

Endocrinological disorders in children with cutis-laxa syndromes

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ABSTRACT

Cutis laxa syndromes is a rare, multisystem disorder, which primary involves the skin, caused by various mutations in genes that code structural or functional components of the elastic fiber, resulting in heterogenous manifestations. Diagnosis is primarily based on the physical examination, but supported by molecular tests, and guides treatment and monitoring of the patients. Endocrinological complications are sparsely described, with short stature, osteoporosis and fractures being the most frequent. The precise mechanisms are not elucidated and reports about condition-specific treatments are rare. This review provides an overview of the endocrinological disturbances reported in association with cutis laxa syndromes.

Keywords: cutis laxa, short stature, osteoporosis

List of abbreviations

adrenocorticotrophic hormone, ACTH; Aldehyde Dehydrogenase 1 Family Member A1, ALDH1A1; Aldehyde Dehydrogenase 18 Family Member A1, ALDH18A1; autosomal dominant, AD; autosomal recessive, AR; ATPase H⁺ transporting V0 subunit a2, ATP6V0A2; ATPase H⁺ Transporting V1 Subunit A, ATP6V1A; ATPase H⁺ Transporting V1 Subunit E1, ATP6V1E1; ATPase Copper Transporting Alpha, ATP7A; arginin vasopressin, AVP; cutis laxa, CL; elastin gene, ELN, fibulin 4 gene, FBLN 4; fibulin 5 gene, FBLN 5; Latent Transforming Growth Factor Beta Binding Protein 4, LTBP4; follicle stimulating hormone, FSH; growth hormone, GH; growth hormone deficiency, GHD; growth hormone insensitivity, GHI; intrauterine growth restriction, insulin-like growth factor 1, IGF-1; IUGR; luteinizing hormone, LH; Macrocephaly, Alopecia, Cutis Laxa and Scoliosis syndrome, MACS syndrome; Pyrroline-5-Carboxylate Reductase 1, PYCR1; Pyrroline-5-carboxylate synthase, P5CS; recombinant human growth hormone, rhGH; Ras And Rab Interactor 2, RIN2; small for gestational age, SGA; Solute Carrier Family 2 Member 10, SLC2A10; N-terminal kinase-like-binding protein 1, SCYL1BP1 (GORAB); thyroid stimulating hormone, TSH;

INTRODUCTION

The name "cutis laxa" (CL) comprises a group of multisystem disorders that have as a common denominator loose, redundant, hypoelastic skin, that give a premature aging appearance [1]. The traditional classification based on mode of inheritance and systemic involvement is burdened by the overlap between disease forms and inconsistent use of eponyms over the course of the years [1]. Although molecular analysis was the turning-point in facili-

tating characterization of multiple disease types, and microscopic findings provided help, up to this moment clinical features form the basis of diagnosis [1].

CL can be subdivided in acquired and congenital forms [inherited as autosomal dominant (AD), autosomal recessive (AR) and X-linked recessive diseases] [1]. Inherited forms are monogenic disorders secondary to structural defects, abnormal maturation and secretion of proteins involved in formation

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of elastic fibers [2], leading to the histological hallmark of fiber fragmentation [1]. Besides the skin abnormalities, inherited forms differ in severity and associated multisystem organ manifestations [2]. Autosomal dominant forms of cutis laxa have a lesser systemic involvement and severity of the disease and usually patients have a normal lifespan, unlike autosomal recessive CL which is often lethal due to severe systemic manifestations [3]. Acquired forms appear secondary to drug administration, allergic reactions, arthropod stings, etc [2] which lead to proneness to elastic fiber degradation [1].

CLINICAL DIAGNOSIS

Because of the wide variety of disorders encompassed under the umbrella-term “cutis laxa syndrome”, the correct diagnosis can be difficult to make. Also, the phenotype can be different in individuals within the same subtypes and some subtypes have been scarcely described because of the rarity of disease (Table 1). There are some pathognomonic features and metabolic alterations described that aid in performing a target genetic diagnosis [2-4]. Endocrinological disturbances might be found in CL children as suggested by few reports (Table 2), but data regarding their prevalence, the association with specific subtypes of CL and their exact mechanisms are scarce. The most frequently encountered is represented by short stature, but its pathogenesis and the most appropriate treatment are not well established.

Thus, the aim of this article is to provide an overview of the endocrinological disturbances associated with CL syndromes in order to help clinician with concise information for a swift diagnosis and early treatment and, therefore, to contribute to the improvement in the quality of life of these patients.

For this review, we performed a PubMed database search with the terms “cutis laxa” and “growth”/“short stature”/“thyroid”/“osteoporosis”/“fractures”/“adrenal”/“genital”. Out of over 60 articles, due to the rarity of the syndrome, and the scarcity of studies focusing exclusively on the association of endocrine complications in CL, we selected 21 in which data regarding complications involving the endocrine system were presented; we subsequently summarized the information. Articles not encompassing any relevant information were excluded.

The endocrinological complications associated with cutis laxa syndromes are summarized in table 2 [1].

GROWTH AND DEVELOPMENT

Intrauterine growth restriction (IUGR) as well as postnatal growth retardation have been frequently

reported in ARCL type 2a, 2b and 3 [1,5]. In addition, postnatal growth restriction is a feature in pts with ARCL type 1b, 1c, 2c/d and progeroid ADCL [1].

Both AD and AR CL forms associated with ALDH18A1 gene variants were reported to present with corpus callosum agenesis [1]. It is known that agenesis of the corpus callosum can be associated with pituitary hypoplasia leading to growth hormone deficiency (GHD) as the most frequent defect and less frequently TSH (thyroid stimulating hormone), ACTH (adrenocorticotrophic hormone), LH (luteinizing hormone), FSH (follicle stimulating hormone) or AVP (arginine vasopressin) deficiency [7]. Currently, there is only one report of GH deficiency and growth hormone treatment in cutis laxa. The patient is a boy with ADCL type 3 with short stature who received treatment with recombinant human growth hormone (rhGH) under the indication of small for gestational age (SGA) and growth hormone deficiency, with a good response and no adverse effects reported [8]. Mutations in ALDH18A1 gene (the gene causing ADCL and ARCL type 3) and PYCR1 gene (responsible for ARCL type 2b) both lead to defects in proline synthesis [9].

The gene causing ADCL and ARCL type 3, ALDH18A1, encodes the Pyrroline-5-carboxylate synthase (P5CS) enzyme which is a crucial catalyst for de novo synthesis of ornithine and proline. Mutations lead to decreased proline levels and subsequently hampered production of collagen and elastin (both of which are proline rich) and might explain bony alteration and detrimental prenatal and postnatal development [10].

Also, impaired proline production may lead to neuroanatomic abnormalities such as corpus callosum atrophy by mechanisms of decreased protein production and reduced antioxidant protection in the central nervous system [10]. PYCR1 gene mutation also leads to defective proline synthesis and affected individuals may experience growth delays and corpus callosum hypoplasia [10]. There is a significant overlap between patients with P5CS deficiency and those with PYCR1 deficiency and the differentiation between the two disorders can only be made by their ultrastructural abnormalities in skin biopsies [9]. Autosomal recessive forms of CL with growth delays have been described in association with congenital hip dislocation [11,12].

Growth hormone insensitivity (GHI) syndrome characterized by short stature, decreased insulin-like growth factor 1 (IGF-1) production and normal or elevated serum growth hormone (GH) concentration, encompasses a spectrum of clinical entities. In their report, Andrews et al. describe a patient with isolated proportionate short stature in which genetic diagnosis revealed a mutation in RIN2 gene responsible for the MACS syndrome [13]. We can con-

TABLE 1. Molecular and phenotypic characterization of cl forms

TYPE OF CUTIS LAXA	GENE	MANIFESTATIONS
A) ACQUIRED CUTIS LAXA		
	– molecular basis unsolved in the majority of patients (1); mild mutations in CL genes may increase susceptibility (5)	– inflammatory reaction of the skin leading to elastolysis (1) – triggers: medications, hematologic malignancies, infections, inflammatory disease, connective tissue disease (1,5) – frequently (young) adults are affected (1,5) – starts on the face and progresses caudally (5) – may have systemic involvement (emphysema, aortic root dilatation, intestinal diverticula, hernias) (1,5)
B) INHERITED CUTIS LAXA SYNDROMES		
B.1) AUTOSOMAL DOMINANT		
ADCL1	ELN (Elastin gene)	– typical facial characteristics (1) – predominant skin involvement (1) – risk of aortic aneurysm and emphysema (1)
ADCL2	FBLN5 (Fibulin 5)	– milder clinical presentation (3) – organ involvement may be absent (3) – macular degeneration (3)
ADCL3	ALDH18A1 (Aldehyde Dehydrogenase 18 Family Member A1)	– progeroid appearance (1,6) – cataract (1,6) – athetoid movements (1) – corpus callosum agenesis (1) – intrauterine growth retardation (6) – postnatal growth retardation (6)
B.2) AUTOSOMAL RECESSIVE		
ARCL type 1	- consists of severe cardiopulmonary complications and systemic involvement (1) - survival to adulthood is exceptional (3)	
ARCL type 1a	FBLN 5	– emphysema (1) – genitourinary/gastrointestinal diverticula (1) – supravalvular aortic stenosis and pulmonary arteries stenosis (1)
ARCL type 1b	FBLN4	– arterial tortuosity/aneurysm (1) – osteopenia/fractures (1) – postnatal growth failure (1)
ARCL type 1c (Urban-Rifkin-Davies sdr)	LTBP4 (Latent Transforming Growth Factor Beta Binding Protein 4)	– similar to type 1a
ARCL type 2		
ARCL type 2a (Debre-type CL, Wrinkly Skin syndrome)	ATP6V0A2 (ATPase H ⁺ transporting V0 subunit a2)	– glycosylation defects (1) – “cobblestone” - like cortical brain malformations (1) – postnatal growth retardation (1) – congenital hip dislocation (1) – scoliosis (1)
ARCL type 2b	PYCR1 (Pyrroline-5-Carboxylate Reductase 1)	– similar to ARCL type 2a
ARCL type 2c	ATP6V1E1 (ATPase H ⁺ Transporting V1 Subunit E1)	– aortic root dilatation (1) – cardiomyopathy (1) – pneumothorax (1) – postnatal growth retardation (1)
ARCL type 2d	ATP6V1A (ATPase H ⁺ Transporting V1 Subunit A)	– similar to ARCL type 2d
ARCL type 3 (de Barys syndrome)		
ARCL type 3a	PYCR1 (Pyrroline-5-Carboxylate Reductase 1)	– progeroid (1) – cataract (1) – athetoid movements (1) – corpus callosum agenesis (1) – postnatal growth retardation (1) – intellectual disability (1)
ARCL type 3b	ALDH1A1 (Aldehyde Dehydrogenase 1 Family Member A1)	– similar to ARCL type 3a
B.3) X-LINKED (Occipital horn syndrome)		
	ATP7A (ATPase Copper Transporting Alpha)	– occipital horns (1) – genito-urinary diverticula (1)

TYPE OF CUTIS LAXA	GENE	MANIFESTATIONS
C) CUTIS-LAXA RELATED DISORDERS		
ARTERIAL TORTUOSITY SYNDROME	SLC2A10 (Solute Carrier Family 2 Member 10)	- severe tortuosity of arteries/aneurysm, stenosis (1) - typical facies (1) - inguinal/diaphragmatic hernia (1)
GERODERMA OSTEODYSPLASTICA (WALT DISNEY DWARFISM)	SCYL1BP1 (GORAB) (N-terminal kinase-like-binding protein 1)	- osteoporosis, fractures (1) - lipodystrophy (1) - distinctive facial features (4) - growth deficiency, short stature (4) - joint hyperlaxity (3)
MACS SYNDROME (MACROCEPHALY, ALOPECIA, CUTIS LAXA AND SCOLIOSIS SDR)	RIN2 (Ras And Rab Interactor 2)	- typical craniofacial features (1) - scoliosis, hyperkyphosis (1) - partial/complete alopecia (4)

TABLE 2. Endocrinological complications in cutis laxa syndromes

ENDOCRINOLOGICAL COMPLICATION	TYPE OF CUTIS LAXA
Intrauterine growth restriction	ARCL type 1a (FBLN4) (1) ARCL type 2a (ATP6V0A2) (1) ARCL type 2b (PYCR1) (1) ARCL type 3 (PYCR1, ALDH1) (1) GO (SCYL1BP1) (22)
Poor post-natal growth	ARCL type 1b (FBLN4) (1) ARCL type 1c (LTBP4) (1) ARCL type 2a (ATP6V0A2) (1) ARCL type 2b (PYCR1) (1) ARCL type 2c (ATP6V1E1) ARCL 2d (ATP6V1A) ARCL type 3 (PYCR1, ALDH1) (1) XLCS (ATP7A) (22) GO (SCYL1BP1) (22)
Abnormal corpus callosum	ADCL (ALDH18A1 mutation) (1) ARCL type 2b (PYCR1) (1)
Osteopenia/fractures	ARCL type 1b (FBLN4) (1,18) ARCL type 2 (no molecular analysis) (17) ARCL type 3 (1) ADCL (ALDH18A1) (1) XLCL (ATP7A) (1) MACS (RIN2) (1)
Thyroid disorders	ADCL (no molecular analysis) (14) ARCL (no molecular analysis) [15]
Adrenal dysfunction	ARCL type 1c (LTBP4) [19]
Genital malformations	ARCL type 2 (no molecular analysis) [20] ARCL type 2b (PYCR1) [21]

clude that GHI may be a contributing factor to development of short stature in some subtypes of CL syndromes and genetic diagnosis may aid in recognizing significant associated comorbidities, especially in patients with mild phenotypic features.

THYROID FUNCTION

Ma et al. described a case of CL, possibly of autosomal dominant inheritance, in a girl who presented with short stature and abnormal thyroid function tests. She presented with high concentrations of thyroid hormones in association with normal thyrotropin, suggestive of thyroid hormone resistance.

She received a short course of thyroid hormone therapy with no improvement in her growth and phenotype, leading to discontinuation of the drug [14].

Another patient with ARCL was reported with congenital hypothyroidism due to isolated thyrotropin deficiency. Due to multiple severe organ involvement, she died soon after birth. Magnetic resonance imaging of the pituitary gland was normal [15].

Whether or not these are chance findings, or they appear secondarily to disease mechanisms is not known and more reports are needed in order to establish this.

OSTEOPOROSIS

Osteoporosis and fractures have been described as features of the disease in ARCL type 1b, and less frequently in other types (ARCL type 3, and progesterone ADCL) [1].

Geroderma osteodysplastica patients are characterized by increased arm span to height ratio and decreased upper to lower body segments ratio possibly due to vertebral fractures and platyspondyly [16]. Osteopenia or osteoporosis with spontaneous fractures is present in the majority of patients [3].

A prospective study on four children, presumably with ARCL type 2, reported decreased bone density in all of the patients, particularly in the lumbar spine associated with spontaneous vertebral and rib fractures. Abnormal connective tissue structure in association with inappropriate physical activity and nutritional support leads to decreased mineralization and fractures in children. All cases were treated with a 2-year course of bisphosphonate therapy with normalization of bone density in three of the patients and stable bone mineral density over the course of follow-up. The patients didn't have any endocrinologic abnormality and puberty was associated with a significant improvement in bone mineral density in one patient. The glycosylation defects associated with ARCL type 2 may be the cause of osteoporosis and fractures in these patients and the

authors recommend follow-up of bone mineral density in all children presenting with this condition [17].

A case of twin pregnancy with a lethal form of osteogenesis imperfecta-like condition was described. At birth they presented with multiple fractures of the limbs, thorax and skull in various states of healing with callus formation. Molecular analysis revealed a mutation in the FBL4 gene (ARCL type 1 b). Absence of the FBLN4 in the extracellular matrix leads to underdevelopment of the elastic fibers and bone maldevelopment with multiple fractures [18].

ADRENAL FUNCTION

There is only one report suggesting the possible involvement of the adrenals in CL. Thus, Urban et al. described a patient with LTBP4 mutation (ARCL type 1c) and multiple systemic malformations that died of respiratory insufficiency at 4 months of age, in whom an autopsy was performed and revealed bilateral adrenal hypoplasia and osteopenia among other findings. No biochemical adrenal tests were reported [19].

GENITAL MALFORMATIONS

There are reports of patients presenting with ambiguous genitalia and CL, but the underlying

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pathophysiological mechanism and their impact on reproductive function is poorly understood [20,21].

CONCLUSIONS

Due to the scarcity of data regarding endocrinological disturbances in patients with CL syndromes, no definitive conclusions can be drawn about the frequency, the whole range of endocrine abnormalities and the mechanism behind their potential association with CL. However, taking into account the molecular basis of some of the CL subtypes, pituitary involvement should be kept in mind as a possible contributor to the spectrum of clinical features in these patients. Especially short stature, a common finding in many CL forms, should be extensively evaluated for the identification of treatable causes such as GH deficiency and small for gestational age which are approved indication for rhGH administration. Although there is no solid ground to systematically screen all the patients with CL for extensive endocrine glands dysfunctions, specific endocrine abnormalities should be suspected in the presence of suggestive clinical picture.

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