A reappraisal of the CHARGE association

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SUMMARY  We describe 14 boys and six girls, including monozygotic twins, with the CHARGE association. All of the children had at least four of the seven major features included in the mnemonic CHARGE and all had ear anomalies or deafness or both and either coloboma or choanal atresia or both. All the boys had evidence of hypogonadism. A characteristic facial appearance (unusually shaped ears, unilateral facial palsy, square face, malar flattening, pinched nostrils) was observed in many of our cases. The aetiology remains unknown. All our cases are sporadic.

The various abnormalities which together comprise the CHARGE association were first described by Hall in 1979. The mnemonic CHARGE (C=coloboma, H=heart defects, A=atresia of the choanae, R=retarded growth and development, G=genital hypoplasia, E=ear anomalies or deafness or both) was not proposed until 1981 when Pagon et al reported a further 21 patients.

There have now been about 150 cases reported and it is evident that although the most consistent features are still those prefixed by the letters CHARGE, there are additional abnormalities which occur frequently. These include facial palsy, renal abnormalities, orofacial clefts, and tracheoesophageal fistulae.

The purpose of this report is to describe a further 20 children in order to try to redefine which major features are necessary to make a diagnosis, to determine how common additional anomalies are, and to look for any specific aetiological factors.

Patients and methods

Ascertainment of our patients was through the genetics clinic and included referrals from general paediatricians, ophthalmologists, and ENT surgeons. Only children with four or more of the major features included in the mnemonic CHARGE were selected.

The 20 children ranged in age when first seen from four days to 14 years. They were all seen and personally examined by at least one of the authors. To look for any aetiological factors, access to the pregnancy and perinatal histories was obtained from hospital records and further information was obtained by direct questioning of the parents.

Results

The clinical findings in the 20 children are summarised in table 1. Only six of the patients are female. One child (patient 10) died at five and a half months of age. Several of the remaining children have continuing major problems.

Patients 17 and 18 are monozygotic twin girls. They are part of triplets and the other triplet is a healthy unaffected boy. Monozygosity was confirmed by tissue typing and blood groups. They had identical HLA antigens and red blood cell markers.

Colobomas

Seventeen of the 20 children had bilateral or unilateral colobomas which usually involved the retina or optic disc or both. There was also involvement of the iris in four cases. None of the 17 had iris colobomas alone. Six had associated microphthalmos. Severe visual handicap was present in nine.

Cardiac defects

Significant structural defects were present in 16 of the 20 cases. As is evident from table 2, no specific heart lesion predominated and many were complex defects. The majority required surgery apart from one with a small ventricular septal defect and another with a vascular ring. Patient 10, with a ventricular septal defect, atrial septal defect, and tricuspid regurgitation, died at five and a half months from persistent postoperative cardiac failure. One other child (patient 12) had evidence of


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†=Normal IQ. +1IQ 50 to 70. ++IQ ≤50.
ND=not done.
$=$Variant Y (see text).

## Table 2. Congenital heart disease in 16 of the 20 patients.

<table>
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<tr>
<th>Patient</th>
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<td>1-15</td>
<td>Pulmonary artery stenosis and vascular ring</td>
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<td>Ventricular septal defect</td>
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<td>17</td>
<td>Patent ductus arteriosis</td>
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<td>18</td>
<td>Patent ductus arteriosis</td>
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<td>19</td>
<td>Patent ductus arteriosis and atrioventricular canal defect</td>
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<td>20</td>
<td>Hypertrophic cardiomyopathy</td>
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## Table 1. Clinical features of 20 cases.

| Choroid plexus calcifications | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

# Choanal Atresia

Thirteen of the 20 children had choanal atresia. Bilateral involvement occurred in eight and seven of these due to bony obstruction in the posterior choanae. The eighth patient had a membranous lesion. A significant finding was polyhydramnios. Bilateral choanal atresia was diagnosed within a few weeks of age.
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hours of birth in seven because of rapid onset of upper airways obstruction. The eighth case (patient 8) was not diagnosed until day 29. He was born at 32 weeks' gestation and was orally intubated and ventilated from birth for hyaline membrane disease.

In two of the patients, following repair of the choanal atresia, difficulties in maintaining an airway necessitated tracheostomy. In one (patient 15), successful decannulation was possible by 18 months of age. However, patient 2 still has a tracheostomy at four years and all attempts to decannulate have been unsuccessful (figs 1 and 2).

The usual presentation of unilateral choanal atresia was persistent nasal discharge. The monozy-

FIG 2 Case 2 aged three and a half years. Note protruding, simple left ear, right facial palsy, lateral tarsorrhaphy of right eye, strabismus, pinched nostrils, prominent columella, and tracheostomy.

FIG 3 (a, b) Growth chart of case 2. Note marked discrepancy in height and weight after 12 months of age.
gotic twins (patients 17 and 18) had unilateral choanal problems; patient 17 had a left choanal stenosis and patient 18 a right choanal atresia.

**Retardation of Growth**

Seventeen of the 20 had significant growth delay although all of the children showed some discrepancy between height and weight early in childhood. The typical growth pattern seen is illustrated in fig 3a and b of patient 2. However, one child (patient 1) showed spontaneous improvement in growth in mid-childhood (fig 4). This growth spurt is still not associated with any physical signs of puberty even at 14 years of age.

All of the children had appropriate birth weight and length (when known) except patient 12 (fig 5) who was born at 36 weeks with a birth weight of 1.7 kg (<3rd centile). No length was recorded but the head circumference was 31.6 cm (10th to 25th centile). There had been concern in the last trimester about intrauterine growth retardation. He is now nine months of age and his growth both in height and weight remains poor although growth velocity is normal. His head circumference is on the 10th centile.

The monozygotic twins were born at 35 weeks; their birth weights were 1.74 kg and 1.89 kg (3rd centile) compared with the unaffected triplet whose birth weight was 1.15 kg. Fig 6 shows the growth of all the triplets.

In two children (patients 3 and 8) growth hormone stimulation studies showed a normal growth hormone response. There was evidence of delayed bone age in those in whom it was looked for (patients 1, 3, and 11). In all 20 children the growth velocity was normal.

**Mental Retardation**

Assessment of the intellectual status of the children was made either by their attendance at normal schools or from results of formal developmental assessments. Mental retardation was evident in 12 of the 20 children. Of these, only three were severely retarded. One of these (patient 2) had major problems after repair of bilateral choanal atresia. He also had a small occipital encephalocele removed after birth. He was not microcephalic. The other severely retarded children were patient 10, who died after cardiac surgery but who was significantly retarded even at a few months of age, and patient 14, in whom a congenital infection was initially suspected as his mother suffered a flu-like illness at 14 weeks' gestation and he was found to have a raised IgM at birth with a normal IgG. Screening for an intrauterine infection was negative. He was also microcephalic.

The remaining nine mildly retarded children had problems, particularly with eye–hand coordination and speech.
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Parenteral testosterone at 12 years of age and this resulted in significant growth of the penis and pubic hair. He is now at Tanner stage 3 at 14 years. Fig 7 of patient 1 shows obvious hypogonadism at 11 years of age.

Patients 3 and 4 received testosterone at three years of age with good response in the growth of the penis. Further testosterone is planned at 10 to 11 years of age to achieve virilisation.

None of the six girls had any obvious hypoplasia of the external genitalia. They are still too young to know whether delayed puberty will occur.

EAR ANOMALIES AND DEAFNESS

All of the 20 children had either abnormally shaped ears or deafness (or both). Sixteen of the 20 had a characteristic shape of the external ear. It can be short and wide and occasionally low set with a small or absent lobe. The ears can also be protruding, lop, or cup shaped, and simple (figs 8 to 11).

Nineteen were deaf and in eight this was profound. The majority had a sensorineural hearing loss, but in three there was conductive loss only; in three, sensorineural and conductive losses were both present.

Five of the 20 children had microcephaly and all of these were retarded, two profoundly (patients 10 and 14).

GENITAL HYPOPLASIA

All of the 14 boys had hypogonadism with micropenis and either absent testes or small undescended testes. In the two boys who had reached the age of adolescence (patients 1 and 6) there had been no signs of puberty and both had a poor response to luteinising releasing hormone (LHRH) and human chorionic gonadotropin (HCG) stimulation tests. Patient 6 was given a short course of
FIG 8  Case 17 aged three years showing asymmetry of ears with protruding simple right ear and low set, cup shaped left ear.

FIG 9  Case 18, twin of case 17, aged three years. Note protruding ears, particularly on right.

FACIAL PALSY (FIGS 12 AND 13 OF PATIENT 6) Facial palsy was the most frequent of the additional findings. It was seen in 11 of the 20 children. It was unilateral and usually present from birth. Patient 5 apparently developed a right facial palsy at six months and this was less marked by 12 months but still evident at four years of age. Similarly, in patient 20 a right facial weakness was only evident at 22 months of age and has persisted.

Several of the other children had facial asymmetry but no detectable facial weakness.

RENAL ANOMALIES Six of the 20 children had renal abnormalities. In five there was evidence of definite renal malformations which were variable, as seen in table 3. The sixth patient had recurrent urinary tract infections with no renal malformation detectable.

OESOPHAGEAL AND LARYNGEAL ABNORMALITIES None of the children had evidence of tracheo-oesophageal fistula. One child (patient 10) had a first degree laryngeal cleft. Five children (patients 2, 7, 10, 12, and 20) had significant feeding difficulties and evidence of either velopharyngeal incoordination or gastro-oesophageal reflux or both.

OTHER FINDINGS None of the patients had any major skeletal abnormalities. Three had evidence of mild thoracolumbar scoliosis with an abnormal x ray in only one (patient
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FIG 10  Case 4 aged one year showing asymmetry of ears with low set, protruding, lop right ear and slightly prominent left ear and right facial palsy.

FIG 11  Case 4 aged one year. Lateral view of right ear showing overfolded helix.

FIG 12  Case 6 aged 10 years. Note right facial palsy and left microphthalmos.

FIG 13  Case 6 aged 10 years. Lateral view showing low set, lop right ear with hearing aid.
4) who had only 11 ribs. Four had mild syndactyly or clinodactyly and two had congenital dislocation of the hips.

Patient 1 had accessory nipples and a median ectopic thyroid but normal thyroid function.

Four children (patients 2, 4, 11, and 16) had short necks. One (patient 16), who was originally thought to have the Klippel-Feil syndrome, had a normal cervical spine on radiological examination.

Two patients had mild micrognathia and three had high arched palates but no evidence of clefting. None had a cleft lip.

AETIOLOGY
All were sporadic cases. One child (patient 5) had a maternal uncle with isolated unilateral choanal atresia.

Four pregnancy histories were of interest. The mother of patient 14 gave a history of a flu-like illness at 14 weeks. Intrauterine infection screen at birth was negative. The mother of patient 15 was taking the fertility drug Clomiphene at the time of her conception. The mother of patient 3 took Debendox during the first trimester but is unsure of the exact time of starting it. The father of patient 2 was apparently heavily contaminated with the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) containing dioxin for frequent periods over several years. The last exposure was 20 years ago.

None of the mothers was diabetic or on anticonvulsant medication.

Sixteen of the children had their karyotypes analysed and 15 had normal blood chromosomes on G banded preparations. Patient 12 had a variant Y due to a pericentric inversion. His father was also shown to have a pericentric inversion in the Y chromosome, confirming that this was a familial variant.

Discussion

The CHARGE association, with the combination of coloboma, heart defects, choanal atresia, growth retardation, mental retardation, hypogonadism, ear anomalies, and deafness, is being more frequently recognised.

The additional features of facial palsy and renal anomalies are seen almost as frequently as the major anomalies and indeed could be useful as confirmatory evidence of the diagnosis.

Pagon et al\textsuperscript{2} proposed that to make a confident diagnosis of the CHARGE association, at least four of the seven major features included in the mnemonic had to be present and these should include either coloboma or choanal atresia or both.

From table 4 it is evident that our 20 patients conform to these criteria, but two other important features were constantly present. Hypogonadism was seen in all our boys and in fact probably accounts for the preponderance of boys in our series as the diagnosis is more readily made in males. In addition, the combination of either ear anomalies or deafness or both was seen in all the children.

Davenport et al\textsuperscript{3} described 15 patients with a rather characteristic 'wedge' pattern audiogram. This was not as clearly evident in our patients but we would agree with their findings that there are very characteristic external ear anomalies which may provide the clinician with a clue to the diagnosis. These are the protruding, cup shaped, simple, or lop ears. One interesting observation is the difference in shape between the two ears, often the most abnormal ear being on the side of the facial palsy. The reason for this is probably quite simple. Protruding ears are thought to be due to absence of the posterior ear muscles which normally hold the ear in towards the head, whereas a lop ear results from absence of the superior ear muscle so that the helix becomes folded over. Experimental studies in rodents\textsuperscript{4} have shown that early denervation of the seventh cranial nerve (which supplies the auricular muscles) results in a simple ear that lacks the usual conchal folds.

The unusually shaped ears, unilateral facial palsy, square face, malar flattening, pinched nostrils, and prominent columella, particularly in those with choanal atresia, which were present in our patients (fig 2) confirm the observation by Davenport et al\textsuperscript{3}.

\begin{table}
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\caption{Renal anomalies in six of the 20 patients.}
\begin{tabular}{|c|c|}
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Patient & Renal abnormality \\
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2 & Renal dysplasia and vesicoureteric reflux \\
6 & Abnormal rotation of kidneys \\
9 & Crossed renal ectopia \\
11 & Horse shoe kidney \\
16 & Duplex renal system \\
5 & Recurrent urinary tract infections, no renal abnormality detected \\
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\begin{table}
\centering
\caption{Summary of the features of the 20 patients.}
\begin{tabular}{|c|c|c|}
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Features & No of patients affected & \% of patients affected \\
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Coloboma & 17/20 & 85 \\
Heart defects & 16/20 & 80 \\
Choanal atresia & 13/20 & 65 \\
Growth retardation & 17/20 & 85 \\
Mental retardation & 12/20 (profound 3/20) & 60 (profound 15) \\
Genital hypoplasia & 14/14 males, 8/16 females & 100 males \\
Ear anomalies/deafness & 20/20 & 100 \\
Facial palsy & 12/20 & 60 \\
Renal anomalies & 6/20 & 30 \\
Microcephaly & 5/20 & 25 \\
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that there is a characteristic facial appearance in the CHARGE association.

Hypogonadism in the males appears to be either pituitary or hypothalamic in origin. The abnormal LHRH stimulation test indicates secondary hypogonadism. Whether any of the females in our series have similar problems has yet to be elucidated.

The significant growth of the penis in our patients after androgen treatment and the concomitant psychological boost are sufficient reasons for considering androgen therapy at an early age. This may need to be repeated in later childhood to achieve virilisation.

Some degree of short stature was present in all our patients during early childhood. There was no correlation between the degree of growth retardation and the other abnormalities. All had normal growth velocities and there was no evidence of growth hormone deficiency in those in whom it was studied. Growth hormone deficiency has been reported in one patient but from her history she had obvious deviation of growth away from the centiles.

Although mild degrees of mental retardation do occur in a proportion of CHARGE children, very few have profound retardation and when this occurs it seems to be related to events arising from the other anomalies.

The aetiology of the CHARGE association remains unknown. All our cases were sporadic but occasional familial cases have been described. Ho et al. reported two girls with iris colobomas, cataracts, congenital heart disease, and one also had a renal anomaly. Their mother had iris colobomas. This might, however, be a separate condition. Hittner et al. reported 10 patients, two of whom were a mother and daughter with colobomatous microphthalmia involving the iris and retina, heart disease, abnormalities of the external ear, and deafness. Pagon et al. described a brother and sister with some features of the CHARGE association. Their parents were normal.

The possibility that a single gene or a chromosomal abnormality might be implicated in the aetiology of the CHARGE association is suggested from our report of concordance in monozygotic twins and a previous report by Levin et al. of monozygotic twin girls with aortic arch anomalies, retinal colobomas, and facial palsy. Our twin girls are strikingly concordant for all of their features and there can be no doubt that both have the CHARGE association. Although concordance does not prove a genetic cause, it does indicate an increased likelihood of a genetic contribution to the occurrence of the defects in some cases.

A common teratogen similar in its action to Thalidomide has been considered as a possible cause, as many of the features seen in the CHARGE association have also been seen in the Thalidomide embryopathy. A similar collection of abnormalities has been reported in infants exposed to hydantoin in utero and also in infants of diabetic mothers. However, none of the mothers in our series was diabetic or on anticonvulsants.

One mother became pregnant on Clomiphene. However, this has not been implicated in causing the types of malformations that occur in the CHARGE association. There have been reports of an increased number of neural tube defects among the children of women taking the drug. However, other factors which might increase their risk of having offspring with neural tube defects were not corrected for.

Another possible teratogen, which has been the subject of much debate over the years, is the herbicide 2,4,5-T. Any possible embryotoxicity is thought to be due to the presence of dioxin impurity. According to one mother in our series, the father of her child used the herbicide which she was told contained dioxin. He was heavily contaminated with it ("it was dripping down his back"). However, from all the studies carried out in the USA and Australia on Vietnam veterans, there has been no confirmatory evidence of the embryotoxicity of dioxin in humans.

Although so far no teratogens have been implicated in the aetiology of the CHARGE association, accurate periconceptional and prenatal histories are necessary if we are eventually to find the cause or causes. Certainly, some form of intrauterine insult is possible as many of the defects (including choanal atresia, coloboma, heart defects, orofacial clefting, and oesophageal atresia) could be attributed to arrested development between days 35 and 45 after conception.

In conclusion it is possible that there are several aetiologies for the CHARGE association but from a practical viewpoint our study confirms that most cases are single and that recurrence risks are small.

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