Cornelia de Lange syndrome

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Abstract :
In this paper we present an 8 years old boy with the classical features of Cornelia de Lange Syndrome which is characterized by retardation and other features namely ,the eyebrows are thick and convergent (synophrys) and eyelashes are markedly hypertrichotic. The patient's face displays a low frontal hairline with a low forehead, frequently covered with vellus hair and low back hairline that extend to the neck, back, and extremities.
Other characteristic facial features include upturned nostrils with a depressed nasal bridge, low-set ears, cutis marmorata and extensive vellus hypertrichosis on the trunk, posterior neck, sacrum, and elbows.

Introduction :
Cornelia de Lange syndrome also known as Brachmann de Lange syndrome is a multisystem developmental disorder characterized by facial dysmorphism, growth and mental retardation, microcephaly, and various malformations. (1)
The distinctive facial features include synophrys , long eyelashes, depressed nasal bridge with an uptilted nasal tip and anteverted nares, thin upper lip with downturned corners of the mouth, and posteriorly rotated low-set ears. Abnormalities in the upper extremities range from subtle changes in the phalanges and metacarpal bones and small hands to oligodactyly and severe reduction defects. Gastrointestinal abnormalities include gastroesophageal reflux, intestinal malrotation, and pyloric stenosis. Additional relatively frequent features include hearing loss, ptosis and myopia, palatal abnormalities, cryptorchidism and hypospadias, cardiac septal defects, and congenital diaphragmatic hernias. Growth retardation is an almost universal finding in CdLS and typically has a prenatal onset. The mental retardation in CdLS is often severe, with a mean IQ of 53 (range 30–86) .Many patients also demonstrate autistic-like behavior and self-injurious behavior. (2)

Etiopathogenesis:
Genetic studies showed mutations in the NIPBL, the human homolog of the Drosophila melanogaster Nipped-B gene,SMC1A, (structural maintenance of chromosomes 1-like 1; or SMC1A)and SMC3 genes cause Cornelia de Lange syndrome. (2,5,6)

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Heterozygous mutations in the NIPBL gene have been detected in approximately 45% of affected individuals. The NIPBL gene is located on the short (p) arm of chromosome 5 at position 13.2. (4,6,7)
This gene provides instructions for making a protein called delangin. Although the exact function of this protein is unknown, it appears to play an essential role in directing development before birth. Delangin regulates the activity of other genes in the developing limbs, face, and other parts of the body. NIPBL mutations lead to the production of an abnormal or nonfunctional version of this protein. These changes disrupt the regulation of genes involved in normal development, leading to the varied signs and symptoms of Cornelia de Lange syndrome.
Mutations in the SMC1A gene (structural maintenance of chromosomes 1-like 1; or SMC1A). appear to be a less common cause of Cornelia de Lange syndrome. Although individuals with mutations in this gene have many of the major features of the condition, the signs and symptoms tend to be milder than those seen with NIPBL mutations. The SMC1A gene (structural maintenance of chromosomes 1-like 1; or SMC1A) provides instructions for making a protein that helps regulate the structure and organization of chromosomes. Like delangin, this protein probably also controls the activity of certain genes that are important for normal development. Mutations in the SMC1A gene may cause features of Cornelia de Lange syndrome by disrupting the regulation of critical genes during early development.
When Cornelia de Lange syndrome is caused by mutations in the NIPBL or SMC3 gene, this condition is considered to have an autosomal dominant pattern of inheritance. Almost all cases result from new mutations in the gene and occur in people with no history of the condition in their family.(1, 2, 4)
Cases of Cornelia de Lange syndrome caused by SMC1A mutations have an X-linked pattern of inheritance. X-linked Cornelia de Lange syndrome appears to affect males and females similarly. Most cases result from new mutations in the SMC1A gene and occur in people with no history of the condition in their family. (9,10)

Case report :
An 8 years old boy presented with Low anterior hair line of forehead and low posterior hairline of the neck, well-defined, and arched eyebrows (as though they had been penciled),Long philtrum ,Anteverted nares ,down-turned angles of the mouth.Thin lip (especially upper vermillion border), short neck , cutis marmorata, relative smallness of the hands (micomelia) is noticed.

Discussion :

We depend mainly on the clinical pictures of the patient for the diagnosis of the syndrome , however laboratory studies are available, such laboratory studies may include:

I- Molecular diagnosis with screening of the NIPBL gene .This testing can confirm the diagnosis, especially in mild or atypical cases, and the results can help in identifying the family-specific mutation for prenatal testing in future pregnancies.

II- High resolution chromosomal studies when the diagnosis is uncertain

III- Thrombocytopenia has been reported in some cases .

IV- Imaging studies may help to reach the diagnosis of Cornelia de lange syndrome (cdls).

A- Radiography may show the following anomalies :

Bone Changes :

Retarded bone age (100%),

Spurs in the anterior angle of the mandible (42%) and a prominent symphysis (66%), Digital abnormalities, which range from acheiria to oligodactyly, Long-bone abnormalities, including ulnar aplasia and/or hypoplasia, aplasia and/or hypoplasia of the radial head,

or fusion of the elbow (When a single forearm bone is present, fusion at the elbow and oligodactyly often occur; this condition makes it difficult to determine if the radius or ulna is absent.),

Hypoplastic first metacarpal (79%), Pelvic abnormalities (33%).

hypoplastic fifth middle phalanx (93%), and clinodactyly (64%) ,

Short sternum with precocious fusion (54%),Thirteen ribs (56%), Thin rib cortices with undulating appearance (33%) , Hiatal hernia , Gastroesophageal reflux (58%) ,

Intestinal obstruction (17%) .[10]

B- Ultrasonography to diagnose to assess the kidney and urinary tract :

(40%) of Cdls may show the following abnormalities:

Horseshoe kidney , Altered corticomedullary differentiation ,

Pelvic dilation , Vesicoureteral reflux,

Small kidneys , Renal cysts , Renal ectopia

C- Echocardiography may be indicated if congenital heart disease is suspected.

Patients with cornelia de lange syndrome need consultation in the field of geneticist, Cardiology , Gastroenterology and Nephrology , opthalmolgy, endocrinology , orthopedic and nutrition plus social and special education care .

Hearing evaluation is recommended as more than 90% of individuals with Cornelia de Lange syndrome have sensorineural hearing loss when properly evaluated.

Patients with Cornelia de Lange Syndrome need special care medically , educationally , socially and psychologically as they are handicapped by hearing loss , visual, other musculoskeletal and systemic affection abnormalities.

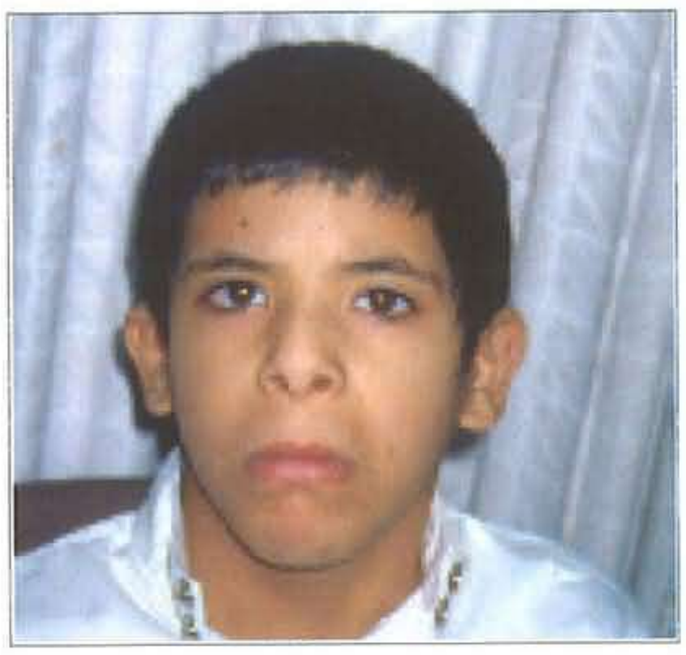

Fig. 1 The distinctive facial features include Low anterior hair line of forehead and low posterior hairline of the neck, well-defined, and arched eyebrows (as though they had been penciled), Long philtrum, Anteverted nares, down-turned angles of the mouth. Thin lip (especially upper vermillion border), short neck.

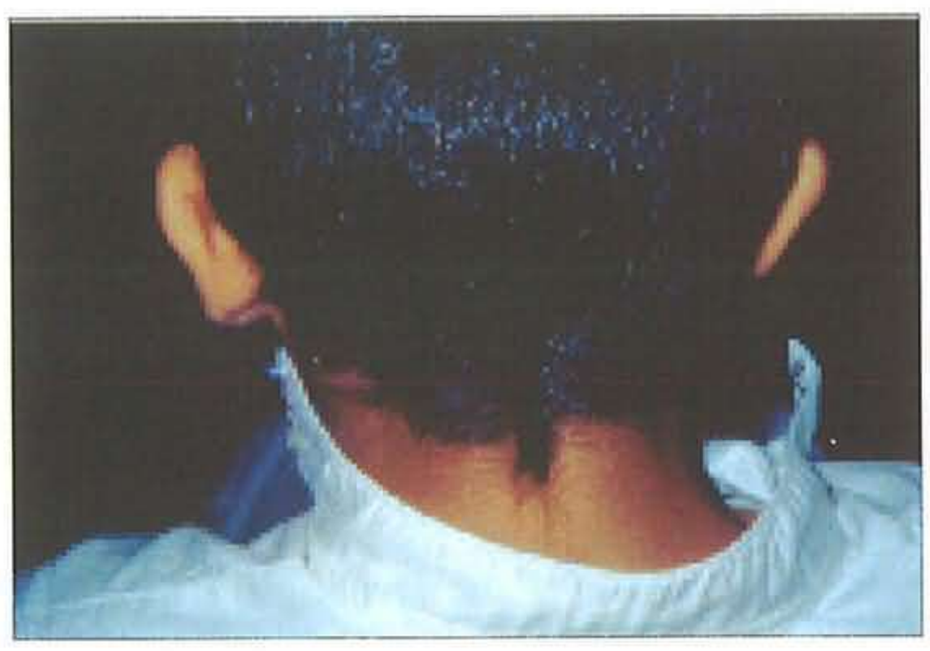

Fig. 2 Low posterior hairline of the neck

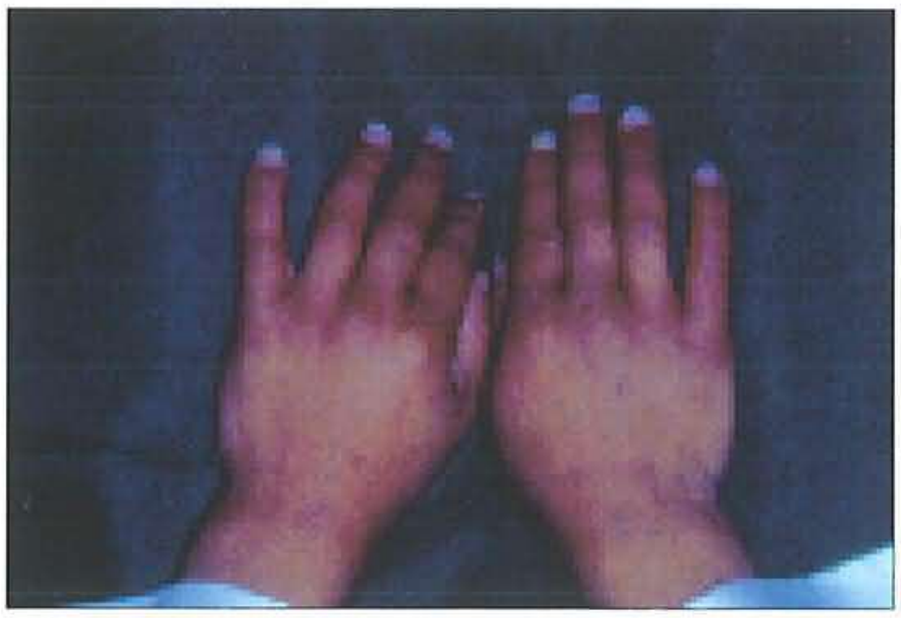

Fig. 3

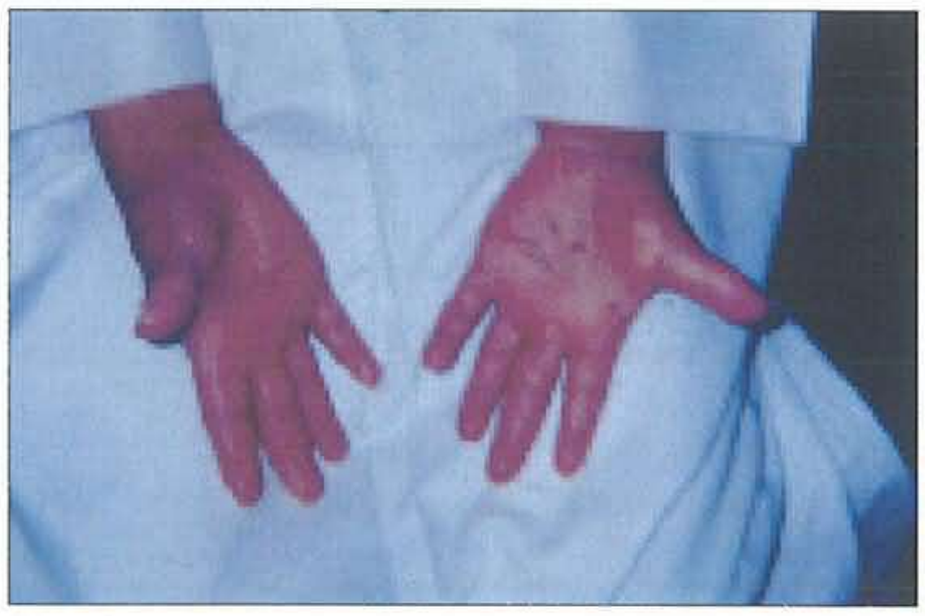

Fig. 4

Relative smallness of the hands (micomelia)

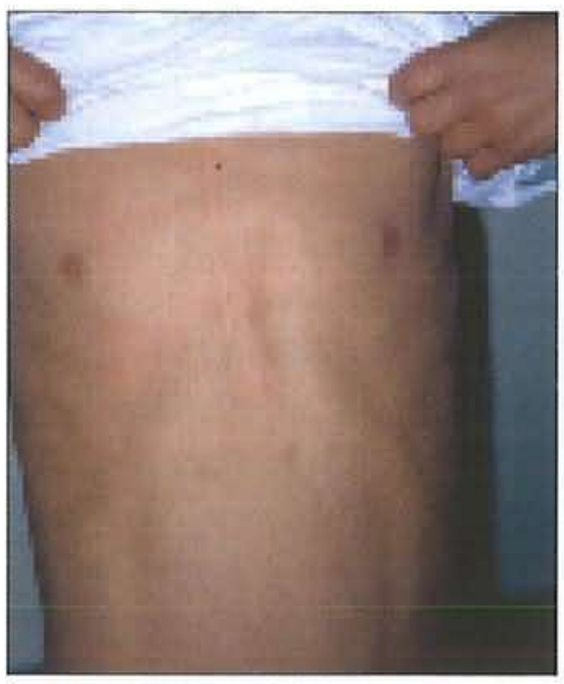

Fig. 5 Cutis Marmorata

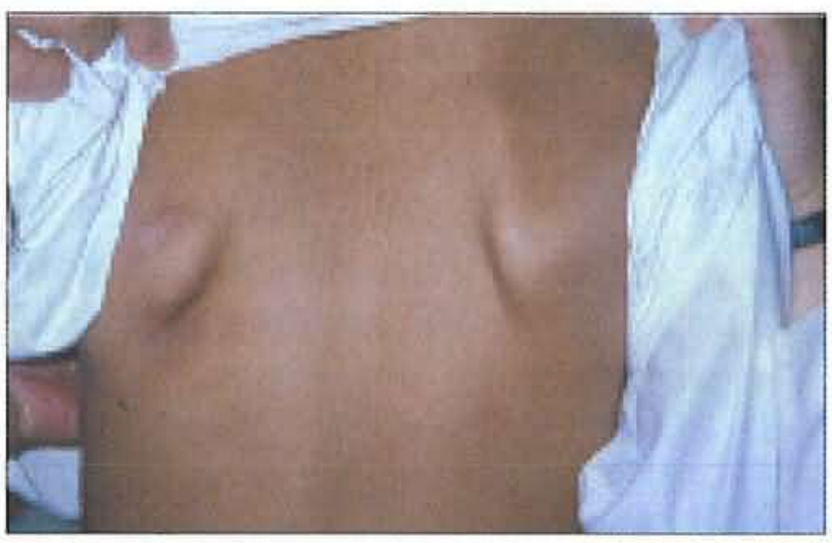

Fig. 6 Winged scapula

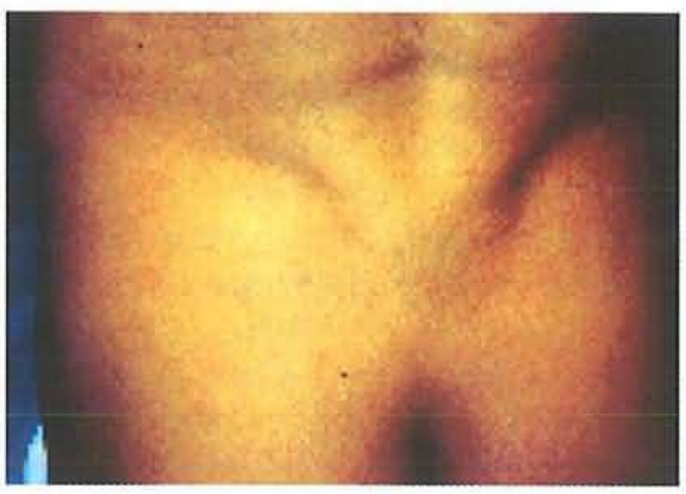

Fig. 7 Hypertrichosis

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