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CASE REPORTS

A Rare Chromosomal Disorder – Isochromosome 18p Syndrome

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ABSTRACT

Background: *Tetrasomy 18p is a very rare chromosomal disorder and is the result of a spontaneous mutation early in embryonic development in most of the cases. This condition is characterised by the presence of a supernumerary 18p isochromosome (i(18p)) in all or some cells of the affected individual. It has a prevalence of 1/180000 live births and affects both genders equally.*

Materials and methods: *In this paper we report a de novo tetrasomy 18p in a 3 months old female dysmorphic child. The clinical features were distinctive with a particular facies, strabismus, microcephaly, growth delay, neonatal hypertonia and talipes varus. An additional small metacentric marker chromosome has been identified after standard cytogenetic analysis, without recognized parental origin of the supplementary genetic material. The child's parents were also tested and their karyotype results were normal. The characterization of the marker chromosome was performed in our genetics laboratory using conventional cytogenetic methods and Fluorescence in Situ Hybridization (FISH) analysis. Also, our patient was compared with other published cases with the same diagnosis.*

Conclusion: *Cytogenetic investigation is an essential step towards the accurate diagnosis of individuals with clinical suspicion of a genetic anomaly. Also, this type of investigation could offer critical information to the practitioner for prognosis of patient and the correct appreciation of the recurrence risk of a certain genetic condition.*

With current advances in preventive and interventional procedures, patients with rare chromosomal disorders can live longer. Therefore, proper medical and behavioural management of each case is important for the enhancement of the quality of life for the patients and their families.

Keywords: rare disease, isochromosome 18p, karyotype, FISH, genetic counseling

INTRODUCTION

Isochromosomes are supernumerary marker chromosomes made up of two copies of the same arm of a chromosome. The presence of an isochromosome in addition to the normal chromosome pair leads to a tetrasomy of the arm involved. The accurate description of such a marker chromosome using only conventional cytogenetic techniques is often difficult, therefore molecular investigations such as FISH (Fluorescence in Situ Hybridization), MLPA (Multiplex Ligation-dependent Probe Amplification), CGH (Comparative

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Genomic Hybridization) are needed for a proper diagnosis.

The existence of a supernumerary isochromome 18p resulting in tetrasomy 18p is associated with moderate to severe mental retardation, microcephaly, hypertonia, typical dysmorphic features and other anomalies. This type of isochromosome appears to be one of the commonest isochromosomes observed in humans (1) with a frequency of 1:180000 liveborn children (2), affecting males and females equally. The majority of reported cases of i(18p) seem to be a result of *de novo* events, although familial cases have been described (3,4). For most of the familial cases of tetrasomy 18p, the i(18p) was found to be of maternal origin (1,5), maternal age being considered a risk factor (1).

In this paper we present the case of a 3 months old female patient carrying a *de novo* supernumerary i(18p), showing typical features for tetrasomy 18p syndrome. ❑

CASE REPORT

Clinical features

The infant was referred to our Genetics Departament at the age of 3 months because of mild facial dysmorphism, microcephaly, growth delay, strabismus and hypertonia of the extremities, with talipes varus. She presented a triangular facies, short palpebral fissures, small asymmetric low-set ears orientated posteriorly with small ear lobes and a particular helix (Figure 1), right preauricular pit and medial posterior cleft palate.

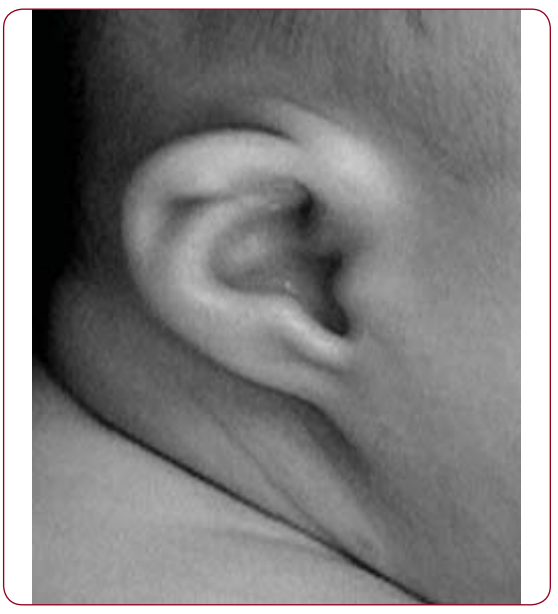

FIGURE 1. The right ear of the proband showing abnormal helix and small ear lobe

She is the first born child of non-consanguineous parents; the family history showed 8 years of infertility before this pregnancy. The mother's age at delivery was 37 years and the father's was 40 years.

The child was born by caesarean delivery at the gestational age of 35-36 weeks, with Apgar score 8, birth weight 2350g (<P5), birth length 47cm (P10). Soon after birth the infant manifested prolonged jaundice. The postnatal evaluation revealed an important growth retardation. Thereby, her weight at the age of 2 months was 2720g (<P5). Medical history excluded seizures up to this age. The cerebral and abdominal ultrasonography evaluations were normal.

Cytogenetics

Peripheral blood specimens have been collected and cytogenetic analysis was performed on GTG-banded metaphase spreads prepared from phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes. The harvesting of the cultures was done after 72h of incubation and 50 GTG-banded metaphases were karyotyped using IKAROS (MetaSystems); chromosomes were analysed according to guidelines provided by the International System for Human Cytogenetic Nomenclature (ISCN 2009) (6).

Further investigations were performed using FISH technique, following the protocol provided by the manufacturer. Two types of DNA FISH probes were used in our study to describe the structure of the marker chromosome observed for the proband: probes for the centromeric region of all chromosomes (Cytocell Chromoprobe Multiprobe®-I, Oxfordshire, UK) and probes for the subtelomeric regions of chromosome 18 (Cytocell Aquarius® Subtelomere Specific Probes for 18p and 18q, Oxfordshire, UK).

The cytogenetic analysis of GTG-banded metaphase spreads for the proband revealed the presence of a small metacentric supernumerary marker chromosome in all 50 metaphases analysed (47,XX,+mar) (Figure 2).

The characterization of the marker chromosome using only conventional cytogenetic methods was difficult. Consequently, the mark-

er was evaluated by molecular cytogenetic techniques applied to metaphase chromosome preparations. Using FISH probes for the centromeric regions of all chromosomes and for the subtelomeric regions of chromosome 18, the marker was identified to be a monocentric isochromosome 18p (Figure 3 and Figure 4).

The mother and father of the proband were also tested to determine if the i(18p) was inherited from one of them and to accurately assess the recurrence risk of the i(18p) for further pregnancies. The karyotype results from their cultured peripheral blood lymphocytes were normal, 46,XX and 46,XY respectively. ❑

DISCUSSION

Tetrasomy 18p is a structural chromosomal anomaly characterized by mental retardation, microcephaly, craniofacial anomalies, skeletal findings and occasionally renal and cardiac malformations.

The isochromosome 18p i(18p) observed for our patient is monocentric, as demonstrated using centromere-specific FISH probes for chromosome 18. Therefore, i(18p) could have been the result of two independent but consecutive events: nondisjunction of omologues and centromeric misdivision (7,8). For the reported cases in literature in which the parental origin of i(18p) could be determined, the i(18p) seems to be of maternal origin (7). Therefore, it could be possible that in most cases encountered the process of nondisjunction of omologues could take place during maternal meiosis II, followed by centromeric misdivision, an event in which maternal age has a considerable contribution. Advanced maternal age is known to have an increased influence in trisomy formation and is one of the determining factors noted in families with a child carrying an additional isochromosome (9). Maternal age can affect the reproductive system in a way that could alter the formation of proper essential proteins needed for accurate meiotic segregation; consequently, a trisomic zygote may occur, followed by a centromeric misdivision or the formation of an isochromosome and the loss of the long arm of the additional chromosome (9). Another possible mechanism is a nondisjunction in meiosis I followed by a post meiotic error or a post zygotic event (8). An alternative mechanism of formation is a U-shaped

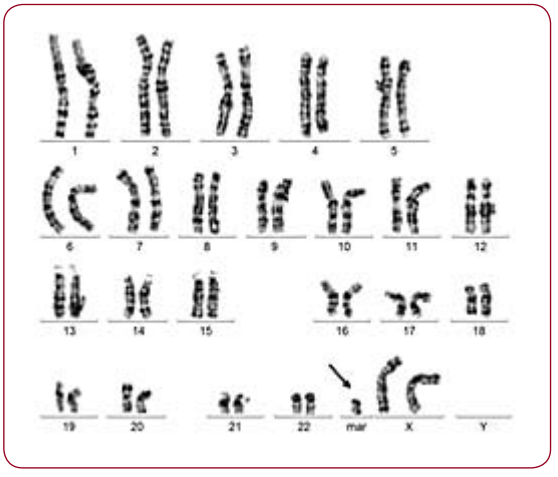

FIGURE 2. Karyogram of the proband showing 47,XX,+mar karyotype

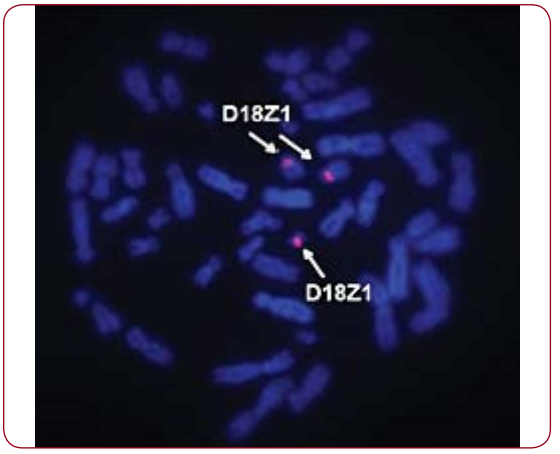

FIGURE 3. FISH result obtained using probes of the centromeric region of chromosome 18; the metaphase spread shows three distinct fluorescent signals, two for the normal 18 pair and one for the marker chromosome

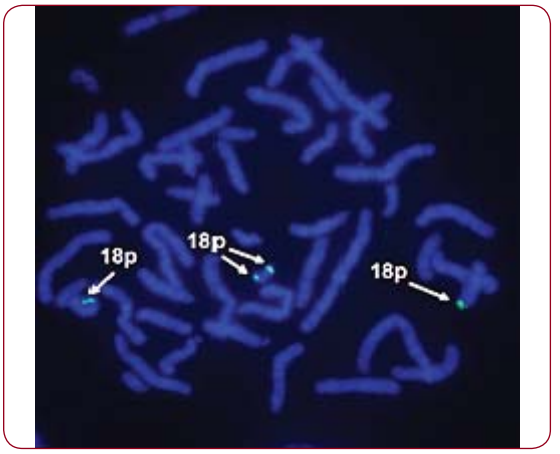

FIGURE 4. FISH result obtained using probes for the telomeric region of the short arm of chromosome 18; four signals can be observed, one for each normal chromosome 18 and two signals for the marker chromosome

exchange resulting in a dicentric marker chromosome (1).

Though it seems that tetrasomy 18p occurs de novo for the majority of cases, several reports have indicated this to be a familial abnormality (3,4,8). Boyle et al (2001) reported a family with two maternal half-sisters that had tetrasomy 18p. The karyotype result and FISH analysis for the mother revealed only normal diploid cells. The authors showed that there might be an abnormal cell line restricted only to the gonad of the mother indicating that the isochromosome was lost in most embryonic precursor cells soon after fertilization (8). For proper assessment of the implications of such an anomaly for recurrence risk is therefore necessary to investigate the parents of the affected individuals. Although for our case the proband's parents did not present a similar marker or any other anomaly detected in metaphase spreads from cultured peripheral blood lymphocytes, it cannot be excluded the possibility of a mosaic in the germline of the mother or father of the patient, especially if we consider the particular reproductive history of this family.

The characteristic features for tetrasomy 18p are particular facies, growth retardation, microcephaly, strabismus, hypertonia, scoliosis or kyphosis and modifications observed on MRI. Sebolt's et al. (2010) study on 43 patients with tetrasomy 18p and the author's thorough review of the current literature on the subject expanded the classical phenotype, adding neonatal jaundice and respiratory distress, recurrent otitis media, hearing loss, seizures, refractive errors, constipation, gastroesophageal reflux, cryptorchidism, heart defects and foot anomalies (7).

Phenotypic features of tetrasomy 18p	Frequency of the features (%)*	Phenotypic features of the proband (3 months old)
Developmental delay	100	+
Mental retardation	100	-
Abnormal muscle tone	73	+
Brain MRI alterations	63	Not performed
Feeding difficulties	56	-
Microcephaly	53	+
Strabismus	45	+
Cryptorchidism	39	-
Scoliosis/kyphosis	37	-
Recurrent otitis media	35	-
Constipation	32	-
Growth retardation	30	+
Jaundice	28	+
Foot anomalies	23	+

TABLE 1. Comparison of the phenotypic aspects observed in our patient with the commonest features of tetrasomy 18p

*Adapted from Sebold et al. (2010) (7)

The phenotypic features of our case match those reported in literature (2,4,7,10) (Table 1). At the age of the evaluation, the patient's phenotype presented only some of the specific features for this disorder. The management for the long-term survival of the patient is very complex because the phenotypic findings can change with age. Some features can disappear and others can become more evident. Therefore, a re-evaluation is necessary at a later age for proper assessment.

Little is known about the behaviour of patients with tetrasomy 18p. Swingle et. al (2006) reported the case of a 41-year-old male diagnosed as a child with "trisomy F syndrome", later confirmed to be a supernumerary 18p isochromosome. The long-term follow-up for this patient revealed profound mental retardation, aggressive, destructive and self-injurious behaviours (11). Also, this type of chromosomal disorder has been associated with high anxiety rates, stereotypic movement disorder and psychosis (12).

Prenatal diagnosis by corionic villus sampling or amniocentesis should be considered for the next pregnancy of the family, firstly due to the advanced maternal age and also for the risk of a gonadal mosaicism which may exist in one of the parents (13).

CONCLUSIONS

Any suspicion of a chromosomal anomaly should be diagnosed by cytogenetic investigation. Genetic testing is an essential step towards the accurate diagnosis of individuals with clinical indication of a genetic disorder. Also, this type of investigation could offer critical information to the practitioner for prognosis of patient and the correct appreciation of the recurrence risk of a certain condition.

In today's time, preventive care and intervention has been improved considerably, helping patients with rare chromosomal disorders live longer. It is therefore necessary to direct efforts for the proper medical and behavioural management of each case in order to enhance the life quality of such individuals and their families. ❑

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