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Long-term outcomes of paediatric Guillain–Barré syndrome

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Abbreviations:

BDI, Beck Depression Inventory fast screen; CDI, Child Depression Inventory short version; FSS, Fatigue Severity Scale; GBS, Guillain–Barre syndrome; GBSDS, Guillain–Barre Syndrome Disability Score; INCATSSS, Inflammatory Neuropathy Cause and Treatment Sensory Sum Score; MSWS, Multiple Sclerosis Walking Scale; ONLS, Overall Neuropathy Limitations Scale.

Abstract

Aim:

To study long-term sequelae in children with Guillain–Barre syndrome (GBS).

Method:

This was a prospective observational study with children from two French tertiary centres. Data were from clinical and several standardized scales or questionnaires.

Results:

Fifty-one patients were included with a median follow-up of 6 years 4 months (range 3–20 years) after the acute phase. The sequelae rate was 67% (95% confidence interval [CI] 53–78) and did not vary with time. Most children had minor sequelae (Guillain–Barre Syndrome Disability Score [GBSDS] = 1); only one was unable to run (GBSDS = 2). The most frequent complaints were paraesthesia (43%), pain (35%), and fatigue (31%). The neurological examination was abnormal in 18% of children, autonomy was compromised in 14%, and symptoms of depression occurred in 34%. The factors associated with late-onset sequelae were correlated with severity during the initial phase (i.e. initial GBSDS >4, odds ratio 6.6, 95% CI 1.8–33; $p = 0.009$). The predictive factors of more severe late-onset conditions were initial severity ($p = 0.002$) and sex (female patients; $p = 0.01$).

Interpretation:

Two-thirds of children with GBS had late-onset sequelae following an episode, often minor, but sometimes with continuing effects on their everyday lives. Particularly affected were those who had severe GBS during the acute phase and who lost the ability to walk.

Guillain–Barre syndrome (GBS) is an acute post-infectious polyradiculoneuropathy with an incidence of 0.34 and 1.34 per 100 000, and is slightly rarer in children than in adults.¹ It has been the primary cause of flaccid paralysis in children since the introduction of the poliomyelitis vaccine.² The mortality rate remains high in the adult population at 3% to 7%,³ whereas it is only 0.2% in the paediatric population.⁴ Motor recovery also seems better, as nearly all children regain the ability to walk, regardless of the electrophysiological form, although axonal forms exhibit a longer recovery time.⁵

In the long term, despite seemingly good motor recovery, approximately 10% of adult patients have severe sequelae,⁶ and nearly two-thirds report different symptoms.⁷ Fatigue is among the most disabling of symptoms in immunological neuropathies.⁸ Some patients also report pain, paraesthesia, feelings of imbalance, etc., which significantly affect their everyday lives. A Dutch study⁹ found that nearly half of patients made negative comments about their psychosocial situation, 38% were forced to change jobs, and 44% had difficulties pursuing recreational activities. In children, motor recovery seems to be better and faster,¹⁰ but only two studies^{11,12} have specifically addressed long-term sequelae following the acute phase of GBS. In these studies, sequelae were frequent and had an impact on patients' everyday lives. The preliminary study identified a rate of highly visible sequelae of approximately 10%, 1 year after the acute phase of GBS in children.

The aim of this study was twofold: first, to estimate the frequency and describe long-term sequelae (at least 3 years after the episode) following GBS where the acute phase occurred during childhood; and second, to identify the factors during the acute phase that predicted an unfavourable long-term development.

METHOD

Participants

In this prospective observational study, we included patients who received care for GBS between January 2000 and June 2016 at the neuropediatric departments of Toulouse and Montpellier University Hospitals. They had all been included in a published study on early GBS sequelae.¹³ In our present study, inclusion criteria were (1) a confirmed clinical diagnosis of GBS determined by the Asbury criteria¹⁴ or a diagnosis of variant forms in the GBS spectrum;¹⁵ (2) a minimum period of 3 years between the acute phase of GBS and the follow-up consultation to ensure an examination of the stabilized sequelae since it is now well known that recovery from GBS can take up to 2 years after the acute period;¹³ (3) age between 0 and 18 years at the time of the acute phase; (4) the absence of an intercurrent event (major neurological or orthopaedic pathologies occurring after GBS); and (5) the absence of chronic polyradiculoneuropathy. Of the 110 families in the previous team's cohort,¹³ 106 matched the criteria and were contacted by two physicians at Toulouse University Hospital (the first and last authors). Fifty-five patients could not be included (lost to follow-up, refusal, etc.) and 51 patients were finally included (Figure S1).

Ethics statement

All parents and children gave their informed oral and written consent after the nature and objectives of the study were thoroughly explained. The local ethics committee (Comite de Protection des Personnes Est III) and the committee on human research Est-III granted authorization to perform this study (sponsor code RC31/19/0311) in accordance with the Declaration of Helsinki.

TABLE 1 Guillain–Barré Syndrome Disability Score (GBS Trial Group 1978).²⁰

Most commonly used measure of levels of activity and participation	
0	Healthy
1	Minor symptoms or sign of neuropathy but capable of manual work/capable of running
2	Able to walk without support of a stick (5m across an open space) but incapable of manual work/running
3	Able to walk with a stick, appliance, or support (5m across an open space)
4	Confined to bed or chair bound
5	Requiring assisted ventilation (for any part of the day or night)
6	Death

Procedure and measurements

Parents were contacted by telephone by a paediatric neurologist and were asked to participate in the study. They were sent a leaflet describing the characteristics of the study, a recruitment letter, and a consent form. When the patients agreed to participate in the study, two paediatric neurologists (BE and EC) gathered information on the patients' clinical and administrative characteristics in the initial phase, using their medical records. All the patients then came for a standard consultation with one of the two paediatric neurologists (BE or EC). They underwent a medical examination to research clinical anomalies, especially cranial nerve impairments, residual ataxia, or pathological deep tendon reflexes. Their complaints were recorded during a semi-structured individual interview. All the patients then underwent the same complete individual evaluation using a comprehensive extensive protocol designed to assess (1) direct GBS sequelae (motor, sensory, and fatigue) and (2) the consequences of sequelae on quality of life. Each area was assessed using one or more self-administered questionnaires, which are listed as follows.

Direct GBS sequelae (motor, sensory, fatigue)

The following tests were used to assess direct GBS sequelae: (1) The Guillain–Barre Syndrome Disability Score (GBSDS)¹⁶ to evaluate overall handicap (Table 1). (2) The Medical Research Council Sum Score¹⁷ to evaluate muscular strength (considered pathological if a muscle group is deficient [Medical Research Council Sum Score < 60]). (3) The Inflammatory Neuropathy Cause and Treatment Sensory Sum Score (INCATSSS)¹⁸ to evaluate sensory disorders (considered abnormal if the score is positive [INCATSSS >0]). (4) The DN4 questionnaire¹⁹ to evaluate the neuropathic aspect of the pain (considered to be positive if the DN4 score ≥ 4). (5) The Fatigue Severity Scale (FSS)²⁰ to evaluate fatigue (considered to be 'significant' if the FSS score ≥ 4 and 'severe' if the FSS score ≥ 5). (6) The Multiple Sclerosis Walking Scale (MSWS),²¹ a self-evaluation questionnaire validated for GBS (considered pathological if the MSWS score >5%) to evaluate walking, cumulated with a 6-minute walking test²² (considered abnormal at -2 standard deviations [SD] from the norm).

Repercussion on everyday life

The following tests were used to assess repercussions on everyday life: (1) the Overall Neuropathy Limitations Scale (ONLS)²³ to evaluate functional limitation in everyday activities (loss of autonomy was considered if ONLS score ≥ 1), (2) the Child Depression Inventory short version (CDI)²⁴ for children older than 7 years, and (3) the Beck Depression Inventory fast screen (BDI)²⁵ for adults were used to screen for depressive symptoms (considered pathological if CDI score >3 or BDI score >4 respectively).

Pathological cut-off for the study

A patient was considered to have late-onset sequelae from the acute phase if the GBSDS was greater than or equal to 1.

The severity of sequelae was evaluated according to the number of domains of complaints: only one motor disorder or sensory disorder complaint or only a complaint of fatigue, or complaints in two or all areas. This classification allowed us to better characterize the sequelae, in particular the heterogeneous group of minor symptoms (GBSDS = 1). Motor disorders were defined as a motor impairment (sensation of muscular weakness noted on the questioning or Medical Research Council Sum Score < 60 or significant infirmity experienced upon walking noted on the MSWS questionnaire or a 6-minute walking test < -2 SD). Sensory disorders were defined as the presence of pain, paraesthesia, cramps, or sensory impairment determined by the INCATSSS. Fatigue was defined by a complaint of fatigue during the medical interview or significant fatigue on the questionnaire (FSS ≥ 4).

The impact of these sequelae on everyday life was defined by the inability to practise sports or receive a normal education or limited autonomy with an abnormal ONLS (score ≥ 1). These sequelae on everyday life were analysed by screening for depression symptoms with a pathological score on the CDI or BDI (CDI >3 or BDI >4).

Statistical analysis

The primary analysis was performed on all patients on complete data (no imputation for missing data). The rate of late-onset sequelae (primary objective) was estimated on the basis of the proportion of patients with a GBSDS ≥ 1 , 3 or more years after the acute phase, with a 95% confidence interval (CI). The characteristics of sequelae were described with numbers and percentages for qualitative variables, and median and first/third quartiles for quantitative variables.

For bivariate comparative analyses, we used Pearson's χ^2 test for qualitative variables (or Fisher's exact test when the conditions for application were not met) and Wilcoxon's non-parametric test for quantitative variables.

To identify predictive factors of late-onset conditions, the judgement criterion was modelled on exposures of interest, one by one, using bivariate logistic regression models after verification of the application conditions. To identify predictive factors of the severity of late-onset conditions, the judgement criterion was modelled on exposures of interest, one by one, using bivariate ordinal logistic regression models after verification of the application conditions.

RESULTS

Population description

One hundred and ten families were contacted. Fifty-five patients could not be included: 44 could not be reached, two refused to participate, and nine did not come to the consultation. Four more patients were not included because they did not meet the inclusion criteria: they had an intercurrent event (serious orthopaedic anomalies not related to GBS [$n = 2$], acute transverse myelitis [$n = 1$], and white matter lesions on brain imagery under exploration with a secondary onset in a child with epilepsy and in utero exposure to sodium valproate [$n = 1$]). Finally, 51 patients were included and analysed (Table 2 and Figure S1).

Among the patients who were included, the median age at diagnosis was 5 years 4 months (IQR 3–10 years, range 1–16 years). There were slightly more males than females (sex ratio 1.3). The initial characteristics at the acute phase of GBS for included patients were compared with those not included to ensure the representativeness of the follow-up cohort in relation to the initial cohort (Table S1 and Figure S1). The individuals who could not be included in the follow-up study were more often the older patients in the cohort ($p < 0.001$). Overall, the other characteristics of those included and those excluded were similar: hospital stay, initial severity, clinical symptoms, demyelination, frequency of transfers to intensive care, and the frequency of intubation. There were more axonal forms in the excluded patients (29.2%) than in the included children (15.6%), but this criterion was not significant ($p = 0.117$).

Description of residual symptoms after 3 years

At the time of the consultation, follow-up after the acute phase of GBS ranged from 3 years to 19 years 6 months, with a median of 6 years 4 months (IQR 5–8 years). The median age at the follow-up consultation was 11 years 6 months (IQR 9–17 years, range 5–31 years). The rate of long-term sequelae, defined by a GBS SDS score of at least 1, was 67% (95% CI 53–78%). No correlation was found between the time since the episode and the sequelae rate ($p = 0.795$). The sequelae therefore seemed to be stable after 3 years and no longer varied with time.

Late-onset characteristics

The late-onset characteristics of the patients are described in Table 3. All patients had regained the ability to walk autonomously. Among those with sequelae ($n = 34$, 67%), most (98%) exhibited minor symptoms but were able to run (GBS SDS score = 1). Only one patient was more severely affected and could not run, although he was still able to walk autonomously for at least 10 metres (GBS SDS score = 2).

With a detailed medical interview, the most common functional signs were paraesthesia (43%), pain (35%), and fatigue (31%). The DN4 questionnaire helped verify the neuropathic nature of pain only in half of the individuals who had pain ($n = 9$ out of 18). Nevertheless, we identified the diagnosis of neuropathic pain thanks to the medical interview in most patients with pain (89% of patients with pain had neuropathic pains such as painful paraesthesia). When measured ($n = 14$), the average pain intensity was 4.9 (SD 1.8) on the Numeric Pain Rating Scale.

TABLE 2 Initial-phase characteristics of the patients included in the follow-up cohort.

	Included (n = 51)	
Centre (n, %)		
Toulouse	33	65%
Montpellier	18	35%
Demographic variables		
Age at diagnosis ^a (years:months)	5:4	2:11; 9:7
Sex (n, %)		
Female	22	43%
Male	29	57%
Initial episode		
Year of the episode (n, %)		
2000–2007	5	10%
2007–2012	17	33%
2012–2014	15	29%
2014–2016	14	28%
GBSDS (n, %)		
1	2	4%
2	14	28%
3	12	23%
4	20	39%
5	3	6%
Interval between onset of symptoms and hospitalisation ^a (days) (n = 50)	5.0	3.0–11.5
Pain complaints (n, %)	39	77%
Paraesthesia complaints (n = 45)	12	27%
Motor impairment complaints (n, %)	45	88%
Sensory impairment complaints (n = 44)	6	14%
Facial paralysis (n, %)	12	24%
Cranial nerve impairments (n, %)	24	47%
Difficulty walking (n, %)	50	98%
Loss of ability to walk (n, %)	22	43%
Asthenia (n, %)	13	26%
Autonomic dysfunction (n, %)	20	39%
Ataxia (n, %)	21	41%
Impairment of consciousness (n, %)	1	2%
Aetiology (n, %)		
Anti-neuronal antibodies (n = 39)	13	33%
Campylobacter (n = 38)	5	13%
Axonal Guillain–Barré syndrome (n = 45)	7	16%
Initial care		
Treatment (n, %)	43	84%
Intubation (n, %)	3	6%
Transfer to intensive care (n, %)	11	22%
Major sequelae following the episode (n = 50)	2	4%
Length of hospitalization ^a (days)	7.0	6.0–14.5

^aQuantitative variables by median and first and third quartiles. Total number is indicated if data are missing.

The detection of a deep tendon reflex anomaly (28%) was not considered as a sequela because it was not clinically relevant. However, the rest of the neurological examination found disabling sequelae (18%) such as ataxia, motor deficit, or cranial nerve impairments.

The FSS questionnaire identified significant fatigue in 20% of patients and severe fatigue in 4%. Infirmity experienced upon walking, measured with the MSWS questionnaire, was significant for 26% of patients. The 6-minute walking test, performed by 46 patients, was below 2 SD for 15% of them. On average, patients had performances of approximately -1.1 SD (1.4 SD) and the distance travelled during this walking test was correlated with the infirmity experienced upon walking measured with the MSWS questionnaire (correlation coefficient -0.6 ; $p < 0.001$).

These symptoms had a significant impact on the everyday lives of the patients in our cohort. In fact, autonomy in everyday activities, as evaluated by the ONLS, was abnormal for 14% of patients. Most children (96%) had been able to receive a normal education, although adaptation to the disability was sometimes needed in the first months after the acute phase of GBS. Three patients (6%) were unable to practise sports because of motor impairment or effort-related susceptibility to fatigue. Symptoms of depression, screened by the CDI or BDI, were detected in 34% of patients (15% male, 57% female). The same patients who reported symptoms of depression also reported fatigue ($p = 0.019$), motor impairment ($p = 0.019$), and complaints ($p = 0.043$).

Combination of complaints and severity score

A GBSDS equal to 1 represents a heterogeneous group of minor symptoms. To clarify this group, we classified the sequelae into three different areas (motor, sensory, and fatigue).

Motor complaints

All patients with a motor impairment (complaints or abnormal motor strength during examination or ataxia) also had difficulty walking, as measured by the MSWS questionnaire or an abnormal 6-minute walk test. Therefore, the MSWS questionnaire and 6-minute walking test detected more patients than the interview or physical examination. These investigations seemed to be the most sensitive method for identifying motor complaints: 14 patients (45%) among patients with minor sequelae (GBSDS = 1).

Sensory complaints

Twenty-seven patients (82%) with minor symptoms were identified as having a sensory disorder (complaint of pain and/or paraesthesia and/or cramps and/or abnormal INCATSSS). The semi-structured medical interview was more sensitive than questionnaires in identifying sensory complaints. In fact, only one patient had an abnormal sensory test (INCATSSS >0).

TABLE 3 Late-onset sequelae.

	Total (n = 51)	
General characteristics (n, %)		
Age ^a (years:months)	11:6	9:2–16:10
Follow-up ^a (years:months)	6:4	4:10–8:5
GBSDS		
0	17	33%
1	33	65%
2	1	2%
Abnormal education	2	4%
Inability to do sports	3	6%
Patient complaints (n, %)		
Fatigue	16	31%
Pain	18	35%
Paraesthesia	22	43%
Motor impairment	3	6%
Cramps (n = 50)	5	10%
Tremors	5	10%
Falling	3	6%
Fine motor disorders	4	8%
Neurological examination (n, %)		
Abnormal DTR	14	28%
Abnormal examination, except abnormal DTR	9	18%
Ataxia	2	4%
Cranial nerve anomalies	1	2%
Abnormal motor strength (MRCSS < 60)	4	8%
Abnormal sensory test (INCATSSS > 0)	1	2%
Standardized tests and questionnaires (n, %)		
Significant fatigue (FSS ≥ 4)	10	20%
Severe fatigue (FSS ≥ 5)	2	4%
Neuropathic pain (DN4 + interview)	16	31%
Neurological disability with loss of autonomy (ONLS ≥ 1)	7	14%
Upper limb disability (ONLS upper limb ≥ 1)	4	8%
Lower limb disability (ONLS lower limb ≥ 1)	4	8%
Depression CDI or BDI (n = 47)	16	34%
Inability to walk (MSWS > 5%)	13	26%
Distance walked < -2 SD (n = 46)	7	15%

^aQuantitative variables by median and first and third quartiles.

Total number is indicated if data are missing.

Abbreviations: BDI, Beck Depression Inventory fast screen; CDI, Child Depression Inventory short version; DTR, deep tendon reflexes; FSS, Fatigue Severity Scale; GBSDS, Guillain-Barré Syndrome Disability Score; INCATSSS, Inflammatory Neuropathy Cause and Treatment Sensory Sum Score; MRCSS, Medical Research Council Sum Score; MSWS, Multiple Sclerosis Walking Scale; ONLS, Overall Neuropathy Limitations Scale; SD, standard deviation.

Fatigue complaints

Once again, the semi-structured medical interview seemed more sensitive than the FSS questionnaire in identifying patients with sequelae of fatigue: 16 patients (49% of those with minor symptoms) were considered to have symptoms of fatigue while the FSS score was only positive (≥ 4) for 12 out of 16 patients.

These different types of complaint were often interconnected. Sometimes, one patient presented with several types of complaint. The patient experiencing the most severe sequelae (GBSDS = 2) experienced fatigue and motor and sensory disorders.

Moreover, a complaint in one domain increased the likelihood of a complaint in another. For example, patients with fatigue more frequently also had a sensory complaint (odds ratio [OR] 4.1, 95% CI 1.1–17.1; $p = 0.034$) or a motor complaint (OR 22.4, 95% CI 5.2–129.9; $p < 0.001$).

We established a severity score based on the number of complaint domains affecting each patient (Table 4). Nine of the 10 patients (90%) with repercussions on their everyday lives (inability to practise sports or receive a normal education or limited autonomy with an abnormal ONLS) were affected in all three areas. On the contrary, 31 patients (78%) without repercussions in their everyday lives had no complaints or were affected in only one area. Therefore, it would seem that the impact on a patient's life increased ($p < 0.001$) with the number of areas affected.

Two patients had no affected domains, but a GBSDS score of 1 due to a ‘fine motor disorder’ and complaints of ‘tremors’ that were not considered in the calculation of the number of domains affected, but which nevertheless are minor complaints.

Initial factors associated with severity of residual symptoms

The initial characteristics associated with the risk of late-onset sequelae (Table 5) are variables related to the severity of the initial episode: an initial GBSDS score of at least 4 (GBSDS ≥ 4 , OR 6.7; $p = 0.009$) and loss of the ability to walk ($p = 0.014$).

The initial characteristics associated with the severity (number of areas of complaint affected) of the late-onset sequelae (Table S1 and Figure S1) are also variables related to the severity of the initial episode: GBSDS at least 4 ($p = 0.002$), loss of the ability to walk ($p = 0.001$), and length of hospitalization ($p = 0.013$). An association was also noted between female sex and a greater number of domains affected ($p = 0.005$).

TABLE 4 GBSDS and repercussions on everyday life based on the number of areas affected.

	n	Number of areas affected							
		0 (n = 18)	1 (n = 13)	2 (n = 6)	3 (n = 14)				
GBSDS									
0	17	17	100.0	0	0.0	0	0.0	0	0.0
1	33	2	6.1	13	39.4	6	18.2	12	36.4
2	1	0	0.0	0	0.0	0	0.0	1	100.0
Repercussions on everyday life									
No	41	18	43.9	13	31.7	5	12.2	5	12.2
Yes	10	0	0.0	0	0.0	1	10.0	9	90.0

Abbreviation: GBSDS, Guillain-Barré Syndrome Disability Score.

DISCUSSION

To our knowledge, this is the largest cohort with the acute phase of GBS occurring during childhood in which long-term sequelae have been examined. In this study, we aimed to estimate the frequency and describe the direct (motor, sensory, and fatigue) and indirect (repercussions on quality of life) long-term sequelae (at least 3 years after the acute phase). We found a rate of 67% of late-onset sequelae after the acute phase. Three areas of complaint were investigated: fatigue disorders, present in 33% of patients; sensory disorders, in 55%; and motor disorders, in 31%. In our study, we also aimed to highlight the characteristics of the acute phase that predicted unfavourable long-term development. It is interesting to understand that the population was derived from a first retrospective study in which the rate of important sequelae in the first year of these patients was estimated at 9%.¹³ Usually, the follow-up of these patients was quickly stopped because of a good overall recovery and the minor sequelae probably went unnoticed. We found that the factors associated with late-onset sequelae are related to the severity at the initial phase: GBSDS of at least 4 and loss of the ability to walk. Female sex seems to be a risk factor of more severe sequelae. Therefore, the predictive factors of the severity of sequelae were initial severity and female sex.

All the patients who were included survived, had recovered the ability to walk autonomously, and most could run (98%). Two-thirds of our patients experienced long-term sequelae. Our results highlighted ‘silent’ late-onset sequelae. In an adult population, 65% of minor sequelae were observed⁶ and comparable rates following childhood GBS, which was in line with previous studies.¹² The nature of complaints was in agreement with those in the literature, particularly paraesthesia, pain, and fatigue, which were the most frequent complaints. We compared the frequencies of the different sequelae in our cohort with previous cohorts (Table 6), especially with two paediatric studies^{11,12} and one mixed paediatric/ young adult study.⁷ Results of late-onset sequelae are fairly heterogeneous between the four studies because of the areas assessed in each. Our study goes deeper, and shows permanent residual sequelae because one-third of the patients exhibited pain and one-third fatigue. Fatigue is a common manifestation of GBS and has been most studied in adults: 60% of adult patients experience fatigue 1 year after the acute phase.²⁶ Our study extends these findings to the paediatric population, highlighting the importance of examining fatigue in children after GBS.

We also noted a strong association between complaints. For example, fatigue was mainly associated with motor complaints. However, it seems difficult to determine the trend and the direction of the relation: does motor disorder induce fatigue or does a child have walking difficulties because of fatigue?

TABLE 5 Initial characteristics associated with late-onset sequelae (bivariate logistic regressions).

Initial characteristics	Presence of sequelae		Bivariate models		
	No	Yes	OR	95% CI	p
Male ^a	n = 17, 65%	n = 34, 53%	0.6	0.2–2.0	0.426
Mean age at diagnosis (SD) (years:months)	6:2 (3:10)	6:7 (4:4)	1.0	0.9–1.2	0.797
Initial symptoms					
Initial GBSDS ≥4	18%	59%	6.6	1.8–33.0	0.009*
Pain	82%	74%	0.6	0.1–2.4	0.487
Paraesthesia	40%	20%	0.4	0.1–1.5	0.160
Motor impairment	82%	91%	2.2	0.4–13.3	0.365
Sensory impairment	6%	18%	3.3	0.5–65.8	0.302
Facial paralysis	18%	27%	1.7	0.4–8.5	0.487
Cranial nerve impairment	47%	47%	1.0	0.3–3.3	0.100
Difficulty walking	100%	97%	—	—	—
Loss of the ability to walk	18%	56%	5.9	1.6–29.2	0.014*
Asthenia	18%	29%	1.9	0.5–9.8	0.368
Autonomic dysfunction	29%	44%	1.9	0.6–7.1	0.314
Ataxia	41%	41%	1.0	0.3–3.4	0.100
Loss of consciousness	0%	3%	—	—	—
Aetiology					
Anti-neuronal antibodies	17%	41%	3.4	0.7–25.3	0.155
Campylobacter	7%	17%	2.6	0.3–53.9	0.415
Axonal Guillain–Barré syndrome	7%	20%	3.5	0.6–69.7	0.268
Management					
Treatment	71%	90%	4.3	0.9–23.8	0.070
Intubation	0%	9%	—	—	—
Transfer to intensive care	12%	27%	2.7	0.6–19.3	0.241
Mean length of hospitalization (SD) (days)	7.9 (4.5)	15.4 (18.6)	1.1	1.0–1.3	0.077

^aAll percentages are those in columns (frequency of the modality in each group defined by the presence or absence of sequelae).

*p < 0.05.

Abbreviations: CI, confidence interval; GBSDS, Guillain–Barré Syndrome Disability Score; OR, odds ratio; SD, standard deviation.

Overall, although only one-third of the children were completely free of sequelae, most patients were considered cured, without sequelae, at the end of the initial follow-up. Our study highlights the need for long-term follow-up for children who have had GBS. Therefore, we recommend a routine consultation at a university centre for evaluation of long-term sequelae 3 years after the acute phase to assess fatigue, sensory impairment (especially pain or paraesthesia), and motor impairment (with the MSWS questionnaire, the most sensitive way of identifying motor disorder). Identifying these sequelae seems significant to effectively inform patients and their families after the acute phase because sequelae can lead to permanent repercussions on everyday life. It may also help to identify appropriate rehabilitation programmes for children. It is known that the symptoms related to GBS can be alleviated in adults after therapy targeting specific activities²⁷ or bicycle exercises,²⁸ with very good results for fatigue and functional scores. Follow-up with rehabilitation physicians seems essential to improve the autonomy and independence of all children who have GBS but there is no evidence-based medical trial about rehabilitation programmes for children after GBS.

Sensory testing with the INCATSSS was almost always normal, which indicates proper large-fibre recovery (tactile discrimination, pallesthesia, and proprioception). On the contrary, the frequency of paraesthesia and neuropathic pain is more indicative of residual small-fibre sequelae. This predominantly small-fibre complaint has been previously demonstrated in adult patients after GBS.²⁹

We aimed to identify the link between direct late-onset sequelae and repercussion on daily life. Overall, we determined that, for a significant proportion of the children with GBS, residual sequelae are part of daily life and for some there is a great impact on quality of life as practising sports is inhibited (6%), and normal schooling (4%) and functional autonomy (in 14% of cases) are compromised.

Therefore, in our study, the severity of the impact on quality of life seemed to be related to the number of areas of complaint affected: sensory, motor, or fatigue. In most instances, patients whose daily lives were impacted were affected in the three domains.

It would be beneficial if future research were to delve further into this relation between these late-onset sequelae and the GBSDS. GBSDS stage 1, 'minor symptoms', is currently non-specific, and could be subdivided according to the type or number of areas of complaint affected (fatigue, sensory disorders, and motor disorders). These areas of complaint could be integrated into the GBSDS. This graduation would be interesting to improve the characterization of this heterogeneous group of patients with minor sequelae.

As many as one out of every three children who had been affected by GBS were at risk for depressive symptoms (34%). Female sex was a predictive factor and more females (57%) than males (15%) had depressive symptoms. Our results did not correspond with previous ones. Although it is well established that autoimmune diseases of the nervous system increase the risk of psychiatric illnesses,³⁰ the rate of depressive symptoms in GBS was close to 7% to 10%.^{12,31} We can explain this by the scales used in our study. Both scales, the CDI²⁴ for children and the BDI²⁵ for adults, were used just for screening and to detect depressive symptoms. Therefore, these should be considered as screening scales not as diagnostic scales. In addition, both scales were short versions, identified to be more sensitive than long versions.²⁴

We identified no association between the frequency of depressive symptoms and age at diagnosis or initial severity. However, we noted a significant association between depressive symptoms and fatigue ($p = 0.019$). The same trend was noted between depressive symptoms and motor complaints ($p = 0.019$). The number of complaints was also found to be associated with the risk of depressive symptoms ($p = 0.043$): the risk of depression increases as the number of complaints increases. We also detected an association between depressive symptoms and indirect complaints (repercussions on quality of life). At equal age, sex, and initial severity, children with GBS repercussions on quality of life were found to be most often depressed (OR = 8.2 [1.3–82.3]; $p = 0.041$). However, because our study was cross-sectional, it was difficult to specify the implication of one or the other, especially which was causing the other. A complementary study would be very important to examine the long-term psychiatric repercussions of GBS in children.

TABLE 6 Comparison of the results with data from the literature.

Population				
Country	France (this study)	Netherlands ¹⁷	Canada ¹⁶	Bangladesh ¹²
Number of patients	51	37	31	38
Median age at diagnosis (years:months)	6:6 (1–16)	9 (0–18)	9 (3–18)	20 (4–39)
Male children (%)	57	51	45	58
Median follow-up time (years)	6 (3–20)	11 (1–22)	5 (3–10)	7 (1–13)
Median age at evaluation (years:months)	11:6 (5–31)	20 (4–39)	—	30 (7–55)
Results				
Residual complaints (GBS SD ≥ 1) (%)	68	65	27	63
Fatigue (%)				
Complaints	34	—	12	—
Significant (FSS >4)	19	—	—	—
Severe (FSS >5)	5	14	—	13
Pain (%)	34	24	8	29
Muscular weakness (MRCSS < 60) (%)	8	8	—	—
Muscular weakness (other tests) (%)	—	—	23	—
Sensory disorder (INCATSSS > 0) (%)	2	14	—	—
Sensory disorder (other tests) (%)	—	—	15	—
Paraesthesia (%)	47	38	—	11
Tremors (%)	9	11	—	—
Cranial nerve impairments (%)	2	3	—	—
Pathological deep tendon reflexes (%)	27	5	27	—
Symptoms of depression (%)	32	7	—	16

Data are expressed as median (range) for quantitative data; otherwise, they are percentages.

Abbreviations: FSS, Fatigue Severity Scale; GBS, Guillain-Barré syndrome; INCATSSS, Inflammatory Neuropathy Cause and Treatment Sensory Sum Score; MRCSS: Medical Research Council Sum Score; SD, standard deviation.

In our study, the presence of late-onset sequelae after the critical phase was significantly related to two factors. First, we found that the initial severity during the acute phase of GBS was correlated with the presence of late-onset sequelae and more severe sequelae (with a larger number of areas of complaint present in the severity score). In adult GBS, the initial clinical severity has been well known to be a predictive factor for late-onset sequelae.³² However, to our knowledge, it is the first time that it has been attested in children. This supports the need for optimal treatment, especially for children with severe forms of GBS in the acute phase because it would seem that they will be the most affected in the long term. Although intravenous immunoglobulins seem to accelerate motor recovery in children, ³³ this treatment may not influence the prognosis in the longer term.^{34,35}

Second, in our study, female sex was a predictive factor for more serious sequelae on the severity score. We found only one study with adult patients that also identified female sex as a predictive factor for a poor long-term prognosis after GBS, regardless of the functional or psychological level.³⁶ Several hypotheses could support this finding. It has been consistently demonstrated in many studies^{37,38} that the GBS incidence was higher among males than females (male: female ratio 1.59:1). Such male predominance is uncommon for an autoimmune disease. Furthermore, GBS incidence is modified during pregnancy,³⁹ which supports the theory of a hormonal action or a genetic/ sex-determination influence. This raises

the question of whether there is also a difference in the sequelae between female and male children.

Lastly, in our study, we detected no association between age at the time of the episode and the rate of sequelae. Therefore, age at the time of GBS is not an explanatory factor for sequelae, nor is it an aggravating or enhancing factor. Consequently, it should be noted that the silent residual sequelae of GBS are generally stable 2 years after the onset of GBS. However, this finding is very important to set the date for follow-up care.

To our knowledge, ours was the largest cohort with the acute phase of GBS occurring during childhood in which long-term sequelae have been examined. Although the number of patients lost to follow-up compared with the original cohort may raise concerns about selection bias, this bias is more likely to be in favour of underestimating the rate of distant sequelae, as it has been shown that initial severity is associated with the risk of sequelae, and the initial involvement of included patients was slightly less severe (non-significant) than that of excluded patients (Table S1 and Figure S1). However, we cannot exclude the possibility that the non-included patients, who had an episode earlier than the others, had different characteristics in other respects and that this influenced the result.

Patient assessment was performed by a single examiner, which helped to homogenize the assessment across patients, but did not eliminate examiner-related measurement bias. However, we used several tests and questionnaires that are validated and standardized. Three types of complaint were investigated: fatigue, sensory disorders, and motor disorders, by means of both a semi-structured interview and standardized scales. The semi-structured interview, even if more subjective and examiner-relative, was more sensitive than the standardized questionnaire scores in assessing fatigue and neuropathic pain. The standardized questionnaires detected less than half of the children complaining of fatigue during a semi-structured interview. Therefore, in clinical practice, for these two domains it seems that identifying the complaint during a semi-structured interview may be preferable to using standardized scales. Conversely, for motor impairment, the scores on the questionnaires seemed more sensitive than recording the complaint in a semi-structured interview. The MSWS questionnaire, especially, seemed to effectively detect patients with a motor and walking disorder with a threshold set at 5%, beyond which the infirmity experienced seemed significant. According to our observations, the DN4 questionnaire was found to be inappropriate for paediatric patients. Indeed, most of the items were too complex for younger patients. This observation is shared by other paediatricians and an adaptation of the DN4 questionnaire using illustrations for younger patients is currently being validated. The ONLS questionnaire was useful in discovering physical functioning, but it could not take account of patients' participation in activities.

In this study, we created a severity score based on the number of domains affected in sensory impairment, motor impairment, and fatigue. This score is interesting because it allows us to better characterize a heterogeneous group of patients with mild sequelae. We have shown that more severe scores have more frequent impacts on activities of daily living. However, for clinical use, these tests and questionnaires should first be validated specifically in other populations, which was not the aim of this study. In terms of identifying predictive factors, this study allowed us to prospectively identify initial characteristics associated with the presence and severity of sequelae. It would be interesting to confirm the relevance and evaluate the performance of these factors, as predictors that could potentially guide clinical decisions, in other studies and other populations. However, from this study, we cannot draw

causal conclusions about the relation between these factors and subsequent disease progression, as neither the study design nor the analysis strategy was designed to do so.

CONCLUSION

We highlight the fact that two-thirds of the children in our study had late-onset sequelae after childhood GBS. These did not improve over time. Late-onset sequelae are often underestimated in children who have recovered the ability to walk and, for the most part, to run after being paralysed in the acute phase of the disease.

The risk of sequelae is related to the initial severity (particularly the loss of the ability to walk during the acute phase of GBS) and to sex (females are more likely than males to have more severe sequelae).

Three areas of complaint are possible: fatigue, sensory disorders, and motor disorders. We have highlighted the fact that silent residual sequelae of GBS limit participation in sports, normal schooling, autonomy, etc., de facto hindering everyday life. The association of several areas of complaint leads to repercussions on everyday lives. Depressive symptoms are also especially common. These conditions could be integrated into the scale to evaluate sequelae after GBS (GBSDS). Stage 1, which is characterized by the rather imprecise term ‘minor sequelae’, could be subdivided. A full follow-up after 2 or 3 years from the acute phase seems essential once the situation has stabilized.

CONFLICT OF INTEREST STATEMENT

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

data are available

REFERENCES

1. McGrogan A, Madle GC, Seaman HE, de Vries CS. The Epidemiology of Guillain-Barre Syndrome Worldwide. *Neuroepidemiology*. 2009;32(2):150–63.
2. WHO-AIREN meeting, World Health Organization. Acute onset flaccid paralysis. Geneva; 1993.
3. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barre syndrome. *The Lancet*. august 2016;388(10045):717–27.
4. Delannoy A, Rudant J, Chaignot C, Bolgert F, Mikaeloff Y, Weill A. Guillain-Barre syndrome in France: a nationwide epidemiological analysis based on hospital discharge data (2008-2013). *J Peripher Nerv Syst*. mars 2017;22(1):51–8.

5. Karalok ZS, Taskin BD, Yanginlar ZB, Gurkas E, Guven A, Degerliyurt A, et al. Guillain-Barre syndrome in children: subtypes and outcome. *Child's Nervous System*. nov 2018;34(11):2291–7.
6. Desforges JF, Ropper AH. The Guillain–Barre Syndrome. *New England Journal of Medicine*. 23 apr 1992;326(17):1130–6.
7. Chowdhury IH, Basher A, Habibullah AK, Asfia KN, Pathan FH, Kamal MM. Evaluation of Post Guillain-Barre Syndrome (GBS) Patients: A Cross Sectional Study. *Mymensingh Med J*. apr 2019;28(2):449–55.
8. Merkies ISJ, Faber CG. Fatigue in immune-mediated neuropathies. *Neuromuscular Disorders*. dec 2012;22:S203-7.
9. Bernsen RAJAM, de Jager AEJ, Schmitz PIM, van der Meche FGA. Long-term impact on work and private life after Guillain–Barre syndrome. *Journal of the Neurological Sciences*. sept 2002;201(1–2): 13–7.
10. Ryan MM. Pediatric Guillain-Barre syndrome: Current Opinion in Pediatrics. dec 2013;25(6):689–93.
11. Vajsar J, Fehlings D, Stephens D. Long-term outcome in children with Guillain-Barre syndrome. *The Journal of Pediatrics*. March 2003;142(3):305–9.
12. Roodbol J, de Wit M-CY, Aarsen FK, Catsman-Berrevoets CE, Jacobs BC. Long-term outcome of Guillain-Barre syndrome in children: Roodbol et al. *Journal of the Peripheral Nervous System*. June 2014;19(2):121–6.
13. Estrade S, Guiomard C, Fabry V, Baudou E, Cances C, Chaix Y, et al. Prognostic factors for the sequelae and severity of Guillain-Barre syndrome in children. *Muscle & Nerve*. dec 2019;60(6):716–23.
14. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barre syndrome. *Ann Neurol*. 1990;27 Suppl:S21-4.
15. The GBS Classification Group, Wakerley BR, Uncini A, Yuki N. Guillain–Barre and Miller Fisher syndromes—new diagnostic classification. *Nature Reviews Neurology*. sept 2014;10(9):537–44.
16. Hughes, R.A., Newsom-Davis, J.M., Perkin, G.D. and Pierce, J.M. (1978) Controlled trial prednisolone in acute polyneuropathy. *Lancet*, 2, 750–3.
17. Compston A. Aids to the Investigation of Peripheral Nerve Injuries. Medical Research Council: Nerve Injuries Research Committee. His Majesty's Stationery Office: 1942
18. Draak THP, Vanhoutte EK, van Nes SI, Gorson KC, Van der Pol W-L, Notermans NC, et al. Comparing the NIS vs. MRC and INCAT sensory scale through Rasch analyses: Comparing the NIS vs. MRC and INCAT. *Journal of the Peripheral Nervous System*. sept 2015;20(3):277–88.

19. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4): Pain. march 2005;114(1):29–36.
20. Krupp LB. The Fatigue Severity Scale: Application to Patients With Multiple Sclerosis and Systemic Lupus Erythematosus. Archives of Neurology. 1 oct 1989;46(10):1121.
21. Graham RC. Clinimetric properties of a walking scale in peripheral neuropathy. Journal of Neurology, Neurosurgery & Psychiatry. 18 may 2006;77(8):977–9.
22. Ulrich S, Hildenbrand FF, Treder U, et al. Reference values for the 6-minute walk test in healthy children and adolescents in Switzerland. BMC Pulm Med 2013;13:49. <https://doi.org/10.1186/1471-2466-13-49>
23. Graham RC. A modified peripheral neuropathy scale: the Overall Neuropathy Limitations Scale. Journal of Neurology, Neurosurgery & Psychiatry. 18 may 2006;77(8):973–6.
24. Allgaier A-K, Fruhe B, Pietsch K, Saravo B, Baethmann M, Schulte-Korne G. Is the Children's Depression Inventory Short version a valid screening tool in pediatric care? A comparison to its full-length version. Journal of Psychosomatic Research. nov 2012;73(5):369–74.
25. Alsaleh M, Lebreuilly R. Validation de la traduction française d'un questionnaire court de dépression de Beck (BDI-FS-Fr). Annales Medico-psychologiques, revue psychiatrique. sept 2017;175(7):608–16.
26. Garssen MPJ, Koningsveld R, Doorn PA. Residual fatigue is independent of antecedent events and disease severity in Guillain-Barre syndrome. Journal of Neurology. sept 2006;253(9):1143–6.
27. Khan F, Pallant J, Amatya B, Ng L, Gorelik A, Brand C. Outcomes of high-and low-intensity rehabilitation programme for persons in chronic phase after Guillain-Barre syndrome: A randomized controlled trial. Journal of Rehabilitation Medicine. 2011;43(7):638–46.
28. Garssen MPJ, Bussmann JBJ, Schmitz PIM, Zandbergen A, Welter TG, Merkies ISJ, et al. Physical training and fatigue, fitness, and quality of life in Guillain-Barre syndrome and CIDP. Neurology. 28 dec 2004;63(12):2393–5.
29. Martinez V, Fletcher D, Martin F, Orlikowski D, Sharshar T, Chauvin M, et al. Small fibre impairment predicts neuropathic pain in Guillain-Barre syndrome: Pain. oct 2010;151(1):53–60.
30. Liu Y, Tang X. Depressive Syndromes in Autoimmune Disorders of the Nervous System: Prevalence, Etiology, and Influence. Front Psychiatry. 2018 Sep 25;9:451.
31. Tzeng NS, Chang HA, Chung CH, Lin FH, Yeh CB, Huang SY, et al. Risk of psychiatric disorders in Guillain-Barre syndrome: A nationwide, population-based, cohort study. J Neurol Sci. oct 2017;381:88–94

32. Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain-Barre syndrome. *Neurology*. 15 march 2011;76(11):968–75.
33. Hughes R, Swan A, van Doorn P. Intravenous immunoglobulin for Guillain-Barre syndrome. *Cochrane Database Syst Rev* Published Online First: 2014.
34. Kalita J, Kumar M, Misra UK. Role of IV Immunoglobulin in Indian Children With Guillain-Barre Syndrome*: *Pediatric Critical Care Medicine*. juill 2019;20(7):652–9.
35. Kuluz JW. Is It Possible That IV Immunoglobulin Does Not Improve Outcome in Children With Guillain-Barre Syndrome? Answer: Yes*. *Pediatric Critical Care Medicine*. juill 2019;20(7):681–2.
36. Khan F, Pallant JF, Ng L, Bhasker A. Factors associated with long-term functional outcomes and psychological sequelae in Guillain–Barre syndrome. *Journal of Neurology*. dec 2010;257(12): 2024–31.
37. Delannoy A, Rudant J, Chaignot C, Bolgert F, Mikaeloff Y, Weill A. Guillain-Barre syndrome in France: a nationwide epidemiological analysis based on hospital discharge data (2008-2013). *Journal of the Peripheral Nervous System*. march 2017;22(1):51–8.
38. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barre syndrome: a systematic review and meta-analysis. *Neuroepidemiology*. 2011;36(2):123–33.
39. Jiang G-X, de Pedro-Cuesta J, Strigard K, Olsson T, Link H. Pregnancy and Guillain-Barre Syndrome: A Nationwide Register Cohort Study. *Neuroepidemiology*. 1996;15(4):192–200.