Nationwide Oral Poliovirus Vaccination Campaign and the Incidence of Guillain-Barré Syndrome

Esko Kinnunen,1 Outi Junttila,1 Jari Haukka,2 and Tapani Hovi2

A retrospective analysis of the incidence of Guillain-Barré syndrome (GBS) in Finland in 1981–1986 was carried out by careful examination of medical records identified from nationwide Hospital Discharge Register data based on a mean total population of 5 million people. Records from 247 patients fulfilled the accepted criteria of GBS corresponding to a mean annual incidence of 0.82 per 100,000 population. Monthly rates showed an increased incidence of GBS in March 1985, following by a few weeks the onset of the nationwide oral poliovirus vaccine campaign and partly overlapping it. Analysis of the time series in depth suggested, however, that a change point in the occurrence of GBS had already taken place before the oral poliovirus vaccine campaign. Widespread circulation of wild-type 3 poliovirus in the population immediately preceded the oral poliovirus vaccine campaign and the peak occurrence of GBS. These results demonstrate a temporal association between poliovirus infection, caused by either wild virus or live attenuated vaccine, and an episode of increased occurrence of GBS, but they cannot prove the suspected cause-effect relation between GBS and oral poliovirus vaccine administration. Am J Epidemiol 1998; 147:69-73.

Guillain-Barré syndrome (GBS) is a relatively rare disease (annual incidence of about 1 per 100,000 population) usually presenting with symmetric progressive paralysis and variable sensory symptoms. The etiology of the disease is unknown. GBS has been frequently reported to be preceded by a nonspecific infection of variable type, usually a few weeks before the onset of neurologic symptoms (1). Other suggested triggering factors include vaccinations (2) or surgical or other types of tissue trauma. No unifying, widely accepted theory exists about the mechanisms of the putative triggering phenomena, and the cause-effect relation, the preceding infections, and GBS cannot be considered unequivocally proven.

A nationwide high coverage campaign with live oral poliovirus vaccine was organized in Finland in 1985 to stop an outbreak of poliomyelitis (3). During and after the campaign, several patients with GBS were admitted to the neurologic units of hospitals. This observation provided the rationale for an epidemiologic survey of the possible effects of the campaign on the incidence of GBS. This was carried out in the province of Uusimaa located in the southern part of the country. When the occurrence of GBS was expressed as the number of cases per quarter of year during the 6-year period from 1981 to 1986, a statistically significant peak was observed in the first quarter of 1985, coinciding with the oral poliovirus vaccine campaign (4). We suggested that this coincidence might indicate that immunization with oral poliovirus vaccine might sometimes trigger GBS like other infections, but we also presented several reservations and confounding factors limiting the value of these results as evidence for the suggested possibility.

Based on the above results only, a recent committee appointed by the US National Institute of Medicine concluded that available evidence favors a causal relation between oral poliovirus vaccine immunization and GBS (5). Since the study was based on a relatively small population of 1.17 million, we decided to extend the survey to the entire country of Finland with a population of about 5 million. This paper reports on the incidence of GBS in 1981–1986, based on careful retrospective analysis of hospital records.

MATERIALS AND METHODS

Source of data on GBS

The mean population of Finland during the period 1981–1986 was 4.95 million. The nationwide Hospital Discharge Register includes all patients treated in
Finnish hospitals since 1972. This was the main source of data on GBS patients with onset of symptoms from January 1, 1981, to December 31, 1986. The records of all patients with a diagnosis of polyradiculitis, coded according to the International Classification of Diseases. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD), were evaluated. The primary screening was carried out by one of the authors (O.J.) with 2 years’ training in neurology and was confirmed by an experienced neurologist (E.K.). Of the 285 records examined, 247 were found to fulfill the criteria of Asbury (6) and Poser (7). The most common reasons for exclusion were association with alcohol abuse or malignant disease. Cases of chronic relapsing polyradiculitis were also excluded. The accepted cases were listed according to the time of onset of symptoms of GBS.

To assess the coverage of this data search, records from Uusimaa were compared with those of the previous study. A 100 percent overlap was found among the patients with confirmed GBS. A comparison was also made with the data collected at the National Public Health Institute in the context of active nationwide surveillance for GBS during and after the outbreak of poliomyelitis in 1985 (E.K., unpublished data). The names of all patients recorded there were also found in the Hospital Discharge Register.

Oral poliovirus vaccine campaign in Finland in 1985

An outbreak of poliomyelitis occurred in Finland in 1984 after 20 years without a single case reported in the country (3). While the number of patients with clinical poliomyelitis was only nine (8), more than 100,000 individuals were considered infected, based on the fact that the epidemic type 3 poliovirus was recovered from both fecal and sewage samples from all over the country (9). An intensive immunization campaign was organized in late 1984 to stop the outbreak. It included a dose of the inactivated poliovirus vaccine, used exclusively in Finland until the outbreak, administered to children 18 years or younger, and a dose of the trivalent oral poliovirus vaccine administered to the entire population. The oral poliovirus vaccine campaign arranged within 5 weeks between February 9 and March 15, 1985, covered 94 percent of the population and was highly successful (3). Figure 1 shows the timing of the outbreak and the vaccination campaigns as well as the timing of the concurrent influenza epidemic. Data for the latter are from unpublished statistics of the National Public Health Institute (Dr. R. Pyhältö, personal communication).

Statistical analysis

The time series formed by the monthly incidence of GBS was analyzed with the methods of Cleveland and Devlin (10) by rearranging the observed monthly rates according to seasons (12 months) and another component. Different smoothing windows were used in the latter variable. Another approach utilized to detect the timing of possible underlying changes in the incidence of GBS was based on the use of the change-point principle and normal approximation (11).
RESULTS

GBS patients

A total of 247 patients with definite GBS (118 women, 129 men) had received hospital treatment in Finland during 1981–1986. This corresponds with a mean annual incidence of 0.84 (range, 0.56–1.25) per 100,000 population. The age ranged from 5 months to 81 years (mean, 42.5 years). The age group-specific incidence of GBS varied from year to year considerably, with 1985 showing the highest numbers in all age groups. In all years, the incidence in the age group of ≥50 years was higher than that in the two other age groups (table 1).

Symptoms or signs of infection (fever and/or acute respiratory, gastrointestinal, urinary tract, or meningeval) during the preceding 10 weeks were reported for 67 percent of patients. A specific microbiologic diagnosis was revealed in only a minority of cases (data not shown). The percentage of GBS patients with a preceding infection was not statistically different (χ² test) in different age groups or in any of the study years or quarters.

Incidence of GBS and cases related to the oral poliovirus vaccine campaign

A highly variable pattern of monthly occurrence, as recorded from the onset of GBS symptoms, was seen with a mean of 3.4 (range, 0–14) cases per month. The highest monthly number of cases in adults was in March 1985 (11) while, in children of ≤18 years, February–March 1985 showed the peak occurrence with four and three recorded cases, respectively (figure 1). As indicated in figure 1, the peak incidence of GBS in both children and adults coincided with both the oral poliovirus vaccine campaign and an influenza epidemic as well. In addition, the nationwide circulation of the wild-type poliovirus continued until the oral poliovirus vaccine campaign and most probably overlapped with the first weeks of the latter. At least one patient in February 1985 caught GBS before receiving vaccination.

Statistical analysis for temporal trends in the occurrence of GBS revealed one major peak period in early 1985, with the onset of an increasing trend in autumn 1984 (figure 2, bottom). Variation of the smoothing window size from 11 to 23 months did not change this basic pattern. A calculated seasonal variation showed only a small amplitude. Change-point analysis revealed a single significant (p = 0.04) event that occurred in November 1984.

Altogether, 27 patients developed GBS within 10 weeks after initiation of the oral poliovirus vaccine vaccination campaign. Additionally, one 53-year-old woman who had refused vaccination developed GBS in February 1985, 2 weeks after diarrhea. Of the 27 cases, 13 (48 percent) had either respiratory infection or diarrhea within the 10 weeks preceding the diagnosis of GBS. In microbiologic studies of the 27 cases associated with the oral poliovirus vaccine campaign, in only one patient was a high serum adenovirus titer discovered. The patient, whose first symptoms of GBS occurred the day after vaccination, had suffered respiratory infection a few weeks earlier. The mean age of the GBS-associated patients was 41.0 (range, 1–73) years.

The geographic distribution of the cases in 12 different provinces of Finland showed a slight excess of cases in the southern province of Uusimaa (total, 71 cases; mean annual incidence, 1.0 per 100,000 population). A more clear excess in this area was seen in cases associated with the oral poliovirus vaccine campaign (10 cases in a population of 1.17 million). No clustering in the other counties was observed (data not shown).

DISCUSSION

Our retrospective analysis of the occurrence of GBS resulted in a mean annual incidence of 0.82, which is well within the range reported from other countries (12, 13). Because there was total overlap of the current survey and our previous study from Uusimaa with the prospective registration of cases during the oral poliovirus vaccine campaign, we believe that not many cases of GBS in Finland were lost from our survey. No marked differences in incidence from various parts of the country were observed, with the exception of a

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>0.24 (3)*</td>
<td>0.65 (6)</td>
<td>0.41 (5)</td>
<td>0.32 (4)</td>
<td>1.13 (14)</td>
<td>0.73 (9)</td>
<td>0.58 (7.2)</td>
</tr>
<tr>
<td>19–49</td>
<td>0.57 (13)</td>
<td>0.66 (15)</td>
<td>0.44 (10)</td>
<td>0.79 (18)</td>
<td>0.83 (19)</td>
<td>0.75 (17)</td>
<td>0.67 (15.3)</td>
</tr>
<tr>
<td>≥50</td>
<td>0.87 (12)</td>
<td>1.45 (20)</td>
<td>1.45 (20)</td>
<td>1.23 (17)</td>
<td>2.03 (28)</td>
<td>1.09 (15)</td>
<td>1.35 (18.7)</td>
</tr>
<tr>
<td>All ages</td>
<td>0.57 (28)</td>
<td>0.88 (43)</td>
<td>0.72 (35)</td>
<td>0.80 (39)</td>
<td>1.25 (61)</td>
<td>0.84 (41)</td>
<td>0.84 (41.2)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, annual number of cases.
slight excess of cases recorded in the southern province of Uusimaa.

As in the previous study of one fifth of the entire population of Finland (4), a peak of monthly or quarterly incidence of GBS occurred in early 1985, approximately coinciding with the oral poliovirus vaccine campaign. Because oral poliovirus vaccine administration results in replication of the attenuated viruses in the vaccinees, this situation might be considered to trigger some cases of GBS as likely as any other subclinical infection. Other explanations than a possible triggering role of oral poliovirus vaccine administration for the peak incidence of GBS must also be considered. Generally, a maximum time of 6–10 weeks preceding the onset of disease is allowed to identify the putative triggering infection of GBS (14). Consequently, one would expect that an increase in the occurrence of the triggering event should have started at the latest in January 1985. Hence, assuming a single major triggering event for the increasing frequency of GBS that peaked in March 1985, something other than the oral poliovirus vaccine campaign is required for explanation. The countrywide circulation of the wild-type 3 poliovirus was evident in late 1984 and continued at least until the onset of the oral poliovirus vaccine campaign. During the epidemic, the virus was recovered from healthy adults almost as frequently as from children, up to 15 percent in some groups (3). The cumulative coverage of the epidemic may have been even higher in some regions because the above percentage is based on a single fecal specimen per tested person only.

Another confounding factor is the influenza epidemic, which briefly preceded and overlapped the oral poliovirus vaccine campaign. The latter epidemic among the Finnish population was also relatively widespread, as judged from the fact that as many as 12 percent of pregnant women showed serologic signs of infection during this epidemic season (Dr. R. Pyhälä, National Public Health Institute, personal communication).

A cluster of GBS cases in Finnish children in 1985 was reported previously (15) and is also evident from the present data. However, a recent case-control study of GBS in children in California gave no support to the suspected association of the syndrome with regular oral poliovirus vaccine immunizations (16).

The extra dose of inactivated poliovirus vaccine was given to children aged ≤18 years between late November 1984 and mid-January 1985, and one could speculate about the possible role of this inactivated poliovirus vaccine campaign in the subsequent increase of GBS incidence. However, the increase was not limited to this age group and, furthermore, the very same inactivated poliovirus vaccine had been used in the previous regular immunizations in Finland without any evidence of increased risk of GBS in the target age.
groups. Hence, the evidence does not support the role of inactivated poliovirus vaccine as a putative triggering factor of GBS.

In conclusion, although a definite peak occurrence of GBS coincided with the oral poliovirus vaccine campaign in Finland in 1985, a careful time series analysis of the data suggests that putative triggering factors occurring before the oral poliovirus vaccine campaign have contributed to the peak occurrence of GBS. The recorded epidemics of wild poliovirus and influenza, although less prevalent than the widespread distribution of oral poliovirus vaccine, are possible candidates. Our data cannot prove the suspected association between oral poliovirus vaccine and GBS.

REFERENCES