PRECOCIOUS PUBERTY ASSOCIATED WITH PARTIAL TRISOMY 18q AND MONOSOMY 11q

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Summary: Precocious puberty associated with partial trisomy 18q and monosomy 11q: We report a 10-years-old female patient with a partial trisomy 18q and monosomy 11q due to a maternal translocation. The phenotype of our proband is partially common with Jacobsen syndrome and duplication 18q but she has also some atypical anomalies such as precocious puberty, a retinal albinism and hypermetropia. Based on cytogenetics and FISH analysis, the karyotype of the proband was 46,XX,der(11)(11;18)(q24;q13). To the best of our knowledge, this is the first report of precocious puberty associated with either dup(18q) or del(11q) syndromes.

Key-words: Central precocious puberty – Partial trisomy 18q – Monosomy 11q – Maternal translocation.

INTRODUCTION

Clinical and cytogenetic characterization of partial trisomy 18q and monosomy 11q have been well documented (7, 4). However, to our knowledge, this is the first report of a combined partial trisomy 18q and monosomy 11q associated with idiopathic central precocious puberty (CPP).

CASE REPORT

The girl was first referred at 33 months of age for genetic evaluation of developmental delay. She was born to non-consanguineous Caucasian parents at 42 weeks of pregnancy. She is the first child of healthy parents. At her birth, the mother and father were 28 and 26-years-old, respectively. Her birth weight was 2150 g (10th percentile), birth length 43 cm (10th percentile) and head circumference 33 cm (25th percentile). There was nothing remarkable during her neonatal period, and no dysmorphic anomaly is mentioned in the records. At 18 months, failure to thrive and developmental delay became obvious. On examination at 33 months, the weight was 10 kg (<3rd percentile), length 81 cm (<3rd percentile), and head circumference was 47 cm (<3rd percentile). She had hypoplasia of the outer part of the eyebrows, trigonocephaly, epi-
canthic folds, mongoloid slant of the palpebral fissures, hypertelorism, broad mouth, long philtrum, upturned and short nose, micrognathia, early eruption and malalignment of teeth with multiple dental caries, low-set malformed ears, short neck, brachydactyly with hyperlaxity of fingers, pectus excavatum, and flat feet (Fig. 1a,b,c,d). She had no cardiac, no renal defects nor hepatosplenomegaly. She had normal female genitalia. At 9.3 years, an idiopathic central precocious puberty (CPP) was diagnosed, according to the method of Tanner and hormone

*Figure 1*: Dysmorphic features of the proband characterized by pectus excavatum and dental caries (A), micrognathia with short neck (B), brachydactyly (C) and trigonocephaly with short stature at 33 months of age (D).
profiles. The GnRH stimulation test induced pubertal gonadotropin responses (basal luteinizing hormone [LH], 3.0 mIU/ml, and peak LH, 14.7 mIU/ml at 30 min; basal follicle-stimulating hormone [FSH], 8.2 mIU/ml, and peak FSH, 19.9 mIU/ml at 60 min) leading to a diagnosis of CPP. The proband has reached pubertal Tanner stage V at 9.3 years of age, with an important development of breasts. She had menarche at that age, axillary and pubic hair. A suppressive treatment of puberty with a gonadotropin-releasing hormone agonist (GnRHa) was administered. She presented also psychomotor and mental retardation (WPPSI-R test). At 9 years of age her weight was 26 kg (-0.6 SD) and her height was 117.4 cm (-2.5 SD). Her head circumference was disproportionately large at the third percentile. Electrocardiogram (ECG), electroencephalogram (EEG), skeletal X-rays, renal investigations, haematological and thyroid analyses were normal. Brain computed tomography (CT) and magnetic resonance imaging (MRI) confirmed trigonocephaly, but were otherwise normal. However, the ophthalmological evaluation revealed a severe hypermetropia associated with a retinal albinism for which corrective lenses were prescribed.

**MATERIAL AND METHODS**

**CYTOGENETIC ANALYSIS**

Standard karyotype was performed on G-banded metaphases spreads prepared from peripheral blood cells by conventional protocols. We used 500 resolution’s level for banding characterization.

**FLUORESCENCE IN SITU HYBRIDIZATION**

Fluorescence in situ hybridization analysis (FISH) was performed on metaphases from the maternal blood sample. Hybridizations were done according to the manufacturer’s recommendations. The BCL2-specific probe (LSI BCL2 Spectrum Orange probe, Vysis, Downers Grove, IL, USA) is normally used for the detection of the translocation t(14;18)(q32;q21) associated with follicular lymphomas. The MLL-specific probe (LSI MLL Dual Color break apart Probe, Vysis, Downers Grove, IL, USA) hybridized to 11q23 band and consists of one centromeric (green) and telomeric (red) probes. It identifies rearrangement of the MLL region in leukemic cells. The telomeric probe of the chromosome 11 (TelVysion 11p and 11q, Vysis, Downers Grove, IL, USA) consists of one p arm specific probe (green) and one q arm specific probe (red).
RESULTS

CYTOGENETIC RESULTS

Cytogenetic examination was performed on peripheral blood lymphocyte culture using G-banding technique. A standard karyotype showed 46,XX,der(11) (Fig. 2). The mother was found to be the carrier of a balanced translocation between chromosome 11 and chromosome 18: 46,XX,t(11;18) (Fig. 3). Fluorescence in situ hybridization analysis (FISH) on maternal blood sample, was performed to define the breakpoints of this chromosomal rearrangement. Firstly, we used BCL2-specific probe which mapped to 18q21 band. One signal was localized on the normal chromosome 18 and the second one was present on the abnormal chromosome 11. We concluded that the breakpoint on 18q arm was more proximal than the q21 band and was localized on 18q13 band (Fig. 4). Secondly, FISH was performed with the MLL-specific probe mapping to 11q23 locus. The signals were present on two chromosomes 11, showing that the breakpoint on 11q arm was more distal than the q23 band and was localized on 11q24 band (Fig. 5). In order to confirm the reciprocal character of the translocation, we performed FISH analysis on chromosome 11 telomeres. Using the specific telomeric paint probe, the red signal corresponding to the long arm of chromosome 11 was present on derivative chromosome 18 (Fig. 6). Therefore, the karyotype of our proband was established; 46,XX, der(11)t(11;18)(q24;q13)mat, thus corresponding to a partial trisomy of chromosome 18 extended between q13 band to qter and a partial deletion of chromosome 11 extended between q24 band to qter.
Figure 4: FISH using the BCL2-18q21 probe. The signal is absent on 18q and present on der(11): the breakpoint on 18q is more proximal than q21 and is localized in q13.

Figure 5: FISH using the MLL-11q23 probe (green, red and yellow fusion signals). The signal is present on der(11) and not 18q-, the breakpoint on 11q is more distal than the band q23 and is localized in 11q24.

Figure 6: FISH using a specific chromosome 11 telomeric probe: the tel 11q is absent on der (11) and on der(18) showing a reciprocal translocation 46,XX,der(11)t(11;18).
DISCUSSION

The dysmorphic aspects described in our patient resemble partially to those observed in the Jacobsen syndrome characterized by partial 11q23 deletion, and to those described in partial trisomy 18 (duplication 18q). As shown by karyotype and FISH analyses, the present case has a combination of genotype and phenotype correlations of trisomy 18q13-pter and monosomy 11q24-pter. However, the presence of idiopathic central precocious puberty (CPP) has not been reported in association with these chromosomal aberrations. The CPP is the premature onset of puberty caused by precocious activation of gonadotropin-releasing hormone (GnRH) neurons in the hypothalamic-pituitary-gonadal (HPG) axis. It accounts for 80% of patients with precocious puberty and is more frequent in girls than in boys (11, 3). Most cases of CPP are idiopathic, whereas an underlying central nervous system (CNS) pathology is diagnosed only in a minority of patients.

In the literature, several chromosomal aberrations associated with the CPP have been reported. Grosso et al. 2001 (8), described a CPP in three girls with duplication of 15 (inv dup[15] chromosome) associated with mental retardation, epilepsy and structural malformations. A maternal uniparental disomy of chromosome 14 (matUPD[14]) was also demonstrated in a patient by haplotype analysis of chromosome 14, showing that the CPP is one of the features caused by mat UPD(14) (11). It has been shown that the matUPD(14) should be considered in the differential diagnosis of CPP associated with characteristic dysmorphism and features frequently described in matUPD(14).

Our patient associates the CPP with mental retardation. A correlation between the chromosomal aberrations in Jacobsen and duplication 18q syndromes, with dysmorphic features and mental retardation, has been suggested by large-scale studies (1, 5, 6, 9, 10). Moreover, the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) responses to gonadotropin-releasing hormone (GnRH) could have hypothalamic-pituitary effects in mental retardation. In a cohort of 56 girls with CPP and mental retardation, it has been shown that the mental retardation is related to an impaired response of the FSH-secreting pituitary cells to their appropriate stimulus; and this feature is present only in the initial pubertal stages, whereas it disappears during sexual development (2). Therefore, it is possible that the chromosomal aberrations observed in this patient are responsible for an important disregulation in CNS development leading to mental retardation and CPP.

In conclusion, our observations confirm that cytogenetic analyses in patients in whom idiopathic CPP is associated with dysmorphic features and mental retardation are mandatory. We described these chro-
mosomes abnormalities, characterized by fluorescent in situ hybridization (FISH) in this proband. We concluded that this rare chromosome abnormality is due to the malsegregation of a maternal balanced translocation between chromosome 18 and chromosome 11. This patient was treated for that precocious puberty. To our knowledge, this is the first report of the idiopathic CPP associated with monosomy 11q and partial trisomy 18q.

ACKNOWLEDGEMENTS

We would like to thank all the members of the Cytogenetic laboratory who have contributed to these investigations. This work was supported by the Center for Human Genetics CHU Liège, Belgium.

REFERENCES


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