RESULTS

The median age at diagnosis was 12 years. Thirteen children were less than 11 years old. Most patients had initially reported nonspecific abdominal pain and were referred because of elevated and serum aminotransferases or abnormal hepatic sonograms. Two patients had diabetes mellitus at diagnosis (one had been on insulin therapy for many years) and two had later development of insulin-dependent diabetes mellitus. Two brothers had Bardet-Biedl syndrome. One patient had a history of recurrent pancreatitis, one had pustular psoriasis (not treated with methotrexate or corticosteroids), and another had dermatomyositis that had been in remission for several years after anti-inflammatory treatment. Two children had some jaundice. Most children were in good health without other medical illness. No patient had a history of significant drug or medication use, and none used ethanol, according to careful history. None had received a blood transfusion. There was no family history of liver disease; only two patients had a family history of maturity-onset diabetes.

Most patients were obese: 30 of 36 patients had weight in higher than the 97th percentile for age and body weight, more than 120% of ideal weight for height. The mean weight was 147% of ideal body weight (mean weight 71 kg, range 32-138 kg). Sixteen patients had hepatomegaly with the liver edge palpable below the right costal margin, and one of these had hepatosplenomegaly. Thirteen patients had acanthosis nigricans observed around the nape of the neck and/or in the axillae; all but one of these were obese. None had typical cutaneous stigmata of chronic liver disease. One had erythema nodosum.

One or both serum aminotransferases were elevated at diagnosis in all but one patient. In 35 patients, the mean value for aspartate aminotransferase (AST) was 104 +- 16 U/1(mean +- SEM; normal <37 U/1); AST was normal or near normal in 4 patients (range, 26-523 U/1) and was not recorded in 1 patient. In 33 patients tested, alanine aminotranserase (ALT) was 179 +- 31 U/1 (normal range, <40 U/1), and 3 patients had normal or near normal ALT (range, 10-644 U/1). There was no correlation between the severity of obesity and the degree of serum aminotransferase elevation. Alkaline phosphatase was normal for age in all patients. One patient had mild, persistent unconjugated hyperbilirubinemia, and another had mild conjugated hyperbilirubinemia. Serum albumin and prothrombin time were normal in all patients. Serum copper and ceruloplasmin, measured in 34 of 36 patients, wre normal. Nonspecific autoantibodies were tested in 21 patients: these were generally not detected. One patient had positive anti-smooth muscle (anti-actin) and anti-mitochondrial antibodies with normal total immunoglobulins; she was also heterozygous for α-antitrypsin deficiency with phenotype PI MZ. Two patients, including the patient with dermatomyositis, had positive anti-nuclear antibodies. Hepatitis B serology obtained in 33 patients and anti-hepatitis C virus antibody (since availability of the test) in 21 patients were uniformly negative.

Fasting blood lipid profiles were determined in 20 patients and found to be abnormal in 18. Seven patients had hypercholesterolemia and 11 had increased serum triglycerides. Four patients had eelevation of both. Fasting serum cholesterol level was 4.43 +- 0.91 mmol/1 (m +- SD; normal, 3.20 –4.40 mmol/1), and tryglyceride was 2.05 +- 1.06 mmol/1 (normal, 0.34-1.58 mmol/1). Except in the two patients with diabetes mellitus, random blood glucose was normal in all patients.

Hepatic sonograms were obtained in 31 of 36 patients. Twenty-four showed abnormalities including hepatomegaly and increased echogenicity suggestive of fatty infiltration.

Percutaneous liver biopsy was obtained in 24 patients. All patients had large-droplet steatosis. Most had inflammation (21, or 88%), and many had fibrosis (17, or 71%). There was inflammatory infiltration and fibrosis of varying severity; the majority showed some degree of both inflammation and fibrosis. Fibrosis was moderately severe in seven patients, including two patients without inflammatory activity. One patient, in addition to these seven, had cirrhosis at diagnosis. None of the biopsy analyses showed any Mallory hyaline. One patient had capillarization of the sinusoids, observed in elctron microscopic examination. A comparison of patients with no fibrosis and patients with severe fibrosis-cirrhosis is shown in Table 1. Thre were no statistically significant differences between these two groups of patients,

although, on average, serum aminotransferases were higher in those with severe fibrosis. The patient with normal aminotransferases, however, had extensive fibrosis suggestive of eary cirrhosis.

Follow-up data were available on 21 patients. The mean duration of follow-up was 18 months (range, 2-65 months). Six patients lost weight, and all had improvement in serum aminotransferase levels. In two of these patients AST and ALT completely normalized. Most patients had great difficulty losing weight. The AST and ALT levels fluctuated in those patients who were not able to achieve weight loss. One patient subsequently had severe hypothyroidism.

TABLE 1. COMPARISON OF PATIENTS WITH SEVERE FIBROSIS OR CIRRHOSIS AND PATIENTS WITHOUT FIBROSIS

	No Fibrosis (n = 6)	*Severe Fibrosis (n = 8)*
Mean age (yr)	*13.2*	*12.1*
Age range (yr)	*9.4 – 15.8*	*10.5 – 14.5*
Obesity (mean % ideal weight for height)	*152*	*150*
Obesity (range % ideal weight for height)	*114 – 192*	*127 – 180*
Mean ALT	*164*	*240*
Range ALT	*76 – 334*	*10 – 644*
Mean AST	*78*	*145*
Range AST	*48 – 114*	*26 – 523*
Acanthosis nigicans	*4*	*2*

ALT, alanine aminotransferase: AST, aspartate aminotransferase.

DISCUSSION

At the time this study began, whether chronic liver disease resembling alcoholic liver disease but occurring in nonalcoholics actually existed was controversial. Identifying this disease in children provided evidence that NASH as such actually existed. Finding a large number of such patients now suggests that it constitutes a significant problem in pediatric hepatology. The diagnosis of NASH rests in part on histologic findings, and we have accepted steatosis with evidence of necroinflammatory activity as the essential histologic criteria for this diagnosis. In many patients, fibrosis is also present. We believe that the term "nonalcoholic steatohepatitis" is unduly restrictive and prefer the term "nonalcoholic fatty liver disease". However, the former terminology appears entrenched.

Despite many case series describing NASH in adults, there have been only a few reports of this disorder in children. Moran et al., describe three children with obesity and steatohepatitis. In a study of 299 obese children, Kinugasa et al., found 36 (13%) to have abnormal aminotranserases. Liver biopsy was performed in 11 of these children, and results confirmed steatohepatitis. One patient had cirrhosis, along with maturity-onset diabetes mellitus and hyperlipidemia. Vajro et al., reported a series of seven obese children with persistently elevated aminotransferases. These children may have had NASH; however, liver biopsy was obtained in only one patient, and the results showed steatohepatitis. Recently Baldridge et al., reported a series of 14 children with idiopathic hepatic steatosis, identified by retrospective review of results of all liver biopsies performed in a tertiary-care pediatric hospital. All were obese, and most had abnormal AST and ALT. Two patients with test results showing normal liver function were discovered incidentally at laparotomy. In a screening study of 310 obese Japanese children Tazawa et al., found that 24% had elevated serum ALT and 83% had a fatty fibrotic pattern observed on hepatic sonography. This same sonographic appearance was found in 19% of children studied who had normal ALT. Although elevated ALT and fatty liver by ultrasound testing appeared to be somewhat more common in older children with more severe obesity, no statistically significan differences were found in different age groups

or with longer duration obesity. An Italian screening study of 195 obese children found fatty liver by sonography in 55%, elevated serum AST or ALT in 20%, and both features in 15%.

In our prospective series of 36 children with NASH, findings were heterogeneous. Obesity was the most common clinical denominator. The average patient had a body weight approximately 50% higher than the ideal for height. Althought the mean weight overall was 71 kg. Of particular concern was the very obese younger child, specifically, 13 children less than 11 years of age who average weight was 56kg. However, six patients were not obese (childhood obesity defined as weight >120% of ideal weight for height). Typically, these children were tall with large bones and proportionately heavy body weight. Unlike some adult series, boys were more common than girls in this series of children. Male predominance was also noted in a Japanese survey of fatty liver detected by sonography in a cohort of 810 children between the ages of 4 and 12 years. Approximately half of all patients in the present study had hepatomegaly, and most had elevated serum aminotransferases. Other liver function test results were normal. Eighteen of 20 patients studied had hyperlipidemia; hypertriglyceridemia was more common and more severe.

Other features of the patients in this series suggest that abnormalities of carbohydrate metabolism may be important in the pathogeneisis of NASH in children. Two of the patients in our series were known to have diabetes, and two other patients had development of diabetes later. A further patient had insulin-dependent diabetes that developed beyond the period of follow-up for this study at a time when his obesity had resolved and serum aminotransferases were normal. Two patients had Bardet-Biedl syndrome, and inherited syndrome characterized by retinal dystrophy, polydactyly, obesity, renal abnormalities and male hypogenitalism. Non-insulin-dependent diabetes mellitus (NIDDM) frequently develops, with insulin resistance due to abnormal insulin receptor function. Alstrom syndrome is a rare condition, phenotypically similar to Bardet-Biedl, but distinquished by sensorineural deafness and absence of mental retardation. Obesity, hyperlipidemia, NIDDM, and acanthosis nigricans commonly occur in Alstrom syndrome. Hepatic involvement with mild steatosis, portal inflammation, and moderate fibrosis has been described in one patient. Yet another report of a rare syndrome in this Bardet-Biedl/Alstrom spectrum has been published, in which one patient had hepatic steatosis and both patients had decreased insulin receptor binding.

CONCLUSION

We conclude that NASH is not limited to adults. Indeed, it may be fairly common in children. It should certainly be suspected in obese children with mildly elevated serum aminotranserases. Moreover, it can occur in nonobese children. Sonography may suggest the diagnos of massive fatty infiltration in the liver, but a liver biopsy is needed to assess the degree of chronic damage. Steatohepatitis can be found in other diseases affecting the liver. Wilson disease must be excluded. Chronic viral hepatitis and drug-induced hepatitis must also be considered in the differential dianosis. Not necessarily a benign disorder, NASH can progress to cirrhosis during childhood and may account for some cases of cirrhosis in adults in whom the cause is obscure. Although there may be diverse causes for NASH in children, we believe that many children have specific and potentially definable disorders of hepatocellular metabolism.

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