Syndrome of the month

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Williams syndrome

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Williams *et al*¹ in 1961 called attention to a syndrome of supravalvular aortic stenosis, mental retardation, and peculiar facial features. In 1962, Beuren *et al*² described the syndrome independently and expanded it to include dental anomalies and peripheral pulmonary artery stenosis, as a result of which some authors prefer the eponym Williams-Beuren syndrome.

Several earlier authors have a claim to posterity. The key cardiac defect, supravalvular aortic stenosis, was first described in 1842 by Chevers,³ was named in 1930 by Mencarelli,⁴ and was shown to be a familial disorder in 1959 by Sissman.⁵ Perhaps the strongest case can be made for Fanconi *et al*⁶ who described what is now known as Fanconi type idiopathic infantile hypercalcaemia (IIH) in 1952, a condition associated with a characteristic dysmorphic syndrome and cardiac defects. Joseph and Parrott⁷ in 1958 made particular reference to the odd facies in these children.

In 1963 Black and Bonham Carter⁸ recognised that the 'elfin facies' of idiopathic infantile hypercalcaemia were the same as those described by Williams *et al*¹ and Beuren *et al*.² In 1964, Garcia *et al*⁹ established this new combined entity with what is still one of the very few fully documented examples of IIH progressing to Williams-Beuren syndrome. A major factor in the preference for the latter term was the recognition that overt hypercalcaemia is an infrequent feature when large series of cases are reviewed.^{10 11}

Clinical features

GENERAL

The classic syndrome is described in all dysmorphology texts: typical facies, supravalvular aortic stenosis, and variable mental retardation with a friendly, outgoing personality. Infantile hypercalcaemia,

when it occurs, may precipitate symptoms such as failure to thrive, vomiting, constipation alternating with diarrhoea, and, in extreme cases, nephrocalcinosis. If hypercalcaemia is overt, skeletal changes in adolescence and adulthood include osteosclerosis of the metaphyses of long bones, the skull vault, or lamina dura of the alveolar bone. Dental anomalies are characteristic with late eruption, reduction in size, and general hypoplasia designated microdontia and rhizomikry (small roots) together with invagination of the incisors, malocclusion, and pathological folding of the buccal mucosa.¹²

FACIAL FEATURES

Whether or not these children have elfin facies is difficult to establish, for while examples of the syndrome are common, this author has never seen an elf. The term should be dropped.

The facial dysmorphic features evolve with age as shown in figs 1 to 4. The key features are a broad forehead, medial eyebrow flare, periorbital fullness, strabismus, stellate iris pattern, flat nasal bridge, malar flattening, full cheeks and lips, a long smooth philtrum, a rather pointed chin, and a wide mouth. The face becomes more coarse with age. None of the features is constant but the characteristic combination for this author is the malar flattening with full lower face, best shown in fig 3b.

CARDIOVASCULAR FEATURES

Cardiovascular anomalies are present in about three-quarters of cases. Intracardiac anomalies, such as septal defects, have been described but are unusual. The characteristic abnormalities are supravalvular aortic stenosis (SVAS) and peripheral pulmonary artery stenosis (PPAS) with other muscular arteries involved less often.

SVAS involves the ascending aorta above the sinuses of Valsalva and, therefore, above the origins of the coronary arteries. These are exposed to the raised pressure and tend to become tortuous and

FIG 1 A female infant at 3 months with typical facies, severe hypercalcaemia, peripheral pulmonary artery stenosis, nephrocalcinosis, failure to thrive, and developmental delay.

thickened with an adverse effect on long term survival without surgery. Two-thirds of cases of SVAS involve an hour glass deformity with the rest divided between a discrete membrane or diffuse hypoplasia. In one-third, the aortic cusps are thickened and in the worst cases become adherent to the area of disorganised aortic media and fibrotic intima.¹³ Valve involvement may add the murmur of aortic incompetence to the systolic murmur transmitted to the carotids. Folger¹⁴ showed the ascending aorta to be unusually short which may be evidence of common pathogenesis with the diffuse hypoplasia of the pulmonary arteries beyond the bifurcation. This shortening may also be significant in embryology, since O'Connor *et al*¹³ noted that haemodynamic factors may influence the site and nature of the narrowing. Another factor of likely importance is the observation that newborn infants may have an infolding or plica at the upper margin of the sinuses of Valsalva which is conspicuous in some and almost

FIG 2 An older girl with classic facies and moderate mental retardation.

absent in others. SVAS may be an exaggeration of this normal structure.¹⁵

Streaming of blood into the innominate artery may give higher blood pressure in the right arm than the left. Clinical features correlate poorly with severity though an ECG pattern of left ventricular hypertrophy with strain indicates a ventricular pressure above 200 mmHG¹⁶ and a worse outlook.

INTELLECT

Intellectual development shows wide variation with most cases falling in the mild to moderately retarded class (mean IQ 56).¹⁰ Suggestions that perceptual and motor function are more impaired than verbal performance were not corroborated by Kataria *et al*.¹⁷ Martin *et al*,¹⁸ in a review of 76 cases of IIH and 41 cases of Williams syndrome, drew attention to hyperacusis which was found in 75% of their cases and proved disabling in some. These authors also noted that the failure to thrive of early months gives way to a tendency to obesity in later childhood, a feature evident in half the group studied.

OTHER FEATURES

Among the other general physical features noted by various authors, of particular value as 'make weight'

FIG 3 (a) A girl of similar age with mild intellectual impairment, outgoing personality, and mild supraaortic stenosis.

findings are mild degrees of short stature and microcephaly, kyphoscoliosis, a long neck, inguinal or umbilical herniae, small nails, hallux valgus, and a hoarse voice. The long term outlook is dependent, usually, on the cardiovascular features dealt with above, but Smith¹⁹ quotes, as a personal communication from B Hall, a tendency to degenerative renal disease. This may be a late consequence of damage related to hypercalcaemia. The adult male reported by Dupont *et al*²⁰ and by Jensen *et al*¹² died at 42 from pancreatic carcinoma. The latter authors reported the postmortem discovery of calcium in the form of hydroxyapatite crystals in the cornea on electron microscopy (EM), and in other tissues, despite the fact that hypercalcaemia had not been reported in life. They suggested that EM of a conjunctival biopsy for calcium deposits may be helpful in diagnosis though this is unlikely to be used often.

The various features of Williams syndrome are arranged and weighted in a diagnostic index by Preus.¹¹

AETIOLOGY AND GENETICS

In the great majority of cases, Williams syndrome is a sporadic event of unknown cause. Two central questions are: first, how does the full syndrome relate to the variable autosomal dominant trait of 'pure' SVAS and, second, is disturbance of fetal calcium homeostasis by an inborn error or environmental stress or both of fundamental importance in its pathogenesis?

The original report of familial SVAS by Sissman *et al*⁵ has been followed by several similar observations.²¹⁻²⁶ Williams syndrome has been described in monozygotic twins²⁷ and in second cousins,²⁸ and Cortada²⁹ reviewed four sib reports

FIG 3 (b) Note malar flattening which exaggerates the full cheeks and lips.

FIG 3 (c) *Strabismus, telecanthus, slight stellate pattern and medial eyebrow flare.*

FIG 4 (a) *An adolescent with severe supraventricular aortic stenosis, moderate mental retardation, and typical, rather coarse facial features.*

and described an affected mother and twin daughters, though the children look more like cases of Noonan syndrome. The latter two reports note normal karyotypes, but it remains possible that such occasional recurrences result from unrecognised chromosome rearrangements.

Many reports of Williams syndrome fail to mention chromosome studies, including the report by Mehes *et al*³⁰ of IIH in a father and two children. Two small chromosome studies^{31 32} were done when techniques were in their infancy. Fryns *et al*³³ described a possible case of Williams syndrome with a deletion of 15p. Martin *et al*¹⁸ found one case of a balanced 9;17 translocation, while Jefferson *et al*³⁴ report in this issue a female infant with features of the syndrome resulting from a deletion of the long arm of chromosome 4.

While such cases may be nothing more than phenocopies, it remains a distinct possibility that Williams syndrome results from a usually submicroscopical deletion of a segment of the chromosome which includes the gene responsible for SVAS. Support for this view is given by the authors who comment on 'elfin facies' in some of the patients with familial SVAS. This case is put most forcefully by Grimm and Wesselhoeft,²⁶ whose major review of 128 families with SVAS or Williams syndrome identified a number of family members in SVAS pedigrees with features of Williams syndrome. They concluded that these clinical phenotypes are ends of a spectrum for an autosomal dominant gene defect of variable penetrance and expression whose gene frequency is at least 1 in 10 000. A criticism levelled at this and earlier reports is that their examples of

FIG 4 (b) Note the lacy stellate iris pattern and wide nose with bulbous tip.

clinical overlap are not supported by clinical photographs. This author was persuaded to their view by the child illustrated in fig 5. His father and paternal uncle had the clinical features of PPAS and SVAS

FIG 5 A boy with SVAS whose brother, father, and paternal uncle had either SVAS or PPAS or both. This child was also hyperactive with mild developmental delay and some of the facial features of Williams syndrome.

respectively, while his brother had SVAS and PPAS. The proband had SVAS and was noted to be hyperactive with evidence of mild developmental delay and facies which resemble the full Williams syndrome. McKusick is sufficiently persuaded by Grimm and Wesselhoeft to have made the syndrome a starred entry in the autosomal dominant catalogue.³⁵

The remaining important issue is the role of disturbed calcium homeostasis in the pathogenesis. Attention in the 1950s was focused on environmental disturbance, in particular the role of maternal ingestion of vitamin D. Following the recognition of an apparent epidemic of infantile hypercalcaemia, an association with vitamin D fortified milk was proposed. Removal of this supplementation was associated with an apparent fall in birth prevalence.³⁶ Persistence of the syndrome and its occurrence in infants definitely not exposed to excess vitamin D led authors to conclude that this teratogenic exposure had exposed fetuses in the population with a pathological sensitivity to the vitamin.

A series of animal experiments by Friedman *et al*³⁷ showed that very large doses of vitamin D in rabbits produced aortic lesions identical to those seen in SVAS, dental anomalies, strabismus, and craniofacial changes closely resembling those seen in Williams syndrome.³⁸ Rather than the calcium disturbances being an epiphenomenon due, for example, to a neural crest abnormality affecting the face, heart, and the ultimobranchial body which gives rise to thyrocalcitonin C cells, this study showed that a phenocopy could be produced by a primary disturbance of fetal calcium homeostasis. Human studies support this interpretation; Becroft and Chambers³⁹ found fibroblasts from affected children to be hypersensitive to vitamin D₂ (25

hydroxycholecalciferol) on the basis of excess cytoplasmic metachromasia, though this is a non-specific marker. Barr and Forfar,⁴⁰ using an oral calcium loading test, showed infants with IIH to have exaggerated and prolonged rises in serum calcium. Older cases with Williams syndrome were less impressive. Forbes *et al*,⁴¹ however, used an intravenous calcium infusion of 10 mg/kg over one hour and found abnormally slow clearance in two cases of IIH and in five of six children with Williams syndrome despite normal resting calcium levels.

The precise defect of hormonal control remains uncertain, and review of the expanding publications on calcium metabolism is not appropriate here. In brief, vitamin D has three basic forms. Cholecalciferol, the dietary form, is converted in the liver to 25 hydroxycholecalciferol which is, in turn, converted by the kidney to the highly potent 1,25 hydroxycholecalciferol. This hormone sustains serum calcium levels by enhanced absorption at bowel and kidney and at the expense of bone. Calcitonin, on the other hand, enhances clearance of calcium from blood and tends to stabilise the important serum concentration while protecting the skeleton. Vitamin D binding protein has been reported to be normal.⁴² Taylor *et al*⁴³ found abnormal regulation of circulating 25 hydroxycholecalciferol, following oral administration, in a small group of patients and in two of four normal sibs. There is a report⁴⁴ of a baby surviving intact ingestion by the mother of massive doses of 1,25 hydroxycholecalciferol though this might have been the result of the genetic resistance in the mother which necessitated the therapy. Forbes *et al*⁴¹ noted reports of normal parathyroid histology and concluded that a defect in calcitonin production, release, or activity was most attractive. The recent localisation of the gene for calcitonin to chromosome 11⁴⁵ makes the possibility of an error in its structure of particular interest. Hutchins *et al*⁴⁶ have obtained thyroid histology in an adult case of Williams syndrome who died at 30 years. There was marked hyperplasia of the C cells which produce calcitonin, which they interpreted as being secondary to chronic stimulation by a persistent error in calcium regulation. An alternative theory is that an abnormal product resulted in chronic feedback stimulation to cell proliferation. The most recent report⁴⁷ is of a defect in calcitonin production in cases of Williams syndrome. Culler *et al*⁴⁷ confirmed, in their controlled investigation of five children with Williams syndrome and no history of hypercalcaemia, a raised baseline serum calcium and a delayed fall after an intravenous calcium bolus. The calcitonin response was blunted with significantly lower calcitonin levels. These authors

raise the possibility that a second product of the calcitonin gene, the calcitonin gene related peptide, may be involved in the cause of retardation in view of the substantial quantities found in normal brain tissue.

Whatever the precise defect, blind restriction of dietary calcium and vitamin D is not advisable. Martin *et al*¹⁸ discovered 41% of their series had been made hypocalcaemic and 9% had radiological evidence of rickets. They recommended reversion to normal diet towards the end of the first year.

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