

Rare association Niemann-pick B syndrome and familial Fanconi syndrome

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ABSTRACT

Recent advancements in therapeutic development have led to a significant breakthrough in the treatment of acid sphingomyelinase deficiency (ASMD), with Olipudase α emerging as the first specific enzyme replacement therapy. This innovative treatment aims to replace the deficient or defective acid sphingomyelinase enzyme, offering hope for patients with this condition. We report the case of a 28-year-old male from a first-degree consanguineous family with a history of Fanconi syndrome and nephrolithiasis, hospitalized for moderate renal impairment and asthenia. Diagnostic evaluation revealed tubular proteinuria, glycosuria, hyperphosphaturia, hyperuricuria, and hypercalciuria, leading to the diagnosis of Fanconi syndrome. Additionally, the patient's distinctive facial features, hepatosplenomegaly, hypertriglyceridemia, and thrombocytopenia prompted further investigation, culminating in the diagnosis of Niemann-Pick type B syndrome (NPBS), confirmed by biochemical and genetic studies. This case highlights the rare association of an autosomal dominant disorder (Fanconi syndrome) and an autosomal recessive disorder (NPBS) in a Maghrebian family, diagnosed late in adulthood, resulting in a significant therapeutic delay.

Keywords: *Toni-Debré Fanconi syndrome; Niemann-Pick B syndrome; Renal failure*

INTRODUCTION

Toni-Debré Fanconi syndrome is a complex renal tubulopathy characterized by generalized dysfunction of the proximal tubule, leading to excessive urinary loss of glomerular filtrate components, including amino acids, glucose, phosphate, bicarbonate, calcium, potassium, uric acid, and other solutes ^{1,2}. This syndrome may arise secondary to intoxication (e.g., mercury, lead), inherited metabolic disorders (e.g., cystinuria, galactosemia), or malignancies (e.g., multiple myeloma). When no underlying cause is identified, it is classified as primary Fanconi syndrome, which can be hereditary and

transmitted in an autosomal dominant manner ^{1,2}. Clinical manifestations, including dehydration, metabolic acidosis, and hypocalcemia, result from renal solute losses and can lead to bone fragility, rickets, growth retardation in children, or osteomalacia in adults. Treatment focuses on addressing the underlying cause when possible, or managing symptoms through rehydration, calcium supplementation, vitamin D, and alkalization therapy.

Niemann-Pick disease, an autosomal recessive disorder, results from acid sphingomyelinase deficiency ³. It is classified into two primary types (A and B) and intermediate forms (A/B). Type B, the less severe form,

lacks neurological involvement and has a variable age of onset, often extending into adulthood. The most consistent feature is hepatosplenomegaly, accompanied by recurrent pulmonary infections, interstitial lung disease, joint pain, diarrhea, growth retardation, and delayed puberty ³. The diagnosis of ASMD is confirmed by detecting biallelic pathogenic variants in the *SMPD1* gene and demonstrating residual acid sphingomyelinase activity below 10% of normal levels in peripheral blood lymphocytes or cultured skin fibroblasts ⁴.

Case Presentation

We report the case of a 28-year-old male (III-1, Figure 1) hospitalized for the evaluation of moderate renal insufficiency, incidentally discovered during an investigation of low back pain and asthenia following the Ramadan period.

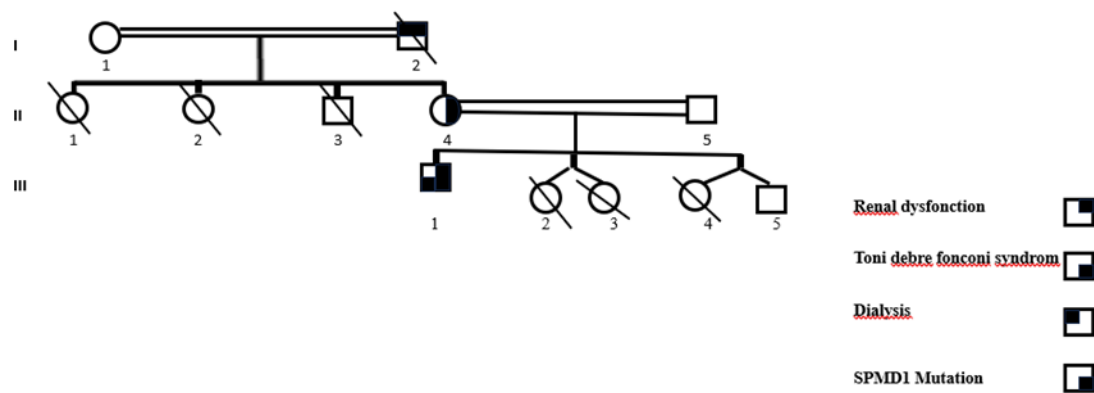


Figure 1: Family pedigree of the Algerian family with clinical Toni-Debré Fanconi syndrome (I 2, II 4 and III 1) associated with Niemann Pick B syndrome (III 1).

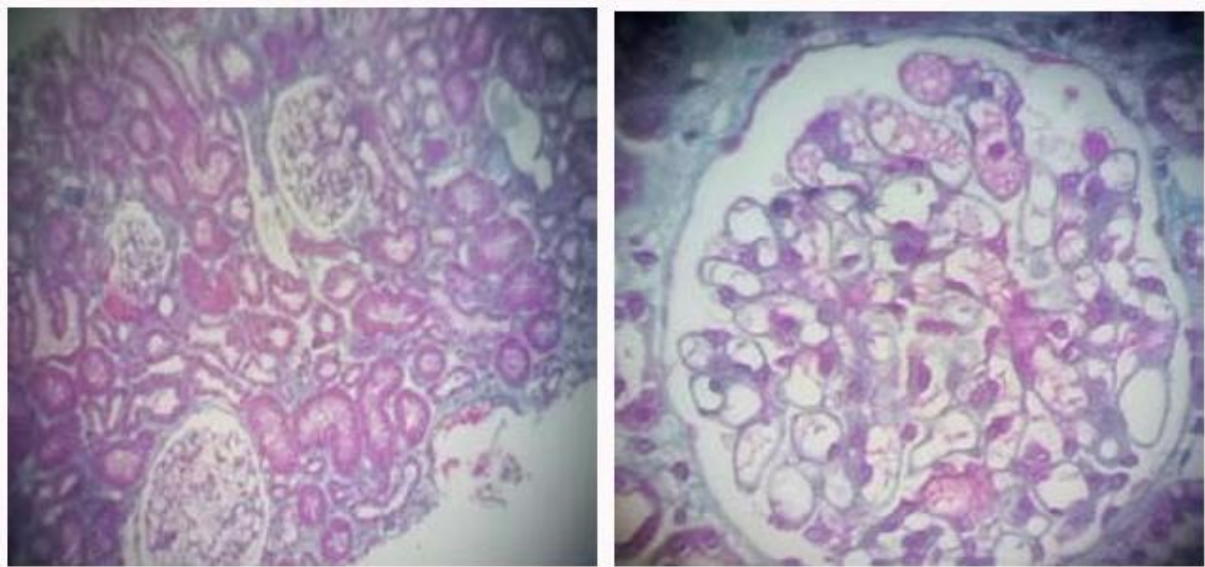


Figure 2: Renal biopsy of the patient (III 1). Optical microscopy with Trichrome Masson stain. Optically normal glomeruli. Non-specific tubulo-interstitial lesions with 02 fibrosis band, one of which contains some atrophic proximal convoluted tubules.



Figure 3: Face of the patient III 1 with a rinophyma and palpebral

The patient's medical history includes prematurity at eight months, polyuria-polydipsia since childhood, and hepatosplenomegaly, which was incidentally identified during a pediatric hospitalization at the age of four. At 17 years of age, the patient developed acne vulgaris, nasal turbinate hypertrophy, and periorbital edema, without lower limb edema.

Clinical examination at 28 Years of age, the patient exhibited normal weight, height, and pubertal development (172 cm, 70 kg). Distinctive facial features included nasal turbinate hypertrophy (rinophyma), a butterfly-wing-shaped facial rash, and periorbital edema (Figure 3). Macules and papules were observed on the chest and back. Abdominal examination revealed a soft abdomen with significant hepatosplenomegaly. Blood pressure was normal at 120/80 mmHg, and the remainder of the clinical examination was unremarkable.

Biochemical evaluation confirmed moderate chronic renal insufficiency, with a serum creatinine level of 2.1 mg/dL and an estimated glomerular filtration rate (eGFR) of 47 mL/min. Urea levels were within normal limits (0.031 g/dL), while uric acid levels were low (2.0 mg/dL). Hypocalcemia (8.1 mg/dL), hyponatremia (126 mEq/L), and hypokalemia (3 mEq/L) were noted, although magnesium, phosphorus, and blood glucose levels were normal. Lipid profile revealed hypertriglyceridemia (327 mg/dL), with normal cholesterol (179 mg/dL), LDL (15 mg/dL), and HDL (6.5 mg/dL) levels. Urinalysis revealed a 24-hour diuresis of 3 liters, with a urinary pH of 5, proteinuria, and glycosuria. Further assessment confirmed proteinuria (1.24 g/24 h), hyperuricuria (780 mg/24 h), hypernatruria (200 mEq/L), hyperkaluria (31 mEq/L), hypercalciuria (435 mg/24 h), and

hyperphosphaturia (1117 mg/24 h). No hematuria or leukocyturia was detected.

Abdominal ultrasound showed slightly reduced kidney size (right kidney: 9 cm; left kidney: 9.2 cm), with mild hyperechogenicity but preserved corticomedullary differentiation. Renal biopsy revealed 8 to 15 glomeruli (Figure 2), two of which were sclerotic, while the others appeared morphologically normal, with no significant immunofluorescence deposits. Small foci of nonspecific interstitial fibrosis were observed, surrounding atrophic proximal convoluted tubules (Figure 2).

Family history: the patient's maternal grandfather (i-2) had a history of polyuria-polydipsia since childhood and developed bilateral renal lithiasis at 35 years of age, treated with extracorporeal lithotripsy. He required hemodialysis from the age of 65 and died at 72. The patient's mother (II-4), a 52-year-old consanguineous individual, reported nycturia until the age of 14, with a childhood diuresis of 3–4 liters/24 hours. She also developed bilateral renal lithiasis, treated with repeated lithotripsy, and complained of lumbar pain and asthenia. Her obstetric history included five pregnancies: two late abortions at five months, two preterm deliveries (6 and 7 months) resulting in neonatal death, and one live birth (the patient) at eight months' gestation with a low birth weight (2.7 kg).

Further Investigations and Diagnosis of Niemann-Pick Disease :given the persistent hepatosplenomegaly, additional investigations were conducted. Liver function tests and viral serologies (HIV, hepatitis B and C) were normal. Antinuclear antibodies were negative. Hematological evaluation revealed thrombocytopenia (92,000/mm³) without anemia or leukopenia. A blood

smear was unremarkable, but bone marrow biopsy identified large foam cells suggestive of a metabolic storage disorder, such as Gaucher disease or Niemann-Pick disease.

The diagnosis of Niemann-Pick disease type B was confirmed by biochemical and genetic studies: a markedly reduced acid sphingomyelinase level (52 pmol/spot/20 h; normal range: 200–3500) and a homozygous deletion in the *SMPD1* gene (c.1829_1831delGCC), resulting in the loss of arginine 608 ($\Delta R608$) in the protein. Both parents were heterozygous carriers of the same mutation.

Imaging and Additional Findings : Chest X-rays revealed diffuse interstitial pulmonary lesions, while echocardiography was normal. Abdominal ultrasound demonstrated heterogeneous hepatomegaly with multiple echogenic nodules and signs of portal hypertension due to intrahepatic block, without decompensation. Rhinoscopy confirmed nasal turbinate hypertrophy without septal deviation, and sinus imaging was unremarkable. Ophthalmological evaluation, including fundoscopy and slit-lamp examination, revealed no abnormalities. Salivary gland biopsy was normal. Re-examination of the renal biopsy with May-Grünwald-Giemsa staining, prompted by the presence of foam cells in the bone marrow, showed no specific deposits in renal cells.

DISCUSSION

The co-occurrence of two genetic disorders one autosomal dominant and the other autosomal recessive is exceptionally rare. Such an association can lead to diagnostic challenges, as one condition may obscure the other. In the case of our patient, the presence of moderate chronic renal failure, a family history of polyuria, and consistent blood and urine test results promptly led to the diagnosis of Toni-Debré Fanconi syndrome, an autosomal dominant disorder ^{2, 5}. Renal biopsy in this context revealed only mild, nonspecific focal tubulointerstitial lesions.

However, several clinical and paraclinical findings in this patient, particularly chronic hepatosplenomegaly and thrombocytopenia, remained unexplained. These findings prompted a bone marrow biopsy, which demonstrated the presence of large foam cells indicative of a metabolic storage disorder, such as Gaucher disease or Niemann-Pick disease, given the patient's adult-onset symptomatology ⁶. Subsequent enzymatic studies ⁷ and genetic testing confirmed the diagnosis of Niemann-Pick disease type B, linked to a mutation in the *SMPD1* gene. The identified mutation in our patient was a homozygous $\Delta R610$ mutation, which is particularly prevalent among Maghrebian patients ^{8, 9}. The clinical presentation associated with this mutation aligns with type B Niemann-Pick disease ¹⁰, the most common and least severe form of the disorder. As reported in the literature,

the diagnosis in this case was delayed until the patient was 28 years old ^{8, 11}.

Cutaneous manifestations, such as the papular lesions observed on the face, back, and thorax in our patient, have been previously described in Niemann-Pick disease ¹². Additionally, the presence of rhinophyma in our patient, though rare, has been reported in association with Niemann-Pick type B ¹³. Radiological assessment revealed diffuse interstitial pulmonary opacities consistent with pneumonitis ^{5, 11}, while abdominal ultrasound demonstrated heterogeneous hepatic parenchyma and a hypoechoic nodule in the right adrenal region. Interestingly, no cellular lipid overload or glomerulopathy was observed in the renal parenchyma, even upon re-examination of biopsy slides following genetic confirmation of Niemann-Pick disease.

In the literature, renal involvement in Niemann-Pick disease is rare. Two cases of renal impairment have been reported in patients with Niemann-Pick type C, but these were considered coincidental associations ^{14, 15}. In contrast, a single case of renal damage directly attributed to Niemann-Pick disease was reported in a patient with type A/B disease ¹⁶. In that case, renal dysfunction was detected at 14 years of age, more than a decade after splenectomy. Renal biopsy revealed glomerular sclerosis, tubular atrophy, and massive lipid accumulation in podocytes and tubular cells, accompanied by interstitial foam cell infiltrates. Electron microscopy identified multiple osmiophilic, lamellar, membrane-bound inclusions in podocytes and, less frequently, in tubular and vascular endothelial cells. These "myelin-like" inclusions resemble those seen in Fabry disease but differ in their distribution, sparing endothelial and mesangial cells ^{17, 18}. Unlike Niemann-Pick disease, renal involvement is more commonly observed in other lipid storage disorders, such as inherited lecithin-cholesterol acyltransferase deficiency, Fabry disease, or metachromatic leukodystrophy ¹⁹. Olipudase alfa, a recombinant human acid sphingomyelinase enzyme replacement therapy, represents a groundbreaking advancement for the treatment of non-central-nervous-system manifestations of acid sphingomyelinase deficiency (ASMD). Supported by over 40 publications in PubMed since 1993, this therapy has demonstrated efficacy in reducing hepatosplenomegaly by 31% and 39%, respectively, while maintaining safety for cardiac and hematological parameters ²⁰. Lipid profiles and elevated liver transaminase levels improved or normalized within one year of treatment and remained stable through two years ²¹.

For this 28-year-old patient with dual pathologies, the long-term prognosis remains guarded. Renal prognosis depends on the progression of Toni-Debré Fanconi syndrome and the risk of recurrent dehydration episodes, which may lead to calcium precipitation, as observed in

the patient's parents. Ensuring adequate daily fluid intake, even during youth, is essential to prevent such complications. Conversely, Niemann-Pick disease predisposes the patient to multiple systemic complications, including cardiac, hemorrhagic, hepatic, and pulmonary sequelae ⁸. Beyond symptomatic management, enzyme replacement therapy represents a promising therapeutic approach, which we consider both necessary and indispensable in our clinical setting.

CONCLUSION

This case report highlights the exceptional co-occurrence of two rare genetic disorders in a single patient: an autosomal dominant condition, Toni-Debré Fanconi syndrome, and an autosomal recessive disorder, Niemann-Pick disease. The diagnostic journey spanned 24 years, and to date, the patient remains on symptomatic treatment only.

This observation underscores the significant challenges posed by hereditary diseases in regions with high rates of consanguinity, such as our country ²². It emphasizes the urgent need to advance family and genetic studies, which are essential for the development and implementation of enzyme replacement therapies. Furthermore, it highlights the importance of promoting genetic counseling to reduce the incidence of these severe inherited disorders and improve patient outcomes.

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Conflict of interest

The authors declare no conflict of interest

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Ethics approval and consent to participate

We have consent to publish and participation in this manuscript.

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