Cri du chat syndrome: a study of two tunisian cases

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ABSTRACT

Cri du chat syndrome (CdCS) also known as Monosomy 5p, was first described by Lejeune et al. in 1963 and was recognized by the characteristic high-pitched cry during their first years of life and the moon shaped face. This rare genetic condition resulting from partial or total deletion of the short arm of chromosome 5. The incidence of this condition at birth is estimated to be between 1/15000 and 1/50000 births. This syndrome is responsible for a set of clinical features such as microcephaly, facial dysmorphism, developmental delay and intellectual disability.

Our purpose was to review different aspects of this syndrome (concept, epidemiology, clinical features, diagnostic methods and prognosis), emphasizing both: the breakthrough in this field introduced by new cytogenetic and molecular techniques, and the orofacial manifestations most frequently reported.

Early identification and medical management are key to improving the quality of life of people with this syndrome.

Appropriate medical and therapeutic interventions can help mitigate the challenges faced by individuals with Cri du Chat Syndrome and promote their optimal development. This condition requires a multidisciplinary approach involving doctors, therapists, and health care practitioners to provide the best possible care to people with this syndrome.

Key words: Cri du chat syndrome, chromosome disorders, orofacial manifestation.

INTRODUCTION

Cri du chat syndrome (CdCS) also known as Monosomy 5p, is a rare genetic condition resulting from partial or total deletion of the short arm of chromosome 5. The incidence of this condition at birth is estimated to be between 1/15000 and 1/50000 births, with a higher prevalence for females (66%) than males [1]. CdCS was first described by Lejeune et al. in 1963 and was recognized by the characteristic high-pitched cry during their first years of life and the moon shaped face. This syndrome is responsible for a set of clinical features such as microcephaly, facial dysmorphism, developmental delay and intellectual disability.

Here we report the observation of two Tunisian patients with CdCS. Our study aims to deepen the understanding of this rare condition from a clinical point of view, by highlighting the clinical characteristics, symptoms and management challenges encountered in these patients.

OBSERVATIONS

Case 1: female, was referred at the age of 3 years for pediatric consultation due to dysmorphism, microcephaly and psychomotor delay. The parents were young (father's age: 37 years, mother's age: 22 years) and not related. The pregnancy was poorly monitored and only one ultrasound finding was done at the third trimester and was normal. The patient's delivery was at term, through cesarean section for default of engagement and a moderate intrauterine growth delay.

She had a severe psychomotor delay (inability to walk independently and the speech is limited to babbling).

On the clinical examination, the patient presented a weak cry, a growth retardation (the weight was at the 3rd percentile, the height was at the 10th percentile) and a microcephaly with a head circumference below the 3rd standard deviation.

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She had facial dysmorphism with dolichocephaly, frontal bossing, bitemporal retraction, upslanted palpebral fissures, telecanthus, bilateral epicanthus, depressed nasal bridge, retrognathism, and normally implanted ears with a right preauricular tag (figure 1).

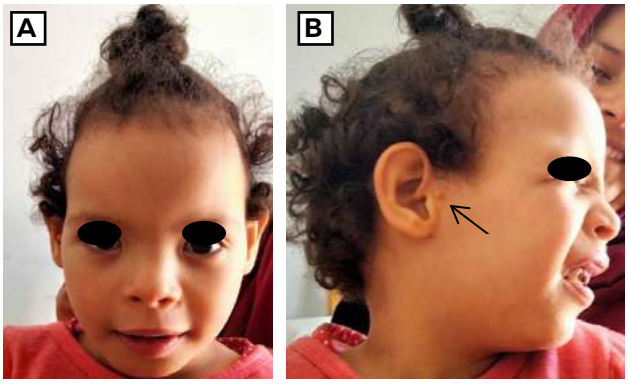

Figure1: Photography of patient 1. A: Frontal view showing long, narrow face, bilateral epican-thus/ B: Lateral view showing dolichocephaly, the arrow shows preauricular tag

Furthermore, the neurological and the rest of the examination were unremarkable.
It is important to note that our patient had an overall developmental delay: She presented a responsive smile at the age of 3 months; she acquired the ability to hold her head at 6 months of age. She was able to sit up with help at 9months, and without help at 1 year.
The patient was referred to the genetic consultation for specific investigations. Cri du Chat syndrome was suspected. A karyotype was requested, which came back normal (46XX); so a further testing with fluorescence in situ hybridization (FISH) was done. It showed a micro deletion of the CTNND2 locus which confirmed the diagnosis OF CDCs (figure2).

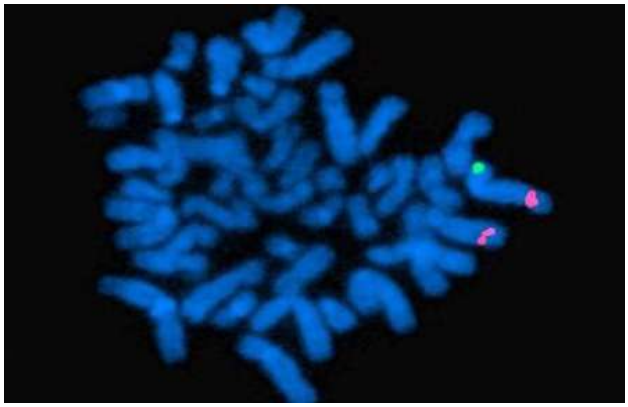

Figure 2: FISH analysis using specific probe critical locus of CDS CTNND2 (spectrum green). Note the only one green signal.

A series of investigations was carried out to look for visceral malformations and to assess the depth of neurosensory damage:
Cardiac and abdominal-renal ultrasounds returned without abnormality.
The auditory brainstem response test and Visual Evoked Potential were normal.
The cranial CT scan showed dysmorphic skull with a dolichocephaly. The brain MRI was normal.
Considering the young parent's age and the potential risk of recurrence in future pregnancies, a genetic counseling was given and Karyotype and FISH testing was recommended for both parents. However, there were not carried out because of poor material condition.
We also recommended an appropriate management which included physiotherapy, ergotherapy and speech therapy, in order to improve the quality of life and child's development; but unfortunately there were not done.

Case 2: A 32 days old female newborn was referred by a private practice pediatrician to our department because of facial dysmorphia with microcephaly.
The mother was 28 years old, she had three previous pregnancies (G3 P3); the father was 37 years old. They weren't related.
The pregnancy proceeded normally without complications. However, a morphological ultrasound performed at 22 weeks and 3 days of gestational age showed decreased amniotic fluid and a small cephalic pole, suggesting a possible developmental issue. The mother underwent an uneventful cesarean delivery, the female infant weight was 2kg500 and the length was 45cm.
At the clinical examination of the newborn, a microcephaly was observed (head circumference was 32.5 cm, which was below the third standard deviations). Dysmorphic facial features were noted including a moon-shaped face, hypertelorism, depressed nasal bridge, small mouth, and small posterior rotated ears with preauricular tag. The patient had a short neck, bilateral transverse palmar creases and bilateral clinodactyly of the 5th finger (figures 3 and 4).

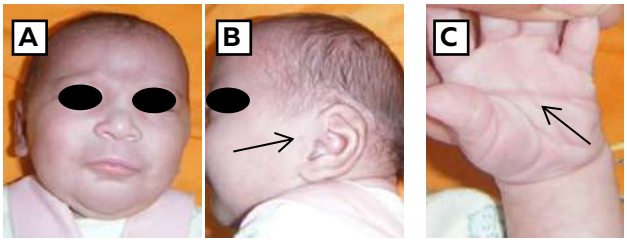

Figure 3: photography of patient 2: A: moon-shaped face/ B: preauricular tag/ C: transverse palmar

The child's neurological state was preserved and cardiac auscultation was normal. She had also hypersomnia, small umbilical hernia, hip dislocation and a high-pitched monochromatic cry evoking a Cri du Chat syndrome.
A malformation assessment was performed and revealed several abnormalities: a persistent atrial canal, a patent foramen ovale, left pyelectasis with normal size and echogenicity of the kidneys. A

transfontanellar ultrasound, abdominal ultrasound, and thyroid assessment did not reveal any abnormalities.
The diagnosis was confirmed by the karyotype which revealed a monosomy 5p (46,XX, del(5)(p13) (Figure 4).

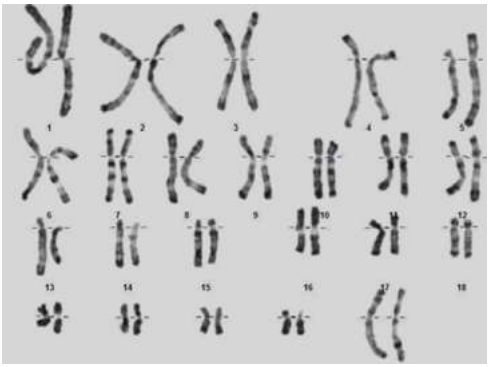

Figure 4: photo of karyotype: a monosomy 5p (46,XX,del(5)(p13)

DISCUSSION

In our study, we described the clinical presentation of two infants with Cri Du Chat syndrome in different ages of life. This syndrome takes its name from one of its most characteristic symptoms: the high-pitched monochromatic cry, like the mewing of the cat. This cry is present from the early weeks of life [2]. It usually disappears within a few months or years. This explains the absence of this sign in our first patient who was consulted at the age of three years; but it was present in the second case that was referred at the age of 32 days. Neverthelx microcephaly. Our patients had low birth weight despite a gestational age close to the norm, the birth length was unspecified for the first case and below 10th percentile for the second case. Postnatal growth delay, with weight more affected than height, is reported in both sexes. This trend continues until later in life, especially in males. Currently, our first patient has normal growth.
Microcephaly is especially evident during the first two years of life. In our study, the head circumference was below the third percentile at birth in both cases and during the follow up.
Craniofacial dysmorphism includes moon shaped face; this symptom is present in 83.5% of the affected newborns. It was observed in the second case. During the growth, the face becomes long and narrow which is observed in 70.8% of patients, the supra-orbital arch becomes prominent (31%), the palpebral fissures tend to be horizontal, the philtrum becomes short (87.8%), the lower lip tends to be full (45.2%) and dental malocclusion was observed in 75% of patients [4]. This evolution of the facial dysmorhia was noticed in our first case.
Other facial alterations widely described in CdCS include the presence of epicanthal folds (90.2% of the patients), observed in our two cases; down-turned corners of the mouth (81%) was detected only in the second case; large nasal bridge (87.2%) observed in our two patients; convex facial profile with mandibular microretrognathia (96.7%) present in the second case and an abnormal dermatoglyphics (92%) [4]. Our two patients had bilateral transverse palmar creases.
The second patient presented small hands and feet due to the shortening of metacarpi and metatarsi which are present in respectively 82.6% and 75% of affected individuals [4].
In addition, minor malformations may be present and require medical or surgical treatment, such as strabismus, gastroesophageal reflux, clubfoot, inguinal hernia, cleft lip or palate, and hip dislocation. Our first case had pes varus at three years eight months and the second case was followed in the orthopedic department because of hip dislocation.
In the medical issue of the first patient, many respiratory tract infections were observed during the two years of her life. This finding was reported in children with this syndrome who can develop also middle ear infections, and constipation. Scoliosis may develop beyond the age of eight [5]. It was observed in our first patient, it can be explained by the fact that muscle hypotonia is replaced by hypertonia while growing [4].
Visceral malformations are rare, involving heart defects, gastrointestinal and renal abnormalities (such as ectopia and renal agenesis). Cryptorchidism and hypogonadism are the main urogenital abnormalities described [6]. Our first patient didn't have any of these malformations; the second one had a persistent atrial canal, a patent foramen oval, left pyelectasis with normal size and echogenicity of the kidneys, which didn't worsen the later vital prognosis. None of our patients had brain malformation or developed seizures.
Patients presented with CDS have severe global developmental delay with the ability to sit after 2 years and independent walking typically before 4 years. Language is often limited to a few words or nonexistent. Intellectual disability is severe to profound; hyperactivity and loss of attention are described in some individuals [5]. Those findings were evident in our first patient; the second patient did not come back after the age of six months.
Severe behavioral problems such as self-mutilation (for example hitting their head and themselves), aggression, and stereotyped movements have been reported in some cases [7].
Physiotherapy, ergotherapy and speech therapy were recommended in our two patients but were not done in order to improve the quality of life and child's development. Prognosis is better for patients who underwent an early educational program with more progress in comprehension of the speech than their ability to communicate. The progress in verbal development is particularly slow [4].
Cri du Chat syndrome is associated with a wide phenotypic variability which is explained by the size of the chromosomal deletion. The critical region of this disorder is located at 5p15.2, but the average size of deletion

ranges from 5 to 40 megabases and may encompass this band. Clinical presentation can be explained by abnormal gene dosage (haploinsufficiency) involving a large number of contiguous genes (figure 5).

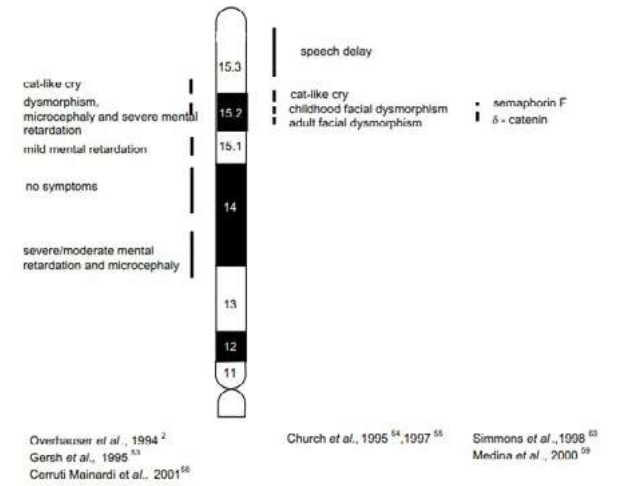

Figure 5: Phenotypic map of 5p. Vertical lines indicate the critical regions for the cry in p15.3, and for the other signs of Cri du Chat syndrome in p15.2. Vertical lines in p15.1, p14 and p13 refer to clinical symptoms reported in individual families with interstitial deletions [4]

Other mechanisms are suggested, such as gene inactivation due to the position effect or rupture of a very large gene. These molecular abnormalities influence the degree of intellectual disability. A more severe phenotype and cognitive impairment was reported to be associated with a larger deletion [2,5].

Our two patients underwent a karyotype, it was normal in the first case; the diagnosis was confirmed by FISH which showed an interstitial deletion of the loci 5p15.2. In the second case a large terminal deletion was observed, it encompassed from 5p13 to 5pter.

The majority of deletions responsible for Cri du Chat syndrome are de novo [8]. The risk of recurrence is practically negligible. However, the possibility of gonadal mosaicism in one of the parents cannot be excluded, so prenatal diagnosis is recommended on cultured amniocytes.

In some cases, a parent may transmit the anomaly if they carry a balanced translocation or a pericentric inversion involving chromosome 5. In these situations, there is an increased risk of transmitting the anomaly to the offspring. So that, parental karyotypes are recommended, genetic counseling is given to those families and prenatal diagnosis is indicated by fetal Karyotype on chorionic villus sampling.

Mortality is reported in 10% of patients affected with this syndrome and 75 to 90% of the cases within the first year of life [4].

Early diagnosis allows healthcare professionals to plan for medical, therapeutic, and educational interventions such as cognitive and behavioral stimulation from birth, which can significantly improve the prognosis for children with Cri du Chat syndrome. The earlier the specific needs of the child are identified and addressed, the better chances of developing their full potential despite the challenges associated with this genetic condition.

CONCLUSION

Deletion of the short arm of chromosome 5 including the critical region 5p15.2, is responsible for Cri du Chat syndrome, which is associated with a well-defined clinical presentation.

Early identification and medical management are key to improving the quality of life of people with this syndrome. Appropriate medical and therapeutic interventions can help mitigate the challenges faced by individuals with Cri du Chat Syndrome and promote their optimal development. This condition requires a multidisciplinary approach involving doctors, therapists, and health care practitioners to provide the best possible care to people with this syndrome.

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