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Case Report

Subfulminant hepatic failure in autoimmune hepatitis type 1: an unusual form of presentation

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Autoimmune hepatitis type 1 is known to progress insidiously and in many cases cirrhosis is already established at the first presentation of symptoms. It affects mostly females, with peaks of incidence around 10 and 50 years of age. Subfulminant hepatic failure is an unusual initial form of presentation of AIH type 1 and it was observed in three post-pubertal female patients. Rapid disease evolution or no response to immunosuppressive therapy led to liver transplantation in all patients. Two did not have cirrhosis, and the third had focal cirrhosis. The occurrence of the unusual subfulminant form of autoimmune hepatitis in three late-pubertal girls (Tanner V) suggests that estrogen may play a role in the severity of the disease.

Key words: **Autoimmune hepatitis type 1; Female adolescent; Subfulminant hepatic failure.**

THREE different subtypes of autoimmune hepatitis (AIH) have been described and classified by the presence of several non-organ-specific autoantibodies. AIH type 1 is characterized by the presence of smooth muscle (SMA) antibodies and anti-nuclear antibodies (ANA), AIH type 2 is characterized by the presence of liver kidney microsome antibodies (LKM1) and liver cytosol (LC1) antibodies, and AIH type 3 by antibodies against soluble liver antigens (SLA). Common features of the different subtypes are: predominance of female patients, hypergammaglobulinemia, and responsiveness to immunosuppressive therapy (1–4). A genetic predisposition seems to exist, as AIH type 1 and 2 affect predominantly women expressing HLA class I A1,B8 and HLA class II DR3 antigens. AIH type 1 is the most frequent form of AIH, with incidence peaks around the age of 10 years and after the age of 50 years (3,5). The mean age of disease onset is 9.8 years (5). The youngest patient described within the pediatric age group, however, was 18 months old (6). In children, AIH presentation is usually insidious with progressive fatigue and jaundice (50–70%) (7,8), while 15% remain asymptomatic (9) and 20–30% present in a form indistinguishable from acute hepatitis (7,8). At presentation, 80% are jaundiced, nearly all patients have hepatomegaly, 50% splenomegaly, and 30–80% already have cirrhosis (8). Other autoimmune diseases are frequently associated with AIH (2). Most AIH type 1 cases show a more favorable response to immunosuppressive treatment (2,10), than other AIH subtypes, both in acute and chronic presentation (11), even if treatment does not prevent the progression of the disease (12). Onset with fulminant hepatic failure (FHF), defined as acute liver failure and encephalopathy within 2 weeks after onset of jaundice (13), has seldom been reported in children with AIH type 2 (3,14,15) and rarely in children with AIH type 1 (16). AIH type 1 evolving to hepatic failure was believed to be mostly associated with a previously known symptomatic disease (17). In this report we describe three cases of AIH type 1 presenting with subfulminant hepatic failure (SFHF), defined as acute liver failure and encephalopathy 2 weeks to 3 months after onset of jaundice (13), unusual in that each case occurred in the postpubertal period.

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Pertinent Clinical Data

Patient 1 was a 16 10/12-year-old white female referred to Sainte-Justine Hospital in May 1993 for subfulmin-

ant hepatic failure. She was an adopted child whose family history was not known. Menarche was at the age of 14. One month before referral to our hospital she developed fatigue, diminished appetite, and intermittent periumbilical and right upper quadrant abdominal pain, and was therefore seen in a peripheral hospital. On examination, she was at Tanner V with scleral icterus. Abdominal ultrasound was normal and liver tests showed elevated transaminases, cholestasis and coagulopathy. She was discharged with the diagnosis of viral hepatitis, although serology results were still pending. Two days before her referral to Sainte-Justine Hospital she was intermittently disoriented and drowsy. At entry, icterus and slight tenderness of the upper right abdominal quadrant were noted. The liver was only 7 cm at percussion, with a small right and an enlarged left lobe. Except for asterixis, her neurological examination was normal.

Patient 2 was a 14 2/12-year-old white female referred to Sainte-Justine Hospital in September 1995 for jaundice. Her cousin was known to have a thyroid disease. Six weeks before referral to our hospital she developed three to four watery, pale stools per day, jaundice, dark urine, poor appetite, weight loss, nausea, fatigue, intermittent arthralgias, ecchymoses and epistaxis. On admission, scleral icterus was present. The liver was 12 cm by percussion with a slight tenderness at the lower border 2 cm below the rib. The spleen was palpable 1 cm below the costal margin. She had some ecchymoses and peripheral edema. The remaining examination, including the neurological examination, was normal and there were no signs of chronic liver disease.

Patient 3 was a 15 2/12-year-old white French female referred to Bicêtre Hospital in February 1988 for fulminant hepatitis. She was the sixth of seven siblings from a family with no previous diseases. Seventeen days before hospitalization scleral icterus was noted, followed by anorexia, diarrhea, fever and dark urine. The jaundice intensified during the next week, after which she was hospitalized in a peripheral hospital. Within 3 weeks of jaundice onset she developed drowsiness, agitation, protracted vomiting, hepatomegaly and increasing coagulopathy. She was then transferred to Bicêtre Hospital. On admission, she had a marked generalized icterus and fetor hepaticus. Examination revealed no hepatosplenomegaly, and there were no signs of chronic liver disease nor of bleeding. She fluctuated between a state of confusion, disorientation and violent agitation, and a normal state of consciousness.

All three patients had had normal psychomotor and intellectual development and their school performance had been good. No drug abuse, regular medication, contact with toxins, foreign travel, prior medical history, surgery or blood transfusion was found in their histories. Patient 1 had had protected sexual intercourse with one partner. Abdominal Doppler-ultrasound excluded any tumoral or thrombotic etiology. Normal blood ceruloplasmin and urine copper before and after D-Penicillamine, normal α1-antitrypsin, and negative serology for hepatitis A,B and C, EBV, CMV, HHV6, measles and rubella excluded Wilson's disease, α1-antitrypsin deficiency and viral hepatitis as possible causes. Anti-liver kidney microsome 1 antibodies, anti-mitochondrial antibodies, anti-parietal cell antibodies, anti-thyroidal microsomal and anti-thyroglobulin antibodies were negative in all three patients.

Tables 1 and 2 illustrate the clinical and laboratory data at entry and before OLT.

Evolution

Patient 1

During the first 4 days after hospitalization her encephalopathy increased despite treatment with lactulose and neomycin. From day 5 onwards, the autoimmune hepatitis was treated with solumedrol 60 mg iv and azathioprine 75 mg per os daily. However, liver failure was too advanced to respond and on day 7 she underwent liver transplantion. The native liver demonstrated a massive parenchymal necrosis and inflammation compatible with AIH, but without cirrhosis. Interestingly, the patient's ANA remained positive during her follow-up of more than 2 years (18).

Patient 2

On day 4 of hospitalization treatment with cyclosporine per os 3 mg/kg per day was initiated. Repeated hypoglycemic episodes and a morning cortisol of 87.1 nmo/l (n=193–690) made an adrenal insufficiency in the context of an autoimmune polyendocrine syndrome probable. T4 and TSH were normal (16 pmol/l (n=8–18) and 1.2 mU/l (n=0.1–5), respectively). After 10 days of cyclosporine with serum levels from 207 to

TABLE 1

Clinical data at entry

Patient	1	2	3
Age	16 10/12	14 2/12	15 9/12
Sex	F	F	F
Age at menarche	14	13	na*
Time from icterus to encephalopathy (weeks)	3	6	2
Pubertal stage (Tanner)	V	V	V
Hepatomegaly	no	yes	no
Splenomegaly	no	yes	no

* na=not available.

TABLE 2

Laboratory data at entry and before OLT*

Patient	1		2		3	
	At entry	Before OLT	At entry	Before OLT	At entry	Before OLT
Total bilirubin μmol/l (mg/l) (*n*=2–18)	251 (14.6)	286 (16.7)	53 (3.09)	217 (12.7)	449 (26.3)	636 (37.2)
Serum ALT U/l (*n*=11–43)	536	231	322	201	1845	1662
Serum AST U/l (*n*=5–34)	1030	326	625	225	1803	1398
Factor V U/ml (*n*=0.5–1.5)	0.23	0.22	0.24	0.15	0.34	0.19
INR** (*n*=0.8–1.35)	5.7	11.4	3.5	4.1	Quick 21% (*n*=70–100)	nd***
Total protein g/l (*n*=60–80)	87	nd	111	nd	nd	nd
Serum albumin g/l (*n*=38–48)	23	nd	21.5	nd	nd	nd
γ-globulin g/l (*n*=7–13)	51.6	nd	21.5	nd	88.7	nd
ANA titers****	1/160	nd	1/5120	nd	1/200	nd
SMA titers****	1/160	nd	1/1280	nd	1/100	nd

* OLT=orthotopic liver transplantation.

** INR=International normalized ratio (prothrombin time (PT) patient/PT control).

*** nd=not done.

**** Anti-nuclear and anti-smooth muscle antibody titers were measured by indirect immunofluorescence on cryostat sections. SMA were of anti-actin filament type, measured by indirect immunofluorescence on HEp2 cells in culture.

360 ng/ml (total blood), transaminases decreased, but serum bilirubin increased and her coagulopathy worsened. Intravenous solumedrol 500 mg daily was added to the therapy. However, within 24 h she developed a low-grade encephalopathy with somnolence, slow speech, and inability to read because of blurred vision possibly due to the catabolic effect of the high-dose steroids. On day 16 of her hospitalization she underwent liver transplantation. Intraoperatively, collateral circulation and abundant clotted blood in the small bowel was noted. The extracted liver had a smooth surface. However, histologically, focal micronodular cirrhosis was present.

Patient 3

The day after admission, encephalopathy deteriorated to grade 3. Simultaneously AST rose to a peak of 2112 U/l, ALT to 1930 U/l and then began to fall, while the bilirubin continued rising. Abdominal ultrasound showed a diminishing liver volume. Gastric aspirates were blood stained. Urgent liver transplantation was performed the same day. The native liver showed no signs of cirrhosis.

For all three patients liver transplantation was decided upon in view of the worsening of jaundice and coagulopathy in the presence of a continuous decrease in transaminases, and encephalopathy.

Discussion

AIH type 1 is the most frequent form of AIH and has an incidence six times higher than AIH type 2 (3,19). It usually presents after an insidious and often symptomless course, with severe impairment of liver cell function and signs of chronicity such as fibrosis or cirrhosis (2). This report describes AIH type 1 in three female patients with Tanner pubertal stage V, presenting with subfulminant hepatic failure without a lengthy history of previous liver disease. In the last 25 years, 38 and 25 patients with AIH type 1 have been diagnosed at Bicêtre and St. Justine Hospital, respectively. Subfulminant hepatic failure as the first disease manifestation has previously been described in children 13 months to 3 years of age, with AIH type 2 (14,15). However, AIH type 1 may also have a fulminant onset (16,20). The three adolescents in this report had normal growth and complete pubertal development. This is consistent with the absence of chronic disease before the development of the first symptoms and supported the absence histologically of cirrhosis in two of the cases and only focal cirrhosis in the macroscopically smooth liver in the other. It is noteworthy that patients 1 and 3 had an unusually sudden disease onset with immediate liver failure, not known until now as a feature of chronic active hepatitis. Yet, the lack of viral etiology, the presence of hypergammaglobulinemia,

typical autoantibodies and corresponding histology made autoimmune hepatitis type 1 the most probable diagnosis. Patient 2 had more typical symptoms, including focal cirrhosis and a low C4 serum level. Moreover, she had adrenal insufficiency, which rarely occurs in association with AIH in the course of an autoimmune polyglandular syndrome (21). Thus, subfulminant hepatic failure may be considered an additional form of presentation for AIH type 1. It was previously believed that AIH type 2 presented more frequently in fulminant hepatitis than AIH type 1 (2,3,7,8,15,22). This distinguishing feature might now be questioned. We prefer the term SHFS (13) rather than FHF (23–25), because in all three patients encephalopathy developed more than 2 weeks but less than 3 months after the presenting symptom of jaundice (13,26). Our experience with these patients reinforces the idea that in any patient with fulminant or subfulminant hepatic failure autoantibodies should be systematically sought. Furthermore, the presence of elevated total protein levels associated with hypoalbuminemia should lead to the suspicion of hypergammaglobulinemia, for which autoimmune hepatitis must be considered. Our patients underwent liver transplantation either before medical therapy could be instituted or because of poor response. In contrast, the three children previously reported with FHF secondary to AIH type 2 all responded well to immunosuppressive therapy (14). There were no particular features in our patients that would predict such an aggressive course of the disease (27). Low C4 in patient 2 could have been caused by a deletion in the C4 gene. Such patients often have an increased disease susceptibility, rapid disease evolution, poor response to treatment and a higher mortality than patients with normal C4 allotypes (28–31). Elevated bilirubin appeared to indicate a bad response to immunosuppressive therapy in patients with AIH.

Our patients had reached pubertal stage Tanner V before the onset of their disease. They were older than the mean age of 9.8 years at the diagnosis of AIH type 1 in pediatric patients. Because AIH type 1 is a rare disease, the small number of patients may result in an association by chance with SFHF in adolescent females. Nevertheless, the possibility exists that the hormonal status of puberty stage Tanner V, particularly estradiol levels, is involved in determining the course of the disease. Some indirect evidence exists that estradiol plays a role. Firstly, prepubertal girls have higher estradiol levels than prepubertal boys (32) and AIH type 1 and 2 are pediatric diseases that affect almost exclusively girls. It has been shown that estradiol levels reach a maximum at the time of menarche and that during the subsequent 4–5 years anovulatory cycles, associated with high or low levels of estradiol (33,34) occur with decreasing frequency (35). Secondly, estradiol has an effect on proliferation and function of peripheral lymphocytes (36–38). These changing estradiol levels could therefore have an impact on the imbalance between permissive and prohibitive factors for autoimmunity and thus favor the particular aggressivity of the disease described. Obviously, serum estradiol was not measured in any of the three patients before disease onset. Measurements of estradiol receptors in the necrotic liver extracted during OLT would probably not have been representative for the pre-disease state.

In summary, we have described SFHF as an unusual form of presentation of AIH type 1 in three postpubertal female patients. Lack of histologic signs of chronicity and failure to ameliorate with immunosuppression characterize the particularly aggressive course of the disease. Further investigation is needed of the influence of pubertal stage and aggressivity of AIH. These cases have shown that subfulminant hepatitis is a form of presentation of AIH type 1. This diagnosis should mainly be considered in female patients at the pubertal age. As the patients seldom respond to immunosuppressive treatment, they need liver transplantation.

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