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Case Report

An eighteen month-old infant with Cornelia de Lange syndrome: a case report

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ABSTRACT

Cornelia de Lange syndrome (CdLS) is an uncommon multiple congenital anomaly with unknown cause and recurrent risk and may be the result of an inheritance metabolic error.

In classical form of the syndrome there is a recognizable facial appearance at birth although in children with mild disease this may be less obvious at birth but become more noticeable over the first three years of life.

In this article we present an infant with multiple congenital anomaly who finally diagnosed as Cornelia de Lange syndrome.

Keywords: Cornelia de Lange syndrome, congenital anomaly, neonate

Introduction

Cornelia de Lange syndrome (CDLS) is a rare dysmorphogenic disorder that occurs in about 1:10,000 to 1:100,000 live births in different population groups. [1]

CDLS was first described by Sir Cornelia de Lange, a Dutch pediatrician in 1933. [2] This syndrome is also called as Brachmann de Lange syndrome (BDLS) since he reported a patient with similar symptoms at autopsy in 1916. [3]

This syndrome is relatively uncommon multiple congenital anomaly with unknown cause and recurrent risk and may be the result of an inheritance metabolic error. [4]

There is no racial predilection. It is slightly more common in females as compared to males (F/M: 1.3/1).

Most children with this syndrome could not live more than 2 years and the main cause of death was pneumonia along with cardiac, respiratory, and gastrointestinal abnormalities. [5]

CDLS is a multisystem developmental disorder characterized by growth and developmental retardation, low birth weight, hirsutism, anomalies in the structure of the upper limbs, gastroesophageal dysfunction, ophthalmologic and genitourinary anomalies, congenital diaphragmatic hernia, cardiac septal defect, distinctive facial features, learning difficulties, and mental retardation. [6]

The facial characteristics are the most diagnostic, with microcephaly, the neat, well-defined, and

arched eyebrows growing across the base of the nose (synophrys or confluent eyebrows), long curly eyelashes, short neck with low anterior and posterior hairlines, long philtrum, generalized hirsutism, thin lips, micrognatia, a small nose with low bridge, low set ears, and crescent-shaped mouth.[7]

Heterozygous mutations in the *NIPBL* and *SMC3* and heterozygous (in females) or homozygous (in males) mutations in *SMC1A* result in Cornelia de Lange syndrome. Most cases are sporadic due to de novo mutations and 10% of the cases present chromosomal alterations, such as a small duplication of the long arm of chromosome 3 or unbalanced chromosomal rearrangement. [8, 9]

This syndrome is mainly between various other rare genetic disorders and fetal alcohol syndrome. The diagnosis is based on a characteristic phenotype. In some cases, molecular analysis of the NIPBL gene allows confirmation of a mutation and provides the basis for prenatal diagnosis in families with transmission from a parent. Investigations may be indicated for the various abnormalities like Hearing screening , Echocardiography and ultrasound screening of the renal tract, CT scanning of the temporal bone can

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be used to identify typical abnormalities of the external auditory meatus, middle and inner ear.[10]

Case presentation

An 18 month-old female infant was born at Mehr hospital with multiple congenital anomalies and seizure. She was the first baby of a non-consanguineous marriage. She was born preterm (30 weeks gestation age), by normal vaginal delivery resultant in vitro fertilities (IVF). She had arched like confluent eyebrows and well-defined, long curly eyelashes, low posterior hairline, short neck, depressed nasal bridge, down-turned angles of the mouth and thin lips, cleft palate, microcephaly, hands deformity include clinodactyly and brachydactyly of left fifth fingers with simian creases, short leg, hypotonicity, and small labia majora. (Figures 1, 2,3).

There were another signs and symptoms include: Renal anomaly (cystic and horseshoe kidney), systolic murmur (2/6), Eye malformation, micriophtalmia and visual disorders, ear deformity and abnormal Auditory Brainstem Response (ABR).

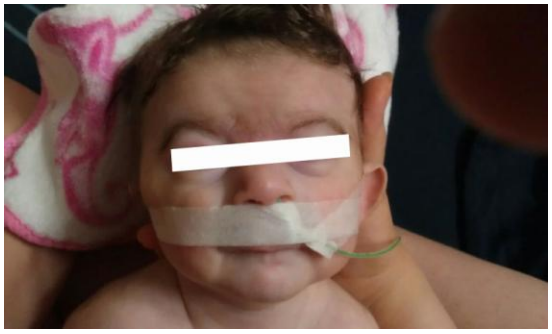

Figure 1: patient face

Laboratory analysis including complete blood count, biochemical parameters and urinalysis were normal. Transthoracic echocardiography showed patent foramen ovale and Fallot's tetralogy (TOF). Cranial magnetic resonance imaging show mild ventricles distention. Chromosomal analysis was done on peripheral blood lymphocytes according to conventional techniques. The Cytogenetic analysis revealed a normal female karyotype (46, XX).

One mutation c. 1973_ 1982 delCAACTGAATG (p. Thr658ThrfsX8: Hom) on NIPBL gene has been detected. Although this mutation has not been reported. The frequency of it in normal population is very low. The mutation leads to termination of the amino acid coding, which is expected to affect the protein's function. NIPBL-Cornelia de Lange syndrome 1 is inherited in autosomal dominant manner.

Figure 2: hand deformity

Discussion

No environmental cause has been discovered. Although an autosomal dominant, autosomal recessive and chromosomal anomaly have been suggested, most cases are sporadic. [11]

Mutations in the NIPBL, SMC1L1, and SMC3 genes cause CdLS. In 2004, two independent groups found that 26–56% of patients with CdLS carry a heterozygous mutation of the NIPBL gene localized on 5p13.2. [12, 13]

The NIPBL gene is the human orthologue of Drosophila Nipped-B and yeast Scc-2 and belongs to the family of chromosomal adherins involved in chromatid cohesion processes and enhancer-promoter communications [14, 15]. An X-linked form of CdLS was reported in three male members from the same family and in one sporadic case, demonstrating the common combination of symptoms in the spectrum of CdLS, caused by mutations in the SMC1L1 gene which encodes a subunit of the cohesion complex [16]. The SMC1L1

Gene provides instructions for making a protein that helps regulate the structure and organization of chromosomes.

Genotype-phenotype correlations in the study of Gillis et al. [17] and Yan et al. [18] showed significant differences between patients with and without mutations in terms of the degree of growth retardation and developmental delay. In a different study on 39 sporadic cases of CdLS from the Netherlands, truncating NIPBL mutations were prevalently detected in CdLS patients of the classical type [19].

Due to the characteristic facial features, the physiological findings, and the presence of a normal karyotype, the patient was diagnosed as CDLS.[20]

In classical disease there is a recognizable facial appearance at birth. In children with mild disease this may be less obvious at birth but become more noticeable over the first three years of life; however, the characteristic face is lost by adulthood.

In some patients, extreme short stature may be caused by growth hormone deficiency. Specific growth curves in Cornelia de Lange syndrome are available. Average adult weight is 30.5 kg in females and 47.6 kg in males; average height is 131 cm in females and 156 cm in males.

Average adult head circumference is 49 cm in both sexes and Microcephaly is common (98%).

classic Facial features are include: Confluent eyebrows (synophrys) (99%), Long curly eyelashes (99%), Low anterior and posterior hairline (92%), Underdeveloped orbital arches (100%), Neat, well-defined, and arched eyebrows (as though they had been penciled), Long philtrum, Anteverted nares (88%), Down-turned angles of the mouth (94%), Thin lip (especially upper vermillion border), Low-set and posteriorly rotated ears, Depressed nasal bridge (83%), High arched palate (86%) and overt or sub mucous cleft palate (20%), Late eruption of widely spaced teeth (86%), Micrognathia (84%), Short neck (66%), Hirsutism (78%), Generalized hirsutism (is observed most easily in dark-haired individuals), Cutis marmorata and perioral cyanosis (56%), Hypoplastic nipples and umbilicus (50%), Micromelia (93%), Severe abnormalities, such as oligodactyly (missing digits) or other deficiencies of the arms, may be present (27%). They usually occur in severely affected patients.

Less-striking limb findings include single palmar flexion crease, clinodactyly of the fifth fingers, proximally placed thumbs, partial syndactyly of the second and third toes, and limitation of elbow extension.

Relative smallness of the hands or feet is almost universal.

Congenital heart disease (25%), typically ventricular septal defect or atrial septal defect: Any lesion may be seen.

Hip abnormalities, including dislocation or dysplasia (10%), scoliosis, tight Achilles tendons and the development of bunions.

Hypo plastic external male genitalia (57%), small labia majora, undescended testes (73%), Hypospadias (33%), are another signs and symptoms.

Ophthalmologic manifestations had seen in 50% of cases includes: Myopia (58%), ptosis (44%), blepharitis (25%), epiphora (22%), microcornea (21%), strabismus (16%), nystagmus (14%) occur.

Although sensorineural hearing loss is a significant cause of auditory impairment in Cornelia de Lange syndrome, a study by Marchisio et al found conductive hearing loss in 26 of 44 (59%) pediatric patients with the syndrome.[21, 22]

Chromosomal analysis was performed to find out if there were chromosomal imbalances or gross rearrangement of the drosophilia nipped B gene (NIPBL) or SMC1L1 gene regions.

Analyses for mutations in these genes are not currently available in Iran.

Nonetheless, based on the clinical features, the present patient was believed to be the first CDLS case reported in the Iran.

Ellaithi *et al.* reported a case of BDLS from Sudan for the first time. The patient was a 7-month-old female infant, who was refereed as a case of malnutrition. Clinical investigation showed that the child was a classic case of BDLS. [18]

Kim *et al.* evaluated ophthalmologic problems, for the first time, in a case of CDLS. They presented a case of CDLS in an 18-year-old female with a superficial keratitis with entropion, ptosis, high myopia, lacrimal cutaneous fistula, and facial appearance.[19] Also, Badoe, Grau Carbó *et al.*, Muhammed *et al.* described cases with clinical features of CDLS.[20–22]

Unfortunately In one series, 68% of cases with major abnormalities were not detected by this method. [23]

However Second trimester maternal serum pregnancy-associated plasma protein-A (PAPP-A) measurements may have predictive value as an addition. [24]

Conclusion

Cornelia de Lange syndrome is a rare syndrome with diagnostic distinctive facial features, limb anomalies and growth retardation that we should attend it in perinatal diagnosis.

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