Congenital atrichia and hypotrichosis

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Background: **Alopecia present from birth includes a broad differential diagnosis and often represents a diagnostic and therapeutic challenge for the involved physician.**

Data sources: **An initial correct diagnosis and classification is essential because structural hair defects may be the expression of a genetic disorder affecting hair growth, part of a congenital syndrome with accompanying hair malformations, or a marker for an underlying metabolic disorder and may impact the mental and physical development of a child. Pathological hair loss rarely occurs in the first year of life; however, it may be a leading symptom of many congenital diseases.**

Results: **In recent years, the clinical and microscopic features of hereditary hair shaft disorders have been characterized and classified. Furthermore, significant progress has been made in our knowledge of genes that control the normal development and differentiation of hair follicles, and thus the research is to define and classify the hair disorders within a genetic basis.**

Conclusions: **In this article we discuss several types of genotrichosis and provide a practical classification based on their clinical features.**

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Key words: **alopecia;**
disorders;
gentrichosis;
hair growth;
hypotrichosis

Introduction

There have been numerous attempts to classify the conditions characterised by congenital alopecia or hypotrichosis. In 1892, Bonnet[1] proposed the first known classification based on embryological principles. It has been widely used until nowadays and roughly divides congenital hypotrichosis with normal ectodermal structures from the ones with associated teeth and nail defects. Afterwards, Cockayne[2] and Muller[3] attempting a more critical analysis proposed a working classification which allowed the currently named syndromes to be identified, and provided a provisional status for those not yet characterized. In 1981 after the Berlin Congress, Sâlamon[4] proposed a classification for the global problem of hair loss that is considered one of the most useful system for the study of congenital hypotrichosis.

In this review, we will follow the practical classification based on the clinical observations proposed by Camacho et al.[5] One should be aware however that within each of the groups there is a large clinical spectrum and that these are not grouped on a pathogenetic basis. The classification scheme shown in Table 1 is largely of didactic value.

When confronted with a child with hair loss, it is important to first determine whether the hair loss is congenital or was acquired. Afterwards, the clinician should evaluate the clinical manifestation profile, the age at onset and the presence of associated symptoms to properly classify the hair disease.

This will not be a comprehensive review of all hypotrichotic syndromes but rather a review of genotrichosis where we will describe their clinical features and the known associated genetic abnormalities.

Generalized congenital alopeciae

I. Genodermatosis with non-scarring hypotrichosis

Genodermatosis with skeletal alterations

Trichorhinophalangeal syndrome

Trichorhinophalangeal syndrome (TRPS) comprises a distinctive combination of hair, facial and bone abnormalities with autosomal dominant inheritance.

a. Trichorhinophalangeal syndrome type I. Type I TRPS is clinically characterized by the presence of a variable congenital hypotrichosis, piriform (pear-shaped) nose, coniform epiphisis, subnasal fold, thin lips, prognatia, and mandibular hypoplasia. The hair alterations consist of diffuse alopecia with a broad forehead and a partial alopecia of the lateral third of the

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Table 1. Classification of generalized congenital and hereditary alopecia

1 Genodermatosis with non-scarring hypotrichosis
1.1 With escheletical alterations
McKusich disease or condrodisplasia
Moynahan disease (hypotrichosis, sindactilia, retinitis)
Trichorhinophalangeal syndromes
Pierre-Robin syndrome
Cardio-facial cutaneous syndrome
Alopecia-contractures-dwarfism (ACD) syndrome with mental retardation
Oculo-dental-digital syndrome
Dubowitz syndrome
Noonan syndrome
Hallemann-Streiff syndrome
1.2 With ectodermic alterations
Ectodermal dysplasias
1.3 With neuroectodermal alterations
Tricothiodystrophy
1.4 With chromosomal alterations
Down syndrome
Klinefelter syndrome
Turner syndrome
1.5 With aminoacid metabolism alterations
Hypotrichosis, hair-shaft defects, hypercysteine hair and glucosuria syndrome
Citrulinemia
Hartnup disease
Homocistinuria
Fenilcetonuria
Tirosinemia I and II
1.6 Other genodermatosis with hypotrichosis
1.6.1 Progeria
Werner syndrome or pangeria
Hutchinson-Gilford or childhood progeria
Variot-Cailleau syndrome or childhood gerodermia
Other progerias
1.6.2 Others
Congenital ichthyosiform eritrodermia
Netherton syndrome
Tay syndrome
Rud syndrome
KID syndrome
Rothmund-Thomson disease
Poikilodermia-alopecia-retrognatism-cleft palate syndrome
Zinsser-Cole-Engman disease
Kallin syndrome or epidermolysis bullosa simplex
1.7 Genodermatosis with hypotrichosis and tumors
Rombo syndrome
Bazex-Dupré-Christol's syndrome
1.8 Hereditary simple hypotrichosis
2 Genodermatosis with scarring hypotrichosis
2.1 Darier disease
2.1 Ichthyosis X
2.3 Distrofic epidermolisis bullosa
2.4 Intontinentia pigmenti
2.5 Poliostotic fibrous dysplasia
2.6 Conradi syndrome
2.7 Happle's syndrome

eyebrows. Scanning electron-microscopic studies of the hair shaft can reveal flattened hair with an elliptoid transverse section pattern. Mechanical behavior of the hair might be abnormal with a significant increase in the viscous parameter, indicating a decreased intermolecular bridging within the keratin matrix.[6]

b. Trichorhinophalangeal syndrome type II (Langer-Giedion syndrome). Patients with TRPS type II usually present hypotrichosis of the scalp hair, piriform nose and redundant skin as the type I, plus multiple cartilaginous exostosis. In a recent article Lu et al[7] described associated alterations to this syndrome including aplasia of the epiglottis and congenital nephrotic syndrome.

c. Trichorhinophalangeal syndrome type III. TRPS type III is a newly defined clinical entity[8] inherited as an autosomal dominant trait and clinically characterized by growth retardation, craniofacial abnormalities, severe brachydactyly and sparse hair. In addition, absence of mental retardation and cartilaginous exostoses are required for the diagnosis of TRPS type III. Other associated abnormalities include a short stature, a thin upper lip and a prominent lower lip, a pear-shaped nose, stubby fingers and toes with cone-shaped epiphyses and sparse scalp hair.

Dubowitz syndrome

First described in 1965,[9] Dubowitz syndrome (DS) is characterized by a peculiar face, infantile eczema, small stature and mild microcephaly. The cutaneous findings consist of an eczematous eruption affecting the face and flexural areas. Scalp hair is sparse and brittle and commonly affects the lateral eyebrows.

Patients affected by DS have a moderate mental deficiency with a tendency toward hyperactivity, short attention span, stubbornness and shyness. They have also been characterized by their high-pitched weak cry.

Hallermann-Streiff syndrome

Hallerman-Streiff syndrome is a rare congenital anomaly characterized by a peculiar bird face, mandibular and maxillary hypoplasia, dyscephaly, congenital cataracts, microphtalmia, hypotrichosis, skin atrophy, and short stature.[10] Dental abnormalities are present in 80% of the cases and include malocclusion, crowding, severe caries, supernumerary and neonatal teeth, enamel hypoplasia, hypodontia, premature eruption of primary dentition, agenesis of permanent teeth, and anterior displacement or absence of condyles.[11]

Genodermatosis with ectodermal alterations

Ectodermal dysplasias

The term ectodermal dysplasia was originally applied to anhidrotic ectodermal dysplasia in which hair, teeth, nails and sweat glands are defective. The classification proposed by Freire-Maya in 1977[12] was based on a primary defect of ectodermal derivatives. Conditions in which the ectodermal changes are secondary, as in xeroderma pigmentosum are thus excluded from the ectodermal dysplasias. According to the Freire-Maia's classifications sub-group 1 is a hair dysplasia, sub-group 2 a dental dysplasia, sub-group 3 a nail dysplasia, sub-group 4 a sweat gland defect, and sub-group 5 a defect of other ectodermal structures.

Solomon and Keuer in 1980[13] defined subgroups of the ectodermal dyplasias based on what ectodermal structures were affected (Table 2).

Anhidrotic ectodermal dysplasia (Christ-Siemen-Touraine syndrome)

In this X-linked syndrome sweat glands and other ectodermal-derived appendages are absent or few in number. The full syndrome only occurs in males. Scalp and body hair is short, fine and very sparse and often bright in colour, but may increase in quantity after puberty. Eyebrows and eyelashes may also be sparse or absent but may be relatively little affected. The prominent square forehead, saddle nose, thick lower lip and the pointed chin produce a distinctive face. The skin around the eyes is finely wrinkled and may be pigmented. The teeth may be absent or few in number, and characteristically the canines and incisors are conical shaped. The absent or reduced sweating leads to heat intolerance, and unexplained pyrexia may be the presenting symptom in infancy. Carrier females may be clinically normal but may show in some degree one or more of the features of the syndrome as conical teeth, hypotrichosis or heat intolerance. Otherwise apparently normal carriers may show dermatoglyphic abnormalities, the presence of which may be a value in diagnosis.[14]

EEC syndrome (ectrodactily, ectodermal dysplasia and cleft lip and palate)

The association of ectrodactyly (lobster-claw deformity), ectodermal dysplasia, and cleft lip and palate is a well defined autosomal dominant syndrome.[14]

Reported EEC syndrome cases show sparse hair, malformed teeth with early caries, ectrodactyly, cleft lip and/or palate, lacrimal duct stenosis and kidney abnormalities, but not all defects are present in all affected individuals within a single family.

Table 2. Ectodermal dysplasia subgoups proposed by Solomon and Keuer

Subgroups 1, 2, 3 and 4 (Hair, teeth, nails and sweating defects)
Anhidrotic ectodermal dysplasia
Rapp-Hodgkin
Ectrodactily-Ectpdermal dysplasia-Cleft palate syndrome
Popliteal web syndrome
Xeroderma-Talipes-Enamel defect syndrome
Subgroups 1, 2 and 3 (Hair, teeth and nail defects)
Clouston dysplasia
Trichodento-osseous syndrome
Ellis-van Creveld syndrome
Ankyloblepharon-Ectodermal defects-Cleft palate syndrome
Basan syndrome
Tooth-nail syndrome
Subgroups 1, 3 and 4 (Hair, nails and sweating defects)
Freire-Maya's syndrome
Subgroups 1 and 2 (Hair and teeth defects)
Orofaciodigital syndrome I
Sensenbrenner syndrome
Trichodental syndrome
Subgroups 1 and 3 (Hair and nail defect)
Curly Hair-Ankyloblepharon-Nail Dysplasia syndrome
Onychotrichodysplasia with neutropenia
Subgroups 1 (Hair defects)
Trichorhinophalangeal syndromes
Dubowitz syndrome
Moynahan syndrome

Familial juvenile macular dystrophy with congenital hypotrichosis capitis

Recently Becker et al[15] described two sisters in a family of consanguineous parents with diffuse hypotrichosis of the head and visual impairment in the context of a tricho-ocular malformation of an ectodermal dysplasia. This newly described entity will probably finally be included as a variant of other ectodermal dysplasia.

Hypotrichosis with aminoacid metabolism alterations ectodermal dysplasia

Hypotrichosis, hair-shaft structure defects, hypercysteine hair and glucosuria

Blume-Peytavi et al[16] reported two Turkish siblings with fragile and sparse scalp hair associated with glucosuria without diabetes or kidney disease. Clinical examination revealed normal physical and mental development, and an analysis of plucked hairs showed dysplastic and broken hair shafts. Polarizing microscopy and scanning electron microscopic studies revealed torsion, irregularities and impressions of the hair shaft, as seen in *pili torti*, trichorrhexis nodosa and pseudomonilethrix (Fig. 1). Analysis of the amino-acid composition of the hair demonstrated a significant reduction of sulphonic cysteic acid and an elevated cysteine and lanthionine content.

Other genodermatosis with hypotrichosis

KID syndrome (keratitis, ichthyosis, deafness)

The KID syndrome is a congenital ectodermal disorder that affects not only the epidermis, but also other ectodermal-derived tissues such as the corneal epithelium and the inner ear. In a classic review,[17] 61 patients who met the criteria for this syndrome were identified. All had cutaneous and auditory abnormalities, and 95% of them also had ophthalmologic defects. The most frequent clinical features were neurosensory deafness (90%), erythrokeratoderma (89%), vascularizing keratitis (79%), alopecia (79%) (Fig. 2A), and reticulated hyperkeratosis of the palms and soles (41%) (Fig. 2B).

In the same article, the authors state that the KID acronym does not accurately define this entity since the disorder is not an ichthyosis, because scaling is not the main cutaneous feature. In addition, not all patients have keratitis. They suggest that this syndrome should be included under the general heading of congenital ectodermal defects as a keratodermatous ectodermal dysplasia (KED).

Genodermatosis with hypotrichosis and tumors

Rombo syndrome

First described by Michaëlsson in 1981,[18] Rombo

syndrome is an autosomal dominant disease clinically characterized by hypotrichosis affecting the eyelashes and yellowish follicular facial papules. They also present cyanotic lips and multiple tricoepiteliomata and basal cell carcinomas.[19]

Bazex-Dupré-Christol's syndrome

Bazex-Dupré-Christol's syndrome (BDCS) is an X-linked dominant disorder of the hair follicle characterized by follicular atrophoderma, multiple basal cell carcinomas, hypotrichosis (Fig. 3A), milia, and localized hypohidrosis.[20] Follicular atrophodermas (FA) are follicular depressions ("ice pick marks") seen most commonly on the dorsum of the hands and elbows (Fig. 3B). In a recent article Kidd et al[21] described a Scottish family with this syndrome, with five affected members through three generations. The reported patients showed hypohidrosis confined to the face, coarse hair, dry skin, milia, and follicular atrophoderma. All the adults had a history of multiple basal cell carcinomas. None of them presented any skeletal feature suggestive of Gorlin's syndrome. The authors thus suggest that the BDCS should be considered as a differential diagnosis in patients with early onset or familial basal cell carcinomas.

In 1994 Goeteyn et al[22] described 20 affected patients of a large family across four generations with typical features of the BDCS. However, the clinical picture in that family differs with regard to gender and age, confirming an X-linked inheritance.

Hereditary simple hypotrichosis

Hereditary simple hipotrichosis (HSH) is an uncommon group of familiar hypotrichias and atrichias, usually non-scarring, which are not associated with other dysplasias neither with internal abnormalities. Although

Fig. 1. Pseudomonilethrix. Scanning electron microscopic studies reveal torsion, irregularities and impressions of the hair shaft.

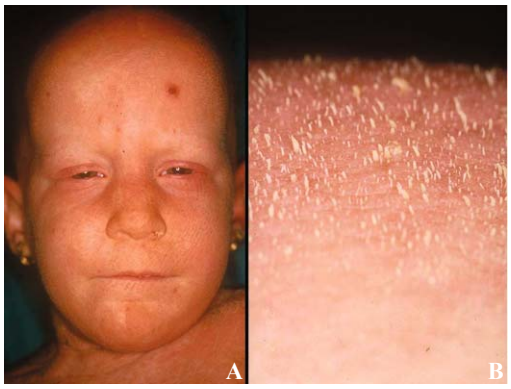

Fig. 2. KID syndrome. **A:** alopecia of the scalp, eyelashes and eyebrows; **B:** palmar keratoderma with a stippled-appearing surface pattern.

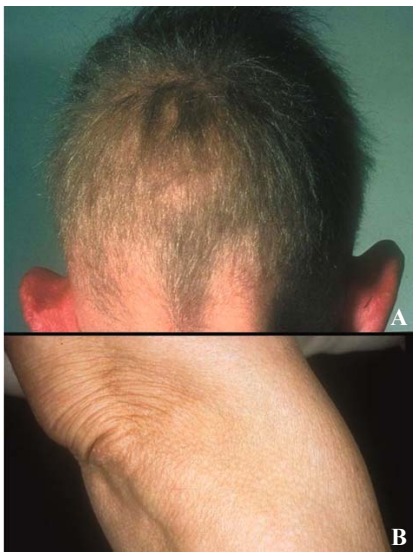

Fig. 3. Bazex-Dupré-Christol's syndrome showing localised hypotrichosis (**A**) and follicular atrophoderma on the elbows (**B**).

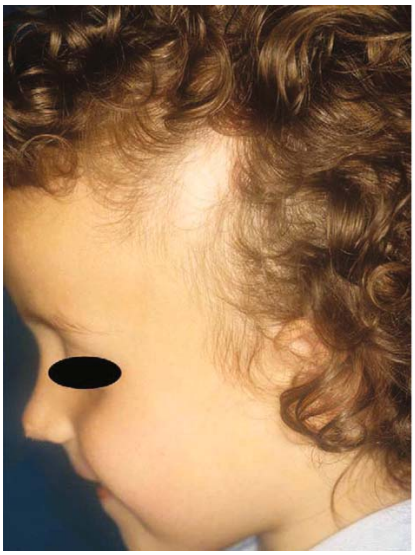

Fig. 4. Brauer's nevus. Congenital unilateral triangular patch of alopecia in the frontotemporal region.

most of them follow an autosomal dominant pattern, some may be recessive.[23]

HSH usually presents as a congenital generalized hypotrichosis or atrichia showing a poor, sparse and dry hair aspect with long, isolated hairs remaining between extensive alopecic areas. Genothypotrichosis of Villafranca de Duero is nearly the only localized form, affecting the scalp hair.[24]

Recently described syndromes (non-classified disorders)

In the last decade, several new hypotrichotic syndromes have been described with the title of "A new genodermatosis?" or "A new syndrome?". These have yet to be classified and included into the older classification schemes.

Congenital ichthyosis with follicular atrophoderma

In a recent article Lestringant et al[25] described five Emirati sibs (three girls and two boys), aged between 4 and 18 years old, with normal stature, diffuse congenital ichthyosis, patchy follicular atrophoderma, generalized and diffuse non-scarring hypotrichosis, and marked hypohidrosis. Steroid sulfatase activity, assessed in the two boys, was found to be normal. Electron microscopic studies of ichthyotic skin did not show any specific abnormality. The patients were thought to have Bazex syndrome; however, ichthyosis is not a component of Bazex syndrome. They concluded that congenital ichthyosis with follicular atrophoderma represents a new autosomal recessive genodermatosis.

Congenital atrichia, palmoplantar hyperkeratosis, mental retardation, and early loss of teeth

Steijlen et al[26] reported four siblings with congenital atrichia, palmoplantar hyperkeratosis, mental retardation, and early loss of teeth. The pedigree in that family suggested an autosomal recessive trait. This combination of findings has not been previously reported and is therefore considered to be a new genetic entity.

Keratoderma, hypotrichosis and leukonychia totalis

Basaran et al[27] reported three relatives with congenital hypotrichosis, characterized by trichorrhexis nodosa and trichoptilosis, dry skin, keratosis pilaris and leukonychia totalis. The described patients also developed a progressive transgrediens type of palmoplantar keratoderma, and hyperkeratotic lesions on the knees, elbows and perianal region.

Alopecia-mental retardation syndrome associated with convulsions and hypergonadotropic hypogonadism

Devriendt et al[28] reported two brothers with total congenital alopecia, mental retardation, childhood convulsions and hypergonadotropic hypogonadism. The authors believe that this association which has not previously been reported represents a new autosomal recessive condition.

Universal congenital alopecia

Complete or partial congenital absence of hair may occur either in isolation or with associated abnormalities. Most of the families with isolated congenital alopecia have been reported to follow an autosomal-recessive inheritance. In an attempt to map the gene for the autosomal recessive form, Nothem et al[29] performed genetic linkage analysis in a large inbred family from Pakistan where affected individuals showed a complete absence of hair. They mapped the gene for this hereditary form of isolated congenital alopecia on chromosome 8p21-22 (ALUNC [alopecia universalis congenitalis]). In a more recent article,[30] they reported an homozygous missense mutation in the *human hairless gene*. In addition, they found that the *human hairless gene* undergoes alternative splicing and that at least two isoforms generated by alternative usage of exon 17 are found in human tissues. Interestingly, the isoform containing exon 17 is the predominant isoform expressed in all tissues except the skin, where they observed exclusive expression of the shorter isoform. The authors speculate that this tissue-specific difference in the proportion of hairless transcripts lacking exon 17 sequences could contribute to the tissue-specific disease phenotype observed in individuals with this type of isolated congenital alopecia.

Congenital hypotrichosis and milia

Patients with congenital hypotrichosis and milia present with coarse sparse hair and multiple milia on the face, chest, axillae and pubic region. There are no abnormalities of teeth and nails. Polarizing light microscopy of hair shows an increased diameter of the hair shaft. Rapelanoro et al[31] reported a large four generations family where individuals presented with congenital hypotrichosis and multiple self-healing milia. The family pedigree was compatible with an autosomal or an X-linked dominant mode of inheritance.

II. Genodermatosis with scarring alopecia

Happle syndrome

Gobello et al[32] described a 13-year-old girl with chondrodysplasia punctata, associated with ichthyosis arranged along Blaschko's lines, follicular atrophoderma, cicatricial alopecia and coarse, lusterless hair. The patient also showed a congenital cataract in the right eye, dysplastic facial appearance and symmetrical shortening of the tubular bones. The pathogenetic concept of

functional X-chromosome mosaicism introduced by Happle is used to name this syndrome.

Localized congenital alopeciae

Congenital triangular alopecia (Brauer's nevus)

Congenital triangular alopecia (CTA)[33] is an unilateral or, less frequently, bilateral patch of alopecia in the frontotemporal region (Fig. 4). The age of onset varies between 3 and 5 year old and CTA should be differentiated from alopecia areata[34] and nevus sebaceous. Only about 47 cases have been reported, probably because the lesion is benign and nonprogressive. A frequency of 0.11% is reported by García-Hernández et al.[35] Males affected by CTA do not require treatment because of the later development of androgenic alopecia, but women might benefit from surgical treatment.

Aplasia cutis congenita (Adams-Oliver syndrome and other associations)

Aplasia cutis congenita is a part of heterogeneous group of disorders characterized by the absence of a portion of skin in a localized or widespread area of the scalp at birth. It most commonly manifests as a solitary defect on the scalp, but sometimes it may occur as multiple lesions.

Adams-Oliver syndrome

Adams-Oliver syndrome depends on the association of aplasia cutis with terminal digital abnormalities namely shortening of fingers and toes, absence of phalangea or more rarely the absence of the entire extremity.

A literature review[36] revealed a rate of 13.4% for congenital heart malformations in individuals with Adams-Oliver syndrome, suggesting that cardiac anomalies are a frequent manifestation of this syndrome. Thus, all patients with Adams-Oliver syndrome should be evaluated for cardiac abnormalities.

Aplasia cutis congenita, high myopia, and cone-rod dysfunction

Recently Gershoni-Baruch et al[37] reported two siblings with congenital nystagmus, cone-rod dysfunction, high myopia, and aplasia cutis congenita on the midline of the scalp vertex. The authors consider this familial oculocutaneous condition as a new unique autosomal recessive disorder.

Nevus sebaceous

Nevus sebaceus of Jadassohn is a benign, congenital hamartoma of the folliculo-sebaceous apocrine unit and epidermis that often presents at birth, appears to regress in childhood, and grows during puberty, suggesting possible hormonal control. In childhood, the lesion consists of a circumscribed hairless yellow-orange-colored, waxy, pebble-like, papule or plaque often linear or round or irregular. In puberty the lesion becomes verrucous and nodular. Nevus sebaceous may develop tumors in adulthood particularly, syringocystadenoma papilliferum and benign hair follicle tumors. Basal cell carcinoma has been observed in about 5% of cases.

Conclusion

Congenital alopecia and hypotrichosis is present in a wide range of genetic conditions. It is important to have a framework of classification when evaluating a newborn with alopecia so that a correct diagnosis can be ascertained in a timely manner. When examining a child with alopecia, one must inspect for associated ectodermal anomalies or skeletal alterations. It is also necessary to have an understanding of the genetic basis of these conditions so that genetic testing can be performed when appropriate.

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