CASE REPORTS

Unbalanced 13;18 translocation and Williams syndrome

A Colley, Y Thakker, H Ward, D Donnai

Abstract

A 2½ year old girl is reported with a *de novo* 13;18 unbalanced translocation and the facial features of Williams syndrome, subaortic stenosis, failure to thrive, and developmental delay. This case provides two candidate locations for the underlying molecular pathology of this sporadic syndrome. Williams syndrome is associated with intellectual and growth retardation, infantile feeding problems which may be associated with hypercalcaemia, cardiovascular abnormalities, a friendly, loquacious personality, and a typical facies. The cause is not known and only a few chromosome abnormalities have been reported in patients with the Williams syndrome phenotype. Many papers fail to mention chromosome studies. We report a girl with an unbalanced 13;18 translocation and the Williams syndrome phenotype.

Case report

The female proband was the third child of unrelated parents (maternal age 26, paternal age 30 years at the time of birth) born at 42 weeks' gestation after a normal pregnancy. The labour was complicated by meconium staining of the liquor and type 1 dips on cardiotocogram. Her Apgar scores were 8 and 10 at one and five minutes respectively, birth weight was 2780 g, and head circumference (OFC) was 33 cm. There were two cord vessels, a sacral dimple, a cardiac murmur thought to be the result of mild pulmonary stenosis, and easily dislocatable hips which were subsequently treated with splints. At the age of 10 days she was readmitted to hospital with vomiting, constipation, and jitteriness. All investigations were normal (calcium 2.5 mmol/l) except Hb 20 g/dl thought to be because of mild dehydration. She continued to be jittery and fed poorly. By the age of 3 months her weight was below the 3rd centile and she was readmitted for investigations. There was no evidence of malabsorption or infection. A subaortic stenosis with a distinct membrane below the aortic valve was seen on echocardiography. There was no cardiac decompensation and the cardiac anomaly was

not thought to be related to her failure to thrive. An abnormal karyotype was found.

At 18 months of age (fig 1) her height, weight, and OFC were all below the 3rd centile. An assessment using the Griffiths Mental Development Scales showed an overall quotient of 85, equivalent to 15 months of age. Conductive deafness owing to recurrent otitis media necessitated myringotomies and her receptive understanding of language surpassed her expressive language.

At 2½ years (fig 2) her height, weight, and OFC were still below the 3rd centile. She had blue irides without a stellate lacy pattern. There was fullness of her periorbital subcutaneous tissues, median eyebrow flare, and epicanthic folds. Her nose was small with a flat nasal bridge, her cheeks full, her philtrum long and smooth, and her mouth remained open with an everted lower lip. She was a very friendly, loquacious child who continued to make developmental progress.

CYTOGENETIC STUDIES

A karyotype was prepared from prometaphase chromosomes obtained from synchronised peripheral blood lymphocyte cultures. G banding showed the absence of one normal 13 and one normal 18, with the presence of an unbalanced derived chromosome 18 arising from a translocation between chromosome 13 and 18 (fig 3). The karyotype was interpreted as 45,XX,-13,-18,+der(18),t(13;18)(q13;q23). Both parents had normal karyotypes.

A skin sample was taken for confirmatory studies and fibroblasts were grown in cultures. Cytogenetic studies were performed on G banded chromosomes obtained from synchronised cultures. The karyotype was identical to that seen in the blood lymphocytes and there was no evidence of mosaicism in 150 cells examined.

Unfortunately, a cell line is not available from this patient.

Discussion

The proband presented the facial features and early history characteristic of Williams syndrome and she had subaortic stenosis. The characteristic cardiovascular abnormalities in patients with Williams syndrome are supravalvular aortic stenosis (SVAS) with the aortic

Department of
Medical Genetics,
St Mary's Hospital,
Manchester M13 0JH.
A Colley
Y Thakker
H Ward
D Donnai

Correspondence to
Dr Donnai.

Received 7 January 1991.
Revised version accepted
18 April 1991.

Figure 1 Patient at 18 months; note puffy infraorbital region, median eyebrow flare, small nose, and everted lower lip.

Figure 2 Patient at 2½ years; note everted lower lip, small teeth, and median eyebrow flare.

valve involved in up to 1/3 of cases, and peripheral pulmonary artery stenosis, with intracardiac anomalies described less often. This girl had a distinct subaortic membrane which although not classical may be related to haemodynamic factors in utero on the same genetic predisposition.

The proband's unbalanced chromosome translocation has resulted in loss of material from the proximal region of the long arm of chromosome 13 and the distal region of the long arm of chromosome 18. One similar case was reported by Suzuki *et al*¹ with the karyotype in lymphocytes apparently 45,XX,-13,-18,+der(18),t(13;18)(q12;q23) de novo. The 6 year old proband was severely mentally retarded with no speech and had dysmorphic features mainly attributed to the 18q deletion (small stature, microcephaly, hypertelorism, and hearing loss). However, other features present (flat nasal bridge, epicanthus, high arched palate, and hypoplastic helix) might have resulted from the 13q deletion. The published photograph of the Japanese proband did

not appear to have the characteristic facies of Williams syndrome and she had no cardiac anomalies.

There have been few other reports of monosomy for proximal 13q and these have been coupled with other chromosome abnormalities as part of translocations. Thus, a distinctive phenotype has not been recognisable. Otto *et al*² reported two first cousins with an unbalanced 13;21 translocation with monosomy for the tip of the long arm of chromosome 21. The published photographs did not show the facies of Williams syndrome, and neither mentally retarded patient had cardiovascular abnormalities. Terminal deletions of the long arm of chromosome 18 have been reported frequently but Williams syndrome has not been associated to the authors' knowledge.

The Williams syndrome phenotype may be causally heterogeneous or linked to changes at a specific chromosome locus. The reports of children with features of Williams syndrome and chromosome anomalies have been few and different chromosomes have been implicated in each case.³⁻⁷ The chromosome anomalies may be coincidental to the children's appearance or each may have produced a phenocopy.

Subjects with Williams syndrome are almost always the only affected members of their family, although affected monozygotic twins have been described.⁸ Familial cases have been reported in sibs and cousins,⁹ but these are not typical.

Recently it has been shown that genomic imprinting has important phenotypic implications. In mice uniparental disomy causes growth and activity disturbances. Since Williams syndrome children are small, developmentally delayed, and often hyperactive, and

Figure 3 Karyotype of patient from cultured lymphocytes showing the small terminal deletion of 18q and the deletion of 13pter→13q13.

45,XX,-13,-18,+der(18),t(13;18)(q13;q23)

concordant monozygotic twins have been described, this genetic mechanism is worthy of investigation. Differential imprinting of a chromosomal region could lead to differences in expression of genes concerned in calcium homeostasis.

Whether because of a submicroscopic deletion, a point mutation, or an anomaly of imprinting, for people working to delineate the genetic mechanism of Williams syndrome, this paper adds to the number of candidate chromosome locations.

- 1 Suzuki Y, Ono K, Oka S, *et al.* A case of (13q;18q) translocation with proximal 13q monosomy. *Hum Genet* 1977; **38**: 337–41.
- 2 Otto PGI, Tolewdo S, Rihien-Costa A, *et al.* Partial monosomy 13 and 21 due to a familial 13/21 translocation. *Hum Genet* 1978; **41**:243–50.
- 3 Eberle P, Beuren AJ. Chromosome studies in patients with supravalvular aortic stenosis. *Lancet* 1963; **ii**:438.
- 4 Jefferson RD, Burn J, Gaunt KL, Hunter S, Davison EV. A terminal deletion of the long arm of chromosome 4 [46,XX,del(4)(q23)] in an infant with phenotypic features of Williams syndrome. *J Med Genet* 1986; **23**:474–80.
- 5 Fryns JP, Van der Hauwaert LG, Dumoulin M, *et al.* The elfin face syndrome and the short arm of chromosome 15. *Ann Genet (Paris)* 1982; **25**:181–2.
- 6 Martin NDT, Snodgrass GJAI, Cohen RD. Idiopathic infantile hypercalcaemia – a continuing enigma. *Arch Dis Child* 1984; **59**:605–13.
- 7 Merritt AD, Palmer CG, Lune PR, *et al.* Supravalvular aortic stenosis: genetic and clinical studies. *J Lab Clin Med* 1963; **62**:995.
- 8 Wiltze HE, Goldblood RB, Antia AV, *et al.* Infantile hypercalcaemia in twins. *N Engl J Med* 1980; **275**:1157–60.
- 9 Burn J. Williams syndrome. *J Med Genet* 1986; **23**:389–95.