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GUILLAIN-BARRÉ SYNDROME AND ATYPICAL VARIANTS IN CHILDREN: A CROATIAN SINGLE TERTIARY CENTER EXPERIENCE

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Aim: To depict heterogeneous clinical features of atypical Guillain-Barré syndrome (GBS) variants overlapping between different GBS types and subtypes. *Methods:* Retrospective analysis of data comprising neurological features, cerebrospinal fluid (CSF) analysis, ganglioside antibody testing results, electromyography (EMG) findings, brain and spinal magnetic resonance imaging (MRI) in all pediatric patients with GBS treated during a 10-year period at a tertiary center. *Results:* Twenty-three children were treated for GBS during the study period. Atypical variants were found in five patients and included bifacial and severe pharyngocervicobrachial weakness of descending type, sixth nerve lesion accompanied with lower extremity paresthesias, sensory atactic neuropathy and facial nerve lesion, acute ptosis with mydriasis and incomplete Miller Fisher syndrome, and bilateral facial nerve paresis (one case each). Initial CSF analysis revealed mostly normal protein level in atypical variants. MRI evaluation was normal in all atypical variants except for enhancement of the cervical nerve roots in a patient with pharyngocervicobrachial subtype. EMG performed in the first two weeks showed prolonged distal latency and proximal conduction block in 3/5 patients, in elicitable nerves and axonal loss on upper extremities in a patient with pharyngocervicobrachial subtype, and absent F-waves and neural potentials in 3/5 patients. Slight decrease of motor conduction velocity was present in 2/5 patients in distal nerve segments. Antiganglioside antibodies were positive in 4/5 patients. *Conclusion:* Clinical manifestations of GBS are very variable, whereas atypical variants/overlaps are not so uncommon. This study supports the proposed hypothesis of continuous spectrum of GBS requiring reconsideration of the existing diagnostic criteria for classic GBS in pediatric population supported by recently proposed (published) diagnostic guidelines.

Key words: Guillain-Barré syndrome, polyneuropathy, atypical, children

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INTRODUCTION

Guillain-Barré syndrome (GBS) is the most common acute peripheral neuropathy in children. Still, its pathogenesis is not yet completely understood, with a broad spectrum of signs and symptoms, nadir within four weeks from onset, and recovery in a few weeks (1,2). The incidence of GBS in children varies between 0.4 and 1.3/100,000 *per* year, being more common in children aged 10-18 years (1-5). GBS is an immune-mediated postinfectious heterogeneous disorder which encompasses different typical (classic) and atypical, localized and incomplete forms indicating a spectrum of disease (6-9). Classic GBS includes acute axonal motor neuropathy (AMAN), acute axonal motor and sensory neuropathy (AMSAN) if additionally sensory fibers are affected, and acute inflammatory demyelinating polyneuropathy (AIDP). Classic variants are characterized by certain clinical features such as history of antecedent infection (respiratory or gastrointestinal), monophasic disease course and rapidly progressive symmetric, bilateral limb weakness with areflexia or hyporeflexia accompanied with a typical finding of cerebrospinal fluid (CSF) albumin cytologic dissociation (raised protein concentration, normal cell count, although normal protein content does not

exclude GBS), positive antiganglioside antibodies, and neurophysiological evidence for axonal and/or demyelinating neuropathy. All mentioned above support the diagnosis of GBS, but are not specific, therefore should not be relied upon, especially at the inception of symptoms (7,10-12). Electrophysiologic abnormalities are often delayed, thus repeated neurophysiologic testing is sometimes needed. As the first electrophysiologic abnormalities occur, i.e. prolongation of F wave and distal latency, repeated testing is not mandatory (4,13). Therefore, diagnosis of GBS is initially dependent on unspecific clinical manifestations including pain, numbness, paresthesias, and ataxia (14). Involvement of respiratory muscles (respiratory failure in up to 20%) or cranial nerves (in 30%-50% of cases) may develop, as well as hyperreflexia or normal reflexes in 10% of cases (4,7,14). Unusual presentations and atypical variants lead to misdiagnosis and delayed management, thus GBS remains a challenge for practitioners (15). Differential diagnosis is rather broad. Certain mimics of acute flaccid paraparesis complicate diagnosis, especially of atypical/incomplete GBS variants due to similarity to the overlapping syndrome (7,8,16). Therefore, neuroimaging plays an important role in diagnostic pathway by excluding other causes of acute neuromuscular paralysis (7). Even though the outcome is generally favorable with self-limitating course of the disease, autonomic system could be affected (cardiac arrythmias, respiratory insufficiency) leading to lethal outcome in 5%-13% of pediatric cases (17). Atypical variants are more likely to have rapid deterioration with increasing severity of disability scores (mean and at nadir), cranial nerve involvement, dysautonomia (Erasmus GBS Respiratory insufficiency score, urinary incontinence) with relative preservation of muscle strength in the extremities (6,7,18-21). Furthermore, chronic demyelinating polyneuropathy (CIDP) may develop in 3%-5% of GBS patients. Therefore, early diagnosis and management is important for timely monitoring of complications and rational therapeutic approach including plasma exchange (PE), intravenous immunoglobulins (IVIG), and supportive measures (physiotherapy, analgesia due to neuropathic pain) (4,7,10,12,21). We conducted this study with the purpose to present clinical pattern and outcome in pediatric patients with GBS and atypical forms, treated in a Croatian tertiary center.

PATIENTS AND METHODS

This was a retrospective case-series single center study. Medical records of all patients with GBS treated from 2005 to 2014 in a pediatric tertiary center (Department of Pediatrics, Zagreb University Hospital Centre) were evaluated. Patients included in the study met diagnostic criteria for GBS (7). Patients with positive medical history of previous neurological signs and symptoms and abnormal psychomotor development were excluded from the study. Pediatric neurologist reviewed medical files of the patients. The following data were extracted from medical files: age, gender, neurological features, CSF findings, ganglioside antibody studies, electromyography (EMG), brain and spinal magnetic resonance imaging (MRI). Serum samples were analyzed for possible causative bacterial (*Campylobacter jejuni*, *Borrelia burgdorferi* and *Mycoplasma pneumoniae*) or viral etiology (Epstein-Barr virus (EBV), cytomegalovirus (CMV)). The GBS classic subtypes or variants according to electroneurographic studies were documented as AMAN and AIDP. EMG was performed by expert pediatric neurologist with concentric needles; motor fibers were studied by needle recording and surface electrode stimulation, while sensory fibers were studied by orthodromic recording from wrist and ankle. Compound muscle action potential amplitude (CMAP), motor nerve conduction velocity (MNCV), neural potential amplitude, sensory nerve conduction velocity (SNCV), F-wave latency, distal latency (DL) and proximal to distal CMAP (P/D) ratio were measured. Recruitment pattern and spontaneous activity were recorded by needle electrode in small hand muscles and extensor brevis muscles. Motor conduction studies were polysegmentally determined and were performed on peroneal, ulnar and median nerves. In each patient, three to four nerves were examined. Normal values and electrophysiologic criteria for demyelination and axonal degeneration were referred to accepted and proposed ones (14). Children's surface body temperature was between 36.9 °C and 37.0 °C axillary. Serum IgG and IgM anti-ganglioside antibodies (anti-GM1, anti-GD1a, anti-GD1b, anti-GQ1b) were measured by enzyme-linked immunosorbent assay (ELISA) (Gan-gliocombi, Bühlmann Laboratories AG, Basel, Switzerland). GBS disability scale was used to assess the severity of disease (18).

RESULTS

Overall, 23 patients with GBS were treated during the ten-year period (Table 1), 18 of them with typical GBS (12 male; age 2 to 15 years). Atypical variants were found in 5 patients (4 male; age 2 to 10 years) and included bifacial and severe pharyngocervicobrachial weakness of descending type, sixth nerve lesion accompanied with lower extremity paresthesias, sensory atactic neuropathy accompanied by facial nerve lesion, acute ptosis with mydriasis and incomplete Miller Fisher syndrome, and bilateral paresis of facial nerve (one case each). Detailed patient characteristics and evaluation is shown in Table 1. Representative cases of atypical variants are presented below.

Case 1
A 9-year-old boy presented with weakness of upper extremities and swallowing. Bilateral facial nerve and unilateral abducent nerve lesion, plegia of upper limbs, hyperreflexia, neck weakness and hyperhidrosis were observed. On day 8 of disease, the patient developed lower limb paresis and weak cough reflex. GBS disability score was categorized as bedridden or chair bound (modified Rankin score 4). His condition deteriorated during the third week of disease. Lower limbs recovered first after four weeks.

Case 2
A 6-year-old boy presented with right eye pain and diplopia. Unilateral lesion of abducent nerve, left leg weakness, bilateral hyperreflexia and paresthesias with positive plantar extensor response on the left foot were observed.

Case 3
A 10-year-old boy presented with progressive generalized ataxia, dizziness and unstable gait. Limb paresthesias and mild bilateral facial nerve lesion, distal limb hypesthesia and decreased pain sensitivity were observed. He was unstable on Romberg test as well. GBS disability score was 4.

Case 4
A 5-year-old boy was admitted due to sudden onset of ophthalmoparesis accompanied by mydriasis and low intensity headache. Anisocoria, ptosis and nystagmus on the right eye were noticed. GBS disability score was 2.

Case 5
A 2-year-old girl presented with bilateral intermittent ptosis on both eyes, asymmetric grimacing, and decreased tendon reflexes on both upper and lower extremities. GBS disability score was 1.

Table 1. *Demographics, clinical profile, evaluation and treatment of studied patients*

Patients treated for GBS (N=23)	Typical („classic") GBS (N=18)	Atypical GBS/GBS variants ("chameleons") (N=5)				
		PCB /GBS – LS	MFS - IF	SAN/MFS - IF	MFS - IF	GBS - LS
Age (years)	Median 6.5 (range 2 -15)	9	6	10	5	2
Gender	12 male, 6 female	Male	Male	Male	Male	Female
Antecedent infection	Respiratory 6/18- 2 *M. pneumoniae*, 1 VZV IgM positive in CSF gastrointestinal 3/18 - 1 *Campylobacter* spp.	Respiratory (mild rhinitis 7 days before); nontypable *N.meningitidis* in tracheal aspirate in week 3	Respiratory	Respiratory	Respiratory	Respiratory infection treated with amoxicillin and clavulanate two weeks before
Bilateral weakness	Ascending type 15/18; cranial nerve involvement 2/18	Upper extremities with generalization in second week	Asymmetric	No	In addition to anisocoria andptosis	Bilateral paresis of facial nerve and ptosis
Deep tendon reflex	Areflexia 10/18; hyporeflexia 3/18; hyperreflexia 4/18; nomal reflexes 1/18	Decreased	Hyperreflexia	Normal	Decreased, positive plantar extensor response	Decreased
Nadir (days)	Median 7 (range 3-28)	6	2	10	8	10
Protein content CSF analysis (g/L)	Median 0.59 (range 0.35-1.98)	Initial normal; Repeated 3rd week 0.39, next 2.2	Normal	Normal	Normal	0.39
EMG findings	AIDP 11/18; AMAN 4/18; both axonal and demyelinating (equivocal) 2/18	AMAN; inelicitable nerves (musculocutaneous nerve) or very low proxymal CMAP in ulnar nerve and median nerve (0.2-0.4 mV) on upper extremities, absent F waves	CMAP 44 m/s; absent F-waves; absent SNAP; prolonged DL; equivocal	Absent SNAPs; absent F-waves; decreased SNCV; prolonged DL	low distal CMAP; F- wave latency; prolonged DL; equivocal	AIDP; decreased MNCV 36 m/s
Antiganglioside antibodies	Positive in 10/12 (8 had positive anti-GM1; 5 had multiple antibodies, 4 had anti-GD1b, anti-GQ1b IgG). Highly specific MFS antibodies were negative in all patients	Anti-GM1, anti-GD1a, anti-GD1b	Anti-GM1	Anti-GM1,GD1a, anti-GD1b	Negative	Anti-GD1b
Brain and spinal cord MRI	-	Initial normal; repeated 4 weeks after disease showed enhancement of cervical nerve roots	Normal	Normal	Normal	Normal
Therapy	IVIG 10/18; IVIG and steroids 4/18; steroids exclusively 1/18, spontaneous recovery 1/18, NA 2/18	PE 5 courses, IVIG 2 courses; spontaneous recovery	IVIG, early recovery	IVIG and steroids, complete recovery	Complete spontaneous recovery after 3 weeks	Early spontaneous recovery

AIDP = acute inflammatory demyelinating polyneuropathy; AMAN = acute axonal motor neuropathy; anti-GM1/anti-GD1a/anti-GD1b/anti-GQ1b = antiganglioside antibodies; CMAP = compound muscle action potential amplitude; CSF = cerebrospinal fluid; DL = distal latency; EMG = electromyography; GBS = Guillain-Barré syndrome; IF = incomplete form; IVIG = intravenous immunoglobulin; LS = localized subtype; MFS = Miller Fisher syndrome; MNCV = motor nerve conduction velocity; MRI = magnetic reasonance imaging; PCB = pharyngo-cervicobrachial; PE = plasma exchange; SAN = sensory ataxic neuropathy; SNCV = sensory nerve conduction velocity; SNAP = sensory nerv action potential; VZV = varicella zoster virus

DISCUSSION

We observed significant clinical variability and serologic heterogeneity of GBS and its atypical variants, which supported the proposed hypothesis of continuous spectrum of GBS and reconsideration of the existing diagnostic criteria for classic GBS in pediatric population (7,9,13). Literature data on atypical GBS in children are scarce. Our study has demonstrated that atypical variants are not uncommon as we thought, similar to a recent small study (22). Our cohort with typical GBS resembled other populations with Caucasian predominance (Europe, United States, Iran, Japan), showing male predominance and AIDP occcurence as the most common neurophysiologic presentation (17,19,23). Antecedent infection was documented in all patients with atypical variants and half of patients with typical GBS, whereas in the literature it rates up to 60%-70% (4,9,24).The majority of infections remained etiologically unproven. GBS is preceded by *Campylobacter* (most frequently), *M. pneumoniae*, CMV, EBV, Zika or influenza virus infection, and recently SARS-Cov-2 infection (13,25-28). Although GBS has been reported as a postimmunization event, vaccination as a provocative factor in our patients was excluded. GBS following previous immunization (rabies, H1N1 vaccine) is rare (1.6 cases *per* 10^6 vaccinations) and probably it is temporally coincidental rather than causative (13,29-31). In one of our study patients, *Neisseria* was isolated from the upper respiratory tract specimen. Currently, there is insufficient data to confirm a link between GBS and non-typable *Neisseria meningitidis* carrier state (6). Recently, a rare case of MFS after *Neisseria meningitidis* has been reported (32). Nadir is reported to be reached at one week, as we also found in our survey, similar in atypical and typical GBS variants (33).

Antiganglioside antibodies become positive early in the course of disease and are found in around one-third of GBS patients (34). In our survey, around half of the patients with typical GBS and atypical variants had positive antiganglioside antibodies (most commonly anti-GM1). Several types of antibodies are more frequently observed in some GBS variants (13). Up to half of the patients with pharyngocervicobrachial GBS subtype (PCB) have positive IgG anti-GT1a antibodies which often cross-react with GQ1b, whereas patients with Miller Fisher syndrome (MFS) carry mostly IgG anti-GQ1b antibodies which cross-react with GT1a (7). Serologic heterogeneity suggests continuous spectrum of GBS and shows more pathogenetic than clinical notability in the evaluation of GBS patients. Also, antiganglioside antibodies could be involved in a variety of other diseases including other neurological diseases (35). CSF findings usually do not differ between typical GBS and its variants, as found in our survey (36). CSF analysis is normal in up to 50% of patients with GBS during the first week of disease, and shows an increased protein level in most cases when obtained one week after the onset of weakness (1,13). Neuroimaging studies are not routinely used. However, due to unusual presentation, all of our patients with atypical GBS underwent brain MRI scans and were normal except for one patient with enhancement of the cervical nerve roots, which is not specific to GBS and occurs in other inflammatory neuropathies (neuroborreliosis) and even in neurodegenerative disorders (33,37,38).

Short-term outcomes were favorable in typical and atypical variants, leading to achievement of full recovery in most patients. Nonlethal outcome was found. The patient described as case 1 showed signs of autonomic dysfunction which may be life-threatening. Swallowing difficulties, low and nasal voice, neck muscle weakness and low blood oxygen might be early signs of respiratory insufficiency. In case of dysphagia and weak cough, intubation is recommended (4). Posterior reversible encephalopathy syndrome and priapism have been rarely described in adolescents with GBS, being more frequent in adults (39). The clinical course was more severe and prolonged in the patient with descending type of PCB. On the contrary, two patients (age 2 and 5 years) with atypical variant recovered spontaneously due to mild form of disease (GBS disability score 1 and 2). Although IVIG and PE have been reported as equally effective, IVIG is preferred due to practical reasons, and thus more frequently used in case of the loss of ability to walk unassisted (modified Rankin score 4). Corticosteroids are indicated and efficient in up to 80% of patients with disease progression over week 4 toward week 8. Further clinical course could be complicated by development of CIDP (when detection of neurofascin 155 IgG4 antibodies against paranodal proteins is considerable), or by the occurrence of disease fluctuation/clinical impairments related to treatment two weeks after IVIG (40,41).

Previous clinical-serologic studies indicate significant overlap between GBS and MFS variants within the GBS spectrum (7,42). In our study, three patients with atypical GBS showed signs of incomplete MFS forms, whereas one patient showed overlap with PCB, as reported by other authors (26). PCB may have fulminant presentation with tetraplegia and altered consciousness overlapping with brainstem encephalitis or with dysphagia and nasal speech with positive anti-GT1a antibodies as incomplete PCB form. The pattern of neuromuscular weakness in patients with botulism also resembles one in MFS and PCB, possibly because of molecular target carbohydrate residues on gangliosides which serve as receptor for botulinum toxin.

There is an increasing number of reported overlaps between GBS and acute disseminated encephalomyelitis, however, not present in our cohort (28,43). Despite some study limitations (modest sample size, single-center experience, retrospective nature of the present study), we believe that our survey contributes to the respective literature by showing interesting insights into GBS and its atypical variants in children.

CONCLUSION

Clinical spectrum of GBS variants might be more common than previously thought, as they tend to be frequently misdiagnosed. The diagnosis is based on clinical history, examination and investigation of evolved clinical/neurological status, which is heterogeneous. As the spectrum of GBS presents with highly variable, atypical and incomplete clinical manifestations, the existing diagnostic criteria for classic GBS in pediatric population should be reconsidered, as supported by the recently proposed and published diagnostic guidelines. Accurate diagnosis is important for rational and timely treatment.

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S A Ž E T A K

GUILLAIN-BARRÉOV SINDROM I ATIPIČNE VARIJANTE U DJECE: ISKUSTVO TERCIJARNOG CENTRA U REPUBLICI HRVATSKOJ

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Cilj: Prikazati heterogene kliničke značajke inačica atipičnog Guillain-Barréova sindroma (GBS) te preklapanje između različitih GBS tipova i podtipova. ***Metode:*** Retrospektivna analiza podataka koji uključuju neurološke značajke, analizu cerebrospinalne tekućine, rezultate ispitivanja antigangliozidnih protutijela, nalaze elektromiografije (EMG), magnetsku rezonanciju mozga i kralježnice (MRI), svih pedijatrijskih bolesnika liječenih zbog GBS-a u tercijarnom centru u 10-godišnjem razdoblju. ***Rezultati:*** Liječeno je ukupno 23 djece zbog GBS-a. Atipične varijante pronađene su u pet bolesnika i uključivale su bifacijalnu i tešku faringo-cerviko-brahijalnu silaznu slabost, leziju šestog živca popraćenu parestezijama donjih ekstremiteta, senzoričku ataktičnu neuropatiju i leziju facijalnog živca, akutnu ptozu s midrijazom i nepotpunim Miller Fisherovim sindromom te bilateralnu parezu facijalnog živca (sve po jedan slučaj). Inicijalna analiza cerebrospinalne tekućine pokazala je većinom normalnu razinu proteina. Radiološka obrada je bila uredna u svim atipičnim varijantama osim u bolesnika s faringo-cerviko-brahijalnom varijantom gdje je nađen pojačan signal u korijenu živaca cervikalne kralježnice. EMG je prva dva tjedna bolesti pokazao produljenu distalnu latenciju i proksimalni blok u 3/5 bolesnika, gubitak aksona na gornjim ekstremitetima u bolesnika s faringo-cerviko-brahijalnim podtipom te odsutne F-valove i neuronske potencijale u 3/5 bolesnika. Blago smanjenje brzine provođenja u distalnim segmentima živaca bilo je prisutno u 2/5 bolesnika. Antigangliozidna protutijela bila su pozitivna u 4/5 bolesnika. ***Zaključak:*** Kliničke manifestacije GBS-a vrlo su varijabilne, a atipične varijante/preklapanja nisu rijetke. Ovo istraživanje podupire predloženu hipotezu o kontinuiranom spektru GBS-a koja zahtijeva preispitivanje postojećih dijagnostičkih kriterija za klasični GBS u dječjoj populaciji te uključenje kriterija za varijante GBS-a koji su nedavno predloženi i objavljeni.

Ključne riječi: Guillain-Barréov sindrom, polineuropatija, atipične varijante, djeca