LETTER TO THE EDITOR

ACQUIRED PERIPHERAL NEUROPATHY: A REPORT ON 20 CHILDREN

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Received January 12, 2012 – Accepted March 15, 2012

Guillain–Barré syndrome (GBS) is an inflammatory polyneuropathy characterized by acute onset, rapid progression, symmetric muscular weakness, pain, and paresthesias. The incidence of GBS in the pediatric age group is 0.8 cases per 100,000; 50%-70% of the cases are preceded by respiratory or gastrointestinal infectious episodes or vaccination. The etiopathogenesis of GBS has been hypothesized to involve a direct immune-mediated mechanism against the peripheral nerves. A series of 20 patients managed in the Department of Pediatrics of the University of Catania between 2003 and 2011 and evaluated according to epidemiologic, clinical, and therapeutic features is reported.

Guillain–Barré syndrome (GBS) is an inflammatory polyneuropathy characterized by an acute onset, rapid progression, symmetric muscular weakness, unstable ambulation, and hypo- or a-reflexia. The weakness in the distal musculature subsequently evolves into flaccid paralysis with involvement of the proximal muscles, and sometimes with caudo-cranial progression and involvement of the respiratory muscles and respiratory insufficiency (1, 2). Distal paresthesias and pain to the lower extremities and the trunk are common; less frequently there is involvement of the cranial nerves (1). The syndrome is preceded in 50%-70% of the cases by respiratory or gastrointestinal infectious episodes, or less frequently by vaccination, and the clinical features reach a peak 1-2 weeks after onset (1, 2).

The diagnosis is made on the basis of neurologic features, cerebrospinal fluid (CSF) and electrophysiologic findings. A relevant diagnostic element is the ratio of elevated CSF protein with no pleocytosis. Albumin-cytologic dissociation is present in approximately 80% of the patients and does not appear to be correlated with the severity of the illness (3, 4). Nerve conduction velocity (NCV) studies and electromyography (EMG) may be useful. Particular interest has recently focused on the role of gangliosides and anti-ganglioside autoantibodies in many cases of GBS (4).

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 20 patients who met the diagnostic criteria for classic GBS (5), ranging in age from 2-14 years, who were admitted to the Department of Pediatrics of the University of Catania between January 2003 and January 2011.

Key words: acute peripheral neuropathy, inflammatory polyneuropathy, childhood

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0394-6320 (2012)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

We considered the events preceding the onset of the neurologic symptoms, age, gender, month of onset, preceding events, clinical features, score during the course of the disease, treatment, and relapses. We evaluated the course of the disease in the short- (1-2 weeks), mid- (2-4 weeks), and long-term (6 months).

Motor and sensory nerve conduction velocity (NCV), performed with an electromyography examination (EMG) of the extremities, and Cerebrospinal fluid (CSF) examination were carried out on 20 patients.

We tested the serum and CSF antibodies of the principal neurotropic agents, such as cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), *Mycoplasma pneumoniae, Borrelia burgdorferi*, enterovirus, adenovirus, and parvovirus B19, as well as anti-ganglioside antibodies. In 9 patients, the presence of viral nucleic acids of HSV, EBV, CMV, enterovirus, adenovirus, and parvovirus B19 in serum and/or CSF was determined by polymerase chain reaction (PCR). Eighteen patients underwent brain and spine magnetic resonance imaging (MRI).

RESULTS

Of the 20 patients, 13 were male and 7 were female. The patient age ranged from 2-14 years, with an average age of 7.2 years. The seasonal incidence showed a peak in the warmest months of the year (spring-summer) with 15 of 20 patients (75%) diagnosed with GBS between April and August.

In 17 patients (85%), an infectious episode preceded the onset of the neurologic symptoms, usually within the 1 or 2 preceding weeks, as follows: upper respiratory tract infections, 14 patients (70%); febrile gastroenteritis, 2 patients (10%); and chickenpox, 1 patient (5%). No preceding events were demonstrated in 3 patients. One patient, at the age of 3 years, was diagnosed with acute lymphoblastic leukemia (ALL) and treated according to the specific chemotherapeutic protocol, and was taken off therapy from 7 years of age.

The most frequent presenting symptom (20 of 20 patients) was weakness of the lower extremities, accompanied by instability in walking. At the peak of disease severity, reached in 1-2 weeks in 80% of the patients, all the patients lost the ability to walk without support. Only one patient had initially severe ataxia. Paresthesias were present in 9 patients (45%) in the lower extremities and sometimes located in the pelvis and the distal aspects of the upper extremities. Nine patients (45%) had involvement of the cranial nerves, with dysarthria and/or dysphagia in 6 (30%), facial paralysis in 5 (25%), palpebral ptosis in 5 (25%), and diplopia in 2 (10%). In 4 patients (20%), the involvement of the cranial nerves had been present from the onset of the illness, together with muscular weakness.

All the patients became hypo or a-reflexic, and one (5%) also presented with involvement of the autonomous nervous system and a crisis of perspiration or intense itch. Two patients (10%) had respiratory insufficiency and required resuscitation maneuvers in the intensive care unit; in particular, one of them had paralysis of the right thoracic diaphragm and broncoscopic removal of a large mucous plug was performed. The average disability score at the nadir was 3.69 (range, 1-5). The results of laboratory, instrumental investigations, preceding diseases and etiology are reported in Table I.

The patients were administered the following therapeutic regimens: 9, IVIG only at a dose of 1 g/kg for 2 or 5 days; 3, IVIG and antiretroviral drug; 5, IVIG and steroids; 3, steroids only. The average disability score was determined at the nadir, and the improvement was quantified measuring the average time (in weeks) in which the clinical score increased at least by one degree. The subgroup treated only with IVIG lasted an average time lag of 1.85 weeks (range, 1-4 weeks) to reach a mild improvement and in all the cases treated with IVIG, with or without steroids, the average time lag for a mild improvement was < 2 weeks (range, 1-4 weeks).

The 20 patients were followed-up with assessments after 2-4 weeks and 6 months from the onset of symptoms. Sixteen patients (80%) completely recovered without any neurologic involvement within 6 months from the onset of symptoms; among these patients, one patient had a relapse 6 weeks after the first therapeutic cycle (IVIG) and was therefore started on a second cycle of IVIG, to which he moderately improved after 1 week and it was necessary to administer a third dose of IVIG after 4 weeks to achieve complete relief of the symptoms. Currently, after 24 months, the patient is in good health and does not show any neurologic symptoms. Two patients (10%) continue to have weakness in the lower extremities with mild instability in ambulation and partial facial paralysis

Table I. *Laboratory and instrumental investigations and preceding infection and etiology.*

Case	CSF examination	MRI scans (brain and spine)	GBS subtypes	Serum- and CSF-specific antibodies*	PCR investigations on blood and CSF**
1	CAD PC: 87.2	Normal	AIDP	Not detected	Not tested
2	CAD PC: 253	Normal	Unclassified	Not detected	Not tested
3	CAD PC: 81	Normal	Unclassified	Not detected	Not tested
4	CAD PC: 61	Normal	AIDP	Not detected	Not tested
5	Normal	Gadolinium enhancement of the cauda equina	AMSAN	Not detected	Not tested
6	CAD PC: 46	Normal	AIDP	Anti-CMV IgM (serum)	Not tested
7	CAD PC: 585	Not performed	AIDP	Anti-VZV IgM (serum)	Not tested
8	Not performed	Not performed	AIDP	Not detected (serum)	Not tested
9	Not performed	Not performed	AIDP	Not detected (serum)	Not tested
10	Increased Pressure	Normal	Unclassified	Not detected	Not tested
11	CAD PC: 98	Normal	AIDP	Not detected	Not tested
12	CAD PC : 61	Normal	AIDP	Not detected	Negative
13	CAD PC: 56	Normal	AIDP	Anti-CMV IgM (serum) Anti-Mycoplasma (serum)	CMV-DNA (CSF)
14	Increased pressure	Normal	AIDP	Not detected	Enterovirus-RNA (CSF)
15	CAD PC: 97	Gadolinium enhancement of the cauda equina	AIDP	Anti-parvovirus B19 (serum)	Parvovirus B19-DNA (serum and CSF)
16	CAD PC: 56	Normal	AMAN	Anti-CMV IgM (serum) Anti-mycoplasma (serum) Anti-chlamydia IgM, IgA (serum)	CMV-DNA (serum)
17	CAD PC: 65	Normal	AIDP	Anti-GM2 IgM (serum) Anti-CMV IgM (serum)	Negative
18	CAD PC: 279	Normal	AIDP	Anti-coxsackie IgG (serum) Anti-mycoplasma (serum)	Enterovirus-RNA (CSF)
19	CAD PC: 55	Gadolinium enhancement of the cauda equina	AIDP	Negative	Negative
20	CAD PC: 50	Normal	AIDP	Negative	Negative

**Included anti-ganglioside antibodies (CMV, HSV, VZV, EBV, Mycoplasma pneumoniae, Borrelia burgdorferi, Enterovirus, Adenovirus, Parvovirus B19)*
***Included: HSV, VZV, EBV, CMV, Enterovirus, Adenovirus, Parvovirus B19*
CAD:cytologic albumin dissociation

6 months after onset of symptoms. One patient, after a rapid but mild improvement with IVIG treatment, had a first relapse after 4 weeks, with a positive response to therapy with IVIG and a second relapse 3 months later, and was treated with the association of IVIG and steroids with good outcome.

DISCUSSION

GBS is an acquired inflammatory demyelinating polyradiculo-neuropathy with acute and/or subacute course, lymphocytic and macrophage infiltrates of the peripheral nerves and of nervous tracts, and myelin disruption. Acute inflammatory demyelinating polyneuropathy (AIDP) is the most frequent form of GBS: the neuropathy is demyelinating, mainly motor, and the prognosis favorable. AMAN, or Motor and sensory axonal neuropathy (AMSAN), is less frequent and the prognosis is usually good (1).

After eradication of polio, GBS is the most

frequent cause of acute flaccid paralysis in children, with an incidence that linearly increases with age, varying from 0.8/100.000 cases/year < 15 years of age until 4/100.000 cases/year in those > 75 years of age, with a risk in the male population 1.5 times higher than females (1). GBS and related disorders are usually linked and subsequent to infectious diseases involving the upper respiratory tract and gastrointestinal tract. Also, vaccinations are reported to be causal events of GBS (5-7).

In our patients, a history of infections preceding the onset of neurologic symptoms was found in 17 patients (85%). In 8 patients, it was possible to identify a possible etiologic agent, as follows: CMV; *Mycoplasma pneumoniae*, enterovirus, and anti-parovirus B19, anti-Chlamydia, anti-Coxsackie virus, and chicken pox. These infectious agents are considered among the most frequent agents associated with GBS. In contrast, no cases of preceding vaccination have been found. Muscular weakness, the main clinical sign, affects the lower extremities with symmetric and bilateral involvement. Among our patients affected by classic GBS, 8 patients initially were only able to walk with support (40%), while the remaining could not walk. In 9 patients (45%), paresthesias were present. No patients presented with papilledema. Eighteen patients submitted to lumbar puncture; 15 patients (75%) had CAD. One patient was likely negative because the lumbar puncture was performed prematurely. The prognosis was good in 90% of the patients, with complete recovery in 2-6 months from the onset of symptoms. In 2 patients, relapses were reported.

From the electrophysiologic findings a clear prevalence of AIDP emerged: as well as the typical signs of demyelization, a few of these children also showed signs of axonal damage, represented by an associated reduction of the CMAP.

Only 2 patients (10%) had a relapse. One of them presented with a first episode of GBS, followed by an early relapse at 6 weeks, before complete recovery which was reached after 1 month. Both of the episodes had the clinical, electrophysiologic, and CSF characteristics of classical AIDP and were treated with IVIG at the dosage of 1g/kg/day for 2 days. The relapse occurred with clinical features more severe than the first episode, showing only signs of improvement after 5 weeks from the second cycle of IVIG (reduction of the clinical score of one point). A third lumbar puncture, performed 6 weeks from the onset and 4 weeks from the relapse, showed a persistent elevation in the albumin-cytologic dissociation. At this point, a third cycle of IVIG was administered at dosing 400mg/kg/day for 5 days, with progressive improvement of the clinical features and attainment of a complete recovery within 4 weeks from the last therapeutic cycle. Early relapse (within the first month from recovery) is considered an uncommon event. This patient had been affected by acute T-lymphoblastic keukemia 10 years previously and treated with vincristine, which caused acute neurotoxicity. It is possible that the vincristine treatment may have predisposed the relapse in our patient.

One patient had two relapses, the first after 4 weeks from the therapy and the second after 3 months; in both cases there was a rapid response to IVIG therapy. Nevertheless, for the onset of an electromyographic pattern of muscular neurogenic features, the patient is currently being followed-up to exclude a possible evolution toward a chronic idiopathic demyielinating polineuropathy (CIDP).

Our data confirm that GBS in the pediatric age group has a more favorable long-term course in comparison to the adult age group, characterized by a higher rate of disability and mortality (10% *vs* 20% and 1-2% *vs* 4-15% respectively) (4). More than 90% of children completely recover within 1-4 months from the onset and only a small percentage of patients develop a mild residual weakness (1, 2).

In contrast to adults, we do not have high number of pediatric patient studies regarding the effectiveness of therapeutic options. The only clinical randomized study involving the results of IVIG in pediatric GBS was conducted by Korinthenberg et al. in 2005 (4) on a small number of patients (52 children). Nevertheless, the data confirm what has been documented by studies performed on the adult population; specifically, treatment with IVIG performed before the loss of ambulation does not improve the gravity of the clinical features, but yields a more rapid recovery. Moreover, in cases in which treatment was initiated after the loss of ambulation, there was not a meaningful difference in the number of days in effectiveness when the overall dose of 2g/kg of IVIG was administered in 2 or 5 days, with an apparent greater frequency of early relapses

after the shorter therapeutic regimen. However, many authors agree that the days of treatment have to be evaluated in relationship to the clinical situation of the patient (8-11).

In children with GBS, the clinical relapse and the possible outcome do not appear to be correlated with those factors that would negatively influence the prognosis in the adult population. In fact, the rapidity of onset of symptoms, the severity of the clinical features at the time of diagnosis, and the disability and prevailing axonal involvement (10, 11) do not interfere with favorable results in children.

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