Undetected Hepatomegaly in Obese Children by Primary Care Physicians: A Pitfall in the Diagnosis of Pediatric Nonalcoholic Fatty Liver Disease
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What is This?
Undetected Hepatomegaly in Obese Children by Primary Care Physicians: A Pitfall in the Diagnosis of Pediatric Nonalcoholic Fatty Liver Disease

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Summary: The diagnostic evaluation of nonalcoholic fatty liver disease (NAFLD) relies on the initial detection of hepatomegaly or elevated serum aminotransferases by the primary care provider. In this investigation, the aptitude of the primary care provider to identify children with hepatomegaly and initiate an evaluation for NAFLD is determined. The physical examination findings and requests for diagnostic testing of 18 primary care physicians (and pediatric gastroenterologists) on 11 obese school-aged children, including a subset of children with hepatomegaly and NAFLD, were analyzed. In children with NAFLD, clinicians detected hepatomegaly in 1.4% of encounters and requested serum liver chemistries in 12.5% of encounters. Hepatomegaly is detected poorly in obese children by primary care physicians and thereby increases the likelihood of a delayed or omitted evaluation for NAFLD. Clin Pediatr. 2005;44:135-141

Introduction

Nonalcoholic fatty liver disease (NAFLD) is present in an estimated 25% to 50% of obese children. The disease often has a silent presentation but hepatomegaly is usually present. In adults with NAFLD, hepatomegaly has been identified in 60% to 100% of individuals. In pediatric studies, hepatomegaly has been identified in 30% to 40% of cases. The prevalence of hepatomegaly is most likely underestimated owing to the body habitus of the affected population.

In a review on NAFLD, Neuschwander-Tetri and Bacon commented that “hepatomegaly is easily missed in obese individuals.” In an effort to determine the validity of this statement, a chart review was undertaken to determine the chief reason for referral to the pediatric gastroenterologist in children eventually diagnosed with fatty liver. Only 6 of 14 children with the disorder were referred initially for evaluation of liver disease. The remaining children were referred for evaluation...
of other gastrointestinal complaints, including constipation or recurrent abdominal pain. The detection of hepatomegaly during routine examination in these previously unsuspecting children by the pediatric gastroenterologist resulted in subsequent evaluation and diagnosis (unpublished data, Fishbein).

In the adult population, a diagnostic evaluation for NAFLD occurs typically after identification of elevated serum aminotransferases in an asymptomatic individual. In the pediatric population, there are no current screening recommendations for NAFLD, and requests for serum liver chemistries arise at the discretion of the primary care provider. Presently, only a minority of pediatricians (11%) request serum liver chemistries in obese children.10 Though requested infrequently, serum aminotransferases appear to be a good marker of fatty liver in children. In a recent investigation by Fishbein et al,11 elevated serum aminotransferases were evident in approximately 95% of obese children with severe steatosis. Yet without detection of hepatomegaly or adequate suspicion of NAFLD, the primary care physician appears unlikely to pursue appropriate diagnostic testing. In this event, a lengthy delay in diagnosis is anticipated, since routine physician visits are recommended annually to every other year in otherwise “healthy” children.12

The present investigation was intended to determine the primary care provider’s aptitude in recognizing the clinical features of NAFLD and pursuing a diagnostic evaluation in suspected individuals. More specifically, establishing the diagnosis of NAFLD depends largely on the detection of hepatomegaly and/or identification of abnormal levels of serum liver chemistries by the primary care provider. In this investigation, the primary care provider’s ability to discern hepatomegaly in a select group of obese children, which included a subset with preestablished fatty liver, was determined. A secondary goal of the study was to determine the coinciding rate of serum liver chemistries and noninvasive hepatic imaging requested by primary care providers.

Methods

Study Population
Entry criteria included obese children (BMI > 95th%), aged 8 to 18 years, without chronic lung disease, neurologic impairment, cardiovascular disease, or developmental delay. Children participating in this study were recruited either by a pediatrician or by a pediatric gastroenterologist. Those children recruited by pediatricians were not identified previously with hepatic steatosis or pre-existing liver disease and did not have any prior contact with the pediatric gastroenterologist. Those children recruited by pediatric gastroenterologists were identified previously with hepatic steatosis and fatty liver. The presence of hepatomegaly was defined as liver edge palpable > 2 cm below right costal margin. Fatty liver or NAFLD was diagnosed in subjects with hepatomegaly by fat quantitation using a rapid magnetic resonance imaging (MRI) technique.11 Severe steatosis was defined as hepatic fat fraction > 18.5%. Pediatricians involved in the recruitment of children did not participate in any other portion of the investigation, including serving as “examiners.” Demographic data collected for this investigation included the child’s height, weight, body mass index (BMI), blood pressure, heart rate, gender, and age. In instances where fatty liver was identified before the investigation, accompanying imaging data and serum liver chemistries were also recorded. A cash stipend was allotted to each child for participation in this study.

Examiners
All primary care physicians (family practitioners and pediatricians) involved in the routine care of school-aged children in Springfield, IL, and surrounding communities were eligible to participate. In order to reduce bias, a pediatric/internal medicine house staff member, rather than the chief investigator (pediatric gastroenterologist), was established as the study coordinator. The study coordinator initiated contact with all primary care physicians through office mail and telephone. Potential examiners were instructed that the purpose of the investigation was “to determine the effects of pediatric obesity on physical examination.” Upon their arrival to the investigation site, examiners were greeted by the study coordinator and provided instructions regarding their tasks. During the investigation, examiners were kept blinded as to the true intent of the study and as to the identity of the chief investigator. Among the examiners, the following data were collected: age, gender, years of practice, and estimated number of children seen in the individual’s practice per week.

Protocol
Each child, accompanied by a parent or guardian, was stationed in a private medical examination room. The child’s identifier was
his/her station assignment. The child remained in the same station for the entire study. Examiners were instructed not to seek medical information from the children, and the children were instructed to withhold any medical information from the examiner. Each examiner was assigned a specific station at the onset of the investigation and was guided to the next station following completion of the examination and corresponding data form. The examiners were allotted 5 to 10 minutes per child. Examiners were instructed to perform a physical examination in accordance with their usual practice. However, examination of the ears, eyes, breasts (female), genitalia, and rectum was excluded. Each station included a standard physical examination form that included a subject identifier, vital statistics, and a brief questionnaire regarding subsequent testing and referrals. For the purpose of this investigation, a physician request for a comprehensive metabolic profile (CPT #80053) was considered equivalent to a request for serum liver chemistries (hepatic function profile, CPT #80076). The examiner was instructed to complete the form in accordance with his/her standard practice with identifiable syntax.

After the primary care physicians had completed their examinations, a pediatric gastroenterologist and an adult gastroenterologist (no other pediatric gastroenterologists were available for comparison) with prior knowledge of the study purpose examined each child’s abdomen separately and recorded their findings privately. For the purpose of this investigation, the clinical examination findings of the pediatric gastroenterologist (possessing 15 years of experience) were utilized to confirm the presence or absence of hepatomegaly (liver edge palpable 2 cm or more below the right costal margin).

Statistical Analysis

One-way analysis of variance and Bonferroni test were used to compare difference between years experience and rate of child encounters per week among specialists. Chi-square analysis was utilized to compare differences in categorical variables between hepatomegaly-present (NAFLD) and hepatomegaly-absent groups and to compare responses among all physician groups. Fisher’s Exact Test was used to compare responses from individual physician groups. Agreement between adult gastroenterologist and pediatric gastroenterologist with regard to the presence or absence of hepatomegaly was established by kappa statistic.

Power analysis: 2 of 11 patients were known a priori to have hepatomegaly. Therefore, the true proportion was assumed to be \( \frac{2}{11} = 0.18 \). The criterion for significance (alpha) was set at 0.05. The test was 2-tailed, indicating that an effect in either direction was interpreted. A sample size of 18 physicians for this investigation possessed a power of 82% to yield a statistically significant result. This computation assumed that the true proportion positive in the population is 0.18 and was tested against a proportion of 0.01. The investigation was approved by a local internal review board and informed consent/assent was obtained for all children.

Results

Eleven children (9M, 2F) participated in the investigation. Subject age was 12.4 ± 3.1 years (range, 8 to 17 years). BMI was 34.0 ± 4.8 kg/m² (range, 28.9 to 42.6 kg/m²). Systolic blood pressure (BP) was 131.1 ± 11.8 mm Hg (range, 115 to 151 mm Hg). Diastolic BP was 64.0 ± 10.5 mm Hg (range, 41 to 78 mm Hg).

Eighteen physicians (pediatricians, n = 6; family practitioners, n = 6; internists/pediatricians, n = 6) served as examiners in the investigation. They had been in practice for 8.6 ± 6.9 years (range, 1 to 24 years) and their rate of child encounters was 63.7 ± 42.7 per week (range, 4 to 150 per week). There was no difference among specialists with regard to duration of practice, but pediatricians experienced more frequent child visits than either family practitioners or internists/pediatricians.

Eleven children were examined by 18 primary care physicians yielding 198 encounters. Hepatomegaly was identified in 1 encounter (0.5%). The most common laboratory tests requested were fasting blood glucose in 46 encounters (23.2%), lipid profile in 40 encounters (20.2%), urinalysis in 24 encounters (12.1%), thyroid function tests in 19 encounters (9.6%), serum electrolytes in 18 encounters (9.1%), and serum liver chemistries in 17 encounters (8.6%). The most common consultations requested were dietary in 91 (46%) encounters and endocrinology in 8 encounters (15.8%). An exercise program was recommended in 8 instances (4%). Abdominal imaging was requested in none of the encounters.

A total of 4 children were identified with hepatomegaly by the pediatric gastroenterologist (2 before the investigation and 2 during the investigation). In each instance, corresponding hepatic fat fraction was greater than 18.5% indicating severe steatosis. Age, BMI, and blood pressure did
not vary between hepatomegaly-present (NAFLD) and hepatomegaly-absent groups. Children with hepatomegaly present (NAFLD) underwent 72 encounters (4 children × 18 examiners) and children with hepatomegaly absent underwent 126 encounters (7 children × 18 examiners). There was no difference between groups with regard to detection of hepatomegaly or requests for specific laboratory tests or consultations. Interobserver agreement between pediatric gastroenterologist and adult gastroenterologist with regard to the presence or absence of hepatomegaly was low (κ = 0.38).

In the hepatomegaly-present (only 1 of 72 encounters [1.4%] NAFLD) group (n = 4), examiners requested serum liver chemistries on 9 occasions (12.5% of encounters). Serum liver chemistries were requested in none of the 4 children by 13 examiners (72.2% of examiners), 1 child by 2 examiners (11.1% of examiners), 2 children by 2 examiners (11.1% of examiners), and 3 children by 1 examiner (5.6% of examiners). Six of 6 family practitioners (100%), 4 of 6 internists/pediatricians (67%), and 3 of 6 pediatricians (50%) failed to request serum liver chemistries in any of the 4 children. The experience of the examiner did not appear influential with regard to the frequency of serum liver chemistries requested.

Discussion

Pediatric care providers have become increasingly aware of the recent epidemic in pediatric obesity. Screening for comorbid conditions such as diabetes, hypertension, and dyslipidemia have received great emphasis. Alternatively, little consideration has been given to NAFLD, a disorder with prevalence as high as 50% in obese children.1

Since fatty liver or NAFLD routinely has a silent presentation, establishing the diagnosis in an affected individual requires the primary care physician to detect hepatomegaly on physical examination and/or order the appropriate diagnostic tests (serum liver chemistries, hepatic ultrasound, computed tomography [CT], or MRI). Hepatomegaly has been recognized as a feature of NAFLD since the original description of the disorder in 1980.3 In a recent study by Fishbein et al, fatty liver was present in 21 of 22 (95%) obese children with hepatomegaly.11 The corresponding relationship between hepatic steatosis and liver size (hepatomegaly) has been shown in obese subjects undergoing gradual weight loss, where a regression of fatty liver coincides with decrement in liver span.14,16 Despite the overt linkage between fatty liver and liver enlargement, hepatomegaly has not been reported universally in NAFLD.

A plausible explanation for the underestimation of hepatomegaly in subjects with NAFLD or fatty liver lies in the body habitus of the affected population. A majority of adults and almost the entire population of children with NAFLD or fatty liver are obese. The popular belief exists that performing abdominal examinations in this population is imprecise, particularly in recognizing hepatomegaly. Two investigations performed in the 1970s have attempted to reconcile this issue. In a study by Sullivan et al,17 the clinical estimation of liver size in obese subjects was impaired by location of the upper border of the liver. However, the estimate of the lower liver border was unaffected, and in cases where a liver was palpable, the estimated clinical liver size was most accurate.17 In a study by Blendis et al, the presence of hepatomegaly, regardless of body habitus, was agreed upon by a majority of observers in 93% of subjects examined.

Various means for estimating liver size are available to the clinician. Among these include the scratch test, light percussion, and deep percussion. Hepatomegaly may be established by liver span or by detection of a liver edge below the right costal margin.19 Gilbert,20 using auscultatory percussion, demonstrated the presence of a liver edge 1 cm or less below the right costal margin in 45 normal individuals. In that same investigation, 2 subjects with diabetes mellitus, abnormal levels of serum liver chemistries, and probable fatty liver had a liver edge palpable 3 cm below the right costal margin. On this basis, Gilbert established a liver edge 2 cm or greater below the right costal margin as an indicator of hepatomegaly.20 Wolf and Lavine21 have defined hepatomegaly in the pediatric population by using the same guidelines. In accordance with these published reports, the pediatric gastroenterologist in the present investigation has interpreted a liver edge 2 cm or greater below the right costal margin as indicative of hepatomegaly.

Aside from examination technique, the clinical experience of the examiner may also be relevant in assessing liver size. In an investigation by Skrainka et al,22 consultants provided a more accurate determination of liver size through percussion and palpation than fellows or medical students did. The accuracy of liver span determination by a single individual was also improved.
Undetected Hepatomegaly in Obese Children

through repeated examinations. In the present study, the clinical experience of the examiner was not influential in the detection of hepatomegaly. A plausible explanation for the poor outcome is due to study design. Clinicians in this investigation were blinded with regard to study purpose and therefore may not have been focused adequately on physical examination of the liver. Perhaps an improvement in the detection of hepatomegaly would have been elicited if clinicians had been given the opportunity to reexamine the children after being unblinded. Yet, in the clinical setting, physicians are not likely to be forewarned or receive a second opportunity to recognize hepatomegaly. These results may have great impact for the affected child since a follow-up examination may not occur for years.

In the modern era, with the advent of noninvasive imaging techniques, the role of the physical examination of the liver has become less clear. In comparing individuals with normal and cirrhotic livers, Zoli et al concluded that there is only a very limited role for physical examination of the liver. Instead, clinicians are becoming more reliant on noninvasive imaging studies to detect liver enlargement or pathology. Indeed, hepatic ultrasound, CT, and MRI are all adequate means to assess liver size and diagnose fatty liver. Yet, in the present investigation, where occult liver disease was unsuspected and hepatomegaly was detected poorly, no requests for hepatic imaging studies were made.

Hepatomegaly was detected in 4 obese children by the pediatric gastroenterologist. Although hepatic imaging studies were not performed routinely in this investigation owing to funding limitations, 3 of these individuals with hepatomegaly underwent MRI that demonstrated hepatic fat fraction greater than 18.5% consistent with severe steatosis (the other child was lost to follow-up and could not be further evaluated). These findings coincide with our prior experience with severe steatosis in obese children, where hepatomegaly is a universal finding.

The adult gastroenterologist agreed with the pediatric gastroenterologist with regard to the presence of hepatomegaly in only 2 subjects and the absence of hepatomegaly in 6 subjects. The slight agreement (κ = 0.38) was not much different than suggested by Espinoza et al looking at the interobserver agreement between gastroenterologists in the physical diagnosis of alcoholic liver disease. These data suggest that despite advanced training, hepatomegaly in obese individuals may still be difficult to detect clinically. In this investigation only 1 experienced pediatric gastroenterologist was able to participate. Additional pediatric gastroenterologists would have been required to confirm ease of detection of hepatomegaly by these subspecialists. Unfortunately, owing to geographical considerations, the participation of other pediatric gastroenterologists was not feasible. However, as noted previously, severe steatosis in 3 of 4 children in the hepatomegaly-present (NAFLD) group verifies the physical examination finding.

Elevated serum aminotransferases have also been useful in pursuing a diagnosis of NAFLD. Several adult studies and a few pediatric studies have demonstrated a consistent pattern of enzyme abnormalities in this disorder. In adults and children, elevated serum aminotransferases are often the first indicator of NAFLD. A noninvasive imaging study or liver biopsy usually follows to establish the diagnosis. Without the detection of hepatomegaly or request for serum aminotransferases, establishing a diagnosis of NAFLD is unlikely. In this investigation, several laboratory tests were selected more preferentially than serum aminotransferases including fasting blood glucose, lipid profile, urinalysis, thyroid function tests, and serum electrolytes. In fact, serum liver chemistries were requested specifically in only 1 instance, coinciding with the detection of hepatomegaly. In all other instances, a request for a comprehensive metabolic profile rather than serum liver chemistries was made. Though considered equivalent for the purpose of this study, the actual intention of the examiner was not further explored. Barlow et al, in a survey filled out by pediatricians, reported a similar pattern of laboratory requests in obese children. In that investigation, total cholesterol, lipid profile, thyroid function test, glucose, insulin, and glucose tolerance tests were ordered more frequently than serum liver chemistries. Only 10.8% of pediatricians requested serum liver chemistries. Both studies indicate an awareness of the primary care physician for the recommended laboratory evaluation guidelines for the obese child including screening for dyslipidemia and insulin/glucose dysregulation, but the low rate of serum liver chemistries requested is suggestive of their inattentiveness or lack of awareness toward the possible existence of NAFLD. In this investigation, approximately 75% of participating physicians failed to request serum liver...
chemistries or hepatic imaging in a single subject with hepatomegaly. In these instances, the affected individual was unlikely to have undergone the necessary further steps toward diagnosis of NAFLD.

Among primary care providers, family practitioners were most likely to omit serum liver chemistries. Their hesitancy to request these may be a result of their relative lack of awareness of NAFLD in the pediatric population as opposed to the adult population. On occasion, even individuals with normal levels of serum aminotransferases may possess severe steatosis, as indicated by subject #10. For this group, which compromises about 5% of afflicted children, detection of hepatomegaly is the only clue to the presence of NAFLD.11

The long-term effect of failing to diagnose NAFLD in children is unknown. However, the long-term prognosis of NAFLD in the adult population is concerning. About 15% of affected individuals are likely to experience disease progression, culminating in cirrhosis.27 Under these circumstances, pediatric care providers need to become increasingly attentive to the abdominal examination of the obese child, and if hepatomegaly is detected (or even suspected), then appropriate diagnostic testing for NAFLD should commence. The most effective therapy for NAFLD is weight loss. Although a majority of primary care providers in this investigation were unaware of the presence of NAFLD in the study group, they were in favor of dietary consultations in about half of the population. The likelihood of a successful weight loss program also varies according to age group. A child involved in a structured weight loss program is more likely to be successful than an adolescent or adult counterpart.28,31

REFERENCES


