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A case of suspected teratogenic holoprosencephaly

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SUMMARY A case of holoprosencephaly is reported in which the mother was prescribed high doses of oestroprogestins during the first 5 months of the pregnancy. Investigation of the family failed to reveal any sign of physical abnormality. A normal karyotype was detected in the proband. The authors suggest that this case may shed some light on the normal and abnormal way in which embryonic fields develop.

The action of teratogenic factors in the aetiology of holoprosencephaly has been studied experimentally using various animals (amphibia, birds, and mammals) and different agents (surgical removal of the

prechordal mesoderm or its destruction by localised x irradiation, vitamin A excess, etc).^{1,2}

The great majority of reports of this condition in man refer to cases with various chromosomal abnormalities,³⁻⁷ or Mendelian aetiology with autosomal dominant transmission in some families⁸⁻¹⁰ and autosomal recessive in others.^{1,11}

Only a very few reported cases¹² have well documented teratogenic mechanisms as causative factors. In the other cases Mendelian or chromosomal aetiology cannot be ruled out.

We report a case of lobar holoprosencephaly with a known exposure to a teratogenic agent.

Case report

The proband (fig 1) was a term newborn male (birth weight 3.5 kg, head circumference 40 cm) who died

FIG 1 The proband.

FIG 2 CT scan showing a large single ventricle.

a few days after birth. He had cebocephaly, hypotelorism, bilateral cleft lip and palate, a nose with a single nostril, hydrocephalus, and left iris coloboma. The karyotype was a normal 46,XY. Serum tests for toxoplasma, rubella, cytomegalovirus, and syphilis were negative. At necropsy a large single ventricle with absent forebrain and its embryological derivatives, optic tracts, and olfactory bulbs were observed.

The family history was not informative. The mother and father were aged 28 and 32 years respectively at the time of conception. They had a normal girl of 9 years. The interpupillary distance in all three first degree relatives was normal and cranial radiographs did not reveal any facial anomaly. The mother was given allyloestrenol (Gestanon), six 5 mg tablets per day, and dihydrogesterone

(Dufaston Depot), one 100 mg injection im per day. Both drugs were given throughout the first 5 months of pregnancy. The drugs were prescribed by an obstetrician because of spontaneous abortion in the previous pregnancy.

Discussion

The question of the teratogenicity in man of oestrogens and progestins, apart from the sexual differentiation of the fetus,^{13 14} is still controversial. In a large series of retrospective studies the use of oestrogen and progesterone during the early months of pregnancy has been found to be significantly associated with neural tube defect,¹⁵ VACTERL association,¹⁶ limb reduction defect,¹⁷ and congenital heart disease.¹⁸ Holoprosencephaly was reported by Batts *et al*¹⁹ but the patient also had trisomy D.

In the prospective survey of Hook *et al*²⁰ in which 50 282 pregnancies were studied, a higher incidence of malformations was found after both early and late exposure to sex hormones in pregnancy. In contrast, a small number of prospective and retrospective studies have failed to confirm the teratogenicity of these drugs.^{21 22}

The embryotoxicity of oestrogens and progestins has been proved in mammals such as mice,²³ rats,²³ and *mus rattus albinus*.²⁴ The most favoured interpretation of the facts is a teratogenic potential conditioned by genetic and other exogenous factors.

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Tracheo-oesophageal anomalies in the Goldenhar anomalad

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SUMMARY A case of the Goldenhar anomalad is presented with a previously undescribed association with oesophageal atresia and tracheo-oesophageal fistula. This is the second instance of a tracheobronchial-oesophageal communication being found in association with the anomalad. Awareness of this combination may facilitate future diagnosis and treatment of the anomaly.

The Goldenhar anomalad is an association of facial and auricular anomalies resulting from errors in morphogenesis of the first and second branchial arches, accompanied sometimes by vertebral, ocular, and visceral malformations.¹ We describe a case with previously undescribed anomalies including tracheo-oesophageal fistula, oesophageal atresia, and hypoplasia of the cerebellum.

Case report

A 2.025 kg female infant was delivered after 36 weeks of uneventful gestation to a 24 year old mother. The parents were unrelated Sephardic Jews and both they and their two children were normal and in good health. The Apgar scores were 6

and 9 at 1 and 5 minutes respectively. Increasing dyspnoea and excessive salivation were soon noted and an attempt to pass an orogastric catheter was unsuccessful.

On examination the baby was noted to have an asymmetrical facies with maxillomandibular hypoplasia, bilateral preauricular skin tags, and microphthalmia with lipodermoids on both lower palpebrae (figure a). The cardiac impulse was felt over the right chest while breath sounds were heard over the left side only. The rest of the examination was considered normal. On chest x-ray a hyperinflated left lung with a complete rightward shift of the mediastinal structures and opacification of the right chest was seen. Extranumerary ribs and hemivertebrae of D1 to D4 were present. The visible tip of the orogastric catheter at D3 and the presence of gastric air suggested the presence of oesophageal atresia with a tracheo-oesophageal fistula. Bronchography showed a complete absence of the right bronchial tree (figure b). The baby died at 20 hours of age.

At necropsy the right lung and the right mainstem bronchus were absent. The left lung had three lobes. The upper portion of the oesophagus was separated from the lower half and ended blindly. The lower portion opened into the trachea. The cardiac chambers and valves were normal. The ductus arteriosus and the foramen ovale were patent. The pulmonary trunk divided into two branches, both supplying the