LEJEUNE SYNDROME – A MICRODELETION SYNDROME – CASE REPORT

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Abstract

Cri du chat syndrome (CdCS) was first described by Lejeune et al in 1963 as a genetic disorder caused by a variable deletion of the short arm of the chromosome 5. CdCS has an estimated incidence of between 1:15,000 and 1:50,000 live births. Among the mentally retarded population, the prevalence may be as high as 1:350. Approximately 90% of cases are the result of a de novo deletion, while the majority of the remaining cases are associated with translocations. We report a female newborn, which was thorough investigated. The fluorescence in situ hybridization (FISH) analysis, confirmed the deletion of the critical region for the Cri du chat syndrome (5p15.2).

Key words: Cri du chat syndrome, microdeletion, fluorescence in situ hybridization.

Introduction

Cri du chat syndrome (CdCS) was first described by Lejeune in 1963 as a genetic disorder caused by a deletion of the short arm of the chromosome 5. CdCS has an estimated incidence of between 1:15,000 and 1:50,000 live births. (Higurashi M, 1990; Niebuhr E, 1978). Among the mentally retarded population, the prevalence may be as high as 1:350 (Niebuhr E, 1978). Approximately 90% of cases are the result of a de novo deletion, while the majority of the remaining cases are associated with translocations.

Various extensions of the deletion of 5p were described in the literature, but the region responsible for the hallmark feature of the syndrome - high-pitched cat like cry - was mapped on 5p15.3 (Gersh et al., 1995). Other significant features, based on which, the syndrome is usually suspected at birth, are: low weight (mean weight 2614 g), microcephaly (mean head circumference 31.8 cm), round face (83.5%), large nasal bridge (87.2%), hypertelorism (81.4%), epicanthal folds (90.2%), downward slanting palpebral fissures (56.9%), down-turned corners of the mouth (81.0%), low-set ears (69.8%), micrognathia (96.7%), abnormal dermatoglyphics (transverse flexion creases) (92%) and the typical cry (95.9%) (percentages from the Italian CdCS Registry (Cerruti, et al, 2006)).

Associated malformations, although not frequent, have been reported: cardiac, neurological and abdominal malformations, as well as hypospadias and chryptorchidism.

Extensive clinical and cytogenetic analysis has been performed on patients with Lejeune syndrome. The characteristic cat-like cry is probably due to anomalies of the larynx (small, narrow, diamond-shaped) and of the epiglottis (flabby, small, hypotonic), as well as to neurological, structural and functional alterations (Niebuhr E, 1978). The examination of clinical features confirms that the cat-like cry represents the most typical sign of the syndrome, not only at birth and in the first years of life, but also later. A longitudinal study carried out in 49 patients showed that the round face generally disappeared, the face becomes narrow, palpebral fissures frequently became horizontal, the nose will be long and coarse, and the patients display dental malocclusion. However, the phenotype remains recognizable in most patients.

Case report

The proband, (Fig. 1a, b; Fig.2) a newborn female is the first child of a healthy, unrelated young couple. Mother's age at birth was 23 years and father's was 24 years. The child was abandoned at the maternity. The newborn had intrauterine growth retardation, at birth the weight was 2530 g, head circumference was 31 cm, length: 48 cm and thoracic circumference: 31 cm. The proband was investigated at birth for high-pitched cry and facial dysmorphy. On examination the following anomalies were observed: microcephaly, round face, facial asymmetry, downwards slanting palpebral fissures, hypertelorism, strabismus, down turned corners of the mouth, low set ears, short neck, simian crease (Fig. 3), clinodactyly. No other associated malformations were noted.

Cytogenetics

Chromosome analysis from peripheral blood lymphocytes was performed. A number of 50 metaphases were analyzed and a deletion of the p arm of chromosome 5 was established (Fig. 4, Fig. 5). The karyotype of the patient is 46,XX,del(5)(p14→pter).

Cytogenetic analysis for the parents should have been performed, but it was not possible because they abandoned the child. This would have been helpful in order to establish whether there is a balanced translocation in one of them, or the deletion is de novo.

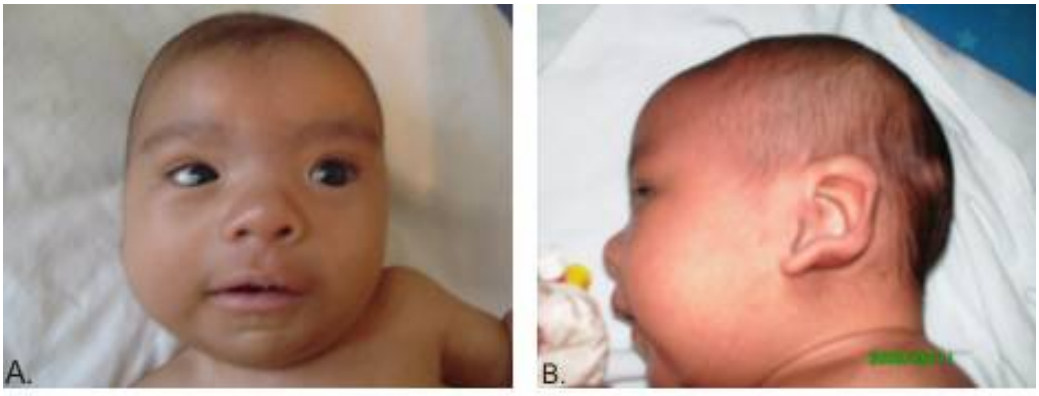

Fig. 1. Patient - facial dysmorphy. (a) front; (b) in profile.

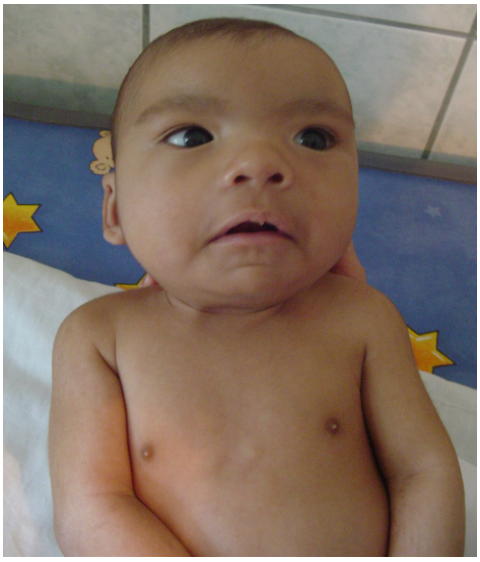

Fig. 2. Patient - clinical features.

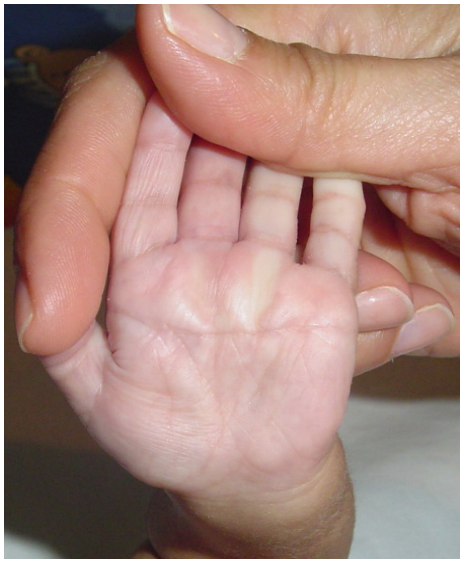

Fig. 3. Patient's hand. Note the simian crease.

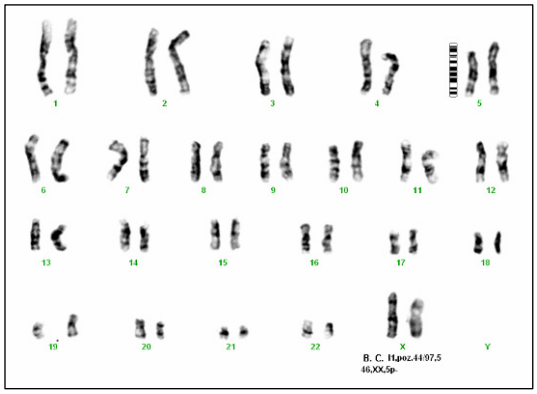

Fig. 4. Karyotype of the patient.
Note deletion of p arm of chromosome 5.

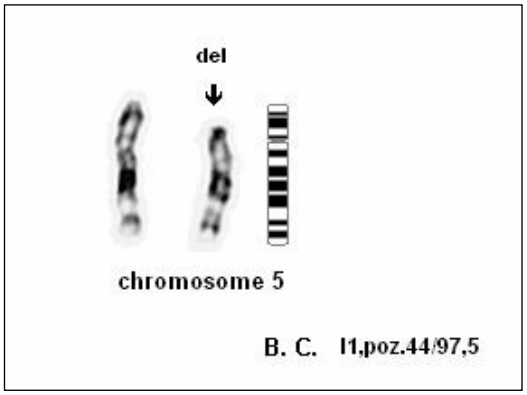

Fig. 5. Ideogram of chromosome 5, 5p deletion and normal chromosome of the pair.

To complete the investigation of the patient, FISH technique was carried out. The probe used was Vysis Cri-du-Chat Region Probe - LSI D5S23, D5S721 Spectrum Green. Slides were analyzed by fluorescence microscope. A total of 50 metaphases (Fig. 6) and 200 interphase nuclei (Fig. 7) were analyzed. Only one signal for the specific probed used could be visualized in all cells analyses. The deletion of the critical region of the syndrome (5p15.2) was made certain.

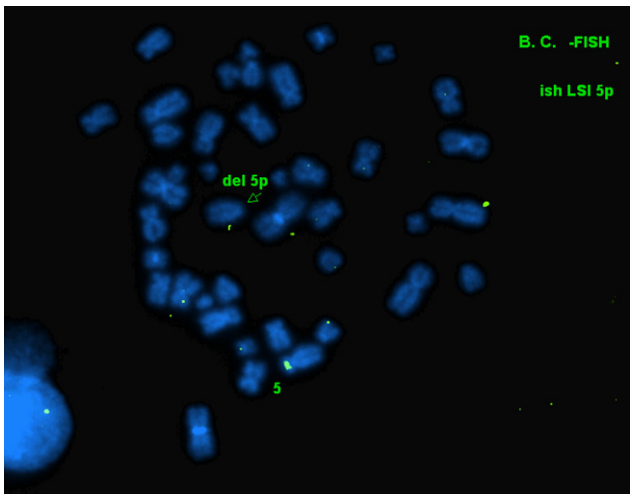

Fig. 6. FISH analysis. Metaphase spread using LSI 5p probe. Note only one green signal for the probe.

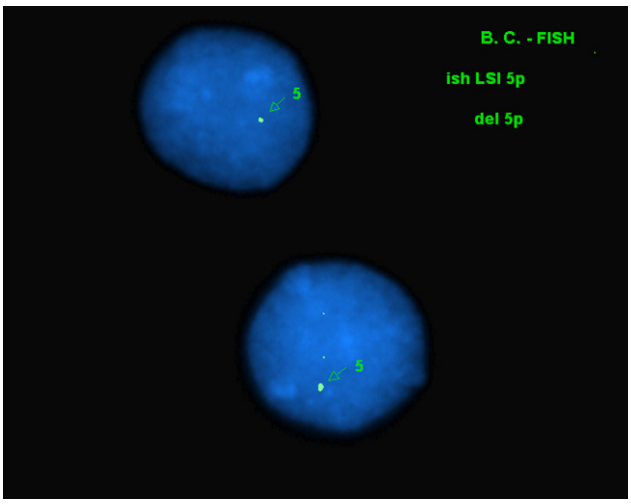

Fig. 7. FISH analysis. Interphase nuclei using LSI 5p probe. Note only one green signal for the probe.

Discussions

Cri du chat syndrome is usually diagnosed at birth due to the specific cat-like cry of the newborns. The diagnosis is first of all clinically if this hallmark is recognized, and also based on facial dysmorphism (facial gestalt).

The fact that the phenotype is well recognizable, in spite of the variability in deletion size, has led to the hypothesis that a critical region causes the characteristic clinical picture when present in a hemizygous situation. Niebuhr (1978) located this region in a narrow area around 5p15.2.

Cytogenetic analysis is important for assessing the diagnosis and molecular cytogenetic analysis (FISH) must be performed for confirming the cases.

Molecular-cytogenetic analysis by fluorescent in situ hybridization (FISH) has renewed the interest in this syndrome and allowed a molecular and phenotypic map of 5p to be defined. Our case could be diagnosed by this cytogenetic molecular technique, which assessed the fact that the critical region for the syndrome was deleted on one of the chromosome number 5. The importance of FISH for a precise diagnosis of 5p deletions was emphasized by the Italian study on 80 patients (Cerruti et al., 2006). Seven of the patients had not been correctly diagnosed by routine cytogenetics. FISH revealed that five of these patients had an interstitial deletion, one had a small terminal deletion and one had mosaicism. Subtelomeric FISH allows 5p cryptic chromosomal rearrangements to be found.

More recent studies identified two new genes, Semaphorine F (SEMAF) (Simmons et al., 1988) and δ-catenine (CTNND2) (Medina et al., 2000), mapped to the "critical regions" involved in cerebral development, and thus their deletion was associated with mental retardation. Recently the telomerase reverse transcriptase (hTERT) gene has been localized in 5p15.33 and its deletion might contribute to the phenotypic changes in CdCS children (Zhang et al., 2003).

Genotype-phenotype studies showed a direct ratio between the clinical severity and the size of the deletion. A more severe phenotype and cognitive impairment were reported to be associated with a larger deletion. There was also identified a distinct region for speech retardation in 5p15.3, and assessed the fact that the condition of patients with a deletion in 5p13 appeared particularly severe.

Regarding the prognosis of the patients, studies have show that after the first years of life, the survival expectation is high and morbidity is low. Mortality, already quite low in previous studies, has decreased in time from 9.67% in 1978 to 6.36% reported by Cerruti et al. in 2006. Also the percent of the children deceased in the first month and in the first year of life decreased meaningful in the later study. Mortality in patients with unbalanced translocations resulting in 5p deletions was higher than in those with isolated deletions, as reported by Wilkins also, because of the higher percent of associated malformations in these patients.

Studies have determined that in the first months of life the child confronts with sucking and feeding difficulties and with respiratory infections. There also have been reported intubations difficulties linked to larynx anomalies.

Psychomotor development is delayed in all patients but there is a variability related to deletion size and type as well as other genetic and environmental factors. Early

rehabilitation (physical therapy, speech therapy) is recommended for the neurological problems such as psychomotor and speech retardation.

Conclusions

Many cases of Lejeune syndrome have been reported in the literature, and a recent study performed by Cerruti el al. (2001) brought much to the phenotype-genotype correlation of the syndrome, as well as for the prognosis of the patients. But, to our knowledge, the case presented in this article is the first Romanian case of Cri du chat syndrome to be thoroughly investigated regarding the cytogenetic analysis, as FISH technique was available to assess the absence of the critical region for the syndrome.

For children with congenital abnormalities, an early clinical diagnosis confirmed through cytogenetic and molecular investigations, is important for providing personalized diagnostic and prognostic evaluation. The thorough investigation is important for genetic counseling regarding the reproductive risk, particularly for patients with parental chromosome translocation involvement.

Studies have shown that several genetic and environmental factors can influence the psychomotor development. The results of Cerruti et al. (2006) showed an improvement in comparison with the past. In addition to the factors previously considered (home-rearing, early starting of physiotherapy), early education, the use of information technology and sport has certainly contributed to this result, also improving social insertion.

Recent studies results show a more optimistic aspect of the disorder than in the past, which may support caregivers and parents to work together in order to improve the quality of life of children and their families.

Our patient remains to be followed up and hopefully given the correct social insertion.

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