

Cri du Chat Syndrome

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[Abstract](#)

[Key-words](#)

[Disease Name and Synonyms](#)

[Definition](#)

[Differential diagnosis](#)

[Incidence](#)

[Clinical description](#)

[Developmental and behavioural profile](#)

[Management](#)

[Etiology](#)

[Phenotype-genotype correlation](#)

[Diagnostic methods](#)

[Genetic counseling](#)

[Prenatal diagnosis](#)

[References](#)

Abstract

The Cri du Chat Syndrome, first described in 1963 by Lejeune et al., is a genetic, chromosomal disease resulting from a deletion of variable size (5-40 Mb) occurring on the short arm of chromosome 5 (5p-). Hallmark clinical features include a high-pitched monochromatic cry (hence the name of the syndrome cry of the cat), microcephaly, broad nasal bridge, epicanthal folds, micrognathia, abnormal dermatoglyphics and a severe psychomotor and mental retardation. The incidence ranges from 1:15,000 to 1:50,000 live-born infants.

The introduction of cytogenetic-molecular analysis (FISH) (Fluorescence In Situ Hybridisation) allowed the definition of a cytogenetic and phenotypic map of 5p.

Recent cytogenetic-molecular and genotype-phenotype correlation studies in patients from the Italian Registry of CdCS showed a clinical and cytogenetic variability. The identification of phenotypic subsets associated with specific size and type of deletion is of great diagnostic and prognostic relevance and is useful for the rehabilitative treatments. Specific growth and psychomotor development charts have been established. Early rehabilitative and educational interventions improved the prognosis and considerable progress has been made in the social adjustment of CdCS patients.

Two genes, Semaphorine F (SEMAF) and δ -catenine (CTNND2), which have been mapped to the "critical regions" are potentially involved in cerebral development and its deletion may be associated with mental retardation in CdCS patients. Also the deletion of the telomerase reverse transcriptase (hTERT) gene localized in 5p15.33 should contribute to the phenotypic changes in CdCS.

Key-words

5p deletion, high-pitched monochromatic cry, Semaphorine F gene (SEMAF), δ -catenine gene (CTNND2), telomerase reverse transcriptase gene (hTERT)

Disease Name and Synonyms

Cri du Chat syndrome

5p deletion

Definition

Cri du Chat Syndrome (CdCS) results from a deletion of the short arm of chromosome 5 (5p-). Lejeune et al.¹ in 1963 first described its clinical and cytogenetic aspects. Hallmark clinical features include a high-pitched cat-like cry,

distinct facial dysmorphisms, microcephaly and a serious psychomotor and mental retardation. The size of the deletion ranges from the entire short arm to the region 5p15.3 (5-40 Mb)^{2,3}.

Differential diagnosis

In most cases the clinical features, in particular the distinct facial phenotype, in combination with the typical cat-like cry and hypotonia, allow to suspect the diagnosis since birth. The karyotype analysis on the peripheral blood will be resolutive. In doubtful cases it will be possible to perform the molecular-cytogenetic analysis (FISH) in order to define the diagnosis. In the following ages, in the mild cases that can escape the diagnosis, it will be the clinical picture again, together with the voice, which remains abnormal and the psychomotor retardation, which will lead to carry out cytogenetic and molecular-cytogenetic analyses.

Incidence

It is a rare disease with an incidence ranging from 1:15,000⁴ to 1:50,000⁵ live-born infants, although it is probably the most frequent autosomal deletion syndrome in humans⁶. In Niebuhr's series mortality was about 10%, 75% of which occurring during the first months of life, and up to 90% within the first year. Survival, after neonatal age, is good. Among the cases described, 3 patients were older than 50 years of age⁵. The oldest patient in the Italian Registry is a 62-year-old woman.

Clinical description

The clinical features at birth^{1 5-15} are low weight, microcephaly, round face, large nasal bridge, hypertelorism, epicanthal folds, downward slanting palpebral fissures, down turned corners of the mouth, low-set ears, micrognathia, abnormal dermatoglyphics^{16 17} and the typical cry (Fig. 1 A, Fig. 1 B). Neonatal problems are asphyxia, cyanotic crises, impaired suction, hypotonia. A serious psychomotor retardation becomes evident during the first year of life. Malformations, not very frequent, may be present: cardiac, neurological, and renal abnormalities; preauricular tags, syndactyly, hypospadias, cryptorchidism. Recurrent respiratory and intestinal infections are reported during the first years of life, although neither clinical nor serologic evidence of a higher sensibility to infections are reported¹⁸. The characteristic cat-like cry is probably due to anomalies of the larynx (small, narrow, diamond-shaped) and of the epiglottis (flabby, small, hypotonic), and to neurological organic and functional alterations⁵. Malformations of the cranial base, which suggest connected anomalies of the brain at rhombencephalic level

and of the larynx during embryonal development, have been recently reported¹⁹.

Specific growth charts for CdCS until then unavailable based on a multicentre study carried out on 374 patients from the United States, Italy, the United Kingdom and Australia, confirmed the existence of pre-natal and post-natal growth retardation^{20 21}. For all ages, median head circumference and weight are near or below, the 2nd and 5th percentile, respectively. Height is less affected than weight from birth up to 2 years of age in both sexes and also later on, especially in males. Difficulties in feeding and gastroesophageal reflux, frequently reported during the first years of life, can be the cause of the low weight²². On the other hand, the slender body shape of many adolescent and adult patients^{5 11 12 23} may also be related to the syndrome.

With age, the face becomes long and narrow, the supra-orbital arch prominent, the filter short, and lower lip full with dental malocclusion (open bite) (Fig. 1 C, Fig. 1 D). Palpebral rimas tend to become horizontal, divergent strabismus is frequent. Metacarpi and metatarsi are short; consequently the hands and feet are small. Prematurely grey hair may be observed^{5-15 23-26}. Myopia and cataract have been reported. Scoliosis, flat foot, pes varus, inguinal hernia and diastasis recti are frequent. Two patients with joints hyperextensibility, skin hyperelasticity and other features of Ehlers-Danlos syndrome⁵ and one patient with both clinical manifestations of CdCS and Marfan syndromes have been reported²⁷.

Cryptorchidism, sometimes present at birth, is rare in adolescent patients and sexual development is generally normal in both sexes. A single case of a CdCS patient's procreation (a mother and a daughter with the typical syndrome) has been reported²⁸.

Muscle hypotonia is replaced by hypertonia, and microcephaly becomes more evident. Convulsive crises are rare at all ages. Magnetic nuclear resonance^{29,30} has shown an atrophy of the brainstem mainly involving pons, cerebellum, median cerebellar peduncles and cerebellar white matter. A CdCS child with an arachnoid cyst causing triventricular hydrocephalus by obstruction of the aqueduct of Silvius has been described³¹. Two studies aiming at the identification of metabolic anomalies in CdCS patients showed a defect in the synthesis of purine nucleotides, which are important neuromediators involved in brain development^{32,33}.

Developmental and behavioural profile

The few data available about the psychomotor development reported a severe psychomotor

and mental retardation in all patients^{5,24}. A better prognosis results from data on home-reared patients who underwent early educational treatments³⁴⁻³⁶. Progress in verbal development is particularly slow^{5,37}. Speech comprehension is higher than the ability to communicate³⁸.

A study on psychomotor development was carried out on 91 patients of the Italian Registry^{14,39}, using the Denver Developmental Screening Test II (DDST II)⁴⁰. This test enabled the percentile distribution of patients on the basis of the age at achievement of the various developmental milestones³⁹. A specific psychomotor development chart has been established. Although these patients present with a range of severe developmental retardation, they can achieve many skills in childhood and continue to learn. This suggests that the new patients have a better outcome than in the past.

CdCS children have mostly a gentle and affectionate personality. Hyper-activity is present in about 50% of patients and sometimes coexists with aggressiveness, which can be modified with adequate educational programs^{5,15,34-41}. The behavioural profile of 27 patients studied by Cornish and Pigrum³⁶ showed self-injury, repetitive movements, hypersensitivity to sounds, clumsiness and obsessive attachment to things. Hyper-activity and distractibility seems specific to CdCS if compared to [Prader-Willi](#) and [Smith-Magenis](#) syndromes⁴². A survey of the prevalence of stereotypy, self-injury and aggression in CdCS children and young adults has been recently carried out by Collins and Cornish⁴³.

Management

There is no treatment in the strict sense of the word for CdCS, since the cerebral damage due to genetic mutation occurs in the early stages of the embryonal development. Nevertheless it is possible to act on the consequences of the genetic alteration, through rehabilitative and educational interventions, to be started as early as possible, in close collaboration with families.

As for the medical aspects, neonatal problems are usually resolved in Neonatal Pathology departments and only occasionally it is necessary to move the newborn to a Neonatal Intensive Care unit. The breast-feeding is possible. For new-borns with difficulties in suction and swallowing it is useful to start a physical therapy right from the first weeks of life. If malformations are present, neonatologists and pediatricians will suggest diagnostic investigations and specialistic examinations.

It is important to highlight the risk of anaesthesiological problems (difficulties in intubation) linked to larynx and epiglottitis

malformations^{44,45}. In Italian series, difficult intubation has been observed in three cases, yet many patients have undergone total anaesthesia without problems.

All compulsory and recommended vaccinations are advised.

About the neurological problems (hypotonia followed by hypertonia) and psychomotor and speech retardation, early rehabilitation (physical therapy, psychomotricity, speech therapy) are recommended.

The report of sensory-neural deafness in some patients and the speech retardation make it necessary an audiometric examination in all CdCS children. For any problems the first interlocutor is the pediatrician who will suggest, if necessary, examinations and/or specialistic interventions.

As important as the rehabilitative interventions are the educational ones in order to improve the social adjustment.

Guidelines for treatment and follow-up have been drawn up^{13,14,46}.

Etiology

The introduction of cytogenetic-molecular analysis (FISH) has allowed to define a cytogenetic and phenotypic map of 5p^{2,47-50}.

The results of the cytogenetic-molecular analysis of 80 patients and 148 parents from the Italian Registry of CdCS showed a 5p terminal deletion in 62 patients (77.50%); an interstitial deletion in 7 patients (8.75%); a *de novo* translocation in 4 patients (5%); a familial translocation in 3 patients (3.75%); a *de novo* mosaic with two rearranged cell lines in 3 patients (3.75%); and a deletion originating from paternal inversion in 1 patient (1.25%)⁵⁰. The breakpoints range from p13 (locus D5S763) to p15.2 (locus D5S18) (Fig. 2). This region shows a large number of repetitive sequences that may account for its instability^{49,51}.

Molecular analysis showed that the deleted chromosome is paternal in most cases: 20/25 (80%)⁵², 10/12 (83.3%)⁴⁸, 55/61 (90.2%)⁵⁰.

The recent studies and the observations of Italian patients suggest that partial aneusomy syndromes like CdCS result from abnormal gene dosage (haploinsufficiency) involving a large number of contiguous genes^{3,49,50,53}. Other mechanisms, such as gene inactivation due to the position effect or rupture of a very large gene, have also been suggested⁵⁴.

A gene for chondrocalcinosis⁵⁵ and a gene for asthma⁵⁶ have been mapped to the critical region defined by Overhauser *et al.*² in 5p15.2. The human Semaphorine F gene (*SEMAF*) covering at least 10% of this critical region was cloned⁵⁷. Because of its role in guiding axons or migrating neuronal precursors during cortical

development in mice, it has been suggested that *SEMAF* deletion may be responsible for some of the features of CdCS. Another gene, human δ -catenine (*CTNND2*), has been mapped to 5p15.2⁵³ where it extends over 25% of the critical region defined by Church *et al.*⁴⁹. δ -catenine is a protein involved in cell motility and is expressed early in neuronal development⁵³. δ -catenine deletion seems to correlate with mental retardation in patients with terminal deletion in this area. The results of a recent study in CdCS patients suggest that the haploinsufficiency of the telomerase reverse transcriptase (*hTERT*) gene localized in 5p15.³³ should contribute to the phenotypic changes in CdCS. *hTERT* gene is the rate-limiting component for telomerase activity that is essential for telomere-length maintenance and sustained cell proliferation⁵⁸.

Phenotype-genotype correlation

Although CdCS is a well-defined clinical entity, individuals with 5p deletion show phenotypic and cytogenetic variability. Few studies, sometimes conflicting, were performed to correlate clinical picture with the deletion size^{5,19,23,59}. A more severe phenotype and cognitive impairment associated with a larger deletion were reported by Wilkins *et al.* and Cornish *et al.*^{15,60}. The fact that the phenotype was well recognisable in spite of the variability of deletion size has led to hypothesise that a critical region causes the characteristic clinical picture when present in a hemizygous situation, and Niebuhr located this region in a narrow area around 5p15.^{25,61}. Such an assumption was supported by findings of individuals with a deletion that did not include 5p15.2 who either did not display the typical CdCS phenotype^{62,63}, or were completely normal⁶⁴.

Cytogenetic-molecular analyses allowed Overhauser *et al.*² and Gersh *et al.*⁴⁷ to identify two distinct regions, one for the typical cry in 5p15.3, and another for the other clinical characteristics in 5p15.2. Church *et al.*⁴⁸ distinguished a region for speech retardation, one for the typical cry, one for face dysmorphism in childhood and one for face dysmorphism in adulthood (Fig. 2).

A phenotype-genotype correlation study has been carried out in 80 patients from the Italian CdCS Registry, who underwent FISH analysis⁵⁰. Results showed a clinical and cytogenetic variability and highlight a correlation between clinical severity and the type and size of deletion. The degree of severity (for microcephaly, dysmorphism, and psychomotor retardation) has been demonstrated to vary between the group of patients with a small deletion in 5p15.2 and 5p15.1 and patients with a larger deletion. The

conditions of patients with deletion in 5p13 appeared particularly severe.

The study of patients with interstitial deletion and with a small terminal deletion has enabled us to confirm the existence of two distinct critical regions, one for dysmorphism, microcephaly and mental retardation in p15.2 and the other one in p15.3 for the typical cry, to narrow the cry region as defined by Overhauser *et al.*² and to support the hypothesis of a distinct region for speech retardation in p15.3⁴⁸. Furthermore it was possible to confirm that not all 5p deletions result in the CdCS phenotype^{62,63}.

In patients with unbalanced translocation, the CdCS phenotype prevails but can be hybrid due to the effect of partial trisomies of the other involved chromosome⁶⁵.

Three patients with *de novo* mosaic showed 2 rearranged cell lines: one with both cell lines deleted, the others with a deleted and a duplicated cell line. In the latter two, the CdCS phenotype prevailed over the effect of the partial 5p trisomy present in part of the cells. The patient showing the largest duplication had a mild clinical picture, which suggested compensation between deleted and duplicated cell lines⁶⁶.

The deleted chromosome was mainly of paternal origin. No phenotypic differences owing to imprinting effects for any of the parameters examined were observed in this group of patients⁵⁰.

The identification of phenotypic subsets associated with specific deletions may be of great diagnostic and prognostic relevance. Furthermore, clinical examination combined with molecular analysis of the deletion results in a more personalised evaluation of the patients useful for rehabilitative and educational interventions.

Diagnostic methods

The importance of FISH for a precise diagnosis of 5p deletions must be emphasized^{50,67}. In the Italian series (80 patients) 7 patients, 5 with interstitial deletion, one with a small terminal deletion and one with a mosaicism had not been correctly diagnosed with routine cytogenetics⁵⁰. An unbalanced cryptic translocation in a family with three mental retarded patients was identified by multiplex FISH telomere integrity assay⁶⁸.

The estimated size of the critical region in 5p15.2 is ranging from 2 Mb^{2,3} and 3.5 Mb^{48,49}. A recent study using array CGH (Comparative Genomic Hybridization)⁶⁹ should locate the cry and facial features to a region of 1.5 Mb at 5p15.3. The combination of FISH, CGH and cytogenetics in a patient with dup5q/del 5p

confirmed that the characteristic cry was due to the deletion at 5p15.3⁷⁰.

Genetic counseling

Genetic counseling indicates that the risk of recurrence is practically negligible in the most frequent cases of *de novo* deletion, while it is higher in cases of balanced familial translocation. The reproductive risk for carriers of translocations involving 5p was defined by the evaluation of personal and reviewed data from 54 pedigrees. The risk of unbalanced offspring according to the pachytene configuration and 5p breakpoint localisation ranges from 8.7% to 18.8%. Risks for male and female carriers are similar⁶⁵.

Prenatal diagnosis

In all cases prenatal diagnosis by cytogenetic and molecular-cytogenetic analyses is available⁷¹⁻⁷⁴. Prenatal diagnoses of CdCS have been performed on the basis of a nonimmune fetal hydrops⁷⁵ and following an abnormal ultrasound finding of isolated moderate bilateral ventriculomegaly⁷⁶. Fetal choroid plexus cysts and/or abnormal maternal serum hCG values in association with Cri du Chat syndrome have been reported⁷⁷⁻⁸⁰.

Yet, it should be considered that not all 5p deletions result in CdCS phenotype. In fact subjects with short terminal deletions in 5p15.3 can show only a mild or moderate psychomotor retardation^{50,62,63,81,82}. Moreover, an interstitial apparently unbalanced deletion in 5p14 observed in prenatal diagnosis for advanced maternal age and later traced through six individuals in three generations resulted in a completely normal phenotype⁶⁴.

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