Cornelia de Lange Syndrome

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This entity was first described in 1933 by the Dutch physician, Cornelia de Lange, who coined the term **Typus Degenerativus Amstelodemensis.**[1] The condition comprises multiple congenital malformations associated with a typical face. It has since been reported from many parts of the world, but, to the best of our knowledge, these are the first cases of the syndrome to be published in this country. In this communication, in addition to reporting two cases, the results of chromosome studies from various parts of the world will be reviewed.

Case I

Case Reports

A five-month-old male infant was brought to Hacettepe Hospital with chief complaints of convulsions, diarrhea and vomiting. His history revealed that he was the product of an eight-month pregnancy and that labor had been prolonged. There had also been frequent vaginal bleeding, especially during the first month of pregnancy, and the mother had had x-ray studies for abdominal pain, for which she was also given medications, but she was unable to inform us what these were. The mother's records at the maternity hospital revealed that the amniotic membranes ruptured ten hours before delivery, and that she had polyhydramnios. She also claimed that the infant's intra-uterine movements were weak.

The patient's birth weight was 2.2 kg and his length 45 cm. He was found to have generalized cyanosis after birth, associated with frequent

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vomiting which resulted in feeding difficulties. It was also found that at the age of six days he had been ill with a high fever for which he was hospitalized for three days, but no information could be obtained as to the nature of this disease.

Family History: The mother was 22 and the father 28 years old, and there was no consanguinity between them. Two female sibs, four and seven and a half years of age, were alive and in good health. The mother had had no abortions. One significant finding was that the child of a maternal uncle was blind, deaf mute and had congenital dislocation of the hip.

Physical Examination: Weight was 3.8 kg (< three percentile), length 52 cm (< three percentile) and chest measurement was 37 cm. The face showed the characteristic findings for Cornelia de Lange Syndrome, including abundant hair, which even covered the forehead, thick eyebrows meeting over the bridge of the nose, long eyelashes, and a small nose with a depressed bridge, which resulted in an increased distance between the lower end of the nose and the upper lip. (Figure 1 - 2) The latter itself was thin and gave the area a certain degree of monkey-like protrusion. The neck was short, the ears larger and lower set

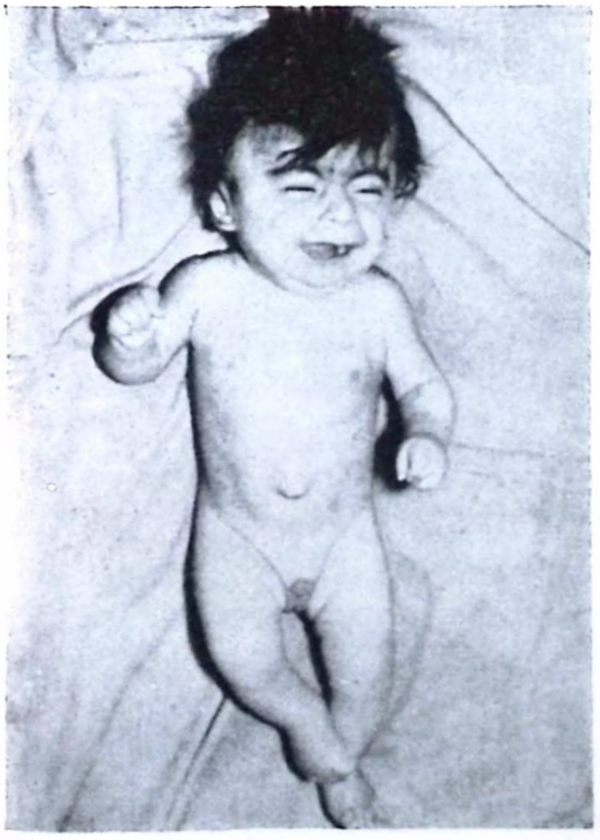

Figure 1

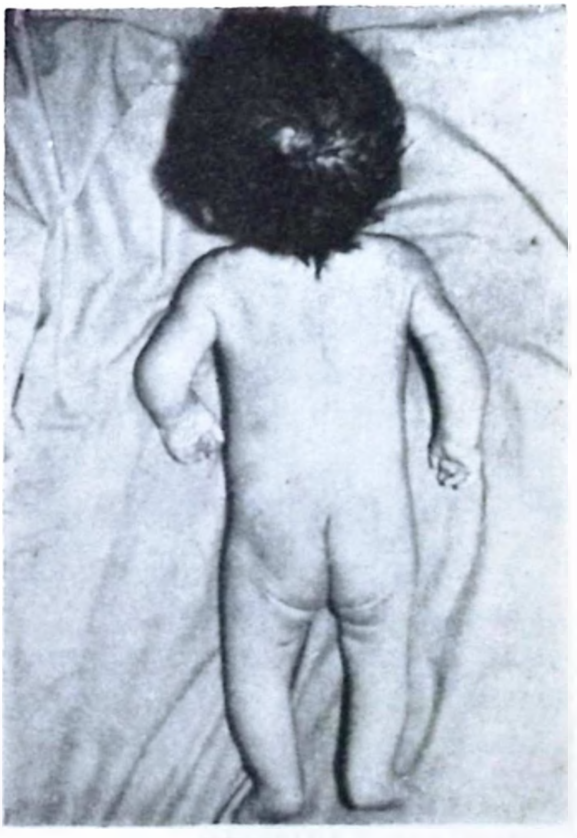

Figure 2

than normal, and the chin was small. (Figure 3 a and b). There was moderate generalized spasticity, and the patient's development was retarded. The extremities were short and the hands, especially, were

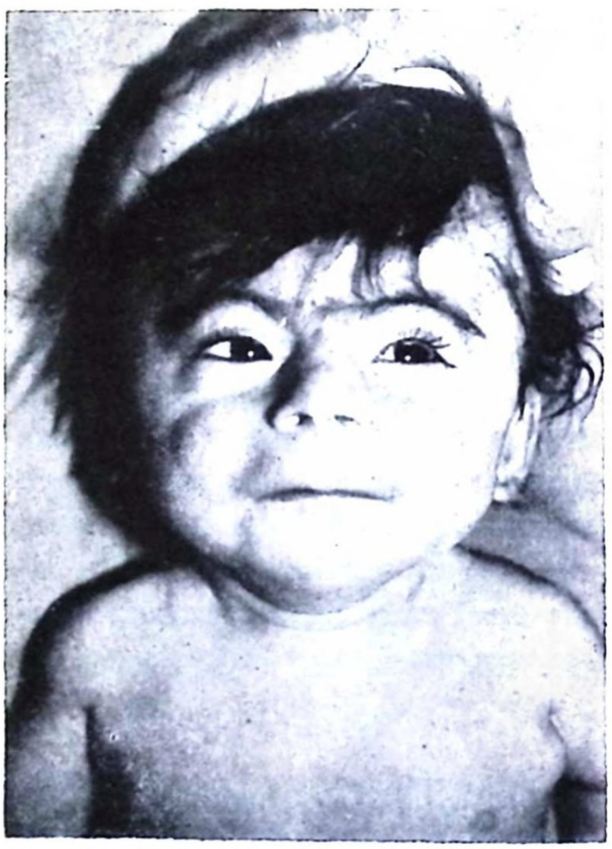

Figure 3 a

Figure 3 b

very small. There was a simian line on the right palm and clinodactyly involving both fifth fingers (Figure 1). The thumbs were low set and both hands and feet were edematous in appearance. There was bilatera cutaneous syndactyly involving the second and third toes (Figure 4). The nippleswere hypoplastic, there was a moderate-sized umbilical hernial and the testes were undescended. The patient had a low-pitched cry. Eye examination showed astygmatism associated with myopia.

Laboratory Findings: Routine blood and urine analysis showed no abnormalities. PBI was 4.36 8/100 ml, BEI was 3.138 8/100 ml, and the other blood chemistry findings were within the normal limits. Buccal smear also showed normal findings for a male (chromatin positive cell number 1 %).

X-ray Findings: There was a butterfly anomaly involving the first and second thoracic vertabrae, and the ribs showed various mild defor-

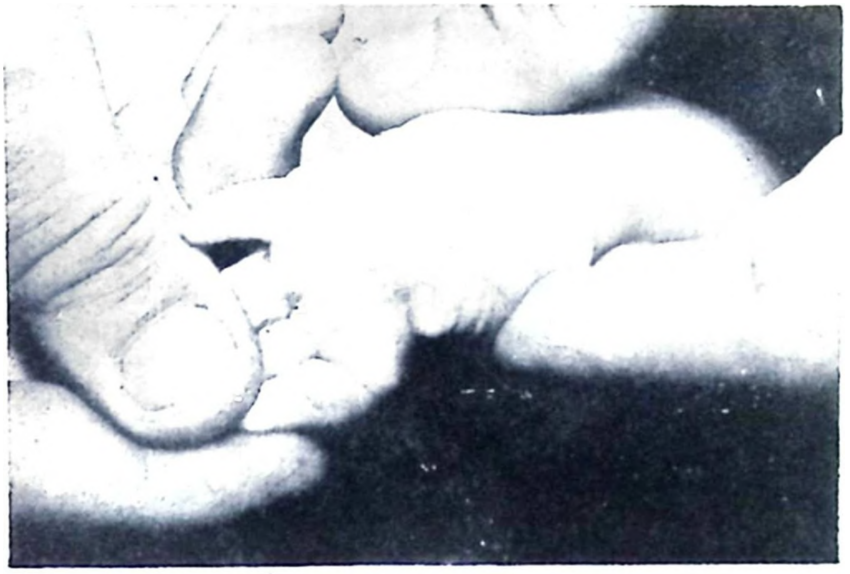

Figure 4

mities. (Figure 5) In the lower extremities a bony hypertrophy was seen involving the femural bones bilaterally adjacent to the trohanter minor. There was also new sub-periosteal bone formation laterally along the diaphysis of the femur. (Figure 6) The maxillary bones, as well as the first metacarpals, revealed bilateral hypoplasia. (Figure 7) Intravenous pyelogram and upper and lower gastro-intestinal series showed no abnormalities The bone age was also within the normal limits. Chromosome studies, using peripheral leukocytes, revealed no aberrations.

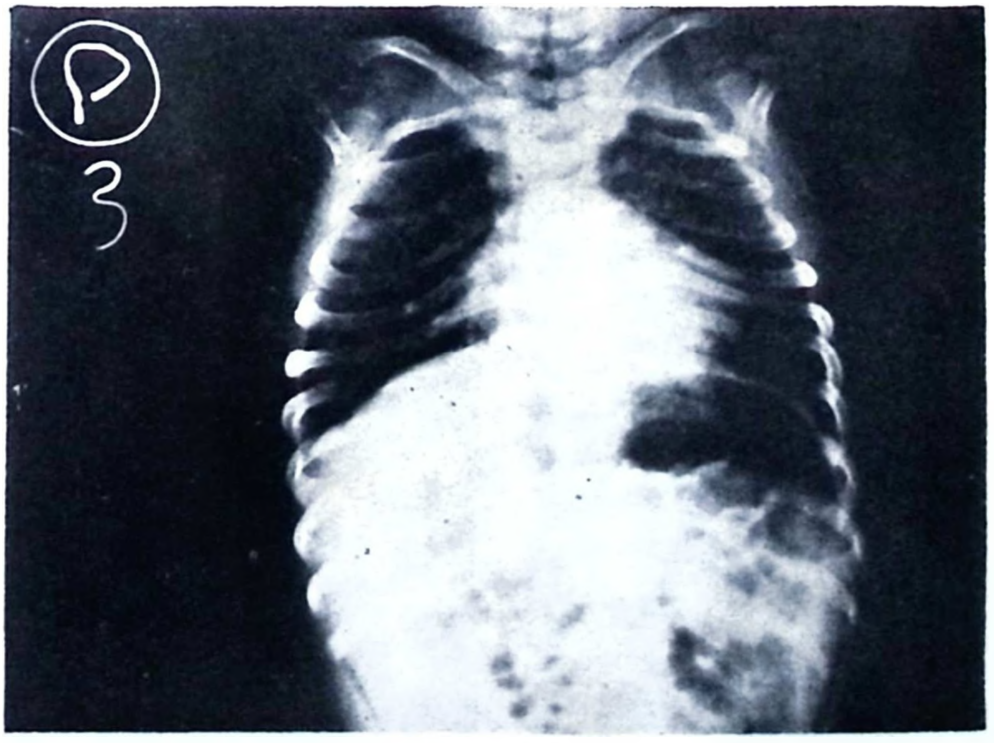

Figure 5

Dermatoglyphic analysis gave the following findings: there were whorls on the first, second and fifth fingers of the left hand, and ulnar loops on the first, second, fourth and fifth fingers of the right hand. The third and fourth fingers of the left hand had low arches, and the third finger of the right also showed a whorl. Axial triradii were in the t'' position bilaterally. The dermal lines in the hypothenar area of the right hand were very hypoplastic, as were the dermal ridges in the hypothenar area of the sole of the left foot. The hallucal areas of both soles showed distal whorl patterns. (Figure 8)

Case II

This five-year-old male was admitted for evaluation of multiple congenital anomalies, recurrent conjunctivitis and failure to thrive. He was born on May 15, 1964 the fifth child of the mother. The pregnancy was uncomplicated, and of normal duration. The mother and father who were healthy, were 30 and 35 years old respectively at the time of the birth. There were four healthy siblings. Consanguinity was present, the mother being a paternal first cousin of the father. The mother had no miscarriages, and no exposure to irradiation or terotogenic substances.

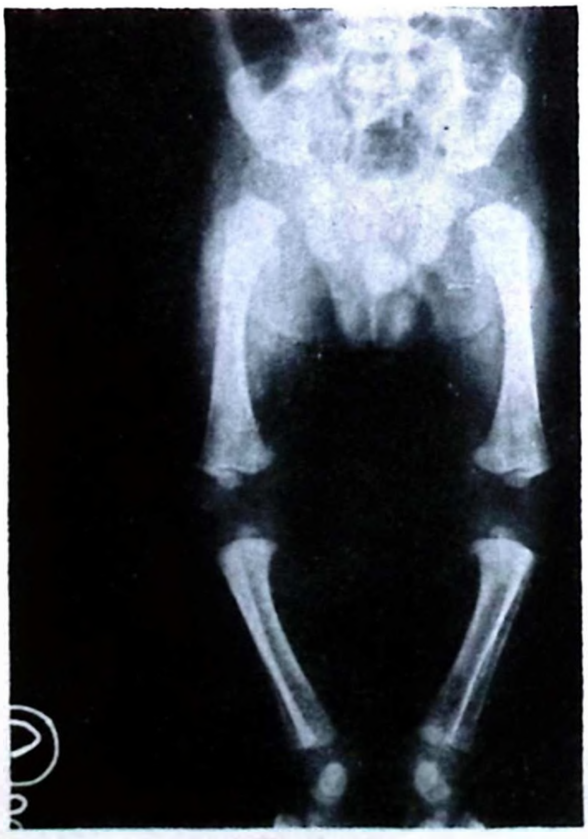

Figure 6

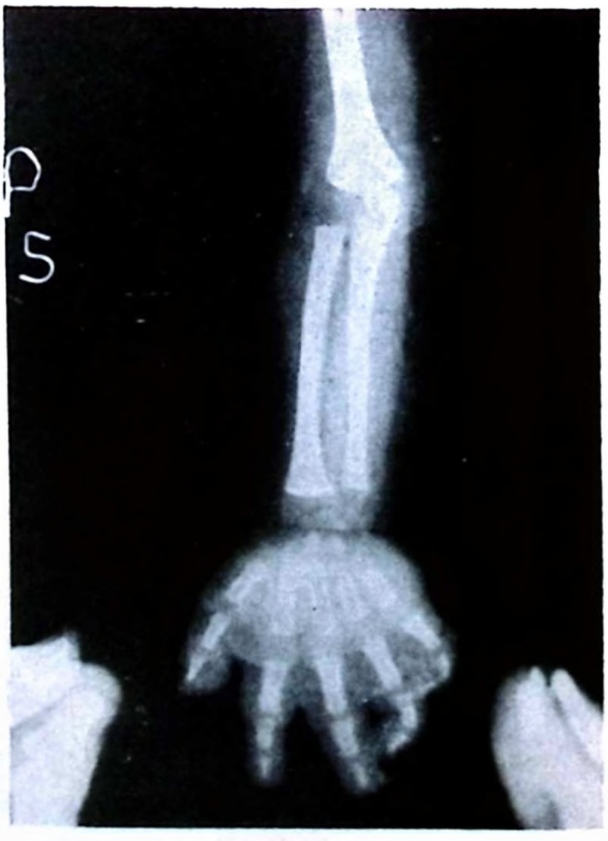

Figure 7

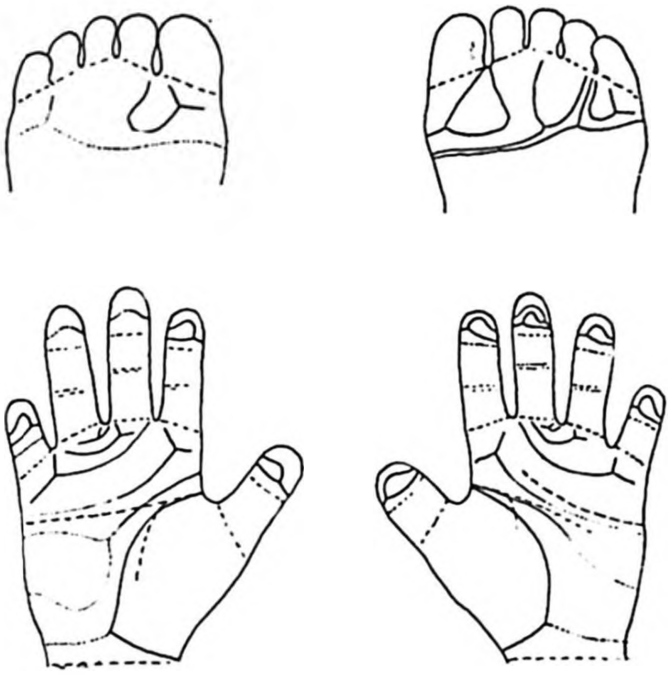

Figure 8

There was no family history of mental defect or retarded growth. The infant has had continual sucking and swallowing difficulties, with regurgitation and episodes of aspiration. Weight gain was very slow and he failed to progress in psychomotor development. There were seizures between the first and second months of life, but no fever at that time. He had polydipsia and polyuria. Psychomotor development was very retarded. He walked at 2 years, and could not speak easily.

Physical examination: At the age of five years the patient's weight was 8 kg., length 79 cm., and head circumference 43,5 cm (all these figures being below the third percentile for his age). The head was microbrachycephalic. He was a small, strong, irritable, retarded child with a weak low-pitched growling cry. (Figure 9) He had generalized hypertonicity, micropthalmia, bushy eyebrows fused at the midline and very long upturned eyelashes. The pupils were eccentrically situated and funduscopic examination revealed a minus 7 diopter myopia. In addition the papilla was very pale. The left eyelid exhibited slight ptosis. (Figure 10) Mild conjunctivitis was present, and had been intermittently since the fourth year of life. Dentition was irregular, and the palate was very high and narrow. The ears were low set but tragi were upturned. The nose was small and the nostrills were anteverted. The maxillary labial region was wide and the lips thin. The umbilicus and nipples were slightly hypoplastic, and he had a left inguinal hernia.

Figure 9

His chest cage was well developed, and the lungs were clear. Heart examination revealed a Grade 2/6 mid-systolic ejection murmur heard best at the left second intercostal space. The femoral pulse was normal.

The fifth finger of the left hand was very long, the fourth finger was absent and the thumbs were proximally placed. There was right simian crease and clino-dactyly. (Figure 11) The right foot showed oligodactyly (the third toe was absent), and the first and second had syndactyly.

Laboratory studies: Hemoglobin, urinalysis, serum alkalin phosphatase, calcium, phosphorous levels and electrophoresis were normal. Albumin globulin ratio was 5,6/2,4 and serum immunoelectrophoresis revealed no abnormality. IgG: 860 mg/100 ml, IgM: 100 mg/100 ml., IgA 76/100 ml.

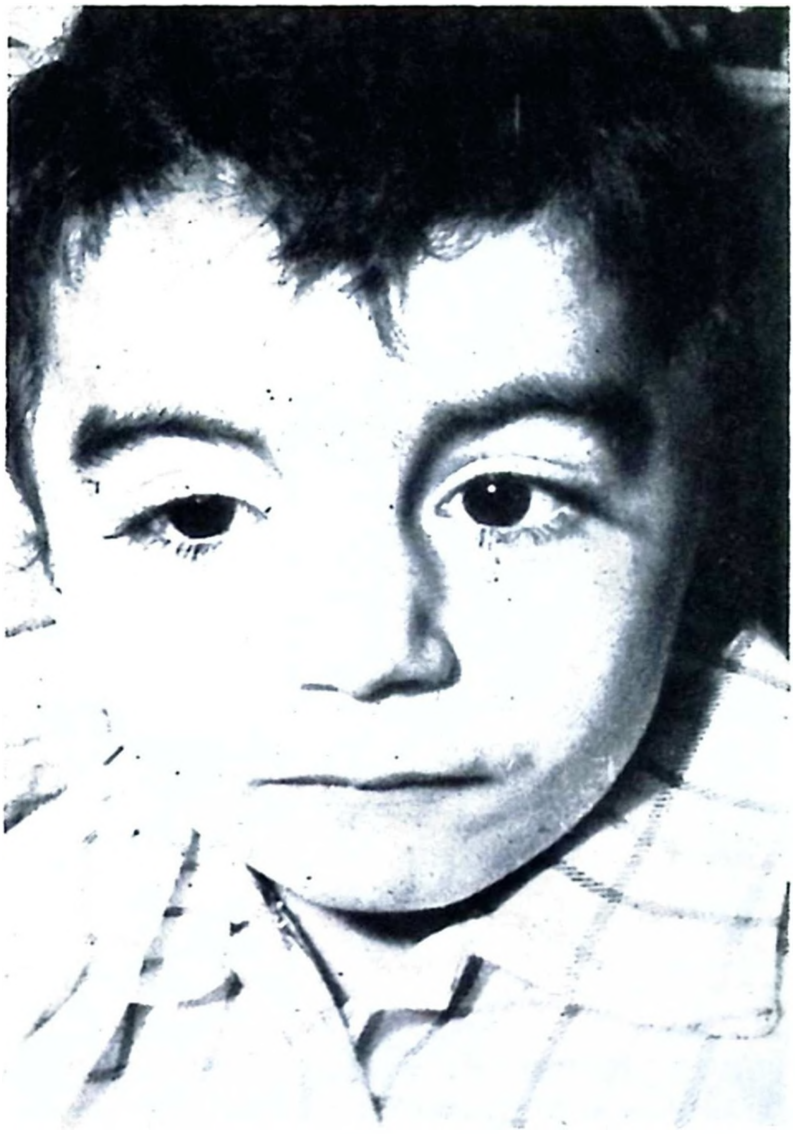

Figure 10

Chromosome studies revealed a normal karyotype. The atd angle was 65° and axial triradus was in an intermedian position at the right hand. In the left palm b, c, and d triradus was absent with aplasia of the fingers. Axial triradus was in a distal position.

The left second ribs showed congenital anomalies and the right first and second ribs had congenital fusion defects, as did, 12 dorsal vertebral and I. lumbal vertebrae.

Discussion

The clinical diagnosis of De Lange's syndrome depends on the accumulation of a number of findings which individually would have little

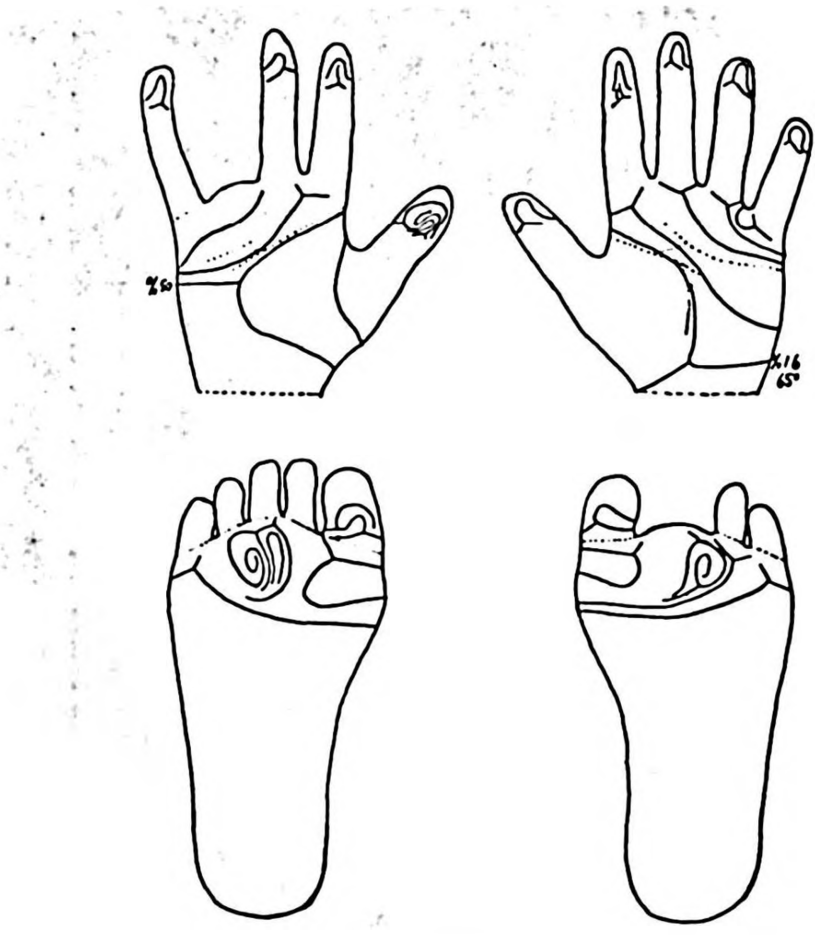

Figure 11

meaning. However, the most significant of these is the typical facial appearence. As in patients with Down's syndrome, patients with De Lange's syndrome resemble each other as closely as brothers and sisters.[2] It was suggested recently that the elevated level of galactose-l-phosphate-uridiltransferase may also be of importance.[3]

Our patients showed most of the significant findings seen in Cornelia de Lange's syndrome (Table 1). It should be noted that some of the findings listed in Table I are not commonly seen, such as congenital heart disease, gastro-intestinal malformations, deafness, choloboma of the iris, etc. Post mortem findings from nine patients have been published. In one of Dr. de Lange's original cases there was sub-arachnoid bleeding and multiple thrombi in the cranial sinuses.[4] Richter reported one case where there were a ventricular septal defect, patent ductus arteriosus, foramen ovale, hemorrhagic pneumonia and widespread bleeding in the adrenals, kidneys, liver and bladder.[5] Schlesinger et al reported brachycephaly, microcephaly, abnormality of the sella turcica, narrowing of the cerebral gyri and widening of the sulcus between the gyri, cortical atrophy, gliosis myelin

TABLE I

CLINICAL FINDINGS ON CORNELIA DE LANGE SYNDROME

Systems	Abnormalities
Growth and development	Retarded body growth and development Retardation of bone development Hypertrichosis
Hair and eye lashes	Long eyelashes Synophris low hair-line at back
Nose	small, short, the nostrils are turned up
Mouth	large filtrum, thin upper lip, fish mouth
Eye	abnormality of eye, near-sighted, color blind
Skin	Cutis Marmoratus, hypoplasia of the nipples and umblicus
Extremities	Micromelia Phocomela and oligodactyly Clinodactyly (5 th finger) Syndactyly (2 nd and 3rd fingers) Joint abnormalities low-set thumbs Simian line
Central Nervous System	Mental retardation Muscular hypertonia
Head	Abnormally shaped Microbrachycephaly
Ears	Low-set
Neck	Short
Urogenital System	Undescended
Others	Rickets, V.S.D., hypospadias, strabismus, pyloric stenosis, colobomo of the iris, scoliosis, arthrogyriposis, spina hifida occulta.

degeneration, absence of basophilic cells in the pituitary and hypoplasia of the thyroid, adrenals and testes. In addition, one of their patients also had malrotation involving both the small and large intestines and cortical nephrocalsinosis, while the other had duplication of the colon.[6]

Ptacek reported developmental retardation involving all the organs except the liver in one case.[1] Hart et al again described a patient with microcephaly, decreasing number of gyri and ganglion cells of the cerebral cortix. There was also hypoplasia of the pituitary, thyroid and adrenal glands, as well as abnormal lobulation of the lungs and malrotation of the intestines.[7] Gans and Thurston reported their post-mortem findings on three cases, one of which showed malrotation of the intestines and thymic

hyperplasia. The second patient had atrial septal defect with hypoplastic aortic valves, small left ventricle, patent ductus arteriosis, polycystic kidneys and fusion of the adrenal glands in front of the aorta. The third case showed the following malformations: ventricular septal defect, endocardial fibroelastosis of the right ventricle, open foramen ovale, hypertrophy of the circular muscles of the stomach and esophagus and multiple renal cysts.[8]

The etiology of Cornelia de Lange's syndrome has yet to the be elucidated; it is claimed, however, that intrauterine events may be of importance. To support this theory it can be seen that in many cases the patients have low birth weights for the length of gestation, and that their fetal movements are also decreased. More interesting, however, is the history of vaginal bleeding during pregnancy in many cases. There are a few which have been reported where mothers were subjected to radiation during pregnancy and one where the mother had measles.

Opitz et al believed the syndrome to be hereditary, and thought that the mode of inheritance was most probably automosamal recessive.[9] To support this it may be pointed out that there are seven families in the literature with more than one case of the condition. However, others claim that these were not in fact genuine cases of de Lange's syndrome. In one pair of identical male twins the syndrome was present in both of them; up to the present consanguinity of the parents has been reported in only one case.[11] Opitz et al, in searching for a solution to the infrequency of consanguinity suggest that the gene causing this condition may be one frequently encountered in the general population.

Chromosomal analysis have been made in about 100 cases, 16 of which showed various abnormalities (Table II). The structural abnormalities seen have not been consistent, and in a few cases one extra minute chromosome has been observed. Chromosome studies in De Lange's syndrome have usually resulted in normal findings, while the abnormalities seen in some cases have varied from patient to patient. It should also be emphasized that many of the cases with chromosomal aberrations have lacked some of the cardinal findings for the syndrome. Some workers in the field, who still believe that a chromosomal aberration is at the basis of the problem, claim that the condition is either the result of a minor abnormality that cannot be detected with techniques presently available, or that it is due to some form of chromosomal imbalance.

The dermatoglyphic findings observed in these patients up to the present are listed below:

McArthur and Edwards showed a hipoplastic pattern on the fifth finger on one side in one case.[23] They also reported the presence of a single flexion line, an axial triradius in the t" position in the palms, loops over the thenar areas, and arch patterns in the hypothenar areas.

G. F. Smith, after analyzing 21 cases of De Lange's syndrome, concludes that dermatoglyphic studies are very valuable in the diagnosis of this condition. He found an increase in the number of radial loops in the fingers associated with a decrease in whorl patterns. He also reported changes in b and c triradii.[24]

Broholm et al found a decrease in the total ridge count on the fingers and an increase in the a t d angle.[22]

Finally one last point should be emphasized. Cornelia de Lange's syndrome is one the more frequent forms of mental retardation, and it is surprising that no case has ever been reported from Turkey before. This may be because publications have been missed, but we believe that in this country specific entities are not recorded as such, but are simply grouped under the title of mental retardation. We hope that our report will prompt other authors to publish their cases so that we will gain a clearer picture of the frequency of this condition in Turkey.

Summary

Two unrelated cases of Cornelia de Lange Syndrome and a review of the world literature especially with regard to the results of chromosome studies in these patients are presented.

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TABLE II

CHROMOSOME ABNORMALITIES FOUND IN CASES OF CORNELIA DE LANGE SYNDROME TO PRESENT DAY

AUTHOR	SEX	TISSUES EXAMINED		CHROMOSOME ABNORMALITIES	STUDIED RELATIVES	
Geudeke et al[12] 1963	M	Leucocyte Fibroblast	100 50	4-5/21-22 translocation majority	Mother Father	Normal
Jervis and Stimpson[13] 1963	M	Leucocyte	44	Extra fragment in 11 cells		
			14	" " in 5 cels		
	M	"		" " in 2 cells		
	M	"		" " in 3 cells		
	M	"				
Hooft et al[14] 1965	M	?	28	Short-arm of 13-15 and 21-22 chromosome consistently showed excess chromosome material		
	M	?	17			
	M					
Bishun and Morton[15] 1965	M	Leucocyte	62	Extra fragment in 17 and 3 cells from leucocyte and fibroblast culture, respectively		
	M	Fibroblast	15			
Craig and Luzzetti[16] 1965	M	Leucocyte	54	2/6-12 Translocation	Mother Father Sister	Normal
Payne and Maeda[17] 1965	M	Leucocyte	17	Possible long-arm deletion of a 6-12 in 3 cells		
	M	Leucocyte	9	4-5/6-12 translocation, plus fragment in 6 cells.		

Massimo and Vianello[18]	F	Leucocyte Leucocyte	15 24	Extra minute chromosome Normal %37		
Cavalier and Garafolo[19] 1966	M	Leucocyte Leucocyte		Breaks in some chromosomes		
Falek and et al[20] 1966	F	Leucocyte Leucocyte	100	Consistent 3/21-22 translocation involving partial trisomy 3	Sister Maternal cousin brother, mother, maternal cousin	The same karyotype and phenotype Balanced 3/21-22 translocation and normal phenotype
Berg et al[21] 1967	M	Leucocyte Leucocyte Fibroblast Leucocyte Fibroblast	30 41 30	Metacentric 6-12 group chromosome in all cells elongated 21-22 chromosomes	Mother brother, step-mother elongated long arms in 21-22 chromosomes in the father one C group chromosome is metacentric	Normal
Broholm et al[22]	F	Leucocyte		4-5/13-15 translocation %100	Father Mother Sister Aunt	Normal

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