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A comparison between plasmapheresis and intravenous immunoglobulin in children with Guillain–Barré syndrome in Upper Egypt

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Abstract

Objective: The aim of our study is to assess the clinico-electrophysiological profile of children with Guillain–Barré syndrome (GBS) in Upper Egypt and to compare the efficacy of plasmapheresis versus other treatment modalities.

Patients and methods: This was a retrospective study of children from January 2010 to October 2014 diagnosed as GBS. It included 62 cases.

Results: Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) was the most prevalent type of GBS in our locality. As regards the treatment, 32 cases received plasmapheresis while 30 patients received intravenous immunoglobulin. We found a significant decrease in the duration of hospitalization and a significant increase in the number of children with complete recovery in cases treated with plasmapheresis.

Conclusion: GBS is not uncommon in children of Upper Egypt, with AIDP the most prevalent type. Plasmapheresis is the best treatment modalities for GBS as it reduces the duration of hospital stay and hastens the recovery of those children.

Keywords: children, Guillain–Barré Syndrome, intravenous immunoglobulin, plasmapheresis, outcome

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Introduction

Guillain–Barré syndrome (GBS) is an acute inflammatory polyneuropathy most commonly characterized by a rapidly progressive, essentially symmetric, ascending flaccid paresis, weakness and areflexia [Chieng *et al.* 2007]. GBS peripheral nerve damage can be classified histopathologically into two main types: demyelinating forms; and axonal-degenerating forms. Motor nerves are more susceptible to disease than sensory ones. In 1995, GBS was subdivided into four distinct forms based on histopathological and neurophysiological basis: acute inflammatory demyelinating polyradiculoneuropathy (AIDP); acute motor axonal neuropathy (AMAN); acute motor and sensory axonal neuropathy (AMSAN); and Miller–Fisher syndrome (MFS) [Hughes, 1995; Kieseier *et al.* 2004]. Most often an unremarkable infection, such as upper respiratory and gastrointestinal infections, often predates the onset of GBS by 14 days [Chiò *et al.* 2003].

To date, the treatment for GBS has been aimed primarily at immunomodulation. In pediatrics, the main therapy of GBS is intravenous immunoglobulin (IVIG). Each batch of IVIG is made of human plasma derived from pools of 3000–10,000 donors [Hughes *et al.* 2003]. Studies in children indicated that plasmapheresis may decrease the severity and shorten the duration of GBS. Between four and five plasmapheresis treatments may be performed over 7–10 days, as described in standard protocols. Both plasmapheresis and IVIG are effective in GBS. The availability of plasmapheresis is generally limited to major referral centers that have the requisite equipment and trained personnel [Shahar, 2006]. Collective data on five trials and 582 patients do not reveal a significant improvement in outcome, either improving faster or more completely with the combination of IVIG and plasmapheresis. The combination exposes the patients to the risks of adverse events from both modalities. There is no

evidence to support the use of both IVIG and plasmapheresis therapies [Randall, 2010].

Patients and methods

This was a retrospective study of the medical records of children diagnosed with GBS who were admitted to the Assiut University Children's Hospital from January 2010 to October 2014 after obtaining approval from Assiut University Ethical Committee. Data collected included age, sex, season, antecedent infection, the need for mechanical ventilation, length of stay in the pediatric intensive care unit, clinical outcome of cases after 6 months of diagnosis, and investigation performed. Investigations included lumbar puncture and electrophysiological studies for AIDP and axonal forms of GBS, which include AMSAN, AMAN and MFS.

The diagnosis of acute GBS was based on the following criteria: an acute progressive symmetric weakness of the extremities with areflexia or hyporeflexia; the cerebral spinal fluid (CSF) showing albuminocytological dissociation; and electrophysiological studies revealing features of demyelinating/axonal neuropathy. Albuminocytological dissociation was defined as CSF with a raised protein and total cell count of $\leqslant 10$ per mm^3 [Asbury and Cornblath, 1990]. Nerve conduction velocity and electromyography were performed within 4 weeks of admission.

The treatment of GBS in our hospital started after confirmation of the diagnosis by clinical manifestations and investigations. Before 2011, the facility for plasmapheresis was not available at our hospital, so treatment of GBS consisted mainly of IVIG in a dose of 0.4 g/kg/day for 5 consecutive days. From 2011, we have used either IVIG or plasmapheresis. For plasmapheresis we use the protocol of the North American trial [Guillain–Barré Syndrome Study Group, 1985] in which a total of 200–250 ml/kg is exchanged over 7–10 days.

Patients who developed use of accessory muscles of breathing, clinical features of respiratory distress and abnormalities on arterial blood gas analysis (hypoxemia and/or hypercapnea) were intubated and provided with mechanical ventilation. The outcome parameters analyzed included in-hospital, recovery, mortality and residual disability.

Statistical analysis

Statistical analysis was performed with SPSS for Windows. Frequencies, percentages, means and standard deviation (SD) were calculated. The Chi-square test and Fisher's exact test were used for comparison between independent groups of categorical data. The unpaired *t*-test was used for numerical data and one-way analysis of variance (ANOVA) was used to compare more than two groups. For all statistical tests, values of $p < 0.05$ (two-tailed) were considered statistically significant.

Results

The demographic and clinical data of the collected cases are presented in Table 1, which shows that the lowest age diagnosed as GBS was 1.5 years and 16 years was the highest age, with the mean age $\pm$ SD being 8.0 $\pm$ 4.7 years. Females (58%) were more affected than males. Summer was the highest season for cases of GBS (58%). Upper respiratory tract infections were the antecedent infection in the majority of patients (67.7%), while 25.8% of patients were preceded by gastrointestinal infection. Viral infection was recorded in four patients (6.5%).

Lumbar punctures were performed in 55 patients (88.7%) within a week of the onset of illness; the rest of patients or parents did not agree to undergo lumbar puncture. Typical albuminocytological dissociation was found in 56 (90.3%). Three samples revealed traumatic taps.

As regards the electrophysiological studies, AIDP was the commonest type being recorded in 40 patients (64.5%); AMAN was the diagnosis in eight patients (13%), AMASN in six patients (9.5%) and MFS in four patients (6.5%). No specific type was detected in four patients, mostly because of their bad general condition.

As regards the treatment groups, Group 1 consisted of 30 patients (48.3%) who received IVIG. The documented side effects of IVIG included mild infusion rate reactions including headache (three patients), myalgia (five patients), flushing (one patient) and paresthesias (five patients). Group 2 consisted of 32 patients; they received only plasmapheresis by central venous catheter. The most important side effects included hypotension (two patients), arrhythmias (two patients), lower limb pain (three patients) and abdominal pain (four patients).

Table 1. Demographic and clinical data of children with Guillain–Barré syndrome.

Parameter	$n = 62$ cases (%)
Age (years): range	1.5–16
Mean ± standard deviation	8.0 ± 4.7 years
Gender (male: female)	26:36 (42/58)
Season	
Summer	36 (58)
Fall	6 (10)
Winter	10 (16)
Spring	10 (16)
Antecedent infection	
Upper respiratory infection	42 (67.7)
Gastrointestinal infection	16 (25.8)
Viral infection	4 (6.5)
Diagnosis	
AIDP	40 (64.5)
AMAN	8 (13)
AMSAN	6 (9.5)
MFS	4 (6.5)
Undefined diagnosis	4 (6.5)
Clinical manifestation	
Autonomic manifestation	11 (17.7)
Cranial nerve affection	15 (24.2)
Facial palsy	17 (27.4)
Bulbar palsy	14 (22.5)
Neck muscle affection	24 (38.7)
Treatment	
IVIG	30 (48.4)
Plasmapheresis	32 (51.6)
Required mechanical ventilation	
Yes	24 (38.7)
No	38 (61.3)
Prognosis	
Complete recovery	26 (42)
Residual deficit	24 (38.7)
Death	12 (19.3)

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory axonal neuropathy; IVIG, intravenous immunoglobulin; MFS, Miller Fisher syndrome.

Mechanical ventilation was used in 24 cases (38.7%) and 38 cases (61.3%) did not need mechanical ventilation. Death was the fate in 12 cases (19.3%), while complete recovery was recorded in 26 cases (42%) and 24 cases (38.7%) were discharged with a residual deficit.

Table 2 compares Group 1 patients treated with IVIG and Group 2 patients treated with plasmapheresis; we found no statistical differences between the two groups as regard to age, sex and death. We found that the mean duration of hospital stay in cases treated with plasmapheresis (Group 2) was significantly lower than the time needed for cases in the other treatment (Group 1) ($p < 0.01$). The number of patients who required mechanical ventilation was significantly higher in Group 1 treated with IVIG ($p < 0.001$). As regard the prognosis, complete recovery was significantly higher in cases treated with plasmapheresis compared with the other group ($p < 0.001$); a residual deficit was significantly higher in cases who did not receive plasmapheresis ($p < 0.01$).

Discussion

GBS is the most common cause of the development of acute flaccid paralysis in children and infants. This study is the first study in Upper Egypt. The occurrence of GBS in children increases with age and it is quite rare in children younger than 2 years-old [Hung *et al.* 2004]; this is in agreement with our series as only one patient was under 2 years (1.5 years).

In our study, females were affected more than males and this is against most of the previous reports which mention that GBS demonstrates a slight male predominance, with a male/female ratio of approximately 1.2–1.5:1 [Pithadia and Kakadia, 2010; Tang *et al.* 2011]. Other researchers in Hong Kong reported a similar predilection between the two sexes [Ma *et al.* 2010].

Summer was the predominance time for the occurrence of cases of GBS in our study and with nearly equal distribution of cases between other seasons. Some studies have indicated a seasonal variation, including studies from China [Ho *et al.* 1995] and Brazil [Rocha *et al.* 2004] which demonstrated a peak incidence in summer and spring. Other studies showed no seasonal variation in GBS incidence [Tang *et al.* 2011].

Many authors believed that the mechanism of GBS involves an abnormal T-cell response precipitated by an infection [Agrawal *et al.* 2007]. Upper respiratory tract infection was the antecedent infection in most of our cases (67.7%), while acute gastroenteritis occurred in 25.8% of cases. It was reported that respiratory infections are the

Table 2. Comparison between children with Guillain–Barré syndrome treated with plasmapheresis and those with other modalities.

	Group 1 Children treated with IVIG $n = 30$	Group 2 Children treated with plasmapheresis $n = 32$	p value
Mean age ± SD	8.0 ± 3.8	8.2 ± 3.9	NS
Sex:			
Female	18	18	NS
Male	12	14	
Duration of hospitalization (days) Mean ± SD	29.4 ± 14.7	15.7 ± 8	$p < 0.01$*
Required mechanical ventilation	20	4	$p < 0.001$*
Outcome at 6 months :			
Complete recovery	7	19	$p < 0.001$*
Residual deficit	17	7	$p < 0.01$*
Death	6	6	NS

* Significant values.
IVIG, intravenous immunoglobulin; NS, not significant; SD, standard deviation.

commonest antecedent infection, occurring in about 40–70% of cases, while 7–20% are gastrointestinal infections [McGrogan *et al.* 2009; Tang *et al.* 2011]. Most of the infections occurred within a month before the onset of the disease [McGrogan *et al.* 2009; Tang *et al.* 2011].

Many antecedent infections have been identified in patients with GBS. *Campylobacter jejuni*, *Mycoplasma pneumoniae* and *Haemophilus influenzae* are frequently found. Cytomegalovirus, Epstein–Barr virus, influenza virus, herpes simplex virus, West Nile virus and human immunodeficiency virus (HIV) have also been found in patients with GBS [Nicolson and Haier, 2010, Meena *et al.* 2011]. Previous investigations reported serological evidence of *C. jejuni* in patients with GBS [Taylor *et al.* 1998]; another study [Gregson *et al.* 1998] found anti-ganglioside GM_1 antibodies that cross-reacted with *C. jejuni* liposaccharide isolates. In India, Gorthi and colleagues reported that 35% of GBS patients had serological evidence of *C. jejuni* and 50% had *M. pneumoniae* infections; moreover, a third of cases showed evidence of both infections [Gorthi *et al.* 2006]. In Japan, Mori and colleagues found that 13% of GBS patients had antibodies against *Haemophilus influenzae* [Mori *et al.* 2000]. Autoantibodies stimulated by infections found in GBS patients can cross-react with nerve cell gangliosides and these are thought to be important in the pathogenesis of GBS [Nicolson and Haier, 2010; Meena *et al.* 2011]. No studies have reported any relationship between treatment modalities and the type of antecedent infections. Further studies are needed to clarify that point. Unfortunately, tests to identify these infective agents as testing for antibodies of *C. jejuni*, cytomegalovirus and Epstein–Barr virus and stool cultures were not routinely performed in GBS patients at our center.

Our findings showed that AIDP was the most common diagnosed subtype by electrophysiological studies in 40 patients (64.5%) compared with AMAN (13%), AMASN (9.5%) and MFS (6.5%). Our results are consistent with other studies from North America and Europe as most GBS children appear to have AIDP [McGrogan *et al.* 2009; Tang *et al.* 2011]. However, the AMAN pattern was the predominant underlying subtype in China, Japan, and Central and South America [McGrogan *et al.* 2009; Tang *et al.* 2011]. This different figure supports the large variations in the incidence of different types of GBS which may be related to seasonal or genetic factors with no support studies explaining this difference until now [McGrogan *et al.* 2009].

Mechanical ventilation was used in 24 patients (38.7%) cases, of whom nine died on the machine mostly due to complications such as pneumonia and septicemia. It was reported that childhood GBS in about a third of all patients needed ventilatory support for respiratory muscle paralysis

and about 10% of the patients died of the disease and its complications [Koul and Alfutaisi, 2008]. The use of mechanical ventilation in our cases is recorded in a higher percentage than mentioned in many studies [Koul and Alfutaisi, 2008; Tang *et al.* 2011]. The high ratio of death between cases connected to mechanical ventilation in our study may be explained by the fact that when most of the cases were referred to our hospital, which is the only tertiary care unit in Upper Egypt, they had complications or the child had become in need for mechanical ventilation.

As regards the evaluation of treatment policy in our hospital, we found that the mean duration of hospital stay and the need for mechanical ventilation in patients treated with plasmapheresis were significantly lower than in cases treated with IVIG; this reduced the cost of hospitalization and intensive care unit (ICU) care in these patients. In addition, complete recovery occurred after 6 months and less residual defects were recorded as being statistically significant in children treated with plasmapheresis than the other group. As regards age and sex, there was no significant difference detected between different groups. Our results are supported by some previous studies that recorded a significant decrease in duration of hospital stay and shorter mechanical ventilation duration which compensate for the cost of plasmapheresis; better secondary outcomes were also achieved [McGrogan *et al.* 2009]. However, some studies suggested that patients who received IVIG treatment had more improvement than those with plasmapheresis [van der Meché *et al.* 1992; Kuwabara *et al.* 2001]. Finally, no significant difference between the two treatments has been shown by other researchers [Diener *et al.* 2001; Nomura *et al.* 2001].

Conclusion

GBS is not uncommon in children in our community, with AIDP being the most prevalent type. Most cases are preceded by upper respiratory tract infection. Plasmapheresis may reduce the duration of hospital stay and hasten the recovery of children with GBS.

Study limitations

As a retrospective study, the data from the cases were not completely available. The small number of cases also made our comparison statistics not valuable enough as significant results.

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Conflict of Interest Statement

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