Case Report

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Griscelli syndrome: a diagnostic challenge of a rare disease: a case report

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Introduction: Griscelli syndrome (GS) is a rare autosomal recessive genetic disorder that primarily manifests as hair and skin hypopigmentation, with three types differentiated by their specific genetic defects as well as by their clinical features. Clinically, GS type 1 is characterized by early neurological alterations, while GS type 2 is characterized by immunodeficiency and could present with neurological symptoms, and type 3 is characterized by a chromosomal anomaly without a specific clinical profile besides hypopigmentation. This article details the challenges faced in the diagnosis of a patient with GS who presents with neurological symptoms followed by immunological deficits.

Case presentation: A 7-month-old female presented with complaints of developmental delay following an otitis media infection. Upon examination, she exhibited signs of psychomotor developmental regression and had pale bronze skin and silvery-gray hair, as well as hepatosplenomegaly. The examination of her hair shaft revealed a pattern consistent with GS. During her hospitalization, the patient developed an intermittent fever and signs of hemophagocytic lymphohistiocytosis (HLH). She subsequently developed recurrent seizures treated with phenytoin and Aciclovir. Shortly she succumbed to respiratory distress syndrome and multisystem failure.

Discussion: The presence of HLH confirms the type of GS. However, in some cases, the HLH criteria could not be fulfilled, presenting a diagnostic challenge.

Conclusion: The genetic examination is the only way to differentiate GS type 1 from type 2. However, when it is not available, the presence of specific symptoms and features may assist in the classification. Furthermore, treatments should be administered when GS type 2 is suspected since they have the potential to improve life quality through treating HLH, delaying and altering the neurological symptoms.

Keywords: genetic disorder, Griscelli syndrome, immunologic dysfunction, neurological alterations, partial albinism

Introduction

Griscelli syndrome (GS) is a rare, inherited autosomal recessive disorder characterized by partial albinism and first described in 1978[1]. GS typically presents between infancy and early childhood[2].

GS is classified into three types based on genetic mutations[3]. Type 1 is caused by a mutation in the MYO5A gene, type 2 results from a mutation in the RAB27A gene, both located on chromosome 15q21 and type 3 is caused by a mutation in the melanophilin gene on chromosome 2q37[3]. All types present with silvery-gray hair and pale skin; however, type 1 is characterized by dominant neurological alterations, while type 2 presents mainly with primary immunodeficiency, and type 3 has no specific features besides hypopigmentation which is a common feature in all GS types[3].

Diagnosis of GS is typically made through genetic testing. When testing is not available, the clinical diagnosis becomes challenging, particularly in cases when a patient presents with a combination of neurological symptoms and immunological deficiency[4]. Despite its rarity, early and accurate diagnosis is crucial as neurological symptoms present in type 2 GS may be treatable[5].

HIGHLIGHTS

- Griscelli syndrome (GS) is a rare autosomal recessive genetic disorder that causes different presentations according to its type.
- The diagnosis of GS is usually established through genetic analysis upon clinical suspicion.
- Access to such tests in war zones might be limited.
- The clinical manifestations, along with the age of presentation, play a crucial role in distinguishing between GS types.
- Early detection and diagnosis can help increase the quality of life.

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In this case report, we discuss the challenges in distinguishing the type of GS in a 7-month-old girl who presented with clinical features indicative of both type 1 and type 2 GS.

Case presentation

A 7-month-old female of Syrian descent, born to consanguineous parents, was referred for evaluation of developmental regression. The onset of developmental regression occurred 20 days prior to presentation following an otitis media infection, which was treated with antibiotics media. The patient's medical history was unremarkable for genetic, metabolic, or hematologic disorders, and there were no reported cases among the patient's parents or siblings.

Differential diagnosis, investigations and treatment

Upon physical examination, the patient exhibited pale bronze skin with silvery-gray hair, hepatosplenomegaly, an open anterior fontanelle measuring 2 × 3 cm, and signs of psychomotor developmental regression, including loss of babbling, rolling over, tracking objects with the eyes, and crawling abilities. Tendon and cutaneous reflexes were normal, and cranial nerve examination revealed no abnormalities. Ultrasound imaging of the abdomen confirmed hepatosplenomegaly, and head ultrasound showed no evidence of hemorrhage or hydrocephalus. The laboratory examinations were insignificant (see Table 1). Microscopic analysis of the patient's hair shafts revealed a pattern consistent with GS. However, genetic testing was not available.

Outcome and follow-up

During admission, the patient developed intermittent fever without a clear source. Bone marrow aspiration revealed a decreased myeloid to erythroid ratio (M: E = 3:1) secondary to decreased granulocytes, and laboratory findings were consistent with hemophagocytic lymphohistiocytosis (HLH), although diagnostic criteria were not fulfilled.

The patient subsequently experienced recurrent seizures, which were partially controlled with phenytoin. Laboratory results indicated possible active infection, as evidenced by an elevated C-reactive protein (CRP) level of 7.3. Antibiotics course of Vancomycin, Ceftriaxone, and sulbactam was initiated. Analysis of cerebrospinal fluid revealed evidence of viral meningitis, and therapy with Acyclovir and Prednisone was implemented. The patient subsequently developed a seizure characterized by central cyanosis, bradycardia, and respiratory failure, likely due to acute intracranial hemorrhage. The patient's condition deteriorated, with decreased hemoglobin and platelet levels and prolonged PT and PTT. Despite interventions infusion of vitamin K, plasma, platelets, and blood transfusion, and applying mechanical ventilation for respiratory distress syndrome (RDS), the patient ultimately succumbed to multisystem failure.

Table 1

laboratory findings upon admission

WBC	5800/µl	Prothrombin time (PT)	92%
Lymphocytes	56%	Partial thromboplastin time (PTT)	27s
Neutrophils	27%	Urea	23 mg/dl
Hemoglobin (HB)	9.6 g/dl	Creatinine	0.6 mg/dl
Mean corpuscular volume (MCV)	75 femtoliter	Fasting glucose	76 mg/dl
Platelets (PLT)	172 000/µl	ESR	21 mm/Hr
Reticulocytes	1.8%	CRP	0.9 mg/dl
Ferritin	180 ng/ml	Na	137 mEq/l
Cholesterol	143 mg/dl	K	4.8 mmol/l
Triacid glycerol	212 mg/dl	Ca	9.5 mg/dl
Total protein	7.1 ng/dl	P	4.2 mg/dl
Albumin	4.2 g/dl	Fibrinogen	165 mg/dl
Blood gases:		Urine analysis:	
PH	7.49	Color	Yellow
Pco2	24 mmHg	Specific gravity	0.015
Po2	67 mmHg	PH	5
Hco3	18 mEq/l	Wight cells	2–3 cells
Sat o2	79%	Red cells	1–2 cells
Direct and indirect coombs tests	Negative	Epithelial cells	1–2 cells
Widal test	Negative		

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

Discussion

Griscelli syndrome is a rare genetic autosomal recessive disorder characterized by multisystem involvement[1]. It has a higher incidence in populations with a high prevalence of consanguineous marriage[6].

The most common symptom among all subtypes of Griscelli syndrome is pigmentary dilution[7]. However, GS type 1 is primarily characterized by dominant neurological impairment, while GS type 2 is characterized by dysfunction of T cells and natural killer cytotoxic cells, leading to immunodeficiency[1,4,8]. Differential diagnoses include Chediak-Higashi syndrome (CHS) and Elejalde syndrome (ES), both of which share some similarities with Griscelli syndrome such as partial albinism[9,10]. Moreover, ES has a genetic link to GS type 1 and also presents with neurological symptoms without immunodeficiency[9]. On the other hand, CHS may mimic the immunodeficiency seen in GS type 2. However, the presence of large clumps of pigment in the hair shaft favors GS type 2 over CHS where more evenly distributed pigment clumps are seen[9,10].

The manifestations of type 1 GS typically consist of neurological manifestations, such as seizures, hypotonia, developmental delay, and intellectual impairments[4,7]. However, similar symptoms can be seen in type 2 GS, despite the difference in the etiology[11,12]. Where it may be caused by central nervous system (CNS) infections or by lymphocytic infiltration in the presence of HLH[13,14]. In our case, the patient had signs of HLH and suffered also from meningitis. However, both presented after the neurological manifestations, which led to difficulties in specifically identifying GS type.

HLH is a significant complication of GS. It is a systemic inflammatory condition caused by high serum levels of cytokines released from cytotoxic T (CTL) and natural killer (NK) cells that lead to macrophage hyperactivation[15]. HLH has two types: Primary HLH; which is hereditary and affects the pediatric population, and typically results in death unless it is treated[15]. Secondary HLH; mostly affects adults and is frequently induced by an infection or cancer[15].

Table 2

laboratory findings after the patient developed seizure and was admitted to the ICU

WBC	7200\ μl dropped to 1700 after 4 days	Albumin	2.4 g/dl
HB	7.9 g/dl	PT	35%
PLT	133 000\ μl dropped to 10 000 after 4 days	PTT	39s
Na	126 mEq/l	CRP	3.9 mg/dl and elevated to 7.3 mg/dl after 4 days
K	3.6 mmol/l	CSF analysis	
Random plasma glucose	141 mg/dl	Cells	140 (63 lymphocytes)
Serum glutamic-oxaloacetic transaminase (SGOT)	195 IU/l	Protein	41 mg/dl
Serum glutamic pyruvic transaminase (SGPT)	81 IU\l	Glucose	55 mg/dl

CRP, C-reactive protein; CSR, cerebrospinal fluid; HB, hemoglobin; PLT, platelets; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell.

To diagnose HLH, there should be either molecular analysis consistent with HLH, or five out of these eight diagnostic criteria should be fulfilled: fever, splenomegaly, cytopenia affecting at least two blood lines, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low or absent NK-cell activity, ferritin level greater than or equal to 500 mg/l, and soluble CD25 greater than or equal to 2400 U/ml[8]. It is worth mention, that the presence of hemophagocytosis is neither necessary nor sufficient for the diagnosis of HLH[16]. Furthermore, fever, splenomegaly, hepatomegaly, cytopenia are the most common symptoms[17]. In our case, the patient had fever, pancytopenia, and splenomegaly. However, not all diagnostic panel was available (see Table 2).

A new method, which includes elevated levels of IFN-γ and IL-10 with only modestly elevated IL-6 levels, has been found to have high accuracy in distinguishing HLH from infection as it reflects T-cell dysfunction[18].

The definitive diagnosis of GS types is based on genetic examination[4]. However, in third-world countries such as in Syria, genetic examination is not always available. Thus, the symptoms play a major role in distinguishing between types 1 and 2 (Fig. 1). However, the signs of immunodeficiency might not always be present as in our case since the patient did not show clear signs of immunodeficiency and had dominant neurological symptoms[7]. Moreover, the type and severity of neurologic symptoms add no diagnostic value[14,19]. However, the presenting time for the neurological symptoms could aid in distinguishing them[4,20]. Where the neurological symptoms in GS type 1 usually present early[4]. On the other hand, in GS type 2, the neurological symptoms usually delay[20]. Moreover, the presence of HLH symptoms, such as fever, splenomegaly/hepatomegaly, and cytopenia, plays a crucial role in distinguishing between GS types 1 and 2, even when the formal HLH criteria are not fulfilled. Another method would be to use Western blot analysis to detect the lack of RAB27A expression, reflecting the impaired T-cell and natural killer cytotoxicity seen in GS type 2[21].

The identification of the specific subtype of GS is of paramount importance, as it has implications for treatments, and potential outcomes. Specifically, while type 1 GS is characterized by the lack of effective therapies and poor prognosis, type 2 GS may be amenable to interventions; that can improve quality of life[8,22]. The primary objective of treatment in type 2 GS is to slow the progression of HLH, as it represents one of the major causes of mortality in these patients[8]. Additionally, early initiation of treatment may mitigate the development of neurological disability[5]. Therefore, treatment must be initiated at the earliest suspicion of type 2 GS, even in the absence of definitive diagnostic criteria for HLH[23]. In our case, the patient, unfortunately, passed away prior to the initiation of any therapeutic

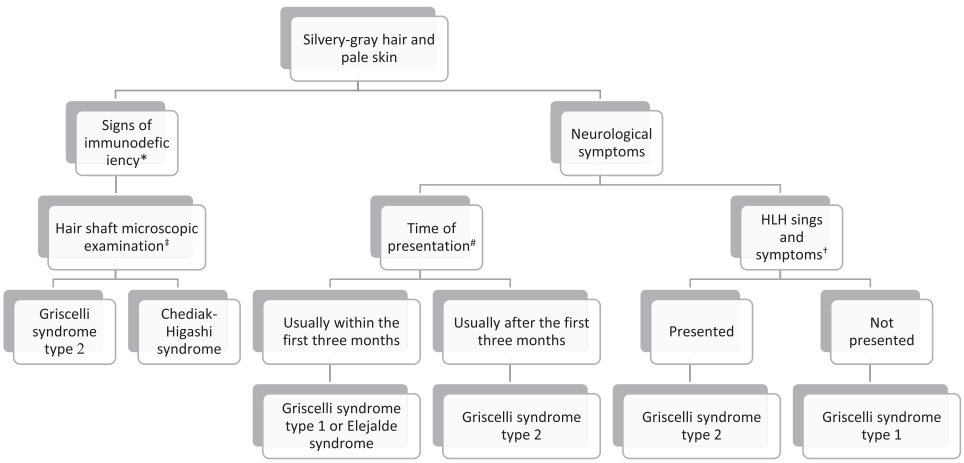

Figure 1. A flow chart demonstrating the diagnostic approach for Griscelli syndrome when genetic analysis is not available. *: recurrent infections and/or persistent infections; †: HLH symptoms include fever, splenomegaly, cytopenia, low T-cells function; ‡: The presence of large clumps of pigment in the hair shaft favors Griscelli Syndrome type 2 over Chediak-Higashi syndrome where more evenly distributed pigment clumps are seen; #: There is no clear threshold to differentiate between Griscelli syndrome types 1 and 2, but the early-life onset (even at birth) of neurological symptoms is indicative of Griscelli syndrome type 1. HLH, hemophagocytic lymphohistiocytosis.

intervention, Due to the delayed suspicion of GS type 2 and the rapid progression of the disease.

The primary therapy for HLH is the administration of dexamethasone[8], which is thought to suppress the pathological activity of HLH and thereby reduce neurological involvement[8]. Prophylactic antibiotics should be considered in the majority of patients to protect against Pneumocystis jirovecii, fungi, and viruses, which could act as triggers for the disorder[23]. However, a recent study proposed the use of intrathecal methotrexate and steroids to manage neurological manifestations, although the effectiveness of this approach has yet to be conclusive[24]. It is worth noting that the use of intrathecal methotrexate carries a significant risk of severe side effects, which may limit its utility[25]. However, hematopoietic stem cell transplantation (HSCT) is still the most effective treatment for HLH, especially if it is done before HLH develops despite the uncertainty of its results and the toxic effects that it might lead to[5,8].

Despite the variety of treatments for GS type 2, the long-term prognosis is poor and death occurs in most cases in the first decade of life[8,12]. The main cause of death is HLH, along with other complications such as RDS and intracranial hemorrhage[8,26,27].

Conclusion

Genetic diseases, like GS, occur more frequently in communities with high rates of consanguineous marriage. Therefore, genetic counseling is important. Additionally, correctly identifying the type of GS is crucial, as treatments for GS type 2 are available and can improve quality of life. Additionally, the symptoms and characteristics of GS may be useful in distinguishing the different types when genetic testing is not available.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patients' parents for publication of this case report.

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Author contribution

S.A., S.K., R.S. drafted the manuscript. M.J. supervised the project. All authors have read and approved the final manuscript.

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The authors declare that they have no competing interests.

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