcephaly, cyclopia, proboscis and anorectal malformations. In view of progressively worsening respiratory distress with recurrent apnoea, the baby was intubated and started on mechanical ventilation. However, she could not survive and succumbed to the illness on the same day. Autopsy was planned to review the cause of death as well as to find any associated anomalies, so that the parents could be properly counselled regarding future pregnancy. The autopsy findings are summarised in tables 1 and 2. At autopsy, gross examination revealed microcephaly, semilobar HPE, absent pituitary and nose, cyclopia, mild scalp oedema, bilateral adrenal agenesis (figures 1 and 2).

INVESTIGATIONS

Deletion of the long arm of chromosome 21q22 was demonstrated on cytogenetic analysis (figure 3), while the karyotype of parents was normal.

DISCUSSION

The characteristic brain findings in semilobar HPE includes—rudimentary cerebral lobes, incomplete interhemispheric division, absence or hypoplasia of olfactory bulbs and tracts, absence of the corpus callosum and varying non-separation of the deep grey nuclei.^{1–4} The facial morphological features include—microcephaly, ocular hypotelorism or hypertelorism, midline or lateral cleft lip and/or

Table 1 Autopsy findings of different organs

Organ	Weight observed	Weight expected	Comments
Thymus	5 g	9.4±2.5 g	Normal
Heart	17 g	19.8±2.8 g	Normal
Lung (bilateral)	28.4 g	42.6±14.9 g	Normal
Liver	95 g	121±39.2 g	Normal
Spleen	7.8 g	10.1±3.5 g	Normal
Kidney (bilateral)	23 g	26.1±4.9 g	Normal
Adrenal (bilateral)	Absent	7.5±2.5 g	—
Brain (prefixation)	245 g	337±91 g	Decreased

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Table 2 Anthropometry at autopsy

Anthropometry	Observed	Expected	Comments
Weight	2105 g	2789±520 gm	Normal
Crown rump length	29.2 cm	34.3±1.9 cm	Normal
Crown heel length	45.5 cm	46.7±4.4 cm	Normal
Toe heel length	6.3 cm	7.5±0.5 cm	Normal
Abdominal circumference	25.8 cm	35.2±1.8 cm	Decreased
Head circumference	25.4 cm	34.6±1.3 cm	Decreased
Chest circumference	26.5 cm	32.9±2 cm	Decreased

Figure 1 Gross examination showing microcephaly, absent nose, cyclopia and proboscis.

palate, flat nose, iris coloboma, single maxillary central incisors and hypoplasia of the pyriform aperture.^{1–4} Besides these, other associated anomalies might be present in such cases, as in the index case with the vestibular anus.

The aetiology of HPE is very heterogeneous. As aforementioned, this pathology can be caused by environmental or metabolic factors. The only formally recognised environmental factors are insulin-dependent diabetes mellitus (1% risk)⁵ and maternal alcoholism with a risk that cumulates with smoking (relative risk of 1.4).⁶ Between 18% and 25% of live births affected by HPE have a recognisable monogenic syndrome, including Smith-Lemli-Opitz, Pallister-Hall, velocardiofacial and Rubinstein-Taybi

syndromes.^{7–10} Chromosomal anomalies have been implicated in 24–45% of live births affected by HPE,^{7–11–12} the most frequently numeric anomalies in chromosomes 13 (70% cases), 18 and 21¹³ and structural anomalies involving 13q, 18p, 7q36, 3p24-pter, 2p21 and 21q22.3.⁷ In the present case, karyotype revealed 21q deletion, which is rare in HPE.

The findings previously described in 21q deletion include: mental and physical retardation, abnormal ears, antimongoloid slant, micrognathia, prominent nasal bridge, skeletal abnormalities, genitor-urinary abnormalities, hypertonia, repeated infections, microcephaly, low birth weight, cardiovascular anomalies, high arched palate, thrombocytopenia/prolonged bleeding time, EEG abnormalities/history of convulsion, eye abnormalities, pyloric stenosis, inguinal hernia, extraribs, renal hypoplasia/aplasia.¹⁴ In the index case, hypotonia, semilobar HPE, absent pituitary and adrenal glands add to the spectrum of 21q22 deletion, not previously documented.

Only few finger countable cases involving chromosome 21q have been described in the literature. Most of the cases are associated with monosomy of 21q with one case reported to have ring chromosome. As reviewed by Estabrooks *et al*,¹⁵ the phenotype of 21q deletion varied from a normal facial appearance to showing all the classical features of HPE. The authors stated that the variation may correlate to the extent of loss in genetic material. Ehling *et al*¹⁶ described two cases of partial deletion of 21q with mild phenotype and showed that the deletion of ETS2 gene, unlike other reported cases having deletion of proximal region, have a more severe manifestation. Our case may have the deletion of the region proximal to ETS2 gene.

The autopsy findings in the index case revealed the absence of pituitary and adrenal glands. Endocrine dysfunctions are common in HPE and correlate with the degree of hypothalamic non-separation. Defects in ventral patterning in HPE may cause hypothalamic dysfunction abnormalities in the hypothalamic-pituitary axis, or pituitary hypoplasia.¹⁷ GLI2 is a transcription factor downstream in sonic hedgehog signalling, acting early in the ventral forebrain and pituitary development. Loss-of-function mutations in this gene are associated with a distinctive phenotype (within the HPE spectrum) whose primary features include defective anterior pituitary formation and panhypopituitarism, with or without overt forebrain cleavage abnormalities, and HPE-like mid-facial hypoplasia.¹⁷ Adrenal hypoplasia is also expected in HPE as in the index case, because the midline malformation affects the development of the hypothalamus and the pituitary gland. However, mutational analysis was not carried out in the index case. In spite of this, the present case is unique in that we were able to demonstrate pituitary and adrenal agenesis simultaneously and additional findings that expand the spectrum of 21q22 deletion.

Figure 2 (A) and (B) Semilobar holoprosencephaly.

Figure 3 Karyotype showing 21q22 deletion.

Learning points

- Only few finger countable cases involving chromosome 21q have been described in the literature.
- Proper antenatal evaluation should be carried out to diagnose this type of case in early pregnancy.
- High-risk mothers should be kept in close follow-up in subsequent pregnancy.

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Competing interests None.

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