Clinical Characteristics of Childhood Guillain-Barré Syndrome

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Abstract

Objectives: To find the incidence, clinical pattern and outcome of Guillain-Barre syndrome in the Sultanate of Oman in children less than 15 years of age.

Methods: All children under fifteen years with acute flaccid paralysis were admitted to identify the underlying cause. The diagnosis of Gullain Barre syndrome was made by clinical criteria, cerebrospinal fluid findings and nerve conduction studies. Intravenous immunoglobulins were given to all and two needed plasmapharesis.

Results: Sixty-one children were diagnosed as Guillan-Barré syndrome and constituted 20% of cases of acute flaccid paralysis. Males 39 (63.9%) outnumbered females (36.1%).The annual incidence below 15 years was 0.45/100,000. Cranial nerves were involved in 31 (50.8%) children. Albumino-cytological dissociation in cerebrospinal fluid was seen in 42/45(93.3%) cases. Acute relapse was seen in six (9.8%) cases. Eleven children (18.3%) needed ventilation. Complete recovery was seen in 45 to 310 days (mean 69.1 days). Three children (4.9%) were left with minimal residual deficit. There was no mortality.

Conclusions: Guillain Barre syndrome is a serious disease, although recovery is the rule in children. The disease is associated with very low mortality and long term morbidity. Immunoglobulins have reduced the duration of hospital stay and the total time needed for recovery.

Keywords: Guillain-Barré Syndrome, Children, Epidemiology, IVIG, Plasmapharesis, Outcome

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Introduction

Guillain-Barré Syndrome (GBS) is an acute monophasic demyelinating neuropathy. The disease is characterized by progressive motor weakness of limbs with areflexia. Preceding antecedent infections, mostly viral, are seen in half of the cases. One third of patients required ventialatory support in the past with about ten percent mortality. Immunoglobulins and plasmapharesis have made a significant change in the course of the illness.[1] For eradication of poliomyelitis in Oman, acute flaccid paralysis surveillance started in 1990.[2] Guillain-Barré syndrome formed a part of this study. The diagnosis of GBS was established on the described criteria.[3, 4] Plasmapharesis and the use of intravenous immunoglobulins (IVIG) result in faster recovery. Fewer numbers of patients need ventilatory support and there are fewer complications. However, some patients develop acute relapse, following initial recovery, which has to be carefully observed. Our study analyzed the outcome of patients who received IVIG (prospective study). In addition, relapse rate was identified and its management is suggested.

Methods

Under the surveillance of AFP in the Sultanate of Oman all cases with acute flaccid paralysis were referred to the Sultan Qaboos University Hospital (SQUH) for workup and management. The Ministry of Health in the country identified this hospital for evaluation of all cases of AFP. This is in order to gain uniform diagnostic evaluation of all cases. All children under 15 years of age with AFP were admitted to SQUH. Data was prospectively collected from all AFH cases as they presented. Subsequently, Guillain-Barré syndrome cases were analyzed separately. All the cases, as they all underwent thorough clinical examinations and several investigations to find the underlying cause. At least 2 stool samples for polio or other viruses were collected from all AFP cases. Serum creatine kinase and sickling test were also done. Other investigations like imaging and immune work up were done when indicated. Most of the children had nerve conduction studies as well. The diagnosis was based on clinical features, lumbar puncture and electrophysiological findings as laid down in the well established criteria.[3, 4] Onset of weakness, duration of weakness, associated or preceding events and progression of the disease were recorded. A detailed neurological examination was recorded in all. The Nerve Conduction velocity (NCV) studies were done within 24 hours of hospitalization. At least one motor and one sensory nerve were tested in upper and lower limbs. F-wave latencies were recorded if there was only mild slowing of nerve conduction velocity. Electromyography (EMG) was not performed in any patient. All confirmed GBS cases were followed up until complete recovery.

Cerebrospinal fluid analysis was done in majority (45) of the cases. The parents of 16 patients refused consent for the test. The severity of the disease was defined on clinical criteria only. Severe form of GBS was defined as the power of 0-1/5 grades in the extremities with or without respiratory muscle involvement. Intravenous immunoglobulins were administered in all cases, in the dose of 400 mg per kg per dose daily for 5 days. Plasmapharesis was done in two children who failed to recover with IVIG, and they were followed until complete recovery. The first signs of improvement were noted meticulously. The patients were also observed for signs of acute relapse, defined as worsening of the clinical condition after the initial improvement for at least a week following the last dose of IVIG. The relapses were treated with three additional doses of IVIG. In addition, children with very slow recovery were given additional doses of IVIG after at least ten days of last infusion. The children were followed up, till complete recovery

Results

The patients presented within 2 days to one month after onset of GBS. Various clinical features, laboratory parameters and outcome are described in table 1. Sixty one children were admitted with GBS. Preceding events were seen in 37(60.6%) children which were in the form of upper respiratory illnesses or fever. Varicella infection (chicken pox) preceding in two and mumps in one child. Cranial nerves were involved in 31(50.8%) children. Facial nerves were involved in 24(39.3%), bulbar in 9(14.7%), and 3rd and 6th nerves in 3(4.9%) each. Autonomic disturbances mostly hypertension were observed in seven (11.50%) cases. Signs of meningeal irritation were elicited in seventeen (29%) children. Severe aches and pains of the body and extremities were seen in about half the cases. Nerve conduction studies were abnormal in all (motor in all and sensory all but five). Of the 61 children, 45 had cerebrospinal fluid (CSF) evaluation. Forty two of the 45 children had albumin-cytological dissociation, and three had normal CSF.

Two patients did not recover with IVIG and underwent plasmapheresis. These were two girls of three and four years of age, who had progressive weakness and initially had some arrest at the disease with IVIG. The weakness worsened needing ventilator support. When there was no recovery over a week, plasmapharesis was done. The first case underwent plasmapharesis in 1992 and showed signs of recovery after 3 cycles, while the second case underwent the procedure plasmapharesis in 2005 with signs of recovery after 2 cycles. The pharesis was continued for 5 days and 7 days in case 1 and case 2 respectively. In view of the complex procedure and difficult venous access at younger age group, the plasmapharesis was not used in all severe cases. Acute relapse/fluctuation was seen in 6 (9.8%). The relapse was seen 6 to 21 days (mean 11.1 days) after first sign of recovery. Five of these relapsed patients responded to the repeat IVIG doses, but one needed ventilation. Two cases showed slow recovery after initial IVIG therapy and were given additional doses after about ten days of the last dose to hasten the recovery. Eleven (18.3%) cases required ventilation from 7 to 71 days (mean 27.9 days). Another child was electively ventilated for four days while being transferred from a far of hospital in Salalah. The hospital stay was from 5 to 116 days, (mean 20.6 days). The time taken for complete recovery ranged from 45 to 310 days (mean 69.1 days). Three (4.9 %) children were left with minimal residual deficit. There was no mortality.

Table 1: Detailed features of Guillain-Barré syndrome children

Number of cases	61 [39 male (63.9%):22 female (26.1%)]
Age range in years	1.5-11.5 years, mean 4.89 years
Onset of weakness in days	1-30 days, mean 8.8 days
Preceding events	37 children (60.6%)
Meningeal irritation signs	17 children (27.8%)
Cranial nerves involvement	31 (50.8%)
Cerebrospinal fluid White blood Cells (lymphocytes) /cmm Range Cells less than 5/cmm No cells	 0-60 cells, mean 17 cells 28, children, (46.6%) 3
Proteins G/L	Range 0.23-8, mean 1.74
Intravenous Immunoglobulin (IVIG) used	All
Plasmapharesis also	2
Ventilation requirement	11 (18.3%)
Relapse	6 (9.8%)
Hospital stay in days	5-116, mean 20.6
Complete recovery in days, (followed up till complete recovery). Range	 45-310, mean 69.1

Discussion

In this study, GBS formed a part of AFP surveillance, an extremely sensitive monitoring system aimed at the global eradication of poliomyelitis, operational in many countries including the Sultanate of Oman, under the guidance of World Health Organization. Guillain-Barré syndrome formed 20% of cases of AFP,[5] and 45% of

all childhood neuropathies.[6] The annual incidence below 15 years in our study was 0.45/100,000. The incidence of GBS has been estimated to range from 0.5 to 1.5 in 100,000 in individuals less than 18 years of age.[7] The age specific incidence was 1.26/100,000 in the age group of 1-4 years and 0.24/100,000 in the 5-9 years age group.[5] Only one case was seen in the 10-15 years age group, hence separate incidence was not calculated. Most of GBS cases are seen below four years of age, worldwide and is believed to be due to exposure to several infections, toxins and increased susceptibility of young myelin to demyelination.[7, 8, 9] Twenty-five (41%) children had severe form of GBS and eleven (18.03%) required ventilation from 7-71 days. Fisher's variant of GBS was seen in three. One of them had features of syndrome of inappropriate secretion of ADH and hypertension. Overall 7 (11.5%) children had hypertension. All of them were treated with beta blockers (5 with propranolol and 2 with atenolol) for one to three months. There were two children with acute motor axonal neuropathy (AMAN) type of GBS in our series, as reported in one study from China.[10]

The earliest recovery sign (improvement by MRC scale grade 1) after IVIG 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 (4th dose of IVIG) 18 patients (30%) had shown signs of recovery. Most of the reports advocate use of IVIG because of the dramatic improvement following treatment,[11, 12, 13] while others favor plasmapharesis.[14] Unfavorable response was seen with both modes of therapy.[14, 15] Intravenous immunoglobulin is preferred in children. It is easy to administer and has less complications. Plasmapharesis is preferred in adults and is cost effective as well. Plasmapheresis was done in two of our patients who failed to respond to IVIG and needed ventilation. Six patients (9.8%) showed initial improvement with IVIG and later relapsed within three weeks. Five of them responded to additional 3 doses of IVIG, while one needed ventilation. Overall 11 (18.03%) children needed ventilation. Ten of them had rapid onset of ascending paralysis and needed ventilatory support within 48-72 hours of weakness. The eleventh case had shown initial improvement to IVIG therapy, but on relapse, required ventilatory support.

When compared with pre IVIG era, there was marked difference in ventilation requirement (17.5% in present series to 18.5-37.5% in the pre IVIG era group).[1] At the same time the mean hospital stay in the IVIG group was markedly reduced, though the range was not different. Complete recovery was also faster in terms of both mean time and longest time in the IVIG group.

Acute relapse was seen in 9.8% of the patients. Acute relapse was not described in pre IVIG era. This clearly indicated the relapse was related to the treatment with IVIG. The relapse in GBS was seen with both IVIG and plasmapheresis. A relapse rate ranging from 1.4%,[13] to 46.7%,[16] was reported with the use of IVIG. Though there were initial reports of more relapses with one mode of treatment as compared to the other, Hughes RA, in his editorial on use of IVIG, plasmapheresis and plasmapheresis followed by IVIG in randomly selected 383 patients divided into 3 groups, suggested that the outcome was similar in all 3 groups after 4 weeks of initial treatment.[17] These 3 regimens also had similar outcome after 48 weeks of follow up.[17]

Acute relapse in GBS has to be differentiated from recurrent GBS and acute presentation of chronic inflammatory demyelinating neuropathy (CIDP). All of these respond to IVIG therapy. The relapse that occurs within 3 weeks of IVIG treatment is more likely to be due to acute GBS while late relapses after 4-6 weeks of IVIG may be the cases of recurrent GBS or CIDP.[18, 19] The acute relapses usually respond to the repeat doses of IVIG, as in 5 of our cases but sometimes there may be relentless progression needing ventilation. We recommend repeating IVIG at 400 mg per kg once daily for 3 days at the earliest sign of relapse. The cause of relapse is related to the mechanism of action and half-life of IVIG.[20, 21] Although the precise mechanism of immunomodulation by IVIG is unknown, it probably directly inactivate myelin specific antibodies and indirectly inhibits its production, inhibit complement binding, hastens recovery leading to improvement in nerve conductions.[20] Other mechanisms include solubilization of immune complexes, neutralization of selected cytokines, possible action on natural killer or suppressor cells and immunomodulation by Fc receptor blockade.[20] The half-life of IVIG is usually 3 weeks.[21] In case where the disease activity persists beyond the half-life of IVIG, relapse sets in. Worldover IVIG therapy has been used either over five days (400mg/kg/day) or two days (1G/kg/day). There are few reports of single dose of 2G/kg use. Relapse and complications were seen more often with the later therapy.[22]

In our study, 17 children (27.8%) had meningeal signs. Two of them had severe signs and the initial impression was meningitis. However, generalized weakness and areflexia along with NCS confirmed the diagnosis of GBS. There was no difference in the clinical profile and CSF cytology/biochemistry of the group with and without meningeal signs. About half of the patients, had severe pain in extremities in addition to meningeal signs. All these children were given analgesics (Ibuprofen) and Gabapentin for about four to six weeks.

Conclusion

The incidence of Guillain Barré Syndrome in children below the age of 15 years in Oman is 0.45/100,000 per year. It represents 20% of cases with acute flaccid paralysis. Cerebrospinal fluid

analysis and Nerve Conduction Studies are important to confirm the diagnosis. IVIG is a safe and effective treatment. If initiated early it reduces the severity of the disease. In addition, duration of the disease, ventilation requirement hospital stay, disability, and mortality are also reduced. Acute relapse following initial recovery with IVIG sometimes occurs and needs to be picked up early. The relapses respond to additional doses of IVIG. There were no complications attributable to IVIG therapy.

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