Original Article

Ten-Year Prospective Study (Clinical Spectrum) of Childhood Guillain-Barré Syndrome in the Arabian Peninsula: Comparison of Outcome in Patients in the Pre– and Post–Intravenous Immunoglobulin Eras

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ABSTRACT

A prospective study of Guillain-Barré syndrome from January 1992 to December 2001 was undertaken. Intravenous immunoglobulins were used in all patients. All patients were followed up until complete recovery. Various parameters, such as onset of weakness, duration of hospital stay, ventilation requirement, residual deficit, and mortality, were recorded. Acute relapses and fluctuations were also noted. The pattern of this group was compared with patients before 1992, who were not given intravenous immunoglobulins in the Sultanate of Oman. Our data were compared with a few studies prior to 1992 from the medical literature. Our study revealed a definite benefit with intravenous immunoglobulins. The disease course and hospital stay were shortened. Fewer patients needed ventilation. There was no mortality, and the residual deficit was less than 5%. Occasional relapses at a later stage in the course of illness have been noted in acute Guillain-Barré syndrome. However, acute relapse, a new phenomenon that was not seen in the pre–intravenous immunoglobulin era, stood at 11.9%. Intravenous immunoglobulins have made a significant difference in the outcome of Guillain-Barré syndrome, but one has to be aware of acute relapses, which usually occur in the first 2 to 3 weeks after administration. (*J Child Neurol* 2003;18:767–771).

Eradication of poliomyelitis has always been one of the top priorities of the World Health Organization. Prompt identification of cases of acute flaccid paralysis is the basic method of identification of acute weakness, leading to the diagnosis of poliomyelitis. Guillain-Barré syndrome constitutes a significant group of cases of acute flaccid paralysis. Acute flaccid paralysis surveillance began in the Sultanate of Oman in 1990.[1] This country has a small population of about 1.5 million and an excellent health care system.[2] The diagnosis of Guillain-Barré syndrome was established on the described criteria.[3,4]

There was no specific treatment for Guillain-Barré syndrome prior to 1990. About a third of all patients needed ventilatory support for respiratory muscle paralysis, and about 10% of patients died of the disease and its complications.

Plasmapharesis and the use of intravenous immunoglobulin therapy started in the late 1980s and early 1990s. These therapies resulted in faster recovery, a fewer number of patients needing ventilatory support, and fewer complications. Although these modalities of treatment significantly improved the outcome of Guillain-Barré syndrome, a new phenomenon emerged: acute relapse following recovery. Our study analyzed the outcome of patients who received intravenous immunoglobulin (prospective study) and compared it with those who were not treated with intravenous immunoglobulin in the Sultanate and elsewhere from available studies in medical literature.[5–14] In addition, the relapse rate was identified and management of Guillain-Barré syndrome was suggested.

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PATIENTS AND METHODS

The Sultan Qaboos University Hospital is one of two tertiary care hospitals in the Sultanate. Pediatric neurology services were established in 1992 in this hospital. The Ministry of Health identified this hospital for evaluation of all cases of acute flaccid paralysis. This was done to have a uniform diagnostic evaluation of all cases. All children under 14 years of age with acute flaccid paralysis were admitted to this hospital. This study was a part of acute flaccid paralysis surveillance, which was aimed at the eradication of poliomyelitis from the Sultanate. The surveillance system and data collection began in January 1990.[1] Under this program, the Ministry of Health implemented acute flaccid paralysis surveillance at all levels of the national health care system involving all government hospitals, health facilities, and private clinics. Training programs for acute flaccid paralysis surveillance were provided to all health care personnel throughout the country, including physicians, nursing staff, and paramedical workers. The patients included were from different parts of the country.

All patients with acute flaccid paralysis underwent blood examination for serum immunoglobulins and polio antibody titer in addition to nerve conduction velocity studies. At least two stool samples for polio or other viruses were collected in all cases. Oman has a population of 1,483,226, of which 714,280 are aged under 15 years, according to the census carried out from November 1992 to January 1993.[2]

The diagnosis of acute Guillain-Barré syndrome was based on the following criteria[3,4]: an acute progressive symmetric weakness of extremities with areflexia, cerebrospinal fluid showing albuminocytologic dissociation, and electrophysiology revealing features of demyelinating/axonal neuropathy. The nerve conduction velocity studies were done within 24 hours of hospitalization. The patients presented within 2 days to 1 month after the onset of Guillain-Barré syndrome. For nerve conduction velocity studies, at least one motor and one sensory nerve was tested in upper and lower limbs. F wave latencies were recorded if there was only mild slowing of nerve conduction velocities. Electromyography was not done in any patient. All cases confirmed to have Guillain-Barré syndrome were followed up prospectively until complete recovery. At the time of admission, onset of weakness, duration of weakness, associated or preceding events, and progression of the disease were recorded. A detailed neurologic examination was recorded in all patients. Cerebrospinal fluid analysis was done in almost all cases except a few, whose parents refused consent for the test. Intravenous immunoglobulins were administered in all cases, 400 mg/kg/dose for five doses. The severity of the disease was defined only on clinical criteria. The severe form of Guillain-Barré syndrome was documented if the power was graded as 0 to 1 of 5 in the extremities with or without respiratory muscle involvement. The first signs of improvement were noted meticulously. The patients were also observed for signs of acute relapse, which was defined as worsening of the clinical condition after the initial improvement for at least a week following the last dose of intravenous immunoglobulin. The relapses were treated with three additional doses of intravenous immunoglobulin.

These data were compared with retrospective data of childhood Guillain-Barré syndrome from the Royal Hospital, the only tertiary care hospital that was functional in the country before the Sultan Qaboos University Hospital was opened. The children with Guillain-Barré syndrome not given intravenous immunoglobulin were analyzed. All children who received intravenous immunoglobulin were excluded. In addition, 10 studies prior to 1992 were chosen from the medical literature for comparison.[5–14]

Table 1. Features of Guillain-Barré Syndrome

Number of cases	42 (24 male, 18 female)
Age group	1.5–11.5 yr, mean 4.6 yr
Onset of weakness	1–30 d, mean 8.9 d
Preceding events	26 children (61.9%)
Meningeal signs	13 children (30.5%)
Cranial nerve involvement	23 (54.7 %)
Cerebrospinal fluid (cells/μL)	0–60, mean 6, less than 5 cells = 25 (59.5%)
Proteins (g/L)	0.23–8, mean 1.83
Intravenous immunoglobulins	All; one had plasmapharesis also
Ventilation requirement	7 (16.7%)
Relapse	5 (11.9%)
Hospital stay (d)	5–116, mean 20.4
Complete recovery in (d)	45–282, mean 73

RESULTS

From January 1992 to December 2001 (10 years), 42 cases of Guillain-Barré syndrome were diagnosed in the country (Table 1). The male-to-female ratio was 24 to 18, with male patients constituting 57.1%. The age at presentation ranged from 1.5 to 11.5 years, with a mean age of 4.6 years. Onset of weakness at admission ranged from 1 to 30 days, with a mean of 8.9 days. There were preceding events in 26 patients (61.9%), with upper respiratory tract infections in 21 and immunization-related (oral polio vaccine in 2 and mumps rubella vaccine in 1) illness in 3 children. Meningeal signs were elicited in 13 patients (30.5%), and cranial nerves were involved in 23 (54.7%), the facial nerve being the most common nerve involved in 19 patients (45.2%). Bulbar palsies were noted in 6 children (14.3%), and third and sixth nerve palsies in 3 children each (7.1%). The autonomic nervous system was affected in 3 children (7.1%), of whom there was hypertension in all and tachycardia in one. Cerebrospinal fluid examination was done at admission time, which meant at least 2 days to 1 month after the onset of Guillain-Barré syndrome. Of 42 patients, 38 had albuminocytologic dissociation and 1 had normal cerebrospinal fluid, and 3 parents refused consent for lumbar puncture. The cerebrospinal fluid cytology ranged from 0 to 60 cells (lymphocytes/μL), with a mean of 6 cells/μL. There were no cells in 9 patients, 0 to 5 cells in 16, 5 to 10 cells in 8, and 6 to 60 cells in 6. The patients with Guillain-Barré syndrome with meningeal signs had 0 to 60 cells/μL, with a mean of 7 cells, whereas the ones without meningeal signs had 0 to 30 cells/μL, with a mean of 6 cells. The cerebrospinal fluid proteins ranged from 0.23 to 8 g/L, with a mean of 1.83 g/L. The proteins in the group with meningeal signs ranged from 0.56 to 4.4 g/L, with a mean of 1.53 g/L, whereas the patients without meningeal signs had 0.48 to 8 g/L, with a mean of 2.14 g/L. All of them had motor nerve conduction abnormalities, but sensory conductions were normal in 4 patients. During

Table 2. Profile of Relapsed Cases of Guillain-Barré Syndrome

Age (yr), Sex	*Onset of Weakness (d)*	*Cranial Nerve Involvement*	*Respiratory Involvement*	*Improvement With IVIG Dose*	*Relapse (d)*	*Repeat IVIG Outcome*
5, F	2	No	No	3rd	10	Improved
2½, M	4	No	Yes	4th	6	Improved
9, M	10	Yes	Yes	4th	11	Improved
3, M	2	Yes	No	4th	21	Improved
7, M	5	Yes	Yes	4th	11	Ventilation required

IVIG = intravenous immunoglobulin.

nerve conduction velocity studies, a conduction block was seen in 28 (66.7%) and a reduction in velocity in 12 (28.6%), and in 2 (4.8%), no nerve could be stimulated. An F wave study was done in 20 cases; 15 had prolonged latencies, whereas 5 had absent F waves. There was no patient with an acute motor axonal neuropathy type of abnormality.

All patients were given intravenous immunoglobulin, 400 mg/kg/day for 5 days; one child underwent plasmapheresis. The recovery after intravenous immunoglobulin was noted from 1 to 21 days after treatment, with a mean of 5.8 days. Only 5 children (11.9%) of 42 relapsed after receiving intravenous immunoglobulin. Acute relapse was seen 6 to 21 days (mean 11.8 days) after the first sign of recovery (Table 2). Four of these relapsed patients responded to repeat doses of intravenous immunoglobulin, but one of these needed ventilation. Seven of 42 children (16.7%) had to be ventilated from 7 to 71 days (mean 27.9 days). The overall duration of hospital stay in all cases of Guillain-Barré syndrome ranged from 5 to 116 days, with a mean of 20.4 days. Of 42 cases, 26 patients (61.9%) were followed up until complete recovery in this hospital. Complete recovery was noted from 45 to 282 days, with a mean of 73 days. The remaining 16 patients were referred back to peripheral hospitals after discharge. Only 2 children were left with a residual weakness in the form of bilateral foot drop even after 2 years of follow-up. However, there was no mortality associated with Guillain-Barré syndrome.

In the retrospective study of Guillain-Barré syndrome, there were only 10 cases, 2 of which were excluded as they had received intravenous immunoglobulin. There was not much difference in the onset of weakness when compared with the prospective study group, but a marked difference in hospitalization, residual deficit, and ventilation requirement was noted. In addition, one child died. When our prospective study of Guillain-Barré syndrome was compared with other studies from the medical literature (Table 3), a favorable difference in the duration of hospital stay, ventilation requirement, and the time required to recover was obvious. Although a higher percentage of mortality was noted in the pre–intravenous immunoglobulin group, there was not much difference in the residual deficit.

DISCUSSION

Our prospective study of Guillain-Barré syndrome in children is unique as all cases in the country were diagnosed at one center and the majority of them were followed up until complete recovery. These cases formed part of acute flaccid paralysis surveillance, an extremely sensitive monitoring system aimed at the global eradication of poliomyelitis that is operational in many countries, including the Sultanate of Oman, under the guidance of the World Health Organization. Guillain-Barré syndrome formed 20% of cases of acute flaccid paralysis[15] and 45% of all cases of childhood

Table 3. Comparison of Patients With Guillain-Barré Syndrome Pre– and Post–Intravenous Immunoglobulin

	SQUH Prospective IVIG Group, 42 Cases	*RH Retrospective and Pre-IVIG Group, 8 Cases*	*Rantala et al,[5] 27 Cases*	*123 Retrospective Cases[7–12]*	*Kleyweg et al,[6] 18 Cases*	*Epstein and Sladky,[13] 14 Cases*	*Bradshaw and Jones,[14] 24 Cases*
Onset of weakness (d)	1–30	7–21	1–33	No data	No data	2–30	2–28
Mean	8.9	7.4	8.5			9.8	12
Ventilation required, n (%)	7 (16.7)	3 (37.5)	5 (18.5)	28 (22.7)	4 (22.2)	1 (7.1)	4 (16.7)
Days	7–71 (27.9)	4–30 (14.7)			16–48 (21.5)	7	1–10 (6.8)
Hospitalization (d)	5–116	13–118	4–70	No data	7–449	No data	11.6 (+ 8.3)
Mean	20.4	45.4	34.1		84		
Relapse, n (%)	5 (11.9)	Nil	Nil	Nil	Nil	Nil	Nil
Complete recovery (d)	45–282	No data	22–660	No data	No data	180	28–450
Mean	73		158				
Residual deficit, n (%)	2 (4.8)	3 (42.8)	1 (3.9)	No data	1 (5.5)	No data	3 (12.5)
Deaths, n (%)	0	1 (12.5)	0	10 (8.1)	2 (11.1)	0	0

IVIG = intravenous immunoglobulin; RH = Royal Hospital; SQUH = Sultan Qaboos University Hospital.

neuropathies.[16] The annual incidence below 15 years in our study was 0.45 in 100,000. The age-specific incidence was 1.26 in 100,000 in the 1 to 4 years age group and 0.24 in 100,000 in the 5 to 9 years age group.[15] Only one case was seen in the 10 to 15 years age group; hence, separate incidence was not calculated. Similar patterns have been well documented and are believed to be attributable to exposure of several infections, toxins, and increased susceptibility of young myelin to demyelination.[17–19] Twenty (47.6%) children had a severe form of Guillain-Barré syndrome, and 7 children required ventilation from 7 to 71 days. The Fisher variant of Guillain-Barré syndrome was seen in 3 children. One of the 3 children had features of the syndrome of inappropriate secretion of antidiuretic hormone, hypertension, and myoclonus.[20] There was no child with the acute motor axonal neuropathy type of Guillain-Barré syndrome in our series, as reported in one study from China.[21]

The earliest recovery sign (improvement by Medical Research Council scale grade 1) after intravenous immunoglobulin was documented after 24 hours of the first dose, and the maximum time needed for onset of recovery was 21 days, with a mean of 5.8 days. By day 4 (the fourth dose of intravenous immunoglobulin), 12 patients (28.6%) had shown signs of recovery. Most of the reports advocating use of intravenous immunoglobulin have documented dramatic improvement following treatment.[22–24] However, there are a few reports with an unfavorable response to intravenous immunoglobulin.[25–27] Plasmapheresis was done in only one of our ventilated patients, who also received intravenous immunoglobulin. Although some authors advocate that plasmapheresis is superior to intravenous immunoglobulin in severe cases,[26] many studies favor intravenous immunoglobulin,[22,23] based on the fact that the group who underwent plasmapheresis had a higher relapse rate compared with the intravenous immunoglobulin group. Five patients showed initial improvement with intravenous immunoglobulin and later relapsed within 3 weeks. Four of them responded to three additional doses of intravenous immunoglobulin, whereas one needed ventilation. Overall, seven (16.7%) children needed ventilation. Six of them had rapid onset of ascending paralysis and needed ventilatory support within 48 to 72 hours of weakness. The seventh case had shown initial improvement to intravenous immunoglobulin therapy but, on relapse, required ventilatory support.

Prior to 1992, the only other tertiary-level hospital in the Sultanate was the Royal Hospital, which did not have any pediatric neurology back-up at that time. All of the cases of Guillain-Barré syndrome from the Royal Hospital prior to 1992 were analyzed. There were 10 cases, 2 of which had received intravenous immunoglobulin. These 2 cases were excluded, and only 8 cases were left for comparison. Although this number is small, in a population of 1.5 million, this could still be significant. Additionally, we found five studies of the pre–intravenous immunoglobulin era with adequate cases of childhood Guillain-Barré syndrome. There may be shortcomings in the form of selection, diagnosis, and treatment bias in comparing the historical case studies with our prospective study. However, on the treatment front, there was nothing available in the past except for the ventilatory support, and often the disease took its natural course.

On comparison, there was not much difference in onset of weakness among the pre– and post–intravenous immunoglobulin era cases. The residual deficit also showed little difference in the two groups, except that our local retrospective study showed a proportionately high residual deficit, which could be attributable to the small number of total cases. However, there was a marked difference in ventilation requirement (16.7% in the intravenous immunoglobulin group of the present series compared with 18.5 to 37.5% in the pre–intravenous immunoglobulin group). At the same time, the mean hospital stay in the intravenous immunoglobulin group was markedly reduced, although the range was not different. Complete recovery was also faster in terms of both mean time and longest time in the intravenous immunoglobulin group.

The only new observation with patients treated with intravenous immunoglobulin was acute relapse in 11.9% of the patients, which was not described in the patients from the pre–intravenous immunoglobulin era. This suggests that relapse was related to the treatment with intravenous immunoglobulin. The relapse in Guillain-Barré syndrome has been seen with both intravenous immunoglobulin and plasmapheresis. A relapse rate ranging from 1.4[24] to 46.7% was reported with the use of intravenous immunoglobulin.[27] Although there were initial reports of more relapse with one mode of treatment compared with the other, Hughes, in his editorial on the use of intravenous immunoglobulin, plasmapheresis, and plasmapheresis followed by intravenous immunoglobulin in randomly selected 383 patients divided into three groups, stated that the outcome was similar in all three groups after 4 weeks of initial treatment.[28] These three regimens also had a similar outcome after 48 weeks of follow-up.[28]

One has to differentiate acute relapses in Guillain-Barré syndrome from recurrent Guillain-Barré syndrome and acute presentation of chronic inflammatory demyelinating neuropathy. All of these forms of Guillain-Barré syndrome may respond to intravenous immunoglobulin therapy. The relapse that occurs within 3 weeks of intravenous immunoglobulin treatment is more likely to be attributable to acute Guillain-Barré syndrome, whereas late relapses after 4 to 6 weeks of intravenous immunoglobulin may be the cases of recurrent Guillain-Barré syndrome or chronic inflammatory demyelinating neuropathy. More than one relapse and late-onset relapse 4 to 6 weeks after intravenous immunoglobulin treatment suggest recurrent Guillain-Barré syndrome.[29,30] The acute relapses may respond to the repeat doses of intravenous immunoglobulin, as was seen in four of our cases, or there may be relentless progression, needing respiratory support. We recommend repeating intravenous immunoglobulin at 400 mg/kg once daily for 3 days at the earliest signs of relapse. The cause of relapse is related to the mechanism of action and half-life of intravenous immunoglobulin.[31,32] Although the precise mechanism of immunomodulation by intravenous immunoglobulin is unknown, it probably directly inactivates myelin-specific antibodies and indirectly inhibits its production, hastening recovery and leading to improvement in nerve conductions.[31] Other mechanisms include solubilization of immune complexes, possible action on natural killer or suppressor cells, and immunomodulation by Fc receptor blockade.[31] The half-life of intravenous immunoglobulin is usually 3 weeks.[32] In case the disease activity persists beyond the half-life of intravenous immunoglobulin, relapse sets in.

In this study, 13 children (30.5%) had meningeal signs. Two of them had severe signs, and the initial impression was meningitis. However, generalized weakness and areflexia, along with nerve conduction velocity studies, confirmed the diagnosis of Guillain-Barré syndrome. Thus, only 2 children of 42 (4.8%) had meningeal signs mimicking the pseudomeningoencephalitic pattern.[14] Further analysis was done to see whether there was any difference in the clinical profile of the group with and without meningeal signs. In the group with meningeal signs, 8 (61.5%) had the severe form of Guillain-Barré syndrome, whereas in the other group, 12 (41.4%) had severe Guillain-Barré syndrome. When cerebrospinal fluid cytology and biochemistry were compared between the two groups, there was no difference.

In conclusion, our study suggests that intravenous immunoglobulin has reduced the duration of the disease, disability, hospital stay, mortality, and ventilation requirement. However, acute relapse remains a disadvantage, which needs to be recognized early and treated accordingly. Overall, the benefits outweigh the risk of relapse. In our entire series, there were no complications attributable to intravenous immunoglobulin therapy.

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