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Original article

Guillain-Barré syndrome in children – High occurrence of Miller Fisher syndrome in East Asian region

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Abstract

Background: Guillain-Barré syndrome (GBS) is a rare acquired immune-mediated polyneuropathy. Updated population-based data concerning paediatric GBS is needed.

Methods: Paediatric patients aged below 18 years diagnosed with GBS between 2009 and 2018 in all 11 paediatric departments in Hong Kong were identified from the Hong Kong Hospital Authority Clinical Data Analysis and Reporting System. The collected data from medical health records were reviewed by paediatric neurologist from each department. Estimated incidence of paediatric GBS was calculated. We also compared our findings with other paediatric GBS studies in Asia.

Abbreviations: GBS, Guillain-Barré syndrome; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory axonal polyneuropathy; MFS, Miller Fisher syndrome; HA, Hospital Authority; CDARS, Clinical Data Analysis and Reporting System; CSF, cerebrospinal fluid; NCS, nerve conduction study; CMAP, compound muscle action potential; SNAP, sensory nerve action potential; LOS, length of stay

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Results: 63 subjects of paediatric GBS were identified, giving an estimated annual incidence of 0.62 per 100,000 population. Half of the subjects had acute inflammatory demyelinating polyneuropathy (AIDP) (n = 31; 49.2%), one quarter had Miller Fisher Syndrome (MFS) (n = 16; 25.4%), one-fifth had axonal types of GBS (n = 12; 19.0%), and four were unclassified. Paediatric subjects with axonal subtypes of GBS compared to the other 2 subtypes, had significantly higher intensive care unit (ICU) admission rates (p = 0.001) and longest length of stay (p = 0.009). With immunomodulating therapy, complete recovery was highest in those with MFS (100%), followed by AIDP (87.1%) and axonal GBS (75%). Our study also confirms a higher MFS rate for paediatric GBS in East Asia region and our study has the highest MFS rate (25.4%).

Conclusion: Our population-based 10-year paediatric GBS study provides updated evidence on estimated incidence, healthcare burden and motor outcome of each subtype of paediatric GBS and confirmed a higher occurrence of paediatric MFS in East Asia.

Keywords: Paediatric; Guillain-Barré syndrome; Acute inflammatory demyelinating polyneuropathy; Acute motor sensory axonal neuropathy; Acute motor axonal neuropathy; Miller Fisher syndrome; Children

1. Introduction

Guillain-Barré syndrome (GBS) is a rare, acquired auto-immune disorder with different clinical and electrophysiological subtypes. Often preceded by antecedent infection or vaccination, it is characterised by acute inflammation and damage to peripheral nerves, nerve roots and sometimes cranial nerves. Classically, it presents as rapidly progressive, ascending flaccid paralysis with diminished or absent reflexes [1].

There are four clinical variants of GBS: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and Miller Fisher syndrome (MFS). Their relative distribution is subjected to regional variation. AIDP is the predominant GBS subtype in Europe and North America, Oceania and Middle East [2], and also in Asia [2–7], and has a demyelinating pattern of motor and sensory nerves in electrophysiological studies. AMAN was previously thought to be the most prevalent subtype amongst Chinese population and was once called the Chinese paralytic syndrome [8]. However, later studies have shown that AMAN is not only common in east Asia [9–11], but also in India [12,13] and Bangladesh [2]. AMSAN resembles AMAN but has an additional sensory component. Whilst MFS is rare amongst Caucasians, it is more common in Asia [5], and has been reported to constitute up to 20–26% of the GBS cases in Taiwan [6] and Japan [7] in their adult patients respectively. MFS/GBS overlapping syndrome is also more common in Asia with incidence rate close to that of classical MFS [5,14].

The incidence of paediatric GBS is likewise subjected to considerable regional variation. The global incidence rate of GBS is estimated to be 0.34–1.34 per 100,000 people per year in children aged 0–15 years [15]. Another global study showed the paediatric estimated incidence rate of GBS were 0.62 and 0.75 per 100,000 people per year for age group 0–9 years and 10–19 years respectively [16]. The regional estimated incidence could be as high as 1.7 per 100,000 people per year in Bangladesh [17], or as low as 0.22–0.5 per 100,000 people per year in Northern China [18].

We performed a 10-year territory-wide retrospective study on Paediatric GBS with the aim to better understand the local incidence, presentation, treatment, and outcome relating to different GBS subtypes in Hong Kong. We have also performed a literature search to study how the local epidemiology of paediatric GBS compares with other Asian regions.

2. Methods

This is a retrospective study of paediatric subjects (<18 years old) with a confirmed diagnosis of GBS admitted to any of the 11 paediatric units of the public hospitals under the Hospital Authority of Hong Kong between 1st January 2009 and 31st December 2018 inclusive. Collectively, the Hospital Authority managed all the public hospitals in Hong Kong that covered more than 85% of all admissions within the whole Hong Kong territory. Moreover, almost all paediatric patients diagnosed with GBS in the private hospitals would be referred to the public hospitals for possible intensive care and rehabilitation care need, so our current study provided a highly representative cohort of paediatric GBS in our region. The Hospital Authority uses diagnostic coding, which contains mapped codes for ICD-10 available via the Clinical Data Analysis and Reporting System (CDARS). All admissions within public hospitals under the Hospital Authority with a specific diagnosis are searchable via the CDARS using ICD-10 codes. Admissions coded with G61.0 Guillain-Barré syndrome (GBS) in subjects aged <18 years inclusive on the day of admissions were retrieved. Duplicated entries due to repeated admissions or patients being

transferred to other hospitals were checked and excluded. Children with other confirmed causes including acute flaccid paralysis, chronic inflammatory demyelinating polyneuropathy and doubtful diagnosis were also excluded from this study.

Systemic evaluation of each patient's past clinical summaries from the electronic medical health records were performed by a paediatric neurologist from each participating hospital when collecting the acquired data. Information on individual subjects' clinical presentation, blood and cerebrospinal fluid (CSF) investigation results, nerve conduction study findings, treatments administered, need for paediatric intensive care admission and ventilation use, and the functional outcome, were collected and analysed. The functional outcome was categorized as (1) able to run; (2) able to walk independently but unable to run; (3) able to walk with support; (4) need wheelchair use. The diagnosis of paediatric GBS in Hong Kong is based on clinical history, physical examination, and the supporting investigations including CSF examinations and electrodiagnostic studies. We have further categorised our cohort using the Brighton Collaboration Diagnostic Criteria for Guillain Barre syndrome (GBS) and Miller Fisher syndrome (MFS) into different level of diagnostic certainty [19,20]. Those with MFS presentation and limb weakness were classified as MFS/GBS overlapping syndrome and evaluated according to the Brighton Collaboration Diagnostic Criteria for GBS.

For the nerve conduction studies (NCS), age-specific reference values were taken into account, especially in the younger pre-adolescent children. The electrophysiological diagnostic criteria adopted to determine the demyelinating sensorimotor polyneuropathy (AIDP subtype), included non-uniform slowing of the conduction velocities of both motor and sensory nerves, prolongation of distal motor latencies, increased F-wave latencies, dispersion of proximally evoked compound motor action potentials, and conduction block. The presence of typical 'sural sparing patterns' with normal sural sensory nerve action potentials, while the median and ulnar sensory nerve action potentials are decreased or absent, was also taken into consideration [20–22]. The electrophysiological diagnostic criteria adopted for axonal motor and sensorimotor polyneuropathy (AMAN and AMSAN subtypes) included profound reductions in the compound muscle action potentials (CMAPs) ± sensory nerve action potentials (SNAPs) with relatively preserved conduction velocities. Reversible transient motor nerve conduction block might be observed [20–22]. Hadden et al. electrodiagnostic criteria for GBS was generally adopted [23]. If the NCS was normal or showed only abnormal late response in F-wave and Hoffman reflexes (H-reflexes), as may be the case early in the disease course, a follow-up study would be performed in the next week where feasible.

Institutional Review Board approval from the Hong Kong West Cluster/University of Hong Kong board was granted (IRB number UW20-360).

2.1. Statistical analysis

The annual incidence of paediatric GBS was estimated using the number of cases in each year, divided by total population aged 0 to <18 years old in each year, using data obtained from the Census Department of Hong Kong [24]. The average incidence of GBS was then calculated using a 10-year average. A simple linear regression analysis of the trend of paediatric GBS incidence from 2009 to 2018 was performed. P-values for categorical comparisons between different subgroups of GBS was calculated using a Chi-Square test. Statistical significance is considered $p < 0.05$ in two tails. Post-test significance was further evaluated using 2×2 Chi-square test. Statistical analysis was performed with IBM SPSS Statistics 27.0 for Windows.

2.2. Literature review

We have also performed literature search with PubMed using search terms 'Guillain-Barré syndrome' and 'children', or 'pediatric/paediatric', with publication dates between 1 January 2000 and 31 December 2019 inclusive. Cohort studies of GBS from Asian regions including China, Taiwan, Korea, Japan, Thailand, India, Iran and Turkey were included for further analysis. Studies with overlapping adult cohorts with no specific paediatric patient data and single case reports were excluded.

3. Results

3.1. Case finding and epidemiology

80 subjects from 11 hospitals were initially identified. Detailed evaluations of each subject's clinical record were performed by a paediatric neurologist of each hospital. Those with overlapping records (n = 4), incomplete records (n = 4), and GBS-mimicking conditions (n = 9) were excluded. The diagnoses of excluded patients included chronic idiopathic demyelinating polyneuropathy, juvenile idiopathic arthritis, and generalized sensory neuropathy.

A total of 63 subjects with confirmed diagnosis of GBS were included in this study for analysis. There were 34 male subjects, giving a male to female ratio of 1.2:1. The age of the subjects ranged from 0.75 to 17.9 years old. The mean duration of follow up was 26.4 months (median 22.5 months). All subjects with AMAN or AMSAN fulfilled level 1 of the Brighton Collaboration Diagnostic Criteria for GBS. Amongst subjects under AIDP subtype that responded promptly to IVIG,

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25/31 (80%) fulfilled level 1 of the Brighton Collaboration Diagnostic Criteria for GBS, with 5/31 (22.6%) fulfilled level 2 of the diagnostic certainty with normal or no NCS but raised CSF protein, and 1/31 (3.2%) fulfilled level 3 of the diagnostic certainty [20]. Half of the subjects (8/16; 50%) with classical MFS, had ophthalmoplegia, ataxia, and areflexia, while the other half (8/16; 50%), had MFS/GBS overlapping presentation. For those with classical MFS, 2/8 (25%) fulfilled level 1 of the Brighton Collaboration Diagnostic Criteria for MFS, and 6/8 (75%) fulfilled level 2 diagnostic certainty with either raised CSF protein or normal NCS. For those with MFS/GBS overlapping syndrome, adopting the Brighton Collaboration Diagnostic Criteria for GBS, 1/8 (12.5%) fulfilled level 1 diagnostic certainty, 6/8(75%) fulfilled level 2 diagnostic certainty with either abnormal NCS or raised CSF protein, and 1/8 (12.5%) fulfilled level 3 diagnostic certainty with normal NCS and CSF protein.

The overall estimated annual incidence of paediatric GBS in Hong Kong from 2009 to 2018 was 0.62 per 100,000 population (Supplementary Table 1). The estimated annual incidence and distribution of cases by subtypes can be found in Fig. 1. Nearly-two-thirds of the subjects were admitted during the spring and summer months (Supplementary Table 2), the warmer seasons in Hong Kong.

3.2. Clinical characteristics and investigations

Among the 63 subjects, half of the subjects had AIDP (n = 31; 49.2%), and one quarter had MFS (n = 16; 25.4%). One fifth of the subjects had axonal types of GBS (n = 12; 19.0%) including AMAN (n = 5; 7.9%) and AMSAN (n = 7; 11.1%). Of the four patients with unclassified subtype, one had Bickerstaff encephalitis, two had normal NCS (one had positive GQ1b antibody, one had elevated protein in cerebrospinal fluid), and one had a mixed axonal and demyelinating picture on NCS.

The characteristics of the three subtypes of GBS is summarised in Table 1. The three subtypes shared similar age of onset and proportions of patients with prodromal illness, none of which involved vaccination. MFS had the highest percentage of cranial nerve involvement, lowest percentage of autonomic disturbance and best motor outcome. Whilst AIDP and MFS had comparable length of stay (LOS), intensive care unit (ICU) admission rate and need for ventilator support, the axonal types of GBS had significantly higher healthcare utilization rate.

Anti-ganglioside antibody testing and contrast MRI spine study were increasingly adopted to aid diagnostic evaluation during the study period. Anti-ganglioside antibody testing including both IgG and IgM of anti-GD1b, anti-GQ1b and anti-GM1. The panel was made available to all our public hospitals only from 2015 onward. The MFS subgroup had the highest testing rate (100%) for anti-gangliosides antibodies, and positive diagnostic rate (87.5%), all of which were for anti-GQ1b. The positive diagnostic rate was much lower in AIDP (10%) and axonal GBS (16.7%) subgroups. Anti-GM1 antibodies were found in all 3 subtypes, with one patient in each subtype. One patient from the MFS subtype was positive for both anti GQ1b and anti-GM1, whereas one patient from the AIDP subtype was positive for both anti-GM1 and anti-GD1b.

3.3. Medical facilities usage, treatment and outcome

No patient with paediatric GBS died during the study period. Overall, two-fifths of the patients (n = 26, 41.2%) required ICU stay, with one-third (n = 9,

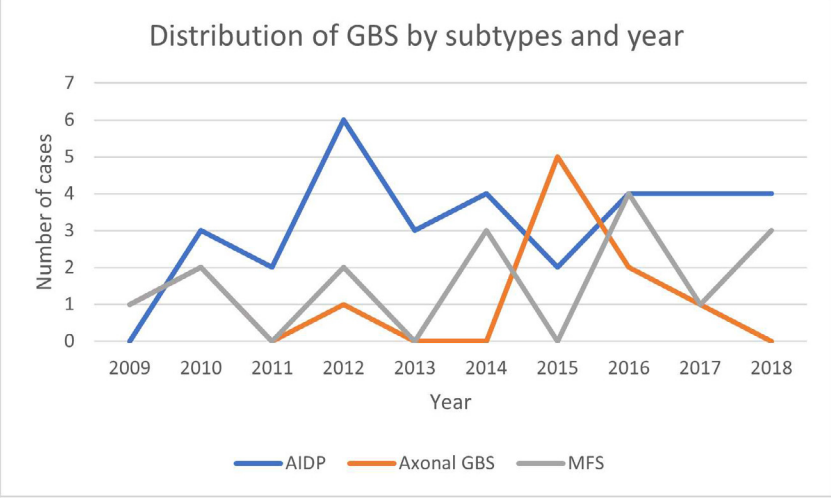

Fig. 1. Distribution of paediatric GBS cases by subtypes and year.

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Table 1
Comparison of clinical presentation, investigation result, treatment, healthcare utilization and outcome of different GBS subtypes.

	AIDP	AMAN/AMSAN	MFS	Chi-Square Test (P value)	Post-test significant findings (P value)
Number of patients (n)	31	12 AMAN: AMSAN 5:7	16 MFS: MFS/GBS Sx 8:8	–	–
Mean age of onset (range) years	8.0 (1.9–17.4)	11.4 (3.3–17.9)	10.2 (2.9–17.6)	–	–
Male to female ratio	0.82 (14/17)	1.4 (7/5)	1.28 (9/7)	0.6515	–
Prodromal illness (n) (%)	24 (77%)	11 (92%)	12 (75%)	0.502	–
Infective agents identified (n) (%)	6 (19.4%)	2 (16.7%)	4 (25%)	0.8466	–
Cranial nerve involvement (n) (%)[#]	6 (19.4%)	5 (41.7%)	14 (87.5%)	<0.001	MFS vs AMAN/AMSAN (0.016)MFS vs AIDP (<0.001)
Autonomic involvement (n) (%)[@]	5 (16.1%)	5 (42%)	1 (6.3%)	0.0512	–
Mean length of stay (range) days	21.9 (3–68)	61.5 (7–199)	23.8 (7–104)	0.009	AMAN/AMSAN vs MFS (0.045) AMAN/AMSAN vs AIDP (0.008)
Required PICU admission (n) (%)	8 (25.8%)	11 (91.7%)	5 (31.3%)	0.001	AMAN/AMSAN vs AIDP (0.0001) AMAN/AMSAN vs MFS (0.002)
Need for ventilator support (n) (%)	2 (6.45%)	4 (33.3%)	2 (12.5%)	0.0687	
Testing for AGA after 2015 (n) (%)	10/14 (71.4%)	6/8 (75%)	8/8 (100%)	0.2506	
Positive yield for AGA after 2015 (n) (%)	1/10 (10%)	1/6 (16.7%)	7/8 (87.5%)	0.002	MFS vs AMAN/AMSAN (0.0256)MFS vs AIDP (0.0029)
AGA findings	Anti-GD1b and anti- GM1	Anti-GM1	Anti-GQ1b (6/7); Anti-GQ1b and anti-GM1(1/7)		
NCS test (n) (%)	28 (90.3%)	12 (100%)	12 (75%)	0.77	
Positive yield for NCS test (n) (%)	25/28 (89.3%)	12/12 (100%)	4/12 (33.3%)	0.037	MFS vs AMAN/AMSAN (0.027)MFS vs AIDP (<0.001)
Testing for MRI spine (contrast) (n) (%)	25 (80.6%)	7 (58.3%)	5 (31.3%)	0.004	
Positive yield of MRI spine for those being tested (%)	18/25 (72%)	5 (71.4%)	1/5 (20%)	0.044	AIDP vs AMAN/AMSAN (0.1459)AIDP vs MFS (0.0472)
Conservative treatment (n) (%)	2 (6.5%)	0 (0%)	1 (6.3%)	0.6677	
1st line – IVIG (n) (%)	29 (93.5%)	12 (100%)	15 (93.8%)	0.6677	
2nd line – Plasmapheresis (n) (%)	3 (9.7%)	3 (25%)	1 (6.3%)	0.272	
Lost to follow up (n) (%)	1 (3.2%)	0 (0%)	0 (0%)	0.6317	
Complete motor recovery (n) (%)	26 (83.9%)	9 (75%)	16 (100%)	0.1337	
Incomplete motor recovery (n) (%)	4 (12.9%)	3 (25.0%)	0 (0%)	0.1246	
• Motor clumsiness (n) (%)	4 (12.9%)	2 (16.7%)	0 (0%)		
• Wheelchair bound (n) (%)	0 (0%)	1 (8.3%)*	0 (0%)	0.2699	
Residual sensory symptoms (n) (%)	0 (0%)	1 (8.3%)	3 (28.7%)	0.0516	

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory axonal neuropathy; MFS, Miller Fisher syndrome; AGA, antiganglioside antibodies; IVIG, intravenous immunoglobulin; NCS, nerve conduction study; PICU, paediatric intensive care unit.
*Declined second line therapy with plasmapheresis.
$P < 0.05$ statistically significant.
[#] Cranial nerve dysfunction included: bulbar dysfunction/palsy, ptosis, external ophthalmoplegia.
[@] Autonomic dysfunction included: urinary retention, hypertension, postural hypotension, bradycardia.

34.6%) of them required ventilator support. The combined acute-and-rehabilitation-associated LOS ranged from 3 to 199 days, with a median LOS of 14 days.

Among the three clinical subtypes, axonal GBS had the highest usage of medical facilities. 91.7% of patients with axonal GBS were admitted to the paediatric ICU ($p = 0.001$) with one-third required ventilator support, i.e. five times that of AIDP. The average LOS of axonal GBS patients was 61.5 days, nearly triple that of AIDP (21.9 days) ($p = 0.009$). All patients with axonal GBS required IVIG and 25% of them also required second-line therapy with plasmapheresis, as compared to 93% of patients with AIDP and MFS required IVIG and <10% of the patients in these 2 subgroups required plasmapheresis. Despite such aggressive treatments, the chance of complete motor recovery in subjects with axonal GBS was lower at 75%, compared to the 87.1% for AIDP and 100% in MFS. No paediatric patients in the AIDP subgroup required wheelchair use. For the child with axonal GBS that could not walk, the family refused plasmapheresis and subsequently defaulted follow-up as the family returned to mainland China in <6 months after onset of symptom, so the outcome in 1 year is not known.

Patients with MFS/GBS overlapping syndrome also demonstrated significantly higher healthcare utilization rates compared to those with classical MFS. The LOS was nearly doubled amongst patients with MFS/GBS overlapping syndrome (average 31.6 days, compared to 16 days for pure MFS). Whereas 62.5% of the patients with MFS/GBS overlapping syndrome required ICU admission, all of those with pure MFS were managed in paediatric general ward ($p = 0.025$). The overall rate of complete recovery, however, was the same in both groups as of 100% (Table 2).

3.4. Literature review

Sixty-three studies were obtained from PubMed search using the search terms 'Guillain-Barré syndrome' and 'children' or 'paediatric/pediatric' with a publication date between 1 January 2000 and 31 December 2019 inclusive. A total of thirteen cohort studies from Asian regions were identified. Two of the identified studies came from the same centre and the study with the shorter duration of study period was excluded. The relevant data is summarized in Supplementary Table 3 [9–13,25–32].

Overall, the proportion of children with prior infective symptoms within this study was comparable to that of neighbouring regions. The overall percentage of AIDP was also comparable to neighbouring regions (32–67.4%).

However, the proportion of MFS cases in this series was highest (25%) in the Asia region, followed by the studies in Korea (12.5%) [9], Taiwan (9%) [25] and Pakistan (4.3%) [30]. While AMAN is more common in Iran, India, Turkey, Japan and south-central China, AMSAN was found to be more common that AMAN in our study (10.9% vs 7.8%) and in Pakistan study (26.1% vs 17%) [30].

4. Discussion

4.1. Estimated incidence of paediatric GBS is similar to neighbouring Asia regions and global studies

Previous systematic reviews showed that the incidence of paediatric GBS ranges from 0.34 to 1.34 per 100,000 population [15]. In neighbouring East Asia regions, the GBS incidence ranges from 0.233 per 100,000 population in Beijing [33] to 0.66 per 100,000 population in Taiwan [34]. Our study showed an average incidence of 0.62 per 100,000 population. As such, the epidemiological findings of our current study in Hong Kong do not differ significantly with regional or worldwide data.

4.2. MFS is more common in paediatric GBS study in East Asia compared to neighbouring Asia regions

While MFS is infrequent in western part of the world accounting for 3–11% of GBS cases in adult patients [5,35,36], it is more frequent in the East Asia accounting for up to 18–26% of GBS cases in adult patients in Taiwan [6,37] and in Japan [7,38].

Likewise, MFS is uncommon in paediatric GBS in Caucasian population and accounts for 2–6% of GBS cases in paediatric patients [39,40]. Our literature review confirmed that MFS is more common in paediatric GBS in East Asia region among neighbouring Asian countries. In the Taiwan GBS study in children, MFS ranged from 6.8% [6] to 9.3% [25]. In the South Korean paediatric GBS study, MFS accounted for up to 12.5% [9]. Our paediatric GBS study found the highest percentage of MFS up to 25.4%.

Table 2
Comparing the healthcare utilization of classical MFS and MFS/GBS overlapping syndrome.

	Classical MFS	MFS/GBS overlapping syndrome	P-value
Mean, median length of stay (range) (days)	16, 13 (7–35)	31.6, 21 (11–104)	0.196
Required PICU admission (n) (%)	0 (0%)	5 (62.5%)	0.0256*
Need for ventilator support (n) (%)	0 (0%)	2/8 (25%)	0.4667

*$P < 0.05$ statistically significant.

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The findings of half of our MFS paediatric patients had overlapping syndrome are comparable to previous reports where MFS/GBS overlapping syndrome accounted for 44% [5] and 49% [14] of the MFS/GBS overlapping syndrome and classical MFS combined. Our paediatric patients with MFS/GBS overlapping syndrome also showed a higher healthcare burden as compared to those with classical MFS syndrome, with more patients required paediatric ICU admission and had a longer length of stay (Table 2). However, our patients with classical MFS and MFS/GBS overlapping syndrome had excellent clinical outcome with full motor recovery (Table 1).

4.3. Higher healthcare burden in axonal GBS subtypes

Amongst the three subtypes of paediatric GBS, the group with axonal types of GBS had the severest clinical presentation, highest rates of healthcare utilization (with longest LOS, highest rates of paediatric ICU admission and ventilator use), as well as lowest rates of complete recovery.

To the contrary of a prior report on adult GBS patients with predominant AIDP subtype where demyelinating feature could be associated with respiratory failure [41], our findings echo adult and paediatric GBS studies performed amongst populations with higher representation of non-AIDP subtypes [42,43] that axonal GBS subtype is associated with higher rates of healthcare utilization and respiratory care need. Children with axonal GBS subtype tended to recover more slowly than those with demyelinating subtype but after 1 year of follow-up, the motor recovery was impressed to be good in both subtypes [42].

Children with axonal types of GBS should thus be managed with higher healthcare vigilance. Close clinical monitoring should be matched with appropriate counselling regarding possibility of deterioration, with timely initiation of second line therapy and ventilatory support. Rehabilitation should also be arranged early in the recovery phase. There should be cautious counselling regarding prognosis and duration of training required.

4.4. Standard of care for patients with GBS

In the past decade, there have been updates in the recommendations regarding the practices for investigations and management of GBS. Use of anti-ganglioside antibodies as diagnostic test has been increasingly adopted. GBS subtypes are often associated with specific panel of antiganglioside antibodies. For instance, patients with AMAN often have IgG antibodies to GM1, GD1a, GalNAc-GD1a, GA1, or LM1/GA1 complex [44]. Patients with MFS have antibodies against GQ1b, which is expressed in the paranodal regions of extraocular motor nerves [45]. In addition, Gal-C and LM1 are expressed in myelin, and the antibodies to those antigens are associated with AIDP [46,47]. GD1b is expressed in the paranodal myelin, so anti-GD1b antibodies could mediate paranodal demyelination resulting in pathophysiological features of AIDP. In contrast, GM1 is localized at the nodes of Ranvier and anti-GM1 antibodies are associated with AMAN phenotype [48].

In Hong Kong, antiganglioside antibodies were made available to all public hospitals from 2015 onward, after which a significant increase in anti-ganglioside antibodies testing rate was observed. However, only a limited panel of antiganglioside antibodies (anti-GD1b, anti-GQ1b, anti-GM1) were offered. Whilst this may explain the lower positive yield in our study, it should also be noted that the positive yield antiganglioside antibodies could be lower amongst paediatric GBS compared to adult GBS [49].

MRI spine with contrast has also become increasingly available in the past decade. Although MRI spine with contrast showing cauda equina enhancement is not necessary in diagnosing GBS, it is especially useful in excluding transverse myelitis, in supporting the diagnosis of GBS in the setting of initially normal conduction study findings, and in cases with atypical presentation such as MFS/GBS overlapping syndrome [50]. In cases with pharyngeal-cervical-brachial weakness and suspected Bickerstaff encephalitis, extended imaging with MRI brain will have diagnostic value.

For the prediction of respiratory risk, documentation of the conduction block with the use of proximal/distal CMAP of studied motor nerves and the serial monitoring of the forced vital capacity will be helpful as both were found to be associated with increased risk of need for ventilation support [41].

In terms of treatment, use of intravenous immunoglobulin (IVIG) early on in the disease course is now proven to be beneficial [51]. Instead of reserving it for only the severe cases, guidelines now encourage earlier empirical use of IVIG when the duration of symptom is short and/or when there is symptom progression [52]. This is reflected in the changes in clinical practice in the management of GBS in our locality, with the proportion of patients with GBS being treated with IVIG surging from 29% in 2010 [4] to 93.7% in this current study. Looking forward, new modalities of treatment for the severe spectrum of GBS are emerging, with use of monoclonal antibodies i.e. eculizumab [53,54] having been explored as third-line treatment for those with suboptimal response to IVIG and plasmapheresis.

5. Limitations of the study

There are a few limitations to this retrospective study. Although international guidelines were generally adhered to by all the paediatric neurology units participating this study, there is no consensus on the adoption of Brighton

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collaboration Diagnostic Criteria on the initial reporting of the GBS subtypes. Moreover, our study period started few years before the validated Brighton collaboration Diagnostic Criteria was established, so the diagnostic certainty of each GBS subtype in this study is assigned through retrospective data collection based on the record keeping. The confirmation of the electrophysiological subtypes by our paediatric neurologists adopted both the narrative approach together with the stated criteria as reference. However, as more than one references [55] for electrophysiological subtyping may be considered for patients in different hospitals during the study period, the current electrophysiological subtyping is not based on a single cut off criteria. Data on the GBS disability score (Hughes functional grading scales) was not included in the analysis of current study as this scale was not used for some of the patients in our study. There is a need to re-emphasize the use of GBS disability scores to document the outcome of paediatric patients with GBS on top of our current documentation using functional motor performance. Anti-ganglioside antibodies diagnostic tests were not routinely available to all public hospitals within the HA before 2015, which may affect the estimation of its testing rate at the early years of the study.

6. Conclusion

Our retrospective territory wide study over 10 years provided detailed estimated incidence rate, clinical presentation, healthcare utilization and motor outcome of different subtypes of paediatric GBS in Hong Kong. Our study showed that the most common paediatric GBS subtype is AIDP, followed by MFS and axonal type of GBS. Compared with other subtypes, patients with axonal types of GBS had the highest rate of PICU admission and ventilator use, and the longest LOS, so the highest healthcare burden. We also found a good overall prognosis and motor recovery for all GBS subtypes with immunomodulating therapy. Compared to neighbouring East Asian regions, we found a highest proportion of paediatric patients with MFS in our region, with half of the MFS group had MFS/GBS overlapping syndrome.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contribution

ATGC was responsible for manuscript preparation (original draft, revision), data collection, curation and analysis. RWKC, MLYY, ACLY, AKFL, SWYL, AMCL, STHF, KHM, CWLL were responsible for patient data collection and curation, manuscript review. MMY, CHK, KWT, CKM, SMT, EKCY, EF, SPW, KLK were responsible for data curation (supervisory), manuscript review. SHSC was responsible for study conceptualization and design, research team invitation, data collection, manuscript preparation (original draft, revision), supervision, project administration.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2022.07.003.

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