

Balanced t(6;8)(6p8p;6q8q) and the CHARGE association

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Abstract

A girl is described with bilateral retinal colobomata, Fallot's tetralogy, unilateral choanal atresia, abnormalities of the external ears, bilateral sensori-neural deafness, a unilateral facial nerve palsy, and a tracheo-oesophageal fistula. A clinical diagnosis of the CHARGE association was made. She had an apparently balanced whole arm translocation involving chromosomes 6 and 8. Parental karyotypes were normal.

Case report

This girl was born at 38 weeks' gestation. Her birth weight was 2640 g, length 49 cm, and head circumference 35 cm. The pregnancy was complicated by premature labour at 30 weeks, which was treated with parenteral tocolytic agents. She had good initial Apgar scores of 10 at one minute and 9 at five minutes, but she rapidly deteriorated at 2 hours of age and required ventilation for hypoxia and circulatory support. In addition, it was suspected that she had a generalised seizure. Dymorphic facial features were noted. She was transferred to a neonatal surgical unit where a tracheo-oesophageal fistula was diagnosed and corrected surgically at 9 hours. Postoperatively her heart size increased and echocardiography showed a large ventricular septal defect, an overriding aorta, and mild infundibular pulmonary stenosis. Her chest x rays also showed hemivertebrae. EEG showed abnormalities in the left hemisphere and an ultrasound examination of the brain indicated a post-partum haemorrhage. Her karyotype was abnormal: 46,XX,t(6;8)(6p8p;6q8q). The parental chromosomes were normal. As her parents were British she

was transferred from Germany to the UK for further management. On examination she was not cyanosed. Her facial appearance is shown in fig 1. She had a round face with a prominent forehead, slightly protruding eyes, retrognathia, and low set, simple, cup shaped ears. The nursing and medical staff were unable to pass any catheters through the left nostril. She had a right facial nerve palsy. She was hypotonic but there were no focal neurological signs. Ophthalmological examination showed bilateral choroidal and mesenchymal colobomata with disc involvement on the left. Her hearing was tested by brain stem evoked response audiometry and there was no response in either ear at 100 dB. She was discharged home but died suddenly. Necropsy confirmed the structural abnormalities described. The cause of death was pneumonia with septicaemia and signs of early meningitis.

Discussion

In 1981, Pagon *et al*¹ coined the term CHARGE to describe the association of choanal atresia with other anomalies. These are C=coloboma of the iris, choroid, or retina, H=heart anomaly, A=atresia choanae, R=retardation of growth and development,

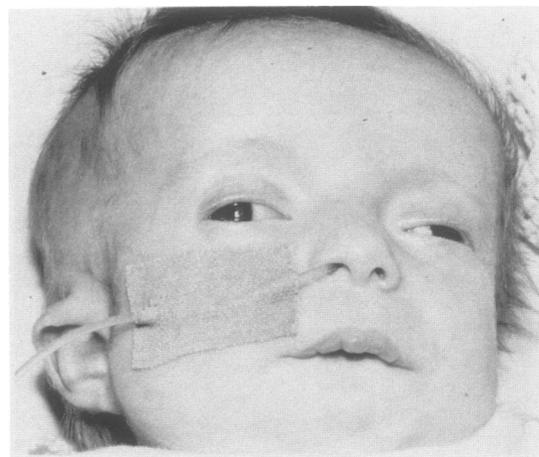


Figure 1 Facial appearance of the proband showing broad forehead, right facial nerve palsy, and simple, low set ears.

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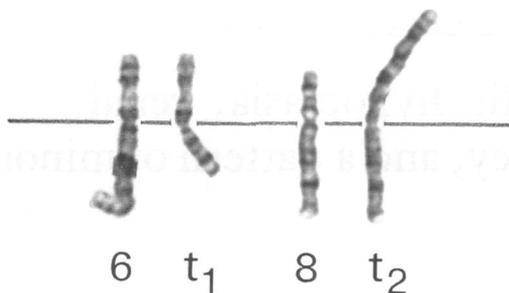


Figure 2 Partial karyotype of the patient showing an apparently balanced whole arm translocation $t(6;8)$, t_1 representing the translocation chromosome $6p8p$ and t_2 representing $6q8q$.

G=genital anomalies in males, E=ear abnormality and deafness. The clinical features of about 100 children with this association have been published, but the aetiology remains unknown. There is an equal sex distribution and the majority of cases are sporadic. Affected monozygous twin girls have been reported and in their original paper Pagon *et al*¹ reported a brother and sister.

The rarity of recurrence in a condition which is being diagnosed with increasing frequency suggests the possibility of either a chromosomal abnormality or a new dominant mutation. There have been no reports of children with 'classical' features of CHARGE and a significant abnormality on karyotype analysis. Children with deletions of the long arm of chromosome 4 show some of the features of CHARGE. Shroff *et al*² described a boy with a tracheo-oesophageal fistula, a patent ductus arteriosus with right ventricular enlargement, cleft palate, anterior ectopic anus,

a large head, and posteriorly rotated ears who had such a deletion of chromosome 4: $46,XY,del(4)(q31)$. A girl reported by Tomkins *et al*³ had choanal atresia and cardiomegaly with a $4(q33-qter)$ deletion, but we do not consider that either child had the CHARGE association. Other published reports of children with some features of CHARGE and a chromosomal anomaly either do not fully satisfy the clinical criteria to make the diagnosis, or the chromosomal change is probably not significant.

In the neonatal period, the differential diagnosis included the VATER association because of the tracheo-oesophageal fistula, Fallot's tetralogy, and hemivertebrae. There is some clinical overlap between the CHARGE and VATER associations but we consider that the diagnosis of the CHARGE association can confidently be made in the girl we report here. Karyotype analysis using G banding techniques showed an apparently balanced translocation between the centromeric areas of chromosomes 6 and 8 (fig 2). Parental chromosomes were normal. Prometaphase banding has not shown any chromosomal loss, but this does not exclude a submicroscopic deletion. Alternatively, the translocation breakpoint may be through a gene of relevance in the aetiology of the CHARGE association. This girl may therefore show the location of the gene or chromosomal change necessary for the development of the CHARGE phenotype.

- 1 Pagon RA, Graham JM, Zonana J, Yong S. Coloboma, congenital heart disease and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* 1981;99:223-7.
- 2 Shroff M, Israel J, Rosenthal F. Congenital anomalies associated with partial deletion of the long arm of chromosome 4 [$46,XY,del(4)(q31)$]. *Am J Hum Genet* 1981;33:122A.
- 3 Tomkins DJ, Hunter AGW, Uchida IA, Roberts MH. Two children with a deletion of the long arm of chromosome 4 with breakpoint at band q33. *Clin Genet* 1982;22:348-55.