CAMPYLOBACTER JEJUNI INFECTION AND CHILDHOOD GUILLAIN-BARRE SYNDROME

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ABSTRACT

Objective: Guillain-Barre syndrome (GBS), acute postinfectious polyneuritis, is the most common cause of acute neuromuscular paralysis. Infection with Campylobacter jejuni is recognized as a common antecedent of the GBS. This study aimed to determine the frequency of this infection in children with GBS and, the clinical and epidemiologic features of this association.

Methodology: We performed a prospective case-control study on a cohort of 47 children with GBS admitted to Tabriz Children’s Hospital in the northwest of Iran between July 2006 and July 2008. Serologic investigations were used to diagnose preceding C. jejuni infection.

Results: We found evidence of recent C. jejuni infection in 40.4% of the patients with GBS, as compared with 6.1% in household controls (odds ratio 10.5, 95% CI: 2.2-49.2, P<0.001). Duration to achieve independent walking was longer in C. jejuni-associated patients (P<0.013). However 95% of C. jejuni-associated GBS patients achieved independent walking at end of one year. The patients with preceding C jejuni infection were more likely to have axonal neuropathy (P<0.05).

Conclusions: Campylobacter jejuni infection is an important antecedent illness in childhood Guillain-Barre syndrome in Iranian children, and is associated with good prognosis.

KEY WORDS: Campylobacter jejuni, Childhood, Guillain-Barre syndrome.

INTRODUCTION

Since the marked decline in poliomyelitis incidence, the Guillain-Barre syndrome (GBS) has become the most common cause of acute flaccid paralysis. The GBS is an acute immune-mediated polyradiculoneuropathy characterized by rapidly progressive, symmetric weakness and areflexia.1 The annual incidence of the disease has been previously reported to be between one to four cases per hundred thousand population in developed countries and about two cases per hundred thousand in Iran.2,3 Considerable evidence suggests that GBS is a postinfectious phenomenon. In approximately two thirds of patients, neurological symptoms follow an infection, often a mild respiratory or
gastrointestinal illness. The organism that has most frequently been described in association with GBS is campylobacter jejuni, a gram-negative rod that is now the most common cause of bacterial gastroenteritis in both developed and developing countries.

Campylobacter jejuni is detectable by stool culture for a median of 16 days from diarrhea onset, but a period of one to four weeks lag between infection and the onset of neurologic symptoms, so the organism may have been cleared by the time many GBS patients are admitted to hospital. The organism was isolated from the stool of 4% of GBS patients. Serological diagnosis is therefore more reliable.

The incidence of C. jejuni infection in GBS patients range from 15% in Italy to 62% in China in case-control studies. By using enzyme-linked immunosorbent assay (ELISA) Barzegar et al found that 23(47.9%) of 48 children with GBS, in North West of Iran, had serologic evidence of C. jejuni infection. However the absence of a control group in this investigation makes it difficult to interpret the results. Therefore to assess the extent to which the GBS is associated with recent C. jejuni infection, we performed serologic screening with defined assays to determine the frequency of C. jejuni antibodies in children with GBS and a control group, in the same region.

**METHODOLOGY**

The setting of the study was Tabriz Children’s Hospital, the largest pediatric medical center in the North West of Iran. This 200-bed acute care university hospital provides tertiary referral care for critically ill patients. Between July 2006 and July 2008, forty seven children with diagnosis of GBS were admitted and recruited in this study. All patients were examined by an expert child neurologist (M.B). The diagnosis of GBS was ascertained based on the criteria defined by Asbury and Cornblath. After obtaining an informed consent from the parents the clinical data were collected. A consecutive sample was used. Control group included 33 healthy children (specifically being a member of the patient’s household).

Poliovirus infection was excluded by cultures that are routinely performed for patients with acute flaccid paralysis as a requirement of the national program of poliomyelitis eradication. For each patient, data was collected with regard to the age, sex, date of onset of the disease, preceding illness, clinical features, results of CSF analysis, electrophysiologic findings, course of disease during hospitalization and outcome. The functional status at the time of maximum deficit was graded according to Hughes scale of disability as follows:

0. Healthy,
1. Minor signs and symptoms and ability to run;
2. Ability to walk 5 meters without assistance, but unable to run.
3. Ability to walk with assistance,
4. Confined to bed or chair bound,
5. Requiring assisted ventilation, and
6. Died.

All patients were followed until they achieved independent walking ability (maximum 12 months). Medical histories of healthy controls were not obtained.

All children underwent at least one electrodiagnostic study at the acute phase of disease. Medelec synergy electromyography machine was used for these studies. Nerve conduction studies included motor nerve conduction (MNC), sensory nerve conduction (SNC) and F-wave response. These assessments were performed using the standard techniques while keeping the temperature under control. MNC studies were carried out on the ulnar, median, tibial and deep peroneal nerves and SNC on median and sural nerves. Each value of nerve conduction was compared with age matched normal data reported by Parano and colleagues. Needle EMG was done for any denervation potentials and motor unit action potentials (MUAP) changes in all patients in at least two proximal and two distal limb muscles. Patients were classified as having either the axonal or demyelinating type on the basis of the electro diagnostic criteria reported by Cornblath and colleagues.
Serum samples were obtained 1-7 days after onset of GBS. Sera from case patients and controls were stored at -80 until tested. Serum samples were screened for IgG and IgM antibodies against C. jejuni by ELISA (ELISA kit, Serion Germany). Patients were considered C. jejuni positive if they had high optical densities for both IgM and IgG classes at serum dilution of 1:1000.

Microbiologic investigations for C. jejuni were not performed in this study. In addition to supportive care, GBS patients with GBS score >3 received either high dose intravenous immunoglobulin or phasmapheresis.

Differences between proportions were statistically tested by Chi-square Fisher’s exact test. All other numerical or quantitative comparisons were performed using student’s unpaired t-test or Mann-Whitney U test. All values were two tailed and were considered statistically significant at P<0.05 level.

This study was approved by the Ethics committee of Tabriz University of Medical Sciences.

RESULTS

We recruited 47 patients with GBS and 33 healthy (household) controls in this study. The mean age of the patients was 5.3±3.8 years; of the control group was 5.4±3.4 years. There was no significant difference in age between two groups (P=0.873). Sex ratio between the patients and controls (the ratio of male to female was 26:21 among the patients and 18:15 among the controls) also was not significant (P=0.256).

Nineteen (40.4%) of GBS patients and two (6.1%) of control had serologic evidence of C. jejuni infection (odds ratio 10.5, 95% CI: 2.2-49.2, P<0.001). C. jejuni antibodies in patients and control groups are shown in Table-I.

Characteristics of C. jejuni positive (19 cases) and C. jejuni (28 cases) are compared in Table-II. None of the following variables was significant: age, gender, disease severity at nadir, preceding infections, clinical features and electrophysiologic pattern. However as regards the outcome we observed that the time to achieve independent walking ability was shorter in C. jejuni negative group (P=0.013). In the follow up, complete recovery was achieved in the 18(94.7%) of C jejuni positive patients and 28 (100%) of C. jejuni negative patients at 12 months and this difference was not significant. Thirty nine cases received specific therapy: plasmapheresis in 6 and high dose immunoglobulin in the 33 cases.

DISCUSSION

This study aimed specifically to determine the frequency and clinical features of C. jejuni-associated childhood GBS. We found that 19(40.4%) of 47 children with GBS had evidence of C. jejuni infection which is similar to our previous study in this region.10 Using the ELISA to determine the frequency of C. jejuni antibodies, Rees et al found that 27(26%) of 96 patients with GBS patients had positive C. jejuni serologic tests, compared with only 2% of household controls and 1% of age-matched hospital controls.14 By a complement fixation technique, Winer et al. found that 14(14%) of 99 patients with GBS had positive C. jejuni serologic test results, compared with only 2% of control.15 In the study by Kaldor and Speed, they found that 38% of 56 GBS patients and none of 57 controls met their criteria for positive serologic responses.16 In a large, blinded, case control study of 118 GBS adult patients and 113 controls in the United States, 36% of GBS patients compared 10% of control had serologic evidence of

Table-I: Campylobacter jejuni antibodies in patients with Guillain-Barre syndrome and healthy controls

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Patients with GBS N=47</th>
<th>Control group N=33</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG (positive)</td>
<td>38(80.9%)</td>
<td>6(18.2)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>IgM(positive)</td>
<td>22(46.8%)</td>
<td>2(6.1%)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>IgM+IgG(positive)</td>
<td>19(40.4%)</td>
<td>2(6.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
C. jejuni Infection and Childhood GBS

Recent C. jejuni infection.17 Serologic evidence of recent C. jejuni infection was found in 92 (45%) of 205 Japanese patients with GBS.18 In Beijing, 62% of GBS patients had evidence of C. jejuni infection.9 In a case control study in India, Kalra et al found evidence of recent C. jejuni infection in 27.7% of children with GBS, as compared with 2.3% in non-neurological controls.19 Antecedent C. jejuni infection in western countries play a less prominent role in childhood GBS than in adult. Serological evidence of C. jejuni infection was found 6 (7%) of 95 patients with childhood GBS in German, Swiss and Austrian countries.20

These findings suggest that the incidence of the C. jejuni infection in GBS varies considerably among countries. The reasons of the higher frequency in our study are not clear. The annual incidence of enteritis in developing countries, especially in children less than five years is higher,21 so the younger age of our patients (mean 5 years) could be a risk factor for campylobacter enteritis. Another explanation may be related to have different genetic background and environmental exposures of various populations. Host factors, including immunologic response to C. jejuni infection that is genetically linked, may predispose patients to development of GBS after C. jejuni infection.2,22 On the other hand, differences in frequencies of C. jejuni-associated GBS might be related to different systems and criteria used for diagnosis of C. jejuni positivity. A comparative study carried out in Japan and the Netherlands on the presence of anti-C. jejuni antibody in GBS showed that serological assay systems vary considerably between laboratories.23 Therefore serologic assays for diagnosis of C. jejuni infections need to be standardized and validated. Our criteria for diagnosis of C. jejuni were made particularly stringent to exclude any false-positive serologic results. It has been reported that isolated IgM response to C. jejuni may also occur after salmonella enteritis. In addition, we excluded patients with elevated levels of a single class of IgG antibody since it has been shown that some people, such as those who regularly drink raw milk, have elevated levels of IgG antibodies.14 By using this criterion (elevated both IgG and IgM) for seropositivity, in our study, the patients with GBS were 10.5 times more likely to have serologic evidence for C. jejuni infection than were the controls.

The timing of occurrence GBS following a preceding C. jejuni infection (1-4 weeks), suggests a humoral immunopathogenic mechanism rather than as a direct effect of organism or one of its toxin. Nevertheless not all infected patients have a measurable antibody response; in our study five patients with history of diarrheal illness in the last month did not have elevated anti-campylobacter antibodies. On the other

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Table-II: Characteristics of patients with Guillain-Barre syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>C. jejuni positive (N=19)</th>
<th>C. jejuni negative (N=28)</th>
<th>P.Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>5.6±4.5</td>
<td>5.1±3.3</td>
<td>0.62</td>
</tr>
<tr>
<td>Male: Female Ratio</td>
<td>9:103.9±2.6</td>
<td>17:114.9±3.3</td>
<td>0.3660.29</td>
</tr>
<tr>
<td>Mean time to reach peak disability (days)</td>
<td>7.0±3.6</td>
<td>5.0±1.8</td>
<td>0.10</td>
</tr>
<tr>
<td>Preceding infection (diarrhea)</td>
<td>7 (36.8%)</td>
<td>5 (17.8%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean GBS score</td>
<td>3.8±0.6</td>
<td>3.9±1.0</td>
<td>0.27</td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td>5 (26.3%)</td>
<td>14 (50%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Axonal pattern</td>
<td>12 (63.2%)</td>
<td>7 (36.8%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean CSF protein (mg/dl)</td>
<td>83.5±61.9</td>
<td>99.2±70.9</td>
<td>0.43</td>
</tr>
<tr>
<td>Duration to achieve Unaided walking (months)</td>
<td>5.3±3.9</td>
<td>2.9±2.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Sensory involvement (pain)</td>
<td>11 (57.9%)</td>
<td>19 (67.9%)</td>
<td>0.48</td>
</tr>
</tbody>
</table>
hand only 7 of 19 C. jejuni-positive patients in our study had definite history of diarrheal illness in the last month, so asymptomatic infection occurred in 12 patients, in whom diagnosis based on serologic results. The incidence of antecedent gastrointestinal symptoms does not necessarily reflect the frequency of preceding C. jejuni infection. Asymptomatic C. jejuni infection is frequent in GBS patients. Rees et al. reported asymptomatic infection in 8 of 27 C. jejuni-positive patients, but they also included patients with elevated levels of isolated IgG antibody and history of diarrheal illness within 12 weeks of neurologic symptoms. In a study on childhood GBS 53.3% of patients had diarrhea within 12 weeks before the onset of the neurologic symptoms. Patients with C. jejuni-associated GBS are more likely than other GBS patients to have primary axonal GBS. We found the patients with preceding C. jejuni infection were more likely to have axonal neuropathy (P<0.05). A large number of cases with C. jejuni associated GBS and axonal pattern have also been reported in children from China, South America and Turkey.

The spectrum of C. jejuni-induced Guillain-Barre syndrome ranges from mild cases of demyelinating neuropathy to a rapidly progressive axonal neuropathy with prolonged recovery and severe residual disability. In general, the younger the patient, the better is the prospect for complete recovery. In a study by Kuroki et al., six of seven patients recovered satisfactorily, and all were <16 years old. In another study on childhood GBS no statistical difference was observed between C. jejuni positive and negative groups with respect to residual paralysis at follow up.

We found that in C. jejuni-associated GBS, clinical features (limb weakness, cranial nerve involvement, sensory involvement, and overall disability) and CSF findings did not differ from C. jejuni negative patients. Although time to achieve independent walking was longer in C. jejuni positive group (P=0.013, 95% of C. jejuni-associated GBS patients achieved independent walking at end of one year.

In accordance with findings in our pervious study in this region, clinical and electrophysiological features of our subjects were relatively similar to other studies reported from Asian countries, especially China. The majority of Chinese patients presenting with acute areflexic paralysis in the summer months met electrodiagnostic criteria for a purely motor axonopathy, but nevertheless made a good recovery. Furthermore, a high percentage of affected children had IgG and IgM antibodies against C jejuni as compared to hospital controls.

**CONCLUSION**

Campylobacter jejuni is a common antecedent infectious agent in children with GBS in Iranian children and is associated with good prognosis.

**ACKNOWLEDGMENT**

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**REFERENCES**


