JAYPEE

Hair and Hair Disorders

Diagnosis & Management

Chief Editor
S Sacchidanand

Co-editors
Savitha AS
Lakshmi DV

Hair and Hair Disorders
Diagnosis & Management

Salient Features

- Text boxes and illustrations in all the chapters to emphasize important points
- The chapters are based on presenting symptoms and signs, differential diagnosis, therapeutics and surgical modalities
- Recent advances in the field of trichology has been covered.

S Sacchidanand MD DVD DHA FRCP (Glasgow) is presently working as Registrar (Evaluation), Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India. He has worked formerly as Professor and Head, Department of Dermatology, STD and Leprosy at Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India. His skills are spread across several domains and he has excelled in teaching, academics, administration, organization and research activities in the last 30 years. He has worked at various levels in Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) and was its Honorary General Secretary (2002–2005) and President during 2008–2009. He has also served as Secretary General of South Asian Regional Association of Dermatologists (SARAD) during 2005–2007 and is currently its Vice-President (2013–2015). He had been Vice-President of Association of Cutaneous Surgeons of India (ACSI, 2011–2013). He is the founder President of Association of Facial Aestheticians and Aesthetic Surgeons of India (AFAASI) and Community Dermatology Society (CDS). He has been a guide to several young postgraduate students of various faculties like Dermatology, Medicine, Pathology, Microbiology, Pharmacology, Community Medicine, Dental and Pharmacy. He has been conferred a Fellowship (FRCP) from the University of Glasgow in 2012. He is a pioneer in starting fellowship courses in Dermatosurgery (2005), Medical Cosmetology (2007), Pediatric Dermatology (2010) and Trichology (2012) at Bangalore Medical College and Research Institute under the aegis of Rajiv Gandhi University of Health Sciences. He has published around 75 articles in indexed journals. He has conducted around 25 conferences so far both at national and international levels (DERMAVISION – 2000, DERMACON – 2009 and PHOTOCON, TRICHOCON, ONYCHOCON, FOTOCON, COSMECON and FACETHETICS, etc.). He has authored several chapters in various textbooks and is currently the Chief Editor of the IV Edition of IADVL Textbook of Dermatology. He has edited and co-authored around 12 undergraduate and postgraduate books in dermatology. The present book on *Hair and Hair Disorders* is another addition to his illustrious career.

Savitha AS MD DNB FRGUHS (Dermatosurgery) has completed her undergraduation and postgraduation and her Fellowship in Dermatosurgery from Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India. She is currently working as Senior Resident in the Department of Dermatology, STD and Leprosy at Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India.

Lakshmi DV DVD FRGUHS (Pediatric Dermatology) has completed her graduation from Dr BR Ambedkar Medical College, and postgraduation and her fellowship in Pediatric Dermatology from Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India. She is currently working as Senior Resident in the Department of Dermatology, STD and Leprosy at Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India.

Hair and Hair Disorders

Diagnosis and Management

Chief Editor

S Sacchidanand MD DVD DHA FRCP (Glasgow)
Registrar (Evaluation)
Rajiv Gandhi University of Health Sciences
Former Professor and Head
Department of Dermatology, STD and Leprosy
Bangalore Medical College and Research Institute
Bengaluru, Karnataka, India

Co-editors

Savitha AS MD DNB FRGUHS (Dermatosurgery)
Senior Resident
Department of Dermatology, STD and Leprosy
Victoria Hospital
Bangalore Medical College and Research Institute
Bengaluru, Karnataka, India

Lakshmi DV DVD FRGUHS (Pediatric Dermatology)
Senior Resident
Department of Dermatology, STD and Leprosy
Victoria Hospital
Bangalore Medical College and Research Institute
Bengaluru, Karnataka, India

JAYPEE *The Health Sciences Publishers*

New Delhi | London | Philadelphia | Panama

Jaypee Brothers Medical Publishers (P) Ltd

Headquarters

Jaypee Brothers Medical Publishers (P) Ltd
4838/24, Ansari Road, Daryaganj
New Delhi 110 002, India
Phone: +91-11-43574357
Fax: +91-11-43574314
Email: jaypee@jaypeebrothers.com

Overseas Offices

J.P. Medical Ltd
83, Victoria Street, London
SW1H 0HW (UK)
Phone: +44 20 3170 8910
Fax: +44 (0)20 3008 6180
Email: info@jpmedpub.com

Jaypee-Highlights Medical Publishers Inc
City of Knowledge, Bld. 237, Clayton
Panama City, Panama
Phone: +1 507-301-0496
Fax: +1 507-301-0499
Email: cservice@jphmedical.com

Jaypee Medical Inc
The Bourse
111 South Independence Mall East
Suite 835, Philadelphia, PA 19106, USA
Phone: +1 267-519-9789
Email: jpmed.us@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd
17/1-B Babar Road, Block-B, Shaymali
Mohammadpur, Dhaka-1207
Bangladesh
Mobile: +08801912003485
Email: jaypeedhaka@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd
Bhotahity, Kathmandu
Nepal
Phone: +977-9741283608
Email: kathmandu@jaypeebrothers.com

Website: www.jaypeebrothers.com
Website: www.jaypeedigital.com

Hair and Hair Disorders: Diagnosis and Management

First Edition: **2015**

ISBN 978-93-5152-340-6

Printed at Replika Press Pvt. Ltd.

Contributors

Anil Abraham MD FAAD FRCP (Glasgow)
Professor
Department of Dermatology STD and Leprosy
St Johns Medical College and Research Center
Bengaluru, Karnataka, India

Anoosha P MD
Consultant Dermatologist
Vee Care DermatoPlastic, Skin, Hair, Laser and
Day Plastic Surgery Clinic
Chennai, Tamil Nadu, India

Aparna Palit MD
Professor
Department of Dermatology, STD and Leprosy
Sri BM Patil Medical College
BLDE University
Bijapur, Karnataka, India

Archana L DVD
(Fellow in Medical Cosmetology)
Department of Dermatology, STD and Leprosy
Bangalore Medical College and
Research Institute
Bengaluru, Karnataka, India

Arun C Inamadar MD, DVD
Professor and Head
Department of Dermatology, STD and Leprosy
Sri BM Patil Medical College
BLDE University
Bijapur, Karnataka, India

Asha GS MD FRGUHS (Dermatosurgery)
Assistant Professor
Department of Dermatology, STD and Leprosy
Victoria Hospital
Bangalore Medical College and
Research Institute
Bengaluru, Karnataka, India

Ashok Kumar Jaiswal MD
Professor and Head
Department of Dermatology, Venereology and Leprosy
Dr BR Ambedkar Medical College
Bengaluru, Karnataka, India

C Janaki MD DD
Professor
Department of Dermatology
Madras Medical College
Chennai, Tamil Nadu, India

D Dinesh Kumar MD
Consultant Dermatologist
Vee Care DermatoPlastic, Skin, Hair, Laser and
Day Plastic Surgery Clinic
Chennai, Tamil Nadu, India

Divya Gorur MD
(Fellow in Dermatosurgery)
Victoria Hospital
Department of Dermatology, STD and Leprosy
Bangalore Medical College and Research Institute
Bengaluru, Karnataka, India

Dolly Gupta MD FIDS Certified in Trichology (USA)
Consultant Dermatologist and Hair Transplant Surgeon
MEDICA Super-specialty Hospital
Kolkata, West Bengal, India

Eshini Perera MBBS
Faculty of Medicine
Dentistry and Health Sciences
The University of Melbourne
Victoria, Australia

Eswari L MD
Assistant Professor (Fellow in Dermatosurgery)
Department of Dermatology, STD and Leprosy
Bangalore Medical College and Research Institute
Bengaluru, Karnataka, India

G Sentamil Selvi MD DD PhD
Professor and Head (Retired)
Department of Dermatology, STD and Leprosy
Madras Medical College
Chennai, Tamil Nadu, India

KC Nischal MD
Consultant Dermatologist
Nirmal Skin and Hair Clinic
Senior Consultant and Associate Manager
Medical Services
Kaya Skin Clinic
Bengaluru, Karnataka, India

Lakshmi DV DVD FRGUHS (Pediatric Dermatology)
Senior Resident, Victoria Hospital
Department of Dermatology, STD and Leprosy
Bangalore Medical College and Research Institute
Bengaluru, Karnataka, India

Leelavathy B MD FRGUHS (Medical Cosmetology)
Associate Professor and Head
Department of Dermatology, STD and Leprosy
Bowring and Lady Curzon Hospital
Bangalore Medical College and Research Institute
Bengaluru, Karnataka, India

Malavika Kohli MD DVD DNB
Director, Skin Secrets
Jaslok Hospital and Research Center
Breach Candy Hospital Trust
Mumbai, Maharashtra, India

Manjunath Shenoy M MD DNB
Professor and Head
Department of Dermatology, STD and Leprosy
Yenepoya Medical College, Deralakatte
Yenepoya University
Mangalore, Karnataka, India

Manoj Khanna MS MCh (Plastic Surgery) FICS (USA)
Fellowship (Cosmetic Surgery) (USA)
Consultant Plastic Surgeon
Enhance Aesthetic and Cosmetic Studios Pvt Ltd
Kolkota, West Bengal, India

Maya Vedamurthy MD FRCP (Glasgow)
Consultant Dermatologist
Anna Nagar, Chennai, Tamil Nadu, India

Neelima Sharma DVD
Consultant Dermatologist
Banaswadi, Bengaluru, Karnataka, India

Prabhakar M Sangolli MD DVD
Former Associate Professor
Dr BR Ambedkar Medical College
Consultant Dermatologist
Skin Care Center
Bengaluru, Karnataka, India

R Madhu MD (Derm) DCH
Senior Assistant Professor
Department of Dermatology (Mycology)
Madras Medical College
Chennai, Tamil Nadu, India

Raghini Ghiya MD
Consultant Dermatologist and Hair Transplant Surgeon
Siddharth Clinic
Surat, Gujarat, India

Rajiv Sharad Joshi MD DVD DNB
Consultant Dermatologist
PD Hinduja Hospital
Mumbai, Maharashtra, India

Ralph M Trüeb MD
Professor
Center for Dermatology and Hair Diseases
Wallisellen, Switzerland

Rodney Sinclair MD FACD
Epworth Hospital, Melbourne
Victoria, Australia

S Sacchidanand MD DVD DHA FRCP (Glasgow)
Registrar (Evaluation)
Rajiv Gandhi University of Health Sciences
Former Professor and Head
Department of Dermatology, STD and Leprosy
Bangalore Medical College and Research Institute
Bengaluru, Karnataka, India

Sanjeev J Aurangabadkar MD
Consultant Dermatologist
Skin and Laser Clinic
Hyderabad, Andhra Pradesh, India

Savitha AS MD DNB FRGUHS (Dermatosurgery)
Senior Resident
Victoria Hospital
Department of Dermatology, STD and Leprosy
Bangalore Medical College and Research Institute
Bengaluru, Karnataka, India

Shashikumar BM MD
Associate Professor
Department of Dermatology, STD and Leprosy
Mandya Institute of Medical Sciences
Mandya, Karnataka, India

Sheena Bansal MD
Consultant Dermatologist
Skin Essence
Kanpur, Uttar Pradesh, India

Shilpa K MD FRGUHS (Dermatosurgery)
Assistant Professor
Victoria Hospital
Department of Dermatology, STD and Leprosy
Bangalore Medical College and Research Institute
Bengaluru, Karnataka, India

Shrutakirthi D Shenoi MD DVD
Professor and Head
Department of Dermatology, STD and Leprosy
Kasturba Medical College
Manipal University
Manipal, Karnataka, India

Smitha Prabhu MD
Department of Dermatology, STD and Leprosy
Kasturba Medical College
Manipal University
Manipal, Karnataka, India

Sudhir Nayak UK MD
Assistant Professor
Department of Dermatology, STD and Leprosy
Kasturba Medical College
Manipal University
Manipal, Karnataka, India

TS Nagesh MD DNB
Associate Professor
Department of Dermatology, STD and Leprosy
Sapthagiri Institute of Medical Sciences and
Research Center
Bengaluru, Karnataka, India

Urmila Nischal MD
Consultant Dermatologist
Nirmal Skin and Hair Clinic
Bengaluru, Karnataka, India

Venkataram Mysore DVD MD DNB DipRCPath (Lond)
FRCP (Glasgow)
Consultant Dermatologist
Dermatopathologist and Hair Transplant Surgeon
Director
Venkat Charmalaya—Center for Advanced
Dermatology and PG Teaching Center
Bengaluru, Karnataka, India

Vishalakshi S Pandit MD
Assistant Professor
Department of Dermatology, STD and Leprosy
Sri BM Patil Medical College
BLDE University
Bijapur, Karnataka, India

Preface

"To study medicine without books is to sail an uncharted sea; while to study books without patients is not to go to sea at all."

—William Osler

"Trichology" refers to study of "hair-related disorders". It is an upcoming branch of dermatology as 10–20% of dermatological out-patients present with hair-related problems. There is an ocean of opportunities for research work in hair-related disorders due to paucity of literature in this subspecialty and also need for a updated book that would throw light on management of hair-related conditions.

Hence, to fill up this void, we have planned to bring out a comprehensive textbook on hair and its related diseases in its entirety.

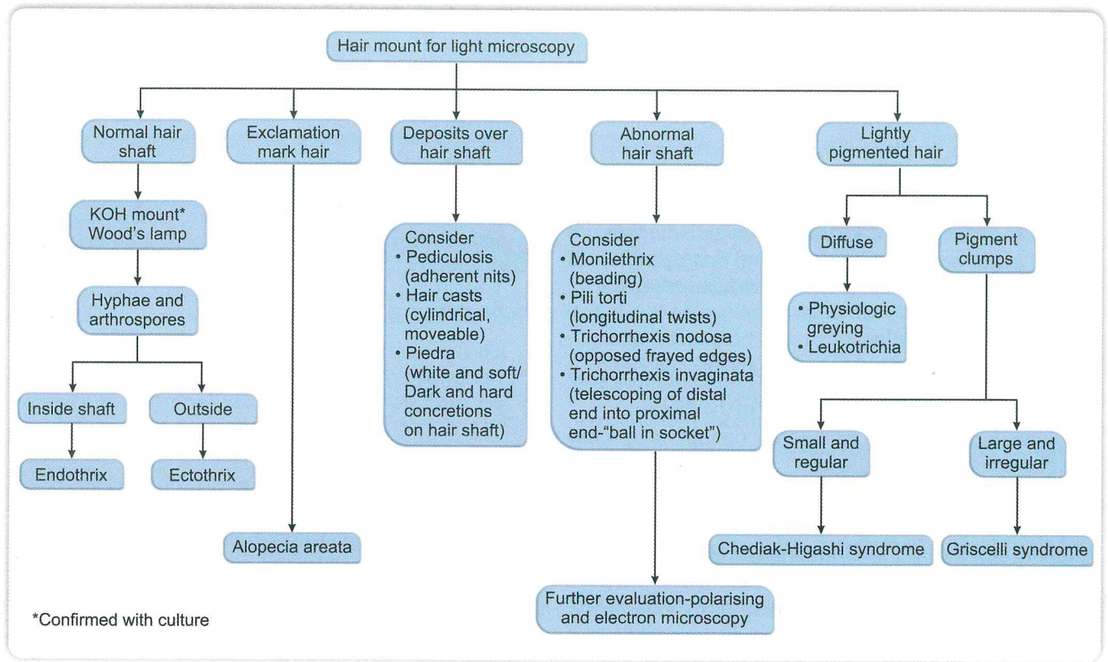
In the first edition of the book, we have aimed to provide an extensive data on hair-related disorders to complement the details available in major textbooks in the field of dermatology. We assure that the work has been sufficiently researched and hopefully would merit further editions. The various sections are based on presenting symptoms and signs, differential diagnosis, therapeutics and surgical modalities highlighted with text boxes and illustrations. Recent advances in the field of trichology have prompted the management of hair and hair disorders enormously, and this is reflected in the descriptions in the relevant sections.

We hope that this treatise will provide the knowledge and confidence to clinicians and postgraduates to untangle the locks of hair and scalp disorders.

We acknowledge the contribution of Sumedha Ballal, Divya Gorur, Chitrika, Shruti C, Varsha Shetty, Kumar Abhishek, Pushpa KR, Shalini, Maheshwari, Amina Asfiya and Linda Robert towards this project.

S Sacchidanand
Savitha AS
Lakshmi DV

Contents



Algorithm 3.6: Hair microscopy

References

1. Dhurat R, Saraogi P. Hair evaluation methods: Merits and demerits. Int J Trichol. 2009;1:108-19.
2. Adya KA, Inamadar AC, Palit A, Shivanna R, Deshmukh NS. Light microscopy of the hair: A simple tool to "untangle" hair disorders. Int J Trichol. 2011;3:46-56.

4

Genetic Hair Disorders

Arun C Inamadar, Vishalakshi S Pandit, Aparna Palit

"My scientific labors have brought me a great deal of satisfaction, and I am convinced that before long the entire world will praise the result of these labors."

—Gregor Mendel

Introdution

Infant with sparse, lusterless, or broken - off hair suggest signs of genetic defect and may signal impending neurological and mental defects. These disorders are not very rare and molecular diagnostic methods are required for definitive diagnosis. Early recognition of genetic hair disorders can be done by simple hair microscopy. Hair mount **(Box 4.1)** is the basic procedure to differentiate between genetic hair disorders due to structural defect and otherwise.

Genetic hair disorders are grouped as given below:

1. Monilethrix
2. Pseudomonilethrix
3. Pili torti
4. Menkes disease
5. Netherton syndrome
6. Trichothiodystrophy
7. Ectodermal dysplasia.

Box 4.1: Hair mount

Hair mount is the basic procedure to differentiate between genetic hair disorders due to structural defect and otherwise

Monilethrix (Synonym: Beaded Hair)

Monilethrix is an autosomal dominant disorder characterized by periodic beading of hair shafts and pronounced hair fragility, leading to hair loss and eventual scarring alopecia.[1] This disorder was first described by Smith in 1879 as a rare nodose condition of the hair and the term "monilethrix" was later coined by Radcliff Crocker.[2]

Pathogenesis

It is an autosomal dominant transmitted disease with variable expressivity.

Around seven different types of mutations have been detected to be associated with monilethrix.[3] The three hair keratin genes proved to be causal for monilethrix encode the type II hair keratins Hb1, Hb3, and Hb6, **(Box 4.2)** and share a completely identical α-helical rod domain and, in line with the ultrastructurally observed disease symptoms, are all expressed in the hair cortex.[4] In these three keratins (hHb1, hHb3 and hHb6), the HTM was the most mutated region while a few HIM mutations occurred only in the hHb6 keratin.[3] There is conceivable evidence that mutation either in the cortex keratins, compromising the keratin–desmoplakin interaction, or in desmoglein 4 (DSG4), abrogating cell–cell adhesion, in cortex cells, entail a similar disease phenotype.[4] The mutation in transmembranous adhesion molecule desmoglein 4, a member of the two desmosomal cadherin subfamilies, desmocollins (DSCs) and desmogleins is implicated in the autosomal recessive pattern of monilethrix **(Figure 4.1)**.[5-7] Singh, et al.[8] have reported a case who showed higher acrocentric association using cytogenetic studies. This association could possibly indicate some predisposing factor between the satellite (acrocentric) chromosomes and mutation in the microsatellite DNA loci region on chromosome 12, containing the type II Keratin gene cluster.

Box 4.2: Genes involved in monilethrix

- hHb1, hHb3 and hHb6—autosomal dominant
- Mutations in desmoglein 4, desmocollins (DSCs)—autosomal recessive
- Mutation in the microsatellite DNA loci region on chromosome 12, containing the type II Keratin gene cluster

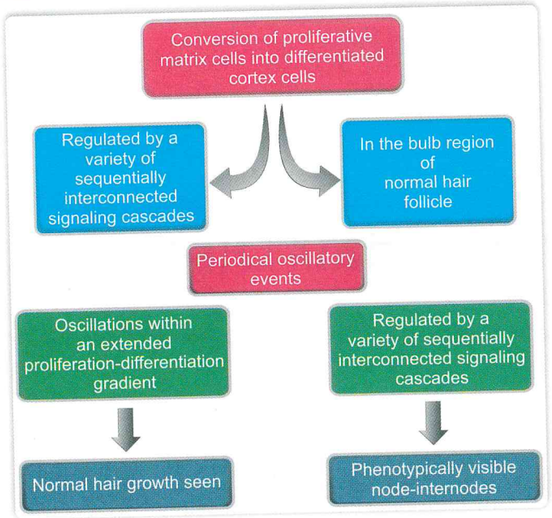


Fig. 4.1: Pathogenetic basis of formation of alternate node and internodes[4]

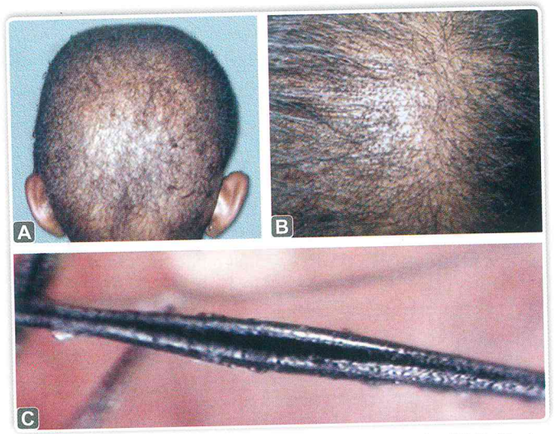
The beading or moniliform appearance of the hair shaft is caused by the nodes and internodal thinning of the shaft. The nodes seem to represent normal growth; the internodes are characterized by the wrinkling of corticle cells leading to fragility of the hair, with an absence of medulla. Ultrastructurally, vacuolation and alterations in the fibrillar structures of lower cortex cells have been described.[9]

Clinical Features (Box 4.3)

Affected individuals usually have normal appearing hair at birth but within the first few months of life, these fibers are replaced by short, fragile and brittle hair. Hairs rarely grow beyond 1 to 2 cm in length because of breakage, resulting in a stubbly appearance. In the mildest form, the disease involves only the occiput and nape of the neck, but in its severe form, the entire scalp, secondary hairs, eyebrows, and eyelashes may also be involved.[4] Alopecia is more severe in areas prone to friction. Perifollicular erythema and follicular hyperkeratosis are commonly observed in the occipital region **(Figure 4.2)**.

Box 4.3: Clinical clues in monilethrix

- *Mild form*—occiput and nape of the neck
- *Severe form*—entire scalp, secondary hairs, eyebrows, and eyelashes
- Perifollicular erythema and follicular hyperkeratosis in the occipital region
- Alopecia in pressure prone areas
- *Associated features*—keratosis pilaris, koilonychia, mental and physical retardation, syndactyly, cataract, teeth and nail anomalies



Figs 4.2A to C: (A) Sparse, fragile hair in monilethrix; (B) Follicular prominence on scalp; (C) Microscopic appearance of hair shaft showing fusiform nodes. (*Courtesy:* Department of Dermatology, STD and Leprosy, BMCRI, Bengaluru)

Lanugo hair is normal in the neonatal period. Clinical signs appear when terminal hair characteristics begin to form. Apart from short, sparse, fragile, non-growing hair, affected patients may have keratosis pilaris, koilonychia and rarely, systemic disturbances such as mental and physical retardation, syndactyly, cataract, teeth and nail anomalies.[10]

Investigations (Figure 4.3)

A diagnosis can be elucidated by examining hairs by light microscopy. It shows hair fibers with regularly spaced elliptical, fusiform or spindle-shaped nodes of normal thickness separated by intermittent abnormal constrictions that are the sites of fracture.[11] Infants with monilethrix may

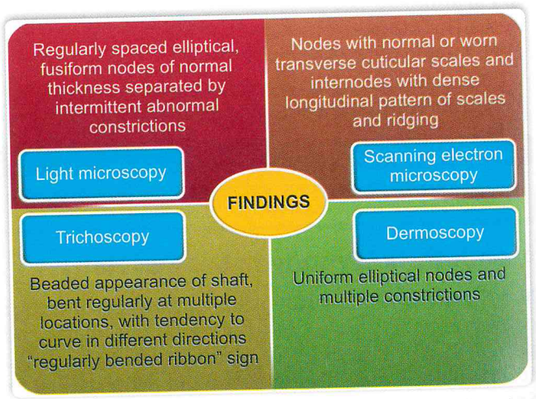


Fig. 4.3: Schematic representation of investigative findings in monilethrix

have a paucity of scalp hair, and it has been suggested that the examination of eyebrow hair may improve the likelihood of making the diagnosis in such settings.[12]

Advantages of simple microscopy: Inexpensive, rapid and non-invasive investigation.[12]

Scanning electron microscopy reveals nodes with normal or worn transverse cuticular scales and internodes with dense longitudinal pattern of scales and ridging. Trichoscopy reveals hair shafts with a beaded appearance, bent regularly at multiple locations, with a tendency to curve in different directions. These findings have been described as "regularly bended ribbon" sign by some authors.[11,13]

Dermoscopy (epiluminescence) of the papules reveals multiple stubs of broken hair arising from them with a similar beaded appearance.[14] Dermoscopy of hair reveals uniform elliptical nodes and multiple constrictions.[14]

Differential Diagnosis

The differential diagnosis between monilethrix and pseudomonilethrix can be made easily by trichoscopy.[15]

Treatment

There is no specific treatment for monilethrix although improvement has been reported with oral steroids, retinoids, griseofulvin and topical minoxidil.[16,17] Occasionally, regrowth of apparently normal hair may occur at the time of puberty or during pregnancy, suggesting some a hormonal influence.[17]

Pseudomonilethrix (Box 4.4)

In this condition, the hair shaft shows irregular flattened expanded areas that have an indented appearance. The beading is produced as an artifact of mounting hairs on glass slides and is of no significance.[18] On scanning electron microscopy, the widened beads can be seen to be an optical illusion. They merely represent artifactual indentations of the shaft viewed in cross section.[18] Although, some families with autosomal dominant transmission have also been described.[19]

Box 4.4: Pseudomonilethrix

Irregular flattened expanded areas on hair shaft with an indented appearance which is an artifact of mounting hairs on glass slides with no significance

Pili Torti (PT) (Synonym: Twisted hair, Corkscrew Hair[18])

In Latin, "pilus-hair", "torti-twisted".[20] It is characterized by hair shafts which are flattened and twisted at angles of about 180° with 4–5 twists at irregular intervals but in the same direction, giving it a spangled (glittering piece of metal) **(Box 4.5)** appearance in reflected light.[20] Fractures occur within the twists, which is the weakest point.[21] Occasional twists of less than 180 degrees do not qualify as true pili torti. These incomplete twists may occasionally occur in normal hair (seen in African hair and in the pubic/axillary hairs of other races).[18] Isolated twisted hairs are also seen in normal scalp, but in PT, the hairs appear in remarkably high number and density.[22]

Pili torti or 'twisting hair dystrophy' may be congenital, sporadic or acquired. Congenital pili torti may be seen as an isolated defect or in association with many different abnormalities and syndromes **(Table 4.1)**.[22]

Pathogenesis

The inheritance patterns can be autosomal dominant, autosomal recessive or sporadic in classic type. A limited number of cases have been reported and no gene defect has been elucidated. An autosomal dominant inheritance is seen in late-onset pili torti.[21] Bjornstad syndrome (congenital sensorineural deafness and PT) has been mapped to chromosome 2q34-36, with autosomal recessive inheritance pattern.[23] Genes encoding the major structural components of hair (cytokeratins and IFAPs) are particularly good candidate for mutations that account for the distinct manifestations of the disease.[23]

Box 4.5: Spangled appearance

- Hair shafts which are flattened and twisted at angles of about 180° with 4–5 twists at irregular intervals but in the same direction, giving it a glittering piece of metal appearance in reflected light
- Fractures occur within the twists, which is the weakest point

Table 4.1: Associations of pili torti

Associations with pili torti
❑ Inherited or congenital:
– Classic pili torti (Ronchese): Early onset
– Beare type: Late-onset PT
❑ Syndromal PT:
– Menke's kinky hair syndrome
– Bjornstad's syndrome
– Bazex syndrome
– Conradi-Hunermann syndrome
– Crandall's syndrome
– Citrullinemia
– Trichothiodystrophy
– Salti-Salem syndrome
– Laron syndrome
– Mitochondrial diseases
– Some ectodermal dysplasias
❑ Acquired:
– Cicatricial alopecia (due to distortion of the hair follicle caused by fibrosis by repeated trauma[21])
– Drugs: Isotretinoin, acitretin

Box 4.6: GRACILE

Growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis and early death

Genetic mapping of the region 2q34-36 revealed a mutation in BCS1L, which encodes an ATPase required for the assembly of a mitochondrial complex.[24] The BCS1L protein plays a role in the assembly of mitochondrial complex III and in the electron-transport chain of energy production.[24] Patients with Bjornstad syndrome have mutations in BCS1L that alter protein-protein interactions, whereas patients with GRACILE **(Box 4.6)** syndrome, a multi-system lethal mitochondrial disorder, have altered adenosine triphosphate binding.[24]

Clinical Features and Types

In pili torti, hair is often normal at birth, but is gradually replaced by abnormal twisted hairs that may be detected as early as the third month. Affected hairs are brittle, fracture easily, and do not grow to any considerable length.[18] Patients present with a sparse and short coarse stubble over the entire scalp and may have a few circumscribed bald patches.

Classic pili torti: It is more common in females, primarily those with thin blond hair.[22] It may also be part of ectodermal dysplasia syndrome, associated with keratosis pilaris, widely spaced teeth, nail dystrophy, corneal opacities, cleft lip/palate and occasionally ichthyosis.[22]

Late-onset variant pili torti: It tends to manifest after puberty with patchy alopecia.[18] In some pedigrees of this type, an association with mental retardation has been reported.[25]

Pili Torti and Deafness

1. **Björnstad syndrome (Box 4.7)** is an autosomal recessive condition characterized by sensorineural hearing loss and pili torti.[24] The hearing loss in the Björnstad syndrome is congenital and of variable severity. Pili torti is recognized early in childhood.[24]
2. **Crandall syndrome** is similar with findings of hypogonadism.[26]

Box 4.7: Bjornstad syndrome

- Autosomal recessive
- Mutation in BCS1L, which encodes an ATPase required for the assembly of a mitochondrial complex (chromosome 2q34-36)
- Congenital sensorineural deafness and PT

Mental retardation is rarely associated with either.[27] The severity of hair shaft abnormality has been shown to correlate with the severity of hearing loss.[27]

Investigations (Figure 4.4)

On light microscopy, groups of three or four (up to 20) regularly spaced twists, each 0.4-0.9 mm in width, may be seen at irregular intervals along the shaft in some hairs within a sample.[28] Light microscopy remains a more flexible tool in terms of adapting the method to allow use of cross-polarized light sources and histological mountant to enhance light penetration and detection of detail within the hair shaft. It also has a greater resolution for smaller or more subtle abnormalities, including fractures (to examine milder forms of monilethrix or pili torti).[29]

Trichoscopy in pili torti shows typical, regular twists of the hair shaft along the long axis, which is best visible at 70-fold and higher magnifications. The 20-fold magnification demonstrates hair shafts with sharp bending at irregular intervals.[15]

Treatment

The twisting hair dystrophies are a diverse group and prognosis is variable. Its frequent association with sensorineural hearing loss (as in Björnstad syndrome and Crandall syndrome) emphasizes the importance of early auditory testing in children with this hair defect. Minimizing trauma is the key aim. There are several cases reports of PT which have improved after an episode of alopecia areata.[20] Patients with true pili torti can be reassured that most will improve at puberty.[18]

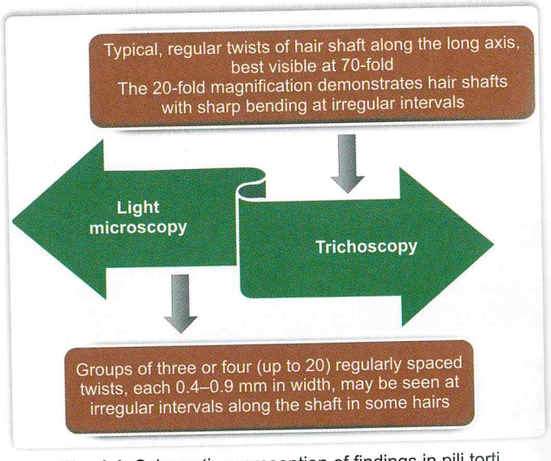


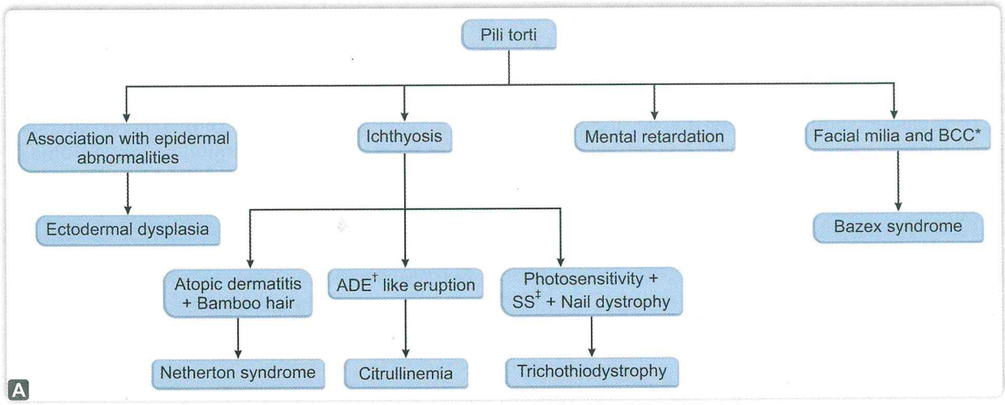
Fig. 4.4: Schematic represention of findings in pili torti

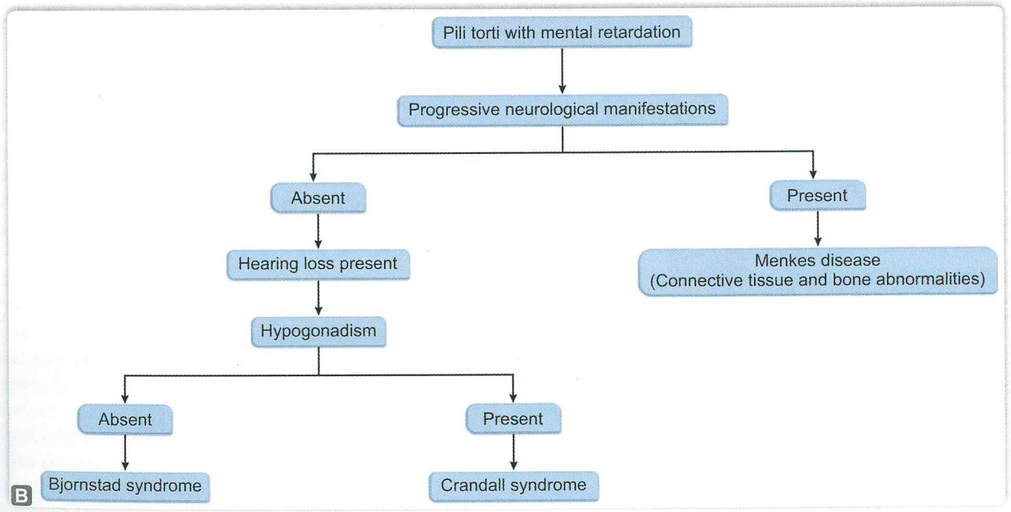
Differential Diagnosis (Figures 4.5A and B shows Algorithm to Diagnose Disease Associated with Pili Torti)

1. Monilethrix: It is often confused with PT, since irregular torsions along the hair shaft resemble the moniliform appearance.[22] Examination of hair with light microscopy or trichoscopy differentiates these two conditions.
2. Spun glass hair or uncombable hair **(Box 4.8)**: Children with this disorder have pili trianguli et canaliculi, which may be confused with the PT.[21] Characteristic findings are triangular or kidney-shaped hairs seen in cross-sections and longitudinal grooves which are responsible for the frizzy, stand-away appearance of uncombable hair.[22] Hair shafts are not twisted as in PT. The hair cannot be combed flat.

Box 4.8: Spun glass hair

- Uncombable hair
- Characterized by pili trianguli et canaliculi-triangular or kidney-shaped hairs seen in cross-sections and longitudinal grooves which are responsible for the frizzy, stand-away appearance





Figs 4.5A and B: Shows the algorithm to diagnose diseases associated with pili torti

*BCC- Basal cell carcinoma, †ADE- Acrodermatitis enteropathica, ‡SS- Short stature

Menkes Disease (Synonyms: Kinky Hair Disease, Trichopoliodystrophy, Steely Hair Disease)

Menkes disease (MD) is a lethal multisystemic disorder of copper metabolism.[30] This is an X-linked recessive condition characterized by skin and hair hypopigmentation, progressive neurologic degeneration with mental retardation, bone and connective tissue alterations with soft doughy skin and joint laxity, and vascular abnormalities, including aneurysms and bladder diverticula.[21]

Pathogenesis

Pili torti with copper deficiency was first described by Menkes, who listed cuproenzymes which may account for features of the disoder **(Table 4.2)**.[22] It is caused by mutations in the ATP7A gene encoding a copper-translocating P-type ATPase, which contains six N-terminal copper-binding sites (CBS1–CBS6).[31] The vast majority of ATP7A mutations are intragenic mutations or partial gene deletions.[30]

ATP7A is an energy-dependent, transmembrane protein, which is expressed in almost all organs except liver where ATP7B is predominantly expressed.[30] ATP7A is involved in the delivery of copper to the secreted copper enzymes, in presence of normal intracellular copper levels and in the export of surplus copper from cells, in the presence of increased copper levels **(Table 4.2 and Figure 4.6)**.[32] Mutations in the MNK gene lead to accumulation of intracellular copper and prevent copper transport to copper dependent enzymes such as lysyl oxidase. With excess intracellular copper, RNA synthesis of metallothionine is triggered, which chelates the accumulated copper to prevent cellular toxicity, but further reducing the transfer of copper to enzymes.[21]

There is no obvious correlation between the mutations and the clinical course of MD. In general patients with a milder phenotype [like occipital horn syndrome (OHS)]

Table 4.2: Cuproenzymes and consequences in their deficiencies

Enzyme	Function	Manifestations in deficiency
1. Lysyl oxidase	Cross-linking of collagen/elastin	Connective tissue abnormalities, laxity of skin/joints, vascular abnormalities, bony abnormalities, and bladder diverticula
2. Tyrosinase	Melanin formation	Depigmentation of hair and skin pallor
3. Cytochrome C oxidase	Electron transport chain	Hypothermia, CNS degeneration, muscle weakness, ataxia and energy deficiency
4. Peptidylglycine α-amidating monooxygenase (PAM)	Neuropeptide processing	Unknown, possible neurodegeneration
5. Superoxide dismutase	Free radial scavenger	Low tolerance of oxidative stress, demyelination
6. Cross-linkase	Cross-linkage of keratin	Coarse, brittle hair
7. Dopamine B hydroxylase	Catecholamine production	Hypothalamic imbalance, hypothermia, hypotension

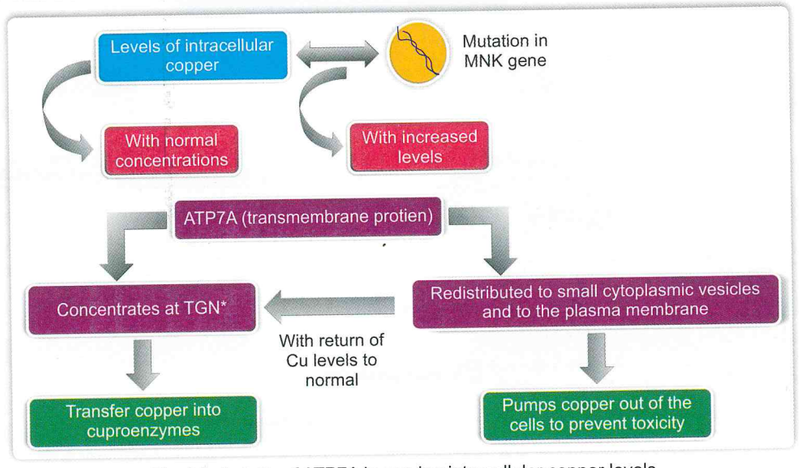


Fig 4.6: Activity of ATP7A in varying intracellular copper levels
*TGN: Trans-Golgi network

have a higher proportion of mutations, which lead to a partially functional protein or result in reduced amounts of an otherwise normal protein.[33]

Clinical Features

MD shows considerable variability in its severity. Classical MD is the most severe form, while OHS is the mildest recognized form.[34]

Classical MS

Affected infants may develop normally until the onset of symptoms, usually between age of 5 weeks and 5 months.[22]

Pregnancy is usually uncomplicated or there may be premature labor and delivery.[30] Cephalohematomas and spontaneous fractures are occasionally observed at birth. In the early neonatal period, patients may present with prolonged jaundice, hypothermia, hypoglycemia and feeding difficulties.[30] Umbilical and inguinal hernias have also been reported.[35]

Affected males have pili torti, growth retardation and progressive psychomotor retardation. Female carriers may have more limited features due to random X inactivation. Affected females demonstrate patchy areas of short, broken, and twisted hairs, along Blaschko's lines on their scalp.[18] As copper is a cofactor for tyrosinase, affected hairs have characteristically hypopigmented "kinky hair" appearance.[35]

The first sign of MD may be unusual sparse and lusterless scalp hair that becomes tangled on the top of the head at the age of 1–2 months. At this time the appearance may be described as being odd, with pale skin, frontal or occipital bossing, micrognathia, pudgy cheeks, and a rather expressionless appearance. However, these changes are often too subtle to attract attention. Initial psychomotor development is usually unremarkable, with normal babbling and smiling up to about 2–4 months of age. The baby then ceases to develop further and gradually loses some of the previously developed skills. The developmental regression becomes obvious around 5–6 months of age.[30]

Subsequently, hypotonia, seizures, failure to thrive, poor eating, vomiting, and diarrhea develop.[36] As the motor dysfunction progresses, spontaneous movements become limited and drowsiness and lethargy emerge. The patients are typically diagnosed at 3–6 months of age, often due to the abnormal hair that is a striking feature of the disease. The hypopigmented or depigmented hair resembles and feels like steel wool; it is lusterless and friable, especially in the areas of the scalp subjected to friction.[30]

Epilepsy is a major feature of Menkes disease; seizure types include focal or multifocal tonic-clonic, myoclonic, infantile spasms, and status epilepticus.[36]

Vascular, urogenital and skeletal abnormalities are numerous.

Urological complications include

1. Congenital—bladder diverticula, hydronephrosis, vesicoureteral reflux, rupture of the bladder diverticulum, hydroureter, obstruction of bladder outflow and rupture of the kidney
2. Acquired—urinary tract infection and bladder calculi.[37]

Skeletal abnormalities include pectus excavatum or pectus carrinatum, and spontaneous fractures due to generalized osteoporosis. The joints are hyperextensive, and loose and dry skin may be observed very early. Thick, scaly seborrheic dermatitis is also a frequent feature.[30] Routine ophthalmoscopy is usually normal, but in later stages patients frequently fail to follow visual stimulus.

Late manifestations of the disease are blindness (secondary to optic atrophy), subdural hematoma, and respiratory failure. Most patients die within the third year of life due to infection, vascular complications (such as sudden and massive cerebral hemorrhage due to vascular rupture), or from the neurological degeneration itself.[30]

Occipital Horn Syndrome (OHS)

The mildest form is primarily characterized by pronounced connective tissue symptoms such as soft doughy lax skin and diverticula, and little neurologic aberration.[31]

It is called OHS because of bony projections (exostoses) which occur on the occipital bone of the skull. These are symmetric exostoses (occipital horns - **Box 4.9**) protruding from the occipital bone and pointing down.[21] These are formed as a result of the calcification in the trapezius and sternocleidomastoid muscles at their attachments to the occipital bone.[38]

The skin may appear wrinkled and loose at birth. The extent of skin laxity is variable and may increase with age, resulting in droopy wrinkles around the trunk. Within days similar to classic MS, neonatal problems such hypothermia, jaundice, hypotonia, and feeding difficulties may develop.[30] Facial appearance gradually becomes distinctive. Unusual features include long, thin face, often with a high forehead, down-slanting eyes, hooked or prominent nose, long philtrum, high arched palate, and prominent large ears **(Box 4.10)**.[30]

Box 4.9: Occipital horns

- Symmetric exostoses protruding from the occipital bone and pointing down
- Result of the calcification in the trapezius and sternocleidomastoid muscles at their attachments to the occipital bone

Box 4.10: Dysmorphic facies of OHS

Long, thin face, often with a high forehead, down-slanting eyes, hooked or prominent nose, long philtrum, high arched palate, and prominent large ears

Motor development is delayed due to muscular hypotonia and is associated with unusual clumsiness. Height is usually normal, while mild disproportion with long trunk, narrow chest and shoulders, thoracolumbar kyphosis or scoliosis, and pectus deformity are common. The joints are hypermobile.[30] Childhood-onset seizures, dysarthric speech, elbow deformities and dislocations, bladder diverticula, recurrence of the inguinal hernia and tortuous vessels are the features of OHS.[38]

Hair is usually not conspicuously abnormal, although some patients may have lusterless and unusually coarse hair. Vascular anomalies, such as varicose veins are common, and arterial aneurysms have also been described. A particular problem is orthostatic hypotension. The intellectual capacity is described as low to borderline normal. Pubertal development is normal.[30]

Central nervous system similarities shared by classic Menkes' syndrome and occipital horn syndrome include generalized cerebral and cerebellar atrophy, cerebellar and cortical neuronal loss, depletion of the central nervous system white matter, and cerebellar heterotopias (reduplication of the cerebral vasculature).[38]

Clinical problems become gradually obvious, and the first signs that bring the child to medical attention may be intractable diarrhea or recurrent urinary tract infections. In spite of these problems, diagnosis of OHS is usually made only around 5–10 years of age.[30]

Investigations

Initial diagnosis of MD is suggested by clinical features (especially typical hair changes) and supported by demonstration of reduced levels of serum copper and ceruloplasmin.[30]

Box 4.11: Rapid diagnostic test of MD in neonatal period

Plasma catecholamine analysis (ratio of DOPA to dihydroxyphenylglycol) indicative of dopamine β-hydroxylase deficiency

The recognition of MD in early neonatal period is difficult and these markers should be interpreted with caution, as their levels may be within the range of normal infants in the first week; they are higher than normal in the cord blood of affected infants and fall gradually after 4 weeks of age.[22] In this period, plasma catecholamine analysis (ratio of DOPA to dihydroxyphenylglycol) indicative of dopamine β-hydroxylase deficiency may be the choice as a rapid diagnostic test **(Box 4.11)**.[39]

Hair Examination (Figure 4.7)

Light microscopy of either eyebrow/scalp hair shows classic short, pale "kinky hairs" with twists, which are completely rotated through 180° around their long axis at irregular intervals in the shaft.[12] Other hair changes include varying hair shaft diameter (monilethrix) and fragmentation at regular intervals (trichorrhexis nodosa).[30] It is important to examine as many strands of hair as possible because not every hair may demonstrate morphological abnormalities in the lengths examined. This may not always be easy, because many infants often have sparse, fine, wispy, blond hair. So, examination of eyebrow hair may improve the likelihood of diagnosis.[12]

Examination of scalp hair using dermoscopy shows twisted hair with greater clarity than with the light microscopic examination.[29]

Different clinical features of MD are detected by using other laboratory investigations like cystourethrography,

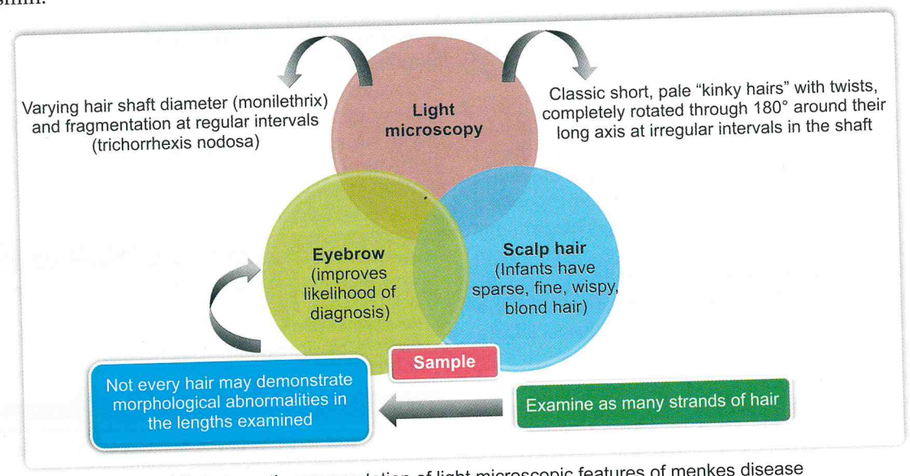


Fig. 4.7: Schematic representation of light microscopic features of menkes disease

arteriography, radiography, computed tomography, and magnetic resonance imaging.

Radiographic features of patient with classical MD includes generalized osteoporosis, metaphyseal flaring and spurs in the long bones, diaphyseal periosteal reaction and thickening, and Wormian bones in the cranial sutures.[30] Other skeletal abnormalities include loss of curvature of the cervical spine, pectus excavatum, short ribs, short and widened clavicles, deformed radii with radial head dislocations and bilateral ulnar deformities.[38] In OHS, multiple horns protruding down from occipital bones and short and broad clavicles are seen.[38]

The CT and MR imaging reports on Menkes disease have shown severe neuronal loss that is manifested by diffuse cerebellar and cortical atrophy, white matter lesions and subdural hematoma or effusions.[35] Magnetic resonance angiography shows tortuosity of cerebral vessels.

EEG findings in MD include absence of age-appropriate features, background slowing and disorganization, polymorphic slow waves, focal or diffuse spike and waves, status epilepticus, and hypsarrhythmia.[36]

The specific diagnostic test for MD is the demonstration of the molecular defect in ATP7A. Detection of the genetic defect in a given family may take time, because of the large size of the gene and the variety of the mutations observed in different families.[30]

Carrier Identification and Prenatal Diagnosis (Table 4.3)

In at-risk families only male fetuses need to be evaluated, and rapid sex determination can be made using Y-chromosome-specific DNA sequences. Carrier determination by measuring radioactive copper accumulation in cultured fibroblasts is not reliable due to random X-inactivation, and mutation analysis should be performed. In informative families, the intragenic polymorphic markers may also be used for carrier detection.[30]

Table 4.3: Carrier detection and prenatal diagnosis

	Diagnostic tests
Carrier detection	Measuring radioactive copper accumulation in cultured fibroblasts, intragenic polymorphic markers
At-risk families	Only male fetuses need to be evaluated, and rapid sex determination made using Y-chromosome-specific DNA sequences
First trimester	The total copper content in chorionic villi can be measured directly by neutron activation analysis and atomic absorption
Second trimester	Copper accumulation is measured in cultured amniotic fluid cells

In at-risk pregnancies where the mutation of the family is unknown, biochemical analysis remains a possibility as identification of the genetic defect may be challenging in limited time. In the first trimester the total copper content in chorionic villi can be measured directly by sensitive and accurate methods like neutron activation analysis and atomic absorption, and in the second trimester copper accumulation is measured in cultured amniotic fluid cells. Although there are potential pitfalls for these analyses, they have been performed routinely at the Kennedy Center in Denmark since 1975.[40]

Differential Diagnosis

The diagnosis of Menkes disease may present problems in early neonatal period. Pili torti may develop later, as the primary fetal hair is usually normal.[22]

The roentenographic signs may not be evident until after 6 weeks of age. Menkes disease should be included in the differential diagnosis of unexplained rib and metaphyseal fractures, sub-dural hematomas, and neurological impairment in infants where the diagnosis of non-accidental injury such as in shaken baby syndrome is considered.[22]

Treatment

MD is a progressive disorder with poor prognosis and most of the patients die within 3 years of life in its severe form.[22] Treatment in major cases is mainly symptomatic. However, careful medical care, and possibly copper administration, may extend life span up to 13 years or even more.[30]

The specific treatment for MD is infusion of copper-histidine **(Box 4.12)**.[21] Objective of this treatment is to provide extra copper to the tissues and copper-dependent enzymes.[30] The full function of copper histidine and how it works is not well characterized. It must be administered early in life, because it may prevent but not reverse permanent neurologic damage.[41,42] Copper-histidine therapy has limited effects on connective tissue abnormalities and many patients subsequently die of these complications.[21]

Box 4.12: Copper histidine

- Specific treatment of MD
- To be administered early in life
- May prevent but not reverse permanent neurologic damage

Netherton Syndrome (Box 4.12) (Synonyms: Netherton's Disease, Bamboo Hair)

Netherton syndrome (NS) is an autosomal recessive inherited disorder characterized by congenital ichthyosis

Box 4.13: Triad of Netherton syndrome

- Trichorrhexis nodosa
- Ichthyosis linearis circumflexa
- Atopic diathesis

(ichthyosis linearis circumflexa ILC), trichorrhexis invaginata, and features of atopic dermatitis (AD) with high serum IgE levels[43] **(Box 4.13)**. Ichthyosis linearis circumflexa (ILC) was first described by Dr Comel in 1949. It consists of migratory polycyclic erythematous patches surrounded by a serpiginous overlying double-edged scale.[44] In 1958, Netherton[45] described a young girl with generalized scaly dermatitis and fragile nodular hair shaft deformities that he termed trichorrhexis nodosa (bamboo hair). Later, this was more appropriately renamed as trichorrhexis invaginata. In 1974, the clinical relationship between ichthyosis linearis circumflexa and Netherton's syndrome was established by Mevorah, et al.[46]

Pathogenesis

The syndrome is caused by the mutation in SPINK 5 gene, which is located on long arm of Chromosome 5. This gene codes for production of a protein LEKT1 (lympho-epithelial Kazal-type related inhibitor), which inhibits the enzyme serine proteinase in the outermost layer of the skin **(Figure 4.8)**.[47] LEKTI is expressed in the stratum granulosum of the epidermis, and it was shown that bioactive LEKTI fragments inhibit 3 major proteases involved in stratum corneum desquamation, kallikreins (KLK) 5, 7, and 14.[48] Lack of LEKTI led to kallikrein 5 (KLK5) and KLK7 proteolytic hyperactivity, resulting in desmoglein-1 degradation and, in turn, to abnormal corneodesmosome cleavage below the stratum corneum.[49] ELA2 is a new epidermal protease which is hyperactive in LEKTI-deficient epidermis.[50] ELA2 directly degrades (pro) filaggrin, promoting skin barrier impairment.

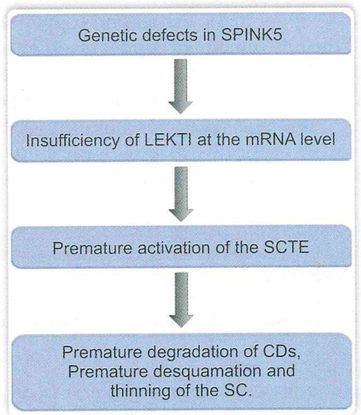


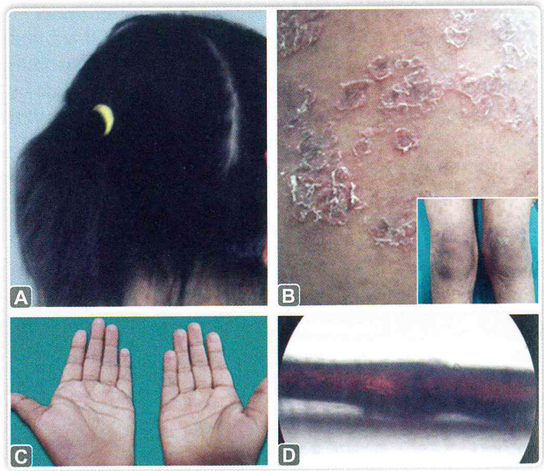
Fig. 4.8: Sequence involved in the pathogenesis of the skin lesions in NS

Abbreviation: SCTE—Stratum corneum tryptic enzyme, CDs—corneodesmosomes, SC—stratum corneum

Clinical Features (Figure 4.9)

At birth, infants exhibit generalized erythroderma and scaling, which is similar to other types of infantile erythroderma.[51] Continuous peeling of the skin can persist in NS similarly to peeling skin syndrome.[52,53] The congenital ichthyosiform erythroderma-like features can persist throughout life in the most severe cases or evolve into a unique milder condition known as ichthyosis linearis circumflexa, consisting of migratory, serpiginous, and erythematous plaques, which are bordered by a peculiar double-edged scale.[54]

Like ichthyosis linearis circumflexa, trichorrhexis invaginata (bamboo hair) is pathognomonic for NS.[47] Trichorrhexis invaginata causes patchy hair thinning, but rarely complete alopecia.[44] Trichorrhexis invaginata is a focal defect of the hair shaft that produces development of torsion nodules and invaginated nodules **(Box 4.14)**. The proximal element of the node overlaps the distal portion, causing an intussusception.[44] Other hair shaft abnormalities manifested as pili torti (twisted hair), helical hair and trichorrhexis nodosa. This may not be detected



Figs 4.9A to D: (A) Sparse brittle hair; (B) Ichthyosis linearis circumflexa- double edge scales (Inset showing scaly lesions over knees; (C) Hyperlinearity of palm noted as a component of atopic diathesis, child also had atopy; (D) Microscopic appearance of bamboo hair. (*Courtesy:* Department of Dematology, STD and Leprosy, BMCRI, Bengaluru)

Box 4.14: Trichorrhexis invaginata ('bamboo hair')

- Pathognomonic for NS
- A focal defect of hair shaft that produces development of torsion nodules and invaginated nodules
- The proximal element of the node overlaps the distal portion, causing an intussusception
- Causes patchy hair thinning, but rarely complete alopecia

at birth and may disappear with age.[55] These hair defects can be found in scalp, eyebrow or eyelash hairs. Ito, et al.[56] have reported the hair shaft abnormality to be secondary to intermittent incomplete formation of disulfide bonds in the keratogenous zone.

Affected individuals have a broad range of atopic manifestations, including eczema-like rashes, hay fever, angioedema, allergic rhinitis, asthma, food allergy, heat intolerance, eosinophilia and high levels of IgE in the serum.[47]

Other associated manifestations include aminoaciduria, recurrent infections, mental and neurological retardation, seizures or spastic diplegia, hyper/hypogammaglobulinemia and impaired cellular immunity.[47] Gastrointestinal involvement in the form of dermopathic enteropathy with villous atrophy and diarrhea may lead to poor weight gaining in early childhood.[55] NS patients with ichthyosis linearis circumflexa have a normal general development, whereas those presenting with generalized exfoliative erythroderma display life-threatening complications such as hypernatremic dehydration, electrolyte imbalances, hypothermia, failure to thrive, and recurrent infections resulting in high postnatal mortality. These complications might be attributed to the severe alteration of the epidermal barrier function.[54]

Investigations

Hair microscopy is crucial for diagnosis of NS and shows **(Box 4.15)**:

1. 'Ball and socket' or 'pencil in cup' configuration with various patterns.
2. Bamboo hair: A shallow invagination of the distal shaft into the proximal part of the shaft.
3. Tulip-like form: A deeper invagination and long sides of the 'cup.'
4. Circumferential strictures: These represent the earliest stage of the invagination.[57]

Box 4.15: Hair findings in NS

- 'Ball and socket' or 'pencil in cup' configuration
- Bamboo hair
- Tulip-like form
- Circumferential strictures

Trichorrhexis nodosa and pili torti also occur. Often only 20–50% of hair is affected; therefore hairs should be cut (not plucked) from multiple areas of the head to be examined. Hairs can also be examined from axillary, pubic, and eyebrow regions for abnormalities.[44]

Histopathologic examination of NS skin reveals a 'psoriasiform' epidermis, hyperplasia of the subcorneal epithelium (acanthosis) with varying degrees of epidermal invaginations into the dermis (papillomatosis).[54]

Electron microscopic examination of skin lesions of NS reveals abnormalities including premature secretion of lamellar bodies, and a less cohesive stratum corneum with loosely packed parakeratotic corneocytes which are often separated by elongated clefts with fewer or greatly reduced numbers of desmosomes and the presence of electron-dense material in the interstices of the stratum corneum.[58]

Peripheral eosinophilia is commonly found.[44] The serum IgE level is often elevated, sometimes to extreme levels. Positive skin tests or RAST responses to environmental and/or food allergens are commonly observed.[59]

Differential Diagnosis

The diagnostic features of NS are helpful in making a differential diagnosis of other causes of neonatal and infantile erythroderma.

Petechiae and purpura due to thrombocytopenia are typical signs in Wiskott-Aldrich syndrome; diarrhea and vesiculobulbous lesions distributed in a periorificial and acral pattern on the face, scalp, hands, feet and the anogenital areas are typical signs in acrodermatitis enteropathica; diarrhea and periorificial eczematous eruption are typical signs in biotinidase deficiency.[60]

Treatment

Many treatments have been attempted in patients with Netherton syndrome. Patients with Netherton syndrome are likely more susceptible to systemic absorption of medication, and are therefore at increased risk to experience adverse reactions to topical therapies.[55]

A crucial point in topical therapy is an intensive skin care by application of hydrophobic creams without additives or with a low dose of urea, for treating only specific parts of the body surface daily.[22]

The cutaneous manifestations of NS are frequently resistant to conventional therapy (emollients and topical corticosteroids).[61] Topical calcineurin inhibitors - tacrolimus and pimecrolimus have been demonstrated to improve the skin findings and quality of life in patients with several chronic dermatoses, including atopic dermatitis. The use of topical tacrolimus has been associated with

significant systemic absorption in children with NS. Use of tacrolimus ointment should be reserved for the short-term management of flares and should be considered only when the benefits outweigh the risks.[22] The absorption of pimecrolimus through the skin in patients with NS is, by contrast, considerably diminished.[61]

Various treatments have been attempted, including low-dose oral corticosteroids, etretinate, and psoralen ultraviolet A therapy.[44] The use of oral retinoids has yielded mixed results.[21]

Trichothiodystrophy (Acronyms: PIBIDS, IBIDS and BIDS)

(From Greek: tricho- meaning hair; thio- sulfur; dys-faulty; trophy- nourishment).

Trichothiodystrophy (TTD) is a heterogeneous group of autosomal recessive disorders characterized by brittle sulfur-deficient hairs.[18] In 1979, Price coined the term "trichothiodystrophy," which encompasses a wide spectrum of neuro-cutaneous findings, to describe the unifying feature.[62]

TTD can be associated with a spectrum of symptoms affecting organs of ectodermal and neuroectodermal origin. These include nail dystrophy, mental and growth retardation, ichthyosis, decreased fertility, and cutaneous photosensitivity, but not cancer.[63] Many terms have been proposed to subcategorize patients by groups of clinical features, which are variable (up to 100). Eight subgroups have been categorized by Itin, et al.[64] and include **(Figure 4.10)**:

1. BIDS - Brittle hair, intellectual impairment, decreased fertility, and short stature
2. IBIDS - BIDS + Ichthyosis
3. PIBIDS - IBIDS +Photosensitivity
4. SIBIDS - Otosclerosis + IBIDS
5. ONMR - Onychotrichodysplasia, chronic neutropenia, and mentral retardation
6. Tay - Brittle hair, intellectual impairment, short stature, Non-bullous congenital ichthyosiform erythroderma
7. Sabinas – Brittle hair, ichthyosis, decreased fertility, ocular abnormalities
8. Pollitt syndromes - Brittle hair, intellectual impairment short stature.

Pathogenesis

TTD is a member of a group of nucleotide excision repair disorders which includes xeroderma pigmentosum (XP).[65] Cells from many TTD patients have defects in nucleotide excision repair (NER) as well as in transcription, which eliminates ultraviolet light induced cyclobutane pyrimidine dimers, pyrimidine pyrimodone photoproducts (6-4PP), and intrastrand crosslinks in the DNA.[66] NER comprises a complex-overlapping network of enzymatic pathways for DNA repair with approximately 30 gene products involved.[21]

TTD patients have abnormal production of transcription factor II H (TFIIH), a general transcription factor active in basal transcription and nucleotide excision repair, due to mutations in genes encoding 3 subunits of TFIIH— ERCC2 (XPD), ERCC3 (XPB), and GTF2H5 (TTDA) - most with mutations of XPD. Photosensitive TTD patients with (~50%) have defective nucleotide excision repair mechanisms

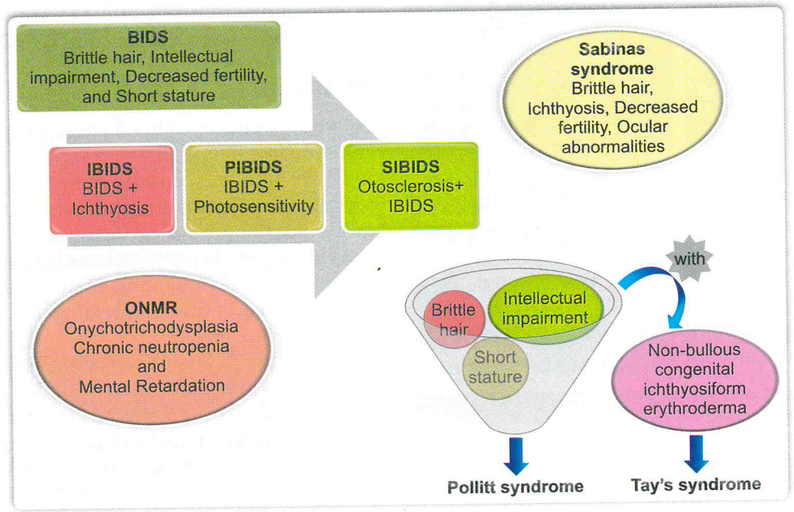


Fig. 4.10: Schematic representation of syndromes associated with trichothiodystrophy

due to reduced amounts of TFIIH, without the increased incidence of skin cancer seen in xeroderma pigmentosum, another autosomal recessive disorder of DNA repair demonstrating mutations in XPB and XPD.[67] The severity of symptoms ranges widely and correlates with the amount of damaged TFIIH and abnormal transcription product.[67]

Nakabayashi K, et al.[68] have identified gene C7orf11 as mutated in patients with non-photosensitive TTD. The protein of this gene demonstrates a nuclear localization, and C7orf11 may have a role in transcriptional processes but have no role in DNA repair.[68]

Clinical Features

The clinical features in different patients are remarkably varied ranging from only hair involvement to severe neurological and somatic developmental abnormalities.

Pregnancy is usually uncomplicated. Many TTD patients were born prematurely or were small for gestational dates.[69]

TTD is associated with several disorders such as mental and physical retardation, low-set and posteriorly rotated ears, nail abnormalities, follicular keratosis, erythroderma, hypohidrosis, ocular dysplasia, dental caries and hypoplasia and cryptorchidism.[70]

Cutaneous Manifestations

Common skin finding is lamellar ichthyosis; many of the patients are born with the collodion membrane. Ichthyosis may be seen in almost all age groups.[62] Crovato and Rebora underlined that if ichthyosis developed in late infancy, patients are affected by IBIDS, and if congenital ichthyosis is present, Tay syndrome must be considered.[71] Follicular keratosis as a sign of ichthyosis, pruritus, eczema, freckles, telangiectasias, and actinic cheilitis have also been found.[70]

Photosensitivity is the second most common skin finding reported with TTD.[62] Photosensitivity may be extreme in patients affected by PIBIDS; in particular photosensitivity to ultraviolet (UV) B and for UVA is impressive.[70] Interestingly, photosensitivity seems to diminish with age, and it does not affect patients with congenital ichthyosis, but only those with ichthyosis that develops later in infancy.[71]

TTD patients, while sun sensitive, do not develop the pigmentary abnormalities of XP and do not have an increased frequency of skin cancer.[69]

Hair Abnormalities

The most frequent hair findings are brittle hair or hair shaft abnormalities. Patients with TTD share the distinctive feature of short, brittle hair. Persistent alopecia is often found; eyebrows, eyelashes and body hair may also be affected.[22] Trichoschisis is characteristically seen on light microscopy. Under polarized light, the characteristic "tiger tail" pattern of alternating bright and dark diagonal bands is seen in most TTD patients and is rarely found in normal individuals **(Box 4.16)**.[21] The underlying cause of the tiger tail pattern is unknown, but it is hypothesized to be secondary to the irregular sulfur content of the hair shaft.[72] This pattern can be seen in utero, but its absence does not exclude the diagnosis. The sulfur and cystine content of the hair is reduced to approximately 50% in both the cuticle and the cortex, with a marked absence of high sulfur content proteins and an increase in low sulfur content proteins in the hair shaft.[21]

Box 4.16: Tiger tail appearance in TTD

- It is a polarized light microscopy feature of hair shaft
- Refers to alternating bright and dark diagonal bands
- Hypothesized to be secondary to the irregular sulfur content of the hair shaft
- Absence does not exclude the diagnosis

Central Nervous System Manifestations

These include microcephaly, spasticity, ataxia, and altered reflexes.[67] Generalized dysmyelination is the most common neuroimaging abnormality in TTD.[67] While TTD patients may have intellectual impairment, they usually are very social and have an outgoing, engaging, friendly personality. Typically, standard intelligence tests appear to underestimate their capability for social interactions. The MRI shows predominantly hypomyelination of the white matter of the cerebrum. Atrophy of the brain is not a major feature. Some patients may have calcification of the basal ganglia.[69] Impaired transcription of structural components of myelin and of high-sulfur content molecules important in central nervous system (CNS) development, such as neurocan and phosphacan, has been implicated in the dysmyelination present in TTD.[67]

Genitourinary System

Hypogonadism, cryptorchidism, delayed pubertal development, poor sexual maturation and partial panhypopituitarism have been reported in few patients of TTD.[62]

Cardiovascular System

Cardiac defects in the form of cardiomyopathy, pulmonic stenosis and ventricular septal defect have been reported in some patients of TTD.[73] Toelle, et al.[73] suggests to monitor TTD patients for developing severe cardiomyopathy using echocardiography.

Nail Abnormalities (Box 4.17)[62]

Box 4.17: Nail changes in TTD

Onychodystrophy, brittle nails, hypoplasia, koilonychia, splitting (onychoschizia), peeling, ridging

Skeletal System

They may have skeletal abnormalities including delayed bone age, peripheral osteopenia and central osteosclerosis.[69] Joint abnormalities including contractures and joint dislocation/subluxation, clinodactyly of 5th finger, short limbs, tapering fingers, syndactyly and joint hypermobility have been noted.[62]

Others

Ophthalmic findings include cicatricial ectropion with bilateral corneal opacities, superficial punctate keratitis and a high frequency of congenital cataracts.[74]

Immunodeficiency with history of multiple infections has also been noted.[69]

Investigations (Figure 4.11)

Light microscopy of scalp hair reveals numerous clean-cut transverse fractures (trichoschisis), trichorrhexis nodosa-like fractures, ribboning and alterations of the cuticle.[75] Higher magnification reveals ridging of the cuticle layer and a cribiform-like shaft surface.[66] Some cases may show spherical hair shaft and abrupt narrowing.[66]

Cross-polarizing microscopy shows the alternating dark and light bands that give the shaft "tiger tail pattern".[75]

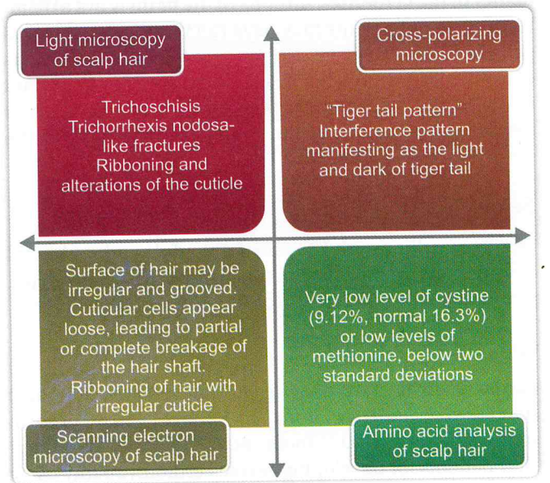


Fig. 4.11: Schematic representation of investigative findings in trichothiodystrophy

This pattern arises through sinusoidal distortion of the weakened cortical keratin fibrils. As they flow through the sine wave morphology they act as polarizing filters in their own right giving rise to the interference pattern manifesting as the light and dark of the tiger tail.[76]

Scanning electron microscopy allows detailed examination of hair shaft abnormalities. The surface of the hair may be irregular and grooved. The cuticular cells appear to be coming loose, leading to partial or complete breakage of the hair shaft. Ribboning of the hair with an intact yet irregular cuticle may also be noted.[66]

Amino acid analysis of scalp hair reveals a very low level of cystine (9.12%; normal value 16.3%)[75] or low levels of methionine, below two standard deviations.[76]

MRI Findings

Magnetic resonance imaging (MRI) discloses diffuse signal hyperintensity throughout the cerebral white matter on T2-weighted images. In normal brain, the signal intensity of white matter on T2-weighted images is dark compared with the cerebral cortex due to myelin sheaths. This finding is compatible with a diffuse hypomyelination of cerebral white matter. The lateral ventricles are moderately dilated, indicating a loss of periventricular tissue, probably as a consequence of hypomyelination.[75]

Other nonspecific structural abnormalities observed in TTD include cortical heterotopias, partial agenesis of the corpus callosum, perimedullary fibrosis of the spinal cord, and intracranial calcifications.[67]

Differential Diagnosis

1. It is important to distinguish tiger tail banding from non-specific banding that occurs without abnormalities or undulation of the hair shaft. All TTD hairs display tiger tail banding with polarizing microscopy and with rotation of the microscope stage.[66]
2. Conditions such as anorexia nervosa and acrodermatitis enteropathica, where malnutrition or malabsorption leads to secondary hair changes share features with TTD. However, with improvement in bowel function, assessment demonstrates normalization of the hair. These diseases are correctable with diet. In acrodermatitis enteropathica, the distinction between the primary disease (e.g. Argininosuccinic aciduria) and the hair features of TTD is important as specific management is required for the primary diagnosis. Urinary amino acids analyses helps in such cases.[76]
3. Differential diagnosis for diffuse dysmyelination **(Box 4.18)** in the absence of gray matter abnormalities in children include Pelizaeus-Merzbacher disease, 18q-syndrome, and Salla disease.[67] Although inborn errors of metabolism may result in delayed myelination mimicking the diffuse dysmyelination present in TTD, atrophy and distinct clinical syndromes generally allow differentiation.[67]

Box 4.18: Diffuse dysmyelination

- TTD
- Pelizaeus-Merzbacher disease
- 18q-syndrome
- Salla disease

Treatment

There is no specific treatment for TTD and there is no trend towards spontaneous resolution.[18] Associated abnormalities require attention, particularly minimizing sun-related skin damage.[22] Dietary cytosine supplementation has been suggested, but its value is unproven.

Ectodermal dysplasia

Ectodermal dysplasia (ED) defines a family of congenital, developmental disorders with primary defects in at least two ectoderm-derived structures.[77] The main tissues of ectodermal origin affected in EDs are hair, teeth, nails and eccrine glands. Hair shaft abnormalities are found in various ectodermal dysplasias. In general, hair may be sparse, curly, and fair. Alopecia may be due to hair shaft anomaly with increased fragility, or to hypotrichosis.[22]

Several classifications have already been proposed on the basis of clinical point of view;[78] molecular genetic data and clinical findings,[79] and the recent one by Lamartine[80] on the basis of functions of genes.

Pathogenesis

Ectodermal dysplasias are the result of molecular causative defects involving, for instance, widely expressed proteins with essential roles in control of cell cycle progression, in replication and/or DNA repair.[79] Embryogenesis is regulated by a number of complex signaling cascades that are critical for normal development.[22] One of the best investigated pathways is the sonic hedgehog, leading to interactions with transcription factors within the Gli family. Dysregulation of this pathway lead to different diseases including some from the spectrum of EDs.[79]

Clinical Features

The spectrum of primary hair shaft abnormalities reported in ectodermal dysplasia ranges from flattened hair, twisted hair, longitudinal impressions to a combination of both twisting and impressions of the hair shaft in pili torti et canaliculi and corkscrew hairs.[77]

These abnormalities often present as alopecia, one of the features of subtypes in EDs.[22] Hair is generally fair, curly and scanty, sometimes brittle and uncombable. Body hair is often diminished or absent. Eyebrows and eyelashes may be lacking.[22]

The different shaft abnormalities may be detected in various ectodermal dysplasias, sometimes in the same patient. Whereas longitudinal grooves are a frequent finding; pili torti et canaliculi appears to be a characteristic finding in ectodermal dysplasias combined with clefting of lip/palate **(Box 4.19)**.[77] There thus seems to be a crescendo in structural abnormalities, with increasing shaft defects associated with the degree of clinical dysmorphology, with corkscrew hairs as an exaggeration of pili torti et canaliculi.[81]

Secondary unspecific changes, such as trichorrhexis nodosa and loss of cuticle, are due to the increased fragility often seen in these hair shaft abnormalities.[77] Differences in the calibre of the hair and cuticular irregularities are other findings previously reported.[82]

Box 4.19: Pili torti et canaliculi

- Longitudinal grooves along hair shaft
- Characteristic finding in ectodermal dysplasias combined with clefting of lip/palate
- Increasing shaft defects associated with degree of clinical dysmorphology in ED, with corkscrew hairs as an exaggeration of pili torti et canaliculi

Treatment

The prognosis and treatment depend on underlying defects, which are heterogenous as the group of EDs itself. In general, maintenance of a cool, ambient temperature is vital in management of these patients. Air-conditioned environments reduce the chances of sudden hyperpyrexia.[83] Light clothing, repeated cold water spray and avoidance of hot food or exertion can help the patient to combat the daily heat stresses of life.

Approach to patient with genetic hair disorder

Given the extensive list of genetic hair disorders, it is imperative that the clinician have an organized approach to the diagnosis of these conditions. It should cover the history, physical examination and laboratory evaluation.

History

Prenatal history: Family history, history of problems during pregnancy like – bleeding, medications and gestational

age are important. Postnatal history of heat intolerance (ectodermal dysplasia), photosensitivity (PIBIDS), skin eruptions (Netherton syndrome), and delayed developmental milestones (Menkes disease) are essential.

Physical examination: Examination of all body part hairs (eyebrow, eyelash and scalp hair), determination of deafness by ENT examination (Bjornstad's syndrome), examination of eye (trichothiodystrophy), teeth (ectodermal dysplasia), nail (trichothiodystrophy) and skin (Netherton syndrome) will throw light on the probable cause of genetic hair disorder.

Investigations

Simple hair microscopy (to see structural hair defect as in monilethrix, pili torti), scanning EM (to see cuticular abnormality in monilethrix, TTD), polarized microscopy ('tiger tail' appearance in TTD), X-ray (Menkes disease), and mutation analysis (as in Netherton syndrome, Bjornstad's syndrome) will add to the diagnostic assay of the genetic hair diseases.

References

1. van Steensel MAM, Steijlen PM, Bladergroen RS, Vermeer M, van Geel M. A missense mutation in the type II hair keratin hHb3 is associated with monilethrix. J Med Genet. 2005;42:e19.
2. Messenger AG, de Barker DAR, Sinclair RD. Disorders of hair. In: Burns T, Breathnach S, Cox N, Griffith C, (eds). Rook's textbook of dermatology, 8th edition. Wiley-Blackwell Publications. 2010;66:1-100.
3. Zhang Shi-de, Meng J, Zhao Jing-jun, Tian W. Mutation E402K of the hHb6 in a Chinese Han family with monilethrix. Euro Jr Derm. 2009;19:508-9.
4. Schweizer J. More than One Gene Involved in Monilethrix: Intracellular but also Extracellular Players. J Invest Dermatol. 2006;126:1216-20.
5. Schaffer JV, Bazzi H, Vitebsky A, Witkiewicz A, Kovich OI, Kamino H, et al. Mutations in the desmoglein 4 gene underlie localized autosomal recessive hypotrichosis with monilethrix hairs and congenital scalp erosions. J Invest Dermatol. 2006;126:1286-91.
6. Shimomura Y, Sakamoto F, Kariya N, Matsunaga K, Ito M. Mutations in the desmoglein 4 gene are associated with monilethrix-like congenital hypotrichosis. J Invest Dermatol. 2006;126:1281-5.
7. Zlotogorski A, Marek D, Horev L, Abu A, Ben-Amitai D, Gerad L, et al. An autosomal recessive form of monilethrix is caused by mutations in DSG4: clinical overlap with localized autosomal recessive hypotrichosis. J Invest Dermatol. 2006;126:1292-6.
8. Singh A, Ambujam S, Srikanth S, Uma AN. Monilethrix: One Step More on the Ladder of Cytogenetics. Int J Trichology. 2010 Jan-Jun;2(1):18-9.
9. Langbein L, Schweizer J. Keratins of the human hair follicle. Int Rev Cytol. 2005;243:1-78.
10. Karincaoglu Y, Basak KC, Muammer ES, Nalan B. Monilethrix Improvement with Acitretin. Am J Clin Dermatol. 2005;6:407-10.
11. Rakowska A, Slowinska M, Czuwara J, Olszewska M, Rudnicka L. Dermoscopy as a tool for rapid diagnosis of monilethrix. J Drugs Dermatol. 2007;6:222-4.
12. Smith VV, Anderson G, Malone M, Sebire NJ. Light microscopic examination of scalp hair samples as an aid in the diagnosis of paediatric disorders: retrospective review of more than 300 cases from a single centre. J Clin Pathol. 2005;58:1294-8.
13. Tosti A. Hair shaft disorders. In: Tosti A, editor. Dermoscopy of hair and scalp: Pathological and clinical correlation, illustrated edition. USA: CRC press; 2007;pp. 51-3.
14. Jain N, Khopkar U. Monilethrix in Pattern Distribution in Siblings: Diagnosis by Trichoscopy. Int J Trichology. 2010 Jan-Jun;2(1):56-9.
15. Rakowska A, Slowinska M, Kowalska-Oledzka E, Rudnicka L. Trichoscopy in genetic hair shaft abnormalities. J Dermatol Case Rep. 2008 July 7;2(2):14-20.
16. Ito M, Hashimoto K, Katsuumi K, Sato Y. Pathogenesis of monilethrix: Computer stereography and electron microscopy. J Invest Dermatol. 1990;95:186-94.
17. Sandhu K, Handa S, Kanwar AJ. Monilethrix. Indian J Dermatol. 2002;47:169-70.
18. Dinh HV, Sinclair RD, Green J. Hair and Scalp Diseases Medical, Surgical, and Cosmetic Treatments. Informa Healthcare USA, Inc. p.149-62.
19. Bentley-Phillips B, Bayles MAH. A previously undescribed hereditary hair anomaly (pseudomonilethrix). Br J Dermatol. 1973;89:688-90.
20. Valia RG, Valia AR. IADVL textbook of Dermatology. Bhalani Publishing House. 3rd edition. 2008.
21. Cheng AS, Bayliss SJ, Louis S. The genetics of hair shaft disorders. J Am Acad Dermatol. 2008;59:1-22.
22. Blume-Peytavi U, Tosti A, Whitling DA, Trüeb R. Hair growth and disorders. Springer International Edition. 2010.
23. Lubianca Neto JF, Lu L, Eavey RD, Flores MA, Caldera RM, Sangwatanaroj S, et al. The Bjornstad syndrome (sensorineural hearing loss and pili torti) disease gene maps to chromosome 2q34-36. Am J Hum Genet. 1998;62:1107-12.
24. Hinson J, Fantin V, Schonberger J, Breivik N, Siem G, McDonough B, et al. Missense mutations in the BCS1L gene as a cause of the Bjornstad syndrome. N Engl J Med. 2007;356:809-19.
25. Beare JM. Congenital pilar defect showing features of pili torti. Br J Dermatol. 1952;64:366-72.
26. Crandall BF, Samec L, Sparkes RS, Wright SW. A familial syndrome of deafness, alopecia, and hypogonadism. J Pediatr. 1973;82:460-5.
27. Voigtlander V. Pili torti with deafness (Bjornstad syndrome). Report of a family. Dermatologica. 1979;159:50-4.
28. de Berker D, Sinclair RD. The hair shaft: normality, abnormality, and genetics. Clin Dermatol. 2001;19:129-34.
29. Wallace MP, de Berker D. Hair diagnoses and signs: the use of dermatoscopy. Clinical and Experimental Dermatology. 2009;35:41-6.

30. Tümer Z, Møller LB. Menkes disease. Eur J Hum Genet. 2010;18(5):511-8.
31. Paulsen M, Lund C, Akram Z, Winther JR, Horn N, Mølle LB. Evidence That Translation Reinitiation Leads to a Partially Functional Menkes Protein Containing Two Copper-Binding Sites. Am. J. Hum. Genet. 2006;79:214-29.
32. Camakaris J, Petris MJ, Bailey L, et al. Gene amplification of the Menkes (MNK; ATP7A) P-type ATPase gene of CHO cells is associated with copper resistance and enhanced copper efflux. Hum Mol Genet. 1995;4:2117-23.
33. Møller LB, Bukrinsky JT, Mølgaard A, et al. Identification and analysis of 21 novel disease-causing amino acid substitutions in the conserved part of ATP7A. Hum Mutat. 2005;26:84-93.
34. Horn N, Tümer Z. Menkes disease and the occipital horn syndromein Royce PM, Steinmann B (eds): Connecitive Tissue and its Heritable Disorders: Molecular, Genetic, and Medical Aspects New York: John Wiley and Sons Inc. 2002. 2nd edn 651-85.685.
35. Lee ES, Ryoo JW, Choi DS, Cho JM, Kwon SH, Shin HS. Diffusion-Weighted MR Imaging of Unusual White Matter Lesion in a Patient with Menkes Disease. Korean J Radiol. 2007 Jan-Feb;8(1):82-5.
36. Kaler SG, Clarissa J. Liew CJ, Donsante A, Hicks JD, Sato S, et al. Molecular correlates of epilepsy in early diagnosed and treated Menkes disease. J Inherit Metab Dis. 2010;33(5):583-9.
37. Zaffanello M, Maffeis C, Fanos V, Franchini M, Zamboni G. Urological complications and copper replacement therapy in childhood Menkes syndrome.
38. Palmer CA. Neuropathology of Occipital Horn Syndrome. Journal of Child Neurology. 2001;16:764-66.
39. Kaler SG. Menkes disease. Adv Ped. 1994;41:263-304.
40. Tümer Z, Horn N. Menkes disease: recent advances and new aspects. J Med Genet. 1997;34:265-74.
41. George DH, Casey RE. Menkes disease after copper histidine replacement therapy: case report. Pediatr Dev Pathol. 2001;4:281-8.
42. Kirodian BG, Gogtay NJ, Udani VP, Kshirsagar NA. Treatment of Menkes disease with parenteral copper histidine. Indian Pediatr. 2002;39:183-5.
43. Hosomi N, Ukai KF, Nakanishi T, Unaki SF, Shii MI. Caspase-1 activity of stratum corneum and serum interleukin-18 level is increased in patients with Netherton syndrome. Br J Dermatol. 2008;159:733-72.
44. Sun JD, Linden KG. Netherton syndrome: a case report and review of the literature. Int J Dermatol. 2006;45:693-7.
45. Netherton EW. A unique case of trichorrhexis nodosa; bamboo hairs. AMA Arch Derm. 1958;78:483.
46. Mevorah B, Frenk E, Brooke EM. Ichthyosis linearis circumflexa comèl. A clinico-statistical approach to its relationship with Netherton's syndrome. Dermatologica. 1974;149:201-9.
47. Salodkar AD, Choudary SV, Jadwani G, Singh A. Int J Trichology. 2009;1:143-4.
48. Deraison C, et al. LEKTI fragments specifically inhibit KLK5, KLK7, and KLK14 and control desquamation through a pH-dependent interaction. Mol Biol Cell. 2007;18(90):3607-19.
49. Descargues P, Deraison C, Bonnart C, Kreft M, Kishibe M, Ishida-Yamamoto A, et al. Spink5-deficient mice mimic Netherton syndrome through degradation of desmoglein 1 by epidermal protease hyperactivity. Nat Genet. 2005;37(1):56-65.
50. Bonnart C, Deraison C, Lacroix M, Uchida Y, Besson C, Robin A et al. Elastase 2 is expressed in human and mouse epidermis and impairs skin barrier function in Netherton syndrome through filaggrin and lipid misprocessing. J Clin Invest. 2010;120(3):871-82.
51. Chavanas S, Garner C, Bodemer C, Ali M, Hamel- Teillac D, Wilkinson J. Localization of the Netherton Syndrome Gene to Chromosome 5q32, by Linkage Analysis and Homozygosity Mapping. Am J Hum Genet. 2000 March;66(3):914-21.
52. Sardy M, Fay A, Karpati S, Horvath A. Comel–Netherton syndrome and peeling skin syndrome type B: overlapping syndromes or one entity? Int J Dermatol. 2002;41:264-8.
53. Schneider I, Sebok B, Kosztolanyi G, Szekeres G. Comel–Netherton syndrome: evolution of manifestation in a 20-year follow-up and phenotypic overlap with peeling skin syndrome type B. Acta Dermatol Venereol. 2000;80:209-10.
54. Descargues P, Deraison C, Prost C, Fraitag S, Mazereeuw-Hautier J, D'Alessio M et al. Corneodesmosomal Cadherins Are Preferential Targets of Stratum Corneum Trypsin- and Chymotrypsin-like Hyperactivity in Netherton Syndrome. J Invest Dermatol. 2006;126:1622-32.
55. Dey VK. Netherton syndrome: A rare genodermatosis. Ind Dermatol Online J. 2011;2:38-9.
56. Ito M, Ito K, Hashimoto K. Pathogenesis in trichorrhexis invaginata (bamboo hair). J Inv Dermatol. 1984;83:1-6.
57. Rogers M. Hair shaft abnormalities: Part II. Australas J Dermatol. 1996;37:1-11.
58. Chao SC, Richard G, Lee J Y-Y. Netherton syndrome: report of two Taiwanese siblings with staphylococcal scalded skin syndrome and mutation of SPINK5. Br J Dermatol. 2005;152:159-65.
59. Smith DL, Smith JG, Wong SW, deShazo RD. Netherton's syndrome: a syndrome of elevated IgE and characteristic skin and hair findings. J Allergy Clin Immunol. 1995;95(1 Part 1):116-23.
60. Kilic G, Guler N, Ones U, Tamay Z, Guzel P. Netherton syndrome: report of identical twins presenting with severe atopic dermatitis. Eur J Pediatr. 2006;165:594-7.
61. Yan AC, Honig PJ, Ming ME, Weber J, Shah KN. The Safety and Efficacy of Pimecrolimus, 1%, Cream for the Treatment of Netherton Syndrome.
62. Faghri S, Tamura D, Kraemer KH, DiGiovanna JJ. Trichothiodystrophy: a systematic review of 112 published cases characterizes a wide spectrum of clinical manifestations. J Med Genet. 2008;45:609-21.
63. Bergmann E, Egly JM. Trichothiodystrophy, a transcription syndrome. Trends Genet. 2001;17:279-86.
64. Itin P, Sarasin A, Pittelkow M. Trichothiodystrophy: update on the sulfur- deficient brittle hair syndromes. J Am Acad Dermatol. 2001;44:891-920.
65. Bootsma D, Kraemer KH, Cleaver JE, Hoeijmakers JHJ. Nucleotide excision repair syndromes: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. In: The Genetic Basis of Human Cancer, 2002 second edition. (Vogelstein B, Kinzler KW, eds) New York: McGraw-Hill, 211-37.