Unusual association of diseases/symptoms

A girl with type 1 diabetes and a yellowish appearance

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Summary

Type 1 diabetes mellitus in children has been associated with other autoimmune diseases, especially coeliac disease and autoimmune thyroiditis. This association may be the result of a common pathogenic background. We describe the case of a girl with type 1 diabetes mellitus who developed icterus due to autoimmune hepatitis, a disease rarely found in children. Thyroiditis-associated and diabetes-associated autoantibodies were also present. Human leucocyte antigen typing revealed DRB1*03 heterozygosity, which has been associated with the occurrence of both autoimmune hepatitis and type 1 diabetes. This finding implies that similar pathogenic pathways may be involved in different autoimmune diseases including type 1 diabetes and autoimmune hepatitis. The patient was successfully treated with prednisolone and azathioprine. Autoimmune hepatitis can be a serious co-occurring disease in patients with type 1 diabetes.

BACKGROUND

Type 1 diabetes mellitus is the predominant form of diabetes in children. It has been estimated that in Europe almost 15 000 children below the age of 15 develop type 1 diabetes annually and their number is increasing.¹ Its aetiology is unclear, but interplay between genetic susceptibility and a triggering environmental agent leading to autoimmune processes seems to be important. Destruction of β cells in the pancreas is the result of direct T cell interaction. Concomitantly, several autoantibodies are frequently found in patients with type 1 diabetes.^{2–5} Furthermore, type 1 diabetes in children has been associated with other autoimmune diseases in addition to diabetes. This association is especially strong for coeliac disease and autoimmune thyroiditis, with coeliac disease-associated autoantibodies being present in 1–10% of type 1 diabetes patients and anti-thyroid autoantibodies being present in 10–19%.² It has been suggested that these associations reflect a common genetic susceptibility.⁴ We here describe the case of a young girl with type 1 diabetes who developed autoimmune hepatitis.

CASE PRESENTATION

Our patient was a 12-year-old girl who had been diagnosed with type 1 diabetes 9 months previously. At the time of diagnosis, C-peptide values were low and anti- β cell autoantibodies were negative. She initially received insulin therapy by subcutaneous injection. Because of varying glucose levels and the patient's expressed wish, she was admitted to hospital to establish safe continuous subcutaneous insulin infusion.

On the first day of admission, her mother mentioned she had noticed her daughter had appeared yellowish for almost a week. She indeed was slightly yellowish and on close examination had icteric sclerae. There had been no history of symptoms, in particular no abdominal pain, nausea, vomiting, diarrhoea or malaise. She did not use drugs

or alcohol. Physical examination did not reveal any abnormalities other than icterus. The family history was negative for autoimmune disorders.

INVESTIGATIONS

Laboratory investigations revealed a hyperbilirubinaemia of 75 $\mu\text{mol/l}$ which consisted mainly of conjugated bilirubin (42 $\mu\text{mol/l}$). Furthermore, increased levels of liver enzymes were found, especially of aspartate aminotransferase (1231 IU/l), alanine aminotransaminase (1373 IU/l) and lactate dehydrogenase (495 IU/l). γ -GT and alkaline phosphatase were 78 IU/l and 267 IU/l, respectively. These results suggested an intrahepatic cause of the icterus.

Additional tests for hepatitis A, B and C were all negative. No evidence of Epstein-Barr virus or cytomegalovirus was found. Negative serum copper tests and normal ceruloplasmin levels made Wilson's disease unlikely. α 1-Antitrypsin levels were normal. IgG levels were increased (35.3 g/l) with normal IgA levels. Liver function was diminished with increased clotting time (INR 1.4, APTT 33.4 s), but albumin and ammonia levels were normal. There were no signs of anaemia (Hb 8.1 mmol/l). Sodium, calcium and phosphate levels were normal. Abdominal ultrasound showed a normal liver size with homogenous aspect and no other signs of abdominal abnormalities.

The girl was referred to the university hospital for a liver biopsy and start of treatment. The biopsy was very suggestive of autoimmune hepatitis, showing chronic, strongly active hepatitis with intra- and periportal infiltrates consisting mainly of plasma cells (figure 1). In addition, signs of parenchymal deterioration were seen as reflected by Councilman bodies and ballooning hepatocytes. Minimal periportal fibrosis was present. There were no signs of bile duct involvement. Copper staining was negative.

Tests for autoimmune hepatitis-associated autoantibodies were performed. Antinuclear antibodies (ANA), antiliver kidney microsomal type 1 (anti-LKM-1)

Figure 1 Hepatocyte ballooning and extensive plasmacytic infiltrate in liver biopsy specimen (haematoxylin and eosin staining; magnification $\times 400$).

antibodies, antiliver cytosol type 1 (anti-LC-1) and soluble liver antigen (SLA) antibodies were negative. Antismooth muscle antibodies (SMA) were not tested at diagnosis, but 6 months later, after therapy was initiated, they were weakly positive. Antineutrophilic cytoplasmic antibodies (ANCA) were negative. MRI-cholangiography showed no sign of sclerosing cholangitis.

Interestingly, antibody tests revealed high levels of antibodies against glutamic acid decarboxylase (GAD) and insulin, which are frequently present in patients with type 1 diabetes, reflecting the autoimmune processes underlying this disease. Insulinoma-associated tyrosine phosphatase (IA2) autoantibody, another autoantibody found in diabetes, was negative. These antibodies were not determined at diagnosis of diabetes mellitus 9 months earlier. Another interesting finding was the increased level of thyroid peroxidase antibodies (193 kU/l). Nonetheless, thyroid function tests were normal. Antiadrenal, antiendomysium and antitissue transglutaminase antibodies were negative. Additional human leucocyte antigen (HLA)-typing showed the following: DRB1*0301/DRB1*07, DQB1*02, DQA1*0201/DQA1*0501.

In conclusion, we describe the case of a 12-year-old girl with insulin-dependent diabetes who developed icterus caused by hepatitis. The scoring list for autoimmune hepatitis issued by the International Autoimmune Hepatitis Group (IAIHG)⁵ revealed a score of 21, leading to a definite diagnosis of autoimmune hepatitis.

DIFFERENTIAL DIAGNOSIS

Because autoimmune hepatitis is rare, other causes of hepatitis should be carefully excluded (box 1), especially if no autoimmune hepatitis-associated autoantibodies are

found. Cholangiographic imaging is necessary to exclude sclerosing cholangitis.

Furthermore, in seronegative cases it should be checked that laboratory testing was performed correctly and what serum dilutions were used. Indirect immunofluorescence is the basic technique for the routine testing of autoantibodies relevant to autoimmune hepatitis. Since a high proportion of healthy adults may show ANA or SMA reactivity at the conventional starting serum dilution of 1:10, the arbitrary dilution of 1:40 or more is considered clinically significant by the IAIHG in the adult population. However, in healthy children reactivity at the conventional starting serum dilution is infrequent, so that titres of 1:20 for ANA and SMA and 1:10 for anti-LKM-1 are clinically relevant.⁶ In the present case, the standardised arbitrary dilution was used by the laboratory, which is 1:40 for ANA and 1:20 for anti-LKM-1, which may explain the negative results.

Box 1 Differential diagnosis of autoimmune hepatitis in children

Viral hepatitis A, B or C, EBV, CMV
Wilson's disease, copper deficiency or copper toxicity
 α 1-Antitrypsin deficiency
PSC or primary biliary cirrhosis
PSC/AIH overlap syndrome
Alcoholic liver disease
Hepatotoxic drug-induced hepatitis (ie, minocyclin)

AIH, autoimmune hepatitis; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PSC, primary sclerosing cholangitis.

TREATMENT AND OUTCOME

Prednisolone therapy was initiated at 40 mg/day with rapid improvement of aminotransaminase levels and bilirubin. However, as a side effect of this therapy the patient developed a cushingoid appearance. During prednisolone treatment her requirement for insulin increased dramatically to up to 93 IU of basal insulin a day with additional boluses of insulin to compensate for carbohydrate intake at a ratio of 1:4, after almost 3 weeks of treatment. Therefore, 50 mg azathioprine (approximately 1 mg/kg/day) was started and prednisolone dose was lowered to 5 mg daily, resulting in continued improvement in liver function and a decrease in insulin requirement.

DISCUSSION

Autoimmune hepatitis is diagnosed in about 2.3–12% of children with liver disease.^{6,7} Diagnosis is based on criteria and the IAIHG scoring system, which was revised in 1999.⁵ Although the criteria were proposed for research purposes, they have been validated in clinical practice with a sensitivity of 97–100%. A liver biopsy is essential to establish the diagnosis of autoimmune hepatitis. Serological requirements for diagnosis, according to the IAIHG, include abnormalities in serum aminotransferases, immunoglobulin G levels elevated more than 1.5-fold and seropositivity for ANA, SMA or anti-LKM-1 antibodies. Negative criteria are the presence of hepatitis A, B or C virus infection, signs of Wilson's disease, abnormal α 1-antitrypsin or ceruloplasmin levels, seropositivity for antimitochondrial antibodies, consumption of more than 25 g/day of alcohol or use of hepatotoxic drugs or other possible aetiological agents.

Two types of childhood autoimmune hepatitis are recognised by the IAIHG: type 1 (about 62% of cases), characterised by the presence of ANA and/or SMA antibodies and type 2 (about 38% of cases), characterised by the presence of anti-LKM-1 antibodies.⁶ The presence of anti-LC-1 has also been associated with autoimmune hepatitis type 2.⁸ Both types occur predominantly in females. Type 2 mainly occurs in children, whereas type 1 also occurs in adults. A third type of autoimmune hepatitis has been described which is characterised by the presence of SLA autoantibodies.⁹ Seronegative autoimmune hepatitis is rare in children and, except for a recent case report,¹⁰ has only been reported in the paediatric literature once in abstract form. In the present case, use of the scoring system means the diagnosis of autoimmune hepatitis is definite. However, whether it is type 1, type 2 or seronegative autoimmune hepatitis is unclear, since autoantibody tests at diagnosis were not complete and were performed according to a protocol standardised for adult testing, which may not be sensitive enough for children. The weak positivity for anti-SMA antibodies after 6 months of therapy indicates the presence of type 1 autoimmune hepatitis.

There are no randomised controlled treatment trials in children with autoimmune hepatitis. Therefore, drugs and treatment regimens are based on research in adults and reflect the preferences of individual centres. In adults 'standard therapy' is considered to be prednisolone combined with azathioprine.¹¹ About 80–85% of all patients with autoimmune hepatitis respond well to this treatment. The overall frequency of azathioprine-related side effects in patients with autoimmune hepatitis is

Learning points

- ▶ Jaundice can be the only presenting symptom of autoimmune hepatitis in children.
- ▶ As paediatric type 1 diabetes mellitus is associated with other concurrent autoimmune diseases, including autoimmune hepatitis, alertness to possible symptoms of autoimmune hepatitis is indicated in children with type 1 diabetes.
- ▶ When autoimmune hepatitis is being considered in children other causes of hepatitis should be carefully excluded.
- ▶ The co-occurrence of different autoimmune diseases and the association between autoimmunity and certain HLA types suggest that different autoimmune diseases have common pathogenic pathways.

10%.¹² Side effects include cholestatic hepatitis, pancreatitis, nausea, emesis, rash, opportunistic infection, bone marrow suppression and, in the long-term, malignancy. Azathioprine treatment should not be started in patients with severe pretreatment cytopenia or known complete deficiency of thiopurine methyltransferase activity. In children, especially those with diabetes, decreasing the prednisolone dose is beneficial. Addition of azathioprine usually means the prednisolone dose can be lowered. Next to azathioprine, other immunosuppressive agents have been suggested and used in patients with autoimmune hepatitis, such as mycophenolate mofetil, tacrolimus and ciclosporin. However, results of the use of these drugs in the treatment of autoimmune hepatitis are restricted to small case series, mostly performed on adults.¹¹ Prognosis in children with autoimmune hepatitis who respond to immunosuppressive therapy is generally good, with most patients surviving long term with excellent quality of life on low-dose medication. However, the development of endstage liver disease requiring liver transplantation despite treatment has been reported 8–14 years after diagnosis in 8.5% of children with autoimmune hepatitis.⁷

Type 1 and type 2 autoimmune hepatitis have a high frequency of associated autoimmune disorders (type 1: 5–20%, type 2: 18–22%) and a family history of autoimmune disease (40–43%).^{7,13} Associated autoimmune disorders include thyroiditis, inflammatory bowel disease, vitiligo, autoimmune haemolytic anaemia, coeliac disease, nephrotic syndrome and type 1 diabetes. However, in these studies the co-occurrence of autoimmune hepatitis with diabetes mellitus in children is rare, comprising 4–6% of all autoimmune hepatitis cases. To our knowledge, our case is only the sixth child ever mentioned in the literature as having both type 1 diabetes and autoimmune hepatitis. Interestingly, in a study on patients with autoimmune hepatitis who were screened for the presence of diabetes-associated autoantibodies, 18.5% had insulin autoantibodies and one had GAD autoantibodies without clinical diabetes.¹⁴

The pathogenesis behind the co-existence of different autoimmune diseases is unclear. Although all autoimmune diseases are characterised by increased autoantibodies, it is unlikely that they play a direct pathogenic role. The presence of autoantibodies merely reflects the

(asymptomatic) phase that occurs after autoimmunity has been initiated, as has been demonstrated in type 1 diabetes.^{3 15 16} The trigger that initiates autoimmunity in the first place, however, is ill-defined. Both in type 1 diabetes and autoimmune hepatitis an underlying genetic predisposition has been suggested, because both diseases are associated with certain HLA, especially HLA DR3 and DR4.^{3 8} For example, in Northern Europe type 1 autoimmune hepatitis is associated with the presence of HLA DRB1*03,¹⁷ for which the girl in the present case was heterozygote. Interestingly, type 1 diabetes is also associated with HLA DRB1*03.^{3 4 15} However, the exact mechanisms involved in this possible common genetic association still need to be unravelled. The fact that multiple genes are associated with disease susceptibility suggests that dysregulation of multiple pathways of self-tolerance is needed for autoimmunity to occur, including dysregulation in central tolerance as in peripheral tolerance.⁵ It could very well be that different autoimmune diseases are induced by common dysregulations in pathways of self-tolerance. An individual with an autoimmune disease may therefore be more susceptible to develop another autoimmune disorder when triggered.

The co-occurrence of autoimmune hepatitis in type 1 diabetes is rare, while type 1 diabetes occurs frequently. Therefore, routine screening for autoimmune hepatitis-associated antibodies does not seem necessary. Nevertheless, alertness to possible symptoms of autoimmune hepatitis is indicated, especially because the clinical patterns of autoimmune hepatitis at onset of disease are various and can range from mild symptoms followed by jaundice to acute hepatic failure with encephalopathy and/or complications of portal hypertension at first presentation.⁶

In summary, we have presented the case of a 12-year-old girl with type 1 diabetes who developed autoimmune hepatitis. Apart from autoimmune hepatitis, patients with type 1 diabetes have a higher occurrence of other autoimmune diseases including autoimmune thyroiditis and coeliac disease. Therefore, there should be a high index of suspicion for other forms of autoimmunity in patients with type 1 diabetes.

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Competing interests None.

Patient consent Obtained.

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