

METAPHASE FISH STUDIES IN TWO CASES OF ATYPICAL DOWN SYNDROME

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REZUMAT

Sunt prezentate două cazuri de sindrom Down atipic, în care diagnosticul a fost stabilit prin analiza cromosomală standard urmată de metoda FISH. Primul caz este o trisomie 21 parțială cu manifestări clinice ușoare, al doilea caz o tetrasomie parțială 21 în mozaic cu trisomie 21 liberă, care prezintă dismorfie cranio-facială caracteristică sindromului Down, fără asocierea unui retard somato-psihiic semnificativ.

Cuvinte cheie: sindrom Down, trisomie 21 parțială, tetrasomie 21 în mozaic.

ABSTRACT

Two cases with atypical Down syndrome are presented, in which the diagnosis was provided by standard chromosome analysis supplemented by FISH technique. The first case is a partial trisomy 21 presenting mild clinical features; the second one is a partial tetrasomy 21 in mosaic with a free trisomy 21, showing a facial dysmorphism characteristic of Down syndrome, with no significant developmental delay.

Key Words: Down syndrome, partial trisomy 21, mosaic tetrasomy 21.

INTRODUCTION

Fluorescence in situ hybridisation (FISH) is a relatively new molecular cytogenetic technique that has found diagnostic application in the detection and definition of both numerical and structural chromosomal abnormalities. It uses fluorescently labelled DNA probes that can be hybridized to both metaphase spreads and interphase nuclei, to detect specific chromosomal segments. The signal given by the hybridized fluorescent probes can then be seen through a fluorescent microscope and the metaphases scored for the presence or absence of the signal.

Metaphase FISH is used to detect specific microdeletions or identify extra material of unknown

origin; it can help in cases when it is difficult or impossible to determine the origin of a marker chromosome by conventional cytogenetic techniques, or to clarify complex chromosomal rearrangements.

Down syndrome or trisomy 21 is the most common chromosomal disorder in humans that result from an extra copy of the long arm of chromosome 21. In 95 % of cases, the trisomy of chromosome 21 involves the whole chromosome through maternal (most frequent) or paternal meiotic non-disjunction. In 4% there is a translocation, mostly Robertsonian t(14;21) or t(21;21). One percent are mosaics with a normal cell line. A very small proportion of cases are the result of partial trisomy of chromosome 21.

We present two cases in which FISH technique was of major help in the clearing up of the underlying chromosome abnormality.

CASE REPORTS

Case 1 is the second child of a 28 years old mother and a 32 years old father. She was born with a birth weight of 2200 g and a length of 46 cm. Affirmatively, the suspicion of Down syndrome was set up on the basis of her facial features at birth. A surgical

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intervention for duodenum stenosis was undertaken at 8 days of age.

Weight gain and growth was satisfactory, on examination at 5 months: she had a weight of 5600 g and a length of 59 cm. Head circumference was 41,5 cm (10th centile). Some of her facial features were reminiscent of Down syndrome (Fig. 1): she had hypertelorism, slightly upwards slanting eyes, epicanthic fold on the right, depressed nasal bridge, downturned mouth with protruding tongue, but some of her features were not consistent with the



Figure 1. Case 1. Facial features, partly reminiscent of Down syndrome.

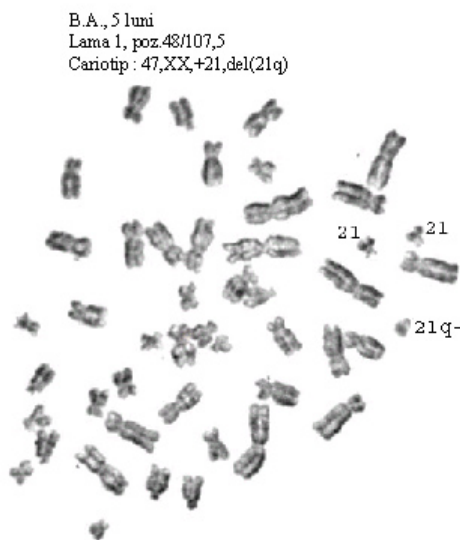


Figure 2. Metaphase showing a supernumerary small chromosome, proved to be a deleted chromosome 21.

Down phenotype, like the large, protruding ears and the prominent occiput. Her fingers were long and she presented with bilateral fifth finger clinodactyly. Psychomotor development was appropriate for her age and she had good head control and manifested interest for the ambiance.

Chromosome analysis of peripheral blood lymphocytes revealed a supernumerary chromosome, smaller than chromosome 21 (Fig. 2) in all of the metaphases. FISH examination with a probe specific for locus 21q22.3 showed three signals (Fig. 3) in all cells. We concluded that the small additional chromosome was a deleted chromosome 21.

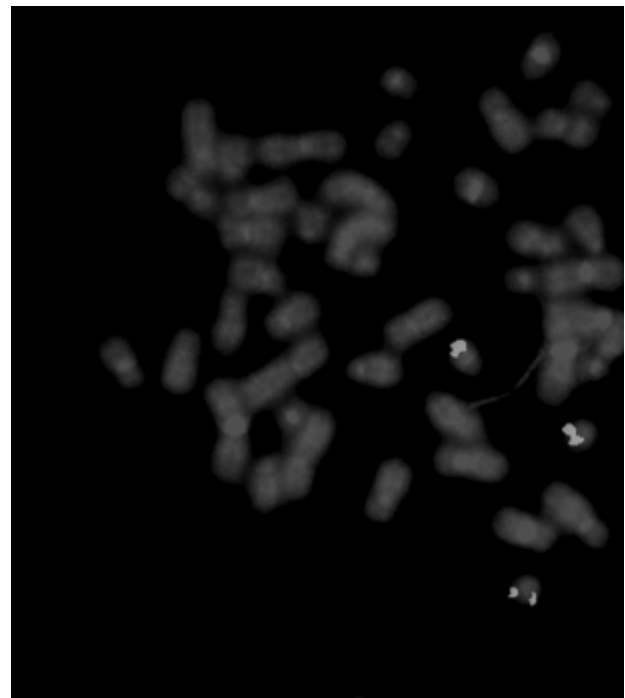


Figure 3. FISH examination with a probe specific for 21q22.3, showing three fluorescent signals. Note that the signals are visible on both chromatids (are doublets).

Case 2, a girl of 15 months old is the first child of a 26 years old mother and a 27 years old father. Weight and length at birth, were 2900 g and 49 cm respectively. There was no history of neonatal hypotonia. On examination at 15 months, height was 76 cm (25th centile), weight 9 kg (15th centile) and head circumference 43 cm (below the 5th centile). Her craniofacial appearance was characteristic of Down syndrome: she had brachycephaly, flat midface, hypertelorism, oblique palpebral fissures, epicanthic folds, small nose with flat nasal bridge, small, low-set ears, microstomia, large protruded tongue and high-arched palate and a short neck. Her hands were small with bilateral simian crease, brachydactyly and clinodactyly of fifth fingers.

Developmental milestones were normal or slightly delayed. She sustained her head at 3 months, sat without support at 6 months and walked alone at the age of 14 months. At 15 months she used 7 words. Neuropsychiatric evaluation revealed mild motor retardation, and normal psychic development.

Cytogenetic analysis showed three copies of chromosome 21 in all metaphases and in two of the 30 examined metaphases an additional marker chromosome. (Fig. 4) We carried out FISH studies with a probe specific for 21q22.3 and we examined 100 metaphases. Six metaphases showed four fluorescent signals (Fig. 5) while the rest of the metaphases showed three signals. Thus, we concluded that the extra marker chromosome had material derived from chromosome 21.

L.B., 15 luni
Lama 3, poz. 64/98
Cariotip : 48,XX,+21,+mar



Figure 4. Metaphase showing three copies of chromosome 21 and an additional marker chromosome.

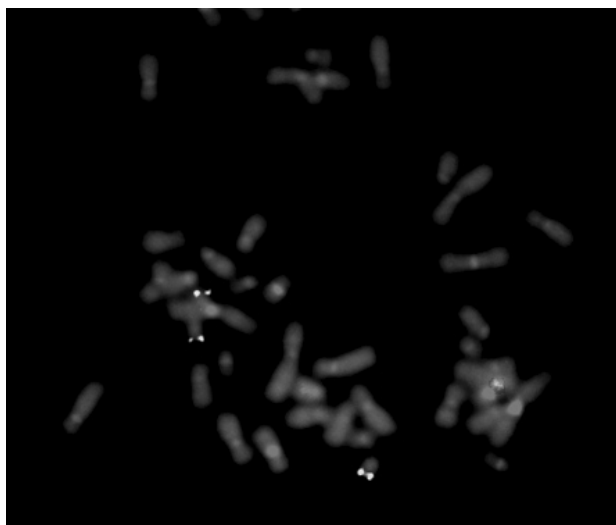


Figure 5. FISH study with a probe for 21q22.3, showing four fluorescent signals.

DISCUSSIONS

Down syndrome is one of the most common and best recognized chromosomal disorders and a leading cause of mental retardation. It is caused by trisomy of chromosome 21. Clinical features of the syndrome are a characteristic facies, hypotonia, growth retardation, varying degree of mental retardation, small hands with brachydactyly and fifth finger clinodactyly, abnormal dermatoglyphs and frequent congenital malformations as heart defects and gastrointestinal anomalies including duodenal stenosis.

Studies carried on to assign the chromosomal regions, which if present in extra copies result in the characteristic phenotypic features of Down syndrome, identified the region 21q22 to be responsible for most of the facial features, hypotonia, short stature, short hands with fifth finger clinodactyly and mental retardation, so this is considered the Down syndrome critical region.¹⁻⁶ However, there is evidence that other genes outside the critical region contribute to some of the phenotypic signs, including the facies, microcephaly, hypotonia and abnormal dermatoglyphs.

Case 1 having a supernumerary deleted chromosome 21, in keeping with other reports of partial 21 trisomies, does not show classical Down phenotype, just several minor anomalies, partly characteristic of Down syndrome, no hypotonia and good motor development.⁷⁻¹⁰

Case 2 presented with a typical Down phenotype, but with a surprisingly good psychomotor development. The unusual chromosome abnormality discovered at chromosomal analysis, namely a supernumerary marker chromosome in addition to three copies of chromosome 21, that by FISH was proved to carry material from chromosome 21 too, has not negatively influenced the phenotype, presumably due to the small percentage of the cells with this abnormality in the critical tissues.

In previously reported cases with non-mosaic partial tetrasomy of chromosome 21 a classical Down phenotype or a more severe clinical picture were described.^{6,11-14} Down syndrome cases with an additional supernumerary marker chromosome have been reported three times in the literature.¹⁵

Although at the time of examination the psychomotor development was not significantly behind of that expected for healthy children of their age in either of the 2 case, there is an obvious need for a careful follow-up of the cognitive development of the children further on, during childhood and adolescence.

CONCLUSION

FISH technique is a valuable tool in the identification of chromosome abnormalities difficult or impossible to be characterized by conventional cytogenetic methods. We described two cases in which FISH had a significant contribution to the clarifying of the underlying chromosomal pathology: a patient with a partial 21q trisomy with a non-characteristic phenotype and a case of partial 21 tetrasomy in mosaic with 21 trisomy, with the characteristic phenotypic features of Down syndrome and a fairly good somatic and psychomotor development.

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