

ZNFX1 Deficiency: An Interferonopathy Mimicking Wilson Disease with Hepatic and Neurologic Manifestations

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Abstract

ZNFX1 deficiency is a recently recognized type I interferonopathy with heterogeneous systemic manifestations. We report a 15-year-old boy presenting with chronic liver disease, hepatic fibrosis, gait disturbance, and persistent proteinuria. Neuroimaging demonstrated bilateral globus pallidus signal changes and diffuse cerebral calcifications, raising suspicion for a metabolic disorder, particularly Wilson disease. However, copper metabolism studies and hepatic copper quantification were normal, and ATP7B sequencing was negative. Liver biopsy showed portal-to-portal bridging fibrosis without steatosis or copper accumulation. Whole-exome sequencing identified a novel homozygous ZNFX1 c.5733del variant, establishing the diagnosis. Over eight years of follow-up, hepatic disease remained stable without progression or hyperinflammatory episodes. This case expands the phenotypic spectrum of ZNFX1 deficiency, emphasizing that interferonopathies may mimic Wilson disease through hepatic and neurologic involvement. Recognition of this overlap is essential for accurate diagnosis, appropriate genetic testing, and long-term surveillance. (Acta gastroenterol belg., 2026, 89, 509-512).

Keywords: Genetic hepatopathy, hepato-neurologic phenotype, liver disease.

Introduction

Type I interferonopathies constitute an expanding group of disorders characterized by dysregulated interferon signaling, resulting in systemic inflammation, multi-organ involvement, and clinical overlap with more established metabolic and infectious diseases (1). Notably, ZNFX1 deficiency represents one of the recently described Type I interferonopathies; ZNFX1 (NFX1-type zinc finger-containing 1), an interferon-stimulated RNA helicase, has recently been implicated in human pathology through biallelic variants that give rise to a remarkably heterogeneous spectrum of manifestations (2). Reported phenotypes range from severe hyperinflammatory syndromes and cytopenias to multiorgan dysfunction involving the liver, central nervous system (CNS), kidneys, and lungs (3). We describe a patient presenting with hepatic fibrosis and neurologic manifestations who was subsequently diagnosed with ZNFX1 deficiency. This case broadens the recognized clinical spectrum of the disorder and highlights the need to consider ZNFX1 deficiency in the differential diagnosis of Wilson disease–like presentations.

Case History

The patient is a 19-year-old male who was initially evaluated at the age of 10 years for chronic liver disease and persistent proteinuria. At the time of the initial presentation, mild proteinuria had been incidentally detected during evaluation for a febrile illness. Abdominal ultrasonography demonstrated hypertrophy of the left hepatic lobe and parenchymal heterogeneity, raising concern for chronic liver disease.

In addition to hepatic involvement, a history of toe-walking since early childhood was reported, predominantly affecting the right side and demonstrating gradual progression. Despite the gait disturbance, cognitive development and academic performance were appropriate for age. The patient had a good appetite but reported difficulty gaining weight despite adequate nutritional intake. He had no history of chronic diarrhea, recurrent or severe infections, and all childhood vaccinations had been completed without complications. The parents were first-degree cousins, and there was no known family history of gait disorders, neurological diseases, or liver disorders.

On physical examination, the patient was cooperative and oriented but displayed hyperactive behavioral traits. He had a markedly asthenic habitus with a body mass index below -3 SD. Additional skeletal findings included pectus carinatum and mild thoracolumbar scoliosis. Hepatosplenomegaly was present, with the liver palpable below the costal margin and percussion dullness over Traube's space. No ascites or edema were observed. Neurological examination revealed a fixed right Achilles tendon contracture, patellar hyperreflexia, and right-sided foot deformities (hammer toe and pes cavus), resulting in an inability to perform heel walking. Cranial nerve, cerebellar, and extrapyramidal functions were intact, and behavioral assessment confirmed hyperactivity with preserved cognition.

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Complete blood count was largely normal except for mild monocytosis (900/ μ L) and eosinophilia (600/ μ L). Biochemical profiling confirmed preserved hepatic function, with bilirubin, aminotransferases, albumin, and coagulation parameters all within reference limits. Evaluation of copper metabolism revealed normal serum ceruloplasmin (20 g/L) and 24-hour urinary copper excretion (42 μ g/24 h). Liver autoantibodies, including antinuclear antibody, anti-smooth muscle antibody, and liver-kidney microsomal type 1 antibody, were negative. Urinalysis showed mild proteinuria, with a 24-hour urinary protein excretion rate of 5.2 mg/m²/hour. Renal ultrasonography demonstrated grade 1 increased echogenicity in both renal parenchymas. Liver ultrasonography revealed an atrophic right hepatic lobe, compensatory hypertrophy of the left lobe, and lobulated liver contours. Portal Doppler ultrasonography was normal, and magnetic resonance cholangiopancreatography confirmed normal biliary tract anatomy. Upper gastrointestinal endoscopy showed no evidence of esophageal varices.

Liver biopsy revealed portal-to-portal bridging fibrosis with architectural distortion and hepatocellular ballooning, consistent with chronic hepatitis progressing toward cirrhosis. Hepatic copper quantification revealed no increase in dry copper weight, and no copper accumulation was identified by rhodanine staining. There was no interface hepatitis or portal plasma cell infiltration; instead, mild portal lymphocytic inflammation was observed. Neither macrovesicular nor microvesicular steatosis was identified.

Brain magnetic resonance imaging revealed T1-weighted hyperintensities in the bilateral globus pallidus and anterior mesencephalon, suggestive of pathological ion deposition (Figure 1). Computed tomography confirmed punctate calcifications in both cerebral hemispheres and the cerebellum (Figure 2).

Analysis of the ATP7B gene revealed no pathogenic

or likely pathogenic variants, thereby confirming the molecular exclusion of Wilson disease. Whole-exome sequencing identified a novel homozygous frameshift variant in ZNFX1 (NM_021035.3): c.5733del, p.(Phe1911Leufs*7). This variant is absent from population databases, including gnomAD exomes and genomes. The deletion results in a frameshift predicted to introduce a premature termination codon, potentially leading to a truncated protein, consistent with a loss-of-function (LOF) mechanism, which is a known disease mechanism for ZNFX1. According to the American College of Medical Genetics and Genomics (ACMG) variant interpretation guidelines, the variant fulfills PVS1 (null variant consistent with a loss-of-function mechanism) and PM2 (absence from population databases) (4). The variant is therefore classified as a variant of uncertain significance with evidence leaning toward pathogenicity (VUS-LP). Segregation analysis demonstrated heterozygosity for the variant in both parents, consistent with autosomal recessive inheritance.

The patient has been followed for nine years since the initial presentation at age 10 years. During longitudinal follow-up, proteinuria remained mild and non-progressive. At the most recent evaluation at age 19 years, the urine protein-to-creatinine ratio was 0.34, serum creatinine levels were within the normal range, and no peripheral edema was observed, indicating preserved renal function without evidence of progressive kidney disease. Serial imaging studies demonstrated stable hepatic morphology without signs of portal hypertension. No additional systemic complications or new organ involvement were observed during follow-up.

Discussion

This patient's phenotype overlapped with metabolic liver diseases, particularly Wilson disease, with hepatic injury, gait abnormalities, and basal ganglia changes

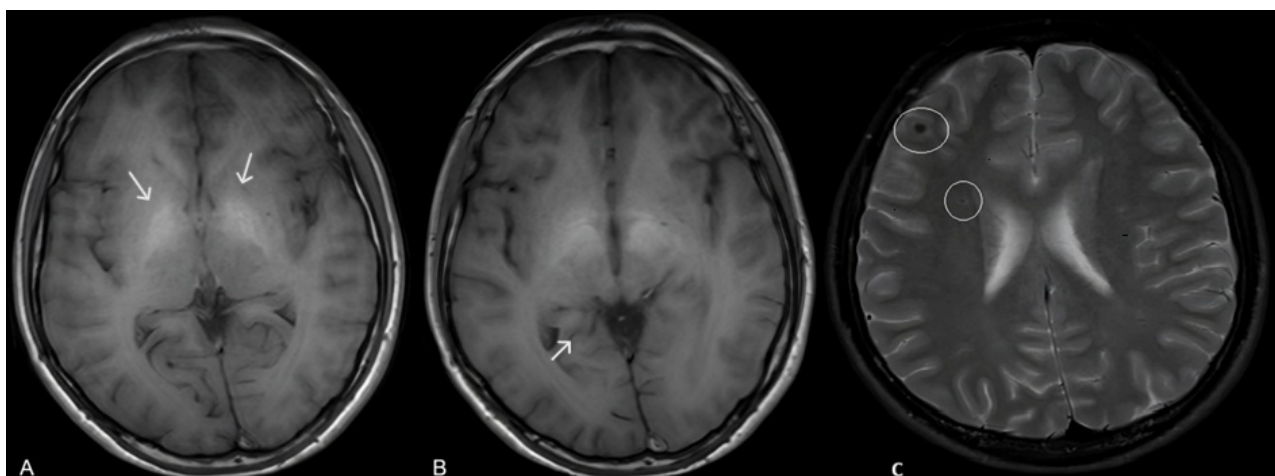


Figure 1. — On axial T1-weighted MRI images, symmetric hyperintense signal changes (arrows) suggestive of ionization or mineral deposition are seen at the bilateral pallidal and capsular levels (A), extending just inferiorly to the level of the cerebral peduncle (arrow) (B). On the axial T2-weighted MRI image at the periventricular cerebral level, signal void foci consistent with millimetric punctate calcifications (circles) are seen (C). MRI; Brain magnetic resonance imaging.

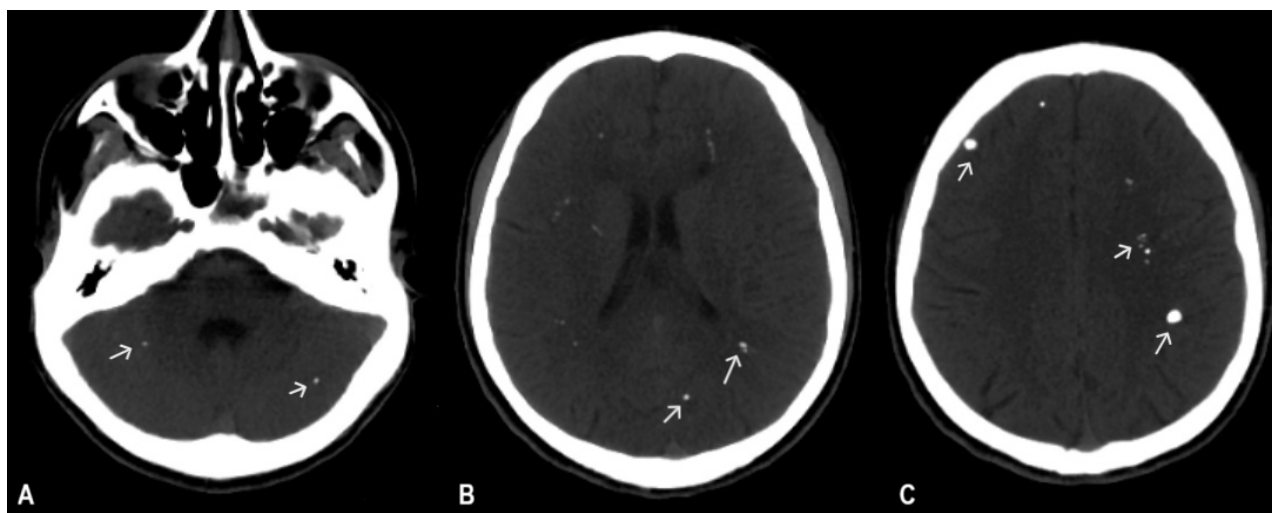


Figure 2. — Parenchymal millimetric punctate calcifications are seen (arrows) on axial CT images at the cerebellar (A), cerebral periventricular (B), and vertex (C) levels. CT; Computed tomography.

resembling its presentation. However, normal copper studies excluded Wilson disease, and unlike Wilson disease—where imaging is usually confined to the basal ganglia—our patient also demonstrated millimetric calcifications in the cerebral parenchyma and cerebellum, with the diagnosis ultimately confirmed by genetic testing. From a practical clinical perspective, several features may help differentiate ZNFX1 deficiency from Wilson disease. In Wilson disease, abnormalities of copper metabolism are typically present, including reduced ceruloplasmin levels, increased urinary copper excretion, and hepatic copper accumulation. In contrast, patients with ZNFX1 deficiency generally have normal copper studies. Neurologically, Wilson disease predominantly affects the basal ganglia and is often associated with movement disorders such as dystonia, tremor, or dysarthria. In ZNFX1 deficiency, neuroimaging abnormalities may extend beyond the basal ganglia and include diffuse cerebral involvement such as calcifications, leukoencephalopathy, or inflammatory changes. In addition, interferonopathies may present with systemic immune dysregulation, including cytopenias, recurrent infections, or hyperinflammatory episodes, although these manifestations are not present in all patients. Therefore, in individuals with unexplained hepatic fibrosis accompanied by atypical neurological findings and normal copper metabolism, genetic interferonopathies such as ZNFX1 deficiency should be considered in the differential diagnosis.

ZNFX1 encodes a mitochondria-associated RNA helicase sensing double-stranded RNA and inducing interferon-stimulated genes via JAK–STAT. Its predominant expression in monocytes, macrophages, and neutrophils underscores its role in innate immunity (2). Biallelic loss-of-function variants confer susceptibility to viral and mycobacterial infections, hyperinflammation, cytopenias, and multiorgan disease. Reported cohorts show striking heterogeneity: neurologic features

(seizures, developmental delay, autism traits), diverse neuroimaging abnormalities (leukoencephalopathy, ischemic lesions, calcifications), and hepatic involvement ranging from mild transaminitis to fulminant failure. Some patients develop systemic hyperinflammatory disease with multiorgan dysfunction and early mortality. Histopathology is nonspecific, typically showing necrosis, extramedullary hematopoiesis, and regenerative changes (3).

In contrast, our patient exhibited a comparatively mild clinical course beginning in childhood, with hepatic fibrosis remaining stable over an eight-year follow-up period and no progression to portal hypertension, and the patient is currently in early adulthood. During this time, no liver-specific therapy was administered, and management consisted of regular clinical and laboratory surveillance. Routine childhood immunizations had been well tolerated, with no evidence of hypersensitivity or adverse reactions. Neurological complications such as seizures, developmental delay, or recurrent viral infections did not develop, and neither hyperinflammatory episodes nor susceptibility to mycobacterial infection were observed, in contrast to the features frequently reported in previously published cohorts (3, 4). Nonetheless, the presence of persistent monocytosis and reduced body weight paralleled findings described in other affected individuals (5, 6). This divergence from fulminant and often fatal presentations highlights the breadth of phenotypic variability and raises the possibility of underlying genotype–phenotype correlations in ZNFX1 deficiency (7). The neurological manifestations in our patient were confined to pyramidal tract signs and gait disturbance secondary to musculoskeletal deformities, accompanied by diffuse cerebral calcifications. These features are consistent with the proposed mechanism whereby loss of ZNFX1 impairs antiviral immunity and drives chronic neuroinflammation, leading to microglial activation, disruption of the blood–brain barrier, and subsequent

neuronal injury (2). Renal involvement represents another recognized component of the ZNFX1 deficiency spectrum, with reported manifestations including proteinuria, nephrotic syndrome, and hemolytic uremic syndrome (6). In our patient, renal pathology was limited to mild proteinuria without evidence of progression to overt renal disease. This finding underscores the variability of organ involvement in ZNFX1 deficiency and the need for long-term surveillance for potential late renal manifestations.

Therapeutic options for ZNFX1 deficiency remain limited. Immunosuppressive regimens have provided only transient or minimal benefit, whereas hematopoietic stem cell transplantation has achieved favorable outcomes in select cases, particularly in those with hyperinflammatory episodes or HLH-like presentations (3). In the present case, the absence of severe inflammatory manifestations or progressive neurological deterioration obviated the need for disease-specific intervention, and a strategy of supportive monitoring was adopted.

This case highlights three considerations. First, ZNFX1 deficiency may mimic Wilson disease through hepatic fibrosis, neurological dysfunction, and basal ganglia changes; with normal copper metabolism, interferonopathies should be considered in liver disease differentials. Second, the spectrum extends from severe systemic to indolent organ-limited forms. Third, novel variants, exemplified by the homozygous c.5733del, expand the genotypic spectrum and refine genotype–phenotype insights.

In conclusion, ZNFX1 deficiency is a rare but increasingly recognized interferonopathy with variable hepatic, neurologic, renal, and immunologic manifestations. Greater awareness of this condition is needed to avoid misdiagnosis, guide appropriate genetic testing, and improve patient care. For hepatologists, interferonopathies should be considered in patients presenting with unexplained hepatic fibrosis or chronic liver disease accompanied by atypical neurological findings, particularly when copper metabolism studies are normal and Wilson disease has been excluded.

Declarations

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