



EPIDEMIOLOGY OF CORNELIA DE LANGE SYNDROME IN EUROPE - POPULATION-BASED DATA

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ABSTRACT

Cornelia de Lange syndrome (CdLS) is a rare genetic disorder characterised by the specific facial dysmorphism, hypertrichosis, upper limb deficiency, intrauterine growth retardation, developmental delay and a variety of associated malformations. The particular clinical features make severe forms of the syndrome easily recognizable.

We have analysed the population-based data extracted from the database of EUROCAT (European Surveillance of Congenital Anomalies), a large European network of birth defect registries that use the same epidemiological methodologies.

The study is based on the 23-year (1980-2002) monitoring covering 8,558,346 births from 16 European countries. We found the prevalence of the classical form of CdLS to be 1.24/100,000 births and estimated the overall CdLS prevalence at 1.6-2.2/100,000 or 1.80/645 births. There were 91.5% (97/106) live born infants with high first week survival (91.4%). Termination of pregnancy following prenatal diagnosis was performed in 5.7% (6/106) cases, and 2.8% (3/106) were foetal deaths. Prenatal detection rate of abnormalities in CdLS cases was 32.1% in the last seven years.

The most frequent associated congenital malformations were limb defects (73.1%), congenital heart defects (45.6%), central nervous system malformations (40.2%) and cleft palate (21.7%). Almost 70% of infants, born after the 37th week of gestation, weighed \leq 2500 g. Low birth weight correlates with a more severe phenotype. All patients were sporadic. Maternal and paternal ages do not seem to be risk factors for CdLS and no evidence of exposure to consistent teratogenic agents was noted.

BACKGROUND

Cornelia de Lange Syndrome (CdLS) is a multiple congenital anomaly/mental retardation (MCA/MR) syndrome consisting of characteristic dysmorphic features, microcephaly, hypertrichosis, upper limb defects, growth retardation, developmental delay and a variety of associated major malformations. The clinical features seen in individuals with the classic form are easily recognizable. In mildly affected patients the diagnosis is often problematic as there is no consensus about the minimal diagnostic criteria for this subgroup of patients.

Based on two surveys of mentally retarded children in Australia and Denmark, the estimated prevalence of CdLS is 0.5 - 1/100,000 livebirths (1,2,3). Opitz (4) estimated the total prevalence of both severe and mild cases to be as high as 1/10,000 livebirths. This figure is usually quoted in published papers dealing with CdLS, but population-based studies that provide reliable epidemiological data on the prevalence of CdLS that could confirm his assumption are lacking.

A description of the epidemiologic characteristics of CdLS is important for an improved understanding of the condition and for clarifying findings from studies of hospital-based series or studies based on the observation of subjects ascertained via support groups.

METHODS

We used data from the EUROCAT, a large European network of birth defect registries with multiple sources of active case ascertainment, to conduct a population-based study of the epidemiological and clinical aspects of the classical form of CdLS. We describe our findings regarding the population-based prevalence (including foetal deaths and termination of pregnancy), prenatal diagnosis, associated congenital malformations and descriptive epidemiology of CdLS syndrome.

The coding systems used for diagnosis by all participating registries are the ICD9/BPA or ICD10/BPA (International Classification of Diseases/ British Paediatrics Association Classification of Diseases) and McKusick. The data for this study were extracted from the central database on the bases of the ICD codes for the confirmed Cornelia de Lange cases (759821, Q8712), unconfirmed cases (75982) and the McKusick code (122470). Medical geneticist reviewed all the cases and contacted the local registries for the confirmation and for text information if missing in the central database.

In the analysis of the anomalies associated with Cornelia de Lange patients, minor anomalies were not included. The malformations were classified according to the EUROCAT subgroups of congenital anomalies (5).

Descriptive data are presented as percentages. Comparisons have been performed using 95% confidence intervals, the Chi-square test and t-test.

RESULTS

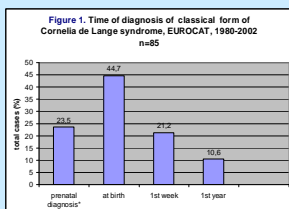
Between January 1980 and December 2002, we monitored a total population of 8,558,346 births, and identified 106 cases with CdL syndrome (Table 1).

Table 1. Prevalence and outcome of pregnancies of Cornelia de Lange syndrome in the EUROCAT birth defect registries, for period 1980-2002

Time period	Total births	Total No of cases (%)	LB (%)	SB (%)	TOP (%)	Birth prevalence per 100,000
1980-2002	8,558,346	106 (1.24)	97 (91.5)	3 (2.8)	6 (5.7)	1.24

The proportion of patients with a mild phenotype is estimated to be 30 - 75% of the total number of cases of CdLS (4,6). Based on this estimate, the overall prevalence for mild and classical cases would be 1.6 - 2.2 per 100,000 or 1:62,000 - 1:45,000.

Of 85 cases with a known time of diagnosis, in 20 (23.5%) cases there was a prenatal suspicion or diagnosis of a congenital anomaly associated with CdLS, as early as at 15 weeks of gestation. In 38 cases (44.7%) diagnosis was made at birth, in 18 (21.2%) in the first week of life, and 9 (10.6%) were diagnosed within one year of life (Figure 1).



*prenatal diagnosis refers to a prenatal suspicion or diagnosis of a congenital anomaly associated with CdLS

All prenatally diagnosed cases were detected by ultrasound. Mean gestational age at discovery was 22.5±4.4 gestational weeks. Of 20 prenatally diagnosed cases, 11 were live born, 3 were foetal deaths (at 23, 29 and 31 week of gestation), and 6 pregnancies were terminated (at 17-26 weeks of gestation).

Karyotype was performed in 63 cases (59.4%) and only three karyotypes were abnormal. In the first case 46, XY del(3)(q12q21), inv(5)(p13q13), the aberration affects the region 5p13, where MIRBL gene is located. The other abnormal karyotype was 46, XX t(X;22)(p11;qter), where the genomic region of the SMC1A is affected. Mutations in SMC1A gene are responsible for a mild, X-linked type of Cornelia de Lange syndrome (7). The karyotype of the third case was not available.

The frequencies of major associated congenital anomalies in 93 cases with available detailed information on malformations are presented in Figure 2.

Of 79 cases in which the survival data was available, 6 (7.6%) cases were terminated, 3 (3.8%) were foetal deaths, 6 (7.6%) died during the first week and 64 (81.0%) survived the first week after birth.

There were 55 females and 50 cases were males, the sex of one case was unknown. The *fm* ratio was 1.1. The mean maternal age was 28.7 ± 4.7 years and the mean paternal age was 31.0 ± 5.1 years. Comparing the maternal age distribution with the distribution in the total EUROCAT population, no significant difference was found (p=0.27).

The mean birth weight in live births was 2,021 ± 645 g for males and 2,153 ± 597 g for females (Table 4). Of 64 cases born after 37 weeks of gestation, 44 (68.8%) weighed less than 2,500 g.

Sex distribution and maternal and paternal age according to the birth weight are given in Table 5. The number of cases with limb anomalies was more frequent in the group weighting \leq 2,500 g (p=0.0022). There were no sex or maternal age differences between two birth weight groups (p=0.27 and p=0.39 respectively).

No sibs or relatives with CdLS were recorded. Among 52 cases for which parental consanguinity data were known, no consanguinity was found. We found 15 reports of various illnesses of mothers before or during pregnancy, but all were different and unspecific (hypertension, thyrotoxicosis, obesity, etc). There was no evidence of exposures to consistent teratogenic agents.

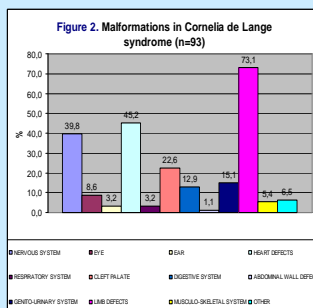


Table 4. Birth weight and gestational age at birth of liveborn children with Cornelia de Lange syndrome

Birth weight	n=97 (liveborn)
under 1500	14 (14.4%)
1500-1999	26 (26.8%)
2,000-2499	32 (33.0%)
2500-2999	17 (17.6%)
> 3000	4 (4.1%)
unknown	4 (4.1%)

Gestational age, wk	n= 97 (liveborn)
< 37	30 (30.9%)
37-41	61 (62.9%)
\geq 42	1 (1.0%)
unknown	5 (5.2%)

Table 5. Sex distribution, maternal and paternal age according to the birth weight in liveborn with CdLS

	Birth weight		Total
	\leq 2,500 g	>2,500 g	
M : F	0.98 (39/40)	0.54 (7/13)	0.87 (46/53)
maternal age	29.1 ± 4.7	27.8 ± 4.8	28.8 ± 4.7
paternal age	31.3 ± 4.9	29.8 ± 5.7	31.0 ± 4.9
limb anomalies	No of cases = 47/61 (77.1%)	No of cases = 7/18 (38.9%)	

CONCLUSIONS

- The prevalence of classical Cornelia de Lange syndrome is 1.24/ 100,000 births
- Estimated overall prevalence for classical and mild cases is 1.6 - 2.2 /100,000 births
- The most frequent major congenital malformations associated with CdLS are limb defects (73.1%), congenital heart defects (45.6%), central nervous system malformations (40.2%) and cleft palate (21.7%)
- Prenatal diagnosis by ultrasound examination accounts for almost a quarter of all diagnosed cases
- Liveborn infants with CdLS have a high first week survival rate
- In the majority of cases the karyotype is normal. Identified abnormal karyotypes may be accidental findings, or responsible for the Cornelia de Lange syndrome by disruption of the gene/genes causing the CdLS phenotype
- Maternal and paternal age do not seem to be risk factors for CdLS
- Almost 80% of cases, born after the 37th week of gestation, weighed less than 2,500 g; low birth weight correlates with a more severe phenotype, including severe limb anomalies
- All cases were sporadic and there was no evidence of exposure to consistent teratogenic agents

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