Dermoscopy as a diagnostic window in Griscelli Syndrome: Expanding the clinical spectrum

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Abstract

Background: Griscelli syndrome (GS) is a rare autosomal recessive disorder rooted in defective melanosome transport, characterized by silvery hair and variable neurological and immunological manifestations. GS Type 2 carries particular clinical significance because of its association with immune dysregulation and hemophagocytic lymphohistiocytosis (HLH). Hair shaft dermoscopy has emerged as a rapid, non-invasive diagnostic tool, particularly in resource-constrained settings where molecular testing may not be readily available.

Aim: To describe the clinic-dermoscopic features of three children with Griscelli syndrome representing different subtypes and to highlight the diagnostic utility of hair shaft dermoscopy.

Materials and Methods: Three pediatric patients presenting with silvery-yellow hair underwent detailed clinical evaluation, relevant laboratory investigations, and hair shaft dermoscopy using a Dino-Lite videodermoscope (×200). Targeted next-generation sequencing was performed in one patient. In the remaining two patients, subtype classification was based on clinicodermoscopic findings in conjunction with the associated systemic manifestations.

Results: All three patients demonstrated a uniform dermoscopic pattern characterized by coarse, irregular melanin clumping along the hair shaft. Two patients exhibited immune dysregulation consistent with Griscelli syndrome Type 2, while one patient showed predominant neurological involvement without immune compromise, consistent with Type 1 disease. Genetic confirmation of a pathogenic *RAB27A* variant was obtained in one patient. Despite similar dermoscopic findings, distinct systemic phenotypes were observed across the three cases.

Conclusion: Hair shaft dermoscopy is a rapid, cost-effective, and non-invasive first-line diagnostic tool for Griscelli syndrome. Although it does not distinguish disease subtypes, it reliably demonstrates the characteristic irregular melanin clumping of the hair shaft and facilitates early diagnosis, particularly in resource-limited settings where genetic testing is inaccessible. Correlation with the systemic clinical phenotype remains essential for accurate subtype classification and appropriate management.

Keywords: Griscelli syndrome; dermoscopy; silvery hair; hemophagocytic lymphohistiocytosis; RAB27A; MYO5A

Introduction

Griscelli syndrome is an uncommon autosomal recessive disorder in which disruption of the molecular machinery governing intracellular vesicle trafficking results in failure of melanosome transfer from melanocytes to keratinocytes[1]. The syndrome is genetically and phenotypically heterogeneous, with three recognized subtypes determined by the affected gene. Type 1, arising from mutations in *MYO5A*, manifests predominantly as severe neurological impairment with relative sparing of immune function. Type 3, caused by *MLPH* mutations, is restricted to pigmentary dilution without systemic consequences. Type 2, the result of biallelic mutations in *RAB27A*[2] is clinically the most consequential, combining the cutaneous signature of the syndrome with profound immune dysregulation and a pronounced predilection for triggering HLH a hyperinflammatory state carrying significant mortality if not recognized and treated expeditiously.

GS present with pigment dilution, featured by silvery-grey hair, eyebrows and eyelashes, as well as light-coloured skin at birth followed by bronzed pigmentation after sun exposure[3]. Microscopic examination of hair

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shaft reveals uneven clusters of aggregated melanin pigments, accumulated mainly in the medullary area of hair shaft[4].

Despite the availability of genetic confirmation in select cases, hair shaft dermoscopy remains an indispensable rapid diagnostic adjunct, particularly where molecular testing infrastructure is limited.

We present three children with GS to illustrate the phenotypic breadth of the condition across subtypes and to underscore the diagnostic utility of dermoscopy as an accessible and reliable tool in clinical practice. Existing literature largely describes individual subtypes or isolated case reports, with limited emphasis on comparative evaluation across subtypes within a single series. This series uniquely correlates dermoscopic findings across multiple subtypes within a single cohort, systematically differentiates closely related syndromes presenting with silvery hair, and highlights the practical role of dermoscopy in settings where genetic confirmation is limited.

Materials and methods

This study includes three pediatric patients presenting with silvery-yellow hair and clinical features suggestive of Griscelli syndrome. Each patient underwent detailed clinical evaluation, including history and physical examination with attention to systemic involvement.

Hair shaft dermoscopy was performed in all cases using a videodermoscope (Dino-Lite Edge Series, Model AF4115ZT + WF20) to assess melanin distribution. Relevant laboratory and ancillary investigations were carried out as clinically indicated. Genetic testing was performed in one patient; in the remaining cases, subtype classification was based on clinical and dermoscopic findings in the context of systemic features.

Informed consent was obtained from the parents of all patients.

Results

All three patients demonstrated a uniform dermoscopic pattern characterized by coarse, irregular melanin clumping along the hair shaft. Despite this shared finding, distinct systemic phenotypes were observed across cases.

Two patients exhibited features of immune dysregulation consistent with Griscelli syndrome Type 2, while one patient showed predominant neurological involvement without immune compromise, aligning with Type 1 disease. This dissociation between consistent dermoscopic findings and variable systemic involvement was a notable observation across the series.

Genetic confirmation was obtained in one case, whereas in the remaining cases, diagnosis and subtype classification were based on clinicodermoscopic correlation and associated clinical features.

Case Reports

Case 1

A male infant was brought to medical attention in early infancy with a history of recurrent lower respiratory tract infections, faltering growth, and repeated hospitalizations since the neonatal period. The parents reported an unusual silvery-yellow coloration of the child's scalp hair since birth, which had not been previously investigated. He was the product of a third-degree consanguineous union. On examination, the child was pale and underweight, with clinical evidence of hepatosplenomegaly. Investigations confirmed anemia alongside laboratory parameters indicative of immune dysfunction. Bone marrow examination demonstrated unequivocal evidence of hemophagocytic lymphohistiocytosis on trephine biopsy.

Cutaneous examination revealed diffusely hypopigmented scalp hair with a characteristic silvery-yellow sheen. Trichoscopic examination demonstrated coarse, irregularly distributed melanin aggregates along the hair shaft, a finding inconsistent with any physiological melanin distribution pattern. Targeted next-generation sequencing subsequently identified a pathogenic variant in the *RAB27A* gene, thereby confirming the diagnosis of Griscelli syndrome Type 2. The child's clinical trajectory was unfavorable; despite institution of supportive and disease-directed measures, progressive systemic deterioration ensued and the child did not survive.

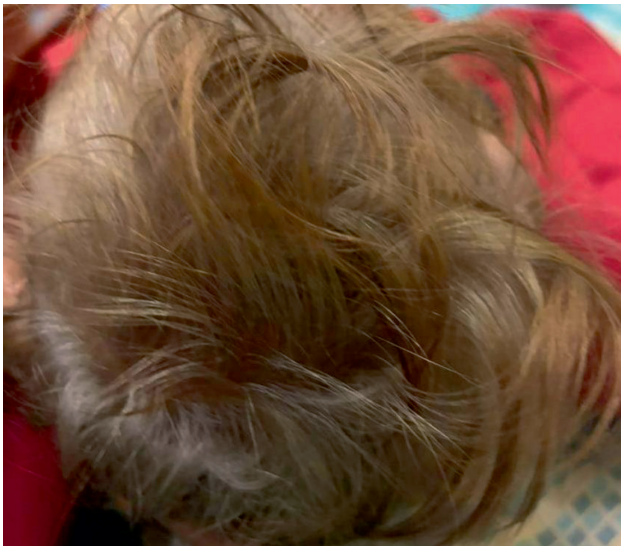

Figure 1: a) Silvery-yellow scalp hair

Case 2

A male child presented with a protracted history of recurrent febrile illnesses, repeated episodes of pneumonia and bacterial meningitis, and a progressive decline in neurodevelopmental milestones manifesting as seizures and developmental regression. The family reported that the child's scalp hair and eyebrows had carried a silvery-yellow discoloration since birth. Repeated hospitalizations had necessitated multiple red cell transfusions for symptomatic anemia. A family history of similar illness was absent, though the child was born of a second-degree consanguineous marriage. Physical examination corroborated hepatosplenomegaly and confirmed the presence of neurodevelopmental impairment.

Dermatological evaluation revealed hypopigmented hair with a pale yellowish sheen involving the scalp and facial adnexae. Hair shaft dermoscopy demonstrated the characteristic pattern of irregular, unevenly distributed melanin clumping along the shaft, mirroring the findings in Case 1. An important observation merits emphasis here: dermoscopic evidence of melanin clumping along the hair shaft is a shared feature across all three subtypes of Griscelli syndrome and therefore cannot, in isolation, determine the subtype. The subtype designation in this case was informed by the accompanying clinical phenotype - specifically, the constellation of recurrent bacterial infections, bacterial meningitis, transfusion-dependent anemia, and hepatosplenomegaly - which collectively constitute a recognizable signature of immune dysregulation characteristic of Type 2 disease. Genetic confirmation was not pursued owing to financial constraints, and the diagnosis of Griscelli syndrome Type 2 was therefore established on clinical and dermoscopic grounds.

Case 3

A 4-year-old child, the offspring of a second-degree consanguineous union, presented with hypopigmentation of the scalp hair, eyelashes, and eyebrows noted since early infancy. Both siblings were phenotypically normal. Beyond the cutaneous findings, the clinical history was notable for repeated episodes of fever, vomiting, and diarrhea, alongside seizures, global developmental delay, moderate intellectual disability, and absence of expressive language attributable to intellectual impairment. Notably, there was no clinical or laboratory evidence of immune dysfunction, and the child had not experienced episodes suggestive of hemophagocytic activation.

Given the nature and progression of neurological symptoms, neuroimaging was obtained. MRI of the brain demonstrated signal abnormalities in a distribution consistent with metabolic encephalopathy, suggesting progressive neurological involvement beyond what might be attributed to a single acute insult. Electroencephalography revealed evolving hypsarrhythmia, a finding of considerable clinical significance that raised the possibility of infantile spasms occurring in the context of an underlying metabolic or neurodegenerative process.

Hematological investigations demonstrated microcytic hypochromic anemia, and thyroid function testing revealed a deranged thyroid profile. Peripheral blood smear examination did not identify giant cytoplasmic granules within leukocytes. Immune function parameters were within acceptable limits, and there was no evidence of HLH on clinical or biochemical assessment.

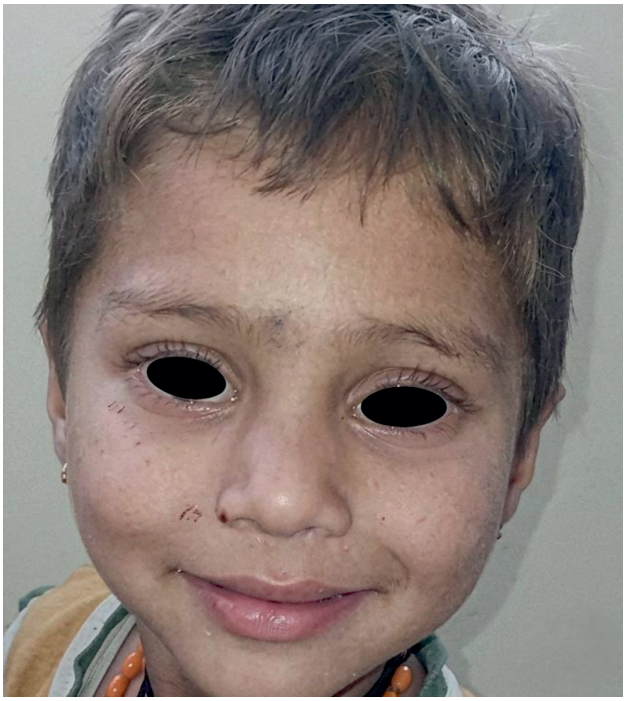

Figure 2: Depigmented hair of eyebrows and eyelashes

Dermoscopy (Dino-Lite, ×200) disclosed the same pattern of coarse, unevenly distributed melanin clumps along the hair shaft as observed in the preceding two cases.

The clinical profile of this child-dominated by severe and progressive neurological impairment, metabolic encephalopathy, evolving hypsarrhythmia, and conspicuous absence of immune compromise - was most consistent with Griscelli syndrome Type 1, arising from mutations in the *MYO5A* gene. In Type 1 GS, neurological involvement constitutes the primary and often exclusive systemic manifestation, with the immune system remaining functionally intact. Molecular confirmation was not obtainable in this

case owing to financial constraints precluding genetic analysis; the subtype designation rests upon the clinical phenotype. This case therefore represents a phenotypically distinct subtype within the series, unified with the other two cases only by the shared dermoscopic hair shaft signature.

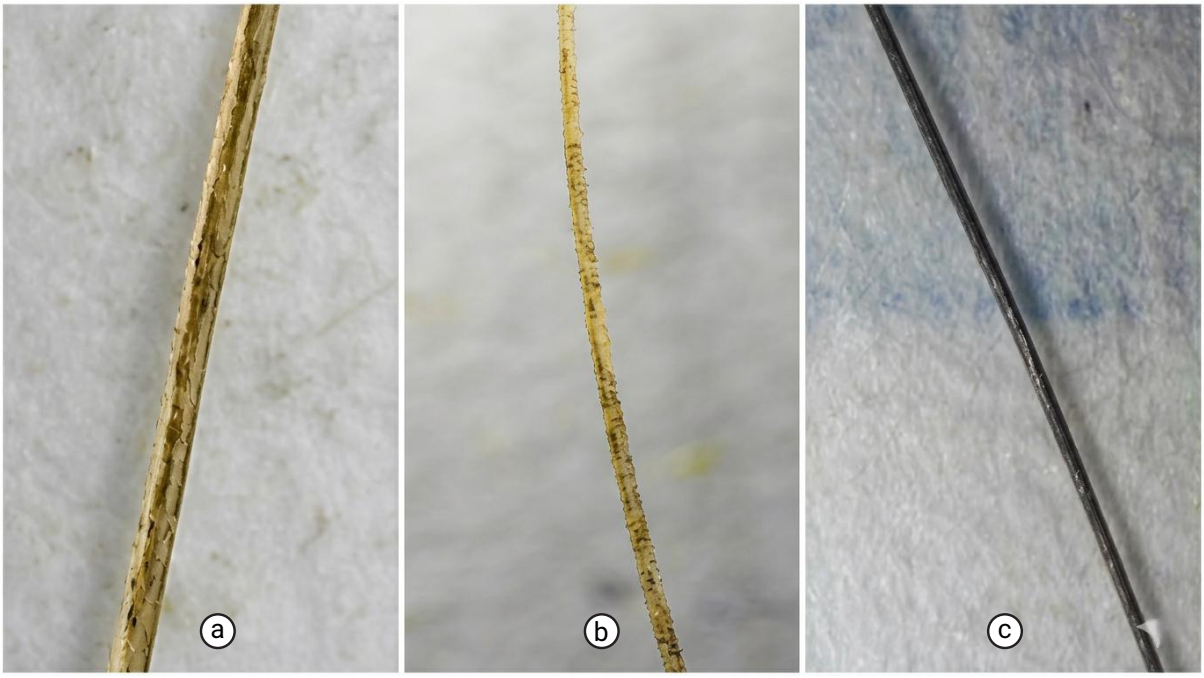

Figure 3 : (a) Hair shaft of Case 1 showing irregular, coarse clumps of melanin along the shaft(Dino-Lite,×200). (b) Hair shaft of Case 2 demonstrating characteristic uneven melanin clumping along the shaft (Dino-Lite,×200). (c) Normal scalp hair showing uniform melanin distribution along the shaft (Dino-Lite, ×200), included for comparison.

Discussion

Griscelli syndrome results from the disruption of a tripartite protein complex - comprising RAB27A, melanophilin (MLPH), and myosin Va (MYO5A) - that orchestrates the transport and anchoring of melanosomes within melanocytes[5]. When any component of this complex is rendered non-functional by biallelic mutation, melanosomes accumulate aberrantly within the melanocyte rather than being transferred to surrounding keratinocytes, producing the characteristic pigmentary dilution of the hair. In Type 2 GS, the defect in RAB27A additionally impairs cytotoxic granule secretion by natural killer cells and cytotoxic T lymphocytes, precipitating the immune deregulatory state and the attendant risk of HLH[6]. Griscelli syndrome type 1 (GS1) is a rare autosomal recessive disorder caused by mutations in MYO5A on chromosome 15q21.2[7].

The dermoscopic signature across all three cases was uniform and diagnostically compelling: coarse melanin aggregates distributed in an irregular and uneven fashion along the hair shaft, without the orderly granular deposition that characterizes normal hair. This trichoscopic pattern, while shared across GS subtypes, serves as a pivotal differentiating feature from other conditions presenting with silvery hair in childhood, and constituted the common diagnostic thread uniting three clinically disparate cases in this series.[3]

The differential diagnostic landscape[8] for silvery hair in a child is narrow but clinically important, and each condition within it carries distinguishing features that permit systematic exclusion:

Table 1: Differential diagnosis of silvery hair in childhood with distinguishing clinical and dermoscopic features

Differentiating Feature	Griscelli Syndrome	Chediak–Higashi Syndrome	Elejalde Syndrome	Oculocutaneous Albinism
Hair color	Silvery-yellow	Silvery-gray	Silvery	White to pale yellow
Dermoscopic melanin pattern	Irregular, coarse clumps	Large, evenly spaced clumps	Irregular clumps	Absent or uniformly sparse
Giant leukocyte granules on smear	Absent	Pathognomonic, present	Absent	Absent
Primary immune dysfunction	Present (Type 2)	Present	Absent	Absent
Neurological involvement	Variable (Types 1 and 2)	Present	Severe and predominant	Absent
Risk of HLH	Significant (Type 2)	Present	Absent	Absent
Causative gene(s)	RAB27A, MYO5A, MLPH	LYST	MYO5A	TYR, OCA2, SLC45A2, others

In the present series, Chediak-Higashi syndrome - the most clinically proximate differential - was systematically excluded in all three children by the absence of the pathognomonic giant cytoplasmic granules within peripheral blood leukocytes[9]. Elejalde syndrome, which shares both the silvery hair phenotype and neurological involvement with GS Type 1, was considered but argued against by the presence of immune dysfunction in Cases 1 and 2, and by the specific electrophysiological and neuroimaging profile in Case 3; Elejalde syndrome characteristically lacks immune compromise and does not predispose to HLH[10]. Oculocutaneous albinism was excluded on the basis of the dermoscopic melanin clumping pattern and the multisystem involvement, neither of which is a feature of that condition.

The three cases presented here collectively illustrate the phenotypic heterogeneity that defines Griscelli syndrome across its subtypes. Case 1 represents the most severe expression of Type 2 disease, with genetically confirmed *RAB27A* mutation, bone marrow-proven HLH, and a fatal outcome - reinforcing the imperative for early diagnosis and prompt consideration of hematopoietic stem cell transplantation in this subtype. Case 2 further elaborates the immunological phenotype of Type 2 GS, with recurrent serious bacterial infections, meningitis, and transfusion-dependent anemia reflecting the depth of immune compromise inherent to this subtype, even in the absence of molecular confirmation. Case 3, by contrast, illustrates Type 1 GS in its characteristic neurological expression: severe global developmental delay, metabolic encephalopathy on MRI, evolving hypsarrhythmia on EEG, and a complete absence of immune dysfunction, consistent with *MYO5A* mutation disrupting neurological rather than immunological function.

This juxtaposition of subtypes within a single case series is instructive. It underscores that while the dermoscopic hair shaft finding of irregular melanin clumping is a shared and reliable diagnostic marker across all GS subtypes, subtype determination is entirely dependent upon the accompanying systemic phenotype and, where available, molecular analysis. A child with silvery hair and predominant neurological impairment without immune dysfunction should prompt consideration of Type 1 GS and investigation directed toward *MYO5A*; immune dysregulation and HLH risk, on the other hand, should direct attention toward Type 2 and *RAB27A* sequencing. This distinction carries direct therapeutic implications: hematopoietic stem cell transplantation is indicated and potentially curative in Type 2 but is not the treatment of choice in Type 1, where neurological management and supportive care take precedence.

These observations collectively reinforce the principle that pigmentary dilution of the hair in a child should not be regarded as an isolated cosmetic finding but as a potential sentinel of serious systemic disease. Dermoscopy of the hair shaft provides a rapid, reproducible, and non-invasive means of identifying the characteristic melanin clumping pattern, serving as a critical bridge between clinical suspicion and definitive molecular confirmation - or, where molecular confirmation is unattainable, as the primary anchor of diagnosis in its own right.

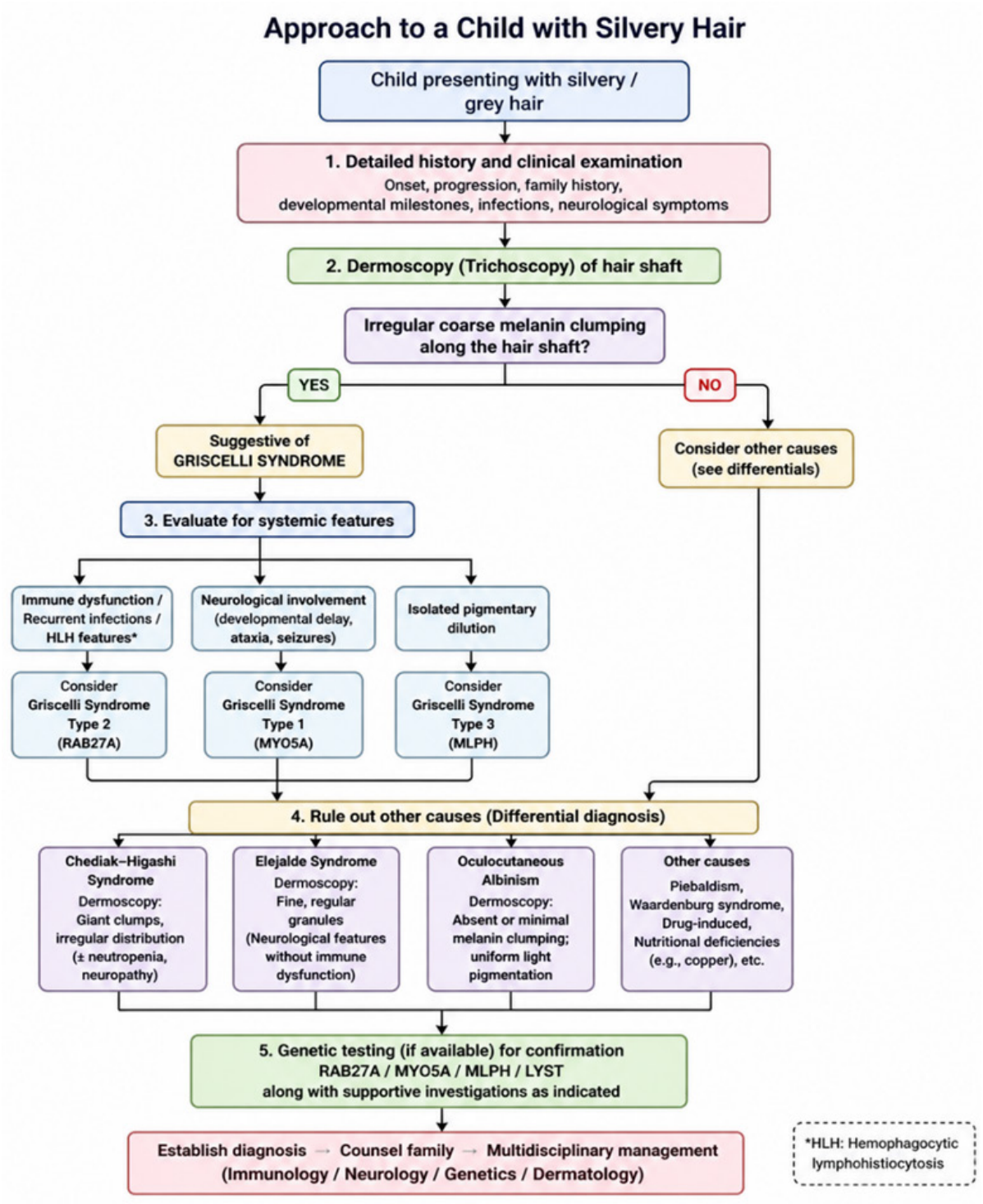

Figure 4 : flow chart on approach to a child with silvery hair

Limitations

Genetic confirmation was available in only one case, while diagnoses in the remaining two relied on clinical phenotyping due to financial constraints, introducing some diagnostic uncertainty. The small sample size limits generalizability, and long-term follow-up was unavailable for two patients, restricting assessment of outcomes. Despite this, study highlights the value of dermoscopy as a practical, non-invasive diagnostic tool, particularly in resource-limited settings where molecular testing may not be feasible.

Conclusion

Griscelli syndrome is a condition of remarkable phenotypic breadth, capable of manifesting as isolated pigmentary change, fulminant immune collapse with

fatal HLH, or severe progressive neurological disease, depending upon the underlying genetic subtype. The three children described in this series illuminate this heterogeneity across subtypes: molecularly confirmed Type 2 GS with fatal HLH progression, profound immune dysregulation with recurrent serious infections in a second Type 2 case, and Type 1 GS presenting with progressive metabolic encephalopathy and evolving hypsarrhythmia in the absence of immune compromise. Each child, irrespective of subtype, shared the unifying dermoscopic signature of irregular hair shaft melanin clumping, affirming dermoscopy as a frontline diagnostic instrument capable of directing clinical suspicion and guiding differential diagnosis at a stage when therapeutic intervention remains viable. Financial constraints limiting genetic analysis in two of three cases further underscore the real-world relevance of dermoscopy as a diagnostic anchor in settings where molecular testing remains inaccessible. Recognition of the subtype-defining systemic phenotype alongside this shared dermoscopic finding is essential, as it determines the investigative pathway, genetic target, and therapeutic strategy for each individual child.

Declarations

Declaration of patient consent: Informed consent was obtained from the parents and legal guardians of all three children for the publication of clinical details and associated images in accordance with institutional guidelines.

Recommendation

In children presenting with silvery hair, early dermoscopic evaluation should be incorporated into routine assessment. Accumulation of similar clinicodermoscopic observations across larger case series may further strengthen diagnostic confidence and aid in subtype differentiation.

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