Features of DiGeorge syndrome and CHARGE association in five patients

Pascale de Lonlay-Debeney, Valérie Cormier-Daire, Jeanne Amiel, Véronique Abadie, Sylvie Odenti, Alain Paupe, Sophie Couderc, Anne-Lorraine Tellier, Damien Bonnet, Marguerite Prieur, Michel Vekemans, Arnold Munnich, Stanislas Lyonnet

Abstract

We report on five patients presenting with features of two congenital disorders, DiGeorge syndrome (DGS) and CHARGE association. CHARGE association is usually sporadic and its origin is as yet unknown. Conversely, more than 90% of DGS patients are monosomic for the 22q11.2 chromosomal region. In each of the five patients, both cytogenetic and molecular analysis for the 22q11.2 region were normal. In view of the broad clinical spectrum and the likely genetic heterogeneity of both disorders, these cases are consistent with the extended phenotype of either DGS without 22q11.2 deletion or CHARGE association, especially as several features of CHARGE association have been reported in rare patients with 22q11.2 deletion associated phenotypes. On the other hand, these could be novel cases of an independent association involving a complex defect of neural crest cells originating from the pharyngeal pouches.

Case reports

Inclusion criteria for DGS were the presence of at least three of the major features: (1) thymic hypoplasia or aplasia, (2) hypocalcaemia or hypoplasia of the parathyroids or both, (3) congenital cardiac malformation, and (4) dysmorphic features including short palpebral fissures, broad nasal bridge, small mouth, low set ears, and micrognathia. Inclusion criteria for the CHARGE association were at least four of the major features, namely, retinal coloboma, choanal atresia, retardation of physical and mental development or cerebral anomaly, genital hypoplasia in males, and ear anomalies/deafness. Velopharyngeal insufficiency, dysmorphic features (square face, shallow orbital ridges), and cranial nerve palsies were considered accessory criteria.

PATIENT 1

Patient 1 was a boy born at term with full blown DGS including tetralogy of Fallot with atrial septal defect, thymic hypoplasia (fig 1) confirmed at necropsy, hypocalcaemia (1.67 mmol/l, normal range 2.2-2.6 mmol/l), a broad nasal bridge, and microretinopathy. T cell lymphocyte count was normal. He also had features of the CHARGE association including unilateral renal coloboma, partial choanal atresia, small and low set ears with an absent lobe, square face, and severe feeding difficulties with poor sucking and velopharyngeal insufficiency. Other features included right renal agenesis, syndactyly of the second and third fingers, malposition of the toes, and agenesis of the 12th ribs. He died at 17 days of age.
PATIENT 2
Patient 2 was a boy born at term with DGS, including truncus arteriosus and ventricular septal defect, thymic hypoplasia confirmed during cardiac surgery, hypocalcaemia (1.39 mmol/l), broad nasal bridge, and small mouth (fig 2A). He also had CHARGE association with left retinal coloboma, right choanal atresia, genital hypoplasia with microopenis, small, undescended testes, and reduced testosterone (0.08 ng/ml, normal range 1-2 ng/ml). The ears were small, low set, and asymmetrical with an absent lobe (fig 2B) and deafness confirmed by auditory evoked potentials. Unilateral facial nerve palsy and retrocoloboma were also observed. Additional features were a posterior cleft palate, proximally set thumbs, and malposition of the toes. Cardiac repair was performed at the age of 1 month, followed by gastrostomy. At the age of 19 months, length and weight were −2 SD and head circumference −1.5 SD. He had retarded psychomotor development and cerebral CT scan showed cortical atrophy.

Patient 3
Patient 3 was a girl with DGS, including facial dysmorphism with a broad nasal bridge, short palpebral fissures (fig 3A), hypocalcaemia shown by seizures on the first day of life (1.38 mmol/l) with very low plasma parathyroid hormone (2.2 pg/ml, normal range 10-65 pg/ml), and thymic agenesis (fig 3C) confirmed by mediastinal ultrasound. Cardiac ultrasound was normal. CHARGE association was also diagnosed with unilateral retinal coloboma, bilateral choanal atresia, and bilateral deafness confirmed by auditory evoked potentials. In addition, she had a square face, shallow orbital ridges, small, low set, and posteriorly angulated ears, velopharyngeal insufficiency, and a hypoplastic right kidney (fig 3B). Owing to severe feeding and respiratory problems, the patient underwent tracheostomy at 1 month of age. At the age of 4 months there was severe developmental delay.

Patient 4
Patient 4 was a boy born at term by caesarean section because of acute fetal distress. He had DGS with thymic agenesis confirmed by mediastinal ultrasound, profoundly decreased T lymphocytes (total white blood cells 5000/ml, T lymphocytes 0%, normal range 6000-7200/ml), hypocalcaemia on the first day of life (1.5 mmol/l) with low plasma parathyroid hormone (14.6 pg/ml, bicuspid aorta, and retrooesophageal left subclavian artery. He also had CHARGE association with right retinal coloboma, square face, malformed, low set ears, shallow orbital ridges (fig 4A, B), micropenis, and bilateral deafness confirmed by auditory evoked potentials. Additional features were left duplicated thumb and micrognathia. Velopharyngeal insufficiency and gastro-oesophageal reflux required tracheostomy with gastrostomy and Nissen procedure. At the age of 6 months, he had postnatal growth deficiency (both height and weight −4 SD).

Patient 5
Patient 5 was a girl born at 33 weeks of gestation by caesarean section because of retroperitoneal haematoma. DGS was diagnosed with hypoplastic aortic arch and ventricular septal defect, congenital hypocalcaemia (1.6 mmol/l), decreased T lymphocytes without thymic hypoplasia (total white blood cells 14 000/ml, lymphocytes 1200/ml), and short palpebral fissures. CHARGE association was also

Figure 2 Patient 2. (A) Face: note the broad nasal bridge, small mouth, and facial asymmetry. (B) Profile: note small, dysplastic ear and micrognathia.
considered with the finding of bilateral retinal coloboma and severely dysplastic ears. She had no choanal atresia but velopharyngeal insufficiency and hydrocephalus. She died on day 13 with sepsis and hepatic abscess.

**Chromosomal investigations**

No abnormality was observed in any of the five children using RGH banding karyotyping. Fluorescence in situ hybridisation (FISH) was performed on at least 20 metaphase spreads from blood lymphocytes and lymphoblastoid cells lines. Probes used for FISH were cosmids clones SC11.1 and 48F8, encompassing a 2 Mb DNA fragment in the DGS critical region. In each of the five patients and their parents, the SC11.1 and 48F8 probes were found to be not deleted.

**Discussion**

Here we report on five patients presenting with features of both DGS and CHARGE association. All patients had at least three of the major features of DGS: conotruncal cardiac malformation, thymic hypoplasia or aplasia, and hypocalcaemia (table 1). In addition, two patients were severely immunodeficient. Patient 3 had some dysmorphic features of DGS, namely broad nasal bridge and short palpebral fissures. None of the five patients had a 22q11.2 deletion which is found in more than 90% of cases with DGS. In addition, each of them had malformations usually found in the CHARGE association, namely coloboma (5/5), choanal atresia (3/5), hypogonadism with micropenis (2/3 boys), deafness (3/3), severe velopharyngeal insufficiency (5/5), and facial palsy (1/5).

Both DGS and CHARGE association have been ascribed to a developmental defect involving structures derived from the third and fourth pharyngeal pouches. In addition, facial anomalies and neonatal brain stem dysfunction have been attributed to a deficiency of neural crest cells derived from the first branchial arch. While only 10% of patients with DGS lack a 22q11.2 deletion, several other chromosomal anomalies have been reported in DGS, in particular monosomy 10p13 and 17p13. These data strongly support genetic heterogeneity of DGS. Moreover, DGS phenocopies have been observed in diabetic, alcoholic, and retinoid embryopathies. In contrast, the origin of CHARGE association remains unknown. The vast majority of cases are sporadic. However, the existence of several familial cases, increased paternal age at birth of the patients, and concordance in monozygotic twins have been reported, indicating that genetic factors are likely to contribute to CHARGE association. In support of this, a small number of cytogenetic abnormalities have been observed in CHARGE patients including partial trisomy 18, unbalanced 2;18 and 3;22 translocations, duplication of 1q, trisomy 8q, and balanced 6;8 translocation. Thus, the patients reported here may represent a novel disorder or, alternatively, the variable expression of either DGS or CHARGE association. Both syndromes do have a broad

---

**Figure 3** Patient 3. (A) Face: note broad nasal bridge, short palpebral fissures, square face, and shallow orbital ridges. (B) Profile: note small, square ear. (C) Thoracic x-ray: note absent thymus.

**Figure 4** Patient 4. (A) Face: note square face and shallow orbital ridges. (B) Profile: note severely dysplastic ear.
Features of DiGeorge syndrome and CHARGE association in five patients

We thank Alan Strickland for his help in preparing this manuscript and Didier Thiéphile (Paris) for helpful discussions.

30. Davis LA, Sadler TW. Effects of vitamin A on endocardial cushion development in the mouse heart. Teratology 1985;31:26A.