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Paediatric Hypotrichosis: A Clinical and Algorithmic Approach to Diagnosis

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ABSTRACT

Paediatric hypotrichosis is the clinical feature of paucity of hair arising congenitally or in early life with the presentation being that of the child whose hair is growing insufficiently. It is a hallmark finding of a diverse group of genodermatoses and sporadic disorders, presenting as either an isolated symptom or in association with syndromic features. Hypotrichoses are rare, with numerous possible differentials requiring a thorough clinical assessment, additional investigations for hair shaft abnormalities and occasionally genetic counselling to reach a diagnosis. We propose a clinical algorithm for the investigation and diagnosis of paediatric hypotrichosis, designed to aid the clinician by utilising key clinical findings in conjunction with the forced hair pull test and trichoscopy to differentiate groups of hair shaft and hair loss disorders. We also discuss in further detail the pathogenesis, phenotypical features and microscopy findings of various types of hypotrichosis.

1 | Introduction

Paediatric hypotrichoses refer to a genetically and phenotypically heterogeneous group of conditions presenting with congenital or early onset hair paucity. They are distinct from atrichias, disorders with complete absence of hair. There is a broad range of differentials for hypotrichoses, including cicatricial alopecia, non-scarring alopecia and inherited and acquired structural hair disorders.

Within syndromic hypotrichoses, there is often considerable heterogeneity even among afflicted members of the same family. The natural history of hypotrichosis syndromes is highly variable with some progressing to sparse adult hair, whereas others, such as loose anagen syndrome, result in normal hair.

While management of genetic hypotrichoses is limited, obtaining an accurate clinical diagnosis may indicate further need for a systemic workup or genetic counselling and obtaining accurate prognostic information.

2 | Clinical Approach

The initial step in diagnosing hypotrichosis disorders is to ascertain whether the hair loss is an isolated symptom or a presentation of a systemic disorder.

A comprehensive patient history and physical examination are vital in narrowing a list of differential diagnoses and developing rapport with the parent and child. A time course may be established with questions about the onset (hair scarcity from birth or age of acquisition), duration, evolution, rate of progression and any history of normal hair. Congenital hair conditions, parental consanguinity or a positive family history may suggest a genotrichosis, whereas childhood onset may have another origin,

such as trichotillomania or alopecia areata. This review focuses on the child who presents never having had normal hair.

3 | Investigations in Addition to Clinical Examination

3.1 | Hair Pull Tests

A 'regular' hair pull test refers to the use of very gentle traction, a gentle combing of the hair with the fingers, to assess active degree of hair shedding. It is a crude test and is dependent on the recent hair styling, combing and washing. A positive hair pull test can help identify telogen hair shedding and is a useful part of the hair loss examination.

In a 'forced hair pull test', the examiner grasps 50–60 hairs strands and pulls them slowly and firmly from the proximal to distal ends. The easy removal of more than 10% of hairs or six hairs, in one pull, or more than three hairs from different areas of the scalp, is considered a positive pull test and indicates active hair loss [1]. The proximal hair shafts can be examined against a contrasting background (white for dark hair, black for light hair) to assess the tip for breakage (blunt tip) or regrowth (tapered tip). Light microscopy may also be used to evaluate the proximal ends for type of hair removed (e.g., telogen, broken, dystrophic). The hair shafts can be further examined for hair thickness, texture, fragility, shape and twists [1].

3.2 | Loose Anagen Hair Pull Test

A 'loose anagen hair pull test' is a specific test for poorly anchored hairs checking for loose anagen syndrome. A total of 10–20 hairs are firmly grasped with fingers close to the scalp and attempt is made to forcibly extract them. For normal hair anchoring, this will tent up the scalp and will not be able to be removed. For those with loose anagen syndrome, the hairs will be easily extracted with little or no pain (Video S1).

Patients and families presenting with hair loss may have reservations about intentionally pulling out additional hair, so it is important to explain the purpose of this procedure and obtain consent before proceeding.

In the assessment of paediatric hypotrichosis, a regular hair pull test is not relevant and we prefer to use the term 'hair pull test' to mean one with force may be required.

3.3 | Trichogram

The trichogram, once a standard test for measuring hair loss, has been largely superseded by trichoscopy in modern practice. Traditionally, a trichogram involves grasping a sample of 25–50 hairs near the root and swiftly pulling them with force in the direction of hair growth. The hair bulbs are then examined using light microscopy on a glass slide to assess the ratio of anagen to telogen phase hairs [2]. A telogen count exceeding 35% (compared to the normal range of 10%–20%) raises concerns for telogen effluvium.

However, the formal trichogram extraction process is often painful and primarily serves to determine telogen counts. Given its traumatic nature, it is rarely performed today and is particularly challenging in both children and adults due to the distress it causes. Instead, if the clinical diagnosis does not necessitate root assessment, a sample of hair cut at the scalp level suffices for evaluating the hair shaft to exclude hair shaft disorders.

3.4 | Trichoscopy

Trichoscopy refers to the non-invasive dermoscopic examination of hair and scalp for analysis of hair shaft abnormalities [3]. A handheld dermatoscope is applied to the scalp, allowing magnification of hair shafts, follicle units, perifollicular epidermis and cutaneous microvessels [3]. It is recommended that trichoscopy serves as the primary diagnostic modality, supplemented by or combined with hair pull tests. Changes under trichoscopy can be reliably used to diagnose loose anagen syndrome (Figure S1) clinically without additional laboratory investigations and hair shaft disorders such as monilethrix (Figure S2) and trichorrhexis nodosa (Figure S3).

When diagnosis remains inconclusive after these three clinical tests, collecting proximal hair clippings for electron microscopy may offer further diagnostic clarification. However, hair electron microscopy services are not readily available across all pathology laboratories due to the need for specialised equipment and expertise of reporting pathologists.

3.5 | Scalp Biopsy

A scalp biopsy can also be obtained as a 4 mm punch biopsy from an actively affected area and is histologically stained [2]. This facilitates examination of the entire hair follicular unit to the subcutaneous fat level, and is useful when considering differential diagnoses of acquired scarring or non-scarring alopecia, androgenetic alopecia and telogen effluvium. Scalp biopsy plays a limited role for the child presenting with congenital chronic hypotrichosis.

3.6 | Genetic Testing

Genetic testing, a rapidly advancing field, is expected to play a progressively crucial role in diagnosing hair shaft disorders. Exome testing, currently offered on a case-by-case basis, can concurrently screen for multiple disorders. The advent of next-generation sequencing has also led to the discovery of multiple inherited hair disorders with defined molecular bases, with the potential to enhancing our understanding of these disorders and identifying new therapeutic targets.

4 | Diagnostic Algorithm

The initial stage of the algorithm involves a clinical assessment, involving history, examination and investigations (Figure 1), aiming to exclude syndromic hypotrichoses from isolated hypotrichosis. If any abnormalities exist in the hair, teeth or nails,

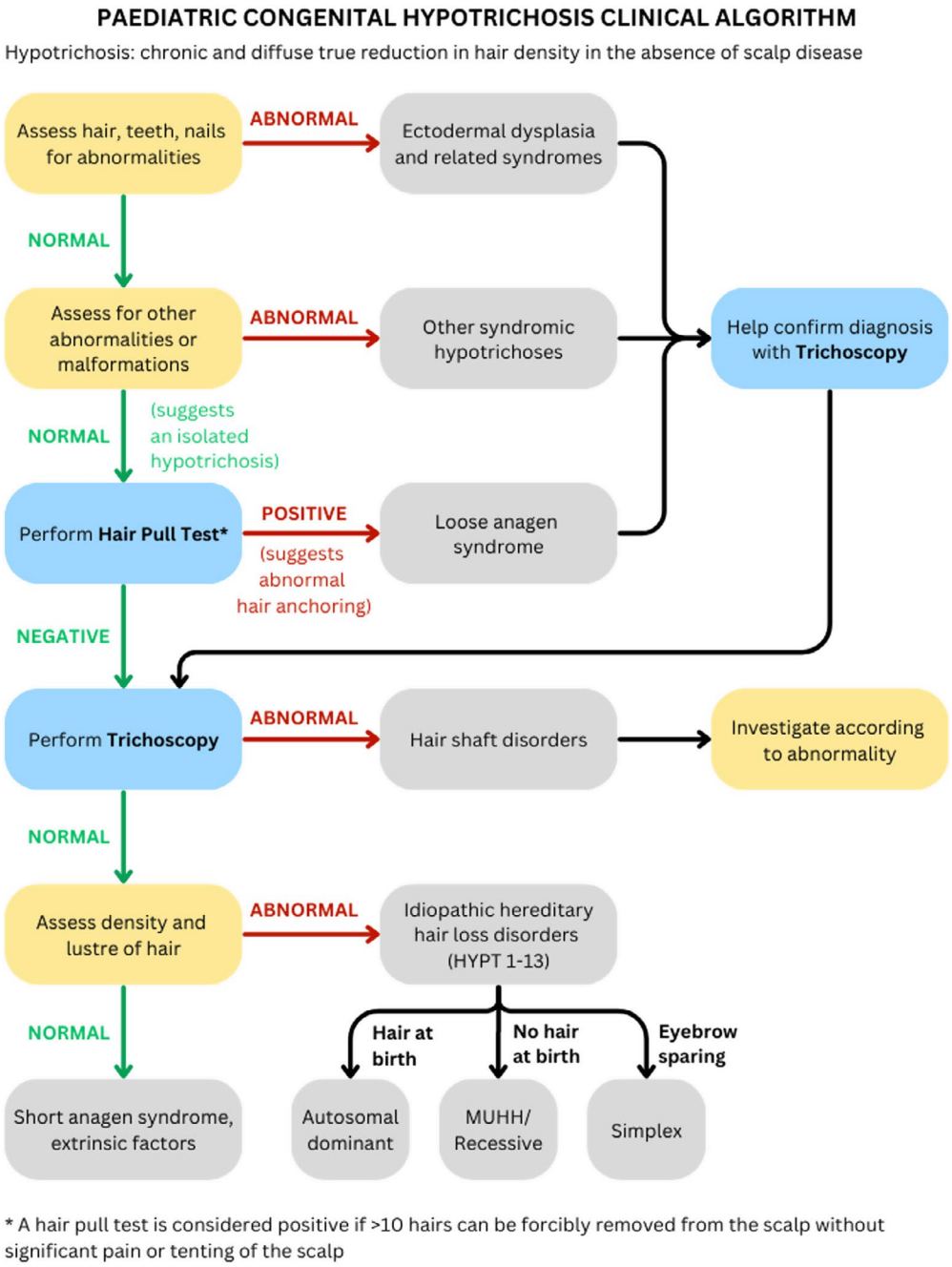

FIGURE 1 | Clinical algorithm for assessment of paediatric hypotrichosis. *A hair pull test is considered positive if > 10 hairs can be forcibly removed from the scalp without significant pain or tenting of the scalp.

this warrants consideration of ectodermal dysplasia (ED) and related syndromes. If any other systemic congenital abnormalities or malformations exist, other syndromes involving hair loss may be considered.

In the absence of syndromic features, we may focus on bedside clinical assessment tools. For example, a loose anagen hair pull test that is positive indicates abnormal hair anchoring seen in loose anagen syndrome. A trichoscopy is useful to corroborate or confirm diagnosis. Abnormal trichoscopy should be investigated according to the type of hair shaft abnormality seen. In the case of normal trichoscopy, hair of normal appearance suggests alternative diagnoses such as short anagen syndrome (SAS) or extrinsic factors, such as traction alopecia or trichotillomania.

Hair with abnormal density, consistency or lustre usually suggests an idiopathic hereditary form of hair loss. In such cases, a history of absent hair from birth is generally associated with an autosomal recessive inheritance pattern or Marie Unna hereditary hypotrichosis (MUHH), hair present at birth suggests autosomal dominance and eyebrow sparing often correlates with a hereditary hypotrichosis simplex (Table 1).

5 | Types of Hypotrichosis

Below we discuss various types of diffuse scalp hypotrichosis seen in a paediatric population, arranged according to the clinical algorithm previously proposed. This discussion will

TABLE 1 | Isolated non-syndromic hereditary hair loss disorders, classified by OMIM naming system.

OMIM Name	Disease	Inheritance	Gene and locus	Phenotype
Hypotrichosis 1 (HYPT1)	Hereditary hypotrichosis simplex type 1 (HHS1)	AD	APCDD1 18p11.22	Normal hair at birth, generalised hypotrichosis progressing from early childhood, with sparse, thin and short hair on scalp and body. Sparing of eyebrow, eyelash and beard hair [4].
Hypotrichosis 2 (HYPT2)	Hereditary hypotrichosis simplex type 2 (HHS2)	AD	CDSN 6p21.3	Normal hair at birth, progressive scalp hair loss from the first decade to diffuse loss by the third decade. Sparse, fine, short scalp hairs. Sparing of eyebrow, eyelash, beard and axillary hair [5].
Hypotrichosis 3 (HYPT3)	Dominant hereditary hypotrichosis 3	AD	KRT74 12q13	Sparse scalp hair from birth, sometimes wiry irregular hair in childhood, with progressive loss to puberty. Sparing of eyebrow, eyelash and facial hair. Normal teeth and nails [6].
Hypotrichosis 4 (HYPT4)	Marie Unna hereditary hypotrichosis 1 (MUHH1)	AD	U2HR 8p21.2	Sparse or absent hair at birth. Slow-growing, variable, coarse, wiry, fragile hair from childhood. Affecting scalp, eyebrows and body hair. Electron microscopy displaying an irregular twisting hair dystrophy and longitudinal grooving [7].
Hypotrichosis 5 (HYPT5)	Marie Unna hereditary hypotrichosis 2 (MUHH2)	AD	EPS8L3 1p13.3	Sparse to absent scalp hair at birth. Wiry, irregular hair in childhood. Thin eyebrows and eyelashes with absence of axillary and pubic hair [8].
Hypotrichosis 6 (HYPT6)	Localised autosomal recessive hypotrichosis 1 (LAH1)	AR	DSG4 18q12	Sparse fragile scalp hairs, affected or absent eyebrows and eyelashes and sparing facial, axillary and pubic hairs. Occasionally hyperkeratotic follicular papules on scalp or other affected areas—an association among LAH phenotypes [9].
Hypotrichosis 7 (HYPT7)	Localised autosomal recessive hypotrichosis 2 (LAH2)	AR	LIPH 3q27.2	Sparse, wiry and twisted to woolly scalp hair. Wide spectrum of body hair phenotype, with individuals affected to different degrees in adulthood [10].
Hypotrichosis 8 (HYPT8)	Localised autosomal recessive hypotrichosis 3 (LAH3)	AR	LPAR6 13q14	Tightly curled, woolly, fragile and slow-growing scalp and trunk hair, and normal to sparse eyebrows and eyelashes [9, 11]. Sparing of beard, and axillary and pubic hairs [11].
Hypotrichosis 9 (HYPT9)	Localised autosomal recessive hypotrichosis 4 (LAH4)	AR	Unknown 10q11.23-q22.3	Thin, sparse hair present from birth on scalp, arms and legs. Sparing of eyebrows and eyelashes, with no other dysmorphic features, no hearing or neurological abnormalities [12].
Hypotrichosis 10 (HYPT10)	Localised autosomal recessive hypotrichosis 5 (LAH5)	AR	Unknown 7p22.3-p21.3	Complete absence of scalp hair from birth. Sparse eyebrow, eyelash, beard and body hair. Papules present on scalp at the termination of hair follicles [13].

(Continues)

TABLE 1 | (Continued)

OMIM Name	Disease	Inheritance	Gene and locus	Phenotype
Hypotrichosis 11 (HYPT11)	Hereditary hypotrichosis simplex type 3 (HSS3)	AD	SNRPE 1q32.1	Sparse to complete absence of scalp, eyelash, eyebrow and axillary and body hair from birth. Pubic hairs spared [14, 15].
Hypotrichosis 12 (HYPT12)	Hereditary hypotrichosis simplex type 4 (HSS4)	AD	RPL21 13q12.2	Normal hair at birth and progressive hair loss 2–6 months of age, progressing to sparse or complete loss of scalp hair. Generalised thin, fragile, dry and sparse hair; some with affected eyebrows, eyelashes and body hair. Sparing of beard hair [16, 17].
Hypotrichosis 13 (HYPT13)	Hypotrichosis with woolly hair	AD	KRT71 12q13.13	Tightly curled scalp woolly hair from birth with limited length. No hair shaft or follicular abnormalities. Affecting scalp, eyebrow and eyelash hairs [18].
Hypotrichosis 14 (HYPT14)	Hypotrichosis 14	AR	LSS 21q22.3	Sparse to absent lanugo-like scalp hair, short brittle eyelashes and eyebrows, and sparse body hair [19].
HYPTSV	Hypotrichosis and recurrent skin vesicles	AR	DSC3 18q12.1	Sparse to absent scalp hair; absence of eyebrows, eyelashes, axillary and body hair and cutaneous vesicles of <1 cm in diameter on scalp and skin [20, 21].
—	Digenic autosomal recessive hypotrichosis	AR	CDH3 16q22.1 & Unknown 12q21.2-q22	Sparse to absent scalp hair from birth, with sparse to normal eyebrows and eyelashes and facial, axillary and body hair [22].

Note: Colours denote broad groups of disease phenotypes.
Abbreviations: AD = autosomal dominant, AR = autosomal recessive [23, 24].

encompass a description of each type, including its unique characteristics, associated symptoms and potential genetic factors.

5.1 | Ectodermal Dysplasias

EDs are a vast group of around 200 hereditary disorders involving the embryonic ectodermal structures and related appendages [25]. Congenital anomalies may involve hair (hypotrichosis, partial or total alopecia), nails (leukonychia, dystrophic, hypertrophic, abnormal keratinisation), teeth (enamel defect, conical teeth, hypodontia, anodontia) and sweat glands (hypoplastic or aplastic apocrine or eccrine glands) [25]. Other tissues of ectodermal origin that may be implicated include eyes, ears, central nervous system, adrenal gland and mammary glands.

The most common form of ED is hypohidrotic ectodermal dysplasia (HED; OMIM: 305100), which occurs secondary to an X-linked recessive mutation in the ectodysplasin encoding gene. HED is characterised by three cardinal features: (1) hypohidrosis or anhidrosis (abnormal eccrine sweat glands leading to reduced ability or inability to sweat and heat intolerance), (2) hypotrichosis (secondary to abnormal follicular development) and (3) hypodontia (abnormal or absent dentition) [26]. The hypotrichosis of HED presents as sparse, thin, fair and slow-growing scalp hair [26], often sparing facial, axillary and pubic hair. Other cutaneous manifestations may include neonatal dermatitis, abnormal sebaceous secretions (as well as nasal and ocular secretions) and absent dermal ridges [26].

Clinical examination of suspected ED should include a review of dentition for hypodontia, underdeveloped alveolar ridges and conical teeth [25]. Trichoscopy may demonstrate hair shaft abnormalities supportive of HED, such as variable thickness, longitudinal grooves, trichorrhexis nodosa, pili torti and decreased follicular units and terminal hair [27].

5.2 | Other Syndromic Hypotrichoses

Other syndromic hypotrichoses to be considered can be divided into two groups: syndromic autosomal dominant hypotrichoses (SADH) and syndromic autosomal recessive hypotrichoses (SARH).

5.2.1 | Syndromic Autosomal Dominant Hypotrichoses

SADH includes trichorhinophalangeal syndrome (TRPS; with Subtypes I, II and III) and connexin disorders. TRPS I (OMIM: 190350) is caused by mutations in TRPS1 gene at 8q23.3 and features sparse scalp hair, a bulbous nasal tip, long flat philtrum, protruding ears, conical epiphyses at phalanges, short stature and skeletal malformations [28]. TRPS III involves a heterozygous mutation at the same TRPS1 gene, however is associated with a greater degree of generalised brachydactyly [29].

TRPS II (Langer–Giedion syndrome; OMIM: 150230) originates from a contiguous gene deletion at 8q24.11–13 causing loss of function at both the TRPS1 gene and multiple exostoses type I (EXT1) genes. TRPS II therefore presents with the phenotypical features of TRPS I as aforementioned, as well as multiple cartilaginous exostoses, intellectual disabilities and occasionally seizures and other skeletal, endocrine and urogenital abnormalities [30].

Connexin disorders are defects of proteins forming intercellular gap junction channels, which may manifest as a range of syndromes causing deafness, dysmorphic facial features, eye anomalies, teeth abnormalities, cleft lip or palate, skeletal malformations or neurological defects [31].

5.2.2 | Syndromic Autosomal Recessive Hypotrichoses

Hypotrichois with juvenile macular dystrophy (HJMD; OMIM 601553) (AR; CDH3 gene mutation at 16q22.1) is a SARH condition presenting with infantile onset of alopecia followed by pubertal regrowth of short, sparse hair and development of progressive macular degeneration to blindness in early adulthood [32].

Autosomal recessive congenital ichthyosis (ARCI) (AR; AT14 gene at 11q24.3) describes a heterogeneous group of genetic disorders in which afflicted individuals are born with collodion membrane, palmoplantar keratoderma and hypotrichosis. Cutaneous phenotypes are a generalised scaling and erythroderma consistent with either lamellar ichthyosis (LI) and nonbullous congenital ichthyosiform erythroderma (NCIE), or an intersection of both [33].

5.2.3 | Others

Others in this category include hypotrichosis with immunodeficiency syndromes (cartilage hair hypoplasia, Omenn syndrome), hypotrichosis with premature ageing syndromes (Hutchinson–Gilford progeria, neonatal progeroid syndrome, Cockayne syndrome, Rothmund–Thomson syndrome), Menkes syndrome, Basex–Dupré–Christol syndrome, Crandall syndrome, Gomez–Lopez–Hernandez syndrome and ichthyosis folicularis alopecia and photophobia syndrome (IFAP) [23, 34]. For these conditions, congenital hypotrichosis is not expected to be the predominant presenting feature.

5.3 | Loose Anagen Syndrome (LAS)

Loose anagen syndrome (OMIM: 600628) most often presents during early childhood (usually aged 2–5 years), and features hair that is usually readily and painlessly pulled from the follicle, due to dysplastic anagen hairs with defective keratinization of root sheaths [35], leading to abnormal hair anchoring. The presentation is primarily in girls due to the desire to grow long hair. Afflicted individuals have a history of short, sparse, slow-growing fair hair that is stiff, unruly, patchy and easily shed and there may be a history of a sibling accidentally removing a clump of hairs. For those girls who tend to twirl their hair, the presentation may be one of patchy, focal hypotrichosis. Clinical diagnosis can often be made with a loose

anagen hair pull test and can be confirmed by trichoscopy demonstrating > 70% loose anagen hairs, often characterised by distorted anagen bulbs, ruffled cuticles and absence of outer root sheath [36]. Loose anagen syndrome is theorised to have an autosomal dominant pattern of inheritance [37] and generally spontaneously improves with age [35]. Therapy is based around minimising hair tension, which usually allows for adequate hair coverage. The prognosis is excellent as the hair becomes more strongly anchored over time.

5.4 | Hair Shaft Structural Abnormalities

Hair shaft structural abnormalities describe a group of genetic conditions characterised by an inherent abnormality of the formation of the hair. They present with a detectable abnormality in hair either clinically, using trichoscopy or electron microscopy. Many of these result in hair fragility and excessive hair breakage and therefore can present with chronic hypotrichosis. These disorders are well detailed in other reviews (need reference) and will be briefly mentioned here only.

5.5 | Monilethrix

Monilethrix (OMIM: 158000) is an autosomal dominant disorder caused by mutations in genes encoding hair keratin (KRT81, KRT83, KRT86). Affected individuals are born with normal hair that after a few months becomes brittle and fragile with perifollicular hyperkeratosis [38]. Milder forms only partially affect the occiput, but in more severe expressions, there may be hypotrichosis of eyebrows, eyelashes, axillary and pubic hair, and hyperkeratosis of the neck, arms and thighs [39]. Under light microscopy, the hair shaft is irregularly narrowed in a hallmark beaded necklace appearance (hence the moniker, an amalgamation of the Latin *monile* for necklace and Greek *thrix* for hair) (Figure S2) [38]. It is at the constricted internode regions that the fragile hair shaft readily breaks. Hair gradually improves with age and may be significantly improved by puberty or young adulthood, or during pregnancy [39].

5.6 | Woolly Hair

Woolly hair (WH) describes a group of hair shaft dystrophies presenting from birth or early childhood with fine, fragile, tightly curled or kinked hair that is short or slow growing due to a truncated anagen phase [40]. Such hair may be hypopigmented and difficult to comb, however, improving with age. Light microscopy is characterised by structural abnormalities such as trichorrhexis nodosa and tapered distal ends [40].

WH has been observed as a feature of several syndromes, such as Noonan syndrome (OMIM: 163950), cardiofaciocutaneous syndrome, keratosis pilaris atrophicans, Naxos disease (a palmoplantar keratoderma and right ventricular cardiomyopathy syndrome) and Carvajal syndrome (a palmoplantar keratoderma and predominantly left ventricular dilated cardiomyopathy syndrome) [41, 42].

Non-syndromic forms of WH have also been found, with the more common form being autosomal dominant woolly hair (ADWH; OMIM: 194300) associated with mutations in the KRT74 gene on 12q13 [40]. Several forms of autosomal recessive woolly hair (ARWH) have been identified: ARWH1/HYPT8 (OMIM: 278150) from a mutation on P2RY5 gene on 13q14, ARWH2/HYPT7 (OMIM: 604379) caused by mutations on LIPH gene at 3q27.2 and ARWH3 (OMIM: 616760) from a homozygous mutation of KRT25 gene on 17q21 [23]. HYPT7 and HYPT8 are described in further detail in Table 1.

5.7 | Uncombable Hair Syndrome

Uncombable hair syndrome (UHS; also *pili trianguli et canaliculi*, *cheveux incoiffables* or spun-glass hair) is a hair shaft disorder presenting in infancy or childhood with dry, coarse, light coloured scalp hair that is kinky, unruly and increasingly uncombable. Hair may be glossy or adopt a spun-glass appearance. Electron microscopy may demonstrate shaft cross sections with a triangular, kidney bean, heart-shaped or flattened appearance. UHS can be inherited as autosomal dominant or autosomal recessive conditions (UHS1 OMIM: 191480; UHS2 OMIM: 617251; UHS3 OMIM: 617252) or occur sporadically, and may likewise spontaneously improve without treatment [43]. The hair is not fragile and adequate length can be achieved. Because the hair looks abnormal, it is included in this review for completeness.

5.8 | Trichorrhexis Nodosa

Trichorrhexis nodosa is a trichoscopy finding rather than being a distinct hair shaft disorder with light microscopy features of spurs at irregular intervals along the hair shaft where the open cuticles expose fragmented corticle fibres [44]. Trichorrhexis nodosa can be congenital in conditions such as Menkes disease (see below), Netherton syndrome (see below), argininosuccinic aciduria (OMIM: 207900) and trichohepatoentric syndrome, or acquired hair damage due to overheating, chemical injury, excessive traction, frequent exposure to chlorinated water or other hair trauma.

5.9 | Trichorrhexis Invaginata and Netherton Syndrome

Trichorrhexis invaginata (also 'bamboo hair' or 'ball and socket' deformity) describes an abnormal invagination appearance of the hair shaft, in which the distal shaft is telescoped against a dilated proximal hair shaft, forming a 'ball and socket' deformity on microscopy. It is otherwise known as 'bamboo hair' due to the appearance of strands with knots being likened to a bamboo stalk. Hair is thin, brittle, short and dull. Trichorrhexis invaginata is a trademark feature of Netherton syndrome and other ichthyosiform disorders.

Netherton syndrome (OMIM: 256500) is a genodermatosis occurring due to an autosomal recessive mutation in the *SPINK5* gene on 5q32, leading to deficiency of serine protease inhibitor LEKTI present on epidermal services [45]. Netherton

syndrome is clinically characterised by a triad of congenital icthyosiform erythroderma, atopic diathesis and trichorrhexis invaginata (detectable on trichoscopy of hair and eyebrows by 1 year of age).

5.10 | Trichothiodystrophy

Trichothiodystrophy (OMIM: 601675) is a rare autosomal recessive condition caused by mutation in *ERCC2/XPD*, wherein patients have short, brittle hair secondary to sulphur deficiency. Sulphur deficiency gives rise to a multisystemic condition with associated features of ichthyosis (often as scaly skin at birth, some with collodion membrane at birth), photosensitivity, nail dystrophy, microcephaly, short stature, intellectual disability, decreased fertility, ocular abnormalities and predisposition to infection and cancer [46]. Associated syndromes include Sabinas syndrome, hair-brain syndrome, Tay syndrome and PIBIDS syndrome.

Deficiency of sulphur in the hair cuticle leads to a range of hair shaft abnormalities. Light dermoscopy or microscopy may identify trichoschisis (transverse fractures of hair) and using polarised light may demonstrate an alternating light and dark birefringence resembling a 'tiger-tail' banding pattern, pathognomonic for trichothiodystrophy [46].

5.11 | Pili Torti and Menkes Disease

Pili torti describes a light microscopy appearance of hair shaft that is flattened with variable diameters, fractures at regular intervals and 180° twisting [47]. Macroscopically, scalp and body hair is short, sparse, fragile and kinky or steel wool like in appearance. Pili torti can occur as an isolated non-syndromic congenital disorder or as a characteristic of other disorders such as Menkes disease, Bjornstad syndrome (OMIM: 262000) and Bazex syndrome (OMIM: 301845).

Menkes disease (OMIM: 309400) is an X-linked recessive metabolic disorder involving an inactivating mutation of the alpha polypeptide gene (ATP7A) causing dysfunction of intestinal copper transport uptake proteins [47]. This leads to severe copper deficiency and secondary deficiency of copper-dependent enzymes. Scalp hair is phenotypically variable but generally characterised by short sparse scalp hair that may be hypopigmented, brittle, kinky or twisted [48]. Light microscopy may reveal pilli torti, monilethrix and trichorrhexis nodosa. Skin may be hypopigmented or mottled in appearance and hyperextensible or lax. The natural history of Menkes disease may include neonatal abnormalities (hypothermia, hypoglycaemia, hypotonia, feeding difficulties) and progressive disease in infancy, including neurological deterioration, epilepsy, ataxia and developmental regression [48]. Treatment with copper replacement has variable efficacy, and mortality usually occurs by late infancy or early childhood [47].

5.12 | Pili Annulati and Pseudopili Annulati

Pili annulati ('ringed hairs'; OMIM: 180600) is an isolated hair shaft disorder that may occur sporadically or inherited as an autosomal dominant disorder (locus 12q24) [49]. It occurs in the context of multiple air-filled cavities arising along the cortex of the scalp hair shaft, causing an alternating light and dark band pattern visible under the microscopy, only macroscopically detectable in lighter hair. There is generally no increased hair breakage with normal growth of hair. Pili annulati is congenital or develops during infancy and is often an incidental finding.

Pseudopili annulati (OMIM: 613241) is considered a normal variant particularly in lighter hair, describing reflection of light against flattened or twisted segments of hair shaft and causing an appearance of light and dark banding on light microscopy.

5.13 | Isolated Hereditary Hair Loss Disorders

In the case of abnormal hair in an otherwise well child without syndromic features, and a normal trichoscopy, consider isolated hereditary hair loss disorders. These are a group of genetically heterogenous non-syndromic hereditary hypotrichoses classified by the Online Mendelian Inheritance in Man (OMIM) naming system—HYPT1 to HYPT12 [23]. Data for these conditions have been informed by case reports and series describing affected families.

5.14 | Short Anagen Syndrome

SAS is a rarely described hypotrichosis presenting as fine, short hair in childhood that does not grow long in the absence of any systemic abnormalities. It is caused by abnormal hair cycling, distinguished by a shortened anagen phase and greater proportion of hairs in the telogen phase, producing a normal (negative) hair pull test and normal trichoscopy. It has been posited to have an autosomal dominant inheritance or may arise in individuals sporadically, and similarly spontaneously resolve in puberty or early adulthood [50].

Reports in the literature have described treatment of SAS with topical minoxidil solution (2%–5% concentration), with aims of extending the duration of anagen phase and preventing telogen effluvium, to improve hair density and length [51, 52]. The evidence for efficacy of minoxidil in SAS has yet to be strongly established. With appropriate counselling regarding risks and potential adverse effects (transient shedding, localised acne, contact dermatitis), it may nonetheless be safely attempted for patients with significant or persisting SAS. There have been reports of combination therapy of topical minoxidil with systemic cyclosporine A to good effect [53]. Oral biotin (a vitamin B7 involved in keratin production) 5 mg/day has also been trialled with reports of significant improvement with minimal side effects, when used alone or in combination with topical minoxidil [51].

Oral minoxidil has also been used to treat and lengthen hair in SAS in children. It appears to be safe and well tolerated at low doses in the range of 0.025–2.5 mg/day [54, 55]. Dosing should be age based and at the discretion of the treating clinician. We recommend starting at a low dose and up-titrating within the dose range depending on age, treatment response and side

FIGURE 2 | Short anagen syndrome treated with oral minoxidil for 2 years (1 year at 0.5 mg/day and then 1 year at 1 mg/day)—before (left, aged 4 years) and after (right, aged 6 years). (Image courtesy of: A/Prof David Orchard, Barkers Road Dermatology).

effects. Patients should be regularly monitored for adverse effects such as undesirable facial or generalised hypertrichosis, hypotension, headaches, elevated LFTs, nausea and rare cardiovascular symptoms (palpitations, dyspnoea, ankle oedema) [55]. In the authors' experience, unwanted facial or body hair is rarely encountered compared to the teenager and adult population (Figure 2).

6 | Principles of Management

The primary step in managing paediatric hypotrichosis is establishing an accurate diagnosis, which subsequently guides genetic analysis and further workup where a syndromic hypotrichosis is suspected. If genotrichosis is suspected, genetics involvement is crucial for providing genetic counselling for individuals and affected family members, and future family planning. Multidisciplinary referrals to paediatricians, surgeons and allied health professions may be required if systemic complications are anticipated.

Conservative management for hypotrichoses focuses on methods of protecting hair through gentle hair products and hair care to avoid trauma causing further hair loss, particularly for conditions of increasing hair fragility or poor anchoring [56]. Cosmetic camouflage through various hairstyling techniques, carefully placed hair extensions, wigs and cosmetic tattooing are instrumental in alleviating the significant psychosocial burden or ostracisation young patients may suffer.

To date, few evidence-based treatments have been well established to be effective in the treatment of genetic hypotrichoses. In several reports, treatments with topical minoxidil, oral biotin and low-dose oral minoxidil have been used with variable degrees of success. Due to the good safety profile of these treatments when applied correctly or commenced at low doses, they may be safely attempted with potential benefits in prolonging anagen phase and increasing hair length and density.

7 | Conclusion

We have presented a diagnostic algorithm for use in the identification of congenital and early onset hypotrichoses arising in the paediatric population. The initial clinical approach should aim to identify the patient's history of hair growth and loss, and the phenotypical features of hair. Abnormal hair that is sparse, short, brittle, fragile is characteristic of a range of isolated hereditary hair shaft disorders, with variable sparing of non-scalp hair. The presence of systemic features suggests syndromic disorder; for example, abnormalities in the skin, hair, nails and teeth are indicative of an ED. Bedside tests such as trichoscopy and a loose anagen hair pull test may yield further valuable diagnostic features and can be followed up with a trichogram or scalp biopsy. Negative findings in the presence of an otherwise systemically well child may suggest an isolated hereditary hypotrichosis (HYPT1-12). Management is generally conservative in nature, with limited but emerging data suggesting a potential role for the use of oral biotin, topical or oral minoxidil and topical retinoids in the treatment of some forms of intractable hypotrichoses.

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Conflicts of Interest

A/Prof David Orchard is an Editorial Board member of *Australasian Journal of Dermatology* and a co-author of this article. To minimise bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.