Cri-du-chat Syndrome: A Topical Overview

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Abstract

Cri-du-chat *syndrome* (CDCS) refers to a unique combination of physical and mental characteristics associated with a loss of genetic material on the distal short arm of the fifth chromosome. Also called 5p- syndrome, 5p monosomy, or Cat Cry syndrome it was first identified by Dr. Jerome Lejeune in 1963, and so named because of the distinctive cry in infancy that resembles the mewing of a cat. This overview present basic phenotypical and genotypical aspects of the syndrome. In addition, it reports the change in prognosis for this population. Finally it offers some insight from researchers familiar with Cri-du-chat Syndrome.

Cri-du-chat Syndrome: A Topical Overview

Cri-du-chat syndrome (CDCS) refers to a unique combination of physical and mental characteristics associated with a loss of genetic material on the distal short arm of the fifth chromosome (Radmer, Bodurtha, Jackson-Cook, Brown, & Wilkins-Huang, 1993). This loss of genetic material is referred to as a deletion. CDCS (also called 5p- syndrome, 5p monosomy, or Cat Cry syndrome) was first identified by Dr. Jerome Lejeune in 1963, and so named because of the distinctive cry in infancy that resembles the mewing of a cat. Other features evident in infancy include characteristic physical features: a small moon-shaped face, epicanthal folds, wide spaced, down-slanting eyes, and a small mouth and chin (micro-retroquathia). Additionally, these children exhibit low muscle tone (hypotonia), slow growth, and significant developmental delays (Carlin, 1983, 1990; Niebuhr, 1978; Radmer, et al., 1993; Wilkins, Brown, & Wolf, 1980; Wilkins, Brown & Nance, 1983). It is the high-pitched, monochromatic cry however, that usually prompts professionals to obtain a chromosome study - the definitive test required to confirm the diagnosis of CDCS.

As children with CDCS grow, the face usually elongates and becomes thinner and more triangular in shape with a broad forehead and a somewhat small pointed and receding lower jaw and chin. The epicantal folds remain and the nasal bridge widens and remains flattened. Baby teeth are often delayed in erupting, are small, and have multiple spaces (diastemas). The growth rate may be normal in the early months or years but frequently slows somewhat during the toddler and schools years resulting in growth parameters that are below average. Developmental milestones usually emerge slowly and show increasing delays with both the increasing age of the child and the complexity of the task.

The term "Classic *Cri-du-chat* syndrome" has sometimes been used in describing individuals with the more common features described above and a deletion involving a specific region located at chromosome 5p15.2. However, many individuals with CDCS show deletions that involve more than the 5p 15.2 region or other 5p genetic material (DNA) and may demonstrate additional or other clinical symptoms. Some common features include microcephaly (smaller than normal cranial circumference) and micrognathia (small jaw). Less common facial features include imbalance in eye muscles or crossed eyes (strabismus); a small, upturned nose; a narrow, high-arched palate; low set and/or posteriorly rotated ears, and skin tags near the ears. Other non-facial characteristics associated with this syndrome include a single transverse palmer crease (simian crease), incurved 5th finger (clinodactyly), webbing of fingers (syndactyly), in turned feet or clubfeet, and dislocated knees and hips. (Carlin, 1983, 1990; Niebuhr, 1978; Radmer, et al., 1993; Wilkins, et al., 1980; Wilkins, et al., 1983).

Most young children with CDCS continue to demonstrate low muscle tone, increased extension, and at least some degree of instability at many joints. As they mature they may develop hypertonia or increased muscle tone. Other physiological manifestations may include limited range of motion in some joints, excessive drooling (sialorrhea), feeding problems, hypersensitive hearing (hyperacusis), tactile defensiveness, nearsightedness, and under development (hypoplasia) of the optic nerve. Differences in dental occlusion have also been reported which can cause an overbite later in life if not corrected (Carlin, 1983, 1990). Many medical or health problems are common in children and of this merit report. Radmer, et al. (1993) reported 20% of the

individuals with CDCS had some form of hearing loss. Cardiac complications are common with about 30% having heart malformations. In addition, an early onset or delayed puberty in females was also reported. Disorders of sleep, feeding problems, constipation (increases with age), infections, and behavior problems are fairly common.

Other medical problems that are sometimes associated with the CDCS (Carlin, 1983,1990; Niebuhr, 1978; Radmer, et al., 1993; Wilkins, et al., 1980; Wilkins, et al., 1983) include:

- low birth weight,
- cleft lip and palate
- respiratory complications including susceptibility to pneumonia,
- gastrointestinal structural differences such as intestinal malrotation,
- gastroesophageal reflux,
- susceptibility to middle ear fluid and infections,
- susceptibility to other infections,
- curvature of the spine (scoliosis),
- inguinal and abdominal hernias,
- orthopedic structural differences,
- slow growth rate,
- differences in various organ systems
- laryngeal structural differences,
- colic, jaundice,
- susceptibility to dehydration,
- kidney and urinary tract problems,
- abnormal urethral opening in male (hypospadias)

Etiology and Prevalence

CDCS is a relatively uncommon syndrome with an incidence rate of between one in 15,000 live births and one in 50,000 (Higurashi, et al., 1990, Niebuhr, 1978, Radmer, et al., 1993). The variation in the rate can be attributed to the epidemiological method. For example, the incidence rate of one in 15,000 estimate emanates from a study of 27,472 live births in a large Tokyo hospital from 1972 to 1985. During this period two individuals were born with Cri-du-chat Syndrome (Higurashi, et al., 1990). Niebuhr (1978) surveyed facilities for individuals with mental retardation in Denmark and tested all individuals who appeared to have the physical traits of CDCS. From this study he concluded that the prevalence or general existence is about 1 in 50,000 for the syndrome. The actual incidence in the population is probably somewhere between these two figures. Most geneticists currently accept a figure of one in 35,000.

The most common form of deletion for individuals with CDCS is a *de novo* terminal deletion on the short arm of chromosome 5 (Radmer, et al., 1993). Terminal deletions occur during meiosis when a portion of a chromosome is lost in the formation of gametes. Between 85-90% of the individuals with CDCS (Radmer, et al., 1993) manifest this nonfamilial form of chromosomal anomaly. Ten to fifteen percent of individuals with CDCS inherit an unbalanced translocated set of chromosomes from one of their parents who is a carrier. In translocations a part of a chromosome detaches and

combines with another chromosome from a different group. In the offspring of a balanced translocation carrier who has inherited an unbalanced translocation, there is missing material from the short arm of the chromosome 5 and some extra material from the other chromosome involved in the translocation.

In diagnosing children with CDCS, the location of the break point on the chromosome appears to have implications for a child's development. Until recently, any individual with a deletion of the short arm of the fifth chromosome was considered to have CDCS (Niebuhr, 1971). As more advanced techniques for locating specific genes on the chromosome were developed, researchers learned that a partial deletion of the fifth chromosome could exist without the traits of CDCS (Overhauser et al., 1994). The short arm of chromosome five is divided into numbered segments from 5p11 to 5p15.3 (Gersh, Goodart, & Overhauser, 1994; Overhauser et al., 1994) Individuals with classic CDCS have a deletion that includes an area at 5p 15.2. Individuals with only part of the critical region from 5p15.2 to 5p15.33 missing may not have the CDCS traits and often do not have the severe language or cognitive delays associated with the syndrome. The relationship between deletion and cognition appears to be a trend toward the greater the deletion the poorer cognitive abilities (Mainardi, et. al; 2001).

Prognosis and Treatment

Prior to the 1980's, research on CDCS consisted primarily of medical studies of individuals who had lived in institutions. Most of these individuals did not have access to a loving family environment, education, or systematic medical care. Consequently, the prognosis for individuals with CDCS reported in early studies was very pessimistic. Parents of children diagnosed early with significant disabilities in the United States were strongly encouraged to place them in institutions and forget them (Robinson, 1997). This was certainly true for individuals with CDCS (Gellis & Fiengold, 1969). Current research on CDCS presents a more optimistic prognosis. When children are provided a positive home environment and access to early intervention programs a more favorable prognosis is expected.

Children with CDCS usually receive primary medical care from a pediatrician, although other specialists routinely involved may include an ear, nose, and throat specialist (ENT), an eye specialist (ophthalmologist), a bone specialist (orthopedist), a dentist, and a geneticist. As mentioned earlier in the paper there are many medical or health problems associated with CDCS. Hospitalization for the treatment of respiratory infections and placement of ear tubes is not uncommon (Radmer, et al., 1993). These health problems notwithstanding, Radmer, et al. (1993) reported individuals with CDCS tend to be relatively healthy. Only 30% experience chronic illness requiring over six medical visits per year, and 56% were considered generally healthy requiring only two to six doctor visits per year. Early reports of significant numbers of deaths in the first year of life are not supported and life expectancy for individuals with this syndrome has been increasing. With routine medical care, individuals with CDCS can be expected to survive into adulthood with many reaching middle age and beyond.

As noted earlier, the prognosis of CDCS prior to recent studies of home-reared children appeared very bleak (Carlin, 1990; Nieburh 1971, 1978; Silber, Engel, & Merrill, 1966; Wilkins et al., 1980; Wilkins, et al., 1983). Prior to the 1980's parents were encouraged to institutionalize their child in infancy. Life expectancy was predicted to be short and parents were told their child would probably not walk or talk, and would be

severely mentally retarded (Nieburh 1971, 1978; Silber et al., 1966). The outlook today is much brighter. Studies of home-reared children, who had access to supportive family environments, early intervention and education, and adequate medical care, demonstrate much better outcomes. Most researchers have challenged the poor prognosis reported in earlier research and are more positive in reporting the prognosis of children with CDCS (Baird, Campbell, Ingram, & Gomez, 2001; Carlin, 1990; Wilkins, et al., 1980; Wilkins, et al., 1983). The information that exists in the medical literature continues to report individuals with CDCS as having very little language, poor cognitive performance, neurological and motor problems, as well as a variety of problematic behaviors (Niebuhr, 1978; Wilkins, et al., 1980). While all of these issues still exist, the research also describes these individuals as happy, friendly, and capable of learning (Carlin, 1990; Wilkins, et al., 1983).

Because of low incidence, little information concerning CDCS exists in the educational literature. Very little systematic research provides insight into educational strategies for individuals with CDCS. In a recent study by Campbell (2002), data from 143 individuals with CDCS was analyzed. On the average, these individuals walked holding hands a year later than typically developing individuals (range: 10 months to 144 months; mean 24 months) and walked independently seven months later (range: 16 months to 144 months; mean 31 months. They rolled over (range: 3 weeks to 36 months; mean 6 months), self-fed using utensils (range: 2.5 months to 108 months; mean 21 months), and drank using a cup (range: 6 months to 120 months; mean 21 months) within the typical age of development. Children who received early education met milestones earlier than those who had not. They averaged rolling over two and one half months earlier, sitting independently eight months earlier, and walking nine months earlier than those in the study without the benefit of early educational interventions.

In the area of communication children in the study required an extra seven months to use gestures to communicate compared to typically developing children. They were on the average 34 months of age when they used their first sign (range: 6 months to 144 months), 48 months for multiple signs (range: 12 months to 168 months), and 45 months when they spoke several words (range: 12 months to 120 months). Those individuals who received early education used gestures 20 months earlier, first signed eight months earlier, used multiple signs ten months earlier, and multiple words 12 months earlier than those who had not received early education. The focus on functional communication provided in most early education programs would certainly be a probable contributing factor to this difference.

Practitioners should recognize that individuals with CDCS have the capacity to learn. Earlier research significantly under estimated the ability of these individuals. Parents should be encouraged to participate in their children's' therapies and never to underestimate their ability.

Having observed hundreds of children with CDCS, the authors feel we can draw several general conclusions. Younger children who have had early intervention seem to have better communication abilities than older individuals without the benefit of these programs. Self-stimulating behaviors, which can be a manifestation of frustration or boredom, seem to be present from a very early age for some children. Practitioners should target behaviors early and consistently.

Many of the issues faced by families, like developing functional communication and redirecting problem behaviors are common. There appears to be a wide variation in the occurrence and severity of problem behaviors from one individual to another. Children served in more inclusive educational environments appear to have a more socially appropriate behavioral pattern. Early education has been shown to help these children reach developmental milestones earlier. Communication interventions should begin in infancy. Sign language should be taught and encouraged along with other total communication methods including picture exchange symbols, augmentative communication, and spoken words. Receptive language skills surpass expressive skills, thus interventions should be targeted at the child's receptive developmental level rather than the expressive. Generally speaking, research findings suggest that effective educational strategies based on empirically based methods likely to maximize the potential gain for children with significant disabilities also work well for children with CDCS. Above all, children with CDCS can learn and the quality of their life is much improved in a home situation with early intervention.

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