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A clinical and electrophysiological study of Guillain-Barré syndrome in Malaysia

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Abstract

Guillain-Barré syndrome is now considered a heterogeneous syndrome with both demyelinating and axonal variants. A prospective study was carried out in patients with Guillain-Barré syndrome admitted to the University of Malaya Medical Centre to determine the electrophysiological subtypes as well as the relationship to antecedent *Campylobacter jejuni* infection, thought to be associated with a predominantly axonal and motor variant of the syndrome. Forty patients were recruited. Excluding patients with clinical Miller-Fisher syndrome, 74.2 per cent had demyelinating polyneuropathy, 12.9 per cent had primary axonopathy and 9.7 per cent were unclassifiable. There was serological evidence of antecedent *C. jejuni* infection in 21.1 per cent of patients as compared to 2.6 per cent of age and sex-matched hospitals (P<0.014). However, all *C. jejuni* positive patients had a demyelinating subtype and had good outcome. Two patients (5 per cent) had poor outcome and one (2.5 per cent) died, all of whom had evidence of axonal degeneration (primary or secondary). This study supports the heterogeneity of Guillain-Barré syndrome in Malaysia. There are differences compared with other populations (e.g. Northern China) and this may suggest differences in risk factors and pathogenetic mechanisms for the syndrome.

Keywords: Guillain-Barré syndrome, electrophysiology, axonal variant, *Campylobacter jejuni*

INTRODUCTION

Guillain-Barré syndrome is an acute polyneuropathy, which is characterised by an ascending paralysis, areflexia and albuminocytological dissociation. With the gradual eradication of poliomyelitis due to immunisation, it is now the most frequent cause of acute flaccid paralysis in most countries.[1, 2] The diagnosis of Guillain-Barré syndrome was based on clinical features[3], supported by features of a demyelinating polyneuropathy on electrophysiology.[4, 5] However it has recently become evident that the syndrome is heterogeneous with distinct pathological entities, including predominantly axonal patterns; a sensorimotor axonal neuropathy now called acute motor-sensory axonal neuropathy (AMSAN) [6] and an acute motor axonal neuropathy (AMAN), a variant occurring mainly in summer epidemics among children in rural Northern China but also seen in other countries as well.[7-9]

Guillain-Barré syndrome is considered to be an immune-mediated disorder and the heterogeneity the syndrome implies several distinctive pathogenetic mechanisms with immunological attack on different antigens of the peripheral nerve.[10,11] In about two-thirds of cases there is some form of preceding infection or event[12, 13], and it has been suggested that the diversity of antecedent infections may give rise to the heterogeneity of the syndrome.[12] The most commonly recognised pathogen is *Campylobacter jejuni*, a major cause of bacterial gastroenteritis. Serological or culture evidence of recent *C. jejuni* infection has ranged from 26 per cent to 66 per cent in various case series.[14–17] Other organisms including cytomegalovirus, Epstein-Barr virus and *Mycoplasma pneumoniae* have been also been implicated.[12] Interestingly, antecedent infection with *C. jejuni* has been found to be associated with the AMAN subtype of Guillain-Barré syndrome in Northern China[17] and predominantly motor and axonal variants with poorer prognosis in other parts of the world.[14,16] There is evidence to suggest that peripheral nerve gangliosides may be the target in some forms of Guillain-Barré syndrome and that molecular mimicry (sharing of identical epitopes) between an infectious agent and neural antigens triggers an autoimmune response against the peripheral nerve.[10, 11] Specifically, antecedent *C. jejuni* infection has been associated with positive anti-GM1 antibodies[16], and

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liposaccharide in some strains of *C. jejuni* exhibit carbohydrate configurations similar to GM1.[18]

Most of our knowledge of Guillain-Barré variants and their relationship with antecedent infections has come from studies in China as well as several Western series. However, different populations around the world would have different exposures to inciting pathogens, with possible differences in subtypes. Determining these differences would be the first step in the further understanding of the pathogenesis and help in identification of the risk factors for the development of the disease.

Malaysia is multiracial developing country in Southeast Asia with a mix of urban and rural populations. We undertook a prospective study of patients with Guillain-Barré syndrome at the University of Malaya Medical Centre, Kuala Lumpur, one of the main tertiary neurology referral centres, to identify the clinical and electrodiagnostic variants of the syndrome seen locally as well as to define its association with antecedent *C. jejuni* infection.

MATERIALS AND METHODS

Patients who fulfilled the clinical criteria for Guillain-Barré syndrome [3] or Miller-Fisher syndrome were included in the study. All patients were reviewed clinically by the investigating neurologist. Cerebrospinal fluid examination was carried out in the majority of patients. We adopted the widely used disability scale of Hughes and colleagues in defining the functional motor deficits of our patients. [19] This was as follows: 0, healthy; 1, the patient has minor symptoms and signs and is able to run; 2, the patient is able to walk 5 m across an open space without assistance but is unable to run; 3, the patient is able to walk 5 m with assistance only; 4, patient is chairbound/ bedbound; 5, patient requiring ventilation and 6, patient is dead. Patients were reassessed clinically on discharge and where possible, followed up periodically until full recovery.

Electrophysiological studies, performed with a Medelec Sapphire® (Oxford Instruments) electromyograph machine, were carried out in one upper and one lower limb using standard nerve conduction techniques, studying four motor and three sensory nerves. Based on the results of electrodiagnostic studies, the pattern of Guillain-Barré syndrome was classified as demyelinating or axonal, using criteria adapted from Ho et al in their study of Guillain-Barré syndrome patients in China. [17] (Table 1) Normal values for our laboratory had been previously established. Studies were considered unclassifiable if they did not fit into either of the above criteria.

Serum samples for *Campylobacter jejuni* serology were collected from patients (before commencing any immunomodulatory treatment) and from age and sex-matched hospital controls with no recent history of diarrhoea or neurological disease. These were stored before being sent in batches to the Victoria Infectious Diseases Reference Laboratory in Melbourne, Australia. An enzyme-linked immunosorbent assay (ELISA) method was used. Test sera were diluted 400 fold in phosphate buffered saline and applied to wells pre-coated with a sonicated mixture of fifteen serotypes of *C. jejuni.* After incubation at 37°C for one hour, the plates were washed and horseradish peroxidase-conjugated rabbit anti-human IgG, IgA or IgM was added and reincubated for a further hour. The plates were read at 410 nm and antibody activity was

TABLE 1: Electrophysiological criteria for classification of Guillain-Barré syndrome (adapted from Ho et al [17])

a.	Diagnosis of demyelination:
•	Present in two or more nerves
i.	Conduction velocity <90% of lower limit normal if amplitude is >50% of lower limit normal; <85% if amplitude <50% of lower limit of normal
ii.	distal latency >110% of upper limit of normal if amplitude normal ; >120% of upper limit of normal, if amplitude is less than lower limit of normal
iii.	evidence of unequivocal temporal dispersion
iv.	F-latency >120% of normal
a.	Diagnosis of primary axonopathy:
i.	No evidence of demyelination as above
ii.	Decrease in CMAP (compound muscle action potential) to <80% of lower limit of normal or
iii.	Denervation changes on needle electromyography

expressed as the mean optical density (OD) of the wells. Increase in antibody activity was defined as an OD value above the mean plus 2 standard deviation (SD) of the reference range of the laboratory, obtained from healthy controls. Seropositivity for *C. jejuni* was defined as high OD values in two or more antibody classes. Stool samples were also taken and positive cultures were regarded as evidence for antecedent *C. jejuni* infection.

Statistical analysis comparing between discrete data was carried out the χ^2 test.

RESULTS

From late 1994 to the end of 1997, 40 patients with Guillain-Barré syndrome were seen. They presented in a sporadic fashion and did not demonstrate any variation in incidence throughout the year. Table 2 summarises the demographic data of the patients. The location and the patient referral pattern of the hospital probably accounts for why the majority of patients were from urban areas (77.5 per cent) and their ethnic breakdown; the Chinese-Malaysian population being generally more urban.

Patients presented to hospital from one day to 28 days (mean nine days) after the onset of initial symptoms. Two patients were referred from another hospital. Antecedent events one month prior to disease onset were noted in 26 patients (65 per cent) of which 23 had preceding upper respiratory tract infection, two had gastroenteritis and one had dengue fever. The clinical features are shown in Table 3. Clinically, at entry, the patients could be divided into pure motor, 19 patients (47.5 percent), sensorimotor, 14 patients (35 per cent), pure sensory, one patient (2.5 per cent) and the Miller-Fisher, six patient (15 per cent) variants. Two patients with sensorimotor involvement also had marked oculomotor and bulbar weakness. The mean time to maximum disability was 7.4 days (range two to 14 days). At nadir the functional classification was grade 5, nine patients (22.5 per cent), grade 4, 12 patients (30 per cent), grade 3, 13 patients (32.5 per cent), grade 2, four patients (10 per cent) and grade 1, two patients (five per cent).

Cerebrospinal fluid examination was carried out 33 patients (82.5 per cent). The mean CSF protein level was 116 mg/dL (range, 14-416 mg/

TABLE 2: Demographic characteristics of Guillain-Barré syndrome patients

	No. of patients N=40
Sex (male/female)	27/13 (67.5% / 32.5%)
Mean age (range) – years	33.6 (2 - 73)
Ethnic group	
Chinese	20 (50%)
Malay	9 (22.5%)
Indian	9 (22.5%)
Others (Bangladeshi)	2 (2.5%)
Area of residence (urban/rural)	31/9 (77.5% / 22.5%)

TABLE 3: Clinical features

	All patients, n=40 no. (per cent)
Limb weakness	
• Distal=proximal	22 (55)
• Distal>proximal	12 (30)
• Distal<proximal	6 (15)
Facial weakness	16 (40)
Bulbar weakness	18 (45)
Extraocular weakness	10 (25)
Respiratory failure	9 (22.5)
Sensory loss	27 (67.5)
Propioceptive loss	9 (22.5)

dL). Protein levels (< 45 mg/dL) were normal in 11 (33.3 per cent).

Electrophysiology: Electrophysiological examinations were carried out in 37 patients (92.5 per cent) between days 6 to 32 (mean, 14 ± 6.8 days) of illness. The electrophysiological diagnoses of the patients with Miller-Fisher syndrome were normal (two), demyelinating (one) and three could not be classified based on electrodiagnostic studies. Among the others, 23 patients (74.2 per cent) were classified as acute inflammatory demyelinating polyneuropathy (AIDP), of which three showed evidence of secondary axonal degeneration (denervation changes on electromyography). Four patients (12.9 per cent) had changes of a primary axonal neuropathy, of which two had pure motor involvement electrophysiologically, thus fulfilling the criteria of AMAN. Interestingly these were the two Bangladeshi patients. A further four patients (9.7 per cent) were unclassifiable.

Antecedent C. jejuni infection: No patient had positive *C. jejuni* stool culture. Thirty-eight patients and an equal number of sex and age-matched (± 5 years) hospital inpatient controls had serum samples sent for *C. jejuni* serology studies. Eight patients (21.1 per cent) were *C. jejuni* positive compared to one hospital control (2.6 per cent, P=0.014). None of the *C. jejuni* positive patients had a preceding diarrhoeal illness, while six had preceding upper respiratory tract illness. Electrophysiologically, all had demyelinating neuropathy. Comparisons between C. jejuni positive and negative patients are summarised in Table 4.

Neurologic outcome: Mean duration of hospitalisation was 16.1 days (range, 1 to 52 days). Ten patients (25 per cent) were treated with intravenous immune globulin infusion, five (12.5 per cent) had plasma exchange while two (5 per cent) had both modalities of immunomodulatory therapy. One patient died from complications of sepsis. Of the remaining patients, functional scores at discharge and at the end of 12 months follow up are shown in Table 5. Thirty-three patients (82.5 per cent) had either full recovery or mild disability (grade 0 to 2) at the end of one year, while three (7.5 per cent) remained severely disabled (grade 3 or worse). Four patients (10 per cent) were lost to follow up but these patients were on discharge (or at 3 months follow up, in one patient) were improving (functional grade 2). It is unlikely that they would have deteriorated or succumbed from the disease and probably had good outcome. Poor outcomes (grade 3 or worse) were seen in one patient (25 per cent) with primary axonal Guillain-Barré syndrome and two patients (8.7 per cent) with AIDP, both of which had secondary axonal degeneration on electrophysiology. All *C. jejuni* positive patients had good outcome.

DISCUSSION

This study of Guillain-Barré syndrome patients from a major tertiary hospital in Malaysia confirms the heterogeneity of the syndrome in the country. The majority of patients had AIDP. The proportion of patients with primary axonal Guillain-Barré syndrome (12.9 per cent) differed from Northern China where the majority (65 per cent) were found to be AMAN [17] but was well within range of the 5.9 to 29.5 per cent of previously reported series from Western Europe and Latin America.[9, 13, 14, 20] As we adopted similar electrophysiological criteria to the Chinese study, the difference could only be accounted for by

TABLE 4: Outcome of Guillain-Barré syndrome patients at discharge and at one year

	At discharge No. (per cent)	One year No.(per cent)
Normal or mildly disabled (Grade 0 or 1)	3 (7.5%)	31 (77.5%)
Moderate disability (Grade 2)	19 (47.5%)	2 (5%)
Severe disability (Grade 3, 4, 5)	17 (42.5%)	2 (5%)
Dead (Grade 6)	1 (2.5%)	1 (2.5%)
Lost to follow-up	0	4 (10%)

TABLE 5: Characteristics of *C. jejuni* positive versus *C. jejuni* negative patients

	***C. jejuni* positive, n=8 No. (per cent)**	***C. jejuni* negative, n=30 No. (per cent)**
Mean age (years)	27.1	35.9
Area of residence		
• Urban	8 (100)	22 (73.3)
• Rural	0	8 (26.7)
Race		
• Chinese	4 (50)	16 (53.3)
• Malay	2 (25)	6 (20)
• Indian	2 (25)	6 (20)
• Others	0	2 (6.7)
Antecedent diarrhoea	0	2 (6.7)
Clinical subtype		
• Motor	6 (75)	12 (40)
• Sensory	0	1 (3.3)
• Sensorimotor	2 (25)	12 (40)
• Miller-Fisher	0	5 (16.7)
Primary axonal subtype on electrophysiology	0	4 (13.3)
Disability grade at nadir:		
• Grade 0-2	0	6 (20)
• Grade 3-6	8 (100)	24 (80)
Outcome at 1 year:		
• Good (grade 0-2)	8 (100)	27 (90)
• Poor (grade 3-6)	0	3 (10)

the differences in the pathogenetic mechanisms operating in the different populations. Some observations suggest that these may be due to differences in their exposure to inciting events. Firstly, Malaysia is a tropical country with little seasonal variation in its climate and we did not demonstrate any peaks in incidence throughout the year. This would suggest that the inciting event (e.g. infection) for Guillain-Barré syndrome in Malaysia occurred sporadically. Secondly, our patients came predominantly from urban areas and may thus be exposed to different antecedent pathogens compared to patients in a rural setting. Although the majority of our patients were Chinese, most Chinese Malaysians are descended from ancestors who came from Southern China and therefore there may be differences in host immunogenetic makeup between the two populations, which may result in different susceptibility for the syndrome.

Antecedent *Campylobacter jejuni* is significantly associated with Guillain-Barré syndrome in Malaysia. There was however little evidence of a previous diarrhoeal illness suggesting that the infecting *C. jejuni* serotype did not cause enteritis. In Japan, most *C. jejuni* isolates from Guillain-Barré syndrome patients were of the Penner serotype 19, which rarely caused enteritis.[21] Serological evidence of previous infection, present in one-fifth of our patient, was fewer compared to Northern Chinese patients (66 per cent). The axonal pattern is believed to be associated with antecedent *C. jejuni* infection.[10, 11] Therefore, it was surprising that none of our *C. jejuni* positive patients were of the axonal subtype. This may be due to our relatively small number of patients studied compared to previous studies but it also demonstrates that the infection is not uniquely associated with the axonal subtype and may differ in various populations

Three patients (7.5 per cent) with poor outcome at the end of one year, including one death, serve to illustrate that this is not an entirely benign disease. All had evidence of axonal degeneration (primary or secondary). However, all *C. jejuni* positive patients had good outcome, but as all these patients had AIDP subtype, it follows that axonal degeneration is the important adverse prognostic factor and antecedent *C. jejuni* infection affects prognosis only in that it may predispose to

axonopathy.

In conclusion, this study supports the heterogeneity of the Guillain-Barré syndrome. Further investigation into other antecedent infections, differences in incidence and subtypes among different populations in the country (e.g. urban versus rural) will be helpful in defining the clinical risk factors for the syndrome in Malaysia.

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