Intellectual Disability: When the Hypertrichosis Is a Clue

Lidia Pezzani1 Donatella Milani2 Gianluca Tadini2,3

1 Pathology Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy
2 Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy
3 Unit of Dermatology, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

Address for correspondence Gianluca Tadini, MD, Unit of Dermatology, Department of Pathophysiology and Transplantation, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Via Pace 9, Milan, Italy (e-mail: gtadinicme@unimi.it).

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Abstract

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The skin and the central and peripheral nervous system both derive from the ectoderm ridge. Therefore, several syndromes characterized by the presence of intellectual disability (ID) can be associated with specific congenital cutaneous manifestations. In this review, we list some of the most frequent diseases characterized by the presence of ID associated with hirsutism, which might be an incentive for the clinicians to pay attention to the ectodermal annexes in patients with ID.

Introduction

Embryologically, the skin and the central and peripheral nervous system share a common source, the ectoderm. Therefore, intellectual disability (ID) can be frequently associated with specific congenital cutaneous manifestations, the discovery of which can facilitate the final diagnosis, leading to specific treatment and/or targeted genetic tests. Careful examination of the skin, hair, and nails by the pediatrician or neurologist is consequently of great importance.1

Terminal hypertrichosis is characterized by the excessive growth of terminal hair that may be generally caused by alteration of its growth cycle, conversion of vellus into terminal hair, or increase in the density of hair follicles. Here we present the most frequent inherited syndromes characterized by hypertrichosis associated with ID, to help nondermatologists to unravel and address the correct diagnosis.

Cornelia de Lange Syndrome

Cornelia de Lange syndrome (CdLS; OMIM 122740, 300590, 610759, and 614701), also known as Brachmann-de Lange syndrome, is a rare genetic disease with an overall prevalence for mild and classical CdLS of approximately 1.6–2.2:100,000.2 This clinically hypervariable disease can be characterized by the presence of typical facial dysmorphisms, microcephaly, pre- and postnatal growth impairment, and multisystemic manifestations particularly ID, limb defects, hirsutism, congenital heart malformations, and gastrointestinal diseases.3 The classical CdLS phenotype typically shows distinctive facial features including low anterior hairline, arched eyebrows, synophrys, thick and long eyelashes, depressed nasal bridge, long philtrum, down-turned corners of the lips, and micrognathia.3 Ears may be thick, dysplastic, low-set, and posteriorly rotated, and the ear canal tends to be narrow or stenotic. Hands and feet are small, with malformed hands in nearly 30% of the patients (from oligodactyly to ulnar deficiency to absent forearm, with digits present just distal to the elbow). In addition, there can be a dislocation of the radial head with radioulnar synostosis. A generalized hirsutism is common (78% of the patients) and most noticeable on the face, back, and extremities.

Development is typically delayed, with a range from borderline IQ with learning disabilities to profound ID, although individuals with IQ in the normal range have been reported. Speech and language are the most severely affected developmental areas, 44 to 53% of patients being...
late talkers, 61 to 67% limited talkers, and 33% are nontalkers.4,5 Epilepsy is frequently reported,6 and typical imaging manifestations of CdLS include skull base dysplasia with coronal clival cleft, cerebral and brainstem volume loss, and gyral simplification.7 Common behavioral issues are hyperactivity, attention deficit disorder with or without hyperactivity, aggression, self-injurious behavior, obsessive-compulsive behaviors, and depression.8

Gastroesophageal reflux disease is extremely common (90%), and often requires medical and/or surgical intervention.9,10 An increased risk of volvulus (2–3%) is seen in patients with CdLS.11 Congenital heart malformations, often a ventricular or atrial septal defect, occur in 20% of the patients.12 Up to 60% of the patients have some degree of sensorineural and conductive hearing loss.13 Myopia, ptosis, and blepharitis are common. Renal malformations are reported in about 40% of cases, with vesicoureteral reflux, pelvic dilatation, or renal dysplasia. Finally, genitalia are dysplastic in up to 60% of affected individuals.3

Mutations in five genes, encoding subunits of the cohesin complex (SMC1A, SMC3, RAD21) and its regulators (NIPBL, HDAC8), account for at least 70% of patients with CdLS or CdLS-like phenotypes. Almost all cases are sporadic and are caused by de novo heterozygous loss-of-function mutations in NIPBL (65%), with mosaic individuals representing a significant proportion (up to 23%).14 While heterozygous mutations in the autosomal genes SMC3 and RAD21 and heterozygous or hemizygous mutations in the X-linked SMC1A and HDAC8 have been reported in approximately 6% of CdLS cases. These cases mostly overlap the classical phenotype caused by mutations in NIPBL, but usually lack limb and internal malformations, and they have less severe growth impairment and the gestalt is milder. In particular, a recent study15 deepened the genotype–phenotype correlation of the patients with missense or in-frame insertions or deletions in SMC3 and found that postnatal microcephaly is present but with a less distinctive craniofacial appearance. In addition, few congenital heart defects, absence of limb deficiencies, and a milder prenatal growth retardation which worsens in childhood can be observed.

Conversely, mutations in HDAC8 seem to be linked to a craniofacial appearance typical of CdLS associated with delayed anterior fontanelle closure, ocular hypertelorism, hooding of the eyelids, a broader nose, and dental anomalies. As complete loss of HDAC8 function appears to be viable in humans, the range of phenotypes varies from more affected males to apparently unaffected carrier females, usually with a heavily skewed X-inactivation.16

All the protein products of the known CdLS genes are part of the cohesin complex, a structure involved in sister chromatid cohesion and in transcriptional regulation in nondividing cells.17,18

Wiedemann-Steiner Syndrome

Wiedemann-Steiner Syndrome (WSS, OMIM#: 605130) is a clinical entity defined by a wide spectrum of associated features accompanied by the hallmark of the disease that should be a localized form of hypertrichosis terminalis of the extensor surfaces of the distal upper arm and proximal forearm, named hypertrichosis cubiti or hairy elbows.19,20 Actually, the recent discovery of the causal gene (KMT2A)21 allowed to expand the phenotype to diffuse hypertrichosis without hairy elbows.22 The additional features that are frequently reported are postnatal growth retardation, ID, mild to moderate developmental delay, and short stature with a thin and muscular build. The facial appearance is typical and characterized by hypertelorism, thick or arched eyebrows, long eyelashes, down slanting and vertically narrow palpebral fissures, broad nasal bridge, and tented upper lip.23–25 Other rarer features observed in some WSS patients include high narrow palate, sacral dimple, tapering fingers, fifth finger clinodactyly, hypotonia, advanced bone age,26 and premature eruption of adult teeth.22

As previously mentioned, haploinsufficiency of KMT2A gene, also known as MLL, has been recently reported to underlie the WSS phenotype, but no KMT2A alterations have been observed in several WSS patients, suggesting a possible locus heterogeneity. KMT2A encodes for a histone methyltransferase that promotes the transcription through the catalysis of the methylation on the histone H3K4. It has been demonstrated that KMT2A is ubiquitously expressed, and in mammalian embryos it maintains the expression of Hox genes,27 which are clusters of primary importance for a proper embryo morphogenesis.28

The hypertrichosis, as well as the other features observed in these patients, is probably the result of the disruption of the genomic distribution and timing of histone-methylation events, causing secondary effects on transcription.

Nicolaides–Baraitser and Coffin–Siris Syndromes

Nicolaides–Baraitser syndrome (NBS; OMIM#601358) and Coffin–Siris syndrome (CSS; OMIM#135900) are two rare congenital multiple malformation syndromes with overlapping clinical characteristics as ID with absent or limited speech, coarsening of the facial features with age, and brachydactyly. Additionally, there may be seizures, feeding difficulties, hypotonia, short stature, and microcephaly, while isolated or multiple congenital anomalies, as heart defects and hearing impairment, seem to be rare,29,30 even if a casuistry estimates that the rate of heart malformations may be approximately 30%.31 Regarding the hair, almost all the patients show low anterior hairline with sparse scalp hair with hair shaft abnormalities including trichoschisis and trichorrhexis nodosa-like defects at light microscopy examination.32 On the contrary, hypertrichosis is usually present all over the body. The facies, as mentioned earlier, becomes progressively coarse, especially in CSS, and it is characterized by a triangular shape with low frontal hairline, bushy eyebrows with or without synophrys, long philtrum, and big mouth with thin upper lip and thick and everted lower lip. Classically, the differential diagnosis between the two syndromes was based on the hands and feet aspect, as NBS patients present prominent finger joints and broad distal
phalanges, while CSS patients display hypo- or aplasia of the fifth finger nails with or without hypoplasia of the phalanges.\textsuperscript{32} However, the diagnosis is often difficult because several CSS and NBS patients have little or no fifth digit involvement, and, for example, mutations of genes classically mutated in CSS patients can also lead to NBS phenotypes.\textsuperscript{33}

In 2012, mutations in genes encoding for members of the SWI/tch/sucrose nonfermentable (SWI/SNF) complex were identified as the cause for CSS\textsuperscript{34,35} and included the genes \textit{ARID1A, ARID1B, SMARCA4, SMARCB1,} and \textit{SMARCE1}. Recently, \textit{SOX11}, a transcription factor downstream of the PAX6-BAF complex, has been added to the list.\textsuperscript{35} Interestingly, mutations in \textit{SMARCA2}, a gene encoding for another subunit of the SWI/SNF complex, have been shown to cause NBS,\textsuperscript{36} underlining the effective molecular as well as clinical overlap between the two syndromes and justifying the difficulties that the clinicians often have to deal with in the differential diagnosis. All these aspects had led to believe that these syndromes might represent a phenotypic spectrum rather than two distinct disorders.

In the last few years, a better genotype–phenotype correlation of some of the causal genes has emerged.\textsuperscript{37,38} For example, \textit{ARID1B} seems to be the major gene involved in CSS and correlates with a milder phenotype.\textsuperscript{33,39} This gene is probably a component of the neuron–specific chromatin remodeling complex and, besides CSS phenotype, haplinsufficiency of this gene can also lead to nonsyndromic ID\textsuperscript{40} or ID, autism, and corpus callosum abnormalities.\textsuperscript{51} Mutations in \textit{SMARCE1} and \textit{SMARCB1} lead to a more severe CSS, with \textit{SMARCE1} causing severe ID, feeding difficulties, seizures, heart defects, and long and slender fingers with hypoplasia of the second and aplasia of the fifth fingernails, while all toenails are often dystrophic. Mutations within exons 8 and 9 of \textit{SMARCB1} seem to lead to severe CSS with midface hypoplasia, up slanting palpebral fissures and tongue protrusion, scoliosis, and visual or hearing impairment. Mutations in the \textit{SMARCA4} gene\textsuperscript{37} classically lead to moderate–severe ID, behavioral abnormalities, fingernails hypoplasia, hirsutism, cardiovascular and gastrointestinal complications and hernia, and sometimes visual or hearing impairment, and patients are prone to infections. Patient with \textit{ARID1A} loss-of-function mutations generally showed a marked hirsutism, hyponatric, and structural CNS abnormalities, severe developmental delay/ID, and serous internal complications that could result in early death, whereas milder phenotypes were also reported.\textsuperscript{37} Finally, de novo loss-of-function mutations in the X chromosomal gene \textit{PHF6} in females seem to lead to a complete CSS phenotype,\textsuperscript{33} although this gene has been previously described as causal gene of Borjeson–Forssman–Lehmann syndrome (MIM 301900).\textsuperscript{42} The gene product interacts with the nucleosome remodeling and deacetylation complex that has similar functions as the SWI/SNF complex in transcriptional regulation.

Of note, in several CSS and NCS patients, no mutations within the SWI/SNF complex have been identified yet, pointing toward further genetic heterogeneity of the disorders.

**Zimmermann–Laband Syndrome**

Zimmermann–Laband syndrome (ZLS; OMIM #135500) belongs to a phenotypically heterogeneous group of conditions characterized by ID with skeletal and mucocutaneous findings as Cantù and DOOR syndromes. Literature review showed that the main features of the syndrome are gingival hypertrophy associated with nails or terminal phalanges hypo/aplasia (100% of patients).\textsuperscript{43–50} In more than 50% of the patients, a typical facial appearance is detectable, characterized by thick ears, large and bulbous nose, and thick lips with or without macrostomia. Common reported clinical features are moreover ID (more than 40%), joints hypermobility (48%), hypertrichosis of the face and/or the body (37%), hepatosplenomegaly (27%), and seizures (13%).\textsuperscript{50} Clinical variability is wide even in the same family, and, as commonly observed, the seriousness of the somatic involvement often does not correlate with the severity of the ID. Several rarer signs have been reported, as pigmentation disorders,\textsuperscript{43,49} supernumerary teeth,\textsuperscript{45,46,49} ocular anomalies,\textsuperscript{47,49} and others.\textsuperscript{45,46,49} This wide spectrum of clinical presentations of ZLS reported in the literature could be partly due to the absence, to date, of any confirmatory diagnostic test aimed at clearly defining the ZLS phenotype as compared with the overlapping conditions (DOOR and Cantù syndromes). However, Kortüm and colleagues\textsuperscript{51} have just reported that heterozygous missense mutations in \textit{KCNH1} leading to gain-of-function effect account for a considerable proportion of ZLS, and that recurrent de novo missense change in \textit{ATP6V1B2} could be a second molecular cause of ZLS. This discovery, together with the recent explanation, although partial, of the molecular bases of Cantù and DOOR syndromes,\textsuperscript{52,53} will permit to better characterize these phenotypes.

**X-Linked Intellectual Disability Type Nascimento**

X-linked syndromic ID type Nascimento (MRXSN, MIM #300860) was first described as a distinct entity in 2006 by Nascimento and colleagues.\textsuperscript{54} The syndrome is clinically characterized by a pronounced ID, seizures in some patients, a recognizable face, macrocephaly, skin abnormalities, and urogenital malformations. The ID is usually severe, with impairment or even absent speech, walking age between 1 and 5 years, or no walking ability, and seizures in about 62% of the patients, while cerebral MRI shows white matter alterations in approximately 50% of cases.\textsuperscript{55,56} In up to 75% of patients, skin abnormalities are detectable and include generalized hirsutism, dry skin with myxedematous appearance, widely spaced nipples, and onychodystrophy, which usually appear at puberty.\textsuperscript{56}

Urogenital findings comprise especially micropenis and ureteral reflux (65% of the reported patients). Regarding the typical craniofacial dysmorphism, the patients show macrocephaly, wide face, prominent supraorbital ridges, synophrys or straight and thick eyebrows, hypertelorism, deep-set and almond-shaped eyes, up slanting palpebral fissures,
depressed nasal bridge, prominent columnella and hypoplastic alae nasi, and macrostomia with downturned corners of the mouth.54,56,57 Other less frequently associated features are recurrent infections with or without neutropenia, heart defects, hearing loss, various digital anomalies (proximally inserted thumbs and short and slender fingers), congenital cataract, and preauricular pits.54,56

Intragenic mutations of UBE2A54,56,58 as well as larger deletions encompassing this gene55–57,59 have been described as causative of the MRXSN clinical phenotype.54 While all affected males show the typical phenotype, all female carriers are clinically unaffected and showed a completely skewed X-inactivation; nevertheless, subtle facial features might be detected.58

Conclusion

This is a small review of the most frequent diseases characterized by the presence of ID associated with hypertrichosis. Obviously, several contiguous gene syndromes, such as duplication 3q26.1–3q28,60 deletion 8q24,61 and other complex chromosomal imbalance, could cause this association, and this review is not exhaustive of this argument, but it might be an incentive for the clinicians to observe the ectodermal annexes in a patient with ID.

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