Cardiac anomalies in Williams-Beuren syndrome

K A HALLIDIE-SMITH AND S KARAS

Royal Postgraduate Medical School, Hammersmith Hospital, London

SUMMARY We have described some of the cardiological findings in 66 patients with Williams-Beuren syndrome and analysed the two dimensional cross sectional echocardiograms in 61 of them in comparison with normal controls. Supravalvar aortic narrowing was shown in all patients examined echocardiographically and may be a useful diagnostic sign. We documented a 7.8% incidence of systemic hypertension, a 15% clinical and echocardiographic incidence of mitral valve prolapse, and a 11.6% incidence of bicuspid aortic valve.

Williams et al in 1961 reported four patients with the triad of characteristic facies, mental retardation, and supravalvar aortic stenosis.1 Subsequently, Beuren et al noted the frequent association of peripheral pulmonary stenoses.2 Although arterial stenoses have been well documented in this group of patients,3 4 intracardiac abnormalities appear to be rare. The object of this study was to make a general clinical cardiological survey of a number of patients with Williams-Beuren syndrome, with regard to the incidence of intracardiac abnormalities and systemic hypertension and with particular reference to the incidence of supravalvar aortic stenosis using two dimensional sector scanning and pulsed Doppler studies of the aortic root. Arterial stenoses were neither documented nor examined. For the purposes of the study we did not differentiate between patients thought to have Williams-Beuren syndrome and those thought to have Fanconi type hypercalcaemia5 as there was no good evidence to suggest a disparity in cardiac findings between the two groups.

Patients and methods

We performed a cardiological examination on a total of 66 patients (31 male, 35 female) aged 8 months to 29 years (mean 9.8 years). Twenty patients were over 16 years of age. Most of these patients were members of the Infantile Hypercalcaemia Foundation, which has been previously reported, and we made no distinction into which of the two subgroups they had been entered.6 Their selection depended on the parents’ willingness to bring their children for examination. Indeed, 18 of the volunteers were thought to have completely normal hearts. Arm and foot pulses were felt and compared and the blood pressures were measured in both arms in the sitting position by two independent observers. The systolic and diastolic pressures were plotted on centile charts7 using the same criteria as in a previously reported series.6 A chest radiograph was taken and 12 lead electrocardiogram recorded. Routine cross sectional echocardiographic studies were carried out using an Advanced Technology Laboratories Mark 100 and 600 echocardiograph with the latter having adaptive pulse wave Doppler facility; 3.5 MHz and 5 MHz transducers were used. Recordings were made in standard echocardiographic planes with the patient either in the supine or 30º left lateral decubitus position. Special emphasis was made on recording the high parasternal long axis view and suprasternal view in order to visualise the aortic root and ascending aorta. Measurements of the internal diameter of the aorta were made in end diastole at the aortic annulus (D1), the sinotubular junction (D2), and distal ascending aorta (D3) (fig 1). The flow patterns were studied at these sites. Identical recordings and measurements were made on 66 normal age matched controls. Anatomical clarification of aortic root abnormality was related to the previously described types—namely, hourglass or segmental, tubular hypoplastic, and membranous supravalvar diaphragm.8 Routine pulsed Doppler flow was made with particular reference to D2 and D3.

Results

Altogether 66 patients were examined: of these seven had had previous cardiac surgery; four had had surgical relief of supravalvar aortic stenosis, one relief of pulmonary valve stenosis, one resection of thoracic coarctation of the aorta, and one closure of
a secundum atrial septal defect. In the particular group of children who volunteered for this study there were no patients awaiting surgery for relief of supravalvar aortic stenosis, and of the seven patients who had had no surgical intervention but had been catheterised, the maximum supravalvar aortic gradient measured was 20 mm Hg. These seven patients had normal electrocardiograms, as did all the other patients who had not had surgery and had no other congenital cardiac defect. In three patients there were no abnormal auscultatory findings. The other 63 patients had systolic murmurs heard bilaterally in the neck, often loudest on the right side. The intensity varied from soft to loud. Eight of these 63 patients (13%) had widespread bilateral systolic murmurs, thought to be due to peripheral pulmonary stenoses. Ten patients (16%) had clinical signs thought to be those of mild mitral incompetence with a click, murmur, or both. One patient had signs indicating pulmonary valve stenosis and a small ventricular septal defect. A further patient had abdominal bruits and had a proven abdominal coarctation of the aorta.

Blood pressure recordings of two observers were compared and when both were definitely taken with the patient at rest, the higher recording was tabulated. In four cases the systolic blood pressure in the right arm was greater than 20 mm above that in the left and the higher reading was charted. Using the criteria of systolic and diastolic blood pressures of over the 95th centile as representing hypertension, which have been previously adopted, we found five patients to be hypertensive (8%). An additional four patients had systolic hypertension. A further three patients had systolic blood pressures at the 90th centile. Of the 12 patients with blood pressures of the 90th centile and above there were nine males and three females. Five patients were over 16 years of age and seven under 16 years of age. Three of the five adult patients had had previous aortic root surgery. One of the children had had aortic root surgery and one relief of thoracic coarctation of aorta; a third had abdominal coarctation of aorta.

**CROSS SECTIONAL ECHOCARDIOGRAPHY**

Many of the patients were hyperactive and five of the 66 recordings could not be completely analysed. The aortic root recordings of the four patients who had had aortic root surgery were excluded from analysis of this structure. Detailed measurements of the aortic root were possible in 57 patients and pulsed Doppler studies were possible in the same number of patients.

Of the 61 recordings, nine (15%) showed mitral valve cusp prolapse— in seven cases prolapse was confined to the anterior cusp and in two both cusps were affected. A small perimembranous ventricular septal defect was shown in one patient, who also had pulmonary valve stenosis. A bicuspid aortic valve was shown in seven patients (11%). Peripheral pulmonary arterial stenoses was shown in only the two patients with proximal branch stenoses.

The 57 aortic root measurements showed a significant narrowing at the sinotubular junction as compared with the aortic annulus (p<0.001) in the patients as compared with the aged matched controls. The internal and diastolic measurements of aortic annulus (D1) in the patients was from 11 mm to 21 mm and the same measured in the control series was between 10 mm and 24 mm (fig 1). Measurement of the sinotubular junction (D2) was recorded between 7 mm and 18 mm in the patients and between 12 mm and 24 mm in the controls (fig 2). The ratio of these two measurements varied between 57% and 90% in the patients and 90% and 120% in the controls (fig 2). In all the patients the measurement of D2 was less than D1 but in none of the controls. In 15 patients the sinuses of Valsalva appeared definitely abnormal. Two categories of aortic root abnormality were detected, namely an hourglass constriction in 51 patients (fig 3) and tubular hypoplasia in six patients.

Pulsed Doppler studies showed dispersion of laminar flow in 48 out of 57 cases at D2 and D3 level (fig 4). Significant flow turbulence was noted in all cases in which the D1:D2 ratio was 70% and less. The measured narrowing at the sinotubular junction and abnormal flow patterns varied with the intensity
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Fig 2 Graph plotting ratio of sinotubular junction to aortic annulus (D2:D1). Patients = ●; controls = △.

Fig 3 Two dimensional scan. Parasternal long axis view of patient with hourglass type of supravalvar aortic stenosis. LA = left atrium; LV = left ventricle; MV = mitral valve; AV = aortic valve; AA = aortic annulus (D1); STJ = sinotubular junction (D2). D1 = 1.7 cm and D2 = 1.3 cm (ratio 76.5%).

of the systolic murmurs recorded, so that the louder murmurs were associated with the greater sinotubular narrowing and the most obviously turbulent flow patterns.

Discussion

Accurate non-invasive measurements of children's blood pressures are notoriously difficult to obtain and the group of children and young adults under survey were particularly fidgety. There is a considerable individual variation in children's blood pressures and this may be a factor determining the lower incidence of hypertension in this series compared with the series previously reported where many of the same patients were studied. Hypertension is well described in Williams syndrome, however, and it is often thought to be due to renal failure secondary to hypercalcaemic nephrocalcinosis or to unknown causes. Attention has been drawn to the peripheral vascular anomalies coexisting in this syndrome and it has been suggested that hypertension may be related to such anomalies relating to the descending aorta and renal arteries. Our findings support this view as three out of our four patients who had aortic root surgery were hypertensive, and it would seem reasonable to suppose that these patients with severe supravalvar aortic narrowing had other established arterial anomalies. Additionally, we found our patients with abdominal coarctation of the aorta and postoperative thoracic coarctation of the aorta to be hypertensive.

M mode echocardiography of a case of supravalvar aortic stenosis was first reported in 1974. Cross sectional two dimensional scanning, however, can give more precise definition of changes in aortic diameter and the exact location and extent of the stenosis. Measurements of aortic root determined in this way compare accurately with angiographic measurements. Using an M mode echocardiogram
derived from the sector scan, calculations of cross sectional area at D1 and D2 can be made and they compare accurately with catheter laboratory measurements of pressure differences.13 Our own findings using cross sectional echocardiography show that supravalvar aortic stenosis is a constant feature of Williams-Beuren syndrome and this may be of useful diagnostic help. Serial aortic root measurements should give adequate information concerning any progression of the supravalvar aortic stenosis in an individual patient. The Doppler recordings were made early in our experience when continuous wave Doppler was not available. The results suggest, however, that Doppler studies should be helpful in assessing severity of stenoses. Preliminary work in progress suggests that continuous wave Doppler may be used to indirectly assess the gradient.

We did not define a case of membranous supravalvar aortic stenosis in our series but confirmed the prevalence of the hourglass type, which is thought to represent thickening of the medial layer of the ascending aorta with narrowing of the corresponding segment of aorta, exaggerated by localised intimal fibrous thickening.8 Abnormalities of the aortic valve are commonly associated with supravalvar aortic stenosis, the most common variation being adhesion of all or part of the free edge of one or more cusp to the aortic intima.8 We did not suspect this in any of our patients but we did not happen to include any patients with significant stenosis in the series examined. We did, however, find an 11.6% incidence of bicuspid aortic valves. The common finding of valvar abnormalities in documented supravalvar aortic stenosis and of bicuspid valves in our patients, all of whom had some degree of supravalvar aortic stenosis, might suggest that such patients should be protected from endocarditis with appropriate antibiotics for dental extractions and other surgical procedures.

Reported studies that concern idiopathic hypercalcaemia in Williams-Beuren syndrome and Fanconi type hypercalcaemia are confusing. We feel that the nomenclature of Williams-Beuren syndrome covers our patients, even though some of them had known hypercalcaemia of infancy and some did not. There is also discussion as to the categorisation of supravalvar aortic stenosis that may occur either in sporadic or familial form in individuals of normal intelligence and appearance as well as in individuals recognisable as having Williams-Beuren syndrome.14 Review of the literature suggests that supravalvar aortic stenosis may also occur in association with facial and other features of Williams-Beuren syndrome, but normal intelligence.14-16 Again, although Williams-Beuren syndrome usually occurs sporadically, familial cases have been reported.17-20

Studies of the histology of supravalvar aortic stenosis have shown that it is common to all types. There is a localised area of disorganised media and of intimal hyperplasia covering narrowing just above the aortic sinuses (hourglass type) and long segment medial induration (hypoplastic type).8 21 It has been suggested that supravalvar aortic stenosis may be an exaggeration of the infolding immediately above the upper margins of the sinuses of Valsalva, which can often be found in normal infants.22 Ultrastructural examination of this area in recognised supravalvar aortic stenosis has shown deficiency of the ground substance and foci of excessive collagen deposition in spaces of the elastic lamina, suggesting abnormal prenatal development.23 Our own finding of supravalvar narrowing, common to all our patients, supports this hypothesis. It has been clearly shown that some newborn rabbits, whose mothers were given large doses of vitamin D, may have supravalvar aortic stenosis23 24 as well as other arterial narrowing and facial and dental abnormalities.25 Broadly, it is accepted that there is a disturbance of fetal calcium homoeostasis, but the exact mechanism and its role in the pathogenesis of supravalvar stenosis has not been exactly defined. The finding of a 15% incidence of mitral valve prolapse in our patients was surprising and has not been commented on previously, although two previous cases of mitral valve prolapse have been documented.16 26

Defective production or structure of collagen has been shown in type IV Ehlers-Danlos syndrome, Marfan’s syndrome, and other hereditary disorders in which mitral valve prolapse commonly occurs.27 28 A raised collagen III:III+1 ratio has been found in skin biopsy specimens of patients with the hypermobility syndrome and floppy mitral valve.29 An increase in collagen type III in the mitral valve tissue of patients in whom there has been mitral valve prolapse has also been shown. In such valves the collagen fibres of the lamina are disorganised.30 It has been suggested that biosynthesis of collagen evaluated by in vitro culture of skin fibroblasts with biochemical characterisation of cell products might provide further information concerning the pathogenesis of the cardiac manifestations of Williams-Beuren syndrome.21

We do not know how Williams-Beuren syndrome relates to the variable autosomal dominant trait of isolated supravalvar aortic stenosis. It has been suggested that the clinical phenotypes of Williams-Beuren syndrome and supravalvar aortic stenosis represent the ends of a range for an autosomal dominant gene defect of variable expression and
penetration.\textsuperscript{31, 32} Finally, a terminal deletion of the long arm of chromosome 4 has been reported in Williams-Beuren syndrome\textsuperscript{33} and localisation of the calcitonin gene to chromosome 11\textsuperscript{14} focuses interest as to whether there is an error in its structure. For the moment, however, the precise causative factors that determine Williams-Beuren syndrome and its cardiac manifestations, particularly supravalvar aortic stenosis as it is seemingly inseparable from this syndrome, remain tantalisingly elusive.

Dr U Balaram contributed much to this work. We should like to thank Miss Esther Fletcher, Dr A Nudazdin, and the cardiology registrar who carried out many of the echocardiographic recordings. We should also like to thank the Infantile Hypercalcaemia Foundation for its financial help and encouragement. Additionally, we are most grateful to the parents and their children who volunteered and to the children’s medical advisers for their collaboration and much valuable information.

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Correspondence to Dr KA Hallidie-Smith, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS.

Accepted 7 March 1988
Cardiac anomalies in Williams-Beuren syndrome.

K A Hallidie-Smith and S Karas

Arch Dis Child 1988 63: 809-813
doi: 10.1136/adc.63.7.809

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