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Case Report

A rare case of 5p-deletion in a child: Cri-du-chat syndrome

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ABSTRACT

The Cri-du-chat syndrome (CdCS; OMIM#123450) is a contiguous gene syndrome caused by a variable deletion of the short arm of the chromosome 5 (5p-). The incidence ranges from 1:15,000 to 1:50,000 live-births. The CdCS diagnosis is suspected in a child with cat like cry during infancy, facial dysmorphisms, hypotonia and delayed psychomotor development. Genotype-phenotype correlation studies shows clinical and cytogenetic variability in CdCS. High resolution G banding karyotyping with chromosomal microarray analysis (CMA) is the definitive method for a precise diagnosis of CdCS. There is no specific therapy for CdCS but early rehabilitative and educational interventions improve the prognosis and is crucial for social rehabilitation. Here the authors reported this case in view of its rarity and classical clinical features and molecular cytogenetic findings.

Keywords: Developmental delay, Dysmorphism, 5p-deletion, Cri-du-chat, Chromosomal microarray, Early intervention

INTRODUCTION

CdCS first described by Jerome Lejune in 1963, characterised mainly by the high-pitched cat like cry.[1] It is a well described partial aneusomy resulting from deletion of short arm of chromosome 5. The size of the deletion is variable, ranging from the entire short arm to the region 5p15.[2] The incidence of CdCS is between 1:15,000 to 1:50,000 live births.

The prevalence is 1.5/1000 in patients with intellectual disability and 1/305 in patients who seek genetic counselling and are analysed cytogenetically.[3,4] Female to male ratio is approximately 1.3:1.[5,6] Most of the CdCS cases are caused by a *de novo* 5p interstitial or terminal deletion, size ranging from 560 Kb to 40 Mb.[7,8]

80-90% of these cases were paternal in origin and 10-15% resulted from an unbalanced parental translocation.[9] Other rarer cytogenetic findings included 5p-mosaicism (1.4%), inversions (0.5%) and ring chromosomes (0.5%).[5,10]

The reported phenotype included high pitched monotonous cat like cry during the first years of life providing the name to the syndrome, facial dysmorphisms, intellectual impairment and development delay.

Here, the authors reported this case in view of its rarity and classical clinical features and molecular cytogenetic findings.

CASE REPORT

A 2 years 6 months old girl child was brought by parents with concerns of motor and language delay. She walked with support, spoke only very few words, indicated needs by gestures, did not address her mother. She was the 2nd born child, term to a non-consanguineous parent,

spontaneous conception, delivered by caesarean section. She cried immediately after birth. Her birth weight was 2.020 kgs. Neonatal period was uneventful. Maternal age was 33 years, paternal age was 34 years respectively at the time of conception. Mother had hypothyroidism during pregnancy. History of excessive crying during infancy was present. She attained head control only at 6 months. At present she was able to sit without support, rose to standing position with support, walked with support, spoke bisyllables, indicated her needs by gestures. No history of seizures. Family history of speech delay and seizure disorder was present in elder sibling.

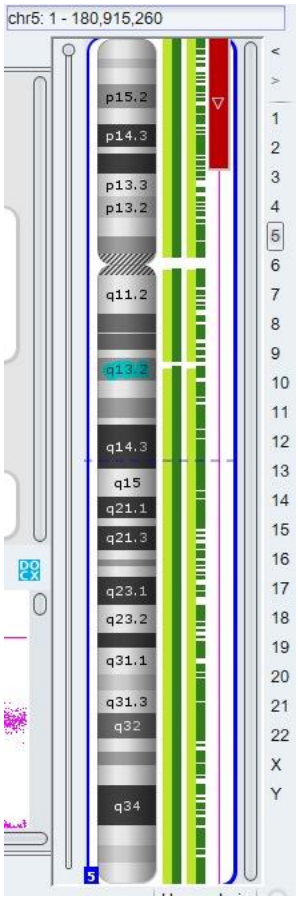

Figure 1: Enlarged view of chromosome 5 depicting location and extent of 5p-deletion (in red).

On examination, she was fidgety, hyperactive, had ill sustained eye contact, reached for objects with both the hands, responded to name, localised sound. She had no pointing and lacked joint attention. She waved bye-bye and shook hands with examiner.

Physical examination revealed microcephaly, strabismus, hypertelorism, broad nasal bridge, hypotonia, flexible joints. Weight, height and head circumference were less than 3rd centile according to WHO charts.

Her motor age was 12 months and language age was 12-15 months. Her M CHAT total score was 8, critical score was 3. Neurological examination revealed hypotonia, normal deep tendon reflexes, normal spine and no focal neurological deficits. Her head circumference was 43 cms. There were no neurocutaneous markers. There was no tongue tie. Other systemic examination was normal. Cardiac evaluation was normal. Ophthalmological evaluation revealed mixed astigmatism.

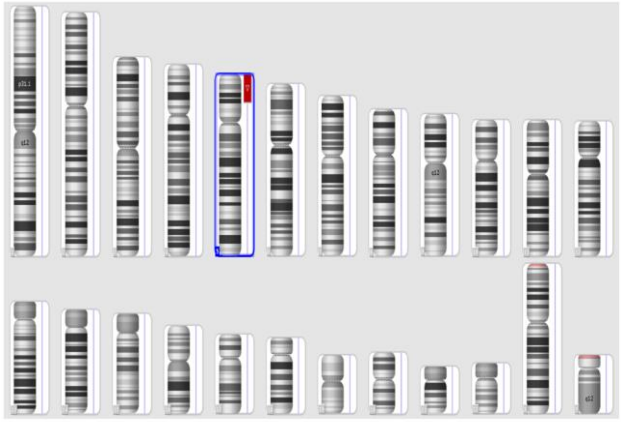

Figure 2: Karyoview of chromosomal microarray showing 5p terminal deletion in chromosome 5.

Her OAE and thyroid function test was normal. BERA showed bilateral peripheral auditory pathway defect, hearing threshold was 40 dB bilaterally. MRI showed right occipital gliosis. Parents were phenotypically normal.

In view of dysmorphic features, global developmental delay, hypotonia, mild hearing impairment, we suggested chromosomal microarray analysis for the child. CMA analysis showed a deletion spanning 27,921kbp (~27.9 MB) on chromosome 5,arr[GRCh37] 5p15.33p14.1 (113577_28034230)x1.According to ACMG guidelines the deletion is classified as pathogenic corresponding to Cri-du-chat syndrome.Number of genes involved in the deletion was 150. CMA was performed using Affymetrix CytoScan Optima microarray. DNA was isolated from the provided sample using a commercial kit that worked on silica-membrane-based DNA purification. Genome version used was Hg 19 for the ChAS and the DGV database was used for analysis.

As cytogenetic analysis by karyotype of both parents can provide more information on whether the copy number variation was inherited or *de novo*, karyotyping for the parents was recommended to check if the parents were carriers for chromosomal rearrangement such as a balanced translocation. In the event of either parent being a translocation carrier, prenatal diagnosis will have to be performed in the subsequent pregnancy.

The child was undergoing physiotherapy, occupational therapy behaviour therapy, speech and communication therapy and was under regular follow up in our child development centre.

DISCUSSION

CdCS (OMIM#123450) is a well-described partial aneusomy, resulting from deletions on the short arm of chromosome 5.[3]

Children with CdCS usually exhibited low weight (mean weight 2614 g), microcephaly (mean head circumference 31.8 cm), micrognathia (96.7%), typical cry (95.9%), abnormal dermatoglyphics (transverse flexion creases) (92%), epicanthal folds (90.2%), large nasal bridge (87.2%), round face (83.5%), hypertelorism (81.4%), down-turned corners of the mouth (81.0%), downward slanting palpebral fissures (56.9%) and low-set ears (69.8%).[6]

The condition may be associated with developmental and cognitive delays, poor spatial awareness, impairment in ambulation and poor sensorimotor skills. Other associated problems described included cardiovascular, renal, gastrointestinal, neurological abnormalities, preauricular tags, syndactyly, hypospadias and cryptorchidism.[6,11] Recent literatures showed that autistic behaviours were common in various genetic disorders.[12]

Partial aneusomy syndromes like CdCS resulted from abnormal gene dosage (haploinsufficiency) involving a large number of contiguous genes. Recent studies have associated some critical regions of 5p with the clinical features of this disorder including haplo insufficiency of 5p15.3 or cat-like cry and speech delay and haploinsufficiency of 5p15.2, for facial dysmorphism, microcephaly and severe intellectual disability.[2,3] Haploinsufficiency was when having a single functioning copy of a gene was not enough for normal function.[5,13]

In our patient, 150 genes were deleted in the 27.9 MB deletion. CTNND2, SEMA5A, TERT were the important genes lost in the deletion for the child.

The delta catenin (CTNND2) was mapped to 5p15.2. The delta catenin codes for a protein involved in cell motility and was expressed in early stages of neuronal development. Delta catenin deletion seemed to correlate with mental retardation in patients with terminal deletion in this area.[14]

Other genes that had been mapped to the CdCS critical region included the Semaphorin 5A (SEMA5 A) gene, which acted as a bifunctional cue, exerting both attractive and inhibitory effects on developing axons.[15]

Semaphorins were a large family of secreted and membrane-associated proteins necessary for wiring of the brain.[15]

Haploinsufficiency of the telomerase reverse transcriptase (hTERT) gene, localized to 5p15. could contribute to the heterogeneous phenotype of CdCS.[33] hTERT was the rate limiting component for the telomerase activity that was essential for telomere-length maintenance and sustained cell proliferation.[16]

The phenotypic variability in CdCS was related to both the location and the extent of deletion that originated, located on the short arm of chromosome 5 (5p15).

Candidate genes such as TERT, MARCH6, CTNND2 and SLC6A3 were considered dose-sensitive or conditionally haploinsufficient.[5]

Haploinsufficiency of the genes mentioned above had been implicated in telomere maintenance dysfunction, cat-like cry, intellectual disability and attention-deficit/hyperactivity disorder, respectively.[17-19]

Thiago et al explored the interaction network of the proteins encoded in the critical region associated with CdCS by combining cytogenomic data and systems biology tools.[20] This study identified and demonstrated the biological processes involving genes previously found to be associated with CdCs such as TERT, SLC6A3 and CTDNND2. Furthermore, through analysis of the protein interaction network, other possible candidate proteins, including CCT5, TPPP, MED10, ADCY2, MTRR, CEP72, NDUFS6 and MRPL36 were identified with potential contributions to the phenotypes observed in CdCS. These candidate genes were also identified amongst the 150 genes deleted in our proband discussed.

Recurrence risk

The risk of recurrence was minimal in cases with *de novo* deletion. However, the possibility of gonadal mosaicism in one of the parents cannot be ignored. The probability was higher and became more important in familial balanced translocation cases that included the 5p fragment.

Recurrence risk was reported to be 15-25% in cases with a parental translocation. Parental karyotype abnormalities resulting in the CdCS occurred fairly frequently and cytogenetic studies of parents should be routinely advised for every affected child in order to prevent recurrence in future pregnancies.

Cerruti et al showed the risk of progeny with unbalanced chromosomal alterations ranges between 8.7% and 18.8% and that it was similar in carriers in both sexes.[6]

A correct diagnosis paves way for early intervention which plays a critical role in improving outcome which is important as CdCS was not associated with reduced life span. Affected patients have been reported to survive more than 50 years from the study on series of five cases from Vellore.[21]

Early intervention followed by consistent behavioral and physical therapy helped these children reach their highest potential. Good home environment, special schooling and

family support helped patient to achieve the abilities of a normal five or six years old. Successful management with conservative rehabilitation plan must be implemented.

CONCLUSION

The CdCS is a contiguous gene syndrome caused by a variable deletion of the short arm of the chromosome 5(5p-). The deletion is predominantly terminal and a *de novo* event. High resolution G banding karyotyping with CMA is the definitive method for a precise diagnosis of CdCS. An accurate diagnosis of CdCS is of paramount importance for genetic counselling and to estimate recurrence risk. Early diagnosis results in early intervention which improves motor, speech, psychological and pre academic skills.

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