Exogenous gangliosides and Guillain–Barré syndrome
An observational study in the Local Health District of Ferrara, Italy

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Summary
A retrospective study was carried out in the Ferrara Local Health District, Italy, for the period 1981–1993 (average resident population: 177,235 inhabitants) to establish whether people exposed to exogenous gangliosides had a higher risk of Guillain–Barré syndrome. The incidence of Guillain–Barré syndrome of 1.9/100,000 population/year [95% confidence interval (CI): 1.3–2.5] reported in Ferrara Local Health District in the same period was used as a reference for comparison. The data bank of Ferrara Local Health District made it possible, first to estimate the number of individuals exposed to gangliosides in the resident population of Ferrara Local Health District (3.7%), the number of ganglioside prescriptions and the number of cases of Guillain–Barré syndrome who had treatment with gangliosides (nine patients, 20.9%), and, secondly, to verify the sequence of events between the ganglioside injection and the onset of the disease. Seven of the nine patients (77.8%) received gangliosides as treatment for peripheral neuropathy (Guillain–Barré syndrome onset before gangliosides were prescribed). For the other two patients (22.2%) a possible appropriate temporal sequence between ganglioside injection and onset of Guillain–Barré syndrome was found. Based on two possible ganglioside-related cases, the risk of Guillain–Barré syndrome was higher in the exposed (0.53/100,000 population/month following ganglioside injection; 95% CI: 0.06–1.91) compared with the unexposed population, but the difference was not statistically significant. When only individuals prescribed with mixed gangliosides were considered (both possible ganglioside-related Guillain–Barré syndrome cases received mixed gangliosides), the risk of Guillain–Barré syndrome was higher (0.64/100,000 population/month following ganglioside injection; 95% CI: 0.08–2.31) but the difference from the risk in unexposed individuals was not statistically significant. The relative risk for the exposure to mixed gangliosides was borderline (relative risk = 4.3; 95% CI: 1.0–17.8). The wide 95% confidence intervals were a consequence of sample size limitations. Considering also that the exposed and unexposed groups differed in age (those exposed were older than those unexposed and the age-specific incidence of Guillain–Barré syndrome in the study population increased with increasing age), the present findings question either a strong increased risk of Guillain–Barré syndrome in people exposed to exogenous gangliosides or an immunogenic role of these agents in humans. However, because of the limited sample size, the results are not conclusive.

Keywords: Guillain–Barré syndrome; exogenous gangliosides

Abbreviation: CI = confidence interval
Introduction

Between 20% and 30% of patients with Guillain–Barré syndrome have high titres of serum anti-ganglioside antibodies, most frequently against GM1 and GD1b (Ilyas et al., 1992; van den Berg et al., 1992). The pathogenetic relevance of anti-ganglioside antibodies in Guillain–Barré syndrome has not yet been established (Kusunoki et al., 1996). It is controversial as to whether these antibodies are markers of a poor prognosis due to axonal degeneration and whether they are associated with Campylobacter jejuni infection (Rees et al., 1995). Gangliosides extracted from bovine brain were extensively prescribed in Italy, mainly for the treatment of peripheral neuropathies, after their introduction in 1975 (Garattini and Garattini, 1993). A neuroprotective role and their potential to promote nerve repair by enhancing nerve sprouting was asserted (Roisen et al., 1981; Ledeen, 1984). Cases of Guillain–Barré syndrome after ganglioside injection have been reported (Schönhüfer, 1991; Figuera et al., 1992; Landi et al., 1993). High titres of anti-GM1 or asialo-GM1 antibodies were found in some of them (Latov et al., 1991; Nobile-Orazio et al., 1992). A causal association between ganglioside injection and Guillain–Barré syndrome was inferred (Behan and Hanifah, 1992) and gangliosides were withdrawn in Italy in December 1993 (Keates, 1994). Although gangliosides are thought to be immunogenic, the mechanism of ganglioside-induced Guillain–Barré syndrome has not yet been established. Moreover, because anti-GM1 antibodies can be non specific, their pathogenetic role in Guillain–Barré syndrome has been questioned (Weller et al., 1992; Mizutamari et al., 1994). Guillain–Barré syndrome following exogenous gangliosides offers an opportunity to investigate their causal relationship in triggering Guillain–Barré syndrome, the immunogenic role of these agents in humans, and the pathogenetic role of antiganglioside antibodies. It would be important to establish whether individuals exposed to exogenous gangliosides have a higher risk of Guillain–Barré syndrome. However, owing to the unknown size of exposed populations, reports on Guillain–Barré syndrome after gangliosides do not include estimates of Guillain–Barré syndrome risk in exposed people. One Guillain–Barré case after gangliosides was reported in 1992 in the Local Health District of Ferrara, Italy (Landi et al., 1993). For this reason, a study has been carried out in Ferrara Local Health District to estimate the risk of Guillain–Barré syndrome in people exposed to gangliosides.

Material and methods

All Italian citizens are assisted by the Italian National Health Service. Prescriptions of drugs included in the National Drug Formulary issued either by general practitioners or by specialists are routinely collected and processed for pharmacy reimbursement. The Italian National Health Service supplied all prescriptions of gangliosides after their introduction in 1975 up to their withdrawal in late December 1993 (Garattini and Garattini, 1993; Keates, 1994). The prescription data were collected in the Local Health Districts (the local agencies of the Italian National Health Service) data banks for financial purposes. Since the Local Health Districts data banks collected only prescriptions of drugs issued by public physicians under contract by the Italian National Health Service, ganglioside prescriptions for private patients could have been missed. However, as the Italian National Health Service dispensed gangliosides free of charge through the Local Health Districts the list of ganglioside prescriptions of the Local Health Districts represented virtually 100% of ganglioside sales in the corresponding geographical area. In fact, it is unlikely that a patient paid for these fairly expensive drugs when he could get them free through the Local Health District. Moreover, since Italian citizens are entitled to the drugs dispensed free of charge by the Italian National Health Service it was normal practice when a private physician advised a patient to take such a drug that the prescription was then issued by a general practitioner. Five drugs containing gangliosides were available on the Italian market: three were a fixed mixture of bovine brain gangliosides (GM1 21%, GD1a 40%, GD1b 16%, GT1b 19%), one was a mixture of the ethers of these four main gangliosides of bovine brain, and the other one contained only GM1.

We submitted the research plan of the present study to the Chief Executive and the Management of Ferrara Local Health District. The research plan was approved and access to Ferrara Local Health District data bank was authorized. The Electronic Data Processing Centre of Ferrara Local Health District supplied us with the data on ganglioside prescriptions in Ferrara Local Health District resident population so that the number of exposed individuals could be estimated. The computerized data base of Ferrara Local Health District supplies the name of the proprietary medical product, the type of package, the number of packages sold, the date of drug prescription, the date of drug sale, the name and the Italian National Health Service identification code of the patient (which being unique for each resident of Ferrara Local Health District makes it possible to know the patient’s personal data), the name and identification code of the physician. The data available made a drug utilization study possible for the 4-year period 1988–1991. The Italian National Health Service identification code allowed us to exclude the prescriptions issued by physicians working in Ferrara Local Health District for non resident individuals.

The incidence of Guillain–Barré syndrome in Ferrara Local Health District resident population in the years 1981–1993 (average population: 177 235 inhabitants) was recently estimated (Govoni et al., 1996) using the diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke (Asbury et al., 1978). The average rate (based on 43 cases) of 1.9/100 000 population/year, with 95% CI (confidence interval) of 1.3–2.5, was similar to that of other community-based studies (Alter, 1990). Neither
Miller Fisher syndromes nor association with Campylobacter jejuni infection were found. One of the 43 cases had already been reported as a case of possible causal association with ganglioside treatment (Landi et al., 1993). The annual number of cases in Ferrara Local Health District resident population was quite stable over the study period and it followed a Poisson distribution (test of goodness-of-fit: $\chi^2(4) = 3.23$, $0.50 < P < 0.60$).

After the research plan was approved by the Chief Executive and the Management of Ferrara Local Health District, the Electronic Data Processing Centre of Ferrara Local Health District was also authorized to provide us with the data on drug prescriptions received by the Guillain–Barré syndrome cases in Ferrara Local Health District resident population during the 3 months (90 days) before their hospital admission for Guillain–Barré syndrome. Moreover, we were authorized to review the clinical files of the cases to obtain anamnestic data. The data were examined only by the authors (each of them is qualified as a specialist in neurology). For each patient the data were assessed using the following criteria: (i) an appropriate temporal sequence between drug administration and onset of neurological symptoms; (ii) presence of other potential aetiological factors or prior illnesses.

The incidence of Guillain–Barré syndrome in Ferrara Local Health District resident population in the years 1981–1993 (Govoni et al., 1996) was used as a reference for comparison. The test of significance for the comparison of the observed and expected number of cases was based on the Poisson distribution. Based on Ferrara Local Health District data we compared the incidence of Guillain–Barré syndrome in the group of individuals exposed to gangliosides and in the group of unexposed individuals of Ferrara Local Health District resident population. A retrospective study over the years considered for the estimate of the Guillain–Barré syndrome incidence (Govoni et al., 1996), that is from January 1, 1981 to December 31, 1993 (when gangliosides were withdrawn), was performed. The 95% CI of incidence rates was computed assuming a Poisson distribution (Schoenberg, 1983). The log-likelihood ratio test was used to compare two rates. The actual difference and the 95% CI associated with the difference in rates were calculated using the Poisson distribution (Rothman, 1986). The relative risk, i.e. the ratio of the incidence rate in the exposed group to the incidence rate in the unexposed group, and the 95% CI associated with the relative risk were also estimated. The $\chi^2$ test for linear trend was used when appropriate (Armitage, 1955).

### Results

The number of individuals in the Ferrara Local Health District resident population treated with gangliosides in the years 1988–1991 was 25,422, the prescriptions of gangliosides 112,563 and the sold packages 196,986 (Table 1). The annual average was 6,355 individuals (3.7% of Ferrara Local Health District resident population), 28,141 prescriptions (162.2 prescriptions per 1000 population), and 49,246 packages (283.9 packages per 1000 population) (Table 2). Based on the available data, we assumed that the proportion of Ferrara Local Health District resident population exposed to gangliosides in the study period 1981–1993 (average resident population: 177,235 inhabitants) was 3.7% and the number of ganglioside prescriptions was 162.2 per 1000 population. Therefore, we assumed that 85,254 individuals of Ferrara Local Health District resident population were exposed to gangliosides in the years 1981–1993 receiving 373,724 ganglioside prescriptions (an average of 4.4 prescriptions for each individual). A 30-day period (~1 month, i.e. 1/12 of 1 year) of presumed increased Guillain–Barré syndrome risk following each ganglioside prescription was considered in agreement with the recommendations for antecedent events in Guillain–Barré syndrome (Larsen et al., 1985; Arnason and Soliven, 1993). In fact, the hypothesis tested was an immunological reaction to the drug, and immunological responses usually manifest within one month of an etiological exposure (Larsen et al., 1985).

The data of the Ferrara Local Health District data bank showed that four of the 43 cases of Guillain–Barré syndrome (9.3%) were prescribed gangliosides within the 3-month period before hospital admission for Guillain–Barré syndrome. In a review of clinical files, no other patient with Guillain–Barré syndrome was found to have been treated with gangliosides before hospital admission. Two of these four patients were prescribed gangliosides by their family doctor, clearly after the onset of Guillain–Barré syndrome. The gangliosides were administered as treatment for early symptoms and signs of peripheral neuropathy due to Guillain–Barré syndrome in the days immediately preceding admission to hospital. The available data showed that Guillain–Barré syndrome had begun 7 and 5 days before gangliosides were administered to these two patients. Since an appropriate temporal sequence between ganglioside administration and onset of neurological symptoms was lacking we did not consider the relationship between gangliosides and Guillain–Barré syndrome to be causal for these two patients. However, for the other two patients there was possibly an appropriate temporal sequence between ganglioside injection and onset of Guillain–Barré syndrome. One patient had a ‘flu-like’ upper respiratory infection with fever for 4 days. After 8 days the patient developed visual loss in the right eye. The eye specialist diagnosed an optic neuritis and prescribed a...
fixed mixture of gangliosides. On the fifth day of treatment the patient developed Guillain–Barré syndrome. This case is the only report of a possible causal association between gangliosides and Guillain–Barré syndrome in Ferrara Local Health District resident population (Landi et al., 1993). The other patient was treated with a fixed mixture of gangliosides and other drugs by the family doctor who suspected otitis (the subject complained of earache and tinnitus). After 8 days of treatment the patient developed Guillain–Barré syndrome. We selected these two patients as possible cases of causal association between gangliosides and Guillain–Barré syndrome in Ferrara Local Health District resident population in the years 1981–1993. The clinical files reported that five other cases of Guillain–Barré syndrome (11.6%) who never had treatment with gangliosides, received gangliosides during hospitalization for Guillain–Barré syndrome (gangliosides were prescribed by the neurologist only after the diagnosis of Guillain–Barré syndrome).

Given the incidence of Guillain–Barré syndrome in the Ferrara Local Health District resident population (1.9/100 000 population/year), the expected number of Guillain–Barré syndrome cases in the group of individuals exposed to gangliosides (85 254 individuals exposed to gangliosides 373 724 times) was 0.6 (Poisson $P$ value for exactly two cases 0.999; Poisson $P$ value for two or fewer cases 0.977). As two individuals of the exposed group had a possible ganglioside-related Guillain–Barré syndrome, the incidence of Guillain–Barré syndrome in that exposed group was 0.53/100 000 population/month following ganglioside injection (95% CI: 0.06–1.91). The other 41 cases did not experience Guillain–Barré syndrome after ganglioside injection so that the incidence of Guillain–Barré syndrome in the unexposed group was 0.15/100 000 population/month (95% CI: 0.11–0.20). The incidence was higher in exposed compared with unexposed individuals, but the difference between the rates (actual difference = 0.38; 95% CI: −0.36 and 1.12) was not statistically significant ($G = 2.22, 0.10 < P < 0.20$). The relative risk was 3.5 (95% CI: 0.8–14.5).

Both the possible ganglioside-related cases received a fixed mixture of gangliosides that were the most frequently prescribed ganglioside drug in the Ferrara Local Health District resident population (85.9% of all exposed individuals, 84.1% of all ganglioside prescriptions). The risk of Guillain–Barré syndrome in the group exposed to mixed gangliosides was estimated. The number of individuals in the Ferrara Local Health District resident population who were prescribed with mixed gangliosides in the years 1988–1991 was 21 843 and the number of prescriptions was 94 668 (Table 1). The annual average was 5461 individuals (3.1% of Ferrara Local Health District resident population) and 23 667 prescriptions (136.4 prescriptions per 1000 population) (Table 2). Based on these data, 71 426 individuals of Ferrara Local Health District resident population were exposed to mixed gangliosides in the years 1981–1993 receiving 314 275 prescriptions. Given the incidence of Guillain–Barré syndrome in Ferrara Local Health District resident population the expected number of Guillain–Barré syndrome cases in the group exposed to mixed gangliosides was 0.5 (Poisson $P$ value for exactly two cases = 0.076; Poisson $P$ value for two or fewer cases = 0.986). The incidence of Guillain–Barré syndrome was higher in exposed (0.64/100 000 population/month following mixed ganglioside injection; 95% CI: 0.08–2.31) compared with unexposed people (0.15/100 000 population/month; 95% CI: 0.11–0.20), but the difference between the rates (actual difference = 0.49; 95% CI: −0.40 and 1.38) was not statistically significant ($G = 2.64, 0.10 < P < 0.20$). However, the relative risk was borderline (relative risk = 4.3; 95% CI: 1.0–17.8).

### Discussion

The present findings confirm that gangliosides were widely prescribed in Italy (Montanaro et al., 1992; Raschetti et al., 1992). Almost all individuals treated in the Ferrara Local Health District resident population were prescribed gangliosides more than once and most of them several times. This was probably a result of the indications for gangliosides (peripheral neuropathies) which are mainly chronic disorders that often have no efficacious treatment. However, gangliosides were probably also prescribed for other reasons outside the sphere of the approved indications and were suspected as being used as coadjuvants or placebos (Montanaro et al., 1992; Garattini and Garattini, 1993). In the present study 20.9% of Guillain–Barré syndrome cases received gangliosides. Most of them (55.5%) began ganglioside treatment in hospital only after the diagnosis of Guillain–Barré syndrome had been confirmed by a neurologist, indicating that gangliosides were often used in Italy for the treatment of Guillain–Barré syndrome. Two of the four patients who received gangliosides before hospital admission showed a temporal sequence between drug injection and onset of neurological symptoms appropriate to the treatment.

### Table 2 Ganglioside use in Ferrara Local Health District, Italy, 1988–1991

<table>
<thead>
<tr>
<th></th>
<th>All ganglioside drugs</th>
<th>Fixed mixture of gangliosides*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribed individuals per 100 population per year</td>
<td>3.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Prescriptions per 1000 population per year</td>
<td>162.2</td>
<td>136.4</td>
</tr>
<tr>
<td>Packages per 1000 population per year</td>
<td>283.9</td>
<td>238.7</td>
</tr>
</tbody>
</table>

*GM1 21%, GD1a 40%, GD1b 16%, GT1b 19%.
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to there being a causal relationship with Guillain–Barré syndrome. One of them has already been reported (Landi et al., 1993). The other case was found thanks to the Ferrara Local Health District data bank. We considered these two patients as cases of possible causal relationships between gangliosides and Guillain–Barré syndrome, but with reservation. The first patient had an optic neuritis that was treated with gangliosides. No serum antibodies against GM1 were found with ELISA (enzyme linked immunosorbent assay), and the patient recovered with no residual neurological deficit. However, since optic neuritis can be a feature of Guillain–Barré syndrome before the visual loss is an upper respiratory infection with fever (suffered by this patient), it is not conclusive that the Guillain–Barré syndrome was attributable to gangliosides in this case. The other possible case was a patient who took other drugs (analgesics/anti-inflammatory and antibiotic drugs) in addition to gangliosides, and in this case another illness (otitis) preceded ganglioside administration. Raised serum anti-GM1 antibodies were found (ELISA). The patient had a moderate residual neurological deficit (able to walk). Since both cases had a potential aetiological factor (an antecedent inflammatory illness) that preceded ganglioside injection, it would seem to be a hasty deduction to consider that these two Guillain–Barré syndrome cases were due to gangliosides. We adopted a cautious attitude and estimated the probability of having two cases in our set of ganglioside-exposed people. Antecedent infections by various agents are reportedly associated with Guillain–Barré syndrome, but how infection triggers the disease is unknown. It is therefore difficult to support a lack of a causal relationship between gangliosides and Guillain–Barré syndrome in some cases, solely on the basis of an antecedent of the common cold, flu, or diarrhoea several days before the onset of symptoms. These two patients were regarded as only possible, not probable, ganglioside-related cases since there was not sufficient evidence to prove or disprove a causal association, and a reasonable doubt as to the existence of this relationship still remains. It is difficult to assess a possible causal relationship when the available data made the sequence of events between the onset of symptoms and use of the drug unclear (Garcia et al., 1993). Prodromal and early symptoms of Guillain–Barré syndrome may be mild and difficult to define, and it is not always easy to establish whether the drug was administered before the onset of neurological disturbances or whether it was prescribed to treat early symptoms. Several of the reported ganglioside-related Guillain–Barré syndrome cases have been questioned, as no definite causal relationship could be established after a review of available data (Diez-Tejedor et al., 1993). Further, a co- incidental association of Guillain–Barré syndrome with ganglioside injection cannot be excluded considering the widespread use of gangliosides, at least in Italy.

The Ferrara Local Health District data bank made it possible to estimate the proportion of Ferrara Local Health District resident population exposed to gangliosides, the number of cases of Guillain–Barré syndrome who had treatment with gangliosides, and to verify the sequence of events between the onset of symptoms and ganglioside injection. The non-concurrent prospective design of the study seemed to be reliable as the geographic mobility of people into and out of Ferrara Local Health District is low (Govoni et al., 1996). Moreover, there was no problem in tracing individuals. A higher risk of Guillain–Barré syndrome in ganglioside-exposed than unexposed people was estimated, especially when mixed gangliosides were considered. However, the difference was not statistically significant, perhaps due to limitations in sample size. In fact, incidence rates in exposed people had a wide 95% CI. The relative risk was borderline for mixed gangliosides. However, exposed and unexposed people differed in age (Table 3). Exposed people in Ferrara Local Health District resident population were older than unexposed people (94.7% of exposed people were >30 years of age compared with only 65.8% in unexposed people). This was predictable since the main indications for administration of gangliosides were peripheral neuropathies or radiculopathies that are for the most part disorders of adult or advanced age. In fact, the proportion of exposed individuals by age-group increased with increasing age ($\chi^2$ test for linear trend $P < 0.0005$). Also age-specific incidence of Guillain–Barré syndrome in Ferrara Local Health District resident population increased with increasing age ($\chi^2$ test for linear trend $P < 0.0005$) (Govoni et al., 1996). As exposed and unexposed people differed in age, a factor which is known to affect the risk of Guillain–Barré syndrome, it is likely that the higher incidence in exposed people was, at least, partially due to the different age distribution. However, because of the limited sample size conclusive results cannot be achieved.

The possible relationship between gangliosides and Guillain–Barré syndrome is an intriguing subject. Gangliosides have been implicated as major autoantigens in the immunopathological reaction of Guillain–Barré syndrome (Ilyas et al., 1992; Illa et al., 1995). No difference in Guillain–Barré syndrome incidence has been reported between areas where use of gangliosides is either low or non-existent compared with those areas in which they are widely used, suggesting that large variations in ganglioside use do not influence Guillain–Barré syndrome incidence (Matias-Guiu et al., 1993). A previous epidemiological study in the area of Ferrara failed to demonstrate an association between exogenous gangliosides and Guillain–Barré syndrome, but the sample was too small to achieve conclusive results (Granieri et al., 1991). The present study, however, did show evidence of a higher risk (although not of statistical significance) of Guillain–Barré syndrome in exposed people.

Immunological studies of comparative groups are essential to clarify the role of gangliosides in Guillain–Barré syndrome. Antibodies against GM1, asialo-GM1, GD1b, and GM2
can be detected in healthy individuals never treated with gangliosides (Mizutamari et al., 1994), and anti-GM1, asialo-GM1, GD1a, and GD1b antibodies have been reported in other human neurological degenerative, infective, and inflammatory disorders as well as other peripheral neuropathies such as diabetic neuropathy (Weller et al., 1992). Anti-ganglioside antibodies could not cause nerve damage in Guillain–Barré syndrome, but might occur in response to axonal injury (Ponzin et al., 1991). Moreover, no correlation between anti-ganglioside antibody titres and clinical or histological involvement of the peripheral nerve has been found (Mithen et al., 1992). However, the serum from one patient with anti-GM1 antibodies induced conduction block following intraneural injection (Santoro et al., 1992), and an increase in anti-GM1 and anti-GD1a antibodies in Guillain–Barré syndrome may have a negative prognostic value (Simone et al., 1993). High titres of anti-GM1 and anti-GD1a antibodies have been found in patients with severe Guillain–Barré syndrome, especially the prominent motor axonal form characterized by axonal degeneration and poor prognosis (Nobile-Carro et al., 1992; van den Berg et al., 1992; Yuki et al., 1992; Gregory et al., 1993). Cases of Guillain–Barré syndrome following ganglioside injection have been severe acute axonal polyneuropathies (Latov et al., 1991; Yuki et al., 1991; Illa et al., 1995), and anti-ganglioside antibodies are more common in axonal Guillain–Barré syndrome (Gregory et al., 1993). Campylobacter jejuni, which bears cross-reactivity with GM1, has been associated with Guillain–Barré syndrome, lending support to the potential role of GM1 as a factor in triggering autoimmune neuropathies (Enders et al., 1993). GM1-reactive epitopes have been identified in the lipopolysaccharides of patients with axonal Guillain–Barré syndrome (Griffin et al., 1996). Furthermore, there is a close association between anti-GQ1b antibodies and Miller Fisher syndrome (Willison et al., 1993) as well as Guillain–Barré syndrome with ophthalmoplegia (Chiba et al., 1993), and many GQ1b antibody-positive sera from Miller Fisher syndrome patients cross-react with GD1b and GT1b (Dalakas and Quarles, 1996).

High antibody titre against GM1, asialo-GM1, GD1b, GD1a, GT1b, and IgG anti-ganglioside antibodies with specificity for motor nerve terminals have recently been demonstrated in cases of acute motor axonal Guillain–Barré syndrome after administration of mixed gangliosides, suggesting that exogenous gangliosides could serve as immunogens against axonal targets and trigger an axonal form of Guillain–Barré syndrome (Illa et al., 1995). The reported association of a high IgG GM1 antibody titre in patients with the acute axonal neuropathy due to Chinese paralytic syndrome is consistent with these data (Kornberg et al., 1994). Mixed gangliosides, which contain only 17–25% GM1, might be more immunogenic than pure GM1 (Schneider and Roeltgen, 1993). Patients receiving long term GM1 for either stroke or acute spinal cord injury showed a lack of immune response to pure GM1 (Yu et al., 1992). Both the two possible ganglioside-related cases in the present study were found in the group exposed to mixed gangliosides. However, if an increased risk of Guillain–Barré syndrome in people exposed to mixed gangliosides does exist it seems to be low and not statistically higher than that in the general population of the Ferrara Local Health District.

At present, Guillain–Barré syndrome is not considered to be a single entity and more than one underlying pathogenic mechanism might be involved (Thomas, 1992). In fact, similar clinical and spinal-fluid patterns can be seen in individuals with quite different electrophysiology and pathology (Griffin et al., 1996). Exogenous gangliosides could be immunogenic only in certain individuals, triggering certain forms of Guillain–Barré syndrome, such as the axonal form. However, it is still unclear why Guillain–Barré syndrome develops in only a small fraction of ganglioside-injected patients. Concomitant muscle injury that exposes presynaptic epitopes, and host susceptibility, might be contributing factors (Illa et al., 1995). As an immune response to gangliosides may be found in normal individuals, the possibility cannot be excluded that in some sensitized subjects exposure to gangliosides may occasionally trigger an antibody response to gangliosides (Pestronk et al., 1990; Sadik et al., 1990). However, whether this may occasionally lead to an acute motor polyneuropathy, presenting as Guillain–Barré syndrome, remains unclear. Based on the present findings this would be a rare event. In fact, the risk of Guillain–Barré syndrome patients cross-react with GD1b and GT1b (Dalakas and Quarles, 1996).

### Table 3

Individuals exposed to gangliosides in Ferrara Local Health District resident population (LHDRP) in the years 1988–1991 by age-group and incidence of Guillain–Barré syndrome (GBS) in Ferrara Local Health District resident population in the years 1981–1993 by age-group

<table>
<thead>
<tr>
<th>Age-group (years)</th>
<th>Number of individuals</th>
<th>Age-distribution (%)</th>
<th>Proportion of Ferrara LHDRP (%)</th>
<th>Number of cases of GBS</th>
<th>Age-distribution of whole population (%)</th>
<th>Age-specific incidence*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–29</td>
<td>1347</td>
<td>5.3</td>
<td>0.5</td>
<td>7</td>
<td>34.2</td>
<td>0.9</td>
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<td>30–59</td>
<td>10 881</td>
<td>42.8</td>
<td>3.6</td>
<td>16</td>
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<td>13 194</td>
<td>51.9</td>
<td>8.2</td>
<td>20</td>
<td>22.7</td>
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<tr>
<td>Total</td>
<td>25 422</td>
<td>100</td>
<td>3.7</td>
<td>43</td>
<td>100</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*χ² test for linear trend (P < 0.0005). † Incidence per 100 000 population per year.
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References


