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Research Paper

Clinical Characteristics and Prognostic Factors of Anti-GM1 Antibody-Positive Guillain-Barré Syndrome Spectrum Disorders in Children

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ABSTRACT

Background: The study aimed to analyze the clinical features and risk factors for poor prognosis of Guillain-Barré syndrome (GBS) spectrum disorders in children positive for anti-tetrahexose monosialoganglioside (GM1) antibody.
Methods: We collected data for children with anti-GM1 antibody-positive GBS spectrum disorders in Affiliated Children's Hospital of Chongqing Medical University between July 2018 and March 2024; 1:1 matching was performed for combined anti-ganglioside or anti-sulfatide antibody. The patients underwent comparative clinical characterization to determine the antibody phenotype-clinical phenotype and to analyze the possible risk factors for the poor prognosis of the disorders.
Results: Thirty-seven pediatric patients were recruited. Anti-GM1 antibody-positive GBS spectrum disorders were preceded by a prodromal event (25 of 37, 67.6%). The first symptom was mainly limb weakness (20 of 37, 54.1%), which could be predominately accompanied by autonomic nerve involvement (21 of 37, 56.8%). Seven features showed statistically significant differences ($P < 0.05$) between the positive group and the negative one, including cranial nerve involvement, bulbar palsy, low lower limb muscle strength at discharge, axonal type of electrophysiological typing, and clinical typing of acute motor axonal neuropathy. The GBS disability scores at discharge and at one month after discharge were higher than those in the control group. The shorter time to peak (<7.5 days) was identified as an independent risk factor for poor short-term prognosis of the disorders.
Conclusions: Anti-GM1 antibody-positive GBS spectrum disorders have a relatively specific antibody phenotype-clinical phenotype. The shorter time to peak (<7.5 days) is an independent risk factor for poor short-term prognosis of the disorders in children.

Introduction

Guillain-Barré syndrome (GBS) in children is a spectrum of autoimmune disorders leading to damage to the central and/or peripheral nervous system resulting from autoimmune dysfunction. The etiology and pathogenesis of GBS are not fully understood and might be related to infections and cellular and humoral immune abnormalities. Clinical manifestations are diverse, including limb weakness, ataxia, autonomic dysfunction, cranial nerve involvement, sensory disturbances, diminished or hyperactive tendon reflexes, and impaired consciousness.[1]

In 1988, Ilyas et al.[2] detected anti-ganglioside antibody (AGA) in the sera of patients with GBS. In 1990, Yuki et al.[3] reported the association of acute motor axonal neuropathy with *Campylobacter jejuni* infection and anti-tetrahexose monosialoganglioside (GM1) antibodies, which linked *C. jejuni* infection with AGA for the first time. Subsequently, studies on the relationship between different serotypes of *C. jejuni*, different AGAs, and different clinical sites of

Ethics approval: This study was approved by the Research Ethics Committee of Children's Hospital of Chongqing Medical University (approved No.178.2024). The participant consent was approved to waive by the ethics committee.

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involvement in GBS were reported.[4-10] Ganglioside (GA) is a lipid molecule present in the cell membrane of neurons, which is involved in the normal functions of nerve cells, such as in neural differentiation and regeneration, brain development, and neuronal cell plasticity and repair.[11] GAs are often named according to the Svennerholm nomenclature[12] and categorized according to the number and location of their glycosyl-bound sialic acid molecules, with one molecule of sialic acid as monosialic acid ganglioside (GM) and two, three, and four molecules of sialic acid being categorized as GD, GT, and GQ, respectively. In addition, GM is classified into GM1, GM2, GM3, and GM4 according to the number and type of hexoses it contains. The specificity of GA tissue provides a cellular histologic basis for the diverse clinical manifestations of GBS subtypes.[11]

GM1 is preferentially exposed on the surface of myelinated fibers in the paraganglionic area; anti-GM1 antibodies are one of the most abundant GA antibodies in nerve membranes[13] and are associated with the pathogenesis of acute motor axonal neuropathy (AMAN) and acute inflammatory demyelinating polyneuropathy.[11] Anti-GM1 antibodies can induce complement-mediated disruption of voltage-gated sodium channels at the Ranvier node, thereby affecting nerve repair.[14] Patients with anti-GM1 IgG antibodies are more likely to have an AMAN-type phenotype and are often preceded by *C. jejuni* infection.[15] Studies have confirmed[16] that *C. jejuni* causes disease by producing anti-GM1 antibodies through a molecular mimic mechanism. Persistent high titers of anti-GM1 antibodies are associated with a poor clinical prognosis in GBS.[17] The detection rate of AGA in patients with GBS is 37%-78%,[18,19] and the positive rate of anti-GM1 antibody is 15%-42.4%.[17,18,20-23] There are currently no reports of anti-GM1 antibody positivity rates in pediatric patients with GBS.

In this study, we retrospectively analyzed the clinical data and follow-up results of 37 children with serum and/or cerebrospinal fluid anti-GM1 antibody-positive GBS spectrum disorders in the Children's Hospital of Chongqing Medical University between July 2018 and March 2024. We summarized the antibody-clinical phenotypic characteristics to explore the risk factors for poor prognosis and to provide a clinical basis for the diagnosis and treatment of this disease.

Methods

Inclusion criteria and exclusion criteria

Patients filtered according to the criteria in Table 1.

Peripheral neuropathy antibody screening methods

The screen was carried out using enzyme-linked immunosorbent assay method (Guangzhou KingMed Diagnostics Medical Research Institute, Guangzhou, China), employing a EUROBlot Master II fully automated immunoblotting instrument.[26]

Neurophysiological examination

The nerves examined included the bilateral tibial nerve, peroneal nerve, median nerve, ulnar nerve, radial nerve, and facial nerve in some children by a Keypoint workstation electromyography/evoked potentials instrument (Dantec, Moreton, UK).[27]

Disease severity assessment

The GBS Disability Score (GBS-DS)[28] was used to assess the severity of the disability. The children were assessed using GBS-DS scores on admission, at discharge, and at one month after discharge.

Prognostic evaluation

Short-term prognosis was categorized according to the GBS-DS score at one month after discharge. Children with poor short-term prognosis (GBS-DS score of 3-6) were followed up for more than six months, and a child with a GBS-DS score that remained $\geq$3 was considered to have poor long-term prognosis.

Data analysis

In this study, data were processed and analyzed using statistical software SPSS (version 27.0; IBM Corp., Armonk, NY, USA) and R (version 4.3.3) and graphing was carried out using R (4.3.3) and Origin (2021; Originlab, Northampton, MA, USA). Measurements were expressed as mean (S.D.) or median (interquartile range), counts as frequencies and percentages, and grades as component ratios.

(1) Clinical characterization: Using a 1:1 matching design,[29] children with GBS in the serum and/or cerebrospinal fluid anti-GM1 antibody-positive group were randomly matched to children with serum and/or cerebrospinal fluid peripheral neuropathy antibody-negative GBS. Children with serum and/or cerebrospinal fluid anti-GM1 antibody-positive

TABLE 1.
Inclusion Criteria and Exclusion Criteria

Inclusion Criteria	
Anti-GM1 antibody-positive group	Anti-GM1 antibody-negative group
(1) Guideline for the diagnosis and treatment of GBS spectrum disorders[24]; the electrophysiological typing criteria of GBS.[25]	(1) Guideline for the diagnosis and treatment of GBS spectrum disorders[24]; the electrophysiological typing criteria of GBS.[25]
(2) Positive serum and/or cerebrospinal fluid for anti-GM1 antibodies.	(2) Negative serum and cerebrospinal fluid for anti-GM1 bodies.
(3) Follow-up was $\geq$1 month after discharge.	(3) Combined anti-ganglioside antibodies and/or anti-sulfatide antibody were the same as in the case group.
(4) Informed consent was obtained from the parents of the children participating in this study.	(4) Follow-up was $\geq$1 month after discharge.
	(5) Informed consent was obtained from the parents of the children participating in this study.
Exclusion criteria	
The possibility of comorbidities with other central nervous system disorders cannot be excluded.	

Abbreviations:
GBS = Guillain-Barré syndrome
GM1 = Tetrahexose monosialoganglioside

combined with other AGA and/or anti-sulfatide antibody-positive GBS were randomly matched to anti-GM1 antibody-negative combined with the same AGA and/or anti-sulfatide antibody-positive GBS. Measurement data were analyzed using a paired *t* test or rank-sum test. The paired *t* test was used for measurements where the difference between the two groups met normality, and a paired Wilcoxon rank-sum test was used for measurements where the difference between the two groups did not meet normality. A paired chi-squared test (McNemar method) was used for count data, and a paired Wilcoxon rank-sum test was used for the ranked data.

(2) Analysis of risk factors for poor prognosis: In response to the data with missing values and a serious imbalance between the two types of (prognostic) data, we perfected missing-value filling and oversampling techniques to correct for this, using the K-nearest neighbor[30] and Synthetic Minority Over-sampling Technique,[31] respectively. The random forest method was used for classification forecasting to improve the accuracy and stability of the model.[32] Least absolute shrinkage and selection operator (LASSO) logistic regression[33] was used for variable selection, and the variables selected by LASSO logistic regression were again included in the binary logistics stepwise forward regression analysis. Then, the variables selected by binary logistic regression and the GBS-DS scores at one month after discharge were used to construct a nomogram prediction model[34] and the receiver operating characteristic curve and the area under the curve[35] were used to assess the predictive performance of the variables on the GBS-DS scores. The Youden[36] index was used to calculate the cutoff value of the variables, and accordingly, a Sankey diagram[37] was drawn to determine the GBS-DS scores of each patient at different times to peak to assess their short-term prognosis. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Clinical features and treatment

A total of 246 patients with GBS spectrum disorders were diagnosed at the Children's Hospital of Chongqing Medical University from July 2018 to March 2024. Thirty-seven children with anti-GM1 antibody-positive GBS were included (15.0%, 37 of 246), including nine cases that were anti-GM1 antibody positive and 28 cases that were anti-GM1 antibody positive combined with positivity for other AGA antibodies and/or anti-sulfatide antibody. Table 2 presents the combined antibodies of anti-GM1 antibody positive group.

In accordance with the 1:1 matching principle,[29] 37 patients on the GBS spectrum were selected as control subjects, including nine patients who were negative for all peripheral neuropathy antibodies and 28 patients who were negative for anti-GM1 antibodies but were positive for other AGA and/or anti-sulfatide antibody antibodies. All children had a monophasic disease course, with the disease reaching its peak within four weeks.

Of the 37 children in the anti-GM1 antibody-positive group, 22 underwent cranial magnetic resonance imaging (MRI) examination, of which nine (nine of 22, 40.9%) showed inflammatory demyelinating lesions (Fig 1A-C), and different degrees of lesion resorption were seen on review after different periods of time (Fig 1D-F). The sites of involvement included the brainstem (four of nine, 44.4%), some of the cerebral sulci (two of nine, 22.2%), bilateral basal ganglia and centrum semiovale (one of nine, 11.1%), cerebellar hemispheres (one of nine, 11.1%), and bilateral dorsal thalamus and posterior branches of the internal capsule (one of nine, 11.1%), which were considered possible inflammatory demyelinating lesions. Three of nine children with single anti-GM1 antibody positivity had normal brain MRI. Of the 37 children in the anti-GM1 antibody-positive group, 26 cases were assessed using cervicothoracic and lumbar magnetic resonance scanning and enhancement examinations, among which 12 cases (12 of 26, 46.2%) suggested linear enhancement of the cauda equina or part of the nerve roots.

Some clinical features showed statistically significant differences between the two groups (Table 3, Fig 2). The anti-GM1 antibody-positive group was less likely to show clinical involvement of cranial nerves (confidence interval [CI] = 0.384-6.718, $P = 0.031$), especially bulbar palsy (CI = 0.358-8.898, $P = 0.013$), and had low lower limb muscle strength at discharge ($P = 0.045$); their electrophysiological typing was more frequent in the axonal type (CI = 0.274-9.166, $P = 0.035$) and the demyelinating type was less common ($P = 0.039$), and clinical typing was more common in those with AMAN (CI = 0.390-59.138, $P = 0.012$); and their GBS-DS was high at discharge ($P = 0.016$) as well as at one month of discharge ($P = 0.013$).

TABLE 2.
Combined Antibodies of Anti-GM1 Antibody Positive Group

Aim Antibody	Other Anti-Ganglioside Antibodies and/or Anti-Sulfatide Antibody	N (%)
Anti-GM1 antibody combined with	Anti-GD1b antibody	6 cases (21.4%)
	Anti-GM2 antibody	4 cases (14.3%)
	Anti-sulfatide antibody	3 cases (10.7%)
	Anti-GD1b + sulfatide antibody	2 cases (7.1%)
	Anti-GD3 antibody	1 case (3.6%)
	Anti-GD3 + sulfatide antibody	1 case (3.6%)
	Anti-GD1b + GM3 antibody	1 case (3.6%)
	Anti-GD2 + GD3 antibody	1 case (3.6%)
	Anti-GD1b + GT1a antibody	1 case (3.6%)
	Anti-GD1b + GD3 + sulfatide antibody	1 case (3.6%)
	Anti-GD3 + GM2 + sulfatide antibody	1 case (3.6%)
	Anti-GD1b + GD2 + GD3 + sulfatide antibody	1 case (3.6%)
	Anti-GD2 + GM2 + GM3 + sulfatide antibody	1 case (3.6%)
	Anti-GD1b + GT1a + GM2 + sulfatide antibody	1 case (3.6%)
	Anti-GD2 + GD3 + sulfatide + GM2 + GM3 + GM4 antibody	1 case (3.6%)
	Anti-GT1a + GQ1b + sulfatide antibody	1 case (3.6%)
	Anti-GM2 + sulfatide antibody	1 case (3.6%)

Abbreviation:
GM1 = Tetrahexose monosialoganglioside

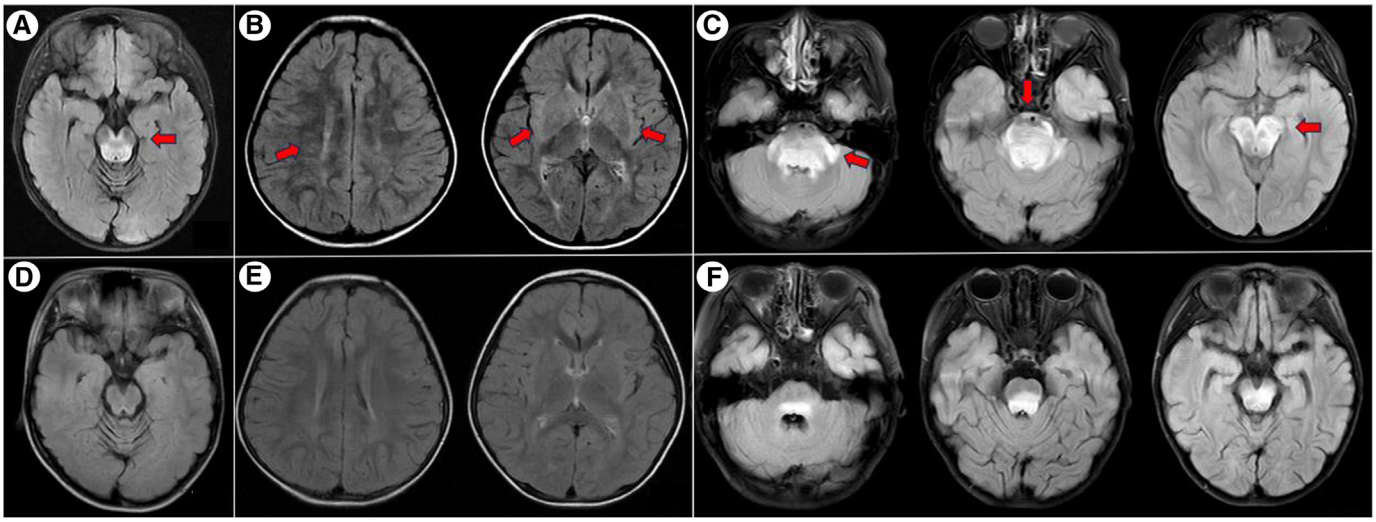

FIGURE 1. Cranial imaging manifestations and follow-up of three children with magnetic resonance imaging abnormalities (where the arrows point). (A) Anti-GM1-combined sulfatide antibody positive: abnormal signal changes in bilateral cerebral peduncles and dorsal midbrain sheets; (B) anti-GM1-combined GM2 antibody positive: abnormal signals in the centers of the semiovals and bilateral basal ganglia regions, considering the possibility of inflammatory demyelination; (C) anti-GM1-combined GM2 + sulfatide antibody positive: abnormal signals in the pontine, midbrain, and midbrain cerebral peduncle did not show significant enhancement, considering the possibility of inflammatory lesions; (D-F) the results of the three cases of children with imaging follow-up after 19 months, 14 months, and 2 weeks, respectively, with different degrees of absorption of abnormal signals. The color version of this figure is available in the online edition.

The treatment regimen included intravenous immunoglobulin (IVIG) in a total amount of 2 g/kg over one to 5 days; some (Table 3) children were treated with a combination of hormone therapy, such as methylprednisolone 20 mg/kg·d for three days and then prednisone 1 -2 mg/kg/d, which was orally tapered off over one to two months. Other treatments included repeated IVIG therapy, mechanically assisted ventilation, and plasma exchange.

Analysis of risk factors for poor prognosis in the anti-GM1 antibody-positive group

Twenty-six (26 of 37, 70.3%) children recovered well and could walk independently at one month after discharge; however, 11 (11 of 37, 29.7%) children still had varying degrees of motor dysfunction at one month after discharge. The 11 children with poor short-term prognosis were followed up for more than 6 months. Among them, 3 (3 of 11, 27.3%) were still unable to walk independently at six months after discharge from the hospital (GBS-DS >2), whereas eight children recovered well and could walk independently (GBS-DS <3). The three patients were all female, with complete paralysis of all limbs and an electrophysiological classification of AMAN. Two cases were accompanied by medullary paralysis, cranial nerve involvement, peripheral respiratory failure, and peak time of 2 to 3 days.

To address the missing values in the data and the serious imbalance between the two groups of data, we used K-nearest neighbor imputation and Synthetic Minority Over-sampling Technique oversampling to fill and equalize the two groups of data and expanded the sample size to a total of 48 cases, of which 22 cases were in the poor prognosis group and 26 cases were in the good prognosis group.[38] Then, the random forest technique was employed for classification prediction, to improve the accuracy and stability of the model. Figure 3A demonstrates the model's prediction accuracy for prognosis using the random forest technique according for the training samples used, which comprised 50%, 60%, and 70% of the total number of samples.[39] The prediction accuracy of most of the samples was more than 80% when using randomized sampling with 100 repetitions, which confirmed the accuracy and stability of the model.

To avoid the problem of multicollinearity in the model, LASSO logistic regression was used to select the variables. Figure 3B shows the shrinkage path of standardized coefficients in the regression with an increasing penalty factor (Lambda). As Lambda increased, the total number of factors whose coefficients in the model shrank to 0 was 11 (their corresponding LASSO logistic regression coefficients can be seen in Table 4), reflecting the relative importance of the 11 factors in the model.

The 11 selected variables were again included in the binary logistics stepwise forward regression analysis, and the time to peak was observed to be significantly different between the two groups ($P = 0.021$), which combined with the negative coefficient of time to peak in the LASSO logistic regression analysis suggested that there is a negative correlation between the time to peak and poor prognosis, i.e., a short time to peak is a risk factor for a poor prognosis of anti-GM1 antibody-positive GBS spectrum diseases.

A nomogram-prediction model was further constructed using the time to peak and the GBS-DS score at one month of discharge (Fig 3C). The resultant column line graph showed that the shorter the time to peak, the lower the total points and the greater the likelihood of a poor short-term prognosis (GBS-DS score >2) for anti-GM1 antibody-positive children. The receiver operating characteristic curve was plotted and the area under the curve was calculated (Fig 3D), which indicated that the predictive performance of our nomogram model was good. Finally, the Youden index was used to calculate the cutoff value of the time to peak, which was 7.5 days, and a Sankey diagram was plotted accordingly (Fig 3E), which showed that patients with a time to peak of <7.5 days had an overall higher GBS-DS score at one-month of discharge.

Discussion

In our study, the positivity rate of anti-GM1 antibodies in children was 15%, which is lower than that in other studies.[17,18,20-23] Considering the reasons, the development of the economy and society as well as the improvement of hygiene conditions are

TABLE 3.
1:1 Paired Analysis of Clinical Characteristics of Children With Serum/Cerebrospinal Fluid Anti-GM1 Antibody-Positive and -Negative GBS Spectrum Disorders

Diagnostic Trait	Anti-GM1 Antibody-Positive Group n = 37	Anti-GM1 Antibody-Negative Group n = 37	Pairing Group	
			Statistical Value	*P* Value
Age	6.18 (3.13)	4.50 (7)	$t = 0.802$	0.493
Sex				1.000
Male	22	21		
Female	15	16		
Time				
Prodrome to onset	6 (4)	4.1 (2.3)	$t = 0.693$	0.428
Time to peak	6.0 (4.9)	6.5 (5.0)	$z = -1.819$	0.069
Season of onset				0.232
Antecedent events	25	21		0.523
Respiratory tract infection	14	15		1.000
Digestive tract infection	6	2		0.289
Vaccinations	1	2		1.000
Other	4	2		0.687
First symptoms				0.351
Weakness of the limbs	20	25		
Pain in the limbs	14	8		
Other	3	4		
Concomitant symptoms				
Weakness of the limbs	33	31		0.754
Autonomic nerve involvement	21	13		0.152
Sensory abnormalities	17	21		0.164
Cranial nerve involvement	14	24		0.031
Bulbar palsy	8	19		0.013
Paralysis of eye muscles	8	9		1.000
Facial nerve involvement	1	3		0.625
Ataxia	8	6		0.774
Impaired consciousness	7	5		0.774
Respiratory muscle involvement	5	1		0.219
Signs				
Decreased or absent tendon reflexes	24	24		1.000
Decreased muscle tone	22	18		0.629
Abdominal wall reflex not elicited	9	6		0.549
Positive nerve root pull sign	9	6		0.581
Positive Babinski sign	3	3		1.000
Muscle strength of the lower limbs				
On admission			$z = -1.024$	0.319
At discharge			$z = -2.005$	0.045
Auxiliary examinations				
Cerebrospinal fluid protein level	0.75 (0.87)	0.69 (1.17)	$z = -0.463$	0.325
Cerebrospinal fluid protein-cell separation	28	26		0.804
Elevated blood CRP or PCT	9	16		0.118
Cranial MRI abnormalities	9	11		0.804
Spinal cord MRI abnormalities	12	8		0.424
Electrophysiological abnormalities				
Decreased CAMP amplitude	28	27		1.000
Slowed-down MCV	13	22		0.049
DML extension	11	17		0.210
SNAP exception	7	14		0.057
Slowed-down SCV	3	2		1.000
F-wave	31	24		0.146
H-reflection	26	26		1.000
Electrophysiological type				
Damage to axon	15	6		0.035
Demyelination	5	13		0.039
Demyelination + damage to axon	8	7		1.000
Unclassifiable	2	3		1.000
Not done/not unusual	7	8		
Clinical typing				
AMAN	12	3		0.012
AIDP	11	18		0.189
MFS	9	8		1.000
AMSAN	3	4		1.000
Other	2	4		
Treatment				
IVIG				0.359
Glucocorticoids				0.607
Glucocorticoids alone	1	1		
Combined with IVIG	10	14		
Plasma exchange	1	1		1.000
Respiratory assistance	4	1		0.375
GBS-DS score				

Table 3 (*continued*)

Diagnostic Trait	Anti-GM1 Antibody-Positive Group n = 37	Anti-GM1 Antibody-Negative Group n = 37	Pairing Group	
			Statistical Value	*P* Value
On admission			$z = -1.579$	0.121
At discharge			$z = -2.390$	0.016
1 month after discharge			$z = -2.489$	0.013
6 months after discharge			$z = -1.197$	0.250

Abbreviations:
AIDP = Acute inflammatory demyelinating polyneuropathy
AMAN = Acute motor axonal neuropathy
AMSAN = Acute motor sensory axonal neuropathy
CAMP = Compound muscle action potential
CRP = C-reactive protein
DML = Distal motor latency
GBS = Guillain-Barré syndrome
GBS-DS = GBS Disability Score
GM1 = Tetrahexose monosialoganglioside
IVIG = Intravenous immunoglobulin
MCV = Motor nerve conduction velocity
MFS = Miller Fisher syndrome
MRI = Magnetic resonance imaging
PCT = Procalcitonin
SCV = Sensory nerve conduction velocity
SNAP = Sensory nerve action potential

important factors leading to the decrease in the incidence of *C. jejuni* infection, and it may also be due to differences in GBS subtypes between children and adults.

In the present study of 37 children with anti-GM1 antibody-positive GBS spectrum disorders, 28 (28 of 37, 75.7%) had a combination of other AGA and/or anti-sulfatide antibodies. The combination of other AGA and/or anti-sulfatide antibodies was the most important confounding factor; we therefore drew on the principles of case-control studies with a paired design[29] to perform 1:1 matching for combined identical AGA and/or anti-sulfatide antibodies, thereby reducing the impact of combined other antibodies in the clinical characterization. The antibodies that appear frequently together with anti-GM1 antibody are anti-GD1b antibody (21.4%), anti-GM2 antibody (14.3%), and anti-sulfatide antibody (10.7%). Similar to Ramos et al.'s study,[40] we speculate that the formation of heteropolymer complexes between a single GA and another GA or lipid can enhance antibody signaling in some serum samples.[1,14]

AGA and/or anti-sulfatide antibodies are considered pathogenic antibodies of GBS and are associated with the occurrence, development, prognosis, and therapeutic efficacy of the disease.[41] The GAs and sulfatide of different subtypes are enriched to varying degrees in nerves of different regions, which may be specifically associated with GBS subtyping.[42-44] Patients with GBS may have both clinical phenotype overlap and antibody overlap, but the corresponding relationship between multiple antibodies and different clinical phenotypes is still unclear. Our study confirms that the clinical manifestations of anti-GM1 antibody-associated peripheral neuropathies have a relatively specific antibody phenotype-clinical phenotype. Children with anti-GM1 antibody-positive GBS spectrum disorders are less likely to present with cranial nerve involvement, especially those involving bulbar palsy; their electrophysiological phenotype is more axonal than demyelinating, and their clinical phenotype is more likely to be AMAN. Moreover, their lower limb muscle strength tends to be low at discharge and their prognosis is poor in the near term. Owing to limited sample size, we were unable to identify predictive factors for GM1 antibody positivity in patients with GBS.

Cranial nerve involvement is one of the clinical manifestations of GBS spectrum disorders and is commonly seen in clinical subtypes, such as Miller Fisher syndrome, Bickerstaff brainstem encephalitis, and bilateral facial nerve palsy with distal sensory abnormalities. In this study, 14 (14 of 37, 37.8%) anti-GM1 antibody-positive children presented with cranial nerve involvement and eight (eight of 37, 21.6%) of them developed bulbar palsy, which was a significantly lower rate than that of the control group, and was similar to that reported previously.[17,45] Sensory abnormalities include muscle pain, limb numbness, and sensory hypersensitivity. GM1 is expressed in both motor and sensory nerve fibers but is mostly distributed on motor nerves, and the concentration in sensory nerve fibers is so low that anti-GM1 antibody seldom binds to the posterior root nerves,[46] since sensory abnormalities are rare.[45,47] In this study, there were 17 cases of sensory abnormalities in the GM1 antibody-positive group and most of them complained of muscle pain (12 of 17, 70.6%); however, only two children with anti-GM1 antibody-positive electrophysiological

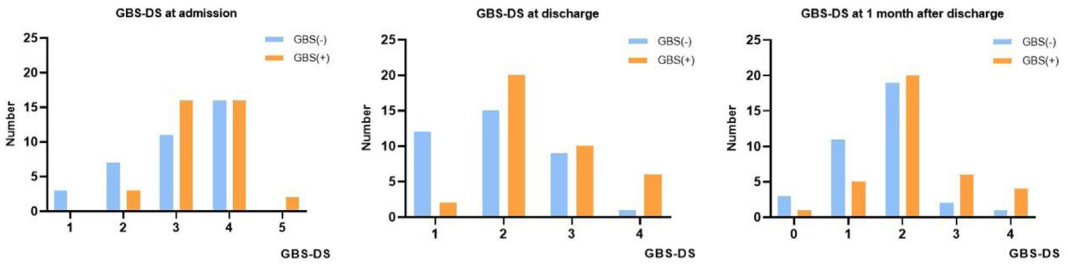

FIGURE 2. Guillain-Barré syndrome Disability Score (GBS-DS) in different courses of disease between the children with positive (GM1+) and negative (GM1-) serum/cerebrospinal fluid anti-GM1 antibodies. The color version of this figure is available in the online edition.

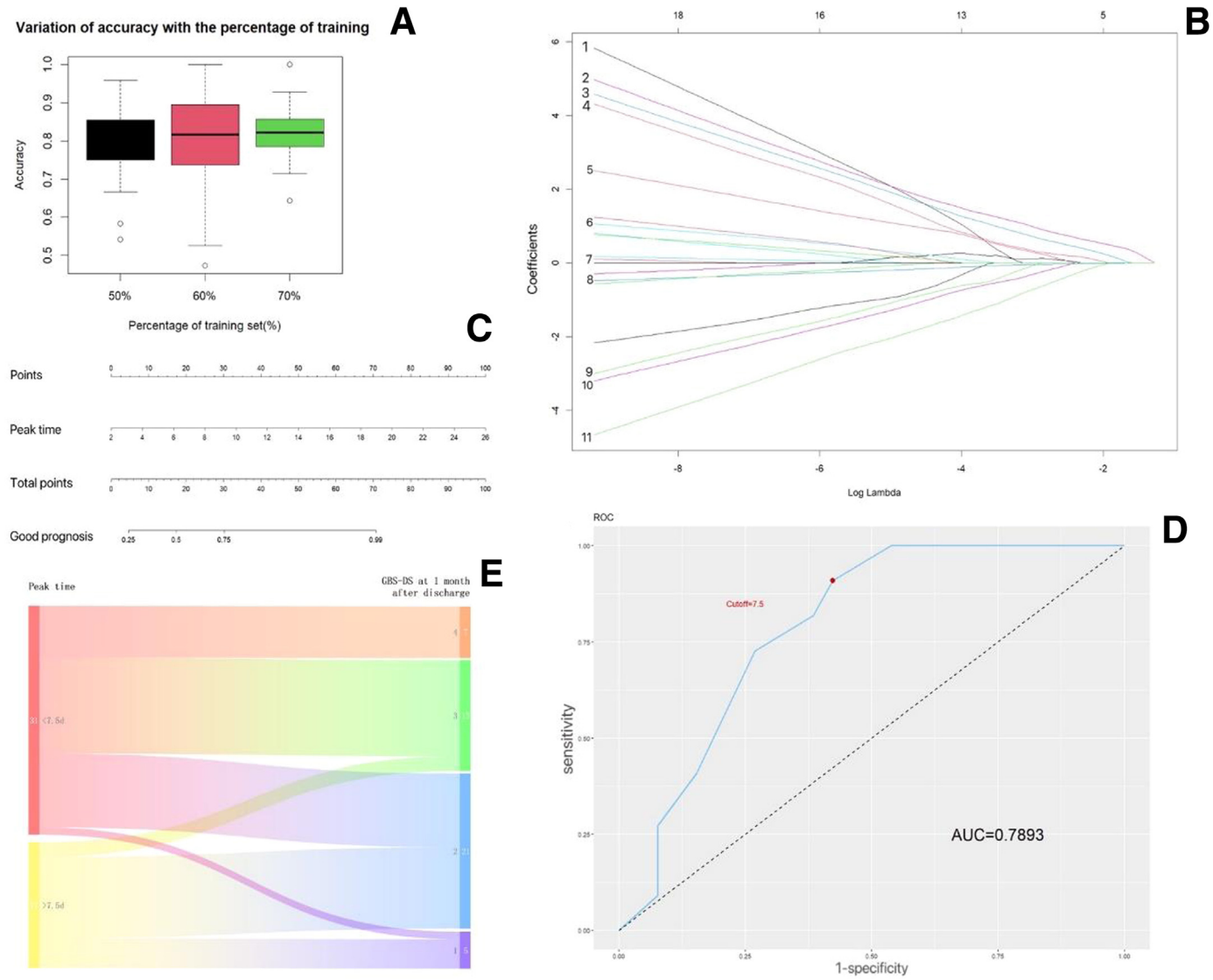

FIGURE 3. Prognostic analysis of children with anti-GM1 antibody-positive Guillain-Barré syndrome (GBS) spectrum disorders. (A) Predictive accuracy of random forest plots for the prognosis of anti-GM1 antibody-positive GBS spectrum disorders. (B) Plot of shrinking paths of standardized coefficients in least absolute shrinkage and selection operator logistic regression with increasing penalty factor (Lambda). (1, ataxia; 2, decreased muscle tone; 3, abnormal cranial magnetic resonance imaging; 4, antecedent respiratory infection; 5, sensory nerve action potential exception; 6, season of onset; 7, antecedent events; 8, time to peak; 9, impaired consciousness; 10, distal motor latency extension; 11, antecedent digestive tract infection). (C) Prognostic nomogram prediction model for children with anti-GM1 antibody-positive GBS spectrum disorders; it shows that the longer the peak time, the greater the possibility of GBS Disability Score (GBS-DS) score <2. (D) Receiver operating characteristic curve evaluation of the nomogram prediction model (area under the curve [AUC]: 0.7893, $P = 0.013$, cutoff value = 7.5). (E) Sankey plot of the time to peak and GBS-DS score at one month after hospital discharge in children with anti-GM1 antibody-positive GBS spectrum disorders. The color version of this figure is available in the online edition.

examination had sensory nerve involvement, which might be related to the inability of some children or their families to accurately describe their conditions. GM1 is enriched in axons and the Ranvier node of peripheral nerves,[15,48] and IgG-type anti-GM1 antibodies bind to P/Q-type and N-type calcium channels in neuromuscular junctions,[39] leading to motor nerve axon damage.[46] Therefore anti-GM1 antibody-positive patients have a predominantly AMAN-type phenotype and are often preceded by *C. jejuni* infection.[15,16] Stefano et al. found severe peripheral neuropathy in anti-GM1 antibody-positive patients, which was associated with distal limb weakness without sensory involvement.[47] In this study, children in the study group had more axonal and less demyelinating electrophysiological typing and more clinical typing of AMAN ($P = 0.012$). The children also showed lower limb muscle strength at discharge compared with the negative group ($P = 0.045$), and a high GBS disability score at discharge ($P = 0.016$), similar to the results of previous studies.[15-17,46,47]

Imaging tests, including cranial and spinal MRI, might assist in the diagnosis of GBS spectrum disorders. In this study, nine children (nine of 22, 40.9%) in the anti-GM1 antibody-positive group had abnormal cranial MRI and 12 children had abnormal spinal cord MRI (12 of 26, 46.2%), which might be related to the fact that GM1 is more abundant in neuronal cell membranes.[13,49] Three of nine children with single anti-GM1 antibody positivity had normal brain MRI. The imaging results and other manifestations may be affected by other combined antibodies, leading to limitations of antibody group variability.[50]

Serum IgG type anti-GM1 antibodies are an independent risk factor for poor prognosis in GBS, especially with sustained persistent high titers.[17,49] We found that children with anti-GM1

TABLE 4.
Analysis of Risk Factors for Poor Prognosis in Children With Anti-GM1 Antibody-Positive GBS Spectrum Disorders

Factors	Anti-GM1 Antibody-Positive Group n = 37	Group With Good Prognosis n = 26	Group with Poor Prognosis n = 11	Lasso Regression Coefficient
Age	6.18 (3.13)	4.91 (1.92)	7.47 (3.29)	
Sex				
Male	22	5	17	
Female	15	6	9	
Time				
Prodrome to onset	6 (4)	2 (6)	2 (4)	
Time to peak	6.0 (4.9)	8.5 (10.0)	5.1 (2.1)	
Season of onset				0.001
Antecedent events	25	15	10	0.201
Respiratory tract infection	14	7	7	0.546
Digestive tract infection	6	5	1	−1.117
Vaccinations	1	0	1	
Else	4	3	1	
First symptoms				
Weakness of the limbs	20	14	6	
Pain in the limbs	14	10	4	
Other	3	2	1	
Concomitant symptoms				
Weakness of the limbs	33	23	10	
Autonomic nerve involvement	21	16	5	
Sensory abnormalities	17	13	4	
Cranial nerve involvement	14	9	5	
Bulbar palsy	8	4	4	
Paralysis of eye muscles	8	7	1	
Facial nerve involvement	1	1	0	
Ataxia	8	6	2	
Impaired consciousness	7	5	2	0.377
Respiratory muscle involvement	5	2	3	−0.435
Signs				
Decreased or absent tendon reflexes	24	9	15	1.244
Decreased muscle tone	22	12	10	
Abdominal wall reflex not elicited	9	4	5	
Positive nerve root pull sign	9	3	6	
Positive Babinski sign	3	1	2	
Muscle strength of the lower limbs				
On admission				
At discharge				
Auxiliary examination				
Cerebrospinal fluid protein level	0.75 (0.87)	1.23 (0.90)	0.75 (0.43)	
Cerebrospinal fluid protein-cell separation	28	19	9	
Elevated blood CRP or PCT	9	5	4	
Cranial MRI abnormalities	9	5	4	
Spinal cord MRI abnormalities	12	8	4	0.996
Electrophysiological abnormalities				
Decreased CAMP amplitude	28	19	9	
Slowed-down MCV	13	8	5	
DML extension	11	9	2	
SNAP exception	7	4	3	
Slowed-down SCV	3	2	1	
F-wave	31	22	9	−0.533
H-reflection	26	18	8	0.517
Treatment				
IVIG				
Glucocorticoids				
Glucocorticoids alone	1	0	1	
Combined with IVIG	10	3	7	

Abbreviations:
AIDP = Acute inflammatory demyelinating polyneuropathy
AMAN = Acute motor axonal neuropathy
AMSAN = Acute motor sensory axonal neuropathy
CAMP = Compound muscle action potential
CRP = C-reactive protein
DML = Distal motor latency
GBS = Guillain-Barré syndrome
GBS-DS = GBS Disability Score
GM1 = Tetrahexose monosialoganglioside
IVIG = Intravenous immunoglobulin
MCV = Motor nerve conduction velocity
MFS = Miller Fisher syndrome
MRI = Magnetic resonance imaging
PCT = Procalcitonin
SCV = Sensory nerve conduction velocity
SNAP = Sensory nerve action potential

antibody-positive GBS spectrum disorders had a poor short-term prognosis compared with control subjects ($P < 0.05$). The 11 children with poor short-term prognosis were followed up for more than six months, and three of them (three of 11, 27.3%) were still unable to walk independently at 6 months after discharge from the hospital. Owing to limitations in research methods, we did not explore the correlation between antibody titers and disease severity and prognosis.

Disorders of cellular and humoral immunity play an important role in the pathogenesis of GBS spectrum diseases. Immunotherapy based on supportive care, especially the early use of high-dose IVIG, as well as plasma exchange,[51] is currently the main recommendation. A randomized controlled trial[52] has shown that administration of corticosteroids alone does not improve recovery or long-term prognosis in GBS. In this study, glucocorticosteroid therapy also did not improve prognosis.

Children with GBS have a shorter course and better prognosis than adults[53] and have a more complete recovery.[54] Most children reach disease peak within 2 weeks, with a few still having motor dysfunction at 6 months after onset.[55] Cranial nerve involvement, autonomic nerve involvement, the need for mechanical ventilation, and elevated levels of cerebrospinal fluid neurofilament light chains[56,57] might be risk factors for poor prognosis in children with GBS spectrum disorders, and rapid disease progression is associated with residual long-term sequelae.[58] In this study, a short time to peak was an independent risk factor for poor short-term prognosis in children with anti-GM1 antibody-positive GBS spectrum disorders. Therefore, children with anti-GM1 antibody-positive GBS spectrum disease who have rapid disease progression, especially with a time to peak of <7.5 days, should be started on standardized immunotherapy and rehabilitation interventions as early as possible.

There are many literature reports on the association between GBS and specific antibodies,[42-44] but most of them have limited value in routine clinical practice; 30%-80% of patients with GBS do not have serum antibodies detected. When inflammatory edema occurs without cell infiltration, especially in the early stages of the disease, the deposition of complement, IgG, and IgM can be seen in neural specimens. Most importantly, its good response to plasma exchange makes the search for pathogenic humoral factors in blood or cerebrospinal fluid a major research direction for GBS. With a deeper understanding of the disease, in addition to clinical phenotype and electrophysiological characteristics, serologic subtyping of GBS may also be a future direction. We recommend testing for AGAs and anti-sulfatide antibodies in GBS children.

Data availability

Data are available on reasonable request.

CRediT authorship contribution statement

Jiaqi Yan: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Project administration, Methodology, Investigation, Formal analysis. **Lamei Chen:** Methodology. **Peijiao Liu:** Software. **Hailun Peng:** Resources. **Li Jiang:** Conceptualization. **Yue Hu:** Review & editing, Supervision, Project administration.

Declaration of competing interest

All individuals listed as authors meet the appropriate authorship criteria, and nobody who qualifies for authorship has been omitted from the list; authors and contributors have approved the acknowledgement of their contributions. All authors had complete access to the study data that support the publication. The authors have stated that they had no interests which might be perceived as posing a conflict or bias.

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