Clinical, Cosmetic and Investigational Dermatology

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CASE SERIES

Recalcitrant Female Pattern Hair Loss Like Alopecia Unveils Unexpected Rare Entity

Ahmed H Nouh[1], Fatma M Elgendy[2], Fatma A Gobran[3], Maryna S Zhuravlova[4]

[1]Al-Azhar University, Faculty of Medicine, Department of Dermatology, Venereology and Andrology, Cairo, Egypt; [2]Ain Shams university, Faculty of medicine, Department of Pathology, Cairo, Egypt; [3]Medical Laboratory at Sharkia Health Directorate, Ministry of Health, Belbeys, Egypt; [4]Lugansk state medical University, Department of Pathology, Rivne, Ukraine

Correspondence: Maryna S Zhuravlova, Email marynazhuravlovamd@gmail.com

Introduction: Marie-Unna hereditary hypotrichosis (MUHH) is an autosomal dominant disorder characterized by a specific pattern of hair loss. Initially described in 1925 by Marie-Unna in a German family spanning over seven generations, MUHH represents a previously unidentified form of congenital hypotrichosis. It typically presents as sparse hair at birth with a coarse texture, followed by regrowth during childhood then, finally, gradual hair loss at puberty, resembling pattern of androgenetic alopecia.

Case Presentation: The study describes two cases from different unrelated families presenting with recalcitrant alopecia resembling female pattern hair loss, with dermoscopic findings consistent with pili torti and yellow dots. Genetic testing confirmed a heterozygous pathogenic variant in the HRURF gene, associated with autosomal dominant Marie Unna Hereditary Hypotrichosis. Up to our knowledge it is first case series reported from Egypt.

Conclusion: While recent literature on MUHH has primarily focused on identifying genetic abnormalities, there are other important questions that warrant consideration. These include histopathological studies, dermoscopic descriptions, and correlating types of genetic mutations with clinical presentations. These data might offer a deeper understanding of MUHH pathophysiology ending in efficacious treatment options.

Plain language summary: Marie-Unna hereditary hypotrichosis (MUHH) is a rare genetic condition that causes a distinct pattern of hair loss. First identified in 1925 in Germany, this condition is passed down through families. In this article, we report two unrelated cases from Egypt, marking the first documented cases of MUHH in the country. Each case involves different genetic mutations, highlighting the variability of the condition.

MUHH typically presents as sparse hair at birth, which becomes coarse in childhood and then gradually thins again during puberty. This hair loss can resemble common male-pattern baldness. While MUHH mainly affects hair, it may also be linked to other conditions such as skin tumors (trichoepithelioma), limb abnormalities, eye issues, wide-spaced teeth, and syndromes like Ehlers-Danlos or atopy.

Because MUHH is so rare, diagnosing it can be difficult, and many healthcare providers may not immediately recognize it. By describing these cases, we aim to raise awareness and improve understanding of MUHH, encouraging clinicians to consider it as a possible diagnosis in similar presentations.

Keywords: hair disorder, rare genetic disorder, alopecia, madarosis, hereditary hypotrichosis

Established Facts and Novel Insights

Marie Unna hereditary hypotrichosis (MUHH) is a rare genetic disorder with an autosomal dominant inheritance pattern, characterized by a distinctive hair loss pattern that varies with age. Genetic factors, altered hair shaft morphology, a decreased number of functional follicles, and abnormal follicle cycling have been suggested as contributors to the disease pathogenesis, with mutations in the U2HR gene, located on chromosome 8p21, identified as the underlying cause. In this study, we identify MUHH in patients from Egypt, contributing to the geographical distribution of this rare condition. Furthermore, we describe varying patterns of hair loss linked to genetic variability (heterogeneity) of the

Received: 17 July 2024
Accepted: 14 January 2025
Published: 22 January 2025

disease. Notably, this is the first report describing the dermoscopic picture of MUHH and the first case series from Egypt, offering novel insights into its clinical features.

Introduction

Marie-Unna hereditary hypotrichosis (MUHH) is a rare autosomal dominant disorder, with a limited number of cases reported worldwide since its initial description, characterized by a specific pattern of hair loss. Initially described in 1925 by Marie-Unna in a German family spanning over seven generations, MUHH represents a previously unidentified form of congenital hypotrichosis. It typically presents as sparse hair at birth with a coarse texture, followed by regrowth during childhood then, finally, gradual hair loss at puberty, resembling pattern of androgenetic alopecia. To the best of our knowledge, there has not been a study examining the correlation between U2HR (U2 small nuclear RNA auxiliary factor (U2AF) 2 hairless Repressor; alternative title HRURF – human hairless gene upstream open reading frame) mutation and MUHH phenotype. The exact function of the HRURF/U2HR gene in hair follicle biology remains largely unknown, adding to the complexity of understanding MUHH pathogenesis. Typically, it manifests as an isolated hair abnormality.[1] However, literature contains limited reports regarding the association or coexistence of MUHH with multiple familial trichoepithelioma (MFT),[2] limb deformities,[3] juvenile macular degeneration (Stargardt's maculopathy),[4] juvenile macular dystrophy,[5] exceptionally wide-spaced upper incisor teeth,[6] and Ehlers–Danlos syndrome and atopy.[7] MUHH poses significant challenges in diagnosis, primarily due to its rarity, which limits awareness and recognition among healthcare providers. To the best of our knowledge, based on a comprehensive search of major medical databases (PubMed, Scopus, Web of Science), this is the first documented case series of MUHH from Egypt.

Case Series Presentation

Case 1

A 22-year-old female complains of abnormal hair shedding started at puberty. A family report denotes that at birth she had an absence of scalp hair; however, she showed hair regrowth during childhood period. She had been diagnosed before as a case of androgenetic alopecia and treated by topical Minoxidil 2% solution without improvement. She is otherwise a healthy female without medical history of concern.

Investigation of her family members reveal individuals affected by a similar condition as illustrated in family pedigree (Figure 1).

Clinical examination: There is a diffuse alopecia predominantly affects the vertex of the scalp (Figure 2), resembling the Ludwig type, with easily epilated, twisted, wiry, and coarse hair shafts. Additionally, there is complete madarosis (Figures 3 and 4) of both eyebrows and eyelashes, along with sparse body hair. Micrognathia was detected in the patient and other affected family members, without any other ectodermal involvement.

Dermoscopic examination (Figure 5) reveals dilated yellow dots, broken hair at different hair length, some black dots, twisted hair, and hair shaft abnormality (Pili torti like picture).

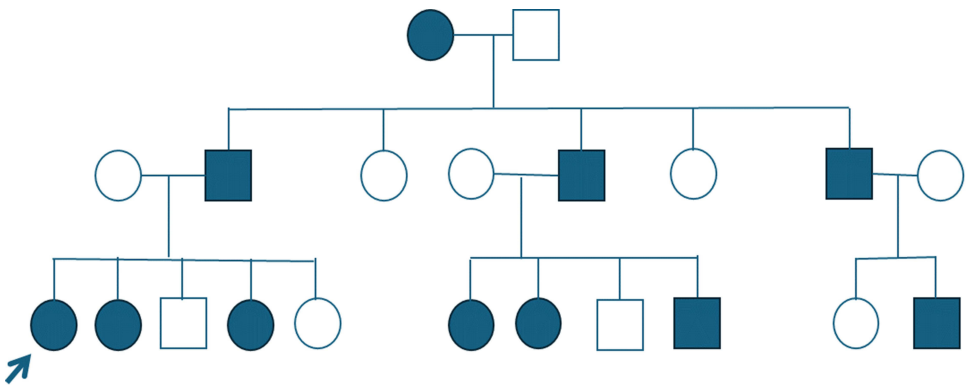

Figure 1 Pedigree of proband from case 1. Circles represent females, squares – males. Affected individuals are colored figures. Proband marked by arrow.

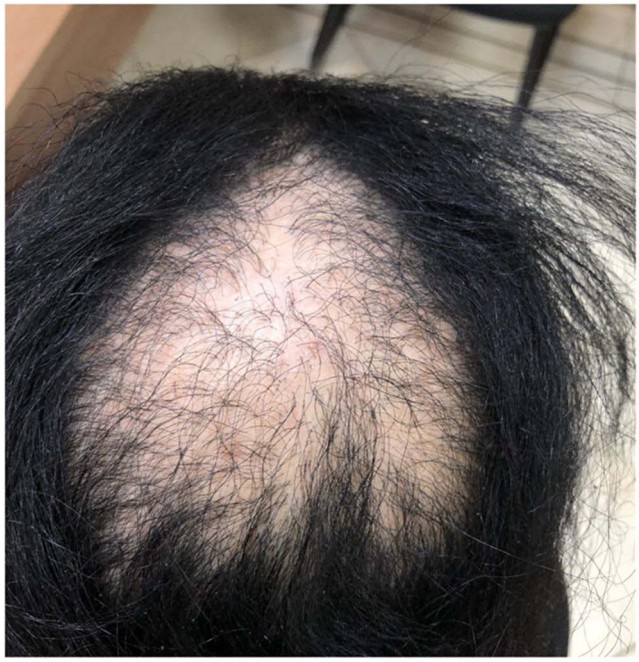

Figure 2 Clinical picture of hair loss pattern from case 1.

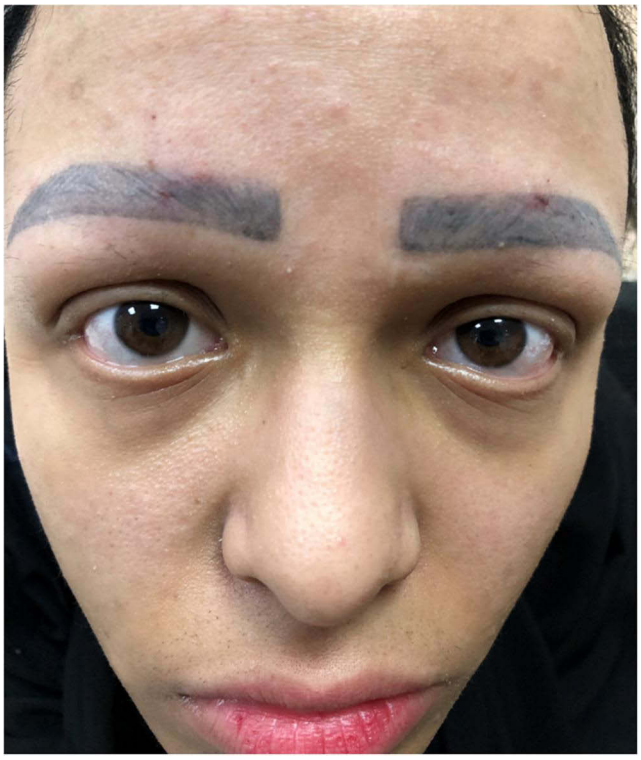

Figure 3 Madarosis clinical picture (cosmetic tattooing) from case 1.

Genetic analysis was conducted using Sanger sequencing, which confirmed a heterozygous pathogenic variant in the HRURF gene (NM_001394132.1:c.2T>C) in compliance with HGVS (Human Genome Variation Society) nomenclature. Variant interpretation followed the ACMG (American College of Medical Genetics and Genomics) guidelines, classifying it as pathogenic and consistent with MUHH.

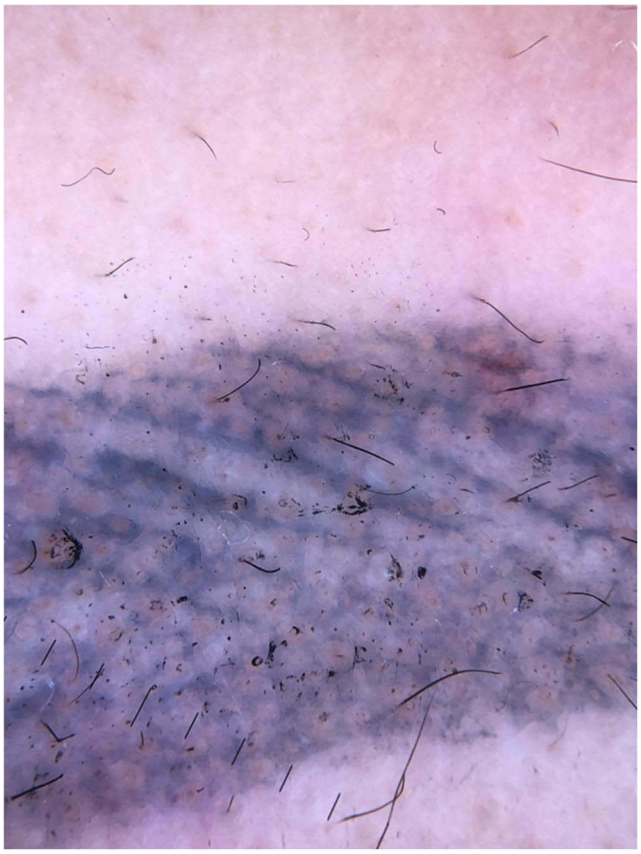

Figure 4 Dermoscopy of madarosis from case 1. Tattoo pigment, very sparse short, broken fine hair.

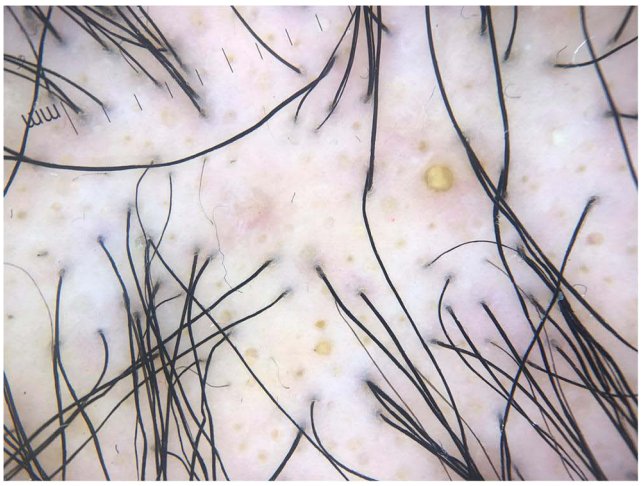

Figure 5 Dermoscopy of hair from case 1.

Case 2

A 19-year-old girl presented with gradual, patterned hair loss that had an insidious onset and a progressive course over the past few years. Her mother reported that the patient was born with an absence of scalp hair, which gradually began to appear during the early years of childhood. After puberty, the patient started complaining of gradual hair loss, mainly in the central frontal area of scalp. Despite many therapeutic trials by different doctors, no effect was observed. She is otherwise a healthy female with no significant medical history.

Investigation of her family members revealed individuals affected by a similar condition, as shown in the family pedigree (Figure 6).

Clinical examination: There is patterned alopecia affecting primarily the central portion of the scalp (Figure 7), with lateral extensions resembling a Christmas tree pattern, accompanied by slight parietal recession. Additionally, there is partial madarosis (Figures 2, 8 and 9) affecting both eyebrows and eyelashes, as well as sparse body hair.

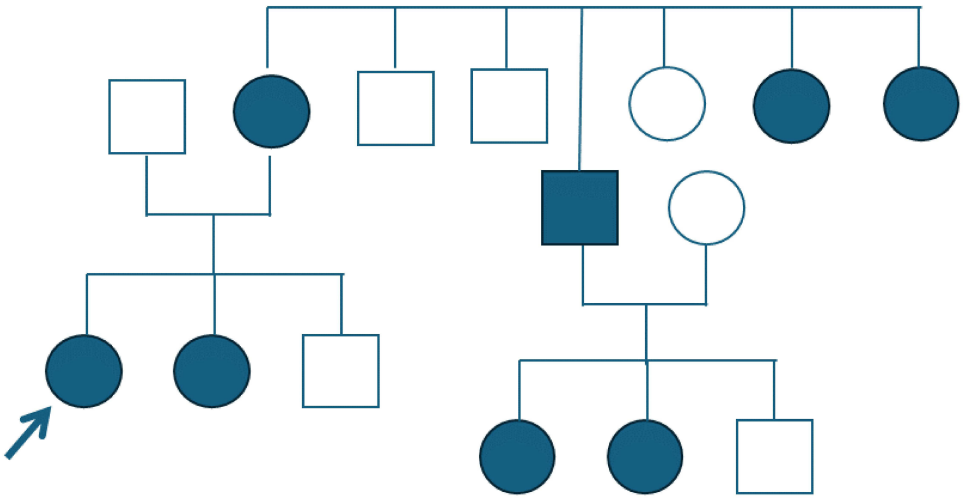

Figure 6 Pedigree of proband from case 2. Circles represent females, squares – males. Affected individuals are colored figures. Proband marked by arrow.

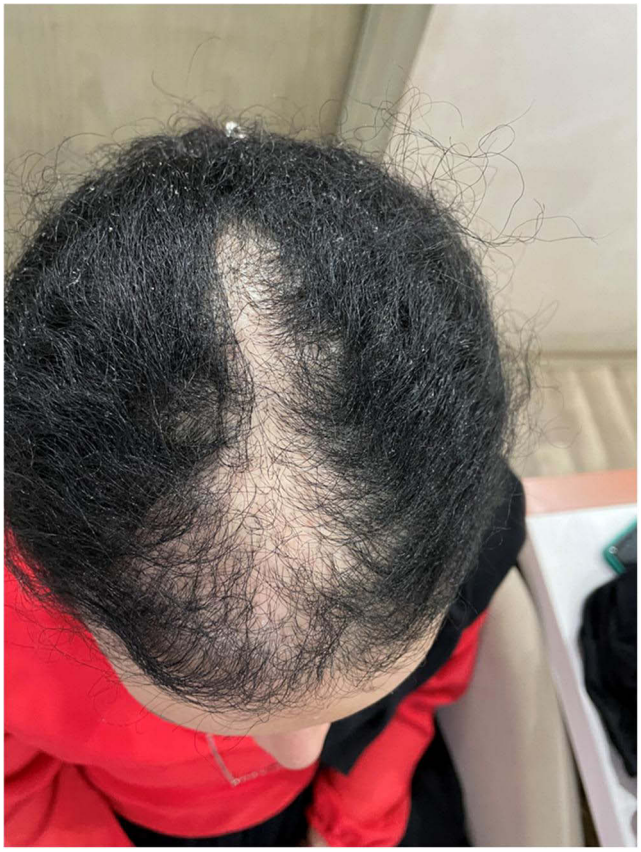

Figure 7 Clinical picture of hair loss pattern from case 2.

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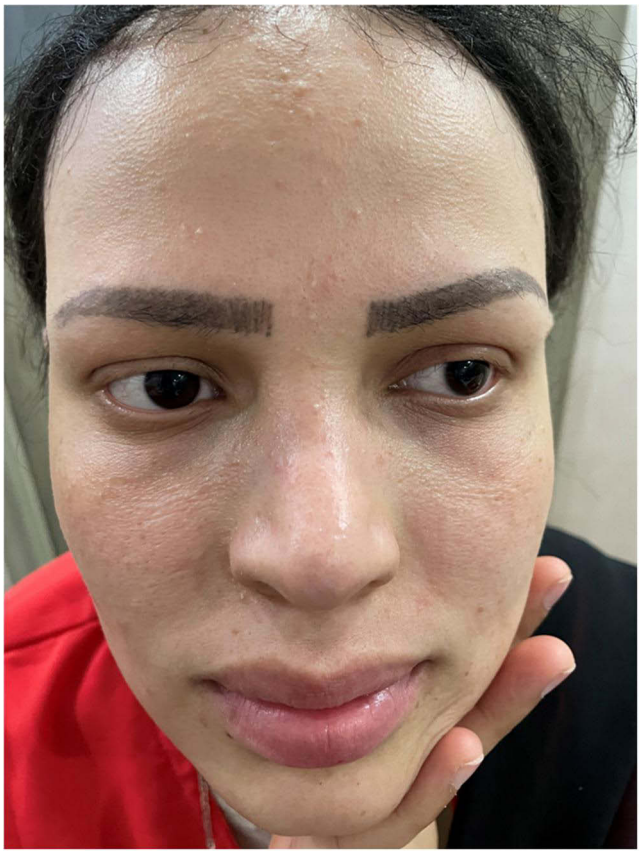

Figure 8 Madarosis clinical picture (cosmetic tattooing) from case 2.

Dermoscopic examination (Figures 10–12) reveal findings included dilated yellow dots, broken hairs of varying lengths, a few hair knots (Trichonodosis), twisted hairs, and hair shaft abnormalities resembling Pili torti.

Genetic testing was validated using Sanger sequencing, identifying a heterozygous pathogenic variant in the HRURF gene (NM_001394132.1:c.74C>G) in compliance with HGVS nomenclature. Variant interpretation followed the ACMG guidelines, confirming its pathogenicity and consistent with MUHH.

Ancestry Information: Both patients belong to Egyptian ancestry, with no evidence of interethnic familial ties, as confirmed through family history analysis.

Light microscopy trichogram (Figure 13) of the hair performed in both cases revealed hairs that were coarse, flattened at irregular intervals with 180° twisting along their longitudinal axis. The hair pull test resulted in the easy extraction of multiple anagen hairs.

Discussion

Since the first report of this disease by German dermatologists Marie Unna in 1925,[8] there have been few case reports from other countries, mainly in Europe. These include studies of hair using light, polarized and electronic microscopy, a few pathological investigations, and mostly just reporting the case with a pedigree. Subsequently, reports have emerged from Turkey, Saudi Arabia, and recently, there have been many from China, Japan, and Korea, focusing on identification of new types of mutations following advancements in gene sequencing technologies.

According to the up-to-date literature, 23 different mutations of the U2HR gene have been identified as a cause of this disorder. This genetic heterogeneity may be linked, in our opinion, to the slightly different patterns of disease manifestation seen in case reports worldwide. In our cases, there are differences in alopecia patterns (resembling Ludwig and Olsen types), as well as in the types of mutations, which support this theory. Another possible reason

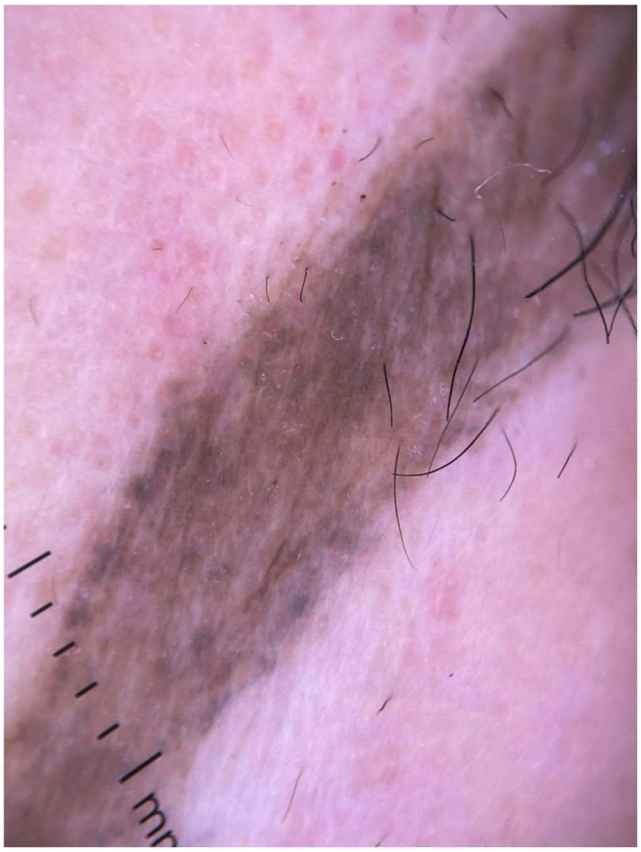

Figure 9 Dermoscopy of madarosis from case 2. Tattoo pigment, sparse broken fine hair.

Figure 10 Dermoscopy of hair from case 2.

could be environmental factors, such as long-term hair combing techniques and hair styling. Given the existence of such differences, madarosis serves as a significant diagnostic indicator for identifying MUHH.

The regrowth of hair during early childhood followed by gradual loss after puberty suggests a role for sex steroid hormones in the pathogenesis of the disease, echoing theories seen in Androgenetic Alopecia. No dermoscopic findings have been described in the existing literature. As illustrated in figures, the dermoscopic findings in our cases exhibit similarities to those seen in Alopecia Areata, including yellow and black dots, broken hairs. These findings may raise

Figure 11 Trichonodosis. Sample pictured here taken from case 2.

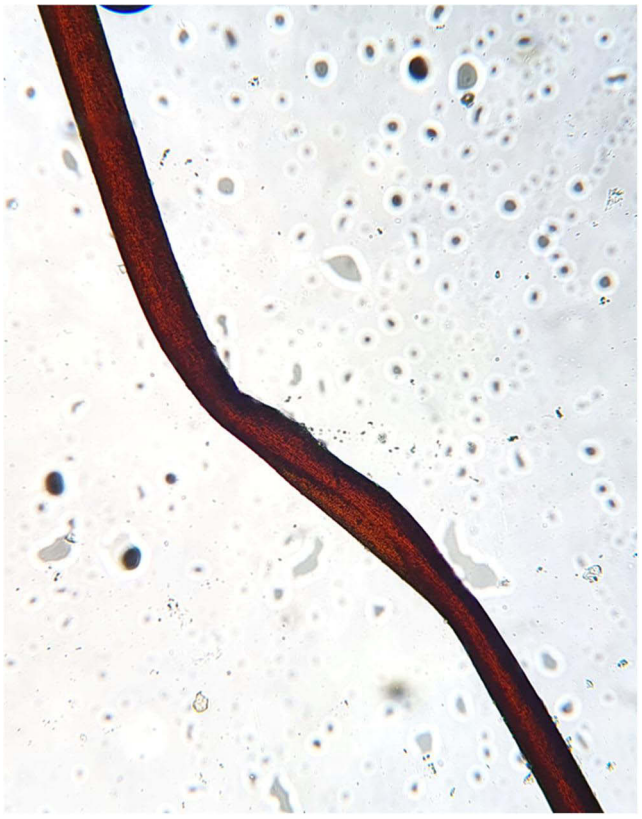

Figure 12 Trichogram: 180 degree twisting point of hair shaft. Sample pictured here taken from case 2.

concerns about the presence of a perifollicular inflammatory infiltrate. Upon closer examination of the yellow dots, they appear slightly more dilated, patulous, and filled with keratin. This observation raises concerns about the level of inflammatory infiltrate and whether it affects the isthmus of the hair follicle. This finding resembles the dilated yellow dots or follicular stippling seen in Discoid Lupus Erythematosus. The abnormality in hair shafts may result from the proliferation of the internal root sheath and the formation of horn cysts in the lower one-third of the follicle. Alternatively, it could be due to the proliferation of the external root sheath in the keratogenous zone, resulting in

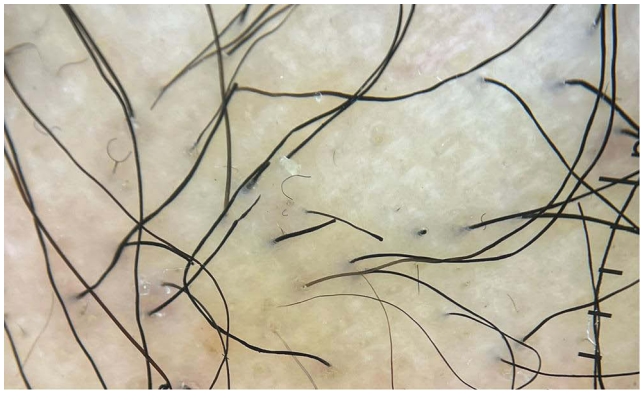

Figure 13 Dermoscopy: Wiry coarse hair shaft with irregular twisting (Pili torti like changes). Sample pictured here taken from case 2.

bulging into the internal root sheath.[9] This can lead to longitudinal grooving or irregularities in the circumference of the hair shaft.[10]

Another point for discussion is the absence or presence of inflammatory signs, either clinical or histological, following the onset of hair shedding after puberty. While some authors describe no inflammation,[6,11–13] others note its occurrence[10,14] to varying degrees. This point appears crucial for both developing effective treatment options and gaining a deeper understanding of the disease's pathogenesis.

We want to analyse clinico-genotypical correlation in previously reported cases with mutations similar to those in our patients. There were 4 reports about c.2 T>C mutations in Turkish,[11] Chinese,[12] Belgian,[15] and German[16] descent families. The mutation c.74 C>G was reported only once from Japan.[17] We cannot phenotypically compare our second case to the case reported from Japan, as they describe and illustrate only the clinical pictures of little boys. As for the first family, the Turkish report differed even in the quality of hair itself (pili torti-like appearance was not reported). The Chinese family exhibited almost complete alopecia, while the Belgian report lacked detailed clinical descriptions except for alopecia mainly on the vertex and some family members exhibiting scarring alopecia. Finally, the German family was described as having male pattern hair loss in affected males and females.

Although genetic diseases like MUHH are not yet treatable, genetic testing remains crucial for accurate diagnosis, family counseling, and further research, particularly for expanding genotype–phenotype correlations and improving global understanding of inherited hair disorders.

Conclusion

While recent literature on MUHH has primarily focused on identifying genetic abnormalities, there are other important questions that warrant consideration. These include histopathological studies, dermoscopic descriptions, and correlating types of genetic mutations with clinical presentations. This data might offer a deeper understanding of MUHH pathophysiology ending in efficacious treatment options.

The current study describes two unrelated Egyptian families with Marie-Unna hereditary hypotrichosis (MUHH), identifying two heterozygous pathogenic variants in the HRURF gene (NM_001394132.1:c.2T>C and NM_001394132.1:c.74C>G). These findings expand the existing genotype–phenotype correlations in MUHH and highlight the clinical variability associated with this rare condition.

While molecular genetic studies, such as the present report, are essential for identifying pathogenic variants, further functional studies are needed to elucidate the precise role of the HRURF gene in hair shaft development and cycling. This remains a key gap in understanding the pathophysiology of MUHH.

Data Sharing Statement

All available data are included in the manuscript.

Study Approval Statement

Approval was not required, as it is a reporting case of rare disease, not an interventional study.

Consent to Publish Statement

Written informed consent was obtained from patients for publication of the details of their medical case and any accompanying images.

Acknowledgment

We extend our heartfelt gratitude to Professor Hussein Hassab El-Naby for his invaluable assistance in the revision of described cases.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was not supported by any sponsor or funder.

Disclosure

The authors have no conflicts of interest to declare for this work.

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