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Cri Du Chat Syndrome-A rare genetic disorder: An overview

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Abstract

Cri du chat Syndrome is an uncommon and unusual hereditary disorder which is caused by a deletion of chromosome 5p. Infants with this condition often have a high-pitched cry that sounds like that of a cat. The disorder is characterized by intellectual disability and delayed development, small head size (microcephaly), low birth weight, and weak muscle tone (hypotonia) in infancy. Affected individuals also have distinctive facial features, including widely set eyes (hypertelorism), low-set ears, a small jaw, and a rounded face. Some children with cri-du-chat syndrome are born with a heart defect. Cri-du-chat syndrome occurs in an estimated 1 in 20,000 to 50,000 newborns. This condition is found in people of all ethnic backgrounds. The aim of present article is to provide in depth knowledge about Cri du chart syndrome which is no doubt, a rare genetic disorder. In this article the author has explained all the clinical aspects related to Cri-du chat syndrome.

Key words: 5P minus syndrome, Le Jeune's syndrome, Cat's-cry syndrome, Chromosome 5p deletion syndrome, cri-du-chat.

Introduction

Normal development of a prenatal baby is something all parents hope for and may sometimes take for granted. When a child is developing before birth, a minute malfunction in DNA replication or chromosome formation can result in an array of genetic disorders. One of these disorders is Cri du chat, or Cat cry syndrome. Discovered by Dr. Lejune in 1963, this disorder is the product of a deletion in the p arm of chromosome 5. The small deletion of a single band of DNA triggers this abnormality. This produces newborns that have a characteristic cry that resembles the mew of a cat as well as other symptoms, which include missed developmental

milestones and microcephaly. Research of Cri du chat has not only brought forth more information about the disorder but also detection techniques. For example, the classic karyotype which provides a view of chromosomes and amniocentesis which allows fetal cells to be acquired and grown in culture are used in the detection of Cri du chat. In addition to detecting Cat Cry Syndrome, these methods have shed light on the disorder and allowed the medical genetics community to reach new conclusions and have provided major results.

Cri du chat syndrome, also known as chromosome 5p deletion syndrome, 5p minus syndrome or Lejeune's syndrome is a rare genetic disorder due to a missing part of chromosome 5. Its name is a French term (cat-cry or call of the cat) referring to the characteristic cat-like cry of affected children. It was first described by Jérôme Lejeune in 1963. The condition affects an estimated 1 in 20,000 to 50,000 live births, strikes all ethnicities, and is more common in females by a 4:3 ratio. Cri du chat syndrome is rare. It happens when genetic information on chromosome 5 is missing. One missing piece, called TERT (telomerase reverse transcriptase) is involved in control of cell growth, and may play a role in how some of the features of this syndrome develop. Most cases are believed to occur during the development of the egg or sperm. A minority of cases result from one parent carrying a rearrangement of chromosome 5 called a translocation and passing this on to the baby. This syndrome may account for up to 1% of individuals with severe mental retardation.

Sign and Symptoms of Cri Du Chat syndrome

The syndrome gets its name from the characteristic cry of affected infants, which is similar to that of a meowing kitten, due to problems with the larynx and nervous system. About 1/3 of children lose the cry by age 2**.** Other symptoms of cri du chat syndrome may include:

- feeding problems because of difficulty swallowing and sucking.
- low birth weight and poor growth.
- severe cognitive, speech, and motor delays.
- behavioral problems such as hyperactivity, aggression, tantrums, and repetitive movements.
- unusual facial features which may change over time.
- excessive drooling.
- Constipation.
- downward slant to the eyes
- Mental retardation
- Partial webbing or fusing of fingers or toes
- Single line in the palm of the hand (simian crease)
- Skin tags just in front of the ear
- Slow or incomplete development of motor skills
- Small head (microcephaly)
- Small jaw (micrognathia)
- Wide-set eyes

Other common findings include hypotonia, microcephaly, growth retardation, a round face with full cheeks, hypertelorism, epicanthal folds, down-slanting palpebral fissures, strabismus, flat nasal bridge, down-turned mouth, micrognathia, low-set ears, short fingers, single palmar creases, and cardiac defects (e.g., ventricular septal defect [VSD], atrial septal defect [ASD], patent ductus arteriosus [PDA], tetralogy of Fallot). People with Cri du chat are fertile and can reproduce.

Less frequently encountered findings include cleft lip and palate, preauricular tags and fistulas, thymic dysplasia, intestinal malrotation, megacolon, inguinal hernia, dislocated hips, cryptorchidism, hypospadias, rare renal malformations(e.g., horseshoe kidneys, renal ectopia or agenesis, hydronephrosis), clinodactyly of the fifth fingers, talipes equinovarus, pes planus, syndactyly of the second and third fingers and toes, oligosyndactyly, and hyperextensible joints. The syndrome may also include various dermatoglyphics, including transverse flexion creases, distal axial triradius, increased whorls and arches on digits, and a (simian crease). Late childhood and adolescence findings include significant intellectual disability, microcephaly, coarsening of facial features, prominent supraorbital ridges, deep-set eyes, hypoplastic nasal bridge, severe malocclusion, and scoliosis.

Affected females reach puberty, develop secondary sex characteristics, and menstruate at the usual time. The genital tract is usually normal in females except for a report of a bicornuate uterus. In males, testes are often small, but spermatogenesis is thought to be normal.

Genetics

Cri du chat syndrome is due to a partial deletion of the short arm of chromosome number 5, also called "5p monosomy". Approximately 90% of cases results from a sporadic, or randomly-occurring, de novo deletion. The remaining 10-15% are due to unequal segregation of a parental balanced translocation where the 5p monosomy is often accompanied by a trisomic portion of the genome. These individuals may have more severe disease than those with isolated monosomy of 5p.

Most cases involve total loss of the most distant 30-60% of the material on the short arm. Fewer than 10% of cases have other rare cytogenetic aberrations (e.g., interstitial deletions, mosaicisms, rings and de novo translocations). The deleted chromosome 5 is paternal in origin in about 80% of *de novo* cases.

Loss of a small region in band 5p15.2 (cri du chat critical region) correlates with all the clinical features of the syndrome with the exception of the catlike cry, which maps to band 5p15.3 (catlike critical region). The results suggest that 2 noncontiguous critical regions contain genes involved in this condition's etiology. Two genes in these regions, Semaphorine F (SEMA5A) and delta catenin (CTNND2) are potentially involved in cerebral development. The deletion of the telomerase reverse transcriptase (hTERT) gene localized in 5p15.33 may contribute to the phenotypic changes in cri du chat syndrome as well.

Pathophysiology

- A partial deletion of the short arm of chromosome 5 is responsible for the characteristic phenotype.
- The characteristic cry is perceptually and acoustically similar to the mewing of kittens. This unusual cry is due to structural abnormalities of the larynx (e.g., laryngeal hypoplasia) and CNS dysfunction. The laryngeal appearance may be normal or may exhibit marked anatomical abnormalities such as floppy epiglottis, small larynx, and asymmetric vocal cords. However, the cause of the characteristic cry cannot be entirely ascribed to the larynx. A developmental field may connect the brain and the affected clivus region of the cranial base with the laryngeal region from which the characteristic cry derives. This area of the brain is probably deformed in patients with cri-du-chat syndrome. The characteristic cry usually disappears over time.
- Genotype-phenotype studies in cri-du-chat syndrome led to the identification of two separate chromosomal regions, hemizygosity for which is associated with specific phenotypes.

Diagnosis and Management

No specific treatment is available for this syndrome. The mental retardation must be addressed, and counselling is recommended for the parents. Parents of a child with this syndrome should have genetic counselling and a karyotype test to determine if one parent has a rearrangement of chromosome 5. Diagnosis is based on the distinctive cry and accompanying physical problems. Genetic counselling and genetic testing may be offered to families with individuals who have cri du chat syndrome. Children may be treated by speech, sound, and occupational therapists. Cardiac abnormalities often require surgical correction.

Medical Care

- Care is supportive. No treatment is available for cri-du-chat syndrome.
- Genetic counseling is indicated.
- Female patients are fertile and can deliver viable affected offspring, with an estimated recurrence risk of 50%.
- Recurrence risk for a de novo case is 1% or less. Rare recurrences in chromosomally healthy parents are probably the result of gonadal mosaicism for the 5p deletion in one of the parents.
- If a parent is a balanced carrier of a structural rearrangement, the risk is substantially high. The risk should be assessed based on the type of structural rearrangement and its pattern of segregation.
- Chronic medical problems such as upper respiratory tract infections, otitis media, and severe constipation require appropriate treatment.
- Use the relatively good receptive skills to encourage language and communicative development rather than relying on traditional verbal methods.
- Early stimulation and introduction to sign language are effective means of developing communication skills (50% of children are able to use sign language to communicate).
- Behaviour modification programs may be successful in managing hyperactivity, short attention span, low threshold for frustration, and self-stimulatory behaviours (e.g., head-banging, hand-waving).
- Visual-motor coordination computerized training improves the visuospatial performance in a child affected by cri-du-chat syndrome.

Surgical Care

- Correction of congenital heart defects may be indicated. Medical problems involving minor malformations such as strabismus and clubfoot may be amenable to surgical correction. Orchiopexy may be necessary in patients with undescended testes.
- Issues important to anesthetic plan include the following:
- Anatomical abnormalities of the airway
- Congenital heart disease
- Hypotonia
- Mental retardation
- Temperature maintenance

Prognosis

- After the first years of life, the mortality (10%) and morbidity rates are low. About 75% of deaths occurred during the first months of life, and as many as 90% occurred within the first year.
- Recent improvements in management and rehabilitation programs have resulted in increased psychomotor development, improved autonomy, and better social adaptation.
- Until recently, little was known about the cognitive function of patients with cri-du-chat syndrome. Recent literature indicates that many children can develop some language and

motor skills. These children attain the developmental and social skills commonly observed in children aged 5-6 years, although their linguistic abilities are seldom as advanced. Older, home-reared children are usually ambulatory, able to communicate verbally or through gestural sign language, and independent in self-care skills.

Patient Education

Families are greatly affected. The main contributor to increased family stress is the child's maladaptive behaviour. However, these families also receive social support from other families, friends, and concerned professionals. Up-to-date information about the syndrome and other resources should be made available.

Special Concerns

- **Genetic counseling**
- Most persons with cri-du-chat syndrome have a de novo deletion, and the risk of recurrence in these individuals is practically negligible. However, the possibility of gonadal mosaicism in one of the parents cannot be excluded, even if no recurrence has been reported.
- In patients with a balanced familial translocation, the recurrence risk is higher. The reproductive risk for producing unbalanced offspring for carriers of translocations that involve 5p ranged from 8.7-18.8%. The risk for male and female carriers is the same.
- **Prenatal diagnosis**
- Prenatal diagnosis of fetuses with cri-du-chat syndrome has been reported in families with a balanced familial translocation.
- Prenatal diagnosis of de novo 5p deletions is not common but has been reported in patients with following conditions:
- Isolated bilateral ventriculomegaly
- Fetal choroid cysts associated with an abnormal maternal serum human chorionic gonadotrophin level
- Microcephaly with cerebellar hypoplasia (a fetus with 5p- mosaicism)
- Dandy-Walker syndrome with agenesis of the corpus callosum
- Encephalocele
- Corpus callosum agenesis

Discussion and Conclusion

Above discussion shows that the Cri-du-chat syndrome is an autosomal deletion syndrome caused by a partial deletion of chromosome 5p and is characterized by a distinctive, high-pitched, cat like cry in infants characterized by microcephaly and facial abnormalities throughout life. No treatment is available for cri-du-chat syndrome. Care is supportive. Genetic counselling is indicated, further consultations of Clinical geneticist, Developmental paediatrician, Neurologist, Cardiologist , Ophthalmologist , Dentist , Orthopaedist , Psychologist, Physical and occupational therapist, Speech language pathologist and Audiologist may be required time to time. Family members of people with Cri-du-chat syndrome will also need help in coping with the stresses of the disease. Social and psychiatric support can help with family relationships and antisocial behaviour. Family therapy and genetic counselling are often useful for alleviating family conflict and stressors related to relationship losses.

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