

The CHARGE association

We read with interest the proposal of a new autosomal recessive syndrome by Hurst *et al* (*J Med Genet* 1989;26:407-9) based on the description of two sibs with ASD, VSD, developmental delay, poor growth, microcephaly, low set, posteriorly rotated ears, and other dysmorphic features. The brother had choanal stenosis and the sister was also suspected to have choanal stenosis, but this was not proven. The authors eliminated CHARGE association because they concluded that it is a sporadic defect. However, there have been several reports of familial CHARGE association, also known as CHARGE syndrome. Metlay *et al*¹ reported one such family and reviewed eight others in published reports. Of these, six appeared most likely to be autosomal dominant, two to be autosomal recessive, and one involved affected monozygotic twins and so could be either dominant or recessive. Two additional sets of affected monozygotic twins have been reported,^{2,3} as well as another family that appears to represent autosomal recessive inheritance.⁴ Thus, CHARGE association appears to be aetiologically heterogeneous with most cases sporadic but a small yet significant percentage familial.

The boy reported by Hurst *et al* satisfies five of the seven major criteria for CHARGE (congenital heart disease, choanal stenosis, growth deficiency, mental deficiency, and ear anomalies) and had two other commonly reported findings (microcephaly and micrognathia). His sister meets four major criteria (congenital heart disease, growth deficiency, mental retardation, and ear anomalies), lacking only the choanal stenosis, although the authors suspected that she also had this. Choanal atresia rather than stenosis is the typical anomaly in CHARGE, but stenosis has been reported as a variant in CHARGE as have some of the dysmorphic features seen in these two patients, that is, long philtrum and high palate.⁵ The published photographs of the sibs both appear to show some degree of facial asymmetry with raised left eyes. Facial asymmetry is commonly observed in children with CHARGE association.² Therefore we suggest that, rather than a new recessive syndrome, the brother and sister appear to have CHARGE syndrome. No ophthalmological or audiological examinations were reported; these

studies are strongly indicated in any child with CHARGE syndrome.

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This letter was shown to Drs Hurst and Berry, who reply as follows.

Thank you for the opportunity to reply to the letter from Drs Bialer and Brown. After careful consideration of the points raised in the letter we do not think that the brother and sister we described have the CHARGE association.

While the CHARGE association was considered in our differential diagnosis, we do not consider that they have sufficient features of that association to make the diagnosis. In particular there were no colobomata, the ears, though posteriorly rotated, were structurally normal, they were not deaf, there was no facial asymmetry or VIIth nerve palsy, the heart lesion is not that which is most commonly found in CHARGE (Fallot or conotruncal lesions), and there were no other commonly associated malformations such as tracheo-oesophageal fistula.

There are many hundreds of children known to have the CHARGE association but only a few reported sib pairs. In the unusual situation of affected brothers and sisters we consider it necessary for both to have the full clinical picture to make a diagnosis of the CHARGE association.

However, there will remain diagnostic difficulty until the underlying gene defect in CHARGE association is identified.

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The Moebius syndrome: aetiology, incidence of mental retardation, and genetics

Kumar, in his summary of the Moebius syndrome (*J Med Genet* 1990;27: 122-6), has made certain contentions with regard to the aetiology, incidence of mental retardation, and genetic transmission of this syndrome which require further examination.

The aetiology of this syndrome has been debated since its original description. Arguments have centred around questions of whether the disorder is primarily degenerative or dysplastic, and the location of the pathology, whether in the brain stem, the peripheral nerves, or the muscle of the face or eye. In addition, to overlap with the hypoglossia-hypodactyly, ankyloglossia, and Charlie M syndromes, there is also association with the Hanhart syndrome. A recent study into the aetiology of the Moebius syndrome has indicated significant events of pregnancy in eight of 15 cases, including hyperthermia, previous uterine surgery, electric shock, failed abortion, prolonged rupture of the membranes, and alcohol abuse.¹ The association with hyperthermia during pregnancy has been confirmed in another study.² In a rat animal model, uterine artery occlusion, handling the uterine vessels, and uterine handling were associated with bilateral brain stem ischaemic lesions and peripheral limb deficiency.³

In this animal study the mothers were treated on day 16 of pregnancy, after organogenesis and lesions were seen in the brain stem and pons. Similar lesions have been seen in a rat animal model of cocaine abuse, the

common mechanism appearing to be decreased blood flow in the uterine vessels with damage to the fetus owing to haemorrhage from the fetal vessels and associated tissue hypoxia.⁴ This is consistent with the proposal of Bouwes-Bavinck and Weaver⁵ that the Moebius syndrome results from an interruption of embryonic blood supply, with the extent and nature of the associated defects dependent on the specific locations of vascular insufficiency. They postulated that premature regression, obstruction, or disruption of the primitive trigeminal arteries before the establishment of sufficient blood supply for the brain stem by the vertebral arteries or obstruction in the basilar or vertebral arteries was the cause of the Moebius syndrome.

They also proposed that the Poland syndrome, Sprengel deformity, and Klippel-Feil anomaly may result from a disruptive vascular insult in early pregnancy and that the pectoralis major, serratus anterior, and vertebral segmentation differentiate at the same time during days 40 to 42 of gestation or horizon 18. The Poland syndrome when associated with Moebius syndrome has had post mortem necrotic brain stem lesions, similar to those demonstrated by Kumar, in the case of Riggs,⁶ in case 2 of Thakkar *et al.*,⁷ and case 15 of Lipson *et al.*¹ Kumar indicated that abnormal brain stem auditory evoked potentials have led to the suggestion of a 'supranuclear' site for the 'acoustic lesion'. This is confusing, or is a typographical error, as the abducens and facial nerve nuclei are not within the auditory pathway and auditory brain stem potentials could be theoretically normal with nuclear lesions. The term supranuclear is not used for the sensory auditory pathway, as there are several nuclei in the auditory pathway—cell bodies in the spiral ganglion, dorsal and central cochlea nuclei in the brainstem, and the inferior colliculus in the midbrain. There is no necropsy report in which the brain stem has been normal in the Moebius syndrome,⁸ including that of Pitner *et al.*,⁹ who dismissed brain stem pathology as resulting from birth trauma.

It is reasonable to assume that the long standing lack of innervation from the motor lesion of the brain stem would result in the fibrosis and atrophy of the muscles resulting in many of the facial dysmorphic features, such as

small palpebral fissures, epicanthic folds, and microstomia.

Animal experimentation is supportive of hypoxic/ischaemic insult mechanisms. Miller and Myers¹⁰ simultaneously occluded the aorta of adult rhesus monkeys for a measured length of time. During arrest of systemic flow, the pulmonary and coronary vessels remained unobstructed allowing the passage of oxygenated blood through the lungs and heart. After termination of timed systemic circulatory arrest each animal's status was monitored by blood pressure measurement and electrocardiogram. The animals who did not have a significant post-arrest hypotension had a typical pattern of brain stem injury, particularly to the cranial nerve nuclei, which spared the cerebrum. Ranck and Windle¹¹ caused asphyxia in near term Macaca Mulatta by detaching the placenta at hysterectomy and keeping the fetal membranes intact. A pattern of brain stem injury affecting the cranial nerve nuclei in particular was observed. Further analysis of human material indicates that similar brain stem lesions, while sparing the cerebrum, can occur after prompt resuscitation for a cardiac arrest in the perinatal¹² and even in the adult patient.¹³ These injuries are hypoxic/ischaemic lesions and are not the result of basilar artery thrombosis associated with birth trauma, as indicated by Kumar.

Although we would agree that the occurrence of Poland syndrome in the Moebius syndrome is probably related to a common pathogenetic mechanism, consideration that it may be "a primary metamer defect" in brain stem nuclei and somite mesoderm of the limb buds is entirely speculative and without human or experimental evidence. The term 'split hand' used by Kumar interchangeably with ectrodactyly is also misleading: no case of the Moebius syndrome has been associated with classical 'split hand'. Kumar, though admittedly indicating that retardation is overdiagnosed, cites an instance of mental retardation of from 10% to 50%. Our own anecdotal experience of two school age children of normal intellectual potential placed in schools for the mentally retarded supports data that the cerebrum is spared and real intellectual impairment is unlikely in the classical Moebius syndrome. The effects are on communication and the lack of facial expression which, in

addition to the speech problems, can have extreme psychological effects.

In addition, Kumar says that it is difficult to offer precise risk estimates for the Moebius syndrome. However, published reports are reasonably precise in this regard. If the Moebius syndrome is associated with limb deficiency the recurrence risk is nil. Cases involving only facial weakness with or without eye paralysis may be familial; either autosomal dominant, X linked, or even recessive inheritance has been suggested.¹⁴⁻¹⁵ The lesion in this latter group may be muscular or of brain stem aetiology.¹⁶ Another rare familial case was associated with arthrogryposis.¹⁷ Rare associations with congenital peripheral neuropathy and hypogonadotrophic hypogonadism¹⁸ and Kallman syndrome¹⁹ have evidence of a Charcot-Marie-Tooth-like disease on EMG and muscle biopsy²⁰ indicating that peripheral nerves as well as muscle disease may be the aetiology in rare cases.

Some reports have indicated isolated limb deficiency in another family member as evidence of a genetic aetiology.²⁰⁻²² These reports are probably coincidental, there being no clear evidence of true vertical or horizontal transmission.

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Royal College of Physicians Report on Prenatal Diagnosis and Genetic Screening. London: RCP. 1989.

The Royal College of Physicians (London) report on Prenatal Diagnosis and Genetic Screening (RCP 1989, 'the screening report') represents a watershed in the development of genetic services in Britain. Traditional patient and family based medicine is confronted by the need for a community wide service for the prevention of genetic disease and radical solutions are required for a potentially vast expansion of screening and prenatal diagnosis. The screening report noted that 2 to 3% of all couples are at high and recurrent risk of having a child with an inherited disorder. The burden of genetic disease is further illustrated by recent estimates from the Department of Health in British Columbia which suggest that 5.5% of the population will develop genetic disease by the age of 25, while 60% may do so in a lifetime.¹

To cope with the needs of genetic patients and families a network of regional genetic centres has been developed in Britain. These centres combine 'under one roof' clinical and laboratory diagnosis, counselling, and genetic registers for the investigation and support of the families. This arrangement follows the pattern of multidisciplinary integration advocated by the Joint Statement from the medical royal colleges in 1986, which was supported by the Department of Health in its reply and in subsequent ministerial statements.

However, new molecular genetic technologies will soon offer tests for all major genetic disorders and permit widespread carrier detection and prenatal diagnosis. Pilot studies for cystic fibrosis population screening are being initiated which, if successful, may eventually involve the entire population of reproductive age in Britain. The demand for genetic diagnosis, counselling, and screening can then be expected to rise rapidly, although this demand already exceeds the capacity of the current establishment of genetic centres. This is shown by another

study by the Royal College of Physicians² which found the equivalent of 156.3 full time clinical genetic staff (including 37.58 consultants) in the UK, representing only 2.75 total clinical staff per million population.

The screening report placed particular stress on the importance of 'community genetics', a new term implying the exposure of persons at low prior genetic risk to population screening programmes. Community genetics is discussed in detail elsewhere in this issue of the journal by Dr Bernadette Modell, who was the Honorary Secretary to the working party that produced the screening report.

The recommendations of the screening report are wide ranging and have important implications for the future of patient and family based medical genetics. While clinical geneticists will appreciate the recommendation that:

“... genetic screening and prenatal diagnosis services should be equally available to the whole community. . . .”

clinical geneticists may wonder if two of the recommendations taken out of context might inhibit specialised pre-pregnancy genetic workup and counselling, frequently necessary before prenatal diagnosis, and might create a new cadre of community geneticists remote from genetic centres. The relevant recommendations are:

“... (genetic screening and prenatal diagnosis services) should be recognised as an intrinsic component of maternal and child health services. . . .”

“... specialist counsellors should be attached to each obstetric unit practising prenatal diagnosis. . . .”

Clinical geneticists are concerned that few doctors have had appropriate undergraduate genetic education and may not yet have acquired adequate postgraduate training. This is shown most clearly by another Royal College of Physicians (London) report³ which indicated very variable teaching of genetics with a mean of 20 hours preclinical (range 2 to 66 hours) and 5.5 hours timetabled clinical teaching. Teaching was given by many different departments and was generally of unknown quality or clinical relevance. The screening report recognised these educational deficiencies and recommended that:

“... professional training in medical genetics and the principles of genetic