CHEST

Official publication of the American College of Chest Physicians

Elevated Serum Aminotransferase Levels in Children at Risk for Obstructive Sleep Apnea*

Leila Kheirandish-Gozal, Oscar Sans Capdevila, Ebrahim Kheirandish and David Gozal

Chest 2008;133;92-99
DOI 10.1378/chest.07-0773

Elevated Serum Aminotransferase Levels in Children at Risk for Obstructive Sleep Apnea*

Leila Kheirandish-Gozal, MD; Oscar Sans Capdevila, MD; Ebrahim Kheirandish, MD; and David Gozal, MD, FCCP

Background: **Fatty liver disease (FLD) is a highly prevalent condition in obese (Ob) children, who are at increased risk for obstructive sleep apnea (OSA). However, the contribution of OSA to FLD remains unknown.**
Design: **Prospective study.**
Setting: **Polysomnographic evaluation and assessment of plasma levels of insulin, glucose, and lipids, and liver function tests.**
Participants: **A total of 518 consecutive snoring children 4 to 17 years of age who were being evaluated for habitual snoring and suspected OSA.**
Results: **A total of 376 children had body mass index z score of < 1.20 (non-Ob children), 3 children (<1%) had elevated serum aminotransferase (LFT) levels, and 248 had OSA (65.9%). Among the 142 overweight/Ob children, 46 had elevated LFT levels (32.4%); of these children, 42 had OSA (91.3%). In contrast, OSA was present in only 71.8% of Ob children without elevated LFT level ($p < 0.01$). Insulin resistance and hyperlipidemia were more likely to occur in children with FLD. Furthermore, FLD was improved after treatment of OSA in 32 of 42 Ob children ($p < 0.0001$).**
Conclusion: **Increased liver enzyme levels are frequently found in Ob snoring children, particularly among those with OSA and/or metabolic dysfunction. Effective treatment of OSA results in improved liver function test results in the vast majority of these patients.**

(CHEST 2008; 133:92–99)

Key words: fatty liver; obesity; sleep apnea

Abbreviations: AHI = apnea-hypopnea index; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; CRP = C-reactive protein; FLD = fatty liver disease; I/G = fasting insulin/fasting glucose; LFT = serum aminotransferase; NOb = nonobese; Ob = obese; OR = odds ratio; OSA = obstructive sleep apnea; SDB = sleep-disordered breathing; Spo_2 = pulse oximetric saturation; T&A = tonsillectomy and adenoidectomy; TNF = tumor necrosis factor; TST = total sleep time

Nonalcoholic fatty liver disease (FLD) is currently considered to be the most common cause of liver disease in children.[1] FLD encompasses a wide spectrum of hepatic abnormalities ranging from simple steatosis to progressive liver inflammation and cell injury, which may ultimately lead to cirrhosis and end-stage liver disease in some children.[2–4] Obesity, insulin resistance, and type 2 diabetes have been identified as risk factors for FLD.[5,6] While the prevalence of FLD has not been firmly established, it appears to affect around 3% of the general population, based on several surveys from around the world.[6–8] However, obese (Ob) children are at much higher risk for FLD, with prevalence rates reported between 6% for overweight children to 23% among Ob children.[6,9]

Obstructive sleep apnea (OSA) has emerged in the past few years as a highly prevalent condition in pediatric populations. Similar to FLD, one of the main risk factors for OSA is obesity. Furthermore, mutual interactions among OSA, obesity, and insulin resistance have emerged, and may involve systemic inflammatory responses.[10–14] However, we are unaware of any study assessing the potential relationship between OSA and FLD in children. In adults, an increased prevalence of OSA symptoms and polysomnographically confirmed

OSA appears to occur among patients with nonalcoholic steatohepatitis,[15,16] and, conversely, among adult patients being evaluated for habitual snoring and suspected OSA, elevated body mass index (BMI) values and the presence of OSA were both independently associated with increased levels of serum aminotransferases (LFTs).[17] Furthermore, it has been reported[18] that the treatment of Ob adults with OSA with nasal continuous positive airway pressure (CPAP) was associated with a decrease in LFT levels.

Based on the aforementioned considerations, we conducted the present study to examine the hypothesis that the prevalence of elevated LFT levels among children with habitual snoring who were being evaluated for suspected OSA would be greatest among Ob snoring children with OSA. Furthermore, we sought to examine whether effective therapy of OSA among children with FLD and OSA would lead to improvements in circulating levels of transaminases.

Materials and Methods

Five hundred eighteen children between the ages of 4 and 17 years who were consecutively evaluated at the Kosair Children's Hospital Sleep Medicine Center for habitual snoring and suspected OSA were recruited into the study. The study was approved by the University of Louisville Human Research Committee. Parental informed consent and child assent, in the presence of a parent, were obtained. Children were excluded if they had any chronic medical condition, were receiving medications known to affect glucose homeostasis or to affect liver function test results, and if they had any genetic or craniofacial syndromes.

A standard overnight multichannel polysomnographic evaluation was performed in the sleep laboratory, as described previously.[19] Sleep architecture was assessed by standard techniques.[20] The proportion of time spent in each sleep stage was expressed as the percentage of total sleep time (TST). Central, obstructive, and mixed apneic events were counted. Obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for a duration of at least two breaths.[19,21] Hypopneas were defined as a decrease in oronasal flow of $\geq 50\%$ with a corresponding decrease in pulse oximetric saturation (Spo_2) of $\geq 4\%$ and/or arousal.[19] The obstructive apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas occurring per hour of TST. Arousals were defined as recommended by the American Sleep Disorders Association Task Force report,[22,23] and included respiratory-related (occurring immediately following an apnea, hypopnea, or snore), technician-induced, and spontaneous arousals. Arousals were expressed as the total number of arousals per hour of sleep time (arousal index). Children with an AHI of ≤ 2 were considered to have habitual snoring, while children with an AHI of > 2 events per hour of TST were considered to have OSA.[19] For treatment purposes, children with OSA were initially referred for tonsillectomy and adenoidectomy (T&A), and 8 to 12 weeks after surgery underwent an additional overnight sleep study. If the postsurgical residual AHI was > 5 events per hour of TST, therapy with CPAP applied via nasal mask was instituted and optimized in the sleep laboratory. Effective adherence to CPAP therapy was considered when children used the CPAP device every night for at least 6 h per night.

BMI

Height and weight were obtained from each child using standard techniques. BMI was then calculated (body mass/height squared) and was expressed as the BMI z score using an online BMI z score calculator (http://www.cdc.gov/epiinfo/). Children with BMI z score values exceeding 1.20 were classified as fulfilling the criteria for overweight/obesity.[24]

Blood Samples

Blood for all of the assays reported was drawn the morning after the sleep study after an overnight fast. Plasma insulin levels were measured using a commercially available radioimmunoassay kit (Coat-A-Count Insulin; Cambridge Diagnostic Products, Inc; Fort Lauderdale, FL). This method has a detection level of 1.2 μIU/mL and exhibits linear behavior up to 350 μIU/mL, with intraassay and interassay coefficients of variability of 3.1% and 4.9%, respectively. Plasma glucose levels were measured using a commercial kit based on the hexokinase-glucose-6-phosphate dehydrogenase method (Flex Reagent Cartridges; Dade Behring; Newark, DE). Insulin sensitivity was assessed using the fasting insulin/fasting glucose (I/G) ratio, as previously reported.[25] Insulin resistance was defined as fasting serum insulin levels of > 25 μIU/mL or an I/G ratio of > 0.30.[25] Serum lipids including total cholesterol, high-density lipoprotein cholesterol, calculated low-density lipoprotein cholesterol, and triglycerides were also assessed (Flex Reagent Cartridges; Dade Behring).

Since serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most commonly used screening tools used to detect FLD, we used these measurements as a surrogate marker for suspected FLD.[26] ALT and AST were determined using a standard automated kinetic enzymatic assay. Although there is no single standard cutoff point for abnormal LFT levels, the most commonly used criterion is a value of ≥ 40 U/L for both ALT and AST.[27] To strengthen the use of ALT and AST as surrogates for FLD, we attempted when possible to exclude other causes of chronic hepatitis, including hepatitis B (hepatitis B surface antigen), hepatitis C (anti-hepatitis C antibody), α_1-antitrypsin deficiency (serum α_1-antitrypsin level), autoimmune hepatitis (antinuclear antibody), and Wilson disease (serum ceruloplasmin). In some cases, ultrasonographic assessment of the liver was conducted for the identification of echogenic evidence of liver steatosis.

*From the Department of Pediatrics (Drs. Kheirandish-Gozal, Sans Capdevila, and Gozal), Division of Pediatric Sleep Medicine, University of Louisville, Louisville, KY; and the Department of Infectious Diseases (Dr. Kheirandish), Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran.
This study was supported by National Institutes of Health grant HL-65270, by The Children's Foundation Endowment for Sleep Research, and by the Commonwealth of Kentucky Challenge for Excellence Trust Fund.
The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Manuscript received March 27, 2007; revision accepted August 8, 2007.

Correspondence to: David Gozal, MD, FCCP, Kosair Children's Hospital Research Institute, University of Louisville, 570 South Preston St, Suite 204, Louisville, KY 40202; e-mail: david.gozal@louisville.edu
DOI: 10.1378/chest.07-0773

Statistical Analysis

Data are presented as the mean ± SD, unless otherwise indicated. All analyses were conducted using a statistical software package (SPSS, version 11.5; SPSS Inc; Chicago, IL). Comparisons of polysomnographic and demographic characteristics according to FLD group assignment were made with independent *t* tests or analysis of variance followed by *post hoc* comparisons, with p values adjusted for unequal variances when appropriate (Levene test for equality of variances), or χ^2 analyses with Fisher exact test (dichotomous outcomes) followed by Mantel-Haenszel corrections. All p values reported are two-tailed with statistical significance set at < 0.05.

Results

Overall, 518 consecutive habitually snoring children with a mean age of 8.4 ± 1.3 years (age range, 4 to 17 years) were recruited into the study, and 343 had evidence of OSA (Table 1). The characteristics of children with and without OSA are shown in Table 1. Among those children with OSA, 44 children had elevated liver function test results (12.8%) compared to only 5 children with elevated serum transaminase levels among the 175 children without OSA (2.8%; $p < 0.0001$; odds ratio [OR], 5.15; 95% confidence interval [CI], 1.95 to 15.06).

Similarly, 376 of the habitually snoring children recruited into the study had BMI z scores of ≤ 1.20 and were considered as non-Ob (NOb). Among the NOb habitually snoring children, 3 children had evidence of elevated ALT or AST levels (< 1%) and 232 fulfilled the polysomnographic criteria for OSA (61.7%) [Table 2]. Two of these three children had severe OSA, and in the third, ALT values returned to normal 2 weeks later without intervention.

Thus, the 142 remaining children fulfilled the criteria for the overweight/Ob category (*ie*, BMI z score, > 1.20). Of these, 111 children (78.2%) had polysomnographic evidence of OSA, and 46 fulfilled the serologic criteria for FLD (32.4%). Of note, most of the children had isolated elevations of ALT, with only 13 of the 46 children also having increased AST levels. Therefore, most of the analyses regarding FLD were conducted using ALT concentrations only. There were no significant relationships between BMI z score and ALT levels for either the whole cohort or for those children with BMI z scores of > 1.20. Among the 46 Ob children with FLD, 34 were evaluated and had no serologic evidence of chronic liver disease. Twelve of the 46 children with suspected FLD also underwent ultrasonographic liver evaluations, and evidence for steatosis was found in all but 1 child. Of the 46 Ob children with FLD, 42 children (91.3%) had polysomnographic evidence of OSA (Table 3). In addition, I/G ratios of > 0.30 were present in 26 children with FLD (56.5%). In contrast, OSA was present in only 69 of the 96 Ob children without elevated LFT levels (71.8%), and elevated I/G ratios occurred in 22 of 96

Table 1—*Demographic, Polysomnographic, and Metabolic Characteristics of 343 Children With OSA Compared to 175 Habitually Snoring Children Without OSA**

Variables	OSA (n = 343)	No OSA (n = 175)	p Value
Age, yr	8.2 ± 1.3	7.9 ± 1.2	NS
Age range, yr	4–17	4–16	
Male sex, %	51	50	NS
African-American race, %	21.6	21.3	NS
BMI, z score	1.22 ± 0.08	1.17 ± 0.10	NS
TST, min	483.4 ± 15.7	484.0 ± 17.1	NS
Sleep efficiency, %	87.9 ± 8.7	88.9 ± 9.6	NS
AHI, events/h TST	7.5 ± 1.6	0.8 ± 0.3	< 0.0000001
Nadir Spo_2, %	80.4.±3.1	91.3 ± 3.5	< 0.000001
$Petco_2$ > 50 mm Hg, % TST	35.7 ± 6.4	12.1 ± 7.1	< 0.000001
Total arousal index, events/h TST	17.5 ± 3.8	9.5 ± 3.0	< 0.00001
Glucose, mg/dL	86.8 ± 9.4	87.4 ± 8.8	NS
Insulin, μU/mL	13.1 ± 2.0	10.5 ± 2.3	< 0.04
Cholesterol, mg/dL	167.2 ± 6.6	156.4 ± 7.1	< 0.04
Triglycerides, mg/dL	90.4 ± 2.6	93.1 ± 2.7	NS
HDL, mg/dL	56.5 ± 1.9	59.7 ± 2.1	< 0.01
LDL, mg/dL	94.5 ± 2.5	90.2 ± 3.6	< 0.01
AST, U/L	15.7 ± 3.3	14.8 ± 3.7	NS
ALT, U/L	18.9 ± 3.7	17.6 ± 3.5	NS
ALT > 40 U/L†	44 (12.8)	5 (2.8)	p < 0.0001‡

*Values are given as the mean ± SD, unless otherwise indicated. NS = not significant; HDL = high-density lipopolysaccharide; LDL = low-density lipopolysaccharide; $Petco_2$ = end-tidal carbon dioxide pressure.

†Values given as No. (%).

‡OR, 5.5; 95% CI, 1.95 to 15.06.

Table 2—*Demographic, Polysomnographic, and Metabolic Characteristics of 142 Overweight or Ob children Compared to 376 NOb Children Referred for Evaluation of Habitual Snoring

Variables	NOb Children (n = 376)	Ob Children (n = 142)	p Value
Age, yr	8.4 ± 1.2	8.5 ± 1.4	NS
Age range, yr	4–17	4–16	
Male sex, %	48	56	NS
African-American race, %	21.8	21.2	NS
BMI, z score	0.97 ± 0.07	1.83 ± 0.12	< 0.00001
TST, min	477.6 ± 11.2	483.7 ± 57.1	NS
Sleep efficiency, %	89.2 ± 9.7	88.6 ± 7.6	NS
AHI of > 2 events/h TST, %	61.7	78.2	< 0.0001†
AHI, events/h TST	7.2 ± 1.3	9.6 ± 1.5	< 0.001
Nadir Spo_2, %	84.2 ± 3.1	80.3 ± 3.5	< 0.01
$PETCO_2$ of > 50 mm Hg, % TST	24.5 ± 4.4	36.2 ± 6.9	< 0.01
Total arousal index, events/h TST	14.7 ± 2.8	15.8 ± 3.1	NS
Glucose, mg/dL	85.6 ± 8.4	88.9 ± 7.8	< 0.04
Insulin, μU/mL	9.4 ± 1.6	16.9 ± 2.1	< 0.0001
I/G ratio > 0.30‡	0 (0)	53 (37.3)	< 0.00001
Cholesterol, mg/dL	157.6 ± 4.6	176.7 ± 6.6	< 0.0001
Triglycerides, mg/dL	89.5 ± 2.6	96.8 ± 2.7	< 0.01
HDL, mg/dL	64.5 ± 1.5	52.4 ± 1.3	< 0.01
LDL, mg/dL	87.5 ± 1.7	109.6 ± 2.6	< 0.001
AST, U/L	17.5 ± 2.8	25.4 ± 4.2	< 0.05
ALT, U/L	22.5 ± 3.2	32.1 ± 4.8	< 0.0001
ALT > 40 U/L‡	3 (< 1)	46 (32.4)	< 0.00005

*Values are given as the mean ± SD, unless otherwise indicated. See Table 1 for abbreviations not used in the text.
†OR, 3.05; 95% CI, 1.78 to 5.25 (OR calculations were made based on the study of Strauss and colleagues[6] in which elevated ALT levels were found in up to 10% of Ob adolescents).
‡Values are given as No. (%).
§OR, 4.31; 95% CI, 1.96 to 9.73 (OR calculations were made based on the study of Strauss and colleagues[6] in which elevated ALT levels were found in up to 10% of Ob adolescents).

children without FLD (22.9%; $p < 0.0001$ [vs FLD]). Thus, the relative risk for OSA was significantly higher among Ob children compared to NOb children (OR, 3.05; 95% CI, 1.78 to 5.25; $p < 0.0001$); furthermore, the risk for OSA among children with FLD was also markedly higher compared to those children without FLD (OR, 4.11; 95% CI, 1.25 to 14.95; $p < 0.01$), even after controlling for age, gender, and race. Similarly, the odds for insulin resistance FLD were significantly higher in the presence of FLD, and mean cholesterol and triglyceride levels were also higher among those

Table 3—*Demographic and Metabolic Characteristics and OSA Frequency in 46 Ob Children With FLD Compared to 96 Ob Children Without FLD

Variables	Ob(+) FLD (+) (n = 46)	Ob(+) FLD (–) (n = 96)	p Value
Age, yr	9.9 ± 1.2	8.1 ± 1.7	< 0.01
Age range, yr	8–17	4–15	
Male sex, %	65.2	50.0	NS
African-American race, %	10.8	26.0	< 0.04
BMI, z score	1.98 ± 0.13	1.84 ± 0.12	NS
AHI, events/h TST	13.7 ± 2.4	7.6 ± 1.5	< 0.001
AHI of > 2 events/h TST, %	91.3	71.8	< 0.01†
I/G ratio > 0.30‡	26 (56.5)	22 (22.9)	< 0.0001§
Cholesterol, mg/dL	197.6 ± 9.1	172.7 ± 10.6	< 0.001
Triglycerides, mg/dL	112.3 ± 5.6	89.7 ± 4.2	< 0.01
HDL, mg/dL	44.9 ± 2.8	55.2 ± 2.2	< 0.01
LDL, mg/dL	119.7 ± 5.2	100.2 ± 3.6	< 0.001

*Values given as the mean ± SD, unless otherwise indicated. + = with; – = without. See Table 1 for abbreviations not used in the text.
†OR, 4.11; 95% CI, 1.25 to 14.95.
‡Values are given as No. (%).
§OR, 4.49; 95% CI, 1.99 to 10.24.

children with FLD ($p < 0.0001$) [Table 3]. Of note, there were no significant relationships between ALT or AST level and AHI, nadir Spo_2, or any other polysomnographic measure. Stepwise logistic regression analysis for the entire cohort indicated that age, ethnicity, fasting I/G ratio, BMI z score of > 1.2, AHI of > 5 events per hour of TST, and nadir Spo_2 of $< 85\%$ all significantly accounted for the variance in ALT levels ($r^2 = 0.68$; $p < 0.0001$).

ALT levels were reassessed within 5 to 12 months in all 42 Ob children with OSA on the morning after polysomnographic studies were conducted following effective treatment of OSA. Table 4 shows the major polysomnographic findings in the 42 children with elevated liver transaminase levels before and after each of the OSA-related therapeutic interventions. OSA interventions that resulted in the normalization of the respiratory disturbances during sleep consisted of either exclusive T&A (8 children) or of T&A followed by CPAP therapy via nasal mask (34 children). Among the latter, the mean CPAP prescribed was 9.7 ± 1.4 cm H_2O, and, based on smartcard CPAP device downloads during the first month of therapy, 88.2% of these children had at least 6-h of CPAP use every night, with all children receiving the prescribed CPAP for > 4 h per night. However, we should also emphasize that among the 21 children receiving CPAP therapy for whom adherence information was available in subsequent months, only 61.9% used the device every night for ≥ 6 h per night. ALT serum levels were below 40 U/L in 32 of these 42 children with FLD ($p < 0.0001$ [before vs after treatment]) in the absence of significant changes in relative BMI values. There was a weak, albeit statistically significant, relationship between the changes in ALT (pretreatment − posttreatment ALT levels) and the corresponding changes (before AHI − after AHI) in the obstructive AHI ($r^2 = 0.17$; $p < 0.02$) and in the nadir oxyhemoglobin saturation ($r^2 = 0.18$; $p < 0.02$).

Discussion

This study shows that FLD is highly prevalent among Ob habitually snoring children. Furthermore, there is a more than threefold increase in the relative risk for FLD in the present cohort compared to previously reported FLD rates among Ob adolescents in the United States,[6] suggesting that respiratory disturbances during sleep may contribute to the underlying mechanisms of hepatic steatosis in the context of obesity. Furthermore, we not only confirm previous observations on the increased frequency of insulin resistance and altered circulating lipid levels among children with FLD,[28] but also show that OSA is extremely frequent and more prevalent among Ob snoring children with elevated ALT levels compared with Ob snoring children without FLD. Finally, our study suggests that the effective treatment of OSA results in significant improvements in ALT abnormalities in a substantial proportion of children with FLD.

Before we further discuss the potential implications of current findings, some methodological issues deserve comment. Our cohort was based on a convenience sample of otherwise healthy children who were being evaluated for the presence of habitual snoring. Thus, we cannot provide accurate estimates of the true prevalence of FLD in Ob children, and estimates of the relative risk for FLD in our population would have to rely on previously published data.[6] Considering the FLD prevalence of 3% as previously reported in Ob children,[6] the relative risk for FLD among our present cohort of Ob habitually snoring children would have been significantly increased (OR, 4.31; 95% CI, 1.96 to 9.73; $p < 0.00005$). Second, although we conducted an evaluation aiming to exclude other causes of elevated liver enzyme levels in the majority of the subjects with increased ALT levels, none of these children underwent liver biopsy to specifically define the histopathologic abnormalities associated with the biochemical alterations identified herein. While such an invasive procedure would undoubtedly be considered unnecessary for clinical purposes and would pose unnecessary and excessive risk, the information obtained might have added further insights into the process of FLD in early childhood. Nevertheless, the reversal of the elevated transaminase levels in the vast majority of children with putative FLD on the implementation of effective treatment for

Table 4—*Polysomnographic Measures in 42 Ob Children With OSA and Elevated AST Levels, at Diagnosis, After T&A, and at the 1-Month Follow-up Sleep Study After CPAP Titration Therapy

Variables	Before Treatment (n = 42)	OSA Resolved After T&A (n = 8)	Residual OSA After T&A (n = 34)	Following CPAP Titration (n = 31)
TST, min	481.3 ± 17.4	474.5 ± 23.5	479.8 ± 21.8	454.2 ± 27.6
AHI, events/h TST	14.9 ± 2.7	1.1 ± 0.7	10.7 ± 1.6	0.2 ± 0.4
Nadir Spo_2, %	78.1 ± 3.3	93.2 ± 1.4	83.4 ± 3.7	95.1.±1.1
$Petco_2$ of > 50 mm Hg, % TST	41.4 ± 6.2	19.4 ± 2.2	35.2 ± 3.9	NA
Total arousal index, events/h TST	17.6 ± 3.2	11.3 ± 2.2	19.7 ± 5.0	14.9 ± 4.1

*Variables are given as the mean ± SD. See Table 1 for abbreviation not used in the text.

the underlying OSA is highly supportive of a link among obesity, OSA, and increased LFT levels.

To date, the pathophysiologic mechanisms underlying FLD remain incompletely understood. It has become apparent that in addition to the initial steatosis, a second injurious process involving insulin resistance, reduced adiponectin responses,[29,30] increased cytokine activity, oxidative stress, and/or mitochondrial dysfunction are necessary for the pathogenesis of nonalcoholic steatohepatitis.[31–34] Conversely, genetically and environmentally modified antioxidant responses and other individual susceptibility factors may also modulate the frequency and severity of FLD, even in the presence of similar adiposity loads.[34–37] As further evidence of the presence of genetic determinants of susceptibility to FLD, we found a reduced frequency of FLD among African-American children, which is similar to the findings of a previously published report.[38]

The remarkable analogy between the putative pathophysiologic mechanisms of FLD and those ascribed to end-organ injury in the presence of OSA, suggest that the coexistence of OSA and obesity could be the determining factor underlying earlier and potentially more severe FLD in young children. To further illustrate the similarity of the mechanisms underlying FLD and OSA-induced end-organ injury, a brief review of such mechanisms in the context of OSA is necessary. For example, increased thiobarbituric acid-reactive substance formation has been repeatedly reported[39–41] in patients with severe sleep-disordered breathing (SDB) compared to healthy subjects; the treatment of OSA will improve the abnormal lipid peroxidation events, and the presence of increased oxidized low-density lipoprotein levels has also been noted in OSA patients.[42,43]

In support of a systemic inflammatory response to OSA, Schultz and colleagues[44] reported markedly enhanced release of superoxide from stimulated polymorphonuclear neutrophils compared to control subjects, and further showed that CPAP therapy resulted in decreased superoxide release. Tumor necrosis factor (TNF)-α levels are increased, and correlate with the degree of sleepiness and the severity of hypoxia in adult patients with OSA.[14] We have reported[45] very similar findings in children with SDB, whereby TNF-α serum levels were not only elevated in a significant proportion of children with polysomnographic evidence of OSA, but also that the magnitude of TNF-α levels correlated with the degree of respiratory event-induced sleep fragmentation as well as with the presence of obesity.[45]

C-reactive protein (CRP) is an important circulating marker of inflammation and is produced in the liver through interleukin-6 activity. Elevations in CRP levels have been rather consistently reported both in adults[46,47] and in children[12,48] with OSA, and CRP levels are reduced with effective treatment.[13,46] Of interest, the presence of concurrent obesity was a major determinant of the variance in CRP responses. In fact, the interactions among the severity of SDB, lifestyle, and environmental conditions, and genetically derived individual susceptibility have now been proposed as the major potential players involved in the magnitude of the oxidative stress and inflammatory responses associated with SDB.[11,49] Taken together, the increased risk for OSA in Ob persons[10] and the overall presumptive inflammatory and oxidative burden accrual derived from the emergence of OSA in the context of obesity appear to interact to increase the probability of FLD. As a corollary to this assumption, the overall risk for OSA was increased among Ob children, in whom the risk of OSA was significantly higher among those who had elevated ALT levels.

In general, Ob children, and more particularly those with FLD, were at risk for insulin resistance and altered serum lipid profiles. However, we have previously shown that obesity rather than OSA appears to be the major driving factor for metabolic dysfunction in the pediatric population.[25] Based on current findings, we now propose that the metabolic alterations initiated by the presence of obesity will either independently or collaboratively with OSA contribute to the emergence of FLD.

In summary, the risk of FLD is markedly increased by the coexistence of OSA in habitually snoring Ob children, and effective treatment of OSA is associated with significant improvements in liver enzyme levels in the vast majority of these patients. Considering the high risk for both FLD and OSA in the context of obesity during childhood, it is likely that these two conditions may be pathophysiologically linked. Based on the current findings, we believe that routine assessment with liver function tests in Ob children with OSA may identify a particularly susceptible group of patients who may benefit from careful evaluation and treatment by the coordinated efforts of pediatric gastroenterologists and sleep practitioners.

ACKNOWLEDGMENT: We thank all sleep technicians at Kosair Children's Hospital Sleep Medicine and Apnea Center for performing the nocturnal polysomnographic recordings.

References

1 Patton HM, Sirlin C, Behlin C, et al. Pediatric nonalcoholic fatty liver disease: a critical appraisal of current data and implications for future research. J Pediatr Gastroenterol Nutr 2006; 43:413–427

2 Moran JR, Ghishan FK, Halter SA, et al. Steatohepatitis in obese children: a cause of chronic liver dysfunction. Am J Gastroenterol 1983; 78:374–377

3 Rashid M, Roberts EA. Nonalcoholic steatohepatitis in children. J Pediatr Gastroenterol Nutr 2000; 30:48–53
4 Molleston JP, White F, Teckman J, et al. Obese children with steatohepatitis can develop cirrhosis in childhood. Am J Gastroenterol 2002; 97:2460–2462
5 Schwimmer JB, Deutsch R, Rauch JB, et al. Obesity, insulin resistance, and other clinicopathological correlates of pediatric nonalcoholic fatty liver disease. J Pediatr 2003; 143:500–505
6 Strauss RS, Barlow SE, Dietz WH. Prevalence of abnormal serum aminotransferase values in overweight and obese adolescents. J Pediatr 2000; 136:727–733
7 Tominaga K, Kurata JH, Chen YK, et al. Prevalence of fatty liver in Japanese children and relationship to obesity: an epidemiological ultrasonographic survey. Dig Dis Sci 1995; 40:2002–2009
8 Park HS, Han JH, Choi KM, et al. Relation between elevated serum alanine aminotransferase and metabolic syndrome in Korean adolescents. Am J Clin Nutr 2005; 82:1046–1051
9 Schwimmer JB, McGreal N, Deutsch R, et al. Influence of gender, race, and ethnicity on suspected fatty liver in obese adolescents. Pediatrics 2005; 115:e561–e565
10 Tauman R, Gozal D. Obesity and obstructive sleep apnea in children. Paediatr Respir Rev 2006; 7:247–259
11 Gozal D, Kheirandish L. Oxidant stress and inflammation in the snoring child: confluent pathways to upper airway pathogenesis and end-organ morbidity. Sleep Med Rev 2006; 10:83–96
12 Tauman R, Ivanenko A, O'Brien LM, et al. Plasma C-reactive protein in children with sleep-disordered breathing. Pediatrics 2004; 113:e564–e569
13 Kheirandish-Gozal L, Sans Capdevila O, Tauman R, et al. Plasma C-reactive protein in non-obese children with obstructive sleep apnea before and after adenotonsillectomy. J Clin Sleep Med 2006; 2:301–304
14 Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 2005; 112:2660–2667
15 Singh H, Pollock R, Uhanova J, et al. Symptoms of obstructive sleep apnea in patients with nonalcoholic fatty liver disease. Dig Dis Sci 2005; 50:2338–2343
16 Tsang SW, Ng WF, Wu BP, et al. Predictors of fibrosis in Asian patients with non-alcoholic steatohepatitis. J Gastroenterol Hepatol 2006; 21:116–121
17 Tanne F, Gagnadoux F, Chazouilleres O, et al. Chronic liver injury during obstructive sleep apnea. Hepatology 2005; 41:1290–1296
18 Chin K, Nakamura T, Takahashi K, et al. Effects of obstructive sleep apnea syndrome on serum aminotransferase levels in obese patients. Am J Med 2003; 114:370–376
19 Montgomery-Downs HE, O'Brien LM, Gulliver TE, et al. Polysomnographic characteristics in normal preschool and early school-age children. Pediatrics 2006; 117:741–753
20 Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring systems for sleep stages of human subject. Washington DC: National Institutes of Health, 1968; Publication No. 204
21 American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. Am J Respir Crit Care Med 1996; 153:866–878
22 American Sleep Disorders Association. EEG arousals: scoring and rules and examples; Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992; 15: 173–184
23 Mograss MA, Ducharme FM, Brouillette RT. Movement/arousals: description, classification, and relationship to sleep apnea in children. Am J Respir Crit Care Med 1994; 150: 1690–1696
24 Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. Adv Data 2000; 8:1–27
25 Tauman R, O'Brien LM, Ivanenko A, et al. Obesity rather than severity of sleep-disordered breathing as the major determinant of insulin resistance and altered lipidemia in snoring children. Pediatrics 2005; 116:e66–e73
26 Yu AS, Keeffe EB. Elevated AST or ALT to nonalcoholic fatty liver disease: accurate predictor of disease prevalence? Am J Gastroenterol 2003; 98:955–956
27 Seist G, Schiele F, Galteau M, et al. Aspartate aminotransferase and alanine aminotransferase activities in plasma: statistical distributions, individual variations, and reference values. Clin Chem 1975; 151:260–265
28 Schwimmer JB, Deutsch R, Rauch JB, et al. Obesity, insulin resistance, and other clinicopathological correlates of pediatric nonalcoholic fatty liver disease. J Pediatr 2003; 143:500–505
29 Louthan MV, Barve S, McClain CJ, et al. Decreased serum adiponectin: an early event in pediatric nonalcoholic fatty liver disease. J Pediatr 2005; 147:835–838
30 Utzschneider KM, Kahn SE. Review: the role of insulin resistance in non-alcoholic fatty liver disease. J Clin Endocrinol Metab 2006; 91; 4753–4761
31 McClain CJ, Mokshagundam SP, Barve SS, et al. Mechanisms of non-alcoholic steatohepatitis. Alcohol 2004; 34:67–79
32 Bugianesi E, Gastaldelli A, Vanni E, et al. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. Diabetologia 2005; 48:634–642
33 Albano E, Mottaran E, Occhino G, et al. Review article: role of oxidative stress in the progression of non-alcoholic steatosis. Aliment Pharmacol Ther 2005; 22(suppl):71–73
34 Malaguarnera L, Madeddu R, Palio E, et al. Heme oxygenase-1 levels and oxidative stress-related parameters in non-alcoholic fatty liver disease patients. J Hepatol 2005; 42:585–591
35 Panasiuk A, Dzieciol J, Panasiuk B, et al. Expression of p53, Bax and Bcl-2 proteins in hepatocytes in non-alcoholic fatty liver disease. World J Gastroenterol 2006; 12:6198–6202
36 Malaguarnera L, Di Rosa M, Zambito AM, et al. Chitotriosidase gene expression in Kupffer cells from patients with non-alcoholic fatty liver disease. Gut 2006; 55:1313–1320
37 Yamazaki Y, Kakizaki S, Horiguchi N, et al. The role of nuclear receptor CAR in the pathogenesis of non-alcoholic steatohepatitis. Gut 2006; 56:565–574
38 Louthan MV, Theriot JA, Zimmerman E, et al. Decreased prevalence of nonalcoholic fatty liver disease in black obese children. J Pediatr Gastroenterol Nutr 2005; 41:426–429
39 Barcelo A, Miralles C, Barbe F, et al. Abnormal lipid peroxidation in patients with sleep apnoea. Eur Respir J 2000; 16:644–647
40 Barcelo A, Barbe F, de la Pena M, et al. Antioxidant status in patients with sleep apnoea and impact of continuous positive airway pressure treatment. Eur Respir J 2006; 27:756–760
41 Lavie L, Vishnevsky A, Lavie P. Evidence for lipid peroxidation in obstructive sleep apnea. Sleep 2004; 27:123–128
42 Tan KC, Chow WS, Lam JC, et al. HDL dysfunction in obstructive sleep apnea. Atherosclerosis 2006; 184:377–382
43 Tan KC, Chow WS, Lam JC, et al. Advanced glycation endproducts in nondiabetic patients with obstructive sleep apnea. Sleep 2006; 29:329–333
44 Schulz R, Mahmoudi S, Hattar K, et al. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea: impact of continuous positive airway pressure therapy. Am J Respir Crit Care Med 2000; 162:566–570

45 Serpero LD, Kheirandish L, Sans Capdevila O, et al. Sleep fragmentation and circulating TNFα levels in children with sleep-disordered breathing [abstract]. Proc Am Thorac Soc 2006; 3:A555
46 Shamsuzzaman AS, Winnicki M, Lanfranchi P, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 2002; 105:2462–2464
47 Kageyama N, Nomura M, Nakaya Y, et al. Relationship between adhesion molecules with hs-CRP and changes therein after ARB (Valsartan) administration in patients with obstructive sleep apnea syndrome. J Med Invest 2006; 53: 134–139
48 Larkin EK, Rosen CL, Kirchner HL, et al. Variation of C-reactive protein levels in adolescents association with sleep-disordered breathing and sleep duration. Circulation 2005; 111:1978–1984
49 Baldwin CM, Bootzin RR, Schwenke DC, et al. Antioxidant nutrient intake and supplements as potential moderators of cognitive decline and cardiovascular disease in obstructive sleep apnea. Sleep Med Rev 2005; 9:459–476

Elevated Serum Aminotransferase Levels in Children at Risk for Obstructive Sleep Apnea *

Leila Kheirandish-Gozal, Oscar Sans Capdevila, Ebrahim Kheirandish and David Gozal

Chest 2008;133; 92-99
DOI 10.1378/chest.07-0773