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Cornelia de Lange syndrome associated with Wilms' tumour and infantile haemangioendothelioma of the liver: report of two autopsy cases

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Summary. Two cases of Cornelia de Lange syndrome associated with infantile haemangioendothelioma of the liver and Wilms' tumour are reported. The patients showed the characteristic facies of the Cornelia de Lange syndrome, with synophrys, long curly eyelashes and small upturned nose, and physical features, including generalized hirsutism, monodactyly, syndactyly and clinodactyly. Post-mortem examination revealed annular pancreas, patency of the foramen ovale, duodenal atresia and evidence of cytomegalic infection. The cases are reported to document a possible association between malformations and neoplasms in this syndrome.

Key words: Cornelia de Lange syndrome – Infantile haemangioendothelioma – Wilms' tumour

Introduction

In 1933, a Dutch pediatrician, Cornelia de Lange described two female infants with curious congenital defects, in Amsterdam. This syndrome has since been referred to as Cornelia de Lange syndrome (CDLS), but was originally described by Brachamann as early as 1916 (It is also called as Brachmann-de Lange syndrome). This readily recognizable but rare syndrome is defined phenotypically by microcephaly, bushy continuous eyebrows, thick eyelashes, low hairline of the forehead and neck, limb malformations and a characteristic appearances of eye, mouth and nose (Ptacek et al. 1963). Only two CDLS associated with neoplasms have been reported to date (Cohen 1982; Sugita et al. 1986) as far as we can determine. We have autopsied two cases of infant CDLS associated with a Wilms' tumour and a infantile haemangioendothelioma of the liver, respectively. Recent investigations have suggested a possible causal relationship between oncogenesis and teratogenesis in early life (Boland 1984). This unusual assocation of CDLS and infantile malignant neoplasms prompted us to report.

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Case reports

Case 1. A Japanese female infant was born in Jan. 1985 with a birth weight of 1432 g after 36 weeks and 3 days gestation complicated by hydramnios. The delivery was uneventful, spontaneous and with cephalic presentation. Her healthy and nonconsanguineous parents had no relatives with CDLS. The clinical diagnosis of CDLS was made on the characteristic facies and upper limb malformation at birth. She suffered from neonatal jaundice and had difficulty in sucking and swallowing since birth, and a tendency to regurgitate. Roentogenographic examination revealed duodenal atresia, but operation was not performed. She gradually wasted because of malnutrition, dying 40 days after birth. Her karyotype was 46,XX without abnormality of chromosomes. A complete autopsy was performed.

The height and weight were 40 cm and 840 grams, respectively at autopsy. Physical examination revealed microcephaly, micrognathia and a characteristic face of CDLS with synophrys meeting in midline, long curly eyelashes, hirsutism and small upturned nose. The right upper limb was tapering and showed monodactylyl. The elbow joints were fixed in flexion. The left upper limb showed syndactyly with three fingers including the proximally placed first a second with a small appendix and the third showing clinodactyly. The nipples and genitalia were normal (Fig. 1).

The liver weighed 37.9 grams and had multiple whitish gray tumours varying 2 to 3 mm in size (Fig. 2). Microscopically these exhibited both irregularly dilated and small compressed vascular spaces lined by a single layer cell with an innocuous cytological appearance. There were neither bile canaliculi nor ductules in the tumour and a pathological diagnosis of infantile haemangioendothelioma was made (Fig. 3). Hepatocytes of non-neoplastic areas showed marked steatosis, thought to be due to hyponutrition and passive congestion. Patency of the foramen ovale was found. The adrenal glands showed small

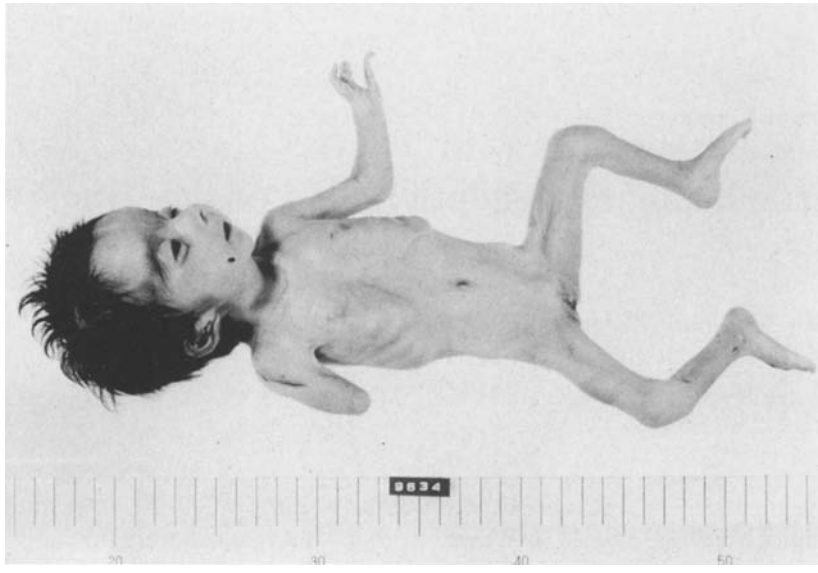


Fig. 1. External appearance of Case 1 showing typical characteristics of Cornelia de Lange syndrome. Note peculiar face, hirsutism and monodactyly in the forearm

cortical nodules. The spleen was atrophic and included haemosiderin deposits. Annular pancreas and mingling of pancreatic and splenic tissue were observed. The atrophic thymus weighed 0.3 grams. The duodenum showed membranous atresia thought to be responsible for the projectile vomiting of the patient. There was histological evidence of bilateral emphysema of the lungs and hypomyelinosis of the brain.

Case 2. The case was a Japanese female infant born in July 1985 as the second child, following an uneventful 39 week and one day gestation. The delivery was via a breech presentation. Her parents were healthy and non-consanguineous and had no relatives with CDLS. She weighed 1890 grams at birth and was a light for date infant. There was no history of neonatal jaundice. The clinical diagnosis of CDLS was made on her characteristic face and upper limb malformation at birth. She was affected by pulmonary infection from the second day after birth and suffered from dyspnoea and convulsion. She died of sepsis 222 days after birth. A karyotype was 46,XX without abnormality. A complete autopsy was performed.

Height and weight were 49 cm and 1780 grams, respectively, at autopsy. The physical examination revealed microcephaly, micrognathia, hirsutism and a characteristic face with bushy eyebrows, synophrys, long curly eyelashes, and a small upturned nose. The right upper limb showed monodactyly and syndactylous left hand consisting of three fingers. The right elbow was fixed in flexion. Both sets of toes showed syndactyly. The nipples and genitalia were normal. The right kidney, weighing 10 grams, bore a witish gray tumour, 2 cm in diameter, with small multiple cysts (Fig. 4).

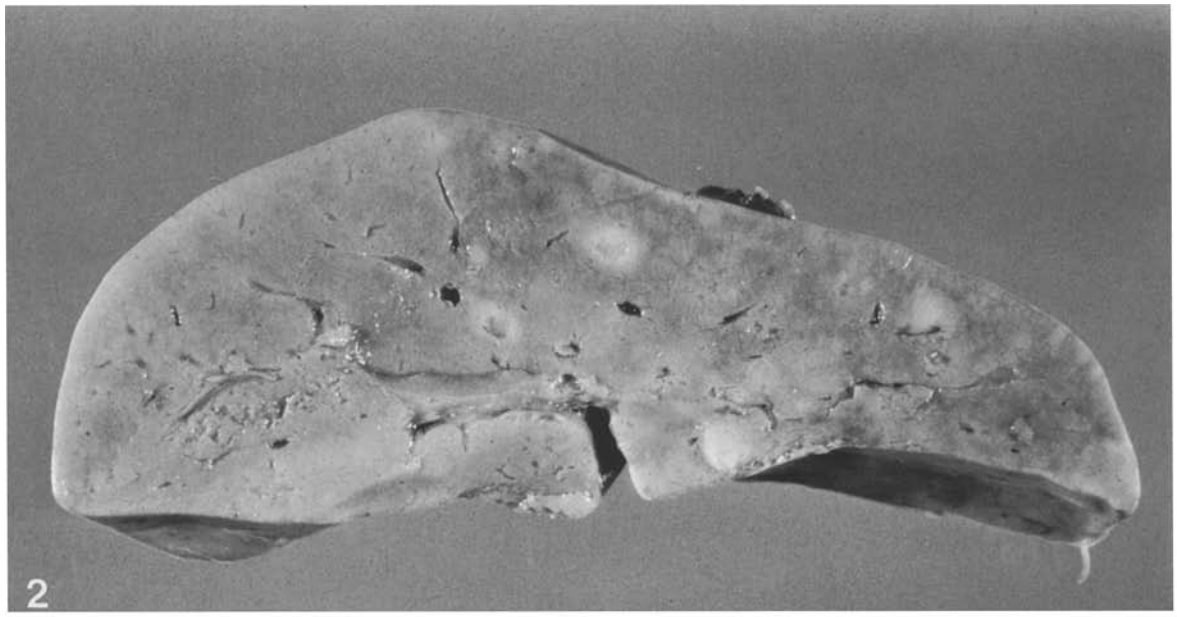
Microscopically the tumour consisted of varying sized and shaped well defined areas of embryonal tubular epithelium, surrounded by a fibrous stroma. The pathological diagnosis of a nephroblastoma was made (Fig. 5). There was no nephroblastosis. The lungs showed bronchopneumonia. Evidence of infection of Pseudomonas aeruginosa and Streptococcus aureus was disclosed by culture of the lung tissue. Cytomegalic inclusions were found in the bilateral lungs and kidneys, the liver, the pancreas, the adrenal glands and some of the lymph nodes. Patent ductus arteriosus and patency of foramen ovale were observed in the heart. There was the mingling of the splenic and pancreatic tissue. Grossly the brain showed microcephaly and histologically, there was zonal necrosis with gliosis in the cortex, thought to be due to hypoxia.

Discussion

Cornelia de Lange reported "Typus degenerativus Amstelodamensis" in 1933. Subsequently more than 250 severely or mildly affected cases have been reported in the literature. In Japan, only 21 cases have been reported. The age of the patients ranges from newborn to puberty. Most CDLS patients are sporadic with an estimated birth prevalence of 1/10000 (Opitz 1985). Monozygotic twins concordant for the syndrome and a few families with several affected siblings suggesting familial occurrence have also been reported (Watson 1979; Beck 1974; Bankier 1986; Kumar et al. 1985; Leavitt et al. 1985). Borghi et al. (1954) suggested dominant inheritance. Autosomal dominant inheritance was also discussed by McArthur and Edwards (1967) and Opitz (1985).

As a possible marker in the classification and prenatal diagnosis of CDLS, Westergaard et al. (1983) proposed the absence of pregnant-associated plasma protein A from both the maternal circulation and from trophoblastic tissue.

Characteristic face, mental retardation, hirsutism and upper limb malformation are hallmarks of the syndrome (Preus and Rex 1983). Furthermore, Schlesinger et al. (1963) and Lachman et al. (1981) described gastrointestinal, cardiac, thymic and cerebral abnormalities all of which were found in the present cases. Despite the paucity of postmortem examinations of CDLS, some show signifi-



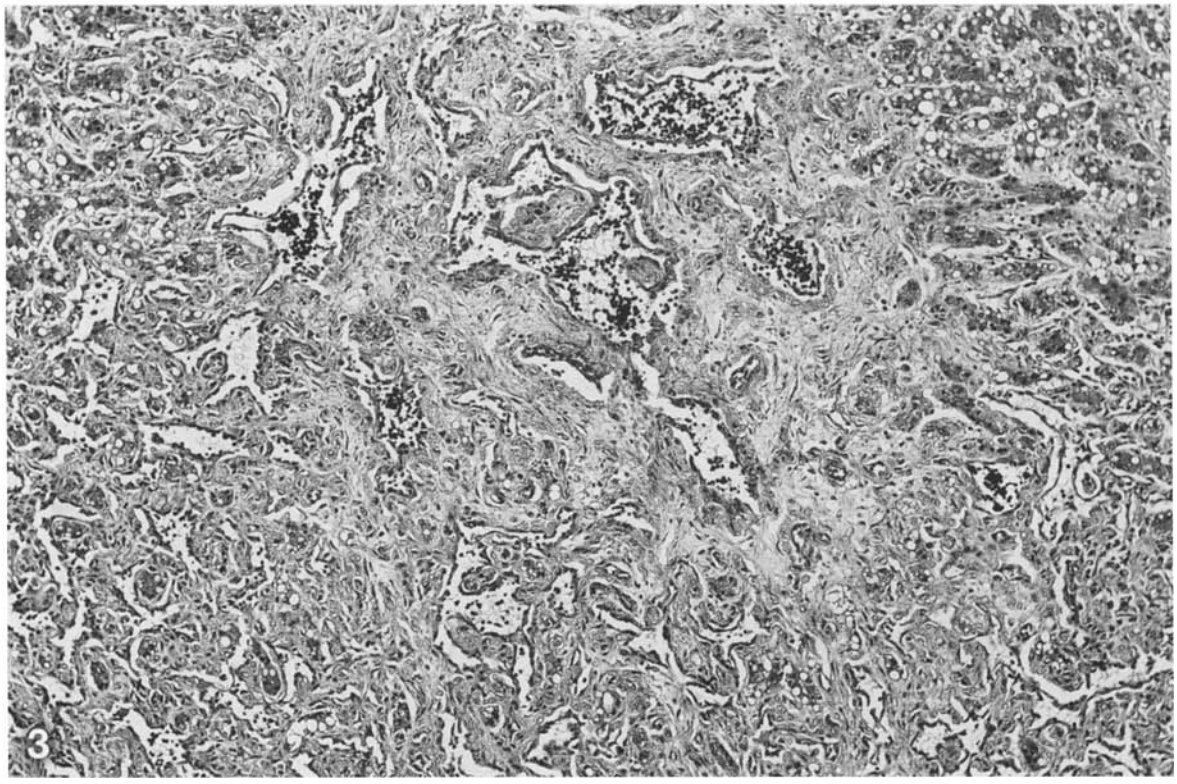
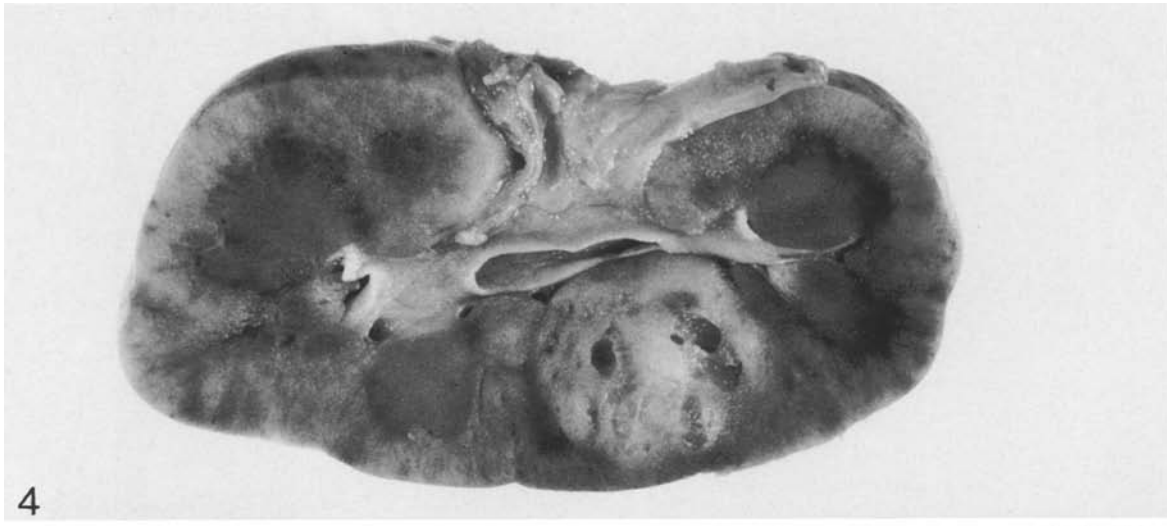


Fig. 2. Multiple whitish gray, well-circumscribed nodules scattered over the cut surface of the liver

Fig. 3. Histological findings of the tumour of Case 1. It is characterized by multiple vascular spaces separated by fibrous stroma. Azan-Mallory stain, × 50

cant similarities. Wick et al. (1982) reported postmortem examination findings including annular pancreas, duodenal obstruction and horseshoe kidney, which features are closely similar to some of those of Case 1. Detailed anatomical study is required to elucidate the cause of the feeding difficulties and other problems of CDLS.

With respect to the association with neoplasm, only two cases of CDLS accompanied by Wilms' tumour and suprasellar germinoma, respectively,



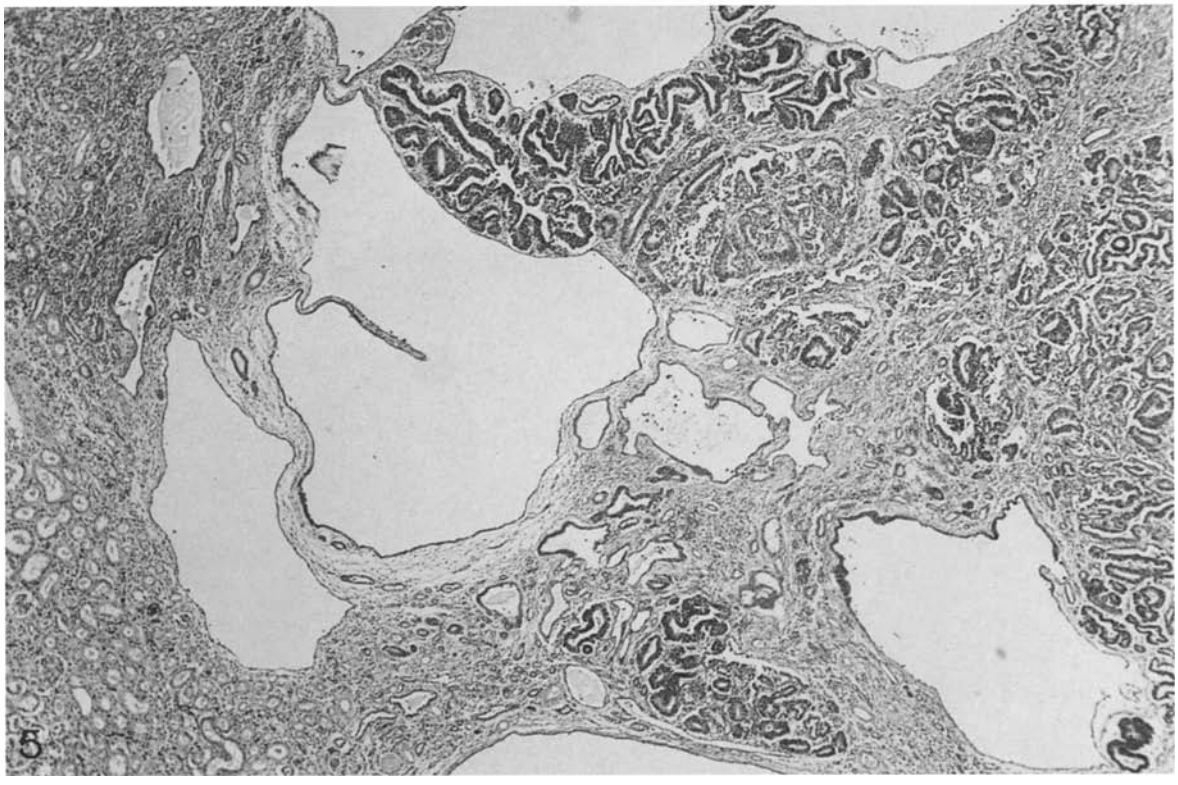


Fig. 4. The solitary and non-encapsulated tumour with small cysts in Case 2. The mass is located in the medulla of right kidney

Fig. 5. The tumour is characterized by embryonal tubular epithelium, a few blastemic lesions and thin-walled cysts. Haematoxylin-eosin stain, × 20

have been described (Cohen 1982; Sugita et al. 1986). Our cases are accompanied by infantile haemangioendothelioma of the liver and Wilms' tumour. The pathological findings in the haemangiondothelioma in Case 1 applied to type 1 in the classification by Dehner and Ishak (1971). They reviewed 30 cases, including 23 cases of infantile haemangioendothelioma and 7 cases of cavernous haemangioma. They described association of these tumours with congenital anomalies in other organ systems and a striking incidence of prematurity among infants. They suggested that the tumour had a potential for involution and regression. The Wilms' tumour seen in Case 2 consisted mostly of

a well differentiated epithelial component. Wilms' tumour is relatively common (Lemerle et al. 1976) and the vast majority represent sporadic occurrences without associated abnormalities or direct transmission from a parent (Riccardi et al. 1978). However, some of them are associated with congenital abnormalities, such as aniridia, hemihypertrophy and Beckwith syndrome. These have been presumed to be genetic or to have resulted from one or more mutational events (Matsunaga 1981). Knudson et al. have proposed a two-hit theory or two-mutation theory to explain the corresponding phenomenon in hereditary retinoblastoma (Knudson 1971). Quoting the "two-hit theory", Bolande (1984) reported the models and concepts derived from human teratogenesis and oncogenesis in early life. Yunis and Ramsey (1978) demonstrated that the development of retinoblastoma is associated with further genetic events resulting in homozygosity for deletion in region of chromosome 13q14 using high resolution banding techniques. In nephroblastoma with aniridia and other malformations, deletion of 11p13 has been demonstrated (Riccardi et al. 1978). These deletions found in retinoblastoma and nephroblastoma are close to known oncogenes and may be involved in controlling their expression (Solomon 1984). Recent work on the Beckwith-Wiedmann syndrome promises to throw light on the relationship between dysmorphic syndrome and cancer. Patients with Beckwith syndrome were thought to have a normal karyotype, but high resolution banding techniques show that at least some individuals are trisomic for part of the short arm of chromosome 11 (Turleau et al. 1984). The segment involved, 11p15, includes the genes coding for insulin, insulin-like growth factor and the oncogene C-H-ras. These preliminary results provide a possible explanation for the abnormalities of growth, carbohydrate metabolism and tumour susceptibility seen in this syndrome.

Some chromosome studies of the patients with CDLS have been undertaken using several different methods (Hersh et al. 1985; Beck and Mikkelsen 1981; Babu et al. 1985). The karyotype exhibited a wide variety of abnormalities. However, no consistent chromosome aberration has been identified and chromosomes of the present cases showed normal karyotypes. Beck and Mikkelsen (1981) consider that if no chromosome abnormality was disclosed, a recurrence rate of 2–5% should be considerated for the CDLS.

It would be difficult to assume that our CDLS cases complicated with neoplasms have a single genetic cause. These might be just co-incidental findings or may be closely related by an undetermined genetic defect, on a single chromosome or on different chromosomes. There have been few reports of CDLS complicated with such neoplasms, and it is important and necessary to accumulate similar cases and perform more detailed pre- and post-mortem examinations, including chromosomal analysis. Hopefully genetic analysis may be possible to establish a relationship between malformation and oncogenesis in CDLS.

References

Babu KA, Verma RS, Rodriguez J, Rosenfeld W, Jhaveri RC (1985) A possible clinical implication of homozygous inversions of 9th regions with Cornelia de Lange syndrome (CLS). Hum Hered 35:265–267

Bankier A (1986) Letter to the editor: Familial occurrence of Brachmann-de Lange syndrome. Am J Med Genet 25:163–165

Beck B (1974) Familial occurrence of Cornelia de Lange syndrome. Acta Pediatr Scand 63:225–231

Beck B, Mikkelsen M (1981) Chromosomes in the Cornelia de Lange syndrome. Hum Genet 59:271–276

Bolande RP (1984) Models and concepts derived from human teratogenesis and oncogenesis in early life. J Histochem Cytochem 32:878–884

Borghi A, Giusti G, Bigozzi U (1954) Nanismo degenerativo tipo di Amsterdam. Presentazione di un caso e considerazioni di orgine genetico. Acta Genet Med Gemellol 3:365

Cohen MM Jr (1982) The child with multiple birth defects. Raven Press, New York

Dehner LP, Ishak KG (1971) Vascular tumors of the liver in infants and children. Arch Path 92:101–111

De Lange C (1933) Sur un type nouveau de degeneration (Typus Amstelodamensis). Arch de Med Enf 36:713–719

Hersh JH, Dale KS, Gerald PS, Yen FF, Weisskopf B, Dinno ND (1985) Dup(4p)del(9p) in a familial mental retardation syndrome: Resemblance to de Lange syndrome detected by high-resolution banding. AJDC 139:81–84

Knudson AG Jr (1971) Mutation and cancer: Statistical study of retinoblastoma. Proc Natl Acad Sci USA 68:820–823

Kumar D, Blank CE, Griffiths BL (1985) Cornelia de Lange syndrome in several members of the same family. J Med Genet 22:296–300

Lachman R, Funamura J, Szalay G (1981) Gastrointestinal abnormalities in the Cornelia de Lange syndrome. Mt Sainai J Med 48:236–240

Leavitt A, Dinno N, Davis C (1985) Cornelia de Lange syndrome in a mother and daughter. Clin Genet 28:157–161

Lemerle J, Tournade MF, Marchant RG, Flamant R, Sarrazin D, Flamant F, Lemerle M, Jundt S, Zucker JM, Schweisguth O (1976) Wilms' tumor: Natural history and prognostic factors. Cancer 37:2557–2566

Matsunaga E (1981) Genetics of Wilms' tumor. Hum Genet 57:231–246

McArthur RG, Edwards JH (1967) De Lange syndrome: Report of 20 cases. Can Med Assoc J 96:1185–1198

Opitz JM (1985) Editorial comment: The Brachamann-de Lange syndrome. Am J Med Genet 22:89–102

Preus M, Rex AP (1983) Definition and diagnosis of the Brachamann-de Lange syndrome. Am J Med Genet 16:301–312

Ptacek LJ, Opitz JH, Smith DW, Gerritsen T, Waisman HA (1963) The Cornelia de Lange syndrome. J Pediatr 63:1000–1020

Riccardi VM, Sujansky E, Smith AC, Francke U (1978) Chromosomal imbalance in the Aniridia-Wilms' tumor associations: 11p interstitial deletion. Pediatr 61:604–610

Schlesinger B, Clayton B, Bodian M, Jones KV (1963) Typus degenerativus amstelodamensis. Arch Dis Child 38:349–357

Solomon E (1984) Recessive mutation in aetiology of Wilms' tumour. Nature 309:111–112

Sugita K, Izumi T, Yamaguchi K, Fukuyama Y, Sato A, Kajita A (1986) Cornelia de Lange syndrome associated with a suprasellar germinoma. Brain Dev 8:541–546

Turleau C, De Grouchy J, Chavin-Colin F, Martelli H, Voyer M, Charlas R (1984) Trisomy 11p15 and Beckwith-Wiedemann syndrome. A report of two cases. Human Genet 62:219–221

Watson A (1979) Cornelia de Lange syndrome: occurrence in twins. Aust J Dermatol 20:7–9

Westergaard JG, Chemnitz J, Teisner B, Poulsen HK, Ipsen L, Beck B, Grudzinskas JG (1983) Pregnancy-associated plasma protein A: A possible marker in the classification and prenatal diagnosis of Cornelia de Lange syndrome. Prenat Diagn 3:225–232

Wick MR, Simmons PS, Ludwig J, Kleinberg F (1982) Duodenal obstruction, annular pancreas and horseshoe kidney in an infant with Cornelia de Lange syndrome. Minn Med 65:539–541

Yunis JJ, Ramsey N (1978) Retinoblastoma and subband deletion of chromosome 13. Am J Dis Child 132:161–163

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