Clinical features of Guillain–Barré syndrome patients with elevated serum creatine kinase levels

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Abstract

Background: It is not well defined whether Guillain–Barré syndrome (GBS) patients with elevated serum creatine kinase (CK) levels have characteristic clinical features and are related to the subgroups of GBS.

Methods: We retrospectively studied 51 consecutive patients with GBS, who visited our hospital, and compared clinical, laboratory and electrophysiological findings between patients with and without elevated CK levels.

Results: Of 51 patients, 14 patients (27%) showed an elevation of serum CK levels. When compared with patients with the normal CK levels, the ratios of male, antecedent infections, and anti-GM1 antibody positivity were significantly higher in patients with elevated CK levels. The ratios of hypoesthesia, cranial nerve involvement, and urinary retention were significantly less in patients with elevated CK levels. There were no significant differences in disability at peak between two groups. In the electrophysiological examination, sensory nerve abnormalities were not observed. Although some patients with elevated CK levels showed prolongation of distal motor latencies (DMLs) and increase of durations in the initial examination, development of the prolongation of DMLs and increase of durations was not observed in the follow-up examinations. The findings were consistent with acute motor axonal neuropathy (AMAN) with reversible conduction failure (RCF) but not acute inflammatory demyelinating polyneuropathy (AIDP).

Conclusions: The results suggest that the GBS patients with elevated CK levels represent not a group of AIDP but a group of AMAN with axonal degeneration or RCF even though the initial electrophysiological examination shows AIDP pattern. Key words: Creatine kinase, Guillain-Barré syndrome, AIDP, AMAN, reversible conduction failure

Introduction

Guillain–Barré syndrome (GBS) is classified into two major subgroups: acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN).[1–6] AMAN is further classified into the subgroups, such as AMAN with axonal degeneration and AMAN with reversible conduction failure (RCF).[7] AMAN with RCF is characterized clinically by rapid improvement.[5, 8, 9] It is important to accurately diagnose the subgroups in patients with GBS for predicting the therapeutic responsiveness.

Although these subgroups are clinically diagnosed by electrophysiological findings, conventional examinations are reported to be often inconsistent with the true subgroup of GBS. 11–41% of patients with GBS failed to judge AIDP or AMAN, because electrophysiological findings did not fulfill the criteria for AIDP or AMAN patterns.[1, 10–12] Additionally, AMAN with RCF is misdiagnosed as AIDP, because electrophysiological examinations at the acute phase indicate the AIDP pattern, such as prolongation of distal motor latencies (DMLs) and increase of durations.[10, 11, 13] This means that the AIDP pattern on electrophysiological examinations reflects two different subgroups, AIDP and AMAN with RCF. However,

previous reports demonstrated that the follow-up electrophysiological examinations are useful for resolving this issue: [11, 12, 14] AMAN with RCF shows rapid improvement of the AIDP pattern,[7, 8, 10, 12] whereas true AIDP shows development of these abnormalities.[15, 16] We previously reported that AMAN with RCF did not show sensory nerve conduction abnormalities in contrast to true AIDP.[17] In this study, we focused on the GBS patients with elevated CK levels. We investigated whether these patients are related to the specific subgroups of GBS by performing repeat electrophysiological examinations.

Material And Methods

Patients

We retrospectively evaluated 51 consecutive GBS patients who visited Osaka Medical College Hospital from January 2005 to December 2016 (31 men, 20 women; mean age 45.9 years, range 17 – 80 years). These patients underwent initial nerve conduction examinations within 17 days of onset. All patients fulfilled the clinical criteria for GBS,[18] except the point regarding areflexia or hyporeflexia. We enrolled these patients, because the presence of GBS patients with normal or exaggerated tendon reflexes was shown previously.[8, 19] Three GBS patients were excluded from this study, because these patients had diabetic neuropathy and it was difficult to appropriately separate abnormalities in the sensory nerve conduction by GBS from those by diabetic neuropathy.

Patient disabilities were evaluated according to the Hughes disability grade scale as follows: grade 0, healthy; grade 1, minor signs and symptoms, able to run; grade 2, able to walk independently; grade 3, able to walk with a walker or support; grade 4, bed or chair bound; grade 5, assisted respiration required for at least part of the day; and grade 6, dead.[20] Elevation of serum CK levels was defined as the values > 200 U/L (normal range 30–200 U/L) for more than 3 days during 4 weeks after onset. CK levels were measured before electromyographic examination, if it was performed.

Electrophysiological examinations

Motor and sensory nerve conduction examinations were performed using MEB-9104 Neuropack mu® (Nihon Kohden, Japan) according to the methods and reference values as described by Kimura *et al.*[21] Motor nerve conduction examinations were performed on the median, ulnar, peroneal, and tibial nerves. Compound action potential (CMAP) duration was defined as the time from the onset of the initial negative phase until the last negative deflection of CMAP returned to the baseline. Antidromic sensory nerve conduction examinations were performed on the median, ulnar, and sural nerves. Based on the results of initial electrophysiological examinations, patients were classified into the AIDP or AMAN pattern according to the criteria of Ho *et al.*[1] Although their criteria set includes unequivocal temporal dispersion for the detection of demyelination, how much temporal dispersion of CMAP should be considered as “unequivocal” one is not defined in the criteria. Therefore, we used a distal CMAP duration > 6.6 ms in the median, > 6.7 ms in the ulnar, > 7.6 ms in the peroneal, and > 8.8 ms in the tibial nerves[22]

or >30% increase in duration ratio of the proximal CMAP to distal one in all nerves.[23] When the electrophysiological findings did not fulfill the criteria for AIDP or AMAN patterns, the patients were designated as unclassified GBS. The absence of F waves was defined as the absence or marked decrease (persistence <20%) of F waves in at least two nerves.[24] Patients were considered to have sensory nerve conduction abnormalities when the sensory nerve action potential amplitude was <50% of the lower limit of normal range in at least two nerves.[25] We further classified the AIDP patterns into motor-sensory AIDP (MS-AIDP) and motor AIDP (M-AIDP) patterns according to the presence and absence of sensory nerve conduction abnormalities, respectively.[17] In this study, the electrophysiological patterns of AIDP and AMAN were expressed as the “AIDP pattern (M-AIDP and MS-AIDP pattern)” and the “AMAN pattern”, respectively.

Statistical analyses

Differences in mean values between two groups were analyzed using the Mann–Whitney U test, and differences in frequencies were analyzed using the Fisher exact probability test. Statistical significance was set at $P < 0.05$. All analyses were performed using GraphPad PRISM version 5.01 (GraphPad Software, San Diego, CA, USA).

Results

Clinical and laboratory features of GBS patients with elevated CK levels

Table 1 shows a comparison of clinical and laboratory findings of GBS patients with and without elevated CK levels. Of 51 patients, 14 (27%) patients showed an elevation of serum CK levels and 37 (73%) patients showed normal CK levels. The ratio of male in patients with elevated CK levels (n=12) were significantly higher than that of patients with normal CK levels (n=19, P=0.029). The incidence of infections prior to the onset of GBS in patients with elevated CK levels (n=13) were significantly higher than that of patients with normal CK levels (n=22, P=0.039). As antecedent infections, the ratio of upper respiratory tract infection in patients with elevated CK levels (n=8) were higher than that of patients with normal CK levels (n=8, P=0.021). Anti-GM1 antibody was measured in 12 and 32 patients with and without elevated CK levels, respectively. The positive ratio of anti-GM1 antibody in patients with elevated CK levels (n=8) were higher than that in patients with normal CK levels (n=8, P=0.016). The incidences of hypoesthesia and cranial nerve involvement in patients with elevated CK levels (n=1 and 2, respectively) were significantly less than those in patients with normal CK levels (n=15 and 19, respectively, P=0.016).

Patients with elevated CK levels showed no urinary retention. There were no significant differences in disability at peak between two groups.

The electrophysiological features at the initial examinations

Based on the initial electrophysiological findings, 51 patients were classified as having the “M-AIDP pattern” (n=15, 29%), the “MS-AIDP pattern” (n=15, 29%), the “AMAN pattern” (n=8, 16%), and electrophysiologically unclassified (n=13, 25%). One patient with the “AMAN pattern” with normal CK levels showed sensory nerve conduction abnormalities, indicating the “acute motor and sensory axonal neuropathy pattern” in the strict sense.[26] Table 2 shows findings in the initial electrophysiological examinations. Although, in patients with elevated CK levels, one patient with the “AMAN pattern” showed hypoesthesia, electrophysiological criteria of sensory nerve abnormality were not fulfilled. There were no GBS patients with elevated CK levels clearly having sensory nerve conduction abnormalities. Consequently, there were no GBS patients showing the “MS-AIDP pattern”. All GBS patients with elevated CK levels showed the “M-AIDP pattern”, the “AMAN pattern”, or unclassified GBS. In contrast, >40% of GBS patients with normal CK levels showed the “MS-AIDP pattern.” Table 3 shows serum CK levels and clinical course of 14 patients with elevated CK levels. To anonymize the identifying information, specific ages were grouped into age ranges. There was no significant relation between CK values and disability grades.

The electrophysiological features at the follow-up examinations

Of 14 patients with elevated CK levels, 12 patients underwent follow-up electrophysiological examinations. Of 37 patients with normal CK levels, 22 patients underwent follow-up electrophysiological examinations. Fig. 1 shows temporal changes of electrophysiological parameters at the right median nerve. Some GBS patients with elevated CK levels showed prolongation of DMLs and increase of durations in the initial examinations. However, none showed development of increased durations and prolonged DMLs in the follow-up examinations, while some GBS patients with normal CK levels did show development.

Discussion

The present study shows that the elevation of CK levels is seen in GBS. 27% of patients had the elevation of CK levels in the first 4 weeks after onset. In this study, GBS patients with elevated CK levels showed

characteristic features in serial electrophysiological examinations. Some GBS patients with elevated CK levels were classified as the “AIDP pattern” in the initial electrophysiological examinations, which showed prolongation of DMLs and increase in durations. However, the development of this prolongation of DMLs and increase of durations in the follow-up examinations were not observed in GBS patients with elevated CK levels. This was inconsistent with true AIDP. On the other hand, it was seen in some GBS patients with normal CK levels. Moreover, our GBS patients with elevated CK levels with “AIDP pattern” showed rapid normalization of increased duration and small extent of demyelinating features, both of which are consistent with AMAN with RCF.[7, 8, 10–13] Therefore, we suggest that the GBS patients with elevated CK levels with “AIDP pattern” in the initial electrophysiological examination represent a group of AMAN with RCF, and that all GBS patients with elevated CK levels represent a group of AMAN with axonal degeneration or RCF.

We previously demonstrated the utility of classifying GBS patients into one of the following four patterns: “AMAN,” “M-AIDP,” “MS-AIDP pattern,” and unclassified.[17, 27] Although patients with “AIDP pattern” include those with both AMAN with RCF and true AIDP, we previously focused on the fact that AMAN patients with RCF as well as axonal degeneration did not show sensory nerve involvement, whereas those with true AIDP did show involvement. After that, we demonstrated the true disease subtype of the “M-AIDP,” “MS-AIDP,” and “AMAN patterns” is AMAN with RCF, true AIDP, and AMAN with axonal degeneration, respectively.[17] We also demonstrated that the true disease subgroup of unclassified GBS is AMAN with RCF.[27] While a limited number of patients undergo serial electrophysiological examinations and these analysis can have biased effect, the analysis using our classification requires only a single electrophysiological examination for almost all GBS patients. Therefore, we analyzed GBS using our classification and found that all GBS patients with elevated CK levels were classified as “M-AIDP,” “AMAN” pattern, or unclassified GBS, of which the former two correspond to AMAN with RCF and the latter to AMAN with axonal degeneration. In contrast, no GBS patient with elevated CK levels is classified as “MS-AIDP pattern,” which corresponds to true AIDP, i.e., the findings also confirm that patients with elevated CK levels represent a group of AMAN but not a group of AIDP.

Several features of GBS patients with elevated CK levels other than electrophysiological findings also confirm that GBS patients with elevated CK levels represent a group of AMAN. In our study, patients with elevated CK levels frequently had antecedent infections and anti-GM1 antibody, rarely had hypoesthesia and cranial nerve involvement, and did not have urinary retention as signs of autonomic failure; all of the features were consistent with AMAN and not true AIDP.[1, 3–5] Conversely, while the most common antecedent infection in AMAN was gastroenteritis, particularly from Campylobacter jejuni, the most common antecedent infection in GBS patients with elevated CK levels in this study was upper respiratory tract infection (URTI). AMAN with antecedent URTI may be a specific feature of GBS patients with elevated CK levels.

To our knowledge, while we found some case reports of GBS patients with elevated CK levels,[28–30] there is only one report of a series of GBS patients in whom CK levels was investigated.[31] That report showed a 52% incidence of the elevation of CK levels in GBS and pain associated with the elevation of

CK levels in GBS patients; however, the authors did not record the disease subgroup of GBS and consequently did not mention the correlation between GBS disease subgroup and the elevation of CK levels. Therefore, our study is the first study of a series of GBS patients in whom correlation between GBS disease subgroup and elevation of CK levels is investigated, demonstrating that GBS patients with elevated CK levels represent a group of AMAN.

Although the mechanism of elevation of CK levels in GBS is still uncertain, a possible mechanism proposed in the literature is that rapid denervation due to axonal damage can result in the release of muscle enzymes.[29] the mechanism could explain our observation that elevation of CK levels occurred in AMAN with RCF as well as AMAN with axonal degeneration but not in AIDP, because the denervation could occur in AMAN with RCF as well as AMAN with axonal degeneration but not in demyelination alone.[32, 33] Moreover, we also found that AMAN with antecedent URTI may be a specific feature of GBS patients with elevated CK levels. The specific pathogen not identified in this study may elicit not only URTI and subsequent AMAN but also additional mechanisms that are specific to elevation of CK levels.

Our study has several limitations including that it is small and retrospective and includes only patients from Japan, where AMAN patients are more frequent than other Western countries. Further large prospective studies in various population groups are needed. Moreover, although serial electrophysiological examinations were performed, the timing, frequency, and period varied for each patient. In some patients, serial examinations were performed only a few times over a short period or not performed at all. Further studies with more frequent electrophysiological assessment at predetermined time points over a longer time period could identify these features in greater detail and with greater confirmation.

Conclusions

We clarified that GBS patients with elevated CK levels represent a group of AMAN. We have also included CK elevation to the clinical features of GBS which differ between AMAN and AIDP. The presence of CK elevation facilitates the accurate diagnosis of the disease subgroup.

Abbreviations

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CK, creatine kinase; CMAP, compound action potential; DML, distal motor latency; GBS, Guillain Barré syndrome; IVIG, intravenous immunoglobulin; RCF, reversible conduction failure; M-AIDP, motor acute inflammatory demyelinating polyneuropathy; MS-AIDP, motor-sensory acute inflammatory demyelinating polyneuropathy; URTI, upper respiratory tract infection

Declarations

Acknowledgment

None.

Authors' Contributors

TH contributed to the conception and design, acquisition of data, analysis and interpretation of data and drafting of the manuscript. HN contributed to the concept and design, acquisition of data, analysis and interpretation of data and critical revision of the manuscript for important intellectual content. TS, YN, ES, AT, KU and SI contributed to acquisition of data. SS contributed to critical revision of the manuscript for important intellectual content. FK contributed to acquisition of data and critical revision of the manuscript for important intellectual content. SA contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All subjects gave their verbal informed consent prior to their inclusion in the study. Written consent to participate was waived as the present study was a retrospective observational study. This study was approved by the Ethics Committee of Osaka Medical College (No. 2074) and was conducted according to the principles expressed in the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Clinical and laboratory features of 51 patients with GBS

	GBS patients with elevated CK levels (n = 14)	GBS patients with normal CK levels (n = 37)	*P*-value
Age, years, mean ± SD	41.2 ± 10.2	47.7 ± 21.1	NS
Males, n (%)	12 (86)	19 (51)	0.029
Antecedent infection, n (%)	13 (93)	22 (59)	0.039
Gastroenteritis, n (%)	5 (35)	14 (38)	NS
Upper respiratory tract infection, n (%)	8 (57)	8 (21)	0.021
Clinical symptoms			
Hypoesthesia, n (%)	1 (7)	15 (41)	0.039
Cranial nerve involvement, n (%)	2 (14)	19 (51)	0.025
Urinary retention, n (%)	0 (0)	12 (32)	0.022
Preserved tendon reflexes, n (%)	9 (64)	16 (43)	NS
Anti-GM1 antibody, n (%)	8/12 (67)	8/32 (25)	0.016
Hughes grade at peak			NS
1	1 (7)	3 (8)	
2	7 (50)	13 (35)	
3	2 (14)	4 (11)	
4	3 (21)	13 (35)	
5	1 (7)	3 (8)	
6	0 (0)	1 (3)	

Abbreviations: GBS, Guillain–Barré syndrome; CK, creatine kinase; NS, not significant

Table 2 Electrophysiological features of the initial nerve conduction examinations of 51 GBS patients

	GBS patients with elevated CK levels (n = 14)	GBS patients with normal CK levels (n = 37)	*P*-value
Electrodiagnosis			
MS-AIDP pattern	0 (0)	15 (41)	0.005
M-AIDP pattern	8 (57)	7 (19)	0.014
AMAN pattern	3 (21)	5 (14)	NS
Unclassified	3 (21)	10 (27)	NS
M-AIDP and AMAN patterns and unclassified	14 (100)	22 (59)	0.005
Sensory nerve conduction abnormality	0 (0)	16 (43)	0.002
Absence of F waves	5 (35)	13 (35)	NS

Abbreviations: GBS, Guillain–Barré syndrome; CK, creatine kinase; MS-AIDP, motor-sensory acute inflammatory demyelinating polyneuropathy; M-AIDP, motor acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; NS, not significant

Table 3 CK levels and clinical features of 14 patients with Guillain–Barré syndrome with elevated CK levels

Patient No.	Age/sex	CK level at peak (U/L)	Cranial nerve involvement	Limb weakness			Treatment	Hughes grade		
				Arm or leg dominant	Proximal or distal dominant	Symmetric or asymmetric		At peak	14 days after onset	28 days after onset
1	20-29/M	1937	None	Arm dominant	Distal dominant	Symmetric	IVIG	2	1	1
2	30-39/M	1264	None	No dominance	No dominance	Symmetric	IVIG	3	2	1
3	30-39/M	795	None	Arm dominant	Distal dominant	Symmetric	IVIG	2	2	1
4	20-29/M	591	None	No dominance	No dominance	Symmetric	IVIG	2	2	1
5	30-39/M	550	Ophthalmoplegia, Facial weakness, bulbar weakness	No dominance	Distal dominant	Symmetric	IVIG steroid pulse	4	2	2
6	40-49/M	515	None	Arm dominant	Distal dominant	Symmetric	IVIG	2	2	2
7	30-39/M	433	None	Arm dominant	Distal dominant	Symmetric	None	2	2	0
8	30-39/M	429	Bulbar weakness	Leg dominant	No dominance	Symmetric	IVIG plasma exchange	5	5	5
9	50-59/M	402	None	Arm dominant	No dominance	Asymmetric	IVIG	1	1	1
10	50-59/M	396	None	No dominance	Distal dominant	Asymmetric	IVIG	4	1	1
11	40-49/F	351	None	No dominance	No dominance	Symmetric	IVIG	2	1	1
12	40-49/M	319	None	No dominance	No dominance	Symmetric	IVIG	2	2	1
13	40-49/M	300	None	No dominance	No dominance	Symmetric	IVIG	4	3	2
14	60-69/F	288	None	No dominance	Distal dominant	Symmetric	IVIG	3	2	1

To anonymize the identifying information, specific ages were grouped into age ranges.

Abbreviations: CK, creatine kinase; IVIG, intravenous immunoglobulin

Figures

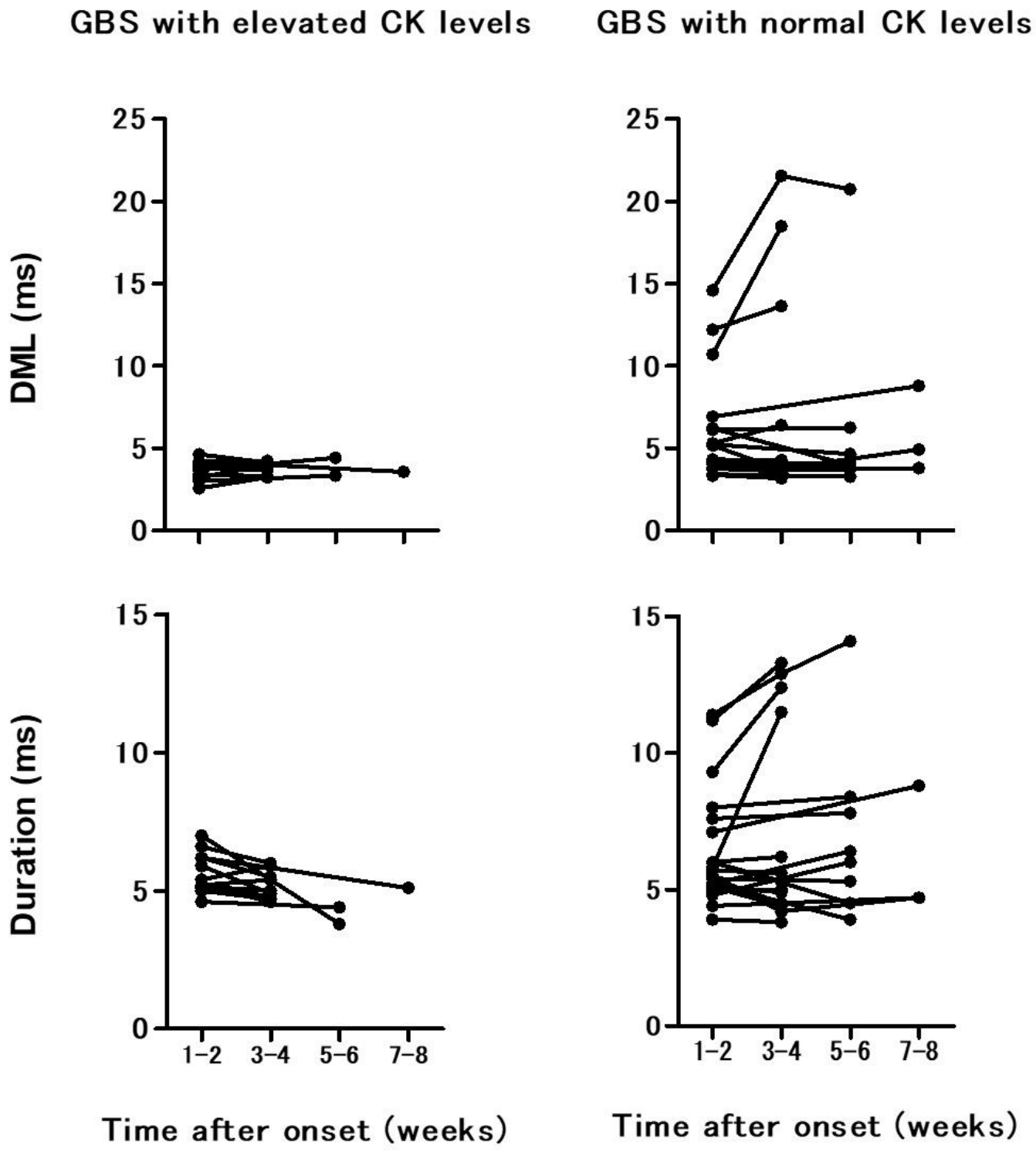

Figure 1

Serial findings of DML and duration in the right median motor nerve of GBS patients with and without elevated CK levels GBS, Guillain–Barré syndrome; CK, creatine kinase; DML, distal motor latency