De novo t(X;21)(q28;q11) in a girl with phenotypic features of Williams-Beuren syndrome

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Abstract

We describe a female infant with mental retardation and some of the phenotypic features of Williams-Beuren syndrome. Chromosome analysis showed t(X;21)(q28;q11). Diagnosis, inactivation of the X chromosome, and possible involvement of the translocation breakpoints in the pathogenesis of this syndrome are discussed.

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Williams-Beuren syndrome (WBS) is characterised by peculiar facial features, mental retardation, hypercalcaemia, and supraaortic stenosis (SVAS) or peripheral pulmonary artery stenosis.^{1,2} However, cardiovascular features and hypercalcaemia are not always present.³⁻⁵

To our knowledge, four chromosomal abnormalities have been described in WBS: de novo t(12;15)(p11;p11) by Fryns *et al*,⁶ del(4)(q33) by Jefferson *et al*,⁷ del(15)(q11q12) by Kaplan *et al*,⁸ and del(6)(q22.2q23) by Bzduch and Lukacova.⁹

A de novo t(X;21)(q28;q11) unbalanced translocation in a girl with mental retardation and some of the phenotypic features of WBS is described, and the involvement of the deleted segments, Xq28→qter and 21pter→q11, in the pathogenesis of this incomplete form of WBS is discussed.

Case report

The female proband was born on 30.1.89 to a 34 year old gravida 1 and her 34 year old husband. Before this pregnancy, the mother had been treated for three years with oestrogen and progesterone for sterility. The pregnancy was complicated by untreated mild systemic arterial hypertension. Delivery was at 38 weeks' gestation. Birth weight and head circumference were 2300 g and 33.5 cm respectively.

At 27 months, the proband showed delayed psychomotor development without motor deficit: she could stand, but did not walk or speak. She had an irritable but friendly and outgoing personality and moderate mental retardation (IQ = 70, Brunet-Lézine scale). The child showed hypotrophy and tonus modifications with limb hypotonia, axial hypertonia, and episodic axial stiffness with sweating but no seizures. Physical examination (fig 1, table

showed dolichocephaly and a prominent occiput. The face was asymmetrical with full cheeks, high and broad forehead, retrognathia, hypertelorism, and strabismus. Ophthalmological examination found increased papillary excavation in the right eye and a small colobomatous abnormality in the left eye. There was no stellate pattern of the iris. The ears were low set with prominent antihelix and small tragus. The nose was short with a depressed nasal bridge, full tip, and anteverted nostrils. The hands and feet showed many abnormalities including tapered fingers in permanent flexion, small nails with hypoplasia of the third phalanx of the left fifth finger, and clinodactyly of the right third, fourth, and fifth toes. The external genitalia were normal in appearance.

The question of ruling out the diagnosis in patients with some features of the syndrome led Preus⁴ to describe a 'diagnostic index for Williams syndrome' for those patients who might be suspected of having the syndrome. The mean (SD) of the WBS total score distribution was +7.18(3.17). In our case, the score was +4.09.

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Figure 1 Face of the proband.

Clinical features of the patient

Performance	Short stature Hypotrophy Limb hypotonia Axial hypertonia
Craniofacial	Dolichocephaly Prominent occiput Facial asymmetry Full cheeks High and broad forehead Temporal depression Malar flattening Retrognathia Short neck
Eyes	Hypertelorism Downward slanting palpebral fissures Epicanthus Strabismus Colobomatous abnormality Blue eyes
Ears	Low set Prominent antihelix Small tragus
Nose	Short Depressed nasal bridge Full tip Anteverted nostrils
Mouth	Long philtrum Wide and open mouth Small and spaced teeth
Hands	Tapered fingers in permanent flexion Ungual hypoplasia Joint stiffness Hypoplasia and permanent flexion of 3rd phalanx of the left 5th finger
Feet	Clinodactyly of right 3rd, 4th, and 5th toes
Others	Horseshoe kidneys Sacrococcygeal dimple

CYTOGENETIC FINDINGS

Lymphocytes were cultured according to a standard method.¹⁰ Banding patterns were analysed using the RHG technique according to Dutrillaux and Lejeune,¹⁰ the CBG technique according to Sumner,¹¹ and the RTBG technique according to Viegas-Pequignot and Dutrillaux.¹²

Chromosome analysis showed a 45,X,-21,der(X)t(X;21)(q28;q11) chromosome complement with RHG and RTBG banding on peripheral blood cultures. Thus, the patient is deleted for segment Xq28→qter and segment 21pter→q11. Cytogenetic investigation of the parents showed that the father and the mother had normal karyotypes. X replication studies were carried out on the child's lymphocytes using the RTBG technique. In 51 mitoses observed, the child's der(X) chromosome was late replicating with the exception of the translocated portion of chromosome 21, which replicated earlier than any other part of the der(X) chromosome and at the same time as the autosomes when observed by the BrdU technique (fig 2). The CBG technique showed a single centromere on the der(X) chromosome.

A cell line from this patient is banked in our department.

LABORATORY EXAMINATIONS

Electrocardiogram and cardiac ultrasound documented a normal heart without any functional abnormality. Calcaemia was normal at 17 months (2.33 mmol/l, normal = 2.45 ± 0.25). Superoxide dismutase (SOD), glucose-6-phosphate dehydrogenase (G6PD), and hypoxanthine phosphoribosyl transferase

(HPRT) enzyme activities were measured to detect gene dosage effects. The copper-superoxide dismutase (Cu-SOD) assays were done on erythrocytes according to the method of Beauchamp and Fridovich,¹³ modified by Sinet *et al.*¹⁴ This enzyme activity was diminished by 30% at 0.99 U/mg Hb (normal = 1.47 ± 0.14), and the G6PD assay was increased by 19% at 15.7 U/I (normal = 10.7 ± 2.5). HPRT was 1.87 nmol (normal = 2.09 ± 0.37).

Radiographs exhibited several skeletal abnormalities including asymmetry and dislocation of the left hip with femoral head dysplasia and absence of the third phalanx of the left fifth finger.

CT and MRI scans showed slightly enlarged ventricles with mild asymmetry of the sylvian fissure. EEG showed asymmetrical activity with rare tempororolandic spikes and slow waves on the right side. Abdominal ultrasound showed horseshoe kidneys. Results of routine blood and urine analyses were normal.

Discussion

The choice of the inactive X in cases of X; autosome translocations has been discussed by many authors in recent years.¹⁵⁻¹⁷ In the majority of cases, the late replicating X is the normal one. The replication pattern is similar to those which lead to minimal genetic imbalance, in the hypothesis of a close relationship between late replication and gene inactivation. Our patient is structurally monosomic for the segment Xq28→Xqter. If the normal X were inactive, she should be functionally nullisomic for this segment of the chromosome. If the full der(X) were inactive, she should be genetically monosomic for chromosome 21. However, we observed that the late replication of the der(X) is not associated with complete inactivation, especially in the translocated chromosome 21 (fig 2). This appears to be the less deleterious situation for the patient, even at the risk of spreading the inactivation to the translocated segment of chromosome 21 in a certain percentage of the cells.

Two deleted segments and two breakpoints are involved in this case. The CBG technique (fig 2) showed only one centromere on the der(X) chromosome. Cu-SOD was diminished by 30%. This could be because of partial inactivation of the SOD gene by spreading of the late replication of the der(X) chromosome. If cytogenetic evidence of late replication is considered indicative of genetic inactivation, then the proband may be partially monosomic for 21pter→q11 as a result of spreading of the inactivation of genes to the translocated segment of chromosome 21 in a certain percentage of cells.

On the other hand, two enzymes, located at Xq26 for HPRT and at Xq28 for G6PD, showed different levels. Only G6PD activity was increased by 19%. This suggests the partial activation of the G6PD gene by spreading of the early replication of the translocated segment of chromosome 21 on der(X). Thus, the breakpoint on the der(X) could be between Xq28 and Xqter.

Figure 2 Chromosomes involved in the translocation.

Although the proband does not have a full blown form of WBS, many phenotypic features are present: peculiar face, irritable but friendly, outgoing personality, mental and growth retardation, characteristic dental malformations, and several skeletal, tone, and kidney abnormalities. In addition, the diagnostic index for WBS of Preus⁴ is positive. However, cardiovascular features, hypercalcaemia, and lacy or stellate pattern of the iris are absent. Generally, in this syndrome cardiovascular features are present in 3/4 of cases³⁻⁵ and in some cases they appear progressively.³ Lacy or stellate pattern of the iris was found in 51% of cases.¹⁸ Hypercalcaemia is always transient.³⁻⁵ For many authors, WBS is characterised by a distinctive facies and habitus and by psychomotor retardation,^{3,4,19} all features present in our patient. We conclude that this case is an incomplete form of WBS.

The patient also shows some features of monosomy 21 including high forehead, depressed nasal bridge with bulbous tip, long philtrum, low set ears, short neck, joint stiffness, finger abnormalities, skeletal abnormalities such as hip dislocation, renal and cerebral abnormalities, mild mental retardation, and abnormalities of tone. Some of these features are common to WBS.

This patient is the first case of WBS reported with an unbalanced $t(X;21)$. In the great majority of cases, WBS is a sporadic event of unknown cause. However, some familial cases have been reported.²⁰ Findings are compatible with X linked dominant,²⁰ autosomal dominant,²¹ or multifactorial inheritance. Our case raises the question of the involvement of the breakpoints on der(X) and der(21) chromosomes in the pathogenesis of this syndrome.

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