Orphanet Journal of
Rare Diseases

RESEARCH

High rate of autonomic neuropathy in Cornelia de Lange Syndrome

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Abstract

Background: Cornelia de Lange Syndrome (CdLS) is a rare congenital disorder characterized by typical facial features, growth failure, limb abnormalities, and gastroesophageal dysfunction that may be caused by mutations in several genes that disrupt gene regulation early in development. Symptoms in individuals with CdLS suggest that the peripheral nervous system (PNS) is involved, yet there is little direct evidence.

Method: Somatic nervous system was evaluated by conventional motor and sensory nerve conduction studies and autonomic nervous system by heart rate variability, sympathetic skin response and sudomotor testing. CdLS Clinical Score and genetic studies were also obtained.

Results: Sympathetic skin response and sudomotor test were pathological in 35% and 34% of the individuals with CdLS, respectively. Nevertheless, normal values in large fiber nerve function studies.

Conclusions: Autonomic nervous system (ANS) dysfunction is found in many individuals with Cornelia de Lange Syndrome, and could be related to premature aging.

Keywords: Cornelia de Lange Syndrome, CdLS, Small fiber nerve, Peripheral neuropathy, Autonomic neuropathy, Sudomotor test, Sweat gland density, NIPBL gene

Background

Cornelia de Lange Syndrome (CdLS) is a genetic disease due to spontaneous mutations in genes of the cohesin protein complex, mainly *NIPBL*, in 70% of the cases [1–4] and *SMC1A*, *SMC3*, *RAD21*, *BRD4*, *HDAC8*, *ANKRD11* and *MAU2* [5–9]. Manifestations of the syndrome differ with mutated gene type, with variants in *NIPBL* often associated with more severe clinical phenotype. The syndrome is characterized by typical facial features, growth failure, limb abnormalities and the involvement of many organs and systems including the central nervous system. Sweating abnormalities, abnormal reactions to cold and heat, and severe gastrointestinal reflux are also prevalent and suggest a compromised peripheral nervous system [1]. More than 80% of individuals with CdLS have some autonomic nervous system dysfunction, while 26% of those have moderate to severe dysfunction as measured by the Compass-31 questionnaire, a validated survey tool for autonomic dysfunction [10]. The aim of this study was to get new insights into neuronal dysfunction in CdLS by analyzing large and small fiber nerves with different techniques.

Patients and methods

All the peripheral nervous system studies, except the sudomotor test, were made in a group of 20 individuals with CdLS (7 male, 13 female, aged 3–37 years). In the sudomotor test the population was broadened to 47 individuals with CdLS (18 male, 29 female, aged 1.5–42 years) and 50 slightly older healthy controls (18 male, 32 female,

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aged 7–48 years). All of the individuals with CdLS and controls were Caucasian, except 3 Latino and 1 Middle East subjects in the CdLS group. The protocol study was approved by the Ethics Committee of Clinical Research from the Government of Aragón (CEICA;PI16/225). All the individuals with CdLS and controls gave informed consent for their participation.

To evaluate the somatic peripheral nervous system, conventional motor and sensory nerve conduction studies [11–15] were carried out in upper and lower limbs (large fiber nerves).

The autonomic nervous system (small fibre nerves) was studied by means of heart rate variability at rest, sympathetic skin response and sudomotor test. Heart rate variability (HRV) at rest was evaluated recording the heart rate for 5 min [16]. Sympathetic skin response (SSR) was studied with electric stimuli over the Median and Posterior Tibial nerves, recording the responses over the palm of both hands (Median) and the sole of both feet (Tibial) [17, 18]. Nerve conduction studies, HRV and SSR were performed by the same group of neurophysiologists with a 5-channel Natus® Electromyography equipment. The sudomotor test, which gives the number of functioning sweat glands per cm^2 (sweat gland density, SGD) was obtained on a silicone mold after pilocarpine iontophoresis stimulation over the foot dorsum [19].

Genetic studies were realized by standard Sanger sequencing and Next Generation Sequencing (NGS) panels. Clinical severity score according to the first international consensus statement [1] was also studied (Table 1). Statistical studies were achieved with the SPSS program version 25.

Results
Conventional motor and sensory nerve conduction studies (large fiber nerves) were normal in all 20 individuals with CdLS analyzed (Additional file 1: Tables 1–3). The study of the autonomic nervous system (small fiber nerves) in HRV at rest was normal as well (Table 2). Nevertheless, SSR revealed mild alterations in lower limbs in 7 of the 20 individuals, with asymmetrical responses (Table 2, Fig. 1). Sudomotor tests evinced reduced SGD in 16 of the 47 individuals with CdLS regarding the control group by decades of life (Table 3). The regression analysis showed that, in spite of dispersion, there were two different populations, with statistically significant differences between the control group and individuals with CdLS ($p < 0.05$ and $p < 0.01$) (Fig. 2). The linear regression showed that the slope of the SGD reduction by age is much more pronounced in individuals with CdLS than in controls (Fig. 2). Independence samples T test showed the results of the mean differences of the sweat gland density (SGD) by age group, with reduction in the

SGD more evident in the individuals with variants in *NIPBL* than in the controls ($p < 0.01$). These differences were found in the whole *NIPBL* group as in all the decades of life, except the first one (Fig. 2, Table 4).

Genetic studies of the 47 individuals with CdLS revealed 31 with variants in *NIPBL*, 4 in *SMC1A*, 2 in *RAD21*, 2 in *HDAC8* and 1 in *SMC3* and negative in 7 individuals (Table 3). In Table 3 there are the CdLS Clinical Scores [1]. No relationship between clinical score or gastroesophageal reflux disease (GERD) and findings of the sudomotor test was found. In Additional file 1: Table 4 is shown the SGD in the control group by decades of life.

Discussion
Though the clinical manifestations of CdLS suggest that the peripheral nervous system is affected, large fiber nerve studies (conventional motor and sensory nerve conduction studies) are within normal limits. However, we have shown evidence, for the first time, for autonomic nervous system dysfunction in individuals with CdLS.

The sympathetic skin response reveals asymmetrical pathological responses in lower limbs in 7 of the 20 individuals (35%), with one of them affected in upper limbs as well. This could be considered a malformative manifestation of the syndrome. However, it is remarkable that the asymmetry is more frequent in lower than in upper limbs, which are often more affected [1–4]. This asymmetry does not seem to be related to GERD or the Clinical Severity Score (CSS), yet all the individuals had mutations in the *NIPBL* gene (Table 2).

Sudomotor testing shows a reduction in the sweat gland density (SGD) in 16 of 47 (34%) of the analyzed individuals with CdLS. These data are further supported by a reduction of the number of sweat droplets imprinted on the silicone after pilocarpine iontophoresis as indirect evidence of decreased postganglionic sudomotor nerve fibers, compared to an unaffected population. Though sweat gland density decreases physiologically with aging, individuals with CdLS show a reduction much greater than should be expected by their age. This decrease is evident from the second decade of life, and is more pronounced at older ages (Table 3, Fig. 2). All of this seems to strengthen the hypothesis that these patients have premature aging. Nevertheless, no relationships were found between SGD reduction and clinical score or GERD.

The reduction in the SGD is evident in individuals with mutations in *NIPBL* (Tables 3, 4), and seems to be similar in individuals with variants in *SMC1A* (3 of the 4 individuals with mutations in *SMC1A* had SGD reduction). However, individuals with variants in *HDAC8* and *RAD 21* are in the first decade of life, so it is early to make an assessment. Surprisingly, there is a high value of sweat

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Table 1 CdLS clinical score (severity)

Individuals with CdLS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Cardinal features (2 points each if present)																								
Synophrys and/or thick eyebrows	+	+	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	–	+	+	+	+	+
Short nose, concave nasal ridge and/or upturned nasal tip	+	–	+	+	+	+	+	–	–	+	+	–	+	+	–	+	–	–	–	+	+	–	+	–
Long and/or smooth philtrum	+	–	–	+	+	+	+	+	–	+	+	+	–	+	+	–	+	–	–	+	+	+	+	–
Thin upper lip vermilion and/or downturned corners of mouth	+	+	–	+	+	+	+	+	–	+	+	+	–	+	+	–	+	–	+	+	+	+	+	–
Hand oligodactyly and/or adactyly	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–
Congenital diaphragmatic hernia	–	–	–	–	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Suggestive features (1 point each if present)																								
Global developmental delay and/or intellectual disability	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Prenatal growth retardation (<2 SD)	+	–	+	+	+	+	+	–	+	–	+	–	–	+	+	–	+	–	+	+	+	+	+	+
Postnatal growth retardation (<2 SD)	+	–	+	+	+	+	+	+	+	–	–	+	–	+	+	+	+	–	+	+	+	+	+	+
Microcephaly (prenatally and/or postnatally)	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–
Small hands and/or feet	–	–	+	+	+	+	–	+	–	+	+	+	+	+	–	+	–	+	–	–	+	+	+	–
Short fifth finger	+	–	+	+	+	+	+	–	–	+	+	+	+	+	+	–	+	–	+	–	+	+	–	+
Hirsutism	+	–	+	+	+	+	–	–	–	+	+	+	+	+	+	–	+	–	–	+	+	+	+	+
Clinical Score	13	5	11	15	15	17	14	7	4	13	14	8	5	15	9	6	11	6	4	16	17	13	14	6

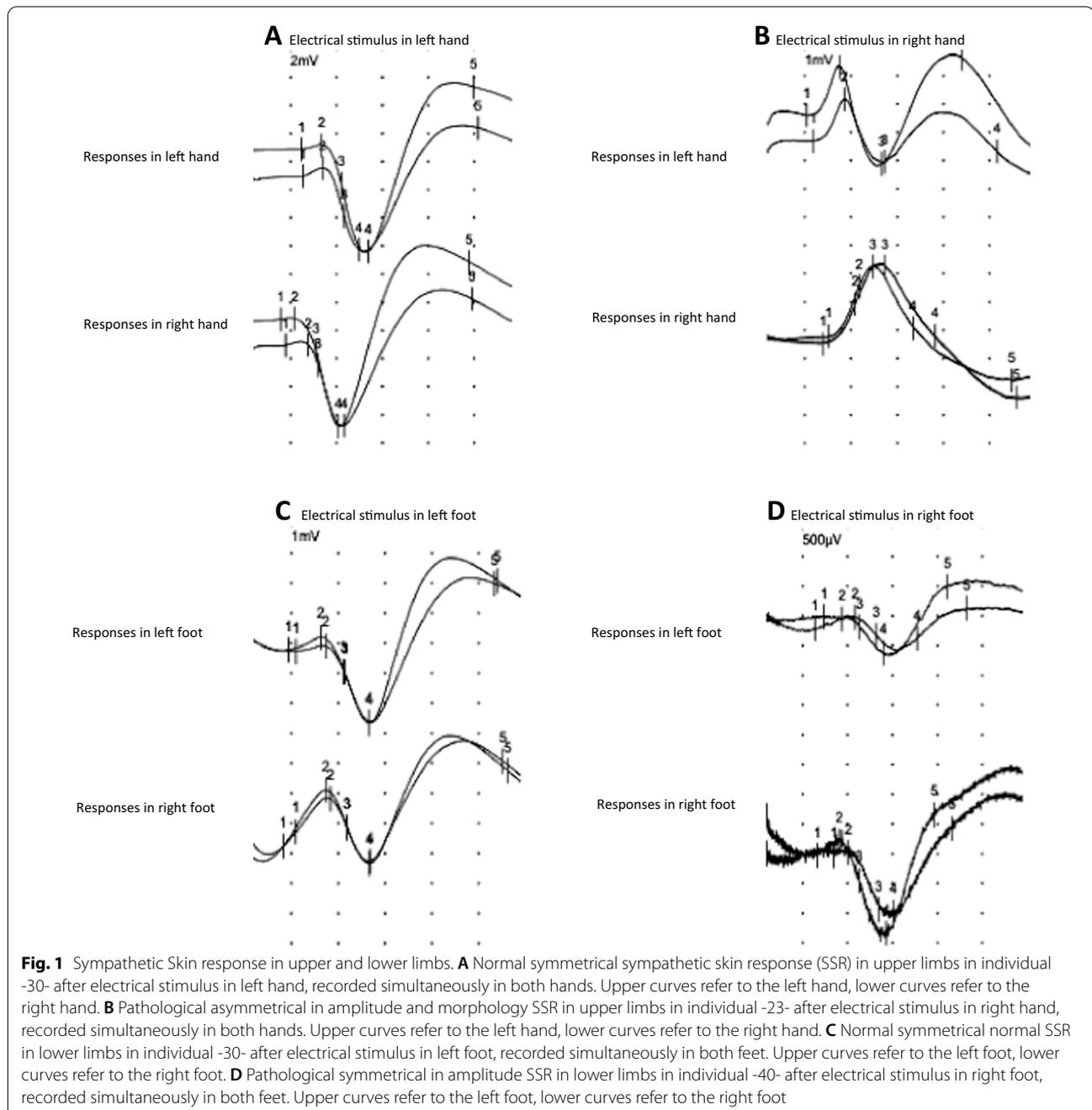| Individuals with CdLS	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47
Cardinal features (2 points each if present)																							
Synophrys and/or thick eyebrows	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Short nose, concave nasal ridge and/or upturned nasal tip	+	+	+	+	+	+	+	–	–	+	–	+	–	+	+	+	+	+	–	+	+	+	+
Long and/or smooth philtrum	+	+	+	+	–	–	+	–	–	+	+	+	–	+	–	–	–	–	+	+	+	–	+
Thin upper lip vermilion and/or downturned corners of mouth	+	+	+	+	+	–	+	–	–	+	+	+	–	+	–	+	–	–	+	+	+	+	+
Hand oligodactyly and/or adactyly	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	+	–	–
Congenital diaphragmatic hernia	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–
Suggestive features (1 point each if present)																							
Global developmental delay and/or intellectual disability	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prenatal growth retardation (<2 SD)	+	–	+	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–
Postnatal growth retardation (<2 SD)	+	–	+	+	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Microcephaly (prenatally and/or postnatally)	+	–	+	+	+	–	+	–	+	+	–	+	–	+	–	+	–	+	+	+	+	+	–
Small hands and/or feet	–	+	+	+	+	+	+	+	+	+	+	–	+	–	–	+	+	+	+	+	+	+	+
Short fifth finger	–	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+
Hirsutism	+	+	+	+	+	+	+	–	+	+	–	+	–	+	–	+	–	–	+	+	–	+	+
Clinical Score	14	11	14	15	8	7	11	8	9	15	9	14	6	16	4	13	7	10	11	16	16	13	13

Clinical Score: ≥ 11 points, which at least 3 cardinal: classic CdLs; 9–10 points, which at least 2 cardinal: non-classic CdLs; 4–8 points, which at least 1 cardinal: molecular testing; < 4 points: insufficient to indicate molecular testing CdLs. Dotted individuals: involved genes different from *NIPBL*

Table 2 Sympathetic skin response and heart rate variability in CdLS

Individuals	Side	SSR hand Lat. (ms)	SSR hand Amp. (µV)		SSR Foot Lat. (ms)	SSR Foot Amp. (µV)		HRV (RMSSD) (ms)
Gender/Age/Gene								
Normal values[7,13,14]		1.3±0.1	800±300		1.9±0.1	600±300		≥16,39ms (<10years)
3	R	0,94	968,7		1,27	1589,3		54,10
M/2y/*HDAC8*	L	0,96	942,71		1,09	1874,8		
4	R	0,89	3352,7		1,11	1019,8	Asymmetrical	64,64
F/3y/*NIPBL*	L	0,88	3198,5		1,26	329,8		
7	R	1,02	758,8		0,94	1285,5	Asymmetrical	48,55
M/3y/*NIPBL*	L	1,18	1062,6		0,93	525,2		
8	R	1,16	696,2		1,39	398,5	Asymmetrical	79,76
M/3y/*NIPBL*	L	1,22	1026,0		1,08	138,9		
12	R	1,04	306,9		1,61	545,0		148,46
F/5y/*RAD21*	L	1,02	396,5		1,69	413,7		
13	R	1,09	2464,1		1,91	745,0		21,68
F/5y/*SMC1A*	L	1,23	3151,1		1,65	868,7		
14	R	1,10	264,1		0,99	764,9		89,16
F/5y/*NIPBL*	L	1,16	236,6		1,28	876,3		
15	R	1,17	3580,2		0,94	5027,5	Asymmetrical	66,49
M/5y/*NIPBL*	L	1,07	4200,0		1,55	1630,5		
18	R	0,88	1016,8		0,85	668,7		74,82
M/7y/*NIPBL*	L	0,99	1050,4		1,27	508,4		
22	R	1,20	658,0		1,36	893,6		58,94
F/8y/*NIPBL*	L	1,20	743,5		0,93	607,6		
23	R	1,05	1022,9	Asymmetrical	1,97		Asymmetrical	54,95
F/9y/*NIPBL*	L	1,19	2062,6		1,79	7255,0 3396,9		
Normal values[7,13,14]		1.3±0.1	800±300		1.9±0.1	600±300		≥16,39ms (<20years)
25	R	1,26	366,4		1,49	706,9		180,41
F/11y/*SMC1A*	L	1,26	355,7		1,61	573,3		
27	R	0,76	1328,2		1,32	404,6		424,88
F/11y/*NIPBL*	L	0,93	1720,6		1,51	371,0		
30	R	0,65	748,1		0,89	543,5		138,36
F/15y/*NIPBL*	L	0,79	578,6		0,94	415,3		
31	R	0,92	957,3		1,42	1019,8		362,04
F/15y/*NIPBL*	L	1,05	879,4		1,14	1305,3		
34	R	1,01	1221,4		1,35	600,0		66,93
F/16y/*NIPBL*	L	1,13	1665,6		1,22	401,5		
36	R	0,88	1016,8		1,39	408,4		126,06
M/17y/*NIPBL*	L	0,99	1050,4		0,85	668,7		
Normal values[7,13,14]		1.3±0.1	800±300		1.9±0.1	600±300		≤14,54ms (≤25years)
40	R	0,93	363,4		1,80	361,8	Asymmetrical	254,66
M/23y/*NIPBL*	L	NE	NE		1,69	167,9		
41	R	0,93	1485,5		NE	NE		57,96
F2/25y/*NIPBL*	L	NE	NE		NE	NE		
Normal values[7,13,14]		1.3±0.1	800±300		1.9±0.1	600±300		≤11,43ms (≤35years)
46	R	1,16	693,9		1,28	164,9	Asymmetrical	51,4
F/37y/*NIPBL*	L	1,15	708,4		1,45	247,3		

Table 2 (continued)

SSR Sympathetic Skin Response; *HRV* Heart Rate Variability; *RMSSD* Root Mean Square of Successive Differences. *Lat* latency; *Amp* Amplitude; *ms* milliseconds; *μV* microvolts; *NE* Not examined. *P40* left arm not studied. *P41* only cooperated for the SSR study in one hand. Asymmetrical: Used to indicate side-to-side differences in amplitude and/or morphology in the Sympathetic Skin Response (SSR) in both upper or lower limbs

Fig. 1 Sympathetic Skin response in upper and lower limbs. **A** Normal symmetrical sympathetic skin response (SSR) in upper limbs in individual -30- after electrical stimulus in left hand, recorded simultaneously in both hands. Upper curves refer to the left hand, lower curves refer to the right hand. **B** Pathological asymmetrical in amplitude and morphology SSR in upper limbs in individual -23- after electrical stimulus in right hand, recorded simultaneously in both hands. Upper curves refer to the left hand, lower curves refer to the right hand. **C** Normal symmetrical normal SSR in lower limbs in individual -30- after electrical stimulus in left foot, recorded simultaneously in both feet. Upper curves refer to the left foot, lower curves refer to the right foot. **D** Pathological symmetrical in amplitude SSR in lower limbs in individual -40- after electrical stimulus in right foot, recorded simultaneously in both feet. Upper curves refer to the left foot, lower curves refer to the right foot
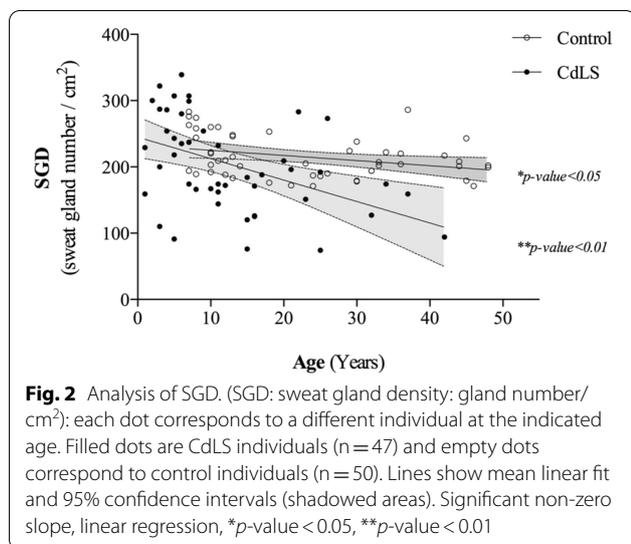
gland density in the only individual with an *SMC3* mutation, who is 39 years old. Regarding the ethnic distribution, only 4 individuals in the *NIPBL* group and none in the control group were not Caucasian, and all of them had normal values in SGD, though they were in the first decade of life. In the group of *NIPBL*, there is a repeated

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Table 3 Genetics, clinical score and sweat gland density (SGD) in individuals with CdLS in different decades of life.

INDIVIDUALS	Control group	1	2	3	4	5	6	7	8	9	10
Age (years)	1-10 years Mean of 13 individuals	1.5	1.5	2	3	3	3	3	3	4	4
Gender		F	M	M	F	M	M	M	M	F	F
Gene Mutation		?	SMC1A	HDAC8 c.305G>A p.Cys102Tyr	NIPBL c.6549_6552delICTCA p.His218Glnfs*13		NIPBL	NIPBL c.3021delA (mosaicism)	NIPBL c.5329-15A>G c.iie1777_Arg1809del	?	?
Clinical Score		13	5	11	15	15	17	14	7	4	13
GERD		++	-		+	-	+++	+	+	++	++
SGD	236.76±33.45	229	159	300	287	322	322	200	110	286	254

INDIVIDUALS	11	12	13	14	15	16	17	18	19	20	21
Age (years)	4	5	5	5	5	6	6	7	7	7	7
Gender	F	F	F	M	F	F	M	M	M	F	F
Gene Mutation	HDAC8	RAD21 c.1382C>T p.Pro395Leu	SMC1A NM_006306:c2096>T	NIPBL	C7736C>T p.Ala2579Val	NIPBL	NIPBL	NIPBL c.5329-15A>G c.iie1777_Arg1809del	RAD21 Arr(GRCh37)8q24.11 (117765326_118270323)x1	NIPBL	NIPBL
Clinical Score	14	8	5	15	9	6	11	6	4	16	17
GERD	++	+	+	+	-	-	++	+	+	+++	-
SGD	235	307	243	218	91	339	280	174	320	299	237

INDIVIDUALS	22	23	24	Control group	25	26	27	28	29	30	31
Age (years)	8	9	10	11-20 years Mean of 11 individuals	11	11	11	11	12	15	15
Gender	F	F	F		F	F	F	M	F	F	F
Gene	NIPBL	NIPBL	SMC1A		SMC1A	NIPBL	NIPBL		NIPBL	NIPBL	NIPBL
Mutation	c.6860T->C p.L2287P	c.5483G>A p.Arg1828Gln			c.2369G>A p.Arg790Gln	Chr 5p 13.1	c.6272G>A p.Cys2091Phe		c.7928-7929delCA	c.5467A>G missense p.Asn182Sp	c.7586A
Clinical Score	13		6		14	11	14	15	8	7	11
GERD	+	+++	++		+	+	+	++	-	-	+++
SGD	166	254	167	217.18±29.99	162	144	232	174	172	184	120

INDIVIDUALS	32	33	34	35	36	37	Control group	38	39	40	41
Age (years)	15	16	16	16	17	20	21-30 years Mean of 10 individuals	21	22	23	25
Gender	M	F	F	M	M	F		M	F	M	F
Gene Mutation	NIPBL Mosaicism	?	NIPBL c.6964_6965insATTTA p.Ala2325*	NIPBL	NIPBL c.6242G->C p.Gly2081Val	NIPBL		NIPBL?	SMC3	NIPBL Delection	NIPBL c.3745AZG
Clinical Score	8	9	15	9	14	6		16	4	13	7
GERD	+++	+	+++	+	+	-		++	+	-	-
SGD	76	171	125	126	188	209	206.40±22.9	196	283	151	192

INDIVIDUALS	42	43	Control group	44	45	46	Control group	47
Age (years)	25	26	31-40 years Mean of 8 individuals	32	34	37	41-50 years Mean of 8 individuals	42
Gender	F	F		F	M	F		M
Gene Mutation	NIPBL	?		NIPBL	NIPBL mosaicism	NIPBL c.5471C>T p.Ser1824Leu		NIPBL
Clinical Score	10	11		15	16	13		13
GERD	+++	-		+	-	-		+++
SGD	74	273	215.28±31.40	127	174	159	202.50±22.16	94

Individuals are differentiated in decades of life by different shading colours from: white: 1st decade of life; light grey: 2nd decade of life; medium grey: 3rd decade of life; grey: 4th decade of life; dark grey: 5th decade of life. *M* male, *F* female, *PNS* Peripheral Nervous System, *GERD* Gastroesophageal reflux disease (− no, + mild, + + moderate, + + + severe), *SGD* Sweat Gland Density: gland number/cm^2

Fig. 2 Analysis of SGD. (SGD: sweat gland density: gland number/cm^2): each dot corresponds to a different individual at the indicated age. Filled dots are CdLS individuals (n = 47) and empty dots correspond to control individuals (n = 50). Lines show mean linear fit and 95% confidence intervals (shadowed areas). Significant non-zero slope, linear regression, *p*-value < 0.05, **p*-value < 0.01

Table 4 SGD by decades of life

	Controls	N	CdLS NIPBL	N	p^{a}
Mean SGD (g/cm^2) ± SD	217.60 ± 30.61	50	178.03 ± 72.53	27	0.001
Mean SGD (g/cm^2) ± SD by decades of life	Controls	N	CdLS NIPBL	N	p^{a}
≤ 10 years	236.76 ± 34.81	13	226.00 ± 86.60	10	0.686
11–20 years	217.18 ± 29.99	11	159.09 ± 45.35	11	0.002
21–30 years	206.40 ± 22.9	10	139.00 ± 59.90	3	0.010
31–40 years	215.28 ± 32.40	8	143.00 ± 22.62	2	0.013
41–50 years	202.50 ± 22.16	8	94.0	1	0.002

Values for sweat gland density in CdLS individuals with variants in *NIPBL* and controls by groups of age

[a] Independent samples t test. There are statistically significant differences (p < 0.05) in the SGD global mean (control group compared to the global NIPBL group) and by decades of life, in all the decades except in the first one

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mutation, a frameshift mutation in 2 siblings. According to the asymmetry in the SSR response, 3 of the *NIPBL* individuals had missense mutations, 2 of them frameshift mutations and 1 of them splicing mutation, but the number of individuals is not big enough to do a correlation with the autonomic neuropathy. Further studies are warranted to look at autonomic nervous system dysfunction and relation to mutated gene and age in individuals with CdLS.

Conclusion

Individuals with CdLS have abnormal autonomic nervous system function, showing asymmetries in the sympathetic responses in lower limbs, and pathological results in the sudomotor test. The degree of dysfunction in postganglionic sudomotor nerve fibers might be related to premature aging. Even though, somatic nervous system function studies were normal.

Abbreviations
CdLS: Cornelia de Lange Syndrome; PNS: Peripheral nervous system; SGD: Sweat gland density; GERD: Gastroesophageal reflux disease; CSS: Clinical severity score.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13023-021-02082-y.

Additional file 1. Tables 1 to 4: Motor and Sensory Nerve Conduction Studies Parameters.

Declarations

Ethics approval and consent to participate
The protocol study was approved by the Ethics Committee of Clinical Research from the Government of Aragón (CEICA; PI16/225). All the individuals with CdLS and controls gave informed consent for their participation.

Consent for publication
All the individuals with CdLS and controls gave informed consent for the publication of this work.

Competing interests
The authors declare that they have no competing interests.

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References
1. Kline AD, Moss JF, Selicorni A, Bisgaard AM, Deardorff MA, Gillett PM, Ishman SL, Kerr LM, Levin AV, Mulder PA, Ramos FJ, Wierzba J, Ajmone PF, Axtell D, Blagowidow N, Cereda A, Costantino A, Cormier-Daire V, FitzPatrick D, Grados M, Groves L, Guthrie W, Huisman S, Kaiser FJ, Koekkoek G, Levis M, Mariani M, McCleery JP, Menke LA, Metrena A, O'Connor J, Oliver C, Pie J, Piening S, Potter CJ, Quaglio AL, Redeker E, Richman D, Rigamonti C, Shi A, Tümer Z, Van Balkom IDC, Hennekam RC. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nat Rev Genet. 2018;19(10):649–66.
2. Pié J, Gil-Rodríguez MC, Ciero M, López-Viñas E, Ribate MP, Arnedo M, Deardorff MA, Puisac B, Legarreta J, de Karam JC, Rubio E, Bueno I, Baldellou A, Calvo MT, Casals N, Olivares JL, Losada A, Hegardt FG, Krantz ID, Gómez-Puertas P, Ramos FJ. Mutations and variants in the cohesion factor genes *NIPBL*, *SMC1A*, and *SMC3* in a cohort of 30 unrelated patients with Cornelia de Lange syndrome. Am J Med Genet A. 2010;152A(4):924–9. https://doi.org/10.1002/ajmg.a.33348.
3. Teresa-Rodrigo ME, Eckhold J, Puisac B, Dalski A, Gil-Rodríguez MC, Braunholz D, Baquero C, Hernández-Marcos M, de Karam JC, Ciero M, Santos-Simarro F, Lapunzina P, Wierzba J, Casale CH, Ramos FJ, Gillessen-Kaesbach G, Kaiser FJ, Pié J. Functional characterization of *NIPBL* physiological splice variants and eight splicing mutations in patients with Cornelia de Lange syndrome. Int J Mol Sci. 2014;15:10350–64.
4. Ramos FJ, Puisac B, Baquero-Montoya C, Gil-Rodríguez MC, Bueno I, Deardorff MA, Hennekam RC, Kaiser FJ, Krantz ID, Musio A, Selicorni A, FitzPatrick DR, Pié J. Clinical utility gene card for: Cornelia de Lange syndrome. Eur J Hum Genet. 2015. https://doi.org/10.1038/ejhg.2014.270.
5. Gil-Rodríguez MC, Deardorff MA, Ansari M, Tan CA, Parenti I, Baquero-Montoya C, Ousager LB, Puisac B, Hernández-Marcos M, Teresa-Rodrigo ME, Marcos-Alcalde I, Wesselink JJ, Lusa-Bernal S, Bijlsma EK, Braunholz D, Bueno-Martinez I, Clark D, Cooper NS, Curry CJ, Fisher R, Fryer A, Ganesh J, Gervasini C, Gillessen-Kaesbach G, Guo Y, Hakonarson H, Hopkin RJ, Kaur M, Keating BJ, Kibaek M, Kinning E, Kleefstra T, Kline AD, Kuchinskaya E, Larizza L, Li YR, Liu X, Mariani M, Picker JD, Pié Á, Pozojevic J, Queralt E, Richer J, Roeder E, Sinha A, Scott RH, So J, Wusik KA, Wilson L, Zhang J, Gómez-Puertas P, Casale CH, Ström L, Selicorni A, Ramos FJ, Jackson LG, Krantz ID, Das S, Hennekam RC, Kaiser FJ, FitzPatrick DR, Pié J. De novo heterozygous mutations in SMC3 cause a range of Cornelia de Lange syndrome-overlapping phenotypes. Hum Mutat. 2015;36(4):454–62. https://doi.org/10.1002/humu.22761.
6. Huisman S, Mulder PA, Redeker E, et al. Phenotypes and genotypes in individuals with *SMC1A* variants. Am J Med Genet A. 2017;173(8):2108–25.

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7. Parenti I, Gervasini C, Pozojevic J, et al. Expanding the clinical spectrum of the *'HDAC8*-phenotype'—implications for molecular diagnostics, counseling and risk prediction. Clin Genet. 2016;89(5):564–73.

8. Cucco F, Sarogni P, Rossato S, Alpa M, Patimo A, Latorre A, Magnani C, Puisac B, Ramos FJ, Pié J, Musio A. Pathogenic variants in EP300 and ANKRD11 in patients with phenotypes overlapping Cornelia de Lange syndrome. Am J Med Genet A. 2020;182(7):1690–6. https://doi.org/10.1002/ajmg.a.61611.

9. Parenti I, Diab F, Gil SR, Mulugeta E, Casa V, Berutti R, Brouwer RWW, Dupé V, Eckhold J, Graf E, Puisac B, Ramos F, Schwarzmayr T, Gines MM, van Staveren T, van IJcken WFJ, Strom TM, Pié J, Watrin E, Kaiser FJ, Wendt KS. MAU2 and NIPBL Variants impair the heterodimerization of the cohesin loader subunits and cause Cornelia de Lange Syndrome. Cell Rep. 2020;31(7):107647. https://doi.org/10.1016/j.celrep.2020.107647.

10. Kerr LM, Jones A, Kline AD, Fischer PR. Compass-31 questionnaire screening in individuals with Cornelia de Lange syndrome. Am J Med Genet A. 2017;173(5):1172–85.

11. Recommendations for the Practice of Clinical Neurophysiology. Guidelines of the International Federation of Clinical Neurophysiology. New York: Elsevier; 1999.

12. Kimura J. Electrodiagnosis in diseases of nerve and muscle. Principles and Practice. Fourth Edition. New York: Oxford University Press; 2013.

13. Ryan CS, Conlee EM, Sharma R, Sorenson EJ, Boon AJ, Laughlin RS. Nerve conduction normal values for electrodiagnosis in pediatric patients. Muscle Nerve. 2019;60(2):155–60.

14. Hylienmark L, Ludvigsson J, Brismar T. Normal values of nerve conduction studies in children and adolescents. Electroencephalogr Clin Neurophysiol. 1995;97(5):208–14.

15. Tekgül H, Polat M, Tosun A, Serdaroğlu G, Gökben S. Electrophysiologic assessment of spasticity in children using H-reflex. Turk J Pediatr. 2013;55:519–23.

16. Ziegler D, Laux G, Dannehl K, Spüler M, Mühlen H, Mayer P, Gries FA. Assessment of cardiovascular autonomic function: age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses. Diabet Med. 1992;9:166–75.

17. Akyuz G, Turkdogan-Sozuer D, Turan B, Canbolat N, Yilmaz I, Us O, Kayhan O. Normative data sympathetic skin response and RR interval variation in Turkish children. Brain Dev 21:99–102.

18. Uncini A, Pullman SL, Lovelace RE, Gambi D. The sympathetic skin response normal values, elucidation of afferent components. J Neurol Sci. 1988;87:299–306.

19. Ferrer T, Ramos MJ, Pérez-Jiménez A, Pérez-Sales P, Álvarez E. Sympathetic sudomotor function and aging. Muscle Nerve. 1995;18(4):395–401.

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