Letters to the Editor


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The Prothrombin G20210A Mutation Is a Risk Factor for Sudden Hearing Loss in Young Patients

Dear Sir,

Idiopathic Sudden Sensorineural Hearing Loss (SSHL) is a frequent disease in otolaryngology with an incidence of approximately 1-2/10,000 per year, and young and otherwise healthy persons are often affected. Nevertheless, the etiology of sudden hearing loss is still unknown. Discussed are mainly circulatory disorders (1-3), viral infection of the labyrinth or the cochlear nerve (4) or autoimmuneologic causes (5). Attempts to find a classification for SSHL, which would correspond to the suspected trigger mechanisms, have not been successful so far.

An impaired cochlear perfusion is a widely accepted hypothesis for the pathogenesis of SSHL, but the location in the temporal bone makes it difficult to investigate the pathophysiological mechanism. Blood viscosity, platelet activation or other parameters possibly linked to an impaired microcirculation might not be representative of the cochlear situation if measured in peripheral blood. Experiments in vivo have been restricted to animals under rather unphysiologic conditions (6). Thus, there are little data available to find proof of an impaired cochlear perfusion in SSHL, although therapeutic concepts are widely based on this assumption.

In recent years, several inherited prothrombotic risk factors have been found. For the two most common, factor V Leiden and the prothrombin G20210A transition, the increased risk of venous thrombosis is well established, while for arterial thrombosis it is currently a matter of debate (7, 8). If thromboembolic events play a role in SSHL, these inherited risk factors might also be found more frequently in patients with SSHL. Genetic association provides a new approach to the pathogenesis of SSHL, with the advantage of being based on invariable parameters.

In 1999, a case-control study was published, investigating 368 patients with deep vein thrombosis for prothrombotic risk factors. Eighteen of them (4.8%) had a history of sudden hearing loss. In addition to the high morbidity of SSHL in this population, which alone gives support to the concept of a thromboembolic pathogenesis, six of the eighteen patients with SSHL were heterozygous carriers of the prothrombin G20210A mutation. In a multiple regression analysis, this mutation appeared as an independent risk factor for sudden hearing loss in these patients (OR 9.3, 95% CI 3.2-27). However, factor V Leiden was not associated with SSHL (9).

For unselected cases of sudden hearing loss the role of the prothrombin mutation has not been reported so far. This prompted us to the present case-control study. We investigated 68 men and 50 women up to the age of 65 years, median age 45.5 years, who were treated for sudden hearing loss in our hospital. 352 healthy blood donors of the same region in southern Germany who were randomly chosen, provided control data. Each case was individually matched with three controls for sex and age except for two cases with only two controls. The maximum age difference between case and control was five years. Statistical methods involved a logistic regression model taking into account the matching of cases and controls (10). To be included in our study, the patient’s hearing loss had to be of acute onset within a few hours and more than 20 dB at two contiguous frequencies. Symptomatic hearing losses were excluded (acoustic neurinoma, rupture of the round window membrane, infectious diseases like influenza or borreliosis and multiple sclerosis). Detection of the G20210A transition in the 3'-untranslated region of the prothrombin gene was performed by polymerase chain reaction (PCR), essentially as described by Poort et al. (11).

Among the 118 case patients, seven subjects (5.9%) were heterozygous carriers of the G20210A mutation, compared to nine subjects (2.6%) in the group of 352 controls (OR = 3.4, 95% CI 0.98 to 11.7; p = 0.052). In a subgroup of 43 patients (28 males, 15 females) in which the first episode of sudden hearing loss occurred before the age of 40, two males and two females (9.3%), aged 20/28/33/35 years, carried the mutation, compared to only two subjects (1.6%) in the control group of 128 healthy blood donors (Table 1). This difference was statistically significant, showing a 16-fold increased risk for SSHL in carriers of the mutation (OR = 16, 95% CI 1.95 to 202; p = 0.0091).

In conclusion, our study demonstrates for the first time that the G20210A-mutation is a strong risk factor for sudden hearing impairment in young, otherwise unselected patients. This finding strengthens the concept of a thromboembolic pathogenesis for SSHL.

Table 1 Prevalence of the prothrombin G20210A mutation in patients with sudden hearing loss and in healthy control subjects

<table>
<thead>
<tr>
<th></th>
<th>Mutation in case-patients</th>
<th>Mutation in controls</th>
<th>Odds ratio, (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total group</td>
<td>7/118 (5.9%)</td>
<td>9/352 (2.6%)</td>
<td>3.4 (0.98-11.7)</td>
<td>0.052</td>
</tr>
<tr>
<td>First SSHL&lt;40 years of age</td>
<td>4/43 (9.3%)</td>
<td>2/128 (1.6%)</td>
<td>16 (1.95-202)</td>
<td>0.0091</td>
</tr>
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</table>

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the assumption of a role of thromboembolic events in the pathogenesis of SSHL. Still, it remains unknown whether SSHL is due to a single pathophysiologic process or whether it is the common end point of various etiologies. Also, knowledge about how the G20210A-transition changes the prothrombin function is still inadequate to draw conclusions on an exact pathomechanism in SSHL. Since prothrombin is involved in plasmatic coagulation as well as in platelet activation, either arteriolar or venular thrombosis or microembolic events may be relevant.

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Inhibitors against Factor VIII Associated with the Use of Interferon-alpha and Fludarabine

Dear Sir,

Conditions most commonly associated with the development of anti-FVIII antibodies include autoimmune disorders, virtually all types of solid and hematologic malignancies and the postpartum state (1-4). Adverse reactions to medications such as penicillin derivatives, phenytoin and sulfa drugs accounted for 5% of all cases of inhibitors in one report (5). The formation of inhibitors to FVIIa following the administration of INF-alpha has been reported in few patients with hemophilia A and chronic active hepatitis (6). Fludarabine, on the other hand, has been recently implicated in the appearance of a true acquired inhibitor in a patient with lymphoma (7).

Between 1993 and 2000, we evaluated the appearance of acquired inhibitors to FVIII following the administration of INF-alpha (4 patients) or fludarabine (3 patients). The presence of FVIII inhibitors was defined as prolonged APTT not corrected in mixing with normal plasma, very low factor VIII activity, detectable anti-FVIII antibodies in the Bethesda assay and normal diluted Russell’s viper venom time (8). Disseminated intravascular coagulation was ruled out by the presence of normal fibrinogen and D-dimer. The characteristics of the patients and type of products used in their management are shown in Table 1. Complete response (CR) to treatment was defined as absence of bleeding, disappearance of inhibitor to FVIII and normalization of FVIII activity.

The median duration of treatment with INF-alpha prior to the appearance of inhibitor was 30.5 weeks and the median dose administered was 7 million units/m². Anti-FVIII antibodies appeared after a median of 4 cycles of chemotherapy with fludarabine administered at 25 mg/kg × 5 days at each cycle. At the time of appearance of inhibitor, the underlying malignancy was in remission in 4 patients while 3 patients had stable metastatic disease. Initial treatment led to CR in 4 patients. In 3 patients, the bleeding episodes were well controlled following treatment of the inhibitor, however, they were rechallenged with INF-alpha prior to the disappearance of inhibitor. The inhibitor titer in these patients rose again an average of 10 days following readministration of the drug.

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