CORNELIA DE LANGE SYNDROME(CdLS) WITH TB ABDOMEN : A RARE CASE REPORT

Dr. Manaswineesahoo, Dr. Sunil Kumar Agarwalla, Dr. Subhranshu Sekhar Dhal & Dr. Debasistapato
Junior Resident, Dept. of Paediatrics, M.K.C.G Medical College, ladies hostel, M.K.C.G Medical College, Berhampur, Ganjam, Odisha, 760004, India
Associate Professor, Dept. of Paediatrics, M.K.C.G Medical College, 1st Lane Jayaprakash Nagar, Ganjam, Odisha, 760010
Junior Resident, Dept. of Paediatrics, M.K.C.G Medical College, Pg Hostel 2, M.K.C.G Medical College, Berhampur, Ganjam, Odisha, 760004, India
Junior Resident, Dept. of Paediatrics, M.K.C.G Medical College, Pg Hostel 2, M.K.C.G Medical College, Berhampur, Ganjam, Odisha, 760004, India

Abstract

Cornelia de Lange syndrome(CdLS) also known as Brachmann de Lange syndrome is a very rare genetic disorder characterized by growth delays; distinctive facial features; malformations of the hands, feet, arms, and/or legs (limb anomalies); other physical abnormalities; intellectual disability; and/or developmental delay. Gastroesophageal reflux disease (GERD) is present in almost all patients. CdLS is genetically heterogeneous and usually sporadic occurring approximately one per 10,000 births. CdLS is caused by gene mutations affecting proteins involved in sister chromatid cohesion. Here we document a case of CdLS who presented to us with TB abdomen

Introduction

Cornelia de Lange syndrome is a genetically heterogeneous disorder affecting multiple aspects of development. It may be highly variable in expression. This variability is highlighted by the earliest reports of this entity by Vrolik in 1849[1] and Brachmann in 1916[2].

The phenotype is distinctly recognizable but can be highly variable in its expression. Almost all organ systems can be affected, but typical involvement includes the craniofacial structures, upper extremities, eyes, gastrointestinal system, hearing and to a lesser degree the heart, diaphragm and genitourinary system.[4,5,6,7]

The main facial characteristics include arched eyebrows, synophrys, ptosis, long eyelashes, microcephaly, anteverted nares, long philtrum and thin upper lip with micrognathia. The consistent facial dysmorphisms have provided the most helpful features in establishing a diagnosis. Developmental delays and mental retardation are close to universal and generally moderate to severe. Gastrointestinal issues include reflux, which is almost universally present. Growth is generally retarded with prenatal onset and mean adult heights in males is 156 cm and 131 cm in females[8]
CdLS is a genetically heterogeneous disorder involving multiple genes, all of which are involved in sister chromatid cohesion. Most CdLS cases are sporadic and dominant. At least half are caused by loss-of-function mutations in the *Nipped-B-Like (NIPBL)* gene on chromosome 5.[9,10,11]

Severe *NIPBL* mutations (such as deletions or truncations) usually cause more severe clinical manifestations than missense mutations. Brain is the organ most sensitive to the perturbations of sister chromatid cohesion factors. They may also be prone to behavioral problems such as hyperactivity, short attention span, and oppositional or repetitive behavior.

The incidence of congenital heart disease in children with CdLS is as high as 20 to 30 percent (compared to 0.8 percent for all births). Language is an area of weakness, and may be compounded by hearing problems. Many individuals with CdLS also have various abnormalities of the gastrointestinal system including gastroesophageal reflux.

**Case presentation**

A 8 years old female child, 1st order, a product of non consanguineous marriage from low socioeconomic status admitted to our hospital with complaints of pain abdomen and constipation for 3 months with low grade intermittent fever associated with weight loss, not associated with vomiting, blood in stool or cough. There is a history of contact with Tuberculosis in the neighbourhood. Family and sibling history nothing suggestive. It’s a neurodevelopmental delay child who is unable to speak with normal hearing and immunised as per age. O/E-child was conscious, oriented, afebrile with HR 88/min, RR 26/min, spo2 92% in room air, BP 90/50 mm Hg in right arm supine position. Anthropometry: Ht=101cm (<-3SD), Wt=11kg (<-3SD), HC=47cm.

On head to toe examination: child is cachectic, having synophrys, long eyelashes, two widely spaced central incisors, angularchelitis, small lateral 3 toes. Having some pallor, no icterus, cyanosis, clubbing, lymphadenopathy or edema. On systemic examination per Abdomen: on inspection: slightly distended, umbilicus central, no scar mark and visible veins, no visible peristalsis. On palpation: tender, mass of 6×8 cm found over right iliac fossa which is deep seated, not moves with respiration with no organomegaly or free fluid found. On auscultation: bowel sounds present. All other systems normal. On investigation: CBC, PS Comment normal, ESR 10 mm, sickling negative. ICTC non reactive. Gastric aspirate for AFB not found. Chest x-ray normal. USG abdomen pelvis shows evidence of ilioceacal tuberculosis (bowel wall thickening, interloop adhesion and interloop fluid) with few enlarged mesenteric lymphnodes (10-20 mm).

**Case discussion**

CdLS is a genetically heterogeneous developmental disorder affecting multiple organs. The phenotype is distinctively recognizable but has a high degree of variability. Affected individuals typically show slow pre- and postnatal growth, and varying degrees of developmental delays and mental retardation at times associated with autistic features.[12,13] It can involve many organs but typical involvement includes the craniofacial structures, upper extremities, eyes, gastrointestinal system, hearing.

They have characteristic abnormalities of the head and facial (craniofacial) area, resulting in a distinctive facial appearance; an unusually small, short head (microbrachycephaly); a prominent vertical groove between the upper lip and nose (philtrum); a depressed nasal bridge; upturned nostrils (anteverted nares); and a protruding upper jaw (maxillary prognathism) with small chin (micrognathia). Other characteristic facial abnormalities may include thin, downturned lips; low-set ears; arched, well-defined eyebrows that grow together across the base of the nose (synophrys); an unusually low hairline on the forehead and the back of the neck; and curly, unusually long eyelashes.

In most infants with CdLS, the hands and feet are small for their size. Fifth fingers that are permanently curved toward the ring finger, and/or, in some people, absence of one or more fingers (oligodactyly). The thumbs may be abnormally positioned (i.e., proximally placed).
CdLS can be inherited as an autosomal dominant condition or an X-linked condition. Five genes have been found to be associated with CdLS including the NIPBL gene on chromosome 5, the SMC1A gene on the X chromosome, the SMC3 gene on chromosome 10, the Rad21 gene on chromosome 8 and the HDAC8 gene on the X chromosome. Most common (50%) is due to loss-of-function mutations in the Nipped-B-Like (NIPBL) gene on chromosome 5.[9,10,11]

NIPBL is required for binding of the cohesin complex that mediates sister chromatid cohesion to chromosomes.[14] CdLS may also be dysrhythmic, meaning they have irregular patterns of behavior in the areas of eating, sleeping and emotional response. The incidence of congenital heart disease in children with CdLS is as high as 20 to 30 percent (compared to 0.8 percent for all births). Individuals with CdLS may have very severe myopia (nearsightedness). So, they need to have a complete ophthalmologic check up. Gastro esophageal reflux is near to universal in these children. Constipation, diarrhea and gaseous distension with cramping are common problems. Speech problems are common. Most children with CdLS exhibit errors in articulation, with sound substitutions and distorted or missing consonants. Augmentative and Alternative Communication (AAC) skill strategies include communication boards; American Sign Language; American Indian Hand Talk or Amer-Ind gestural code; Blissymbolics; Total Communication; Pantomime; a manual alphabet; eye-blinking encoding; or electronic communication aids.

Most children with CdLS are diagnosed clinically after birth or in childhood based upon a thorough clinical evaluation and identification of characteristic physical findings. Molecular genetic testing for mutations in the five genes associated with CdLS is available to confirm the diagnosis. Prenatal diagnosis is available if a specific NIPBL, SMC1A, SMC3, Rad21 or HDAC8 gene mutation has been identified.

Treatment may require the efforts of a team of specialists working together including pediatricians; geneticists; surgeons; orthopedists, plastic surgeons; orthopedic surgeons; gastroenterologists, urologists, otorlaryngologists; speech pathologist, audiologists, physical and occupational therapists; and/or other health care professionals. Specific therapies for the treatment of CdLS are symptomatic and supportive. Early intervention is important in ensuring that children with CdLS reach their highest potential. Genetic counseling is recommended for affected individuals and their families. Other treatment is symptomatic and supportive.

Conclusion
It is a very rare genetic syndrome usually diagnosed by its typical phenotypic features. Normally G.I. complaints are common in the children but our case presented with pain abdomen with mass in right iliac fossa. After investigation found to have tubercular abdomen. There should be high degree of suspicion of TB in a case presenting with cachexia, pain abdomen, unexplained fever for 3 months and mass abdomen. Child was advised ATT, CAT -1 (as per RNTCP) for 6 months and counseled for speech therapy and follow up. After two months child became afebrile, no further pain abdomen, mass in right iliac fossa decreased in size, regained appetite. After 6 month followup, she regained 5kg weight and became free from abdominal symptoms. Any child with short stature, mental retardation, microcephaly having typical features like synophrys, long eyelashes one has to suspect CdLS.

References