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Causes and consequences of diagnostic delay in Guillain-Barré syndrome in a U.K. tertiary centre

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Abstract:

Introduction/Aims: Understanding the potential causes and consequences of diagnostic delay in Guillain-Barré syndrome (GBS) could improve quality of care and outcomes. We aimed to determine these.

Methods: We retrospectively reviewed records of subjects with GBS, admitted to our centre at University Hospitals Birmingham, U.K., between January 2005 and December 2020. We evaluated time to diagnosis from presentation, factors associated with diagnostic delay and its potential consequences.

Results: We included 119 consecutive subjects. Diagnostic delay >5 days from first presentation occurred in 27/119 (22.7%) of patients. Diagnostic delay was associated with age >60 years (OR: 3.58; 95% CI: 1.44-8.85), pre-existing cardiac/respiratory disease (OR: 4.10; 95% CI: 1.46-11.54), pre-existing diabetes (OR: 10.38; 95% CI: 2.47-43.69), documented normal initial neurological examination (OR: 2.49; 95% CI: 1.03-6.02), initial assessment by primary care (OR: 3.33; 95% CI: 1.22-9.10) and >1 visit for medical attention (OR: 10.29; 95% CI: 3.81-27.77). Diagnostic delay was not associated with length of in-patient stay, ICU admission, ventilation, ability to walk at discharge, or in-patient mortality. Independent associations with diagnostic delay were observed for >1 visit for medical attention (OR: 10.15; 95% CI: 3.64-28.32) and pre-existing cardiac/respiratory disease (OR: 3.98; 95% CI: 1.19-13.28). An association of diagnostic delay with in-patient mortality was ascertained specifically in subjects with classic GBS (OR: 5.33; 95% CI: 1.1-25.87).

Discussion: Diagnostic delay in GBS results from patient-specific factors and patient pathways. A high index of suspicion is appropriate for certain patient groups. Prospective studies are needed to further investigate this topic.

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Introduction.

Guillain-Barré syndrome (GBS) is relatively common neurological emergency requiring early recognition for adequate safe management and treatment (1). Although GBS typically causes a symmetric, flaccid, areflexic paralysis, the clinical presentation may be heterogeneous (2). Distal paraesthesiae, numbness or pain in the limbs, lumbar pain and cranial nerve involvement may all be part of the presenting symptoms.

Few studies have been conducted to date on diagnostic delay in GBS. In one North American study, it was found that delay in formal review by a neurologist as well as atypical clinical features including neuropathic pain and preserved deep tendon reflexes, may be contributory to diagnostic delay (3). In the United Kingdom (U.K.), primary care general practitioners are the first point medical encounter for acutely ill patients for what initially may appear to be non-life-threatening presentations. The distal sensory symptoms and weakness in early GBS are often wrongly considered as within that spectrum. Acute admissions occur through Accident & Emergency (A&E), directly accessible to patients or through Medical Assessment Units (MAU), accessible through primary care referral. In large hospitals with neuroscience units, neurological opinions are then sought from trainee neurologists, who have a variable level of experience in the speciality, supported by fully trained consultant neurologists, who, themselves, do not always see all patients straight on admission. Most U.K. District General Hospitals (DGH) do not have a specialist neurological presence every day of the week or neurological on-call teams on site. Acutely ill neurological patients are as a result, initially evaluated by general physicians and other specialists (4). There is a documented lack of neurologists both qualified and in training in the U.K. compared to other

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developed nations, and considerable variations exist from one region to another (5). Hence, there are several logistic reasons that may cause delayed diagnosis of GBS.

The aim of our study was to evaluate the potential factors responsible for delay in the diagnosis of GBS in our population. We also attempted to determine the potential effects of delay of the diagnosis of GBS in this cohort.

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Methods.

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We reviewed records of patients admitted to our institution at Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham, U.K., between January 2005 and December 2020 with a diagnosis of GBS. All potential cases admitted during this period were reviewed, with only those meeting recently published clinical diagnostic criteria (2), retained. This study was reviewed, approved and registered by our Institutional Review Board (CARMS No. 16360, 23rd August 2020).

We ascertained demographics, detailed history of the presenting complaint and resulting medical attention sought. Hence, we determined the first visit to any medical facility by each patient, the number of visits, the time of diagnosis of GBS and the time from the first attendance to the time of diagnosis, defined for the purposes of this analysis, as the "diagnostic delay". We arbitrarily considered that a 5-day time frame was the maximal acceptable for a GBS diagnosis which remains clinically based and for which investigations such as electrophysiology and cerebrospinal fluid (CSF) examination, are not essential for diagnosis and treatment initiation. In relation to possible causes of diagnostic delay, we first considered past medical history in each case and evaluated the presence or absence of (i) previous cardiac/respiratory disease (defined as ischaemic heart disease, myocardial infarction, chronic obstructive pulmonary disease or asthma) (ii) previous history of diabetes mellitus (iii) previous history of any malignancy (iv) antecedent infectious illness in the 6 weeks prior to symptom onset (v) any vaccination in the 6 weeks prior to symptom onset. Regarding clinical presentation, we considered the type of GBS i.e. classic vs. non-classic (3). We also in each case determined neurological status as documented at first assessment (normal or abnormal neurological examination) and the presence of (i) limb weakness (ii) sensory symptoms (iii) facial weakness (iv) oculomotor weakness (v) bulbar weakness (vi) lumbar pain, and (vii) dysautonomia. Finally, we considered potential consequences of delayed admission through: (i) length of hospital stay >10 days (ii) need for ICU admission

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(iii) need for mechanical ventilation, (iv) ability to walk (aided or unaided) at hospital discharge and, (v) hospital in-patient mortality rate.

Statistical analyses were performed using SPSS 25.0 software (IBM, Armonk, NY). Simple and multiple logistic regression analyses were used to determine associations. Statistical significance was set at $p<0.05$. We calculated, for each variable included in the multiple regression analysis, the variance inflation factor (VIF).

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Results.

We included 119 patients with a final diagnosis of GBS. A majority had a classic GBS presentation and the remainder had other forms of GBS. This included Miller Fisher Syndrome (MFS) in 11, GBS/MFS overlap in 1, paraparetic GBS in 2, pharyngocervicobrachial (PCB) variant in 1, and GBS/PCB overlap, in 2. Table 1. summarizes the patients' characteristics at baseline.

In this cohort 92 (77.3%) subjects were diagnosed ≤5 days after initial presentation. Hence, 27 subjects (22.7%), were diagnosed with delay of >5 days. Ten patients (8.4%) had attended a DGH before transfer to our institution. Of the 27 subjects who were diagnosed with diagnostic delay> 5 days, the initial diagnosis was of another neuropathy in 9 (33.3%) of another non-neuropathic neurological disorder in 11 (40.7%) and of a non-neurological condition in 7 (25.9%).

Tables 2 and 3 summarize the results of the simple regression analysis of the association of delay in diagnosis with the explored variables. Age >60 years, preceding cardiac/respiratory illness and a previous diagnosis of diabetes mellitus were associated with diagnostic delay >5 days. Multiple other clinical factors were not.. Patients whose initial medical encounter was with their general practitioner were more commonly diagnosed with delay of >5 days compared to those went straight to hospital as were those with recorded normal neurological examination findings at their initial visit. Finally, patients who had attended any medical facility more than once were diagnosed more frequently with delay of >5 days, than those who had been admitted at their first visit. In relation to potential consequences of diagnostic delay >5 days, we found no associations..

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Multiple logistic regression analysis (Table 4) showed that preceding cardiac/respiratory illness and more than one visit at any clinical care facility before GBS diagnosis were independently associated with diagnostic delay >5 days. VIF values (Table 4) were all around 1.

In view of the large proportion of subjects with MFS, which is of known better prognosis, in the non-classic GBS subgroup, we studied the correlates of diagnostic delay in the classic GBS subgroup (102 patients) and found similar associations with diagnostic delay >5 days, to those of the whole cohort. However, in addition, we found that in-patient mortality was also associated with diagnostic delay >5 days (OR: 5.33; 95% CI: 1.1-25.87).

Discussion.

In this study, we found that diagnostic delay >5 days from first presentation occurred in over one fifth of patients. Diagnostic delay was associated with greater age and pre-existing co-morbidities. A documented normal initial neurological examination, initial attendance to primary care and repeated attendance for medical attention, were all associated with diagnostic delay. No potential consequences of diagnostic delay was identified in the whole cohort, although specifically in subjects with classic GBS, an association with in-patient

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mortality, was demonstrated. Independent associations with diagnostic delay were observed for >1 visit for medical attention and pre-existing cardiac/respiratory disease.

One previous study specifically analysed the causes of diagnostic delay of GBS. This North American study of 69 patients had found that neuropathic pain and preserved reflexes were associated with diagnostic delay (2). This is, in part, consistent with our findings that a normal neurological examination, implying preserved reflexes, was associated with diagnostic delay. We believe it is likely that under-recognition of subtle abnormalities such as mild weakness, patchy distal sensory loss and hyporeflexia, may have been present in a proportion of cases, in view of the subsequent abnormal findings subsequently described in the records. This may highlight the value of thorough early neurological evaluations to reduce rates of delayed diagnosis. Dubey et al. found that lack of early evaluation by a neurologist resulted in diagnostic delay, as was the number of visits to the Emergency Department (2). The latter is in keeping with our findings, although the former was not of definite clear relevance to our analysis in a tertiary neuroscience centre, where an on-call neurology service is present on-site. Importantly, in the U.K. context, we believe it is likely that multiple visits before diagnosis otherwise relate more commonly to physician under-recognition of GBS at visit, rather than to patient-driven multiple attendance.

It is possible that early non-recognition of subtle clinical abnormalities and lower index of suspicion for GBS may partly account for our findings of associations of diagnostic delay with multiple visits and documented normal initial examination. Similarly, and possibly linked to the above, age and co-morbidities also appear, from our results, to have played an important role in the under-recognition of GBS.

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Our study findings differ partly with those of Dubey at al. Using residual motor weakness at discharge, Dubey et al. found worse outcomes after delayed diagnosis (3). The relevance of this measure, particularly in the short timeframe of in-patient hospital stays, small sample size and lack of inter-rater reliability of MRC score ratings, as has been documented previously (6), is uncertain. This may explain the difference between our results.

We found that rates of ICU admission and ventilation were unaffected by diagnostic delay >5 days, but inpatient mortality was, of concern, associated with diagnostic delay exclusively in the classic GBS group. This could not be explained by multicollinearity between interdependent variables, as demonstrated by VIF values. This sub-analysis allowed the exclusion of MFS patients who represented almost two-thirds of the non-classic GBS subgroup. It is possible that delayed diagnosis in the context of greater age and presence of co-morbidities played a role in treatment response and/or in clinical management decisions.

In view of our findings, it may be appropriate to consider advising primary care physicians to direct patients with suggestive early symptoms straight to hospital rather than arrange an out-patient visit. This is already in existence for suspected stroke (7), and despite the much lower incidence of GBS, may also be suitable in suspected cases. Also, in view of the association of diagnostic delay with the number of attendances, increased awareness of general practitioners and of A&E physicians appears appropriate for adequate attention to be given to repeat attenders with compatible presentations.

Regrettably, although GBS is of higher prevalence in older age groups (1), diagnostic delay was commoner in subjects >60 years in our cohort. Those with previous cardiac/respiratory disease and diabetes also appeared at greater risk of receiving a delayed diagnosis, consistent

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with the high proportion of non-neurological diagnoses (25.9%) made in those with diagnostic delay >5 days. These findings may highlight the lack of attention paid to relevant symptoms in affected, (although not exclusively older) subjects, in whom they are frequently inappropriately attributed to co-morbidities (8).

Our study is limited by its retrospective and single-centre design as well as number of included subjects. Our institution is a tertiary regional center and this may explain part of the findings. Numerous other subjects with GBS were seen and managed in their local DGHs during the study period, without being referred to us. We estimate that in view of the current regional population that our institution serves (2.9 million), and GBS incidence rates, that the studied cohort represents about 25% of all cases of GBS seen in our region, (West Midlands, U.K.) during the study period. Hence, selection bias may have impacted upon the results.

In conclusion, diagnostic delay in GBS is multifactorial and relates to both patient-specific and patient-pathway issues. Delay as defined in this analysis occurred in over one patient in 5. We believe that this figure is likely to be higher in hospitals without neuroscience centres. The factors implicated in diagnostic delay may be remediable by enhanced awareness of general practitioners, general physicians and neurologists, as well as patients themselves. A higher index of suspicion appears advisable in subjects with co-morbidities, especially but not exclusively the elderly, in the adequate clinical setting. Of concern, we found evidence of adverse effects on in-patient mortality, of diagnostic delay >5 days, specifically in patients with classic GBS. Longer prospective studies are needed to establish whether this finding may be replicated and whether, therefore, diagnostic delay and its causes, may represent additional factors of poor prognosis in GBS (9).

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Abbreviations: GBS: Guillain-Barre syndrome; MFS: Miller Fisher Syndrome; DGH: District General Hospital.

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Table 1: Patients' baseline characteristics: Consecutive cases of Guillain-Barre syndrome admitted 2005-2020 at University Hospitals Birmingham, Birmingham, U.K.

Number of patients	119
Mean age, (SD), years	51.7(19.44)
Median time to first attendance, (IQR), (days)	6(12)
Median time to diagnosis, (IQR), (days)	8(14)
Male: Female ratio	79:40
Co-morbidities	
Cardio/respiratory	19
Diabetes mellitus	10
Malignancy	10
Antecedent illness	60
Vaccination	7
Clinical presentation	
Weakness	99
Sensory symptoms	87
Facial weakness	31
Ocular symptoms	14
Bulbar symptoms	16
Lumbar pain	25
Classification	
Classic	102
Non-classic	17
Initial Documented Clinical examination	
Abnormal	81
Normal examination	38
Place of first attendance	
GP	21
ED	98
Outcome	
Able to walk at discharge	77
Unable to walk at discharge	23
Alive at discharge	111
Death during in-patient stay	8

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Table 2: Factors associated with GBS diagnostic delay >5 days: simple logistic regression

Variable	Time delay diagnosis, days <5	≥5	Crude OR (95% CI)	*p*-value
Age				***0.006***
<60 years	59	9	1(ref)	
≥60 years	33	18	3.58(1.44-8.85)	
Gender				0.619
Male	60	19	1.27(0.50,3.21)	
Female	32	8	1(ref)	
Cardiac/respiratory disease				***0.008***
Yes	10	9	4.10 (1.46-11.54)	
No	82	18	1(ref)	
Diabetes				***0.001***
Yes	3	7	10.38(2.47,43.69)	
No	89	20	1(ref)	
Malignancy				0.566
Yes	7	3	1.52(0.37,6.32)	
No	85	24	1(ref)	
Antecedent illness				0.481
Yes	48	12	0.73(0.31,1.74)	
No	44	15	1(ref)	
Vaccination				0.205
Yes	4	3	2.75(0.58,13.13)	
No	88	24	1(ref)	
Weakness				0.753
Yes	76	23	1.21(0.37,3.98)	
No	16	4	1(ref)	
Sensory symptoms				0.715
Yes	68	19	0.84(0.33,2.16)	
No	24	8	1(ref)	
Facial weakness				0.607
Yes	25	6	0.77(0.28,2.12)	
No	67	21	1(ref)	
Ocular symptoms				0.905
Yes	11	3	0.91(0.24,3.57)	
No	81	24	1(ref)	
Bulbar symptoms				0.383
Yes	11	5	1.67(0.53,5.33)	
No	81	22	1(ref)	
Lumbar pain				0.477
Yes	18	7	1.44(0.53,3.92)	
No	74	20	1(ref)	
Classification				0.929
Classic	79	23	0.95(0.28,3.18)	
Non-classic	13	4	1(ref)	

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Clinical examination				**0.043**
Abnormal	67	14	1(ref)	
Normal	25	13	2.49(1.03,6.02)	
Place of first attendance				***0.019***
GP	12	9	3.33(1.22,9.1)	
ED	80	18	1(ref)	
Number of visits				***<0.001***
1	72	7	1 (ref)	
>1	20	20	10.29 (3.81, 27.77	

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Table 3. Potential Consequences of Diagnostic Delay: simple logistic regression

Variable	Time delay diagnosis, days		Crude OR (95% CI)	*p*-value
	≤5	>5		
ICU admission				0.397
Yes	20	8	1.52(0.58,3.97)	
No	72	19	1(ref)	
Ventilation				0.205
Yes	14	7	1.95(0.70,5.47)	
No	78	20	1(ref)	
Length of stay, (days)				0.194
≤ 10	29	5	1(ref)	
> 10	63	22	2.03(0.70,5.88)	
Functional outcome				0.246
Able to walk	58	19	2.18(0.58,8.17)	
Unable to walk	20	3	1(ref)	
Final outcome				0.072
Alive	88	23	1(ref)	
Death during in-patient stay	4	4	3.83(0.89,16.47)	

Note:
Crude OR: Crude Odd ratios
95% CI: 95% Confidence Interval

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Table 4: Factors independently associated with diagnostic delay >5 days: multiple logistic regression.

Variable	Time delay diagnosis, days		Adj. OR (95% CI)	*p*-value	VIF
	≤5	>5			
Age				0.11	1.165
<60 years	59	9	1(ref)		
≥60 years	33	18	2.46(0.82,7.42)		
Diabetes mellitus				0.098	1.138
Yes	3	7	3.8(0.78,18.53)		
No	89	20	1(ref)		
Cardiorespiratory disease				***0.025***	1.149
Yes	10	9	3.98(1.19,13.28)		
No	82	18	1(ref)		
Clinical examination				0.726	1.239
Abnormal	67	14	1(ref)		
Normal/not done	25	13	1.23(0.39,3.87)		
Place of first attendance				0.91	1.487
GP	12	9	1.08(0.27,4.36)		
ED	80	18	1(ref)		
Number of visits				***<0.001***	1.59
1	72	7	1(ref)		
> 1	20	20	10.15(3.64,28.32)		

Note:
Adj OR: Adjusted Odd ratios
95% CI: 95% Confidence Interval
VIF: Variation inflation Factors

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