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An Endocrinological approach to Cornelia de Lange Syndrome

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ABSTRACT

Cornelia de Lange syndrome is a developmental disorder with a great degree of clinical and genetical variability characterized by typical facial features, growth impairment and multi-organ anomalies. It is caused by mutations in the cohesin complex that is involved in regulation of gene expression. Growth disturbances are a major feature of the syndrome and have various underlying mechanisms. Other associations regarding endocrine function are represented by disturbances in the hypothalamic-pituitary axis, decreased bone density associated with fractures and genital malformations associated with menstrual irregularities and altered fertility.

Keywords: Cornelia de Lange syndrome, endocrinological complications, growth

List of abbreviations
adrenocorticotropic hormone, ACTH; ankyrin repeat domain containing protein 11, ANKR11; Bromodomain-containing protein 4, BRD4; Cornelia de Lange syndrome, CdLS; growth hormone – insulin-like growth factor 1, GH-IGF1; Histone deacetylase 8, HDAC8; Nipped-B-like Protein, NIPBL; recombinant human growth hormone, rhGH; Repair protein rad21 homologue, RAD21; Structural Maintenance Of Chromosomes 1A, SMC1A; Structural Maintenance Of Chromosomes 3, SMC3; thyroid stimulating hormone, TSH;

INTRODUCTION

Cornelia de Lange syndrome (CdLS) is a multisystem congenital developmental disorder characterized by distinctive facial features, multi-system anomalies and growth retardation [1].

Since the first description of the syndrome by Dutch pediatrician Cornelia de Lange, the evolution of knowledge of the clinical expression and biologic basis has largely expanded. The estimated prevalence, between 1 in 10.000 and 1 in 30.000 live births [2] may not be entirely accurate because of the possible misdiagnosis of mild cases and the complexity, variability and dynamic changes with time of various phenotypes [2,3,4].

The development of molecular diagnosis provided the means to genetically characterize CdLS patients, previously diagnosed on a clinical basis only. It is now known that the biological basis of the syndrome resides in mutations in genes encoding the cohesin pathway [2]. Cohesin is a multi-subunit protein complex involved in chromosome function, gene regulation and DNA-repair [1].

The molecular basis of CdLS shows a great genetic heterogeneity, with genes identified as structural or regulatory components of the cohesin complex [Nipped-B-like Protein (NIPBL), Structural Maintenance Of Chromosomes 1A (SMC1A), Structural Maintenance Of Chromosomes 3 (SMC3), Repair protein rad21 homologue (RAD21), Bromodomain-containing protein 4 (BRD4), Histone deacetylase 8 (HDAC8), ankyrin repeat domain containing protein 11 (ANKR11)] [2].

Mutations in these genes lead at a cellular level to cell growth arrest, apoptosis, genome instability

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and premature aging as a result of increased levels of oxidative stress [5]. Although most cases are sporadic, autosomal dominant or X-linked inheritance patterns have also been described [6].

Clinical practice and molecular diagnosis intertwine in thorough characterization of CdLS spectrum with subsequent division in classic CdLS phenotype - which does not require obligatory molecular confirmation and non-classic CdLS phenotype in whom the diagnosis in established only after identification of a pathogenic variant in the cohesin-relevant gene. Individuals in whom a mutation in a cohesin complex gene is found, but do not harbor a resemblance with the classic phenotype, fall outside the CdLS spectrum and into the larger family of "cohesinopathies" [2].

DIAGNOSIS

The spectrum of findings ranges from mild to severe, which lead some authors to divide this syndrome in subtypes, but the cardinal feature of the syndrome is the facial gestalt "once seen, never forgotten" [7] with bushy eyebrows and synophrys, anteverted nares with depressed nasal bridge, thin lips and hirsute forehead [1,2].

According to the International consensus statement published in 2018, classical phenotype includes characteristic facial features and non-facial cardinal features such as hand oligo/adactyly and congenital diaphragmatic hernia. Also, suggestive features (global developmental delay, prenatal/intrauterine growth retardation, microcephaly, small hands, short fifth finger, hirsutism) are included into a clinical score. The diagnosis of CdLS is then determined based on the summed score detailed in Table 1 [2].

In aid of diagnosing individuals with a milder phenotype and less striking clinical features facial analysis technology is evolving as an important tool in establishing diagnosis [8].

Accompanying the characteristic facial features, limb abnormalities and growth retardation, there have been described a variety of multi-organ malformations: gastrointestinal involvement with accompanying feeding problems, congenital heart anomalies, otolaryngological impairment, kidney, genitalia and urinary tract malformations, neurologic abnormalities, cognitive and behavioral issues have been reported [2].

Despite early interest in the endocrine system involvement in CdLS, few investigators have focused on endocrinological dysfunction in CdLS patients and standardized protocols regarding treatment have not yet been implemented. Thus, the purpose of this review is to summarize the current knowledge regarding endocrinological disturbances in CDL patients and their determinant pathophysiological mechanisms.

TABLE 1. Clinical score according to the first international consensus statement

Cardinal features (2 points each)	• 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)	• 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 • Classic CdLS >; > 11 points, of which at least 3 are cardinal • Non-classic CdLS: 9 or 10 points, of which at least 2 are cardinal • Molecular testing for CdLS indicated: 4-8 points, of which at least 1 is cardinal • Insufficient to indicate molecular testing for CdLS: <4 points	

We searched the PubMed database using the terms "Cornelia de lange", "growth", "endocrinological complications". We also performed a search of relevant articles in the references used by other authors. Out of 49 articles, we selected 19 which contained data regarding endocrinological complications and summarized the information.

GROWTH

A cardinal feature of CdLS syndrome is represented by both prenatal and postnatal growth retardation [2].

Proportionate short stature originates in the prenatal period with intrauterine growth retardation being reported in the vast majority of patients. Birth parameters such as height, weight, and head circumference are below the 5th percentile throughout life, with an accentuation of growth delay after 6 months. Although maximal pubertal growth spurt occurs at 15 years in males and 13 years in females, comparable with normal individuals, height velocity is normal until adolescence when it slows and there is a slower pubertal growth, finally reaching a mean adult height of 156 cm for males and 131 cm for females with head circumference consistent to relative microcephaly. Skeletal maturation also appears to be delayed. Growth velocity is reported to be slow but consistent over the course of the years, thus specific growth charts have been implemented to properly follow these patients [9].

There is inconsistency regarding the etiology of short stature in CdLS with a number of factors being

cited as contributors: feeding difficulties, gastrointestinal problems, thyroid dysfunction and growth hormone – insulin-like growth factor 1(GH-IGF1) axis disturbances or as an intrinsic feature of the syndrome [2]. The causative genetic variant also appears to be of influence with individuals with NIPBL variant being more affected [2]. Also, short stature is an important clinical clue in the diagnosis of individuals with SMC3 variant [2,10].

Regarding the involvement of GH-IGF1 axis, reports have been inconsistent, with some reporting normal GH secretion in most children [4]. End-organ resistance to GH was suspected as a contributing factor due to increased IGF-1 concentration on a regular recombinant human growth hormone (rhGH) dose in one patient [4], and low levels of IGF-1 in association with discordant result at stimulation testing in another [11].

Although thin body habitus is a major manifestation of the syndrome in the case of children [9], adult patients progress to truncal obesity, possibly induced by high-caloric food intake and limited physical activity [2].

Despite some cases reporting favorable outcomes on rhGH treatment [4,12], at present, somatropin in not regarded as a commonly accepted treatment of short stature in CdLS and is suggested to be considered only in the case of severe hypoglycemia [5] and if growth delay exceeds that presented in growth charts for CdLS patients and weighted against the burden of daily subcutaneous injections, increased cost and the lack of a positive impact of increased adult height on the quality of life of most individuals with CdLS [2,12]. Also, addressing concurrent conditions such as failure to thrive due to gastroesophageal reflux disease, feeding difficulties and thyroid hormone dysfunction need to be addressed in order to improve growth [13].

Hypothalamic-pituitary dysfunction

Schwartz et al described variable endocrinological dysfunctions in their cohort of CdLS patients and proposed an the hypothesis of thyroid, adrenal and growth hormone involvement in the mental retardation, susceptibility to infection and growth failure respectively, frequently observed in these patients. Small sized thyroid, adrenal, ovaries and testicles are suggested to occur secondary to dysfunction in the hypothalamo-pituitary axis or structural and histological abnormalities: pituitary hypoplasia and absence of basophilic cells responsible for adrenocorticotropic hormone (ACTH) secretion. Endocrine function tests showing evidence of hypopituitarism were also reported [14].

Disorders of water metabolism have been described in a patient with hypernatremia and polydipsia and in another with salt wasting possible secondary to intravenous rehydration [15]. A case of suprasellar germinoma with growth retardation, amenorrhea and diabetes insipidus has also been described [16].

Adrenal and thyroid function

Early in the description of the syndrome, De Lange performed an autopsy of a CdLS subject which showed absence of colloid in the thyroid gland on microscopic examination [17]. Also, Zweymuller, using ^{131}I, demonstrated deficient radiotracer uptake which increased after thyroid stimulating hormone (TSH) stimulation, suggesting secondary hypothyroidism could be associated with CdLS [17], observations that were also consistent with the findings of Li et al which reported a patient with low thyroid hormone levels and normal TSH [12]. Thyroid ectopia in association with TSH deficiency was also described in a patient [14].

Similar, if adrenal insufficiency is present, although rarely encountered, it is likely secondary to hypopituitarism [14,17].

Reproductive function

Malformations of the genital system such as hypospadias, cryptorchidism, micropenis are present in boys and bicornuate uterus can be found in 19-25% of females [2], with clitoromegaly or hypoplastic labia majora being an infrequent finding [18]. Most females develop breast tissue (80%) [2]. Variable dysregulation of the hypothalamic-pituitary-gonadal axis may be the cause of hypoplastic genitalia and disordered sexual development in some of these patients [14].

Although there is a minor delay in the onset of puberty (mean age of onset 15 years for boys and 13 years for girls), the majority of CdLS individuals go through puberty, but girls frequently experience irregular menstrual cycles [2]. Behavioral changes, encountered in CdLS can be exacerbated by the occurrence of premenstrual syndrome and dysmenorrhea [2].

Pregnancy has been reported in CdLS syndrome, although most of them had non-classical phenotype and fatherhood has also been reported, but reliable data on fertility are not available [2].

Osteoporosis

Low bone density is frequently encountered in CdLS patients and is possibly related with hypogonadism, nutritional deficiency, insufficient physical exercise, delayed skeletal maturity and premature aging secondary to defective DNA repair due to abnormal gene expression and osteoporosis is expected to appear at a younger age (mid-teens). Although fractures occur in CdLS patients, most of

them are documented in patients without evidence of osteopenia and/or osteoporosis [19].

Monitoring

When the finding of short stature accompanies other multisystem abnormalities such as various hand deformities, poor language and intellectual disability or other organ involvement, the possibility of a genetic cause should be thoroughly investigated.

Because of the striking facial features and phenotype, the diagnosis of CdLS may be apparent from birth. Diagnosing the specific molecular defect provides the possibility of investigating and if needed appropriately treating major malformations. Multidisciplinary care should be implemented in all children diagnosed with CdLS and it involves management of the feeding difficulties, dental problems, gastrointestinal disorders, of which the most frequently encountered is gastro-esophageal reflux disease, which often requires medical or surgical intervention. Ultrasound of the heart and renal system should be performed routinely, and imagistic investigation of the central nervous system is performed in the case of neurological symptoms. Also, ophthalmologic features and ear abnormalities should be treated and monitored appropriately. Musculoskeletal problems are common and may require physical therapy or medical intervention. Psychotherapy is also an integral part of the management of such patients, because of intellectual disabilities, difficulties in sensory processing communication and language skills, and behavioral issues [2]. Finally, close clinical follow-up of growth and sexual development is needed, in order to offer a timely diagnosis and appropriate treatment.

CONCLUSION

A spectrum of endocrinopathies can be seen in patients with CdLS. By far the most frequent, disorders of growth development are multifactorial and specific treatment may be required in some of the patients. CdLS patients may also be at risk of dysfunction of pituitary and hypothalamic axis. Also, malformations of the reproductive system and fertility issues need to be approached on an individual basis. Low bone density may result from associated endocrine deficits and nutritional factors and its presence at a younger age along with increased risk of fractures justifies close monitoring and timely intervention.

Although not at all a chance finding, the endocrinological milieu encountered in CdLS is not well characterized and further and newer studies are needed with an emphasis on treatment for the proper diagnosis and management of these patients.

This review highlights the importance of continuous monitoring of CdLS patients for endocrinological abnormalities, with a particular focus in childhood on hypothalamic-pituitary dysfunction as a possible modifiable contributor to the cardinal feature of the syndrome, the short stature.

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REFERENCES

1. Avagliano L, Parenti I, Grazioli P et al. Chromatinopathies: A focus on Cornelia de Lange syndrome. *Clin Genet.* 2020;97(1):3-11.
2. Kline AD, Moss JF, Selicorni A et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. *Nat Rev Genet.* 2018;19(10):649-666.
3. Mikolajewska E. Interdisciplinary therapy in Cornelia de Lange syndrome - review of the literature. *Adv Clin Exp Med.* 2013;22(4):571-7.
4. de Graaf M, Kant SG, Wit JM et al. Successful Growth Hormone Therapy in Cornelia de Lange Syndrome. *J Clin Res Pediatr Endocrinol.* 2017;9(4):366-370.
5. Sarogni P, Pallotta MM, Musio A. Cornelia de Lange syndrome: from molecular diagnosis to therapeutic approach. *J Med Genet.* 2020;57(5):289-295.
6. Kline AD, Krantz ID, Sommer A et al. Cornelia de Lange syndrome: clinical review, diagnostic and scoring systems, and anticipatory guidance. *Am J Med Genet.* 2007;143A(12):1287-96.
7. Kousseff BG, Thomson-Meares J, Newkirk P et al. Physical growth in Brachmann-de Lange syndrome. *Am J Med Genet.* 1993;47(7):1050-2.
8. Dowsett L, Porras AR, Kruszka P et al. Cornelia de Lange syndrome in diverse populations. *Am J Med Genet A.* 2019;179(2):150-158.
9. Kline AD, Barr M, Jackson LG. Growth manifestations in the Brachmann-de Lange syndrome. *Am J Med Genet.* 1993;47(7):1042-9.
10. Li R, Tian B, Liang H et al. A Chinese Case of Cornelia de Lange Syndrome Caused by a Pathogenic Variant in SMC3 and a Literature Review. *Front Endocrinol (Lausanne).* 2021;12(604500).
11. McArthur RG, Edwards JH. De Lange syndrome: report of 20 cases. *Can Med Assoc J.* 1967;96(17):1185-98.
12. Liu C, Li X, Cui J. Analysis of clinical and genetic characteristics in 10 Chinese individuals with Cornelia de Lange syndrome and literature review. *Mol Genet Genomic Med.* 2020;8(10):e1471.
13. Deardorff MA, Noon SE, Krantz ID. Cornelia de Lange Syndrome. *Gene rev,* 2005 [updated 2020].
14. Schwartz ID, Schwartz KJ, Kousseff BG et al. Endocrinopathies in Cornelia de Lange syndrome. *J Pediatr.* 1990;117(6):920-3.
15. Tonini G, Marinoni S. Neonatal-onset panhypopituitarism in a girl with Brachmann-De Lange syndrome. *Am J Med Genet.* 1990;36(1):102-3.
16. Sugita K, Izumi T, Yamaguchi K et al. Cornelia de Lange syndrome associated with a suprasellar germinoma. *Brain Dev.* 1986;8(5):541-6.
17. Schlesinger B, Clayton B, Bodian M et al. Typus Degenerativus Amstelodamensis. *Arch Dis Child.* 1963;38(200):349-57.
18. Mariani M, Decimi V, Bettini LR et al. Adolescents and adults affected by Cornelia de Lange syndrome: A report of 73 Italian patients. *Am J Med Genet C Semin Med Genet.* 2016;172(2):206-13.
19. Kline AD, Grados M, Sponseller P et al. Natural history of aging in Cornelia de Lange syndrome. *Am J Med Genet C Semin Med Genet.* 2007;145C(3):248-60.