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Unraveling the Diagnostic Puzzle of Hermansky-Pudlak Syndrome: Lessons From Two Brothers with Growth Failure

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ABSTRACT

Short stature (SS) is a common reason for consultation in pediatric endocrinology. Its etiologies are varied, with general causes predominating, while endocrine causes account for only about 10% of cases. More rarely, SS may occur in a syndromic context, making diagnosis more complex. Early identification of such cases is crucial for appropriate management and to limit long-term repercussions. We report the cases of two brothers, aged 7 and 9 years, referred for evaluation of SS. Both presented with height and weight below -2 standard deviations for age and sex. Clinical and radiological examinations revealed recurrent epistaxis, micrognathia with broad nasal bridge, oculocutaneous albinism, a polymalformative syndrome including spondyloepiphyseal dysplasia, dorsolumbar scoliosis, and equinovarus foot, and limited joint mobility in the upper and lower limbs. IGF-1 levels were below age- and sex-matched norms. A stimulation test with Avlocardyl®-glucagon confirmed growth hormone (GH) deficiency. Hypothalamic-pituitary MRI was normal. The short stature in these two brothers occurs in a complex syndromic context. The association of oculocutaneous albinism, osteoarticular malformations, and growth hormone deficiency strongly suggests Hermansky-Pudlak syndrome (HPS), a rare genetic disease characterized by albinism and other systemic anomalies. To our knowledge, this is the first report of HPS presenting with growth hormone deficiency in two brothers from North Africa. Diagnosis relies on multidisciplinary evaluation and ideally genetic confirmation. Management requires orthopedic correction of malformations, specialized ophthalmological follow-up, and psychosocial support. GH replacement therapy is contraindicated due to the risk of aggravating bone abnormalities. Early recognition of a rare etiology like Hermansky-Pudlak syndrome enables targeted management, which is essential to improve functional prognosis and quality of life.

KEYWORDS: Hermansky-Pudlak Syndrome, Short Stature, Oculocutaneous Albinism, Growth Hormone Deficiency, Spondyloepiphyseal Dysplasia, Rare Disease, Pediatric Endocrinology.

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1. Introduction

Short stature (SS) is a frequent cause of referral in pediatric endocrinology, with diverse etiologies. While most cases are attributed to general causes such as familial short stature, constitutional delay, or chronic diseases, endocrine etiologies account for only about 10% of cases [1]. In a subset of patients, SS is part of a syndromic disorder, complicating the diagnostic process. Early recognition of such syndromic presentations is critical to ensure timely intervention and prevent long-term complications.

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder characterized by oculocutaneous albinism, bleeding diathesis due to platelet dysfunction, and, in some subtypes, pulmonary or renal involvement [2]. Although growth failure has been occasionally reported in HPS, its association with isolated growth hormone (GH) deficiency is uncommon. Here, we describe two brothers with SS, oculocutaneous albinism, and skeletal anomalies, in whom the clinical picture strongly suggests HPS with GH deficiency. To our knowledge, this is the first report of HPS presenting with growth hormone deficiency in two brothers from North Africa.

2. Case Reports

2.1 Case 1

A 9-year-old boy was referred for evaluation of short stature. His height was 110 cm (-3 standard deviations [SD]), and weight was 18 kg (-2.5 SD) for age and sex. He had a history of recurrent epistaxis since early childhood. Clinical examination revealed micrognathia, a broad nasal bridge, and hypopigmentation of the skin and hair. He also had limited joint mobility in the upper and lower limbs. Radiological examination showed spondyloepiphyseal dysplasia, dorsolumbar scoliosis, and bilateral equinovarus foot.

Laboratory investigations revealed low IGF-1 levels (80 ng/mL, normal range >150 ng/mL for age). A GH stimulation test using Avlocardyl®-glucagon confirmed GH deficiency (peak GH 3.2 ng/mL, normal >10 ng/mL). Hypothalamic-pituitary MRI was normal.

2.2 Case 2

The 7-year-old younger brother presented with similar features. His height was 105 cm (-3.5 SD), and weight was 16 kg (-2.8 SD). Clinical findings included oculocutaneous albinism, micrognathia, and joint limitations. Radiographs confirmed dysplasia and scoliosis (Figure 1). IGF-1 was 60 ng/mL, and GH stimulation showed deficiency (peak GH 2.8 ng/mL). MRI of the hypothalamic-pituitary region was normal.

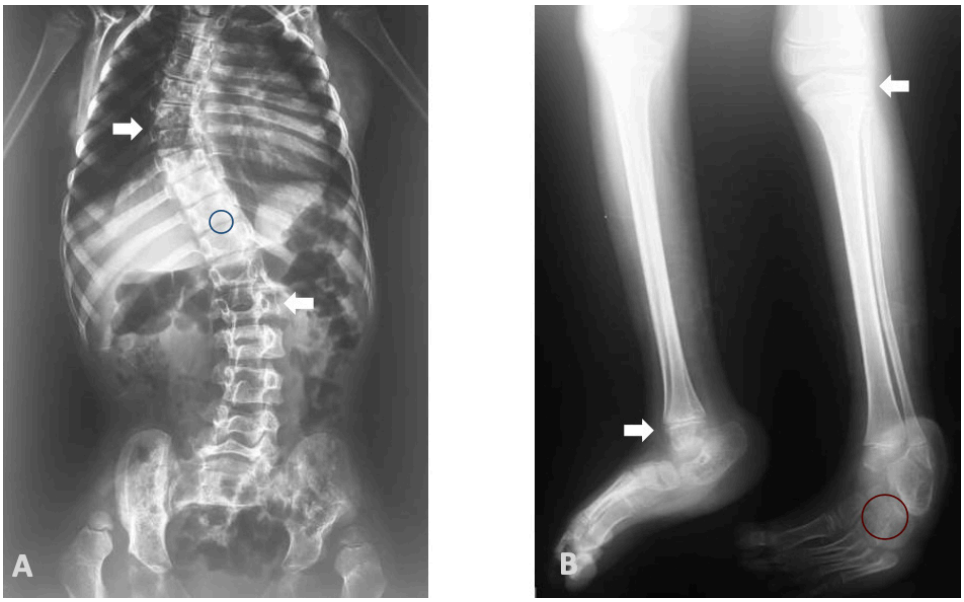

Figure 1. Radiographs of the spine and lower limbs of Brother B (younger sibling) showing dorsolumbar scoliosis with spondyloepiphyseal dysplasia.

1.A. Spine radiograph, anteroposterior view, showing a dorsolumbar scoliosis (white arrows), vertebral endplate irregularities with reduced vertebral body height (blue circle).

1.B. Lower limbs radiograph, showing enlargement of the proximal and distal tibial epiphyses with a lamellated appearance (white arrows) and an oval-shaped appearance of the foot bones (red circle).

2.3 Family History

Both parents had short stature but no albinism. There was no known consanguinity. The paternal grandfather had a history of bleeding tendency.

3. Results:

3.1 Clinical and Biological Characteristics

Table 1: Clinical and Biological Characteristics of the Two Brothers

PARAMETER	CASE 1 (9 YEARS)	CASE 2 (7 YEARS)	AGE-MATCHED NORMS
Height (cm)	110 (-3 SD)	105 (-3.5 SD)	>125
Weight (kg)	18 (-2.5 SD)	16 (-2.8 SD)	>22
IGF-1 (ng/mL)	80	60	>150
GH stimulation (peak ng/mL)	3.2	2.8	>10
MRI hypophysis	Normal	Normal	No lesions
Epistaxis	Recurrent	Recurrent	Non-pathological
Oculocutaneous albinism	Yes	Yes	Not described
Micrognathia	Yes	Yes	Not described
Joint limitation	Yes	Yes	Not described

3.2 Diagnostic Criteria for HPS

Table 2: Diagnostic Criteria for Hermansky-Pudlak Syndrome (HPS)

CRITERION	PRESENT IN OUR PATIENTS	FREQUENCY IN LITERATURE	DIAGNOSTIC VALUE
Oculocutaneous albinism	Yes	100%	Major criterion
Recurrent epistaxis	Yes	80–90%	Major criterion
Growth hormone deficiency	Yes	<5%	Minor criterion
Skeletal malformations	Yes	30–50%	Minor criterion
Scoliosis	Yes	20–30%	Minor criterion
Equinovarus foot	Yes	10–20%	Minor criterion
Genetic confirmation	Not performed	Essential	Gold standard

3.3 Differential Diagnosis

Table 3: Differential Diagnosis of Syndromes with Albinism and Short Stature

SYNDROME	MAIN FEATURES	DIFFERENCES FROM HPS
Hermansky-Pudlak	Albinism, epistaxis, skeletal dysplasia	Presence of skeletal dysplasia
Chédiak-Higashi	Albinism, recurrent infections, lymphocyte anomalies	Severe infections
Griscelli	Albinism, immunodeficiency, neurologic symptoms	Major neurologic involvement
Waardenburg	Albinism, deafness, atypical pigmentation	No epistaxis or dysplasia
Rothmund-Thomson	Poikiloderma, short stature, cataracts	No typical albinism

4. Discussion

4.1 Clinical Diagnosis of HPS

The association of oculocutaneous albinism, skeletal dysplasia, and growth failure in these two brothers is highly suggestive of HPS. HPS is caused by mutations in genes involved in biogenesis of lysosome-related organelles (LROs), leading to defects in melanosomes, platelet dense granules, and other organelles [3]. The most common subtypes, HPS-1 and HPS-4, are associated with pulmonary fibrosis, whereas HPS-3 may present with milder systemic involvement [4].

4.2 Growth Hormone Deficiency in HPS

While growth failure is reported in HPS, isolated GH deficiency is rare. A review by Gahl et al. [5] noted that only 5% of HPS patients have documented GH deficiency, often associated with pituitary abnormalities. In our cases, the absence of structural lesions on MRI suggests a functional or genetic basis for GH deficiency.

4.3 Management Recommendations

Management of HPS requires a multidisciplinary approach. Ophthalmological monitoring is essential for vision correction, and orthopedic interventions may be needed for skeletal deformities. GH replacement is contraindicated due to the risk of aggravating bone dysplasia [6]. Genetic testing should be pursued for confirmation and family counseling.

Table 4: Management Recommendations for Hermansky-Pudlak Syndrome

DOMAIN	RECOMMENDATIONS	GOALS
Ophthalmology	Annual monitoring, visual correction	Prevent vision loss
Orthopedics	Radiologic assessment, deformity correction	Improve function
Endocrinology	Hormonal monitoring, GH replacement contraindicated	Avoid bone aggravation
Hematology	Platelet monitoring, avoid NSAIDs	Prevent bleeding
Genetics	Molecular testing, genetic counseling	Confirm diagnosis, family advice
Psychosocial support	Psychological help, school integration	Improve quality of life

4.4 Novelty and Regional Context

This report is the first to describe HPS with GH deficiency in siblings from North Africa, highlighting the need for increased awareness and genetic testing resources in the region.

5. Conclusion

Hermansky-Pudlak syndrome should be considered in children with short stature, oculocutaneous albinism, and skeletal anomalies. Early recognition allows for tailored management, including avoidance of GH therapy, and facilitates genetic counseling. Further studies are needed to elucidate the genetic basis of GH deficiency in HPS.

6. Conflict of Interest Statement

The authors declare no conflict of interest.

7. Ethical Considerations

This study was designed as a retrospective and observational case report. This case report is not a clinical trial and does not involve data from experimental interventions. The information was collected from medical records as part of routine clinical follow-up. As a retrospective observational study, it did not require formal approval by a research ethics committee, in accordance with national and institutional guidelines for this type of publication. All procedures adhered to the ethical principles of the 2013 Helsinki Declaration, ensuring patient confidentiality, anonymity, and respect.

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