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Cornelia de Lange Syndrome A Case Report

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Abstract:

*Cornelia de Lange syndrome (CdLS) is a rare syndrome of multisystem disorder. Almost every system is involved in this disorder having growth retardation, facial dysmorphism, short stature, psychomotor delay and behavioral problems. Diagnosis is made on the basis of clinical observations, physical examination, laboratory tests and X-rays; chromosome analysis is usually conducted before a diagnosis is made. DNA testing is helpful for confirmation of the clinical diagnosis. A 10 year old boy presented with short stature, facial dysmorphism, microcephaly, mental retardation and micromelia. DNA analysis revealed heterozygous mutation in **NIBPL** gene. Patient was counseled about the diagnosis and treatment was given. We reported the case due to rarity of the disease.*

Key-words: *Cornelia de Lange syndrome (CdLS); growth retardation; dysmorphism; Nipped-B-Like (NIPBL)*

Introduction:

Cornelia de Lange syndrome (CdLS), also known as Brachmann de Lange syndrome, is a multisystem disorder involving various congenital malformations, growth retardation, and neurodevelopmental delay.[1] The incidence is 1 case per 10,000 to 50,000 births.[2] There is no race or gender predilection. Most of the children usually die by 2 year of age and the main cause of death is pneumonia along with cardiac, respiratory and gastrointestinal abnormalities.[3] Most cases are sporadic, but an autosomal dominant hereditary pattern has also been reported. It was first reported by Dr. Cornelia de lange, a dutch pediatrician in 1933. Brachmann in 1916 had observed similar features with additional feature of deficiencies of upper limb in child with autopsy.[4]

CdLS has been characterized by retardation in growth, distinctive facial dysmorphism, primordial short stature, psychomotor delay, behavioral problems, hirsutism and upper limb reduction defects that range from subtle phalangeal abnormalities to oligodactyly.[5] Craniofacial features of CdLS include micro brachycephaly, synophrys, arched eyebrows, long eyelashes, depressed nasal bridge, anteverted nares, long philtrum, thin upper lip, high arched palate, late eruption of small widely spaced teeth, micrognathia, spurs in the anterior angle of mandible and prominent symphysis.[6] Currently diagnosis is made on the basis of clinical observations. DNA testing is helpful for confirmation of a clinical diagnosis, but the sensitivity is only 50% for mutations in NIPBL. There is the potential for CdLS to be caused by other genes which have yet to be identified.[7] Here we report a case of CdLS due to rarity of the disease.

Case Report:

A 10 year old boy came to our OPD with the complaints of not growing well since birth. History revealed that the child had low birth weight (1.5 kg), history of convulsions at 17 days of life, delayed milestones and autistic behavior. On examination he had microcephaly (OFC: 44.5 cm) (Z score:-3.4), mental retardation, delayed milestones, can walk at present without support, indicates body parts, obeys simple commands, can speak in sentence of 2-3 words. Facial features revealed: bushy & arched eyebrows, synophrys, long and curly eyelashes, depressed nasal bridge**,** anteverted nares, long philtrum, thin upper lip, downturned angles of mouth, high-arched palate, delayed eruption & crowding of teeth in maxillary arch, low set ear and micrognathia**.** *Hands and feet showed m*icromelia, clinodactyly of fifth finger, syndactyly of 2nd, 3rd and 4th fingers. He had hirsutism and genitalia showed hypoplasia & undescended testes (right side). Anthropometry revealed his height was 123 cm (Z score:-3.1), weight was 28 kg (on 10th centile), BMI was 18kg/m² (50-75th centile).

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Fig.-1: *Craniofacial features of the syndrome*

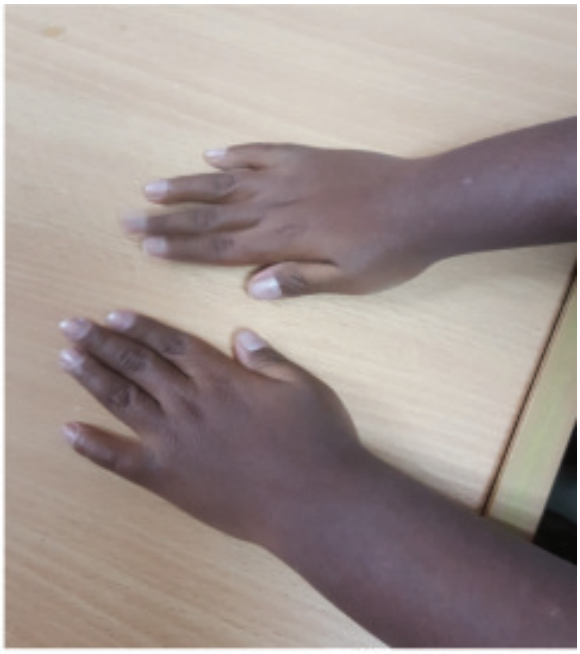

Fig-2: Micromelia.

His karyotype report was 46,XY. His DNA test report (clinical exome) revealed: heterozygous mutation in *NIBPL* gene [a heterozygous 5¹ splice-site variation in intron 2 the *NIBPL* gene (chr5:36953863; G>G/A; Depth: 93x) that affects the invariant GT donor splice-site of exon 2 (c.64+1G>G/A;ENST 00000282516) was detected].

Discussion:

CdLS is a complex congenital anomaly of unknown cause. No age, race, or sex predilection has been reported. The estimation of exact prevalence is difficult because of unknown proportion of milder cases; however, it occurs one in every 10,000 live births, and approximately one third of them have premature birth. The diagnosis is primarily clinical and is based on signs and symptoms of a distinct phenotype, mainly in the face and limbs.[8] Previous studies suggested that the etiology is related to mutations in the Nipped-B-Like (NIPBL) gene which has been identified in 26% to 56% of cases.[9]

The symptoms affect the entire body including cardiac, skeletal, gastrointestinal, visual, and auditory systems. Facial features are the hallmark of the syndrome which includes microbrachycephaly, high forehead, short neck, bushy eyebrows, long curled eyelashes, ptosis, strabismus, small nose, anteverted nostrils, thin upper lip, fish like mouth, long philtrum, cleft palate, micrognathic mandible, prominent symphysis, and spurs in the anterior angle of the mandible. Oral manifestations include cleft palate, macroglossia, microdontia, partial anodontia, and delayed dental eruption.[10,11] Skeletal features include short stature, clinodactyly of toes and fingers, hirsutism, and proximally placed thumbs. Gastrointestinal problems mainly include gastro-esophageal reflux disease (GERD), vomiting, belching, heartburn, or intermittent poor appetite. Visual problems include nystagmus, strabismus, ptosis, or myopia. Auditory defect includes mild to moderate or even severe hearing loss. They have narrow ear canals leading to problem with chronic ear drainage. Cardiac defect includes congenital heart disease, most common being ventricular septal defect. Mental issues are common with average IQ score being 53 which is within the mild to moderate range of mental. Other less frequent findings are seizures, hyperactivity, irritability, sleep disturbances, and self-injurious behaviors.[12,13]

In 2004, the research teams led by Ian Krantz at The Children's Hospital of Philadelphia (CHOP) and Tom Strachan at the Institute of Human Genetics (University of Newcastle), reported the identification of a heterozygous mutation in a gene named NIPBL in a group of individuals with CdLS.[3] The NIPBL is the human homolog of the Drosophila Melanogaster Nipped-B gene, located on chromosome 5, which encodes a protein named delangin. Although its exact function is still unknown, its homologous in other living species is involved in developmental regulation and

in the cohesion of sister chromatids.[3,9] This condition is thought to be inherited by autosomal dominant pattern.[14,15] Almost all cases result from new mutations in the gene and occur in people with no familial history.[16,17]

There is no specific treatment. Management is done by team approach including dental surgeon, cardiologist, gastroenterologist, endocrinologist, urologist, and ENT specialist. Also paediatric neurologist and psychologist consultation are needed for seizures and /or behavior problems and speech/ occupational therapy is needed for rehabilitation. Family support is very much important, specially at the time of diagnosis. It is necessary to provide information to the family about the syndrome, which will help them to cope emotionally and cooperate for the child's treatment.[18]

Our patient is non-consanguinous and has no family history of such problems. He has history of prematurity, low birth weight, seizure, growth retardation, gross developmental delay, behavioral problem, hirsitism and facial dysmorphism which typically consistent with findings in case reported by Gupta D & Goyal S.[5] Features of Craniofacial dysmorphism eg arched eyebrows, long eyelashes, depressed nasal bridge, anteverted nares, high arched palate, late eruption of small widely spaced teeth, micrognathia, and limb deformity like clinodactyly, syndactyly was found in our case which is similar to observation by Beck B & Fenger K.[6] His karyotype was 46, XY and DNA analysis reveals: heterozygous mutation in ***NIBPL*** gene. He was managed with proper counseling about the diagnosis & prognosis, as well as pediatric neurological, endocrinological and surgical consultation was taken and treated accordingly.

Conclusion:

CdLS is a rare syndrome but have well defined features. Affected children suffer from multiple congenital anomalies, developmental delay, psychological and behavioral problems. Karyotype reports are usually normal and some patients have mutation in NIBPL gene. A multidisciplinary team is required to diagnose and treat such a patient.

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