Association of Symptoms of Chronic Bronchitis and Frequent Flu-Like Illnesses With Stroke

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Background and Purpose—Acute and several chronic infectious diseases increase the risk of stroke. We tested the hypothesis that chronic bronchitis and frequent flu-like illnesses are independently associated with the risk of stroke or transient ischemic attack (TIA).

Methods—We assessed symptoms of chronic bronchitis, frequency of flu-like illnesses, and behavior during acute febrile infection in 370 consecutive patients with ischemic or hemorrhagic stroke or TIA and 370 age- and sex-matched control subjects randomly selected from the population.

Results—Cough with phlegm during ≥3 months per year (grade 2 symptoms of chronic bronchitis) was associated with stroke or TIA independent from smoking history, other risk factors, and school education (odds ratio [OR] 2.63, 95% confidence interval [CI] 1.17 to 5.94; \( P = 0.021 \)). There was also an independent association between frequent flu-like infections (≥2 per yr) and stroke/TIA (OR 3.54; 95% CI 1.52 to 8.27; \( P = 0.003 \)). Simultaneous assessment of chronic bronchitis and frequent flu-like infections did not attenuate the effect of either factor. Patients reported more often than control subjects to continue to work despite febrile infection (OR 3.68, 95% CI 1.80 to 7.52, multivariate analysis).

Conclusions—Our results suggest that chronic bronchitis is among those chronic infections that increase the risk of stroke. Independent from chronic bronchitis, a high frequency of flu-like illnesses may also be a stroke risk factor. Infection-related behavior may differ between stroke patients and control subjects. (Stroke. 2009;40:00-00.)

Key Words: stroke ■ prevention ■ risk factor ■ infection

Several studies convincingly show that acute infection and particularly respiratory tract infection temporarily increases the risk of stroke.1 Common chronic infections such as periodontitis or infection with Helicobacter pylori may also increase stroke risk.2 In a large cohort study, symptoms of chronic bronchitis independently predicted both incidence and mortality of coronary heart disease.3 Data on chronic respiratory infection and stroke are scarce. Two previous case–control studies reported that a history of recurrent or chronic bronchitis is associated with stroke risk.4,5 Chronic bronchitis is characterized by excessive tracheobronchial mucus production sufficient to cause cough with expectoration for at least 3 months of the year. Bronchitic inflammation predominantly consists of neutrophils and is associated with systemic inflammation. There is a continuum and overlap between chronic bronchitis and chronic obstructive lung disease (COLD), emphysema, or asthma.6

We performed a case–control study7,8 to investigate whether symptoms of chronic bronchitis or frequent acute flu-like illnesses are independently associated with the risk of stroke or TIA.

Methods

We investigated 370 consecutive patients admitted to the Neurology Department of the University of Heidelberg for ischemic or hemorrhagic stroke or TIA and 370 control subjects randomly selected from the general population between November 2001 and April 2003. Exclusion criteria were age >80 years (>75 years after the first 6 months of the study), residence outside the study area (city of Heidelberg and the neighboring county), and inability to give informed consent. Among 385 eligible patients, 370 (96.1%) agreed to study participation. All patients received a cranial CT or MRI scan, extra- and transcranial Doppler sonography, ECG, and in most cases transthoracic or transesophageal echocardiography and Holter monitoring. Ischemic stroke was defined as either a central nervous deficit lasting ≥24 hours without evidence for nonvascular cause or cerebral hemorrhage or by a new ischemic lesion on neuroimaging (including abnormalities on diffusion-weighted images unless only detected after the first hours post ischemia) corresponding to acute neurological symptoms regardless of duration of symptoms. Diagnosis of intracerebral hemorrhage was based on neuroradiological evidence. TIA was diagnosed if a neurological deficit of vascular origin lasted <24 hours without new corresponding vascular lesion on neuroimaging. The TOAST criteria were used for further subtyping cerebral ischemia.9

From the Inhabitant Registration Administration of our area we received a list containing name, age, sex, and address of a random sample of 2% of all adult inhabitants aged ≤80 years. All inhabitants
have to be registered there according to German law. Control subjects were randomly selected from this sample and matched to patients one-to-one for age (±2 years), sex, and area of residence. Within 1 week after a patient was included the first matching subject that could be identified in the random sample was contacted by mail and thereafter by phone. Among 430 subjects who could be contacted by phone, 370 (86.0%) agreed to study participation. The Neurology Department of University of Heidelberg is the only neurological hospital in the area, and most younger patients with stroke/TIA (<75 years) are admitted there. Therefore, the patients examined are reflective of the population of the surrounding area. All subjects were interviewed by trained interviewers using a structured questionnaire. Interviews were performed face-to-face in patients and by phone in control subjects. To avoid any classification bias between groups, self-reported risk factors and diseases were acknowledged if subjects affirmed that a physician had made the respective diagnosis before stroke or interview. The ethics committee approved the study protocol. All subjects gave informed consent.

Symptoms of chronic bronchitis were assessed by 3 questions using the modification by Jousilahti and coworkers of the respiratory questionnaire by Rose and Blackburn: (1) Do you usually have cough with phlegm in the mornings in the winter? (2) Do you usually have cough with phlegm during the day or at night in the winter? (3) And do you cough like this on most days or nights as much as 3 months each year? Positive answers in either or both of the 2 first questions were classified as grade-1 symptoms, positive answers in the third question were classified as grade-2 symptoms of chronic bronchitis. Participants were furthermore asked how often they suffered from acute respiratory tract infection or flu-like illness on average during the last 5 years. Acute respiratory tract infection or flu-like illness was defined as any combination of fever or shivering, cough, hoarseness, running nose, or sore throat lasting ≥3 days. To assess infection-related behavior, subjects were asked the following question: Imagine you develop symptoms of a flu with fever of 39°C, malaise, and arthralgia on one evening. What would you do if symptoms (OR 2.35, 95% CI 1.44 to 3.83; P<0.001) and fever (OR 2.67, 95% CI 1.37 to 5.18; P=0.008) of chronic bronchitis (Table 1). Table 1 also depicts other risk factors and diseases, many of which show significant differences between groups. After adjustment for all covariables, grade 2 symptoms of chronic bronchitis were significantly associated with stroke or TIA (OR 2.63, 95% CI 1.17 to 5.94; 0.008).

### Statistical Analysis
Dichotomous variables were compared using χ² test. Odds ratios and 95% confidence intervals (CI) are given for all risk factors. Conditional logistic regression analysis for matched pairs was used to adjust for other variables and included all generally accepted stroke risk factors and associated diseases (hypertension, diabetes mellitus, smoking, previous stroke/TIA, hyperlipidemia, coronary heart disease) plus all those factors that were significant (P<0.05) in univariate analysis. For analyses of an interaction between parameters, an interaction term was introduced into the model. Because of lower numbers of subjects, a reduced model was used for subgroup analyses containing only those risk factors that were significant in multivariable analyses with all subjects. Patients with missing values were excluded from the analyses. Data were analyzed using the software package SAS.

### Results
Among the 370 patients, 244 had ischemic stroke, 76 had a TIA, and 44 suffered from hemorrhagic stroke. As compared to control subjects patients reported more often grade 1 symptoms (OR 2.35, 95% CI 1.44 to 3.83; P=0.001) and grade 2 symptoms (OR 2.67; 95% CI 1.37 to 5.18; P=0.008) of chronic bronchitis (Table 1). Table 1 also depicts other risk factors and diseases, many of which show significant differences between groups. After adjustment for all covariables, grade 2 symptoms of chronic bronchitis were significantly associated with stroke or TIA (OR 2.63, 95% CI 1.17 to 5.94; 0.008).
Grade 1 symptoms of chronic bronchitis were also independently correlated with stroke/TIA (OR 3.11; 95% CI 1.64 to 5.91; P < 0.0005). Effect size of symptoms of chronic bronchitis was not different between younger and older patients. Prevalence of chronic bronchitis was lower in women than in men in both groups, and chronic bronchitis was associated with stroke/TIA in men but not in women (Table 3).

Symptoms of chronic bronchitis increased the odds of stroke/TIA independent of current or previous smoking and within the model of Table 2 current smoking and symptoms of chronic bronchitis did not interact with each other (P = 0.89). Frequency of chronic bronchitis was highest in current smokers and lowest in never smokers among patients, and a similar trend was seen in control subjects (Table 3). The mean number of cigarettes currently smoked by patients (19.4 ± 11.7 per day) and control subjects (16.5 ± 11.3 per day) was not different (P = 0.10). Symptoms of chronic bronchitis tended to be associated with increased odds of stroke/TIA in current smokers, previous smokers, and never smokers, however a significant association was only found in previous smokers in univariate analysis (Table 3).

Symptoms of chronic bronchitis increased the odds of stroke/TIA in subjects with lower level school education in univariate analysis and a strong trend was present after adjustment for potential confounders, whereas no such effect was present in better educated subjects (Table 3). Grade 2 symptoms of chronic bronchitis were associated with increased odds of ischemic stroke and of stroke/TIA attributable to large artery atherosclerosis and tended to increase the odds of cardioembolic stroke/TIA (Table 3).

Addition of influenza or pneumococcal vaccination during the last year to the model in Table 2 attenuates the risk

### Table 2. Multivariate Analysis With Symptoms of Chronic Bronchitis and Other Variables

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic bronchitis (Grade 2 symptoms)</td>
<td>2.63</td>
<td>1.17–5.94</td>
<td>0.020</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.98</td>
<td>1.32–2.98</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.14</td>
<td>0.63–2.04</td>
<td>0.67</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.23</td>
<td>0.81–1.87</td>
<td>0.33</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>6.29</td>
<td>3.36–11.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>0.97</td>
<td>0.54–1.72</td>
<td>0.91</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.74</td>
<td>1.05–2.91</td>
<td>0.033</td>
</tr>
<tr>
<td>Previous smoking</td>
<td>0.98</td>
<td>0.59–1.63</td>
<td>0.94</td>
</tr>
<tr>
<td>Alcohol abstinence</td>
<td>1.81</td>
<td>1.06–3.10</td>
<td>0.031</td>
</tr>
<tr>
<td>High alcohol consumption</td>
<td>2.71</td>
<td>1.18–6.24</td>
<td>0.019</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>1.65</td>
<td>1.04–2.61</td>
<td>0.032</td>
</tr>
<tr>
<td>School education &lt;10 years</td>
<td>1.53</td>
<td>1.01–2.33</td>
<td>0.046</td>
</tr>
</tbody>
</table>

### Table 3. Symptoms (Grade 2) of Chronic Bronchitis and Risk of Stroke/TIA: Subgroup Analyses

<table>
<thead>
<tr>
<th>Group of Subjects</th>
<th>Prevalence of Chronic Bronchitis (Patients)</th>
<th>Control Subjects (Univariate Analysis)</th>
<th>Odds Ratio (Multivariate Analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;60 years (n=149)</td>
<td>10.1%</td>
<td>4.1%</td>
<td>3.00 (0.97–9.30)</td>
</tr>
<tr>
<td>Age ≥60 years (n=221)</td>
<td>10.1%</td>
<td>5.4%</td>
<td>2.37 (1.04–5.42)</td>
</tr>
<tr>
<td>Women (n=115)</td>
<td>4.4%</td>
<td>3.5%</td>
<td>1.33 (0.30–5.96)</td>
</tr>
<tr>
<td>Men (n=155)</td>
<td>12.7%</td>
<td>5.5%</td>
<td>3.11 (1.47–6.99)</td>
</tr>
<tr>
<td>Current smokers (n=105)</td>
<td>15.2%</td>
<td>10.0%</td>
<td>1.62 (0.63–4.16)</td>
</tr>
<tr>
<td>Prev. smokers (n=126)</td>
<td>11.2%</td>
<td>3.9%</td>
<td>3.13 (1.09–8.96)</td>
</tr>
<tr>
<td>Never smokers (n=106)</td>
<td>5.1%</td>
<td>3.6%</td>
<td>1.55 (0.49–4.94)</td>
</tr>
<tr>
<td>Low-level school education (n=256)</td>
<td>11.0%</td>
<td>5.5%</td>
<td>2.12 (1.05–4.27)</td>
</tr>
<tr>
<td>Medium-/high–level school education (n=103)</td>
<td>7.8%</td>
<td>4.1%</td>
<td>1.33 (0.46–3.84)</td>
</tr>
</tbody>
</table>

**Etiologic subgroups**

- **Ischemic stroke (n=244)**
  - 11.5% (6.2%) 2.30 (1.09–4.83) 2.45 (1.10–5.46)
- **TIA (n=76)**
  - 5.3% (1.3%) 4.00 (0.45–35.8) 3.32 (0.23–48.4)
- **Hemorrhagic stroke (n=44)**
  - 12.5% (5.0%) 4.99 (0.58–42.8) 8.66 (0.52–144)

**Etiologic subgroups of ischemic stroke/TIA**

- **Large artery atherosclerosis (n=130)**
  - 11.5% (5.4%) 3.00 (0.97–9.3) 4.77 (1.18–19.3)
- **Cardioembolism (n=63)**
  - 12.7% (1.6%) 8.00 (1.00–64) 6.75 (0.76–59.9)
- **Microangiopathy (n=30)**
  - 6.7% (3.3%) 2.00 (0.18–22.1) 1.85 (0.09–39.9)
- **Other etiologies (n=25)**
  - 4.0% (12.0%) 0.33 (0.04–3.21) 0.27 (0.019–3.93)
- **Cryptogenic (n=72)**
  - 8.5% (5.6%) 2.00 (0.37–10.9) 1.45 (0.19–10.9)

*Adjusted for arterial hypertension, current smoking, alcohol abstinence, high alcohol consumption, family history of stroke, school education.
associated with grade 2 symptoms of chronic bronchitis to a borderline significant level (OR 2.31; 95% CI 0.99 to 5.38). Symptoms of chronic bronchitis were associated with increased risk of stroke/TIA during winter months (November through April, n = 261; OR 4.58; 95% CI 1.73 to 12.1) but not significantly with those during summer months (n = 106; OR 2.39; 95% CI 0.53 to 10.8) in multivariate analysis.

Patients reported more often than control subjects to suffer on average from >2 episodes of flu-like illnesses annually during the last 5 years (OR 2.14; 95% CI 1.14 to 4.04; \(P = 0.019\); Table 1). High frequency of flu-like illnesses was independently associated with the odds of stroke/TIA after adjustment for the covariates in Table 2 (OR 3.54; 95% CI 1.52 to 8.27; \(P = 0.003\)). Chronic bronchitis (OR 2.83; 95% CI 1.16 to 6.91) and frequent flu-like illnesses (OR 3.22; 95% CI 1.39 to 7.49) were independently associated with stroke/TIA when simultaneously entered in the model in Table 2.

The self-estimated reaction to symptoms of febrile infection was different between groups (Table 1). More patients than control subjects reported that they would continue as usual, including continuation of work despite high fever (OR 2.68, 95% CI 1.59 to 4.55), and such behavioral pattern remained associated with stroke/TIA in multivariate analysis (OR 3.68, 95% CI 1.80 to 7.52). In contrast, less patients reported to use self-medication and to rest (OR 0.48, 95% CI 0.35 to 0.66) and such self-reported attitude was also independently associated with reduced odds of stroke/TIA (0.46; 95% CI 0.30 to 0.68).

**Discussion**

Our results support the hypothesis that chronic bronchial inflammation is a risk factor for stroke. This finding strengthens the concept that chronic infectious diseases of different origin may increase stroke risk.

The diagnosis of chronic bronchitis is made by history and commonly applied diagnostic criteria were used in our study. Cough and sputum are nonspecific symptoms that can also result from other airway diseases or from cardiac disease. Therefore, we use the term "symptoms of chronic bronchitis" in accordance with previous epidemiological studies. Several confounders could explain the association between chronic bronchitis and stroke, particularly smoking and low socioeconomic status. As shown previously, prevalence of chronic bronchitis varied along smoking status and was highest in current smokers and lowest in never smokers in both groups. Symptoms of chronic bronchitis remained associated with stroke/TIA when smoking status was adjusted for. Smoking and chronic obstructive airway disease both independently increase the level of inflammatory markers such as C-reactive protein, which is also a predictor of stroke. A genetically determined strong inflammatory response appears to be linked with both stroke and COLD and also influences the association between smoking and stroke. We had hypothesized that chronic bronchitis and smoking interact with each other in the sense that those current or previous smokers who react with stronger bronchial inflammation and develop symptoms of chronic bronchitis may have a particularly high risk of stroke; however, our data do not support such interaction.

Lower socioeconomic status may be associated with higher risk of respiratory infections. Our data suggest that chronic bronchitis may play a more important role as stroke risk factor in subjects with lower than in those with higher education levels. Less educated subjects may reside in areas with more disadvantageous living conditions (eg, with higher air pollution). Air pollution is an important risk factor for chronic bronchitis, and an association with stroke was also shown recently.

Symptoms of chronic bronchitis were independently associated with ischemic stroke but not with TIA and intracerebral hemorrhage who both represented smaller groups of subjects. In general, subgroup analyses have to be viewed with caution because of insufficient statistical power and only possess hypothesis-generating character. A significant association was found for stroke/TIA attributable to large artery atherosclerosis. Atherosclerosis is an inflammatory disease, and chronic inflammatory conditions (eg, rheumatoid arthritis) may promote atherogenesis and its complications. Proinflammatory changes as in chronic bronchitis can cause a procoagulant state, thereby potentially increasing the risk of thromboembolism (eg, cardioembolism and increased proteolytic activity) and potentially augmenting the risk of injury to the vascular wall and consecutive hemorrhage. However, significant associations with cardioembolism and intracerebral hemorrhage could not be shown in our study.

Acute respiratory infection transiently increases the risk of ischemic stroke. Therefore, a higher number of infectious episodes could augment the risk of cerebral ischemia. In our study, high frequency of respiratory infections was independently associated with stroke/TIA. These results are based on subjects' self-estimation and were not correlated with medical records. However, uncomplicated respiratory infection does often not prompt a doctoral visit; therefore, verification may be difficult. To the best of our knowledge, an association between higher rates of infection and stroke risk has not been reported before. The cause of a higher rate of infections among patients is unknown; living conditions (eg, poorer housing), environmental factors (eg, higher air pollution), lifestyle factors (eg, inappropriate clothing), or genetically determined higher susceptibility to infection are among potential explanations.

Acute respiratory infections are a risk factor for chronic bronchitis, and vice-versa patients with chronic bronchitis more often suffer from acute exacerbations of upper airway disease. Therefore, high frequency of respiratory infections could influence the association between chronic bronchitis and stroke. However, frequent infections and chronic bronchitis remained both significantly associated with stroke/TIA in a combined model indicating an independent influence of both inflammatory conditions.

The role of infections as vascular risk factor could be influenced by the way subjects react to emerging infections. Furthermore, reaction to infections may reflect subjects' health-related lifestyle. We found that more stroke patients would continue to work and fewer stroke patients would use self-medication in acute febrile illness. Self-medication would not include antibiotics, as those require prescription in Germany. If such self-report is not biased by the experience...
of stroke and in fact reflects prestroke behavior, it may represent an attitude in stroke patients that reflects greater ignorance regarding health issues and less confidence in their own medical competence but possibly also more socioeconomic pressure (eg, fear of unemployment).

Patients and control subjects originate from the same source population, and control subjects would have become inpatients in the Neurology department with high probability if they suffered a stroke, constituting the comparability between both groups. But several limitations exist regarding our study. We had to exclude severely disabled patients, therefore results cannot be generalized to very severe and lethal strokes. Smoking history was detailed regarding current smoking whereas calculation of pack-years was not possible here. We relied on patients’ self-report, and cross-checking with medical records was not performed in our study. Residual confounding by factors not assessed, such as non-infectious inflammatory conditions, is possible. Furthermore, differences in the interview situation and differences in the recall of previous minor diseases could have biased our results.

In summary, our study supports the hypothesis that chronic bronchitis is among those chronic infections that independently increase the risk of stroke. It is possible that treatment of chronic bronchitis, recently improved by the use of broad spectrum antibiotics, has contributed to the decline of stroke during the last decades. It is also possible that chronic bronchitis that was associated with stroke only in winter months in our study contributes to the seasonal variation of stroke incidence, with a peak during colder months that was found in most respective studies. Such hypotheses deserve analysis in future studies.

Disclosures

None.

References

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