

Graves' disease, celiac disease and liver function abnormalities in a patient — clinical manifestation and diagnostic difficulties

Magdalena Góra-Gębka¹✉, Małgorzata Woźniak², Joanna Cielecka-Kuszyk³, Maria Korpalszczyrska⁴, Katarzyna Sznurkowska¹, Maciej Zagierski¹, Irena Jankowska², Katarzyna Plata-Nazar¹, Barbara Kamińska¹ and Anna Liberek⁵

¹Department of Pediatrics, Pediatric Gastroenterology, Hepatology and Nutrition, Medical University of Gdansk, Gdańsk, Poland; ²Department of Gastroenterology, Hepatology and Eating Disorders Children's Memorial Hospital in Warsaw, Warsaw, Poland; ³Department of Patology, Children's Memorial Hospital in Warsaw, Warsaw, Poland; ⁴Department of Pediatrics, Hematology, Oncology and Endocrinology, Medical University of Gdansk, Gdańsk, Poland; ⁵Faculty of Health Sciences with Subfaculty of Nursing Medical University of Gdansk, Gdańsk, Poland

Autoimmune diseases due to probable common pathogenesis tend to coexist in some patients. Complex clinical presentation with diverse timing of particular symptoms and sophisticated treatment with numerous side effects, may cause diagnostic difficulties, especially in children. The paper presents diagnostic difficulties and pitfalls in a child with Graves' disease, celiac disease and liver function abnormalities.

Key words: autoimmune disease, Graves' disease, celiac disease, liver abnormalities, children

Received: 13 October, 2013; revised: 12 March, 2014; accepted: 06 April, 2014; available on-line: 06 June, 2014

INTRODUCTION

Graves' disease is a common autoimmune disease with a prevalence of 1/1000 in children (Jacobson *et al.*, 1997). Autoimmune diseases such as Graves' disease, celiac disease and autoimmune hepatitis, due to probable common etiopathogenesis tend to coexist in some patients (Meloni *et al.*, 2001; Strassburger *et al.*, 2002).

Complex clinical presentation with diverse timing of occurrence of particular symptoms and treatment with numerous side effects, may cause diagnostic difficulties. Liver function abnormalities are common in this group of patients. Children appear to be a special group of patients with immature immune system, altered pharmacokinetics of some drugs and compliance.

The aim of this paper is to present diagnostic difficulties and pitfalls in a child with Graves' disease, celiac disease and liver function abnormalities.

CASE REPORT

A 12-year-old girl with no evident burden in perinatal and familial medical history is presented. At the age of 8 the diagnosis of Graves' hyperthyroidism was established — with thyroid hormone fT₄ 50 pmol/l, undetectable thyroid stimulating hormone (TSH), anti-thyroid peroxidase (TPO) antibodies — 598 IU/ml, anti-thyroglobulin (TG) antibodies 1837 IU/ml, and no nodules in the ultrasound scan of thyroid gland. Screening for celiac disease was negative by then and decreased IgA level-0, 16 g/l was noted. Initially, the patient was treated with methimazol (no consent for surgical therapy was ob-

tained), and next, because of an ophthalmopathy the steroids were introduced in a primary full dose of 40 mg (1 mg/kg/d) for 6 weeks, and then in the reduced doses for 4 months. Although the therapy brought some improvement, full remission was not achieved - every attempt to withdraw from methimazol was unsuccessful. Still, no consent for surgical therapy was obtained. After 3 years propylthiouracyl (PTU) and Levothyroxine sodium were introduced.

At the age of 12 the girl was transferred to our department from Department of Pediatric Endocrinology because of liver injury with cholestasis. In medical history infection of respiratory tract with cephalosporins therapy prior to the occurrence of jaundice was noted. On admission the girl was jaundiced, with enlargement of thyroid gland, exophthalmos and hepatosplenomegaly. Laboratory tests showed increased transaminases activity (AIAT 977 U/l, Aspat 629 U/l), bilirubin levels (2, 3 mg/dl, direct bilirubin 1, 7mg/dl), increased activity of gamma-glutamyl transpeptidase (GGTP 120 U/l) and bile acids levels (179 micromol/l). The full blood count, acute phase proteins, sedimentation rate, protein pattern, coagulation and thyroid function tests were within normal ranges; merely elevated immunoglobulin G level (IgG 17, 43 g/l), and slightly decreased immunoglobulin A (IgA-0, 2 g/l) were noted. The ultrasound scans showed enlarged liver with no features of cholestasis, no lymphadenopathy. In the further investigations the most common infectious (HBV, HCV, HAV, CMV, E-BV, HSV-1, HSV-2, *Toxoplasma gondii*) and metabolic (alpha-1-antitrypsin deficiency, Wilson's disease) diseases were excluded. Immunological tests were negative for anti-liver-kidney microsomal (LKM-1), anti-smooth muscle (SMA), anti-nuclear (ANA), anti-neutrophil cytoplasmic (ANCA), bile ductless (BDA) antibodies next to the test for anti-transglutaminase (tTG) and anti-endomysium (IgG-EMA) antibodies. Due to normal thyroid gland

✉ e-mail: mgora@gumed.edu.pl

Abbreviations: AILD, autoimmune liver disease; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; ANA, anti-nuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; AIAT, alanine aminotransferase; Aspat, aspartate aminotransferase; BDA, bile ductless antibodies; CD, celiac disease; CMV, cytomegalovirus; EMA, anti-endomysium antibodies; E-BV, Epstein-Barr virus; fT₄, free thyroxine 4; GGTP, gamma-glutamyl transpeptidase; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; IgA, immunoglobulin A; LKM, anti-liver-kidney microsomal antibodies; PTU, propylthiouracyl; SMA, anti-smooth muscle antibodies; TSH, thyroid stimulating hormone; TPO, thyroid peroxidase; TG, thyroglobulin; tTG, anti-transglutaminase antibodies

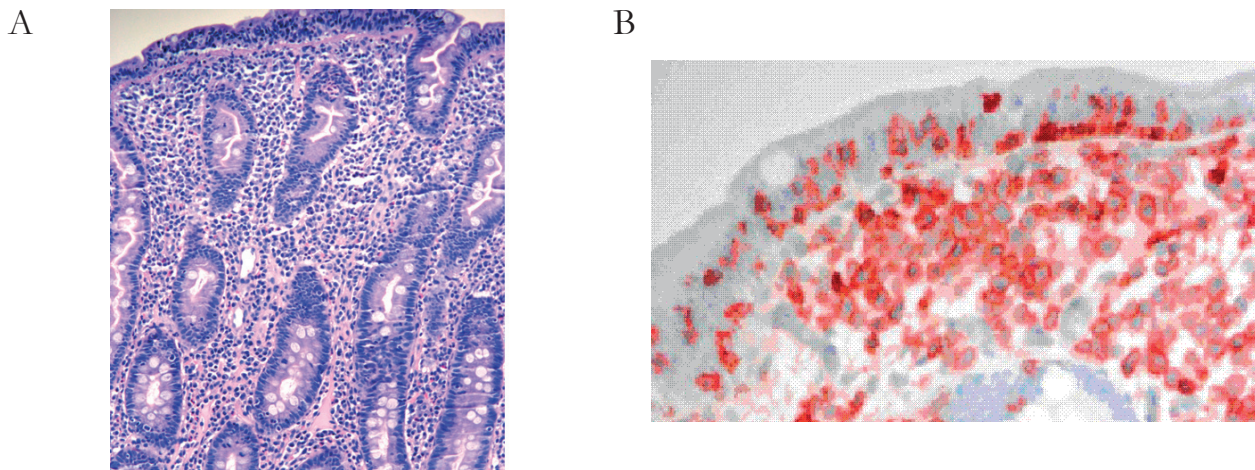


Figure 1. Duodenal biopsy no 91848: (A) Villous atrophy with crypt hyperplasia (H&E); (B) Increased number of intraepithelial lymphocytes (Immunohistochemical stain with CD3).

function test and possible risk of side effects, PTU was withdrawn and conservative hepatoprotective therapy (ursodeoxycholic acid, ornithine, essential fosfolipids, dextrose infusions) were introduced to the cure, which resulted in the fast liver function tests normalization.

In 2 months time the patient was admitted again to the hospital, because of the hyperthyroidism (fT4 35 pmol/l) and elevated transaminases activity (AlAT up to 300 U/l with no cholestasis in laboratory tests). Laboratory tests showed no features of infectious disease. Tests for the autoimmune processes showed the presence of anti-smooth muscle (SMA, 1:640) and anti-nuclear (ANA; 1:320) antibodies as well as the presence of anti-transglutaminase (tTG) and anti-endomysium (IgG-EMA) antibodies. The diagnosis of celiac disease was confirmed by the histopathological changes within the intestinal mucosa — grade III in Marsh scale (Fig. 1) — villous atrophy, crypt hyperplasia, increased density of intraepithelial γ/δ T-cells (Marsh, 1992). After the initial treatment with thyrostatics (methimazol) and gluten free diet, strumectomy (accompanied with the liver biopsy) was performed. Liver histopathological findings showed inflammatory (grading 2 in the Batts' scale) and fibrotic (staging 2) changes with no evident features of autoimmune process such as portal bridging necrosis and fibrosis with massive inflammatory infiltrates of lymphocytes and plasma cells and interface hepatitis (Fig. 2) (Batts *et al.*, 1995). Consecutive substitutive hormonal therapy

and gluten free diet finally resulted in euthyrosis, normal liver function tests. Control liver biopsy performed in 4 months time showed full regression of inflammatory changes and minor fibrous changes (staging S0/S1) (Fig. 3).

DISCUSSION

Liver function abnormalities were noted few times in the course of the Graves' disease in our patient. Laboratory abnormalities ranged from the increase in aminotransferases activity with cholestasis in the time of PTU treatment, euthyroidism and respiratory tract infection treated with antibiotics to high activity of liver enzymes next to hyperthyroidism and tissue antibodies presence strongly suggestive of some other autoimmune diseases. Sophisticated and comprehensive diagnostic approach was warranted along with side effects of some drugs, which had to be taken under consideration.

Thyrotoxicosis stands for one of the potential causes of liver dysfunction in patients with Graves' disease. The combination of increased oxygen consumption and inadequate perfusion leading to hepatocyte hypoxia is regarded as the main pathogenic mechanism of liver damage in these patients (Shimizu, 2008). However, in the presented case the timing of liver function abnormalities was poorly correlated with high levels of thyroxin.

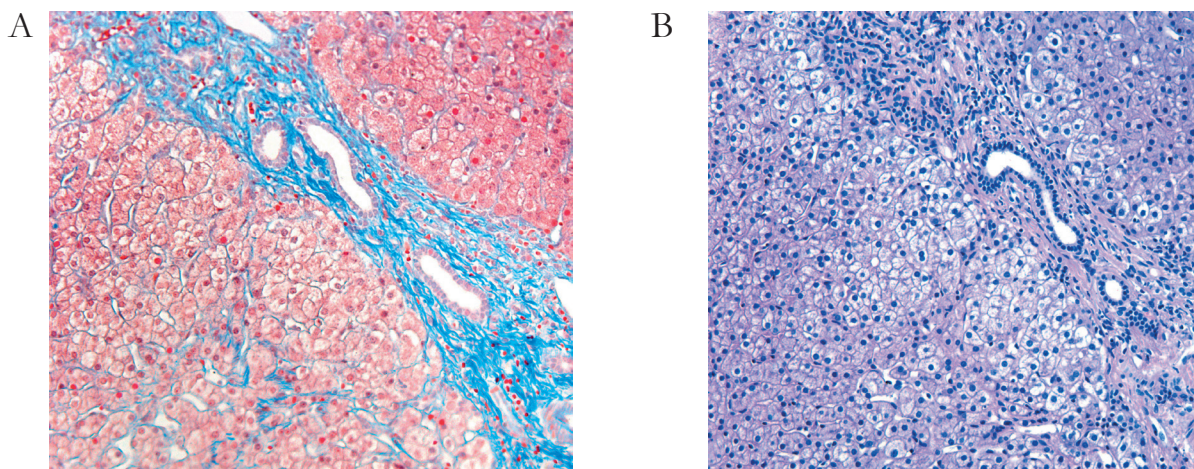


Figure 2. Liver biopsy (I) no 90643: (A) Portal tract with fibrous septa (Azan stain), (B) Portal tract with mild inflammation and fibrosis (H&E).

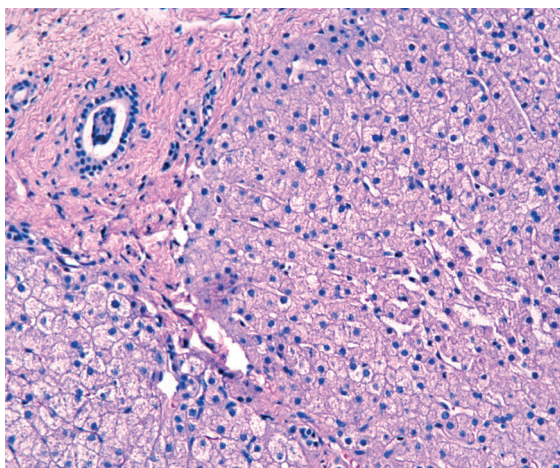


Figure 3. Control liver biopsy after 4 months (II) no. 91207: Portal tract is enlarged with fibrosis without inflammatory infiltrates (H&E).

Methimazol and propylthiouracyl with some side effects, like increase in liver enzymes, are the antithyroid drugs commonly used in Graves' disease. Most cases of PTU-induced hepatic injury occur in the first few months of PTU therapy (Lazar *et al.*, 2000; Kim *et al.*, 2001). The PTU-induced hepatic injury is manifested histologically as acute cholestatic, hepatocellular or mixed forms. In pediatric patients adverse reactions related to PTU therapy, including moderate increase of liver function tests, are noted in 71% of pre-pubertal vs. 25% of post-pubertal children (Lazar *et al.*, 2000; Kim *et al.*, 2001). Among children receiving transplants due to drug-induced acute liver failure, PTU appears to be the third cause following acetaminophen and isoniazid (Russo *et al.*, 2004). Clinical manifestation, the results of laboratory tests, the histology of the liver tissue, and the effect of PTU withdrawal are strongly suggestive of this mechanism of liver injury, which was noted at the time of euthyroidism in our patient.

There is a high frequency of anti-neutrophil cytoplasmic (ANCA) antibodies in patients with Graves' disease treated with PTU. However, in few cases only, a classical ANCA associated vasculitis with kidney or liver manifestation (type 1 autoimmune hepatitis) is observed (Targan *et al.*, 1995; Cui *et al.*, 2003; Sato *et al.*, 2004). Little is still known about some other antibodies in this clinical entity, which may or may not have clinical significance. No ANCA was detected in our patient who also presented with normal kidney function. The presence of SMA and ANA was noted in our patient and appeared to be suggestive of the autoimmune process like autoimmune hepatitis type 1. Autoimmune hepatitis type 2, with the presence of LKM antibodies is reported to appear more often in either children with AIH or patients with Graves' disease (Targan *et al.*, 1995; Cui *et al.*, 2003; Sato *et al.*, 2004). According to the autoimmune hepatitis score system, our patient did not fulfilled the score criteria for the definite diagnosis of AIH. The liver histopathological findings showed no evident features of autoimmune process like portal bridging necrosis and fibrosis with per-portal inflammatory infiltrate of lymphocytes, plasma cells and neutrophils. No glucocorticoids was administered prior to the liver biopsy, which could have abolished the characteristic lymphoplasmacytic infiltrate typical for AIH.

Three types of liver disease are described in celiac disease: mild, transient liver dysfunction, chronic liver disease (with severe fibrosis especially in patients with CD and HCV infection) and autoimmune liver disease (AILD) (Davidson, 2002; Freeman, 2006). They may be within the spectrum of the clinical manifestation of the same disease, where congenital factors and gluten exposure may influence the pattern of liver dysfunction, or may reflect liver abnormalities of different pathogenesis. Non-specific hepatitis with moderate increase in aminotransferases activity is a quite common clinical entity in celiac disease (CD) (Lindberg *et al.*, 1978; Maggiore *et al.*, 1994).

In most cases, aminotransferase normalize with 12 months of gluten-free diet (Novacek *et al.*, 1999; Bardella *et al.*, 1999). Histological changes are mild and include Kupffer cell hyperplasia, mononuclear cell infiltration, steatosis and mild fibrosis (Novacek *et al.*, 1999; Bardella *et al.*, 1999). The latter finding was probably the one, which was noted in the control biopsy in our patient.

In the course of disease and treatment our patient presented with liver injury with the presence of SMA and ANA, but also with the features of cholestasis, which may be suggestive of either autoimmune hepatitis, primary sclerosing cholangitis (PSC) and autoimmune sclerosing cholangitis (AISC). LKM appear to be the most frequently noted autoantibodies in AIH in the course of either CD or Graves' disease (Volta *et al.*, 1998; Davidson *et al.*, 2002; Cui *et al.*, 2003). However, in some recent studies AIH type 1 is reported to coexist more often with CD even in pediatric group of patients (Rubio-Tapaia *et al.*, 2007; Diamanti *et al.*, 2008). Although according to the autoimmune hepatitis score system, we should have been suspicious of AIH in our patient, the liver histopathological findings showed no typical features of AIH, like portal bridging necrosis and fibrosis with peri-portal inflammatory infiltrate of lymphocytes, plasma cells and neutrophils. Some studies report the prevalence of PSC in CD patients to be increased 4-fold to 8-fold than in individuals without CD (Rubio-Tapaia *et al.*, 2007; Ludvigsson *et al.*, 2007). In other, the prevalence of CD is 1.6% in the group of PSC patients (Volta *et al.*, 1997; Rubio-Tapaia *et al.*, 2007). Liver histology showed no typical features of cholestasis and lymphocytic portal inflammatory process with increased intra-epithelial lymphocytes in biliary ductal epithelium (Frejman *et al.*, 1994; Freeman, 2006).

In summary we highlight the wide range of probable mechanisms involved in the liver injury in the course of Graves' disease and CD. The diagnosis of autoimmune liver disease may cause some difficulties and some other pathogenetic mechanisms should be taken under consideration.

Conflicts of interest and source of funding: none declared.

REFERENCES

- Bardella MT, Vecchi M, Conte D, Del Nino E, Fraquelli M, Pacchetti S, Minola E, Landoni M, Cesana BM, De Franchis R(1999) Chronic unexplained hypertransaminasaemia may be caused by the occult celiac disease. *Hepatology* **29**: 654–657.
- Batts KP, Ludwig J (1995) Chronic Hepatitis. An Update on Terminology and Reporting. *Am J Surg Pathol* **19**: 1409–1417.
- Cui B, Abe M, Hidata S, Nakanishi S, Matsuura B, Michitaka K, Yamamoto K, Horiike N, Onji M (2003) Autoimmune hepatitis associated with Graves' disease. *Intern Med* **42**: 331–333.
- Davidson S (2002) Coeliac disease and liver dysfunction. *Arch Dis Child* **87**: 293–296.

- Diamanti A, Basso MS, Pietrobatista A, Nobili V (2008) Prevalence of celiac disease in children with autoimmune hepatitis. *Dig Liv Dis* **40**: 965.
- Freeman HJ (2006) Hepatobiliary and pancreatic disorders in celiac disease. *World J Gastroenterol* **12**: 1503–1508.
- Frejman HJ, Kwan WC (1994) Occult celiac disease associated with lymphocytic sclerosing cholangitis. *Can J Gastroenterol* **8**: 249–252.
- Jacobson DL, Gange SJ, Rose NR, Graham NM. (1997) Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* **84**: 223–243.
- Kim HJ, Kim BH, Han YS, Yang I, Kim KJ, Dong SH, Kim HJ, Chang YW, Lee JI, Chang R (2001) The incidence and clinical characteristics of symptomatic propylthiouracil-induced hepatic injury in patients with hyperthyroidism: a single-center retrospective study. *Am J Gastroenterol* **96**: 165–169.
- Lazar L, Kalter-Leibovici O, Pertzalan A, Weintrob N, Josefsberg Z, Phillip M (2000) Thyrotoxicosis in prepubertal children compared to with pubertal and postpubertal patients, *J Clin Endocrinol Metab* **85**: 3678–3682.
- Lindberg T, Berg NO, Borulf S, Jacobson I. (1978) Liver damage in coeliac disease or other food intolerance in childhood. *Lancet* **1**: 390–391.
- Ludvigsson JF, Elfstrom P, Broome U, Ekblom A, Montgomery SM. (2007) Celiac disease and risk of liver disease: a general population-based study. *Clin Gastroenterol Hepatol* **5**: 63–69.
- Maggiore G, Ceccarelli M, Colombo Giacomo C De, Virgili S De, Musumeci S, Ventura A (1994) 141 Hepatic lesions in childhood celiac disease: a multicentric retrospective study. *J Pediatr Gastroenterol Nutr* **19**: 691–696.
- Marsh M (1002) Gluten, major histocompatibility complex and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology* **102**: 330–354.
- Meloni GF, Thomasi PA, Bertocelli A, Fanciulli G, Delitala G, Meloni T (2001) Prevalence of silent celiac disease in patients with autoimmune thyroiditis from Northern Sardinia. *J Endocrinol Invest* **24**: 298–302.
- Novacek G, Miehsler W, Wrba F, Ferenci P, Penner E., Vogelsang H (1999) Prevalence and clinical importance of hypertransaminasaemia in celiac disease. *Eur J Gastroenterol Hepatol* **11**: 283–288.
- Rubio-Tapia A, Murray J (2007) The liver in Celiac Disease. *Hepatology* **46**: 1650–1658
- Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. (2004) Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transplant* **10**: 1018–1023.
- Sato H, Hattori M, Fujieda M, Sugihara S, Inomata H, Hoshi M, Miyamoto S (2000) High prevalence of antineutrophil cytoplasmatic antibody in childhood onset Graves' disease treatment with propylthiouracil. *J Clin Endocrinol Metab* **85**: 4270–4273.
- Shimizu Y (2008). Liver in systemic disease *World J Gastroenterol* **14**: 4111–4119.
- Strassburg CP, Manns MP (2002) Autoantibodies and autoantigens in autoimmune hepatitis. *Sem Liver Dis* **22**: 339–352.
- Targan SR, Landers C, Vidrich A, Czaja AJ (1995) High-titer antineutrophil cytoplasmatic antibodies in type-1 autoimmune hepatitis. *Gastroenterology* **108**: 1159–1166.
- Volta U, De Franceschi L, Molinaro N, Cassani F, Muratori L, Lenzi M, Bianchi FB, Czaja AJ (1998) Frequency and significance of anti-gliadin and anti-endomysial antibodies in autoimmune hepatitis. *Dig Dis Sci* **43**: 2190–2195.