Fibrinogen Levels and Obstructive Sleep Apnea in Ischemic Stroke

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The plasma level of fibrinogen is felt to be an independent risk factor for vascular events. Obstructive sleep apnea (OSA) has a high prevalence in patients with stroke and may also be an independent risk factor. The aim of our study was to determine the association between OSA and plasma levels of fibrinogen in patients with stroke. Polysomnography was performed during neurological rehabilitation in 113 patients (82 men, 31 women, age 58 ± 11.1 yr, mean ± SD) with ischemic stroke. OSA was absent (RDI < 5) in 44 patients, 42 had mild OSA (5 ≤ RDI < 20), and 27 had moderate to severe OSA (RDI ≥ 20). Parameters of OSA (respiratory disturbance index [RDI], oxygen indices) were correlated to plasma levels of fibrinogen, measured in the morning after admission to rehabilitation. Fibrinogen was positively correlated with RDI (r = 0.24, p = 0.007), duration of the longest apnea (r = 0.18, p = 0.049), and negatively correlated with several oxygen indices including average minimal oxygen saturation (r = -0.41, p < 0.001). Correlation coefficients were slightly higher when excluding patients with stroke of presumed cardiac origin. Multiple linear regression identified minimal mean oxygen saturation and sex as independent predictors of fibrinogen level. The correlation between severity of coexisting OSA and fibrinogen level in patients with stroke suggests a possible pathophysiological mechanism for an increased risk of stroke in patients with OSA.

Epidemiological studies indicate that the plasma level of fibrinogen is an important independent risk factor for vascular events, including myocardial infarction and stroke (1–3). The prevalence of sleep-disordered breathing (SDB), mainly obstructive sleep apnea (OSA), among patients with cerebrovascular accident (CVA) is high (4). In most cases there is evidence that OSA preceded the cerebrovascular event (5–7). Several studies have suggested that OSA is also a risk factor for vascular disease. OSA is associated with worse functional outcome (8) and higher mortality in stroke victims (9). Morning plasma fibrinogen levels and whole blood viscosity are attenuated by effective treatment of OSA with nasal continuous positive airway pressure (nCPAP) (10), raising the possibility, that the treatment may reduce the risk of subsequent vascular morbidity and mortality.

The purpose of our study was to investigate the relationship between plasma fibrinogen levels and the degree of coexisting OSA as determined by full polysomnography in patients with ischemic stroke.

METHODS

Two hundred forty-five consecutive patients admitted for neurological rehabilitation with all forms of ischemic stroke were considered for inclusion in the study: The diagnosis of stroke was confirmed by two neurologists, a complete neurological history, and examination and brain imaging including computed tomography (CT) and/or magnetic resonance imaging (MRI). Patients with signs of acute or chronic inflammation at the time of investigation, as determined by an elevated erythrocyte sedimentation rate > 15 mm/h, were excluded from further analysis (n = 122). Central apnea was regarded as a possible sequela of stroke (7). Hence, all patients with predominant central apnea (defined as a respiratory disturbance index [RDI] ≥ 20 with more central than obstructive or mixed events, n = 10) were excluded. Final analysis was performed on 113 patients with stroke (82 men, 31 women, age 58 ± 11.1 yr, body mass index [BMI] 27 ± 4 kg/m²). Because the pathophysiological mechanism of stroke may be different, a separate analysis was performed for patients with all forms of ischemic stroke and after exclusion of those with probable cardiac or cardioembolic origin of the stroke (n = 21). For this analysis ischemic events were classified according to the TOAST classification (11). The classification was performed by a board-certified neurologist unaware of the results of the sleep studies.

Blood was drawn at 8:00 A.M. on the day after admission to the rehabilitation department after overnight fasting. Plasma levels of fibrinogen were determined using a commercially available assay (Fibrinogen Kinetic, Boehringer Mannheim, Germany). Median time of blood sampling and sleep study was 7 A.M. and polysomnography 37 A.M.

Complete overnight polysomnography (Compumedics, Melbourne, Australia) was performed between 10:00 P.M. and 7:00 A.M. Two-channel electroencephalogram, electrooculogram, and chin electromyogram were registered using standard methods. Oronasal airflow was recorded by thermistor, and thoracic and abdominal respiratory efforts were measured by impedance plethysmography. Oxygen saturation was measured by finger pulse oximetry (ResMed Model 305A, San Diego, CA), and the electrocardiogram (ECG) from a precordial lead. Sleep data were staged manually according to standard criteria (12, 13).

An apnea was defined as cessation of airflow or reduction of thermistor signal to less than 10% of the normal flow with a duration of at least 10 s. Apneas shorter than 10 s were counted if they were followed by either an arousal or an oxygen desaturation of ≥ 4%. Differentiation was made between obstructive (clear obstructive or mixed with a clear obstructive component in the event) and central apneas according to the respiratory effort channels (absence of ribcage and abdominal movement). Hypopnea was defined as a discernible reduction of airflow of at least 10 s duration followed by either an arousal or a desaturation of ≥ 4%. The RDI was calculated as the number of all respiratory events per hour sleep. Clear SaO₂ artifacts were excluded manually. Oxygen indices were then calculated from the SaO₂ curve with the minimal oxygen saturation being the lowest saturation reached during sleep and the average minimal oxygen saturation being the mean of all saturation values reached during all respiratory events. An RDI of ≥ 20 was defined as significant SDB and an RDI of less than 5 was used to rule out relevant SDB.

Statistics

Association between levels of fibrinogen and various parameters of OSA (RDI, oxygen indices) was determined by Pearson’s product correlation. To assess the magnitude of difference in fibrinogen levels, the levels of patients with OSA (RDI of ≥ 20/h) and without OSA...
(RDI < 5/h) were compared using descriptive statistics with 95% confidence intervals [95 CI] and unpaired t tests. To assess the independent effect of different parameters on fibrinogen levels, stepwise multiple linear regression was performed. Sex, age, body mass index, systolic blood pressure (mean of three standardized measurements during the first 2 d), smoking (categorized as nonsmoker, ex-smoker, and smoker at least until the stroke), RDI, and average minimal oxygen saturation were used as independent variables and the fibrinogen level as the dependent variable. A level of p < 0.05 was considered significant. Data are given as mean ± SD.

RESULTS

Positive correlations were found between plasma fibrinogen levels and RDI and between fibrinogen and longest apnea duration. Negative correlations were found between fibrinogen level and several oxygen indices including average minimal oxygen saturation, minimal oxygen saturation, and average oxygen desaturation per event. Correlation coefficients range between 0.2 and 0.5 (Table 1).

After exclusion of all stroke victims with presumed cardiac origin (n = 21), correlation coefficients are slightly higher: The RDI (Figure 1) and the duration of the longest apneas as well as the average desaturation per event (apneas and hypopneas) were positively correlated with fibrinogen level. There was also a moderate negative correlation between fibrinogen and the average minimal oxygen saturation (Figure 2) and the minimal oxygen saturation.

The difference in fibrinogen levels between patients with OSA (RDI of ≥ 20/h, n = 27) and without (RDI < 5/h, n = 44) was 54 (372 mg/dl [95 CI 329; 415] versus 318 mg/dl [288; 347], p = 0.031). After exclusion of patients with cardiac and cardioembolic strokes the difference was slightly higher reaching 78 (382 mg/dl [337; 427] versus 304 mg/dl [276; 332], p = 0.002).

Stepwise multiple linear regression showed the minimal average oxygen saturation and sex to be independent predictors of fibrinogen level. Age, BMI, systolic blood pressure, RDI, and smoking were not found to be predictors of fibrinogen levels (R² for the overall model 0.239, F = 4.7, df = 7,105, p < 0.001; beta for average minimal SaO₂ = 0.31, beta for sex = −0.20).

The distribution of age, sex, BMI, and parameters of OSA according to fibrinogen quartiles is given in the online data supplement to this article on the Journal’s website at www.atsjournals.org.

DISCUSSION

This study demonstrates an association between the severity of OSA in patients with stroke and the plasma level of fibrinogen. Fibrinogen level was positively correlated to number and length of respiratory events and negatively correlated to minimal and average minimal oxygen saturation, as measured by polysomnography. The magnitude of these correlations is in the range of 0.20 to 0.50, indicating a fair degree of relationship. The correlation between OSA and fibrinogen has not been accounted for in epidemiological studies investigating the association of fibrinogen as a possible risk factor for stroke.

There are two major implications of our results: First, the described relationship offers possible evidence for a pathophysiological link between sleep apnea and stroke. Second, given the results of other studies about fibrinogen as a risk factor, the higher levels among patients with stroke with OSA

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>RDI</th>
<th>Average Minimal SaO₂</th>
<th>Minimal SaO₂</th>
<th>Average Desaturation</th>
<th>Longest Apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 113 (all ischemic strokes)</td>
<td>0.24 (0.011)</td>
<td>−0.41 (&lt; 0.001)</td>
<td>−0.23 (0.019)</td>
<td>0.19 (0.046)</td>
<td>0.20 (0.049)</td>
</tr>
<tr>
<td>n = 92 (cardiac origin excluded)</td>
<td>0.32 (0.002)</td>
<td>−0.49 (&lt; 0.001)</td>
<td>−0.26 (0.013)</td>
<td>0.26 (0.013)</td>
<td>0.19 (0.055)</td>
</tr>
</tbody>
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Definition of abbreviation: RDI = respiratory disturbance index.

* Pearson correlation coefficients between fibrinogen levels and indices of severity of obstructive sleep apnea (Average minimal SaO₂) for all ischemic strokes (n = 113) and after exclusion of patients with probable cardiac/cardioembolic origin (n = 92). p Values are given in parentheses.
may identify them as being at a higher risk of stroke recurrence and other vascular events including myocardial infarction. Therefore, treatment of OSA may be warranted even if subjective symptoms (e.g., sleepiness) are not the predominant problem.

Fibrinogen affects blood coagulation, blood rheology, and platelet aggregation. In addition, it has direct effects on the vascular wall and is a prominent acute-phase reactant. In addition, fibrinogen is closely linked to atherosclerosis and prospective epidemiological trials suggest this association represents a major independent cardiovascular risk factor (14).

The Framingham study showed that an elevated level of fibrinogen is associated with a risk of cardiovascular events (1). The impact of fibrinogen level, considered as a separate variable, on cardiovascular disease was comparable with other major risk factors, such as blood pressure, hematocrit, obesity, cigarette smoking, and diabetes. Fibrinogen values were also significantly related to these risk factors.

In a case–control study among a cohort of survivors of a first stroke, the odds ratios for a second stroke were significantly increased in patients with elevated fibrinogen (odds ratio 3.67) (15). Based on these findings the authors conclude that hyperfibrinogenemia is an independent risk factor for cardiovascular events in stroke survivors.

In the Northwick Park Heart study the elevation of one standard deviation in fibrinogen concentration was associated with an 84% increase in the risk of ischemic heart disease within the next 5 yr (16). In our study we note the fibrinogen between patients with and without OSA is in the range between 50 and 80 mg/dl, slightly less than one standard deviation.

The results of our study may have implications for the current treatment of ischemic CVAs. Direct interventions to lower the fibrinogen level have been discussed as possible prevention for vascular events: One can speculate that these interventions are more difficult if coexisting SDB is left untreated. Also, as the relative antiaggregatory effect of ticlopidine is decreased with higher plasma fibrinogen concentrations, this form of treatment may not have the same benefits as in patients without SDB. Higher plasma fibrinogen concentrations may be in part responsible for the individual response to treatment with ticlopidine (17). This hypothesis, however, needs further investigation.

It has been demonstrated that effective treatment of OSA with nCPAP decreases morning fibrinogen levels in patients with OSA without stroke (10). In patients with stroke with OSA, implementation of nCPAP may therefore be an important part of prevention of further cerebrovascular events.

The measured fibrinogen levels in this study do not reflect the true levels at the time of the cerebrovascular event. There was a significant time delay of 6–7 wk between the vascular event and the measurement of fibrinogen: It is possible that the association between fibrinogen levels at the time of stroke and OSA may even be stronger. Despite these limitations, we feel our results suggest that OSA is a causative factor in the elevated fibrinogen levels in our patients.

Patients with stroke often have overt or hidden infections in the poststroke phase (e.g., urinary tract infections) that are often acquired acutely in the hospital. Fibrinogen levels are highly dependent on any acute inflammatory process with a reported 2- to 20-fold increase with acute stress. We therefore prospectively excluded patients with any evidence of infection as determined by an elevated erythrocyte sedimentation rate. The sedimentation rate is a sensitive but nonspecific marker for infection. Thus, patients without infection may have been excluded by this criterion, but this would not be expected to bias the data.

Fibrinogen and OSA may share some common biological pathway. Even after exclusion of patients with clinical and laboratory signs of infection, the higher fibrinogen levels may reflect inflammation: There is strong epidemiological, biochemical, and cell biological evidence implicating inflammation in the process of atherosclerosis and, ultimately, clinical cardiovascular disease (18, 19). There is recent clinical evidence supporting a link between sleep breathing disorders and the pathogenesis of atherosclerotic lesions (20). However, further speculation is beyond the scope of this article.

Association does not necessarily mean causation, and, theoretically, it is possible that high fibrinogen levels may even cause OSA, although this consideration seems unlikely. The only epidemiological study so far linking sleep to fibrinogen shows a weak inverse correlation (r = −0.10, p < 0.05) between sleep disturbance and fibrinogen levels in nonsmokers (21). However, sleep disturbances were only evaluated with a questionnaire and not with objective measurements. Furthermore, in our study population patients did not complain about sleeping problems (6).

Our discussion is based on the hypothesis that OSA, although diagnosed after the CVA, was present before the stroke. This was not addressed in our study and has not been proven in the studies conducted so far (cross-sectional surveys and case–cohort studies). However, several points suggest that obstructive sleep-disordered breathing preceded the stroke in most cases. A history of snoring and breathing pauses prior to stroke is more common in stroke patients with OSA, and the anthropometric data of patients with stroke with OSA are similar to OSA populations without stroke (6). Furthermore, the prevalence of SDB among patients with transient ischemic attacks and stroke is similar (5) and in a recent follow-up study among patients with first-ever stroke the authors found that no correlation exists between the site of stroke and the diagnosis of OSA (7).

We do not want to overemphasize the magnitude of association between stroke and fibrinogen levels as our regression model explains only about 25% of the variation in fibrinogen levels. It must be stressed, however, that none of the epidemiological studies considered SDB as relevant covariable.

In conclusion, patients with ischemic stroke and OSA have elevated fibrinogen levels, which correlate positively with indices of sleep apnea severity. The increased rate of coagulation activity and vasoreactivity may represent a possible pathophysiological mechanism behind the increased vascular morbidity of patients with OSA. We suggest that in future studies on fibrinogen as vascular risk factor coexisting sleep-disordered breathing should be taken into account. Further studies are necessary to investigate the impact of OSA treatment on fibrinogen levels in patients with ischemic stroke.

References


