Plasma C-Reactive Protein in Nonobese Children With Obstructive Sleep Apnea Before and After Adenotonsillectomy

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Study Objective: Sleep-disordered breathing (SDB) is a prevalent condition in children and is associated with increased cardiovascular morbidity. Circulating levels of C-reactive protein (CRP), a proinflammatory protein, are associated with increased risk for atherosclerosis. Plasma CRP levels in snoring children have yielded conflicting results, such that it remains unclear whether OSA is mechanistically involved in such elevations of CRP.

Methods: Consecutive nonobese children with polysomnographically demonstrated obstructive sleep apnea underwent blood draws in the morning after their corresponding sleep studies on 2 occasions, namely at diagnosis of obstructive sleep apnea and 10 to 14 weeks after adenotonsillectomy. High-sensitivity CRP serum concentrations were determined within 2 to 3 hours after collection, using a particle-enhanced turbidimetric immunoassay technique.

Results: Twenty children with obstructive sleep apnea (mean age 7.3 ± 1.9 years; 55% boys; relative body mass index: 88% ± 12.0%) with a mean apnea-hypopnea index at diagnosis of 15.6 ± 2.9 events per hour of total sleep time and nadir SaO₂ of 82.3% ± 2.5% were included. Mean initial CRP levels at obstructive sleep apnea diagnosis were 0.67 ± 0.21 mg/dL and decreased to 0.23 ± 0.07 mg/dL after adenotonsillectomy (p < .05), along with significant decreases in measured apnea-hypopnea index (2.2 ± 0.8 events/h of total sleep time ; p < .01) and improved oxygenation (mean nadir SaO₂ values: 88.6% ± 1.9%; p < .01).

Conclusions: Obstructive sleep apnea is frequently associated with increases in CRP levels that are reversible upon treatment. Thus, obstructive sleep apnea induces a systemic inflammatory response in children, which, if left untreated, may potentially lead to cardiovascular morbidity.

Keywords: C-reactive protein, sleep-disordered breathing, children, inflammation, obstructive sleep apnea

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Sleep-disordered breathing (SDB) is a frequent disorder in children, with an estimated prevalence of 2% to 3%,1,2 which has been associated with increased risk for cardiovascular morbidities. Nocturnal elevations of systemic blood pressure and sustained diurnal hypertension3,4 and severity-dependent changes in left-ventricular geometry and function5 have all been recently reported in children with SDB and have been ascribed to the concurrent presence of sustained sympathetic activation6-8 and platelet-leukocyte-endothelial interactions leading to initiation and propagation of atherogenesis-related processes.9-11

C-reactive protein (CRP), an important circulating marker of inflammation, is now considered as a reliable marker for subsequent cardiovascular morbidity.12-14 This protein, which is synthesized in the liver in response to upstream inflammatory signaling pathways involving interleukin-6, has also been shown to directly participate in atheromatous lesion formation.15 In a previous study, we showed that plasma CRP levels were increased in children with SDB, compared with controls, and that CRP concentrations were significantly correlated with disease-severity measures, such as hypoxemia and sleep fragmentation.16 Furthermore, we found that these correlations were still valid after adjusting for the degree of obesity.16 Similar to our findings, Larkin and colleagues further reported elevated plasma CRP levels in adolescents with SDB who were free of any known cardiovascular disease, thereby suggesting that SDB in children may apportion an additional risk for cardiovascular morbidity beyond that imposed by the presence of obesity.17 Notwithstanding such findings, normal levels of plasma CRP have also been reported in Greek children with SDB,18 suggesting that the causal relationship between CRP elevations and SDB may not be always operational. Therefore, in order to better understand the contribution of SDB to the inflammatory process ultimately leading to increased cardiovascular risk, we examined the plasma levels of CRP in children with SDB before and following treatment.

METHODS

Consecutive nonobese children diagnosed with SDB were enrolled in the study and were studied twice, namely at the time of SDB diagnosis and 10 to 14 weeks after undergoing curative adenotonsillectomy. Exclusion criteria were the presence of genetic disorders, cerebral palsy, neuromuscular diseases, or any under-
lying systemic diseases or acute infectious processes. Blood was
drawn the morning after the child underwent a standard polysom-
ographic evaluation in the sleep laboratory at the Kosair Chil-
dren’s Hospital. Plasma CRP was measured within 2 to 3 hours
after collection using the Flex reagent Cartridge (Date Behring,
Newark, DE), which is based on a particle-enhanced turbidimet-
ric immunoassay technique. This method has a detection level of
0.05 mg/dL and exhibits linear behavior up to 255 mg/dL, with in-
traassay and interassay coefficients of variability of 9% and 18%,
respectively. Plasma was obtained from the blood sample and was
stored at -80°C until assayed.
A standard overnight multichannel polysomnographic evalu-
ation was performed in the sleep laboratory on 2 different occa-
sions, specifically during the initial diagnostic study and 10 to 14
weeks after undergoing adenotonsillectomy. Children were stud-
ied for up to 12 hours in a quiet darkened room with an ambient
temperature of 24°C and in the company of 1 of their parents.
No drugs were used to induce sleep. The following parameters
were measured: chest and abdominal wall movement by respira-
atory impedance or inductance plethysmography; heart rate by
electrocardiogram; air flow by a sidestream end-tidal capnograph,
which also provided breath-by-breath assessment of end-tidal
CO2 levels (PetCO2; BCI SC-300, Menomonee Falls, WI); naso-
ral pressure catheter; and an oronasal thermistor. Arterial oxygen
saturation (SpO2) was assessed by pulse oximetry (Nellcor N 100;
Nellcor Inc., Hayward, CA); with simultaneous recording of the
pulse waveform. The bilateral electrooculogram, 8 channels of
electroencephalogram, chin and anterior tibial electromyograms,
and analog output from a body-position sensor (Braebon Medical
Corporation, NY) were also monitored. All measures were digi-
tized using a commercially available polysomnography system
(Rembrandt, MedCare diagnostics, Amsterdam). Tracheal sound
was monitored with a microphone sensor (Sleepmate, VA), and a
digital time-synchronized video recording was performed.
All overnight sleep studies were scored in a blinded fashion
without a priori knowledge of the patient’s identity or treatment
status. Sleep architecture was assessed by standard techniques.19
The proportion of time spent in each sleep stage was expressed
as percentage of total sleep time (TST). The apnea index was de-
defined as the number of apneas per hour of TST. Central, obstruc-
tive, and mixed apneic events were counted. Obstructive apnea
was defined as the absence of airflow with continued chest wall
and abdominal movement for duration of at least 2 breaths.20-22
Hypopneas were defined as a decrease in oronasal flow of at least
50%, with a corresponding decrease in SpO2 of 4% or greater
and/or an arousal.22 The obstructive apnea-hypopnea index (AHI)
was defined as the number of apneas and hypopneas per hour of
TST. Children with an initial AHI of 5 or more events per hour of
TST were considered to have SDB and were referred for surgical
removal of enlarged tonsils and adenoids. Complete resolution of
SDB after surgery was defined as a postsurgical AHI < 1 per hour
of TST.
The mean oxygen saturation, as measured by pulse oximetry
(SpO2) in the presence of a pulse waveform signal void of motion
artifact, and the nadir SpO2 were recorded. Since criteria for
arousals have not yet been developed for children, arousals were
defined as recommended by the American Sleep Disorders As-
sociation Task Force report23 using the 3-second rule and/or the
presence of movement arousal.24
Height and weight were obtained from each child. Body mass

| Table 1—Demographic and Polysomnographic Characteristics of 20
  Children with Sleep-Disordered Breathing Before and Following Adenotonsillectomy |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Before adenotonsillectomy</td>
<td>After adenotonsillectomy</td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>7.3 ± 1.9 (4-10)</td>
<td>7.9 ± 2.0 (5-10)</td>
<td>NS</td>
</tr>
<tr>
<td>Boys, %</td>
<td>55</td>
<td>55</td>
<td>.NS</td>
</tr>
<tr>
<td>Relative BMI, %</td>
<td>88 ± 18.0</td>
<td>92.4 ± 17.8</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>15.6 ± 2.9</td>
<td>2.2 ± 0.8</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>SpO2, nadir, %</td>
<td>82.3 ± 2.5</td>
<td>86.6 ± 1.9</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>PETCO2, mmHg</td>
<td>56.3 ± 4.8</td>
<td>52.8 ± 4.1</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>Arousal Index, events/h</td>
<td>16.8 ± 3.2</td>
<td>6.4 ± 2.1</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>TST, min</td>
<td>523.9 ± 24.7</td>
<td>531.6 ± 26.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>91.2 ± 4.5</td>
<td>90.3 ± 5.4</td>
<td>NS</td>
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<tr>
<td>Sleep stage, %</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13.6 ± 6.7</td>
<td>8.5 ± 7.5</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>2</td>
<td>47.0 ± 12.2</td>
<td>43.8 ± 11.9</td>
<td>NS</td>
</tr>
<tr>
<td>SWS</td>
<td>23.8 ± 8.1</td>
<td>26.4 ± 9.3</td>
<td>NS</td>
</tr>
<tr>
<td>REM</td>
<td>14.7 ± 5.2</td>
<td>17.6 ± 6.6</td>
<td>NS</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>0.67 ± 0.21</td>
<td>0.23 ± 0.07</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD unless otherwise indicated. BMI
refers to body mass index; AHI, apnea-hypopnea index; PetCO2, en-
tid CO2, TST, total sleep time; SWS, slow-wave sleep; REM, rapid
eye movement; CRP, C-reactive protein.

Results were calculated and also expressed as relative BMI (relative BM
index (BMI) was calculated and also expressed as relative BMI
(relative BMI), using the following formula: (BMI/BMI of the 50th
percentile for age and sex) × 100, based on standardized
percentile curves.25 Obesity was defined as a BMI greater than
the 95th percentile for sex and age and led to exclusion from the
study.

Data Analysis

Data are presented as means ± SD unless otherwise indicated.
All analyses were conducted using SPSS software (version 11.5;
SPSS Inc., Chicago, IL). Comparisons between pretreatment and
posttreatment measures were made with paired t-tests. All p val-
ues reported are 2-tailed, with statistical significance set at < .05.

RESULTS

Twenty children with SDB were included. Subject sleep char-
acteristics are shown in the Table. In brief, their mean age was
7.3 ± 1.9 years, 55% were boys, and their mean relative BMI
was 88% ± 12.0%. Their mean AHI at diagnosis (before the ad-
enotonsillectomy) was 15.6 ± 2.9 events per hour of TST, and
their nadir SaO2 was 82.3% ± 2.5%; adenotonsillectomy was as-
associated with significant improvements in respiratory disturbance
(AHI post adenotonsillectomy: 2.2 ± 0.8 events per hour of TST;
p < .01, and nadir SaO2 post adenotonsillectomy: 88.6% ± 1.9%;
p < .01), with mild, albeit significant, increases in relative BMI
(92.4% ± 17.8%; p < .05).

Mean initial CRP levels at SDB diagnosis were 0.67 ± 0.21
mg/dL and decreased to 0.23 ± 0.07 mg/dL after adenosil-
lectomy (Figure; p < .05). As in our previous study,9 there
was a statistically significant linear correlation between logAHI and
logCRP (r2: 0.22; p < .03). Of the 20 children studied, 15 children
exhibited higher CRP levels at diagnosis, 3 had no changes in
their CRP levels over time, and 2 children showed mild insignifi-
of note, elevated plasma levels of adhesion molecules occur in children with SDB, and, remarkably analogous to adults with SDB, they are significantly correlated with the degree of hypoxemia and sleep fragmentation. Thus, SDB appears to induce or amplify an inflammatory-response cascade that ultimately potentiates the pathophysiologic mechanisms underlying atherogenesis. If these assumptions are correct, it is somewhat reassuring to observe a decline in such inflammatory activity with effective treatment, as suggested by our current findings.

Although a major strength of our study lies in the prospective and paired study design, it would be interesting to further determine whether the concurrent presence of obesity would affect the effect size of the response to treatment. Similarly, it will be critical to determine in future studies whether SDB elicits differential responses in children born to families with a high prevalence of cardiovascular disease and whether treatment will abrogate CRP elevations in such high-risk patients. Indeed, despite a linear correlation between CRP levels and the severity of SDB (expressed as AHI) there was substantial interindividual variability in the degree of CRP changes associated with the presence of SDB, suggesting that genetic and environmental factors may account for a substantial proportion of the variance in the magnitude of the systemic inflammatory response to SDB.

In addition, our study population consisted of patients with relatively severe SDB, such that the magnitude of systemic inflammation ascribable to SDB in milder cases remains undefined.

In summary, children with SDB commonly display reversible increases in plasma CRP even in the absence of concurrent obesity. These findings support the hypothesis that SDB in childhood imposes an independent risk for development of subclinical inflammation and that the latter may underlie the onset and progression of atherosclerosis, particularly in risk-prone populations.

ACKNOWLEDGEMENTS

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