

Revista de Psiquiatría y Salud Mental

www.elsevier.es/ saludmental



SHORT ORIGINAL ARTICLE

X tetrasomy (48,XXXX karyotype) in a girl with altered behaviour

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Received February 8, 2010; accepted March 31, 2010

KEYWORDS

X-tetrasomy;
Mental retardation;
Karyotype;
Altered behaviour

PALABRAS CLAVE

Tetrasomía X;
Retraso mental;
Cariotipo;
Alteración de conducta

Abstract

Introduction: We report the case of a 14-year-old girl with mental retardation and dysmorphic features referred to child psychiatry because of altered behaviour at school.

Material and methods: Karyotyping (GTG banding), in situ fluorescent hybridisation (FISH) and molecular study of parental origin by polymorphic STS were performed.

Results: Genetic study revealed a 48,XXXX karyotype with a maternal origin of the X-tetrasomy. The mechanism was successive non-dysjunction at meiosis I and II.

Conclusions: The interest of this case lies in the rarity of the chromosomal anomaly and its late diagnosis, leading to a failure to adapt the girl's education to her needs, with consequences for her psyche.

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Tetrasomía X (cariotipo 48,XXXX) en una niña con trastorno de conducta

Resumen

Introducción: Adolescente de 14 años con retraso mental y rasgos dismórficos, derivada a psiquiatría infantil por alteraciones de conducta en el medio escolar.

Material y métodos: Cariotipo (bandas GTG), hibridación in situ fluorescente (FISH), estudio molecular del origen parental mediante STS polimórficos.

Resultados: El estudio genético reveló un cariotipo 48,XXXX, con un origen materno de la tetrasomía X por no-disyunción sucesiva en meiosis I y II.

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Conclusiones: El interés del caso reside en la rareza de la alteración cromosómica y en su diagnóstico tardío, lo cual impidió una adecuación de las necesidades educativas con la consiguiente repercusión en el psiquismo de la niña.
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Abnormalities in the number of sex chromosomes occur in 1 in 400 births. The most common karyotypes are 47,XXX, 47,XXY, 47,XYY, and 45,X, and there is a lot of information about them in the specialised literature.¹ However, the same is not true for other polysomies. Around 50 cases of the 48,XXXX karyotype have been reported,²⁻⁴ this being a very heterogeneous phenotype. Few of these reports study the patient's behaviour,^{3,5} or detect the parental origin of the polysomy.^{4,6-9}

Case report

A 14-year-old who was in conflict with her peers and teachers (negative attitude, aggression) making her time at school difficult. At home, she was defiant and aggressive towards her pets and younger siblings.

History of psychological problems and previous consultations

At 9 years of age, due to learning difficulties at school she was given an adapted curriculum and began to attend the support classroom. At present, she is in the 2nd year of Spanish secondary education, but her level is that of a child in the first year of primary school.

Since she was 10 she has had a disability of 33% due to slight mental retardation, but her parents provided no medical report of a previous assessment.

Mental state

She is an adolescent with a slim physique. She maintained eye contact. In the first few interviews she had a negative attitude, not responding verbally and looked to her mother to respond for her. She was able to be alone without feeling distress and/or fear, and performs childish activities when alone. When asked her age, she responded by raising and counting with her fingers. The psychopathological examination was impeded by her language limitations, although she was never mistrustful, and thought content disorders were not suspected. Her diction was poor, with levels of expression and comprehension below those appropriate for her age. After doing a free drawing (fig. 1), she created a story with a paucity of ideas, in accordance with a mental age below her chronological age. There were no symptoms of depression.

Interviews with her parents revealed an interest in childish activities and a preference for playing with younger children. Repetitive behaviour was not described.

Personal history

Her mother gave birth to her naturally at 42 weeks, and she weighed 3.3kg. It was the first pregnancy of a young, non blood-related couple (father: 22 years; mother: 23 years). She began walking at 2 years and said her first words at 2 years of age. She has a limited vocabulary for her chronological age, only forming simple sentences. Anal sphincter control at 2 years of age and daytime urinary control at 4, with persistent primary nocturnal enuresis. Regarding her social development, she mixed with younger children. Between 7 and 8 years of age, oppositional and negative behaviour were described at school; this hindered learning and became worse with age. She can eat without help, but her personal hygiene requires supervision. Outside of the family environment she does not perform activities independently.

Psychological examination

This was performed using the WISC-R, and the Inventory for Client and Agency Planning (ICAP) to assess adaptability. Her intelligence quotient is 40 (VIQ 44, MIQ 44). Oral communication: understands simple instructions and gets the gist of simple texts, having difficulties with abstract concepts. Syllabic reading with comprehension problems. She can count to 100, and recognise concepts such as up, down, in, out, near and far. Her coordination is limited with regard to body-mind integration.



Figure 1 Pictures drawn by the patient at different stages of the treatment.

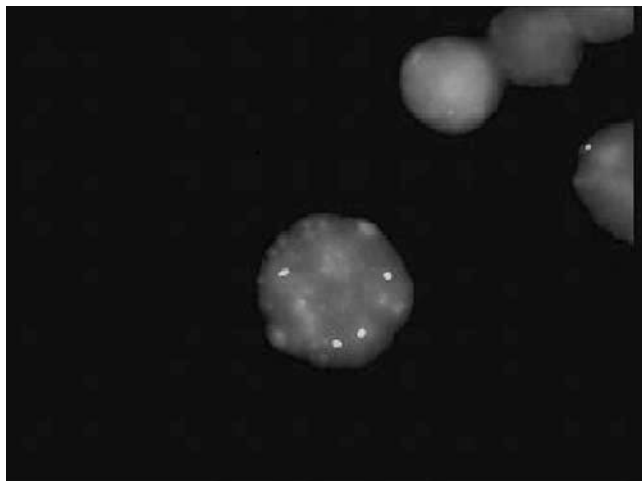


Figure 2 Hybrid interphase nucleus with centromeric probe for X chromosome, showing 4 hybridisation signals.

Physical examination

Weight: 53.4kg (P61); height 1.58m (P50); head circumference: 53.5cm (-0.4 SDS); body mass index: 22kg/m²; Shukla nutritional index: 105%.

She had a notably inexpressive facies with mild epicanthus, an ogival palate, and poor tooth enamel. Normal blood and hormone biochemistry, and haematology profile. An MRI scan revealed marked dilation of the lateral ventricles. Electro-encephalogram was normal. Normal female external genitalia (Tanner: S4, P4).

Genetic study

Karyotyping (GTG banding) showed a 48,XXXX karyotype. This was confirmed with fluorescent in situ hybridisation (FISH) using a centromeric probe for the X chromosome in interphase and metaphase nuclei (fig. 2).

To study the origin of the X polysomy, an analysis was performed of the polymorphic markers on the X chromosome (X22, DXS15, DXS48, and DXS1073) in the patient and her parents. The patient's allele pattern was identical to her mother's (X22: 200/209; DXS15: 128/130; DXS48: 99/101; DXS1073: 126/139), and no paternal allele was found. The allele pattern and the intensity of the electrophoretic peaks showed the polysomy was maternal in origin due to successive non-disjunction at meiosis I and II.

Evolution and treatment

Treatment with risperidone (1.5mg/day) was begun, observing improved behaviour. She began to attend a centre for children with disabilities, leading to improvements in behaviour. She remained rather defiant in her family environment, partly caused by a lack of clear and definite rules.

Comments

The phenotype of the 48,XXXX chromosome is extraordinarily variable, with no pathognomonic characteristics.

Chromosome studies are generally recommended due to mental retardation (present in all cases to varying degrees) and non-specific dysmorphic features. However, as these patients' behaviour is not described, it is impossible to establish a common pattern. However, in the 2 cases with detailed descriptions,^{5,10} and in our patient, social integration problems were notable, as well as socially inappropriate and even aggressive behaviour. Despite the limited number of descriptions, the similarity between the cases suggests that the behaviour alterations could imply a characteristic phenotypical feature of the X tetrasomy.

Performing a review of molecular studies of the origin of the X tetrasomy, we found 21 cases including our own (15 with 49,XXXXY karyotype; 6 with 48,XXXX karyotype). In the cases with the 49,XXXXY karyotype, the X chromosomes were maternal in origin and in 2 homologous pairs (due to a successive non-disjunction at meiosis I and II). In cases with the 48,XXXX karyotype we found different mechanisms, the most common being the father providing one X chromosome and the mother 3, normally 2 the same and one different (caused by non-disjunction at meiosis I). Our case is the second to be reported in which the 4 X chromosomes are maternal in origin and in 2 homologous pairs (as in the 49,XXXXY cases), implying not only a double successive maternal non-disjunction at meiosis, but also, the sperm must have been nullisomic for sex chromosomes. As has been described for triple X syndrome, the most common cause of meiotic non-disjunction of the X chromosomes is absent recombination and, therefore, the formation of achiasmatic tetrads, incompatible with normal chromosome segregation.¹¹ This mechanism has no connection with the mother's age.

In our opinion, the presence of any degree of mental retardation together with dysmorphic features and antisocial or aggressive behaviour would make it recommendable to carry out a chromosome study to rule out X chromosome polysomy. We believe that with this type of patients it is essential to include a detailed psychological description to enable comparative studies to be performed and thus improve our knowledge of this phenotype.

Conflict of interests

The authors affirm that they have no conflict of interests.

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