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.

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 to 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 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, aged 7–48 years). 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 mean 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 minutes [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 cm² (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 2). Statistical studies were achieved with the SPSS program version 25.
Table 2
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   |
|-------------|---------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Age (years) | 1–10 years    | 1.5 | 1.5 | 2   | 3   | 3   | 3   | 3   | 3   |
| Gender      | Mean of 13    | F   | M   | M   | F   | M   | M   | M   |
| Gene        | individuals   | ?   | SMC1A| HDAC8| NIPBL| NIPBL| NIPBL| NIPBL| NIPBL|
| Mutation    | c.305G>A      | p.Cys102Tyr | c.6549_6552delICTCA | p.His218Glnfs*13 | c.3021delA fibroblast (mosaicism) |
| Clinical Score | 13  | 5   | 11  | 15  | 15  | 17  | 14  |
| GERD        | ++           | -   | +   | -   | ++  | +   |
| SGD         | 236.76±33.45 | 229 | 159 | 300 | 287 | 322 | 322 | 200 |
| INDIVIDUALS | 11            | 12  | 13  | 14  | 15  | 16  | 17  | 18  |
| Age (years) | 4             | 5   | 5   | 5   | 5   | 6   | 6   | 7   |
| Gender      | F             | F   | F   | M   | F   | M   | M   | M   |
| Gene        | HDAC8         | RAD21| SMC1A| NIPBL| NIPBL| NIPBL| NIPBL| NIPBL| NIPBL|
| Mutation    | c.1382C>T     | heterozygous | NM_006306:c2096>T | C7736C>T | p.Ala2579Val missense (exon45) | c.5329-15A>G |
| Clinical Score | 14 | 8   | 5   | 15  | 9   | 6   | 11  | 6   |
| GERD        | ++           | +   | +   | -   | ++  | +   |
| SGD         | 235          | 307 | 243 | 218 | 91  | 339 | 280 | 174 |
| INDIVIDUALS | 22            | 23  | 24  | Control group | 25  | 26  | 27  | 28  |
| Age (years) | 8             | 9   | 10  | 11–20 years | 11  | 11  | 11  | 11  |
| Gender      | F             | F   | F   | Mean of 11 | F   | F   | F   | M   |
| Gene        | NIPBL         | NIPBL| SMC1A| individuals | SMC1A| NIPBL| NIPBL| NIPBL|
| Mutation    | c.6860T>C     | p.L2287P | c.5483G>A | c.2369G>A | Chr 5p | c.6272G>A | exon29 | exon15 | exon 36 |
| Clinical Score | 13 | 6   | 14  | 11  | 14  | 15  |
| GERD        | +            | +++ | ++  | +   | +   | ++  |
| SGD         | 166          | 254 | 167 | 217.18±29.99 | 162 | 144 | 232 | 174 |
| INDIVIDUALS | 32            | 33  | 34  | 35  | 36  | 37  | Control group | 38  |
| Age (years) | 15            | 16  | 16  | 16  | 17  | 20  | 21–30 years | 21  |
| Gender      | M             | F   | F   | M   | M   | F   | Mean of 10 | M   |
| Gene        | NIPBL         | ?   | NIPBL| NIPBL| NIPBL| NIPBL| NIPBL| individuals |
| Mutation    | Mosaicism     | c.6964_6965insATTTA | c.6242G>C | p.G2081A Exon35 |

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; dark grey: 4th decade of life. PNS: Peripheral Nervous System, GERD: Gastroesophageal reflux disease (– no, + mild, ++ moderate, +++ severe), SGD: Sweat Gland Density: gland number/c
| INDIVIDUALS | Control group | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|-------------|---------------|---|---|---|---|---|---|---|---|
| Clinical Score | 8 | 9 | 15 | 9 | 14 | 6 | 16 | |
| GERD | +++ | + | +++ | + | + | - | ++ | |
| SGD | 76 | 171 | 125 | 126 | 188 | 209 | 206.40 ± 22.9 | 196 |
| INDIVIDUALS | 42 | 43 | Control group | 44 | 45 | 46 | Control group | 47 |
| Age (years) | 25 | 26 | 31–40 years | 32 | 34 | 37 | 41–50 years | 42 |
| Gender | F | F | Mean of 8 | F | M | F | Mean of 8 | M |
| Gene | NIPBL | ? | individuals | NIPBL | NIPBL mosaicism | NIPBL | individuals | NIPBL |
| Mutation | c.5471C > T | p.S1824L | Exon29 | |
| 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 de

PNS: Peripheral Nervous System, GERD: Gastroesophageal reflux disease (- no, + mild, ++ moderate, +++ severe), SGD: Sweat Gland Density: gland number/cm²

Results

Conventional motor and sensory nerve conduction studies (large fiber nerves) were normal in all 20 individuals with CdLS analyzed (Tables 1 to 3 of supplementary material). The study of the autonomic nervous system (small fiber nerves) in HRV at rest was normal as well (Table 1). Nevertheless, SSR revealed mild alterations in lower limbs in 7 of the 20 individuals, with asymmetrical responses (Table 1, Fig. 1). Sudomotor tests evinced reduced SGD in 16 of the 47 individuals with CdLS regarding the control group by decades of life (Table 2). 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. 2A). The linear regression showed that the slope of the SGD reduction by age is much pronounced in individuals with CdLS than in controls (Fig. 2A). 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 as in the whole NIPBL group as in all the decades of life, except the first one (Fig. 2B).
| Individuals | SSR hand | SSR Foot | HRV (RMSSD) |
|-------------|----------|----------|-------------|
| Gender/Age/Gene | Side | Lat. (ms) | Amp. (µV) (µV) | Lat. (ms) | Amp. (µV) | (ms) |
| Normal values | | | | | | |
| | | 1.3±0.1 | 800±300 | 1.9±0.1 | 600±300 | ≥ 16,39ms (< 10years) |
| 3 | M/2y/HDAC8 | R | 0.94 | 968,7 | 1.27 | 1589,3 | 54,10 |
| | | L | 0.96 | 942,71 | 1.09 | 1874,8 |
| 4 | F/3y/NIPBL | R | 0.89 | 3352,7 | 1,11 | 1019,8 | Assymetrical 64,64 |
| | | L | 0.88 | 3198,5 | 1.26 | 329,8 |
| 7 | M/3y/NIPBL | R | 1.02 | 758,8 | 0.94 | 1285,5 | Assymetrical 48,55 |
| | | L | 1.18 | 1062,6 | 0.93 | 525,2 |
| 8 | M/3y/NIPBL | R | 1.16 | 696,2 | 1.39 | 398,5 | Assymetrical 79,76 |
| | | L | 1.22 | 1026,0 | 1.08 | 138,9 |
| 12 | F/5y/RAD21 | R | 1.04 | 306,9 | 1.61 | 545,0 | 148,46 |
| | | L | 1.02 | 396,5 | 1.69 | 413,7 |
| 13 | F/5y/SMC1A | R | 1.09 | 2464,1 | 1.91 | 745,0 | 21,68 |
| | | L | 1.23 | 3151,1 | 1.65 | 868,7 |
| 14 | F/5y/NIPBL | R | 1.10 | 264,1 | 0.99 | 764,9 | 89,16 |
| | | L | 1.16 | 236,6 | 1.28 | 876,3 |
| 15 | M/5y/NIPBL | R | 1.17 | 3580,2 | 0.94 | 5027,5 | Assymetrical 66,49 |
| | | L | 1.07 | 4200,0 | 1.55 | 1630,5 |
| 18 | M/7y/NIPBL | R | 0.88 | 1016,8 | 0.85 | 668,7 | 74,82 |
| | | L | 0.99 | 1050,4 | 1.27 | 508,4 |
| 22 | F/8y/NIPBL | R | 1.20 | 658,0 | 1.36 | 893,6 | 58,94 |
| | | L | 1.20 | 743,5 | 0.93 | 607,6 |
| 23 | F/9y/NIPBL | R | 1.05 | 1022,9 | Assymetrical 1,97 | 7255,0 | Assymetrical 54,95 |
| | | L | 1.19 | 2062,6 | 1.79 | 3396,9 |
| Normal values | | 1.3±0.1 | 800±300 | 1.9±0.1 | 600±300 | ≥ 14,54ms (≤ 25years) |
| 25 | F/11y/SMC1A | R | 1.26 | 366,4 | 1.49 | 706,9 | 180,41 |
| | | L | 1.26 | 355,7 | 1.61 | 573,3 |
| 27 | F/11y/NIPBL | R | 0.76 | 1328,2 | 1.32 | 404,6 | 424,88 |
| | | L | 0.93 | 1720,6 | 1.51 | 371,0 |
| 30 | F/15y/NIPBL | R | 0.65 | 748,1 | 0.89 | 543,5 | 138,36 |
| | | L | 0.79 | 578,6 | 0.94 | 415,3 |
| 31 | F/15y/NIPBL | R | 0.92 | 957,3 | 1.42 | 1019,8 | 362,04 |
| | | L | 1.05 | 879,4 | 1.14 | 1305,3 |
| 34 | F/16y/NIPBL | R | 1.01 | 1221,4 | 1.35 | 600,0 | 66,93 |
| | | L | 1.13 | 1665,6 | 1.22 | 401,5 |
| 36 | M/17y/NIPBL | R | 0.88 | 1016,8 | 1.39 | 408,4 | 126,06 |
| | | L | 0.99 | 1050,4 | 0.85 | 668,7 |
| Normal values | | 1.3±0.1 | 800±300 | 1.9±0.1 | 600±300 | ≤ 14,54ms (≤ 25years) |
| 40 | M/23y/NIPBL | R | 0.93 | 363,4 | 1.80 | 361,8 | Assymetrical 254,66 |

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.
| Individuals | SSR hand | SSR Foot | HRV (RMSSD) |
|-------------|----------|----------|-------------|
|             | 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 values7,13,14 | 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       | 51.4       |             |
| F/37y/NIPBL | L 1.15   | 708.4    | 1.45        | 247.3       |             |             |

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.
### Table 3
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 | 15 | 17 | 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 |

**AL Hand – Two channel. B Hand - Two channel**
### Table 1: Genetic Studies of the 47 Individuals with CdLS

| 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  |
|-----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Synaphe 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  | 15  | 16  | 13  | 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 gene different than NIPBL.

A L Hand - Two channel. B R Hand - Two channel

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 2). 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 Table 4 of the supplementary material 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 consider 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 not be related to GERD or the Clinical Severity Score (CSS), yet all the individuals had mutations in NIPBL gene. (Table 1).

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 2, Fig. 2A). 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 (Table 2, Fig. 2B), and seems to be similar in individuals with variants in SMC1A. 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 gland density in the only individual with an SMC3 mutation, who is 39 years old. 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

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.

Availability of data and material

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Competing interests

Non-financial competing interests.

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Authors’ contributions
Conceptualization, M.J.P., F.R., J.P., and B.P.; nerve conduction studies, PP, M.H.; autonomic nervous system studies, M.J.P., I.B., L.M.K.; clinical studies, F.R., G.B.L., L.T., F.J.K., S.A.H. and A.D.K.; genetics, A.L.P., M.A., S.A.H. and F.J.K.; writing—original draft preparation, M.J.P., J.P. and B.P.; writing—review, L.M.K., S.A.H., F.J.K., F.R., A.D.K., J.P. and B.P.; writing—editing, M.J.P., PP, M.H., I.B., A.L.P., M.A., L.T., G.B.L., L.M.K., S.A.H., F.J.K., F.R., A.D.K., J.P. and B.P. All authors have read and agreed to the published version of the manuscript.

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Figures
Figure 1

Sympathetic Skin response in upper and lower limbs. A: Normal symmetrical sympathetic skin response (SSR) in upper limbs in individual 30. B: Pathological asymmetrical in amplitude and morphology SSR in upper limbs in individual 23. C: Normal symmetrical normal SSR in lower limbs in individual 30. D: Pathological symmetrical in amplitude SSR in lower limbs in individual 40.
Figure 2

A: Analysis of SGD. (SGD: sweat gland density: gland number/cm²): 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, ***p-value<0.001. B: SGD by decades of life. Values for sweat gland density in CdLS individuals with variants in NIPBL and controls by groups of age. aIndependent 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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