



Factors Associated with Respiratory Insufficiency in Children with Guillain–Barré Syndrome

Rui-di Sun¹ Jun Jiang¹ Xiao-long Deng²

¹Department of Electrophysiology, Wuhan Children's Hospital (Wuhan Maternal and Children's Healthcare Center), Wuhan, People's Republic of China

²Department of Pediatric Neurology, Wuhan Children's Hospital (Wuhan Maternal and Children's Healthcare Center), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

Address for correspondence: Xiaolong-Deng, MD, Department of Pediatric Neurology, Wuhan Children's Hospital, Jiangnan District 430016, People's Republic of China (e-mail: honey@163.com).

Neuropediatrics 2024;55:112–116.

Abstract

Objective The risk factors for respiratory insufficiency in children with Guillain–Barré syndrome (GBS) are poorly known. This study aimed to investigate the factors associated with respiratory insufficiency in children with GBS.

Methods This retrospective study included children diagnosed with GBS by pediatric neurologists and admitted at the Wuhan Children's Hospital and other hospitals from January 2013 to October 2022. The patients were divided into the respiratory insufficiency and nonrespiratory insufficiency groups according to whether they received assist breathing during treatment.

Results The median (interquartile range) age of onset of 103 patients were 5 (3.1–8.5) years, 69 (67%) were male, and 64 (62.1%) had a history of precursor infection. Compared with the nonrespiratory insufficiency group, the respiratory insufficiency group showed more facial and/or bulbar weakness ($p = 0.002$), a higher Hughes Functional Grading Scale (HFGS) at admission ($p < 0.001$), and a shorter onset-to-admission interval ($p = 0.017$). Compared with the acute motor axonal neuropathy (AMAN) subtype, the acute inflammatory demyelinating polyneuropathy (AIDP) subtype showed longer days from onset to lumbar ($p = 0.000$), lower HFGS at admission ($p = 0.04$), longer onset-to-admission interval ($p = 0.001$), and more cranial nerve involvement ($p = 0.04$). The incidence of respiratory insufficiency between AIDP and AMAN showed no statistical difference ($p > 0.05$).

Conclusion In conclusion, facial and/or bulbar weakness, HFGS at admission, and onset-to-admission interval were associated with respiratory insufficiency and might be useful prognostic markers in children with GBS.

Keywords

- Guillain–Barré syndrome
- respiratory insufficiency
- prognosis
- muscle weakness
- physical functional performance
- cerebrospinal fluid

received
June 5, 2023
accepted after revision
November 9, 2023
article published online
January 22, 2024

DOI <https://doi.org/10.1055/s-0043-1777767>.
ISSN 0174-304X.

© 2024. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Introduction

Guillain-Barré syndrome (GBS) is a rare autoimmune acute polyradiculoneuropathy with potentially severe symptoms, usually presenting with bilateral weakness in limbs starting from distal to proximal.^{1,2} The annual incidence is 0.8 to 1.9 cases/100,000 persons, increasing with age. The anatomical distribution of the initial symptomatic involvement in the peripheral nervous system varies widely and typically does not follow a distal-to-proximal gradient. GBS is clinically heterogeneous: the classic presentation of GBS features progressive (ascending) limb weakness associated with reduced or absent reflexes. However, patients can present with localized weakness and these variants include a pharyngeal-cervical-brachial variant and facial diplegia with paraesthesia. Patients can also present with completely different sets of clinical features to classic GBS but can share similar serological biomarkers. These disorders related to GBS include Miller Fisher syndrome (MFS) and Bickerstaff brainstem encephalitis. Recognizing the clinical patterns categorized under the wide umbrella of GBS allows for more timely and accurate diagnosis, and for treatment to be initiated without delay.³

The diagnosis of GBS is based on clinical features and auxiliary examinations. Nerve conduction study and cerebrospinal fluid (CSF) examination are essential for diagnosing GBS.^{1,2} At the early stages of disease, nerve conduction can be normal, but in most patients there is evidence of a neuropathy. Some early studies on nerve conduction changes in GBS include absent Hoffmann reflexes and F waves, and abundant A waves.³⁻⁵ The selective rise in CSF total protein (CSF-TP), historically labeled “albuminocytologic dissociation,” is time-dependent.^{1,2}

GBS is one of the leading causes of acute flaccid paralysis in children and pain may be the primary symptom leading to a consultation with the pediatrician.⁶ Although most children with GBS have a favorable prognosis, respiratory insufficiency is one of the most severe complications of GBS.^{1,2} Respiratory insufficiency is a potential life-threatening complication of GBS and it is associated with higher incidence of morbidity.^{1,2,7,8} Therefore, predicting respiratory insufficiency is necessary for the proper management of children with GBS. The validated predictors of respiratory insufficiency include serum albumin, forced vital capacity (FVC), negative inspiratory force, and the Erasmus GBS Respiratory Insufficiency Scale (EGRIS), as well as rapid disease progression, inability to cough, stand, or raise the head, bulbar dysfunction, bilateral facial weakness, insufficient foot flexion (at the end of immunotherapy), and dystonia.⁹⁻¹³ The prognostic value of CSF-TP for respiratory insufficiency in GBS remains controversial.¹⁴⁻¹⁶

To date, very few studies investigated the predictors of respiratory insufficiency in childhood. Therefore, the present study investigated the factors associated with respiratory insufficiency in childhood GBS. The results could help guide the management of children with GBS.

Material and Methods

This retrospective study included children diagnosed with GBS by pediatric neurologists¹⁷ and admitted at the Wuhan

Children's Hospital, and Pediatric Union unit from January 2013 to October 2022. The inclusion criteria were (1) 1 to 18 years of age and (2) diagnosed with GBS. The exclusion criteria were (1) diagnosis of acute onset of chronic inflammatory demyelinating polyneuropathy, (2) diagnosis of other autoimmune diseases, (3) diagnosis of central nervous system infections, or (4) alternative diagnosis should be excluded after follow-up. The study was approved by the Wuhan Children's Hospital ethics committee (#2021R110-E02) and was performed in accordance with the Helsinki Declaration. The patients were divided into the respiratory insufficiency and nonrespiratory insufficiency groups according to whether they received assisted breathing (mechanical ventilation) during treatment.

Demographic and disease-specific data, including electrophysiological subtypes, cranial nerve involvement, sensory nerve involvement, autonomic nerve involvement, history of precursor infection, treatments, and CSF-TP, were collected from the patient charts and pediatric neurology clinic records. The functional status was graded at onset according to the Hughes Functional Grading Scale (HFGS): grade 0 = normal, grade 1 = minor signs and symptoms, grade 2 = walks 5 m without a walker or support, grade 3 = walks 5 m with a walker or support, grade 4 = bed rest or wheelchair required, grade 5 = assisted ventilation required, and grade 6 = death.¹⁸

The children were classified as acute inflammatory demyelinating polyneuropathy (AIDP), axonal subtype (acute motor axonal neuropathy [AMAN] or acute motor and sensory axonal neuropathy), or equivocal subtype based on the existing electrodiagnostic criteria.¹⁹ If a patient had two nerve conduction studies during the hospital stay, we based on the Second one. According to clinical criterion, GBS was classified into classical GBS and MFS.¹⁷

All analyses were performed using SPSS 21.0 (IBM, Armonk, New York, United States). Continuous data were tested for normal distribution using the Kolmogorov-Smirnov test. The continuous variables with a normal distribution were described as means \pm standard deviations and tested using Student's *t*-test. The continuous variables with a skewed distribution were presented as median (interquartile range [IQR]) and compared using the Mann-Whitney *U* test. The categorical variables were described as *n* (%) and compared using the chi-square test or Fisher's test. Two-sided *p*-values of < 0.05 were considered statistically significant.

Results

The median (IQR) age of onset of 103 patients were 5 (3.1–8.5) years, 69 (67%) were male, and 64 (62%) had a history of precursor infection. There were no differences in median age of onset and sex between the two groups (all *p* > 0.05) (► **Table 1**).

Autonomic dysfunction was observed in 16 (15.5%) patients. All the patients had nerve conduction study, 50 patients had more than two nerve conduction studies. The interval from onset to first nerve conduction study ranged from 7 to 30 days and the interval from onset to the second

Table 1 The clinical features between GBS with respiratory insufficiency and without respiratory insufficiency

	All, <i>n</i> = 103	GBS with respiratory insufficiency, <i>n</i> = 9	GBS without respiratory insufficiency, <i>n</i> = 94	<i>p</i>
Age of onset (y), median (IQR)	5 (3.1–8.5)	7.3 (3.25–10.4)	4.96 (2.88–8.5)	0.6
Male, <i>n</i> (%)	69 (67.0)	7 (77.8)	62 (66.0)	0.5
History of precursor infection, <i>n</i> (%)	64 (62.1)	6 (66.7)	58 (61.7)	0.8
CSF-TP (g/L), median (IQR)	0.93 (0.65–1.5)	1.8 (0.68–2.60)	0.9 (0.61–1.28)	0.08
Days from onset to lumbar, median (IQR)	11 (7–15)	11 (7.8–12.5)	11 (7–15)	0.5
Autonomic dysfunction, <i>n</i> (%)	16 (15.5)	1 (11.1)	15 (16.0)	0.7
AIDP, <i>n</i> (%)	63 (61.2)	6 (66.7)	57 (60.6)	
AMAN, <i>n</i> (%)	22 (21.4)	2 (22.2)	20 (21.3)	
Equivocal subtype, <i>n</i> (%)	9 (8.7)	1 (11.1)	8 (8.5)	
MFS, <i>n</i> (%)	9 (8.7)	0	9 (9.6)	0.8
HFGS at admission, median (IQR)	2 (2–3)	4 (3.75–4)	2 (2–3)	< 0.001
Onset to admission interval, median (IQR)	7 (4–12)	4 (2.8–4)	7 (4–13.5)	0.017
Facial and/or bulbar weakness, <i>n</i> (%)	32 (31.1)	7 (77.8)	25 (26.6)	0.002

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CSF-TP, cerebrospinal fluid-total protein; GBS, Guillain-Barré syndrome; HFGS, Hughes Functional Grading Scale; IQR, interquartile range; MFS, Miller Fisher syndrome.

Note: Bold indicates statistical significance.

nerve conduction study ranged from 28 to 60 days. According to the second nerve conduction result, there were 63 classified as AIDP, 22 classified as AMAN, 9 classified as equivocal subtype among classic GBS. 3 MFS had absent Hoffmann reflexes in nerve conduction study, and 6 MFS had normal nerve conduction study. Nine patients had mechanical ventilation and 3 of them had tracheotomy. Among all 103 children, 15 (14.6%) showed no increase in CSF protein, while 88 (85.4%) had albumin cytological dissociation in CSF. The CSF-TP levels of the 103 children were 0.93 (0.65–1.50) g/L. The interval from onset to lumbar puncture was 11 (7–15) days. Compared with the nonrespiratory insufficiency group, the

respiratory insufficiency group showed a higher HFGS at admission ($p < 0.001$), more facial and/or bulbar weakness ($p = 0.002$), and shorter onset to admission interval ($p = 0.017$) (► **Table 1**, ► **Figs. 1–2**).

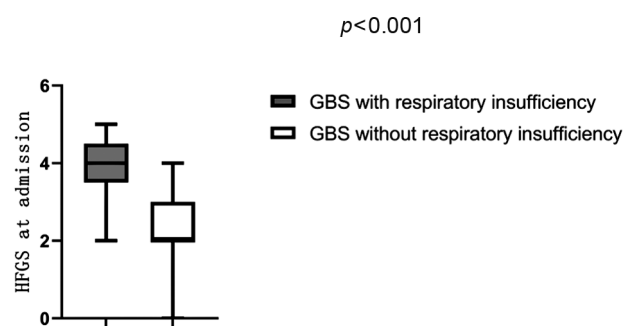


Fig. 1 HFGS at admission between the two groups. Boxes represent the medians and the 25th and 75th quartiles. Mann-Whitney *U* test was used to analyze the data. HFGS, Hughes Functional Grading Scale.

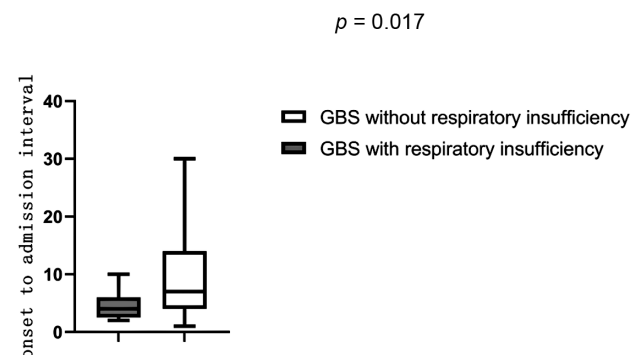


Fig. 2 Interval from onset to admission between the two groups. Boxes represent the medians and the 25th and 75th quartiles. Mann-Whitney *U* test was used to analyze the data.

The comparison between AMAN subtype and AIDP subtype: Compared with the AMAN subtype, the AIDP subtype had longer days from onset to lumbar ($p = 0.000$), lower HFGS at admission ($p = 0.04$), longer onset-to-admission interval ($p = 0.001$), and more cranial nerve involvement ($p = 0.04$) (► **Table 2**).

Discussion

The results suggest that facial and/or bulbar weakness, HFGS at admission, and onset-to-admission interval were associated with respiratory insufficiency in children with GBS.

The EGRIS is a model based on the time from onset of weakness to hospital admission, presence of facial or bulbar weakness, and the Medical Research Council sum score at admission that was found to predict the possibility of respiratory failure within the first week of admission in

Table 2 The comparison between axonal subtype and AIDP

	AMAN (<i>n</i> = 22)	AIDP (<i>n</i> = 63)	<i>p</i>
Age of onset (y), median (IQR)	5 (2.6–7.9)	5.4 (3.3–10)	0.43
Male, <i>n</i> (%)	13 (59)	46 (73)	0.22
History of precursor infection, <i>n</i> (%)	17 (77)	36 (57)	0.09
CSF-TP (g/L), median (IQR)	0.87 (0.59–1.32)	1.1 (0.77–1.99)	0.06
Days from onset to lumbar, median (IQR)	8 (5–10.3)	12 (8–17)	0.000
Autonomic dysfunction, <i>n</i> (%)	4 (18)	11 (17)	0.9
HFGS at admission, median (IQR)	3 (2–4)	2 (2–3)	0.04
Onset to admission interval, median (IQR)	4 (3–7)	7 (4–14)	0.001
Cranial nerve involvement, <i>n</i> (%)	5 (22.7)	30 (47.6)	0.04
Respiratory insufficiency	2 (9)	6 (10)	0.9

Abbreviations: AIDP acute inflammatory demyelinating polyneuropathy; AMAN acute motor axonal neuropathy; CSF-TP cerebrospinal fluid-total protein; HFGS, Hughes Functional Grading Scale; IQR, interquartile range.

Note: Bold indicates statistical significance.

patients with GBS.²⁰ In the present study, facial and/or bulbar weakness associated with respiratory insufficiency, as supported by the EGRIS model and previous studies.^{11,12,20} In addition, the HFGS at admission was also associated with respiratory insufficiency. The HFGS is related to the severity of GBS.²¹ The HFGS was included in a predictive score for mechanical ventilation in GBS.²² Therefore, facial and/or bulbar weakness and HFGS at admission could be useful and easy-to-assess indicators of respiratory insufficiency. Sometimes pain may be the chief complain among pediatric GBS,^{23,24} it could influence the symptoms that can be observed at admission. Future studies should quantify and analyze the progression of the symptoms in time and their association with the eventual requirement for respiratory insufficiency during hospitalization.

Albumin cytological dissociation in CSF is an important parameter for diagnosing GBS. The association between CSF-TP and the requirement for respiratory insufficiency in patients with GBS is controversial.^{14,25} In the present study, CSF-TP was not associated with respiratory insufficiency. Various reasons could be responsible for the discrepancies, including the patients' condition, age, and interval to lumbar puncture. Especially, this interval is controlled in a retrospective study and relies on the original clinical decisions, possibly attenuating the association.

AMAN and AIDP were the main subtype in GBS. In contrast to AIDP, AMAN have been described to have a more rapid progression with less frequent cranial nerve and autonomic involvement than AIDP.²⁶ Our findings are slightly different from the results of previous reports in adults.²⁶ This may be partially explained by autonomic involvement such as blood pressure are not routine examination item among pediatric GBS. Electrophysiological subtype as a prognostic factor in respiratory insufficiency has been controversial. Pediatric GBS-indicated axonal type is associated with increased risk for mechanical ventilation in children with GBS.²⁰ No difference was found in the requirement of mechanical ventilation between children with acute inflammatory demyelinating

polyradiculoneuropathy and AMAN in a study conducted in childhood GBS of India.²⁷ These inconsistencies between studies indicate that the value of electrophysiological characteristics in predicting the need for mechanical ventilation in patients with GBS is yet to be validated. This may be partially explained by regional differences in electrophysiological subtypes of GBS: the demyelinating subtype is reported to be the predominant subtype in Europe and South America, while the axonal type is more common in Asian countries.²⁸

There are several limitations in the present study. It was conducted with a limited number of patients. As a retrospective study, these results cannot be used to determine clinical practice. Multicenter prospective studies with large number of patients are needed to develop a model to predict respiratory insufficiency in children with GBS. Unable to get necessary equipment and poor cooperation in young children, the observation of autonomic dysfunction was difficult to be found during disease, respiratory function such as negative respiratory force and FVC were not available in this investigation. Unable to get serial conduction studies in all patients may lead to incorrect subtype in some patients. Unable to get antibody at admission is also our limitation, since the correlation between severity of GBS and antibody status could teach us a lot about the pathogenesis.

Conclusion

In conclusion, facial and/or bulbar weakness, HFGS at admission, and onset-to-admission interval were associated with the need for respiratory insufficiency and might be useful prognostic markers in children with GBS. Once confirmed, these results could help guide the management of children with GBS.

Ethical Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Authors' Contributions

S.R.D. and D.X.L. conceptualized the study; J.J. helped in data analysis and manuscript writing, referencing etc.; S. R.D. and D.X.L. finalized the manuscript.

Funding

This work was supported by the Wuhan Health Commission Project under Grant [WX21B06]; Hubei Provincial Science and Technology Plan Project for Clinical Research Center of Neurodevelopmental Disorders in Children under Grant [No. 2022DCC020].

Conflict of Interest

None declared.

Acknowledgments

The authors thank Union Hospital of Pediatrics for referring to patients.

References

- Donofrio PD. Guillain-Barré syndrome. *Continuum (Minneapolis)* 2017;23(5, Peripheral Nerve and Motor Neuron Disorders): 1295–1309
- Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet* 2016;388(10045):717–727
- Shahrizaila N, Lehmann HC, Kuwabara S. Guillain-Barré syndrome. *Lancet* 2021;397(10280):1214–1228
- Gordon PH, Wilbourn AJ. Early electrodiagnostic findings in Guillain-Barré syndrome. *Arch Neurol* 2001;58(06):913–917
- Vucic S, Cairns KD, Black KR, Chong PS, Cros D. Neurophysiologic findings in early acute inflammatory demyelinating polyradiculoneuropathy. *Clin Neurophysiol* 2004;115(10):2329–2335
- Karalok ZS, Taskin BD, Yanginlar ZB, et al. Guillain-Barré syndrome in children: subtypes and outcome. *Childs Nerv Syst* 2018; 34(11):2291–2297
- Miller AG, Scott BL. 2021 year in review: pediatric mechanical ventilation. *Respir Care* 2022;67(11):1476–1488
- Zielińska M, Zieliński S, Sniatkowska-Bartkowska A. Mechanical ventilation in children – problems and issues. *Advances in clinical and experimental medicine: official organ Wroclaw. Adv Clin Exp Med* 2014;23(05):843–848
- Fokkink WR, Walgaard C, Kuitwaard K, Tio-Gillen AP, van Doorn PA, Jacobs BC. Association of albumin levels with outcome in intravenous immunoglobulin-treated Guillain-Barré syndrome. *JAMA Neurol* 2017;74(02):189–196
- Sharshar T, Chevret S, Bourdain F, Raphaël JCFrench Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Early predictors of mechanical ventilation in Guillain-Barré syndrome. *Crit Care Med* 2003;31(01):278–283
- Walgaard C, Lingsma HF, Ruts L, et al. Prediction of respiratory insufficiency in Guillain-Barré syndrome. *Ann Neurol* 2010;67 (06):781–787
- Lawn ND, Fletcher DD, Henderson RD, Wolter TD, Wijdsicks EF. Anticipating mechanical ventilation in Guillain-Barré syndrome. *Arch Neurol* 2001;58(06):893–898
- Fourrier F, Robriquet L, Hurtevent JF, Spagnolo S. A simple functional marker to predict the need for prolonged mechanical ventilation in patients with Guillain-Barré syndrome. *Crit Care* 2011;15(01):R65
- Davalos L, Nowacek D, Elsheikh B, Reynolds EL, Maher Stino A. Cerebrospinal fluid protein level and mechanical ventilation in Guillain-Barré syndrome patients. *J Neuromuscul Dis* 2021;8(02): 299–303
- Bourque PR, Brooks J, Warman-Chardon J, Breiner A. Cerebrospinal fluid total protein in Guillain-Barré syndrome variants: correlations with clinical category, severity, and electrophysiology. *J Neurol* 2020;267(03):746–751
- Petzold A, Brettschneider J, Jin K, et al. CSF protein biomarkers for proximal axonal damage improve prognostic accuracy in the acute phase of Guillain-Barré syndrome. *Muscle Nerve* 2009;40 (01):42–49
- Wakerley BR, Uncini A, Yuki NGBS Classification Group GBS Classification Group. Guillain-Barré and Miller Fisher syndromes—new diagnostic classification. *Nat Rev Neurol* 2014;10 (09):537–544
- Konuşkan B, Okuyaz Ç, Taşdelen B, Kurul SH, Anlar B Turkish Childhood Guillain-Barre Syndrome Study Group. Electrophysiological subtypes and prognostic factors of childhood Guillain-Barré syndrome. *Noro Psikiyatri Arsivi* 2018;55(03):199–204
- Gupta D, Nair M, Baheti NN, Sarma PS, Kuruvilla ADiplomate-American Board. Electrodiagnostic and clinical aspects of Guillain-Barré syndrome: an analysis of 142 cases. *J Clin Neuromuscul Dis* 2008;10(02):42–51
- Luo H, Hong S, Li M, Wang L, Jiang L. Risk factors for mechanical ventilation in children with Guillain-Barré syndrome. *Muscle Nerve* 2020;62(02):214–218
- Wang Y, Shang P, Xin M, Bai J, Zhou C, Zhang HL. The usefulness of chief complaints to predict severity, ventilator dependence, treatment option, and short-term outcome of patients with Guillain-Barré syndrome: a retrospective study. *BMC Neurol* 2017;17(01):200
- Ning P, Yang B, Yang X, et al. A nomogram to predict mechanical ventilation in Guillain-Barré syndrome patients. *Acta Neurol Scand* 2020;142(05):466–474
- Barzegar M, Toopchizadeh V, Gholizadeh D, Pirani A, Jahanjoo F. A predictive model for respiratory failure and determining the risk factors of prolonged mechanical ventilation in children with Guillain-Barre syndrome. *Iran J Child Neurol* 2020;14(03):33–46
- Hasan I, Papri N, Hayat S, et al. Clinical and serological prognostic factors in childhood Guillain-Barré syndrome: a prospective cohort study in Bangladesh. *J Peripher Nerv Syst* 2021;26(01):83–89
- El-Bayoumi MA, El-Refaey AM, Abdelkader AM, El-Assmy MM, Alwakeel AA, El-Tahan HM. Comparison of intravenous immunoglobulin and plasma exchange in treatment of mechanically ventilated children with Guillain Barré syndrome: a randomized study. *Crit Care* 2011;15(04):R164
- Kuwabara S, Yuki N. Axonal Guillain-Barré syndrome: concepts and controversies. *Lancet Neurol* 2013;12(12):1180–1188
- Kalita J, Kumar M, Misra UK. Prospective comparison of acute motor axonal neuropathy and acute inflammatory demyelinating polyradiculoneuropathy in 140 children with Guillain-Barré syndrome in India. *Muscle Nerve* 2018;57(05):761–765
- Doets AY, Verboon C, van den Berg B, et al; IGOS Consortium. Regional variation of Guillain-Barré syndrome. *Brain* 2018;141 (10):2866–2877