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A new case report of autoimmune liver disease in a patient with Noonan syndrome: Risk factors, presentation and management

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Keywords: Noonan syndrome; RASopathies; Autoimmune hepatitis; Hypertransaminasemia; Autoantibodies.

Abbreviations: NS: Noonan syndrome; AIH: Autoimmune hepatitis; ANA: Anti-nuclear Antibodies; SMA: Smooth Muscle Antibodies anti-LKM1: anti-Liver-Kidney Microsomal type 1 antibodies; GH: Growth Hormone; AST: Aspartate Aminotransferase ALT: Alanine AminoTransferase; ɣGT: ɣ Glutamyl Transferase.

Abstract

Background: Noonan syndrome (NS, MIM 163950) is an autosomal dominant multisystem disorder which is included among the RASopathies, and is characterized by short stature, typical facial features and multiorgan involvement. Autoimmune hepatitis is a chronic necroinflammatory disease of the liver, commonly characterized by hypergammaglobulinemia (Ig), circulating autoantibodies, and compatible histological findings (interface hepatitis).

The association between Noonan syndrome and susceptibility to autoimmune diseases is known, however only two cases of Noonan syndrome and autoimmune hepatitis have previously been reported.

Case presentation: We report the case of a 15-year-old boy with Noonan syndrome due to a mutation in PTPN11 who developed autoimmune hepatitis type 1. The occasional finding of hypertransaminasemia led to the discovery of clinical manifestations such as chronic fatigue and recurrent bouts of headache, the presence of serum antinuclear antibody and borderline smooth muscle antibodies, histological findings (pattern of acute hepatitis with moderate chronic inflammatory infiltrate, neoductulogenesis and ductular metaplasia), and exogenous risk factors.

We describe the diagnostic pathway and treatment management (prednisone and azathioprine) and analyze the role of possible co-factors and the rationale behind the therapeutic choice.

Conclusion: The liver could be a further target of the immune dysfunction in Noonan syndrome, therefore any signs or symptoms causing suspicion of autoimmune disease require careful evaluation in the management and follow-up of patients with Noonan syndrome and related conditions (RASopathies).

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Background

Noonan syndrome (NS, MIM 163950), the most common RASopathy caused by germline mutations in several genes of the RAS/MAPK pathway [1,2], is a multisystem disorder characterized by short stature, peculiar facial features, congenital heart disease, renal anomalies, lymphatic malformations, developmental involvement, and bleeding defects [3].

Autoimmune Hepatitis (AIH) is a cryptogenic and progressive disease of the liver, commonly characterized by hypergammaglobulinemia (Ig), circulating autoantibodies, and compatible histological findings (interface hepatitis). Most cases of AIH respond to immunosuppressants (prednisone and azathioprine) [4]. AIH occurs at all ages and within all ethnic groups, and its manifestation is influenced by ethnicity [5]. Anti-Nuclear Antibodies (ANA), Smooth Muscle Antibodies (SMA), and anti-Liver-Kidney Microsomal type 1 Antibodies (anti-LKM1) are the serological biomarkers for the diagnosis of AIH [6].

Overall, 55,839 patients with AIH have been reported from 18 countries across five continents with a prevalence of 15.65 cases per 100,000 inhabitants, of which 2.04 (1.01-4.14) cases were in children [7]. AIH has been sporadically reported in NS, although genetic syndromes may be more susceptible [8-10].

We report the case of a 15-year-old caucasian male, a novel presentation of AIH in an NS patient during Growth Hormone (GH) treatment.

Case presentation

The male patient was born at 38 weeks of gestation following an uneventful pregnancy and caesarian delivery due to podalic presentation. Birth weight was 3.425 g (72nd centile, +0.58 DS), length 50 cm (60th centile, +0.26 DS), OFC 36 cm (94th centile, +1.57 DS). The parents were not consanguineous.

In his second year of life, the patient underwent surgery for bilateral cryptorchidism, and mild pulmonary valve stenosis was diagnosed. At 3 years of age, he was referred to our outpatient clinic due to growth delay. On physical examination, downslanting palpebral fissures, ptosis, epicantal folds, webbed neck, low set ears, and chest abnormalities were observed, and, given the organ involvement (pulmonary valve stenosis, cryptorchidism, short stature), molecular analysis was performed which revealed a heterozygous mutation c.189 A>G (tyr63cys) in exon 3 of the PTPN11 gene.

At 7 years of age, growth rate deflection (height-2.12 SD, growth velocity-3.63 SD) occurred leading to a diagnosis of GH deficiency (peak clonidine test 3.48 ng/ml, peak arginine test 2.8 ng/ml) and GH therapy was initiated. As part of the routine diagnostic pathway, a cerebral MRI was performed, which showed some large perivascular spaces with a para and retrotrigonal location with a tendency to confluence, and high FLAIR intensity in the white matter. To obtain further diagnostic elements, a 3 Tesla brain MRI was performed, which confirmed the presence of some large perivascular spaces. The patient attended regular 6 monthly follow up visits and during this time no major events occurred, neuroradiological follow-up remained unchanged, abdominal ultrasound follow-up was normal (accessory spleen was reported) and his thyroid gland was at the lower limits for size and thyroid function was within the normal range.

During a follow up evaluation at the age of 13 years and 11 months, hypertransaminasemia was detected: aspartate aminotransferase (AST) 126 U/L (nv<37), alanine aminotransferase (ALT) 214 U/L (nv <40), normal ɣ glutamyl transferase (ɣGT), total bil 2.49 mg/dl (nv<1.1), direct bilirubin 0.68 mg/dl (nv<0.3). During the month prior to the visit, the patient had received a Coronavirus (Covid-19) vaccination. After that, he reported chronic fatigue and recurrent bouts of headache for which he took multiple doses of acetaminophen. His liver was palpable 3 cm from the costal arch, the lower splenic pole was appreciable at the point of peak inspiration. No itching, no changes in bowel movements or night sweats were reported. Acetaminophen was suspended and a cycle of N- Acetyl Cysteine (NAC) was started. Liver function tests (LFTs) were monitored and worsened steadily: AST 1221 U/l (nv<37), ALT 1784 U/l (nv<40), ɣGT 184 U/l (nv<55), total bil 2.83 mg/dl (nv<1.1), direct bilirubin 0.98 (nv<0.3) mg/dl, indirect bilirubin 1.85 mg/dl. Inflammatory markers (C-reactive protein and hemosedimentation rate) were normal. Alpha 1-antitrypsin, ceruloplasmin, serological tests for hepatitis B and C, other hepatotropic infective agents (EBV, Parvovirus, Toxoplasma, CMV) and those causing immunodeficiency diseases, ammonia and lactic acid were all within the normal ranges. Quantiferon test, celiac disease reflex, gastric parietal cell autoantibodies, and anti-neutrophil cytoplasmic antibodies were all negative. Urine and serum levels of copper, as well as ferritin, were also within normal ranges. The presence of Antinuclear Antibody (ANA) (homogeneous and granular cytoplasmic pattern 1:160) and borderline smooth muscle antibodies (SMA 1:80) were detected, as well as low titer immunoglobulin IgE sensitization to parasites such as roundworms and anizakis. SMA increased to 1:320 in the following month along with immunoglobulin IgG 2167 mg/dl (normal range <1600), immunoglobulin G1 1514 mg/dl, and gammaglobulin 26.2% (range 11.1-18.8). Human Leukocyte Antigens (HLA) testing revealed HLA-DRB1 *03 *07 positivity.

The ultrasound evaluation showed findings of acute liver damage in an enlarged liver (long diameter of the right lobe 16.3 cm), with regular profiles and homogeneous echostructure, no focal lesions, and a slight accentuation of the peribiliary fibrosis which gave a starry sky appearance. The elastography study showed an increased stiffness (13.3 kPa), which, however, cannot be considered a hallmark of fibrosis due to the high LFTs. An ultrasound-guided biopsy was performed which showed a pattern of acute hepatitis with moderate (D=2) chronic inflammatory infiltrate, modest plasma cell component and eosinophilic granulocytes; the presence of neo-ductulogenesis and ductular metaplasia and mild focal (A=1) piecemeal necrosis was noted. Numerous (C=5) foci of spray necrosis with acidophilic bodies were observed in the lobule along with PASD positive macrophages, confluent necrosis in zone 3 and occasional foci of porto-central necrosis (B=4). No accumulation of iron or copper was seen.

To exclude the overlap with Autoimmune Sclerosing Cholangitis (ASC), magnetic resonance cholangiography was performed, which showed no significant alterations in the calibers, profiles, or signal of the intrahepatic bile ducts. A molecular

analysis of familial cholestasis was also performed which revealed a heterozygous mutation in the SLC25A13 gene (missense variant p.Asn.38ser c.113A>G, exon3); this variant is very rare, it has not been previously reported in association with a pathological phenotype, and is considered to be of uncertain pathogenic significance.

Pharmacological therapy with methylprednisolone at a dose of 1 mg/kg/d was started, plus the addition of ursodeoxycholic acid (15 mg/kg/d) given the increase in bilirubin levels. GH therapy was discontinued. The patient was instructed to take acetaminophen only occasionally.

Subsequent blood tests showed a progressive improvement in his LFTs even after steroid tapering (8 mg/d). However, the patient's compliance was not always guaranteed, and, after a year, liver markers showed fluctuations. To maintain a low dose corticosteroid therapy (4 mg/d), the addition of azathioprine (1 mg/kg/d) was required. Subsequently, the liver markers returned to within the normal range and the patient was symptom-free.

Discussion and conclusion

Autoimmune hepatitis is a necroinflammatory liver disease of unknown aetiology.

Typical autoimmune characteristics are hypergammaglobulinemia (Ig), the presence of circulating autoantibodies, a histological pattern of hepatitis, and response to immunosuppressant drugs such as prednisone and azathioprine [4].

Two subgroups have been identified: AIH type 1 is defined by the presence of SMA and/or ANA; AIH type 2 is defined by the presence of anti-LKM autoantibodies. In many cases, patients have a personal or family history positive for other autoimmune diseases. The diagnostic algorithm for the evaluation of suspected AIH after the exclusion of viral, drug-induced, hereditary, and metabolic diseases, with specific indications for the pediatric age group, was also performed [5]. Quaio et al described [8] two NS patients with positive anti-SMA and/or anti-mitochondria antibodies without evidence of autoimmune hepatitis and one patient affected by NS with multiple lentigines with AIH characterized by abdominal pain, hepatosplenomegaly and high levels of liver enzymes, positive levels of anti-SMA, histological findings of inflammatory infiltrate, fibrosis, and disorganization of the liver architecture. After the administration of azathioprine and corticosteroids, laboratory parameters and clinical symptoms improved.

A second patient was described by Loddo et al [9]. This patient presented with weakness and fever, increased liver volume, high levels of liver enzymes, positive anti SMA and ANA and negative anti-LKM-1, and a histological pattern of acute hepatitis. The biliary tree had a normal appearance at MRI. After 4 weeks of treatment with prednisone and azathioprine, complete biochemical remission was reported.

Our NS patient had a biochemical and histological pattern compatible with AIH type 1 and a good response to the steroid and azathioprine therapy. Although his clinical, laboratory, and histological presentation, and therapeutic response was similar to the other two cases reported in the literature, there were a few differences. First, the patient is an HLA-DRB1 *03 *07 carrier. DRB1*03 appears to be more frequent in children with AIH-1 (relative risk of 8.88) and, when in a homozygous state, can be associated with more severe fibrosis at disease onset. DRB1*07 is associated with AIH-2 (relative risk 3.72) [11]. Genetic predisposition to AIH in adults is associated with possession of HLA class I (A*01, B*08) and class II alleles (DRB1*03, -04, -07 or -13), depending on the geographic area. Second, he was identified as being heterozygous for the gene SLC25A13 (missense variant p.Asn.38ser c.113A>G, exon3). This variant is very rare and has not yet been correlated to specific diseases. However, SLC25A13 (Solute Carrier Family 25 Member 13), a member of the mitochondrial carrier family, is a Protein Coding gene associated with diseases involving liver function such as citrullinemia, type II, neonatal- or adult-onset. Peroxisomal lipid metabolism and glycolysis are among its related pathways.

As regards the therapy, azathioprine was not added at the beginning to avoid major immune suppression and to test the efficacy of steroids alone. NS patients are 3.5-8 times more prone to developing cancer than the general population due the presence of the PTPN11 gene [12,13]. Some PTPN11 mutations expose patients to juvenile chronic myelomonocytic leukemia or acute myeloid leukemia [14]. NS patients are also at risk of developing brain tumors and neuroblastoma. Steroids, in the range of 8-16 mg/d of methylprednisolone, were able to control the LFTs. However, it was deemed inadequate when other factors were considered: his young age and his bone health, the presence of steroid side effects in his face and body, and a lack of treatment compliance.

Finally, it is worth mentioning the other potential factors including drugs, infective agents such as parasites, and the Coronavirus vaccine. All could have contributed to the development of AIH in this NS boy. Acetaminophen is a well-known cause of liver toxicity. As for GH therapy, only one case report is present in the literature which describes the development of cholestatic hepatitis during GH treatment with resolution upon discontinuation [15]. Hepato-biliary ascariasis has been described in India and can spread to the liver and biliary tract leading to recurrent cholangitis [16]. Regarding the Coronavirus vaccine, several cases of AIH have been reported following COVID-19 vaccination and the numbers seem to have been increasing lately, although the ethiopatogenetic mechanisms remain unclear. The liver injury in our patient occurred within the time frame identified in the Efe study [18]. In this study, liver injury was diagnosed a median 15 (range: 3-65) days after vaccination [18].

The association between NS and susceptibility to autoimmune diseases is known.

Quaio et al [8] reported autoimmune [8] diseases such as autoimmune thyroiditis, systemic lupus erythematosus, celiac disease, antiphospholipid syndrome, vitiligo, and autoimmune hepatitis in 14% of a group of 42 patients affected by RASopathies, particularly in the major subgroup carrying a PTPN11 mutation. Cases of autoimmune diseases have been reported anecdotally, such as systemic lupus erythematosus [19-21] and sporadic cases of autoimmune liver disease [8,9]. To date, our patient represents the third case of autoimmune hepatitis in NS described in the literature. Therefore, we believe that any signs or symptoms causing suspicion of autoimmune pathology require careful evaluation in the follow-up of patients with NS and related conditions (RASopathies). The liver could be a further target of the immune dysfunction reported in these patients, so special attention should be paid when potential risk factors such as infections and drugs present.

Declarations

Consent for publication: Written informed consent for publication of clinical details was obtained from the parent of the patient.

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interest: The authors declare that they have no competing interests.

Author contribution statement: FT, ES. MLF, ML designed, and wrote the case report. FT, ES, MLF, CS, EO and AP cared for the patients and coordinated all clinical investigation. CR carried out molecular analysis.

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