Evaluation of gastrointestinal symptoms as primary sign of severe invasive group A streptococcal infections

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Background & objectives: Severe invasive infections caused by group A Streptococcus (GAS) are often associated with shock and organ failure. We describe epidemiological and disease related data from the national surveillance of invasive GAS infection in Denmark in addition to three fatal cases that occurred in Denmark in 2002 with gastrointestinal (GI) symptoms as the dominating preliminary signs.

Methods: As the National Streptococcal Reference Centre The Streptococcus Unit, Statens Serum Institut (SSI) receives the vast majority of the invasive GAS isolates from patients admitted to all the hospitals in Denmark. The isolates were T-typed by slide agglutination test emm-squencing and pulsed field gel electrophoresis (PFGE) were also performed.

Results: During January 2002 three patients died at home and GAS were found at autopsy. Cases 1 (12 yr) and 3 (25 yr) had been ill for less than two days with nausea, diarrhoea and vomiting. Case 2 (25 yr) had the same symptoms for two weeks. None of the three had any underlying diseases. The GAS isolates from cases 1 and 2 were T-type 3-13-B3264, emm89 and SpeA-, SpeC-. The third isolate was T-type 1, emm1 and SpeA+, SpeC-. PFGE could not discriminate between the two isolates with T-type 3-13-B3264. The PFGE patterns of the three isolates were similar to those identified from GAS isolated elsewhere in Denmark at different times and from non-fatal cases. In 1999-2002, SSI received 409 isolates from patients with invasive GAS infection, and the mortality rate was 18 per cent. In 40 patients the primary symptoms were gastrointestinal, and in 30 per cent of these the outcome was fatal.

Interpretation & conclusion: The various early clinical manifestations of severe GAS infections are still a major challenge for clinicians because of the importance of a fast and appropriate diagnosis and immediate start of treatment.

Key words: Denmark - diarrhoea - gastrointestinal symptoms - group A streptococcal - invasive streptococcal infections - Streptococcus pyogenes - surveillance - vomiting

Streptococcus pyogenes, group A Streptococcus (GAS), has been described as an emerging cause of severe infections with septic shock, organ failure and soft tissue infections [myositis and necrotizing fasciitis (NF)]. The patients with streptococcal toxic shock syndrome (STSS) were described as young without predisposing factors and had flu-like complaints as the primary symptoms1-4. In January 2002, three unexpected deaths due to invasive GAS infections occurred in Denmark. None of the patients were admitted to the hospital and the three patients had predominated gastrointestinal (GI) symptoms. In the present study, epidemiological and disease related data from the national surveillance of invasive GAS infections in Denmark are described to evaluate gastrointestinal complaints as a primary sign of severe invasive GAS infections. Information on the three fatal cases with invasive GAS infections was also described.
Material & Methods

National surveillance: The invasive GAS isolates included in this study were from blood and cerebrospinal fluid (CSF) collected from patients admitted to various hospitals in Denmark from January 1, 1999 to June 30, 2002. The Streptococcus Unit serves as the National Streptococcus Reference Centre and receives the vast majority of the invasive streptococcal isolates as part of the national surveillance. The 15 local clinical microbiological departments voluntarily submit invasive GAS isolates to the Streptococcus Unit to be serotyped.

Typing of the isolates: After a confirmatory identification of the group A antigen, the isolates were T-typed by slide agglutination test with rabbit antibodies produced by Statens Serum Institut, Denmark. Non-typeable strains were designated NT5. emm-sequencing was performed on the isolates from the three fatal cases and identification of SpeA, SpeB and SpeC were performed on the 40 isolates from patients with gastrointestinal complaints as the primary symptoms. Both molecular methods were carried out as described elsewhere.

Questionnaire: A questionnaire was sent to the clinical wards where the patients were admitted and filled in by the doctors responsible for the treatment of the patients. Of the three patients (2 males, 1 female), the first was a 12 yr old boy (died on January 6, 2002). The second case (25 yr old woman) was found dead at home on January 16, 2002, while the third case (25 yr old man) died on February 1, 2002. All these patients had diarrhoea and vomiting. The isolates obtained from the patients were tested by T-typing, emm-sequencing and identification of the exotoxins (SpeA, SpeB and SpeC). Pulsed field gel electrophoresis (PFGE) was also performed.

Statistical analysis: Fischer’s exact test and Mann-Whitney U tests were used for statistical analysis. P < 0.05 was considered significant. The SAS System, Release 8.02 (SAS Institute Inc. Cary, NC, USA) was used for all analysis.

Results

GAS T-type 3-13-B3264/emm89 was identified in the lungs, heart and CSF of the first patient. The strain was SpeA+, SpeB+ and SpeC-. At autopsy of the second patient, GAS T-type 3-13-B3264/emm89 was identified in tissue from CSF, lungs, peritoneum, blood and rectum. The strain was mucoid and was SpeA-, SpeB+ and SpeC+. T-type 1 emm1 was identified in tissue from heart, lungs, CSF, tonsils, skin and pharynx from the third patients. The strain was SpeA+, SpeB+ and SpeC-.

Epidemiological data on invasive GAS infections in Denmark: During the study, the Streptococcus Unit at Statens Serum Institut received 409 isolates from patients with invasive GAS infections admitted to various hospitals in Denmark. In relation to every invasive isolate, a questionnaire was sent out to the clinician responsible for the treatment of that patient and the Streptococcus Unit received 397 questionnaires in return. Fifty four per cent of the patients were females; the gender was not stated in 10 cases (2%). The overall mortality rate was 18 per cent, while the annual mortality rates for 1999, 2000, 2001 and 2002 were 15, 19, 15 and 25 per cent, respectively. The median age of the patients who died was 78.1 yr (range 4.4-95.7 yr). The survivors had a median age of 56.2 yr (range 0.4-97.4 yr). Stratification for age was not used in the analysis. T-types 1, 3-13-B3264, 28 and NT constituted 26, 22, 11 and 19 per cent respectively of the GAS isolates from dead patients, and 19, 24, 16 and 10 per cent respectively of the GAS isolates from the survivors. Of the fatal cases, 96 per cent of the isolates were from blood in comparison with 99 per cent of the non-fatal cases. The remaining isolates were from CSF.

A significantly larger number of the fatal cases had only GI-complaints as the primary symptom compared to the non-fatal cases (P<0.05). A similar pattern could be noticed for bacteraemia without any focus (P<0.05). Septic shock occurred in 60 per cent of the fatal cases compared to 17 per cent of the non-fatal cases (P<0.001) while STSS or NF occurred in 21 per cent of the fatal and in 9 per cent of the non-fatal cases (P<0.05). Treatment in the intensive care unit and use of mechanical ventilation occurred significantly more often in the cases with fatal outcome (P<0.05 and P<0.01, respectively) (Table).

GI-complaints as the primary symptom: The primary symptoms were gastrointestinal in 40 patients, and in 12 (30%) of these the outcome was fatal. The outcome and primary symptoms were independent of female : male ratio. The median age was 75.3 yr (range 12.4-85.0 yr) and 67.2 yr (range 5.5-89.8 yr) for patients who died or survived respectively. T-type 1 constituted 25 per cent, T3-13-B3264 14 per cent, T28 0 per cent and NT 8 per cent of the isolates from the fatal cases, in
comparison 14, 29, 18 and 11 per cent from the non-fatal cases. Three of the 12 cases with fatal outcome had meningitis, and only 1 of 28 survivors had GAS isolated from CSF. Seventy five per cent of the isolates from the fatal cases and 96 per cent from the non-fatal cases were from blood. There were no significant differences between the dead and survived patients regarding other primary symptoms, clinical presentations or treatment not mentioned here, but included in the questionnaire (data not shown).

**PFGE:** The PFGE patterns of the isolates from the three patients presented here were similar to the PFGE patterns obtained from GAS isolated elsewhere in Denmark at different times and from non-fatal cases (data not shown). PFGE could not discriminate between the two isolates with T3-13-B3264. The 40 isolates from patients with GI-complaints as the primary symptom regardless of outcome revealed 29 PFGE-patterns (data not shown).

**Table.** Data from the national surveillance regarding invasive GAS infections in Denmark (January 1999 to June 2002)

<table>
<thead>
<tr>
<th></th>
<th>Dead</th>
<th>Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>72 (18)</td>
<td>325 (82)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (58)</td>
<td>169 (52)</td>
</tr>
<tr>
<td>Median age (range) yr</td>
<td>78.1 (4.4-95.7)</td>
<td>56.5 (0.4-97.4)</td>
</tr>
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</table>

**Microbiology**

<table>
<thead>
<tr>
<th>T-type</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>T-type 1</td>
<td>18 (26)</td>
<td>63 (19)</td>
</tr>
<tr>
<td>T-type 3-13-B3264</td>
<td>16 (22)</td>
<td>78 (24)</td>
</tr>
<tr>
<td>T-type 28</td>
<td>8 (11)</td>
<td>51 (16)</td>
</tr>
<tr>
<td>NT</td>
<td>14 (19)</td>
<td>33 (10)</td>
</tr>
<tr>
<td>Other T-types</td>
<td>16 (22)</td>
<td>100 (31)</td>
</tr>
<tr>
<td>Blood</td>
<td>69 (96)</td>
<td>321 (99)</td>
</tr>
<tr>
<td>CSF</td>
<td>3 (4)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

**Primary symptoms**

<table>
<thead>
<tr>
<th></th>
<th>Dead (n)</th>
<th>Alive (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI-complaints</td>
<td>12 (17)</td>
<td>28 (9)</td>
</tr>
<tr>
<td>Bacteraemia without focus</td>
<td>28 (38)</td>
<td>74 (23)*</td>
</tr>
<tr>
<td>STSS and NF</td>
<td>15 (21)</td>
<td>30 (9)*</td>
</tr>
<tr>
<td>Treated in ICU</td>
<td>25 (36)</td>
<td>68 (20)*</td>
</tr>
<tr>
<td>Surgery</td>
<td>15 (21)</td>
<td>93 (28)*</td>
</tr>
<tr>
<td>Artificial ventilation</td>
<td>17 (23)</td>
<td>33 (10)*</td>
</tr>
<tr>
<td>Septic shock</td>
<td>43 (60)</td>
<td>56 (17)*</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; GI, gastrointestinal; NF, necrotizing fasciitis; ICU, Intensive Care Unit

*P<0.05 compared to dead

**SpeA, B and C:** Ten isolates (25%) were identified as SpeA*, SpeB* and SpeC and this pattern constituted 21 and 33 per cent of the isolates from fatal and non-fatal cases, respectively. In eleven isolates (28%) SpeA*, SpeB* and SpeC were identified and this pattern was found in 33 per cent of the isolates from fatal cases and in 25 per cent of the isolates from non-fatal cases.

**Discussion**

Three fatal cases of invasive GAS infection occurred in Denmark during January 2002. All patients were young (12-25 yr old) and without predisposing factors. Clusters of invasive GAS infections were primarily described in institutions for elderly or mentally disabled but could be observed elsewhere7-10. Though PFGE could not discriminate two of the isolates with T-type 3-13-B3264, it was concluded that there were no relatedness between the cases. The PFGE patterns were identical to the patterns of other both fatal and non-fatal isolates identified in Denmark independent of time and place (data not shown). PFGE analysis of the 40 isolates from patients with GI-complaints showed the presence of several clones rather than few virulent T-type-specific clones. Of the 40 infectious episodes, 12 had a fatal outcome and no clusters were found regarding to the T-type distribution and time of occurrence (data not shown).

The patient related data were collected as part of the national surveillance of invasive GAS infections. In 1999-2001 the response rate to the questionnaire was 99 per cent. Because of the delay of clinicians answer the response rate was 85 per cent in 2002 at the time of data counting. Questionnaire response rates in other studies varied from 57-95 per cent11,12.

The overall mortality was 18 per cent, which was similar to what has been described earlier in Denmark, Sweden and Norway13-15 but higher than described elsewhere16-19. The mortality rate of 30 per cent among patients with GI-complaints was comparable to what has been reported for patients with STSS or meningitis4,18,20,21. Patients with STSS often have GI complaints3,22, more often in patients in the middle age group than in the elderly and very young24. Only 18 per cent of our patients with GI symptoms had STSS or necrotizing fasciitis (NF), regardless of the outcome. Despite the young age of the three fatal cases, in general the group of patients with GI symptoms was older than...
the patients with invasive GAS infections disregarding the primary symptoms. Though this underlines the fact that increasing age might be a risk factor for fatal outcome, it emphasizes the characteristics of the three young patients presented here. The various early clinical manifestations of severe GAS infections are still the major challenges for clinicians because of the importance of a fast and appropriate diagnosis and immediate treatment. This also emphasises the importance of national and international surveillance of invasive GAS infections.

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References


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