CLINICAL QUIZ (p237) ANSWER

What is the diagnosis?

The girl presented with microcephaly, poor feeding, failure to thrive, a floppy larynx, hypotonia, and global severe developmental delay. She had craniofacial dysmorphic features including hypertelorism, epicanthic folds, low-set ears, wide and flat nasal bridge, downturned corners of mouth and a small lower jaw. Most characteristically, she had a monotonous weak high-pitched cry. The overall features are compatible with Cri du Chat syndrome. Karyotype testing confirmed terminal deletion of the short arm of chromosome 5 at breakpoint band 5p14. Parental karyotype testing confirmed that the deletion was de novo.

What are the clinical features?

Cri du Chat (French for "cry of the cat") syndrome [OMIM #123450] is one of the most common chromosomal anomalies, with reported incidence ranging from 1 in 15,000 to 1 in 50,000 liveborn infants.[1]

As its name suggests, Cri du Chat syndrome classically presents with a high-pitched, monotonous cat-like cry during infancy. The atypical cry is primarily attributed to structural abnormalities of the larynx, including floppy supraglottic larynx, underdevelopment of the larynx, asymmetry of the vocal cords, and widening of the space between vocal cords posteriorly, as well as neurological alterations.[2]

The other clinical features present at birth are low birthweight, microcephaly, breathing difficulties, low muscle tone, and weak sucking ability. Patients commonly present with craniofacial malformations such as moon face, widely spaced eyes, prominent epicanthic folds, large nasal bridge, downturned mouth angles, short philtrum, premature gray hair, single transverse palmar crease and a small lower jaw. The following features evolve with age: microcephaly and the bony ridge above eyes become prominent, moon face elongates vertically in adulthood, weak muscle tone transitions to increased muscle tone, malaligned dentition, exotropia and scoliosis develop. Less frequent malformations are cardiac, renal, neurological anomalies, presence of rudimentary skin tags anterior to the ear, syndactyly, malpositioned urethral opening, and undescended testes in male.[1]

Regarding growth, the median head circumference and weight consistently fall at or below the 2nd and 5th percentiles, respectively, across all age groups.[1] Feeding difficulties (because of hypotonia, poor sucking, dysphagia) and gastroesophageal reflux, both of which are commonly observed in early childhood, may account for the low body weight.[3] Patients also present with developmental delay and intellectual disability.[4] Individuals may exhibit behavioral characteristics such as overactivity, self-inflicted injury, stereotypic movements, an affable demeanor, excessive attachment to specific objects. Besides, patients' ability to comprehend spoken language often exceeds their capacity for verbal expression.[5]

What is the genetic basis of Cri du Chat syndrome?

Cri du Chat syndrome is caused by a deletion, either partial or complete, of the short arm of chromosome 5 (5p). It arises from terminal deletion in over 80% of cases, in which the majority occur de novo during gamete formation and are paternal in origin.[6] Patients show variable phenotype and severity depending on the size and region of deletion, as well as whether it is terminal or interstitial deletion.[1] Two critical chromosomal regions were identified from cytogenetic studies to account for the clinical features: 5p15.3 deletion results in the high-pitched cry, and 5p15.2 deletion is associated with microcephaly, distinctive facial features and intellectual disability.[1] A separate region at 5p15.3 was found to be associated with speech delay.[1]

At writing, the complete map of responsible genes in this syndrome is not fully understood. However, it has been suggested that there might be some critical regions that are associated with certain clinical features. It has been suggested that the loss of multiple genes in the deleted critical regions would result in the phenotype. Mapped to 5p15.2, the genes Semaphorin F (*SEMAF*) and human δ-catenin (*CTNND2*) are implicated in cognitive development, and their deletion potentially contributes to intellectual disability observed in individuals with Cri du Chat syndrome.[1] Loss of the telomerase reverse transcriptase (*hTERT*) gene, located at 5p15.33, may play a role in the varied presentation of the syndrome.[1]

On the other hand, Nevado et al[7] mapped the high-pitched cry and severe intellectual disability at 5p14.3-5p13.2. Their study revealed that the cadherin genes (*CDH*), mapped at 5p15.1-5p14.1, are strongly associated with stereotypies, aggression, cardiac defects, sleeping and breathing difficulties, while the regions 5p14.1-5p13.2 are associated with dysmorphism and aggression.[7]

What is the management of Cri du Chat syndrome?

Management is mainly supportive, early multidisciplinary care involving paediatricians, otorhinolaryngeal surgeons, cardiologists, respiratory medicine specialists, orthopaedic surgeons, ophthalmologists, clinical geneticists, dental surgeons, speech therapists, physiotherapists, occupational therapists, dietitians, and special education teachers is crucial for the comprehensive management of patients with Cri du Chat syndrome.[7]

While the vast majority of affected individuals enjoy a normal life expectancy, there remains a 10% mortality among patients with Cri du Chat syndrome,[8] with 90% of death occurring within the first year of life.[4] The early mortality is most commonly attributed to pneumonia, congenital heart defect, respiratory distress syndrome, and aspiration pneumonia. The contributory respiratory risk factors include the anatomical anomalies, neuromuscular hypotonia, neurological alternations and immature immunity in early infancy. The rate of mortality tends to decline after the early years of life, beyond which remains comparable to that of the general population.[8] Early diagnosis, structured rehabilitation, and ongoing monitoring are vital components in optimising outcomes and prognosis for individuals with Cri du Chat syndrome.

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Declaration of interest

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