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Cri Du Chat Syndrome: A Case Study

H. Bella[1*], A. Ourrai[1], A. Radi[1], A. Hassani[1], A. Agadr[1], R. Abilkassem[1]

[1]Mohamed V Military Teaching Hospital - Rabat, Morocco

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***Corresponding author:** Houda Bella
Mohamed V Military Teaching Hospital - Rabat, Morocco

Abstract **Case Report**

Cri du Chat syndrome (CdCS) is a chromosomal abnormality resulting from a deletion of variable size at the end of the short arm of chromosome 5 (5p), including a critical region located at p15.2. It is one of the most common chromosomal deletions, with an incidence in the general population of between 1:20,000 and 1:50,000. Clinical features include an acute monochromatic cry, microcephaly, characteristic craniofacial dysmorphia progressing with age and significant mental and psychomotor retardation. The size of the deletion varies, and treatment depends on the various symptoms. Parental chromosomal rearrangement is found in 12% of cases and the majority of deletions responsible for cri-du-chat disease occur de novo. We present an observation of a Cri du Chat syndrome, confirmed by metaphasic karyotype (46, XY,del(5)(p13) de novo). Through this observation we will update the scientific news of this rare syndrome, as well as the place of cytogenetic explorations in the precise diagnosis and genetic counselling of dysmorphic syndromes.

Keywords: Cri du Chat, karyotype, genetics, chromosome, Morocco.

INTRODUCTION

Introduction Cri du Chat syndrome (CdCS) is a chromosomal anomaly resulting from a variable-sized deletion of the short arm of chromosome 5 (5p), including a critical region located at p15.2 [1]. It is one of the most common chromosomal deletions, with an incidence in the general population ranging from 1 in 20,000 to 1 in 50,000 [1]. Clinical features include a high-pitched monochromatic cry, microcephaly, characteristic craniofacial dysmorphism that evolves with age, and significant intellectual and psychomotor delay [1]. The size of the deletion varies, and treatment depends on the specific symptoms. Parental chromosomal rearrangement is found in 12% of cases, and most deletions responsible for Cri du Chat syndrome occur de novo [2]. We present a case of Cri du Chat syndrome, confirmed by metaphase karyotype (46, XY, del (5) (p13) de novo). Through this case presentation, we will provide updates on the current scientific knowledge about this rare syndrome, as well as the role of cytogenetic investigations in accurate diagnosis and genetic counseling for dysmorphic syndromes.

OBSERVATION

An 11-month-old male infant (Figure 1) was referred to a medical genetics consultation due to dysmorphism and psychomotor delay. He was born to non-consanguineous parents from an unmonitored pregnancy estimated to be at full term.

The mother had experienced a miscarriage at the age of 23 during her first marriage. She remarried at the age of 39. The father, aged 76, was a former smoker and alcoholic, with multiple comorbidities (lung cancer under treatment, ankylosing spondylitis under NSAIDs). The mother, currently 43 years old, had an uneventful pregnancy without the need for radiological investigations or medication, and with a negative infectious history. The delivery was conducted vaginally, and the birth weight was 2.4 kg. The infant had a weak cry and experienced feeding difficulties, leading to stagnant weight at 2.4 kg until 3 months of age. Psychomotor development was disrupted, with the ability to sit unsupported acquired at 1 year and 6 months, but with no ability to stand up to the present.

Clinical examination revealed global hypotonia, delayed language development, stunted growth (weight and height were -2 standard deviations), and microcephaly. Facial dysmorphism was evident, including a round face, hypertelorism, micrognathia, a wide and flat nasal bridge, a globular nasal tip, epicanthus, and eyebrows slanting towards the middle of the face. The patient also exhibited strabismus (Figure 1). The fourth toes of both feet consistently rested on the

fifth and fourth toes (Figure 2). The remainder of the clinical examination showed no abnormalities. An initial assessment for malformations (digestive and renal) was conducted, but no anomalies were found.

Metaphase karyotyping with R-banding of our patient revealed a 5p deletion (Figure 3): 46,XY, del(5)(p13p15) in all three analyzed mitoses. Parental karyotype analysis showed no abnormalities, confirming the de novo nature of the 5p deletion.

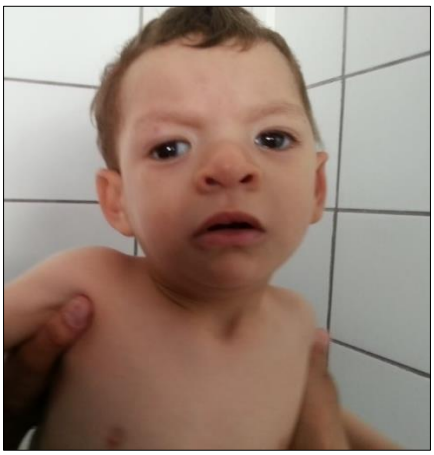

Fig-1

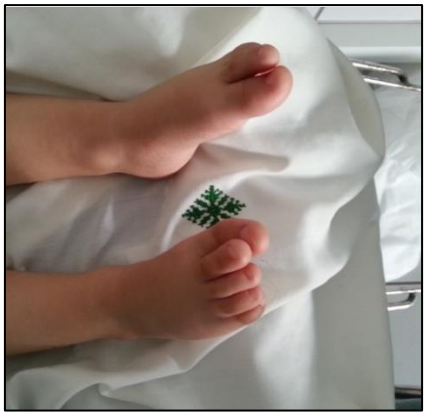

Fig-2

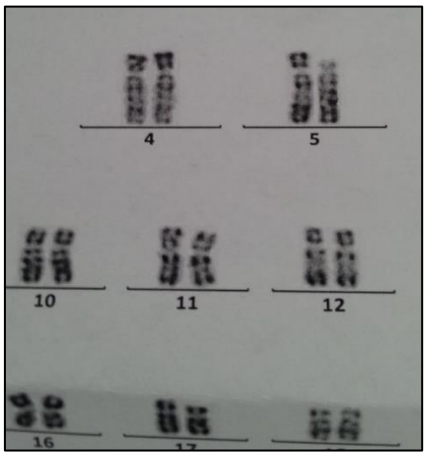

Fig-3

DISCUSSION

Cri du Chat syndrome, or deletion of the short arm of chromosome 5 (5p-), affects a critical region located at p15.2 [3, 4]. The first clinical and cytogenetic observations were described by Lejeune and colleagues in 1963 [1]. The most significant clinical features include a high-pitched monochromatic cry, microcephaly, facial dysmorphism (broad nasal bridge, epicanthus, micrognathia), as well as significant intellectual and psychomotor delay.

The incidence in the general population ranges from 1 in 20,000 to 1 in 50,000, making it one of the most common chromosomal deletions. The prevalence among individuals with intellectual disability and an IQ below 50 is estimated to be around 1 in 350 [1]. 90% of newborns have a birth weight below average, and over half have a head circumference below the 10th percentile. Respiratory and feeding problems are common in the neonatal period. Weight, height, and head circumference remain below average [1]. The most remarkable sign is a monotonous, high-pitched, plaintive cry, reminiscent of a kitten's meow. It is present during the first weeks of life and changes over time [5]. Facial appearance is highly characteristic and evolves with age. Facial dysmorphism is characterized by hypertelorism, micrognathia, a very broad and flat nasal bridge, epicanthus, and strabismus. As the child ages, the face becomes long and thin with the jaw angles becoming less pronounced. Hypotonia is constant in the neonatal and early childhood period but disappears later. Psychomotor milestones are delayed, with independent sitting achieved after the age of 2 years and independent walking rarely before the age of 4. Language is usually limited to a few words or absent. Intellectual delay is evident from the first months and ranges from severe to profound [3].

Minor malformations that can be addressed medically or surgically may also exist, including strabismus, malocclusion, gastroesophageal reflux, clubfoot, inguinal hernia, cleft lip or palate, and hip dislocation. Common medical problems in childhood include upper respiratory tract infections, middle ear infections, severe constipation, and hyperactivity with self-mutilation. Scoliosis is relatively common after the age of 8 [3]. Serious visceral malformations are rare and mostly observed in cases of unbalanced translocation, particularly involving cardiac and gastrointestinal anomalies. Urogenital anomalies are rare, including cryptorchidism and hypogonadism [6]. Renal ectopias, agenesis, or horseshoe kidneys have been described. Sexual development is normal for both sexes, and only one case of maternity has been reported in the worldwide literature [3]. Severe behavioral problems, such as self-mutilation, aggression, and stereotyped movements, have been reported in several cases [7].

Metaphase karyotyping (R-banding and/or G-banding) confirms the diagnosis. The size of the deletion varies from the entire 5p to a deletion limited to the region 5p15.2-15.3. It is usually present in all cells, although some mosaic cases are known. 5p ring chromosome and unbalanced de novo translocations have also been reported. In some cases, prometaphase karyotyping and/or FISH (Fluorescence in Situ Hybridization) with a specific probe for the region may be necessary to identify a very short deletion or to more precisely analyze a deletion of the short arm of chromosome 5 with an unusual clinical presentation [1]. Recent techniques, such as comparative genomic hybridization array (CGH array) and quantitative polymerase chain reaction (qPCR), mainly used in research, allow the characterization of breakpoints and microrearrangements [3].

Cri du Chat syndrome is a well-defined clinical entity characterized by significant phenotypic variability, which can be explained by the variable size of the deletion, ranging from the entire 5p to a deletion limited to the region 5p15.2-15.3 [1]. The critical region for Cri du Chat syndrome (CDCCR, Cri Du Chat Critical Region) is approximately 2 Mb in size and is located at 5p15.2. The average deletion size ranges from 5 to 40 Mb, encompassing this band. Intellectual delay and growth are partly dependent on the size of the deletion [1]. Models have been established to predict specific growth and psychomotor development. Two genes, Semaphorin F (SEMAF) and delta-catenin (CTNND2), located within the "critical regions," are potentially involved in brain development, and their deletion could be associated with intellectual deficit in Cri du Chat syndrome patients. Deletion of the telomerase reverse transcriptase gene (hTERT) located at 5p15.33 could contribute to the observed phenotypic manifestations in patients [3].

The majority of deletions responsible for Cri du Chat syndrome occur de novo, likely during gametogenesis. There is no known causal factor, and the average parental age is not increased. In 10 to 15% of cases, the abnormal chromosome is transmitted by one of the parents, who is a carrier of a balanced translocation involving chromosome 5 and another chromosome, or more rarely, a pericentric inversion of chromosome 5 or parental mosaicism [2]. Parental karyotyping is necessary. Genetic counseling is reassuring when the parental karyotype is normal. In cases of parental translocation, prenatal or preimplantation genetic diagnosis (PGD) is possible [1]. Treatment depends on the specific symptoms. Early intervention with rehabilitation (physical therapy, psychomotor therapy, speech therapy) has significantly improved the prognosis for psychomotor disorders [3].

Life expectancy is high, and morbidity is low after the first years of life. Mortality most often occurs during the first months of life, primarily due to visceral malformations. Three reported patients have lived for over 50 years [1]. We report the first observation from our medical genetics unit of Cri du Chat syndrome, confirmed by metaphase karyotype: 46, XY, del (5) (p13) in all 11 analyzed mitoses (Figure 2). Our 11-month-old patient exhibited signs commonly seen in this syndrome, including hypotonia, delayed psychomotor development, microcephaly, a round face, hypertelorism, micrognathia, epicanthus, strabismus, esophageal atresia type III, bilateral testicular ectopia, and rarely reported horseshoe kidney. Unfortunately, our patient passed away one month after diagnosis, due to urinary tract infection and general deterioration. The parents are young, and genetic counseling is reassuring as the 5p deletion is de novo (parental karyotype is normal). Nonetheless, obstetrical follow-up and prenatal cytogenetic diagnosis are advisable.

CONCLUSION

Deletion of the short arm of chromosome 5, particularly when it involves a critical region at p15.2, is responsible for a well-defined syndrome known as Cri du Chat syndrome. This syndrome includes characteristic craniofacial dysmorphism that evolves with age, and in its typical form, it is associated with severe intellectual disability. Visceral malformations are relatively rare and nonspecific. The size of the deletion varies. We present a typical case of 5p deletion syndrome, and the precise diagnosis allowed us to provide the young couple with appropriate genetic counseling.

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