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Guillain-Barré Syndrome with Discharges Following Compound Muscle Action Potentials: A-waves, M Dispersion or After-Discharges?

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ABSTRACT

In the very early days of Guillain-Barré syndrome (GBS), electrophysiological findings may be scarce but mostly required for the substantiation of nerve and/or nerve root pathology. Abnormal F-waves, absence of H reflexes, multiple A-waves and sural sparing are the best-known early findings of the disease. In this report, we present two cases with GBS in whom the early electrophysiology revealed discharges following the compound muscle action potentials. We propose that these discharges may be another early sign of GBS and may reflect early peripheral nerve demyelination and/or hyperexcitability.

Keywords: After-discharges, A-wave, demyelination, Guillain-Barré syndrome, hyperexcitability

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INTRODUCTION

At the very early stages of Guillain-Barré syndrome (GBS), electrophysiological findings may be scarce and mostly devoid of the classical findings of GBS. Abnormalities of F-waves, H responses and sural sparing may help (1). A-waves have also been shown to be associated with the early stages of GBS, particularly with AIDP (2–4). Still, the scarcity of the electrophysiological findings or their unconformity to the common patterns may cause missing out the abnormality and a mild case with a rare electrophysiological abnormality can recover spontaneously without having a proper electrodiagnosis. We herein describe two patients who presented with mild clinical features compatible with GBS, and with limited electrophysiological findings, one of which was the 'discharges following compound muscle action potentials (CMAPs)' . We chose this term because some of the discharges that follow the CMAPs in our patients did not conform to the well described characteristics of the A-waves, causing a relatively changing appearance of these discharges in successive stimulations.

Highlights

- **Discharges following CMAPs can be an early electrophysiologic sign of GBS.**
- **Discharges following CMAPs indicate demyelination/ hyperexcitability of nerves.**
- **Late response studies may provide helpful additional information in early GBS.**

CASE 1

A 40-year-old woman developed progressive weakness over a week with some sensory complaints on feet and hands. She was feeling clumsy while walking and climbing upstairs. She did not describe any complaints about sphincter control. Neurological examination revealed slight to moderate symmetrical weakness of distal lower extremity muscles (ankle and toe extensor muscles were MRC grade 4). All deep tendon reflexes were absent. Decreased superficial sensation to pinprick and touch was found distal to her ankles. No pyramidal signs were observed. There was no history of an antecedent immune attack.

In electrophysiological examination performed on the 7th day of her initial complaints, sensory nerve conduction studies were normal. The distal CMAP negative peak durations of bilateral median and right peroneal nerves were slightly prolonged (7.1 ms, 6.9 ms, 10.2 ms; respectively). Motor nerve conduction studies were otherwise normal. F-wave minimal latencies, persistence and chronodispersions of bilateral median nerves and right-sided ulnar nerve were also normal. However, F-waves couldn't be discriminated by stimulating left ulnar nerve and bilateral

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tibial nerves; 'discharges following CMAPs' were recorded instead. It was notable that while some of those discharges matched the well described characteristics of A-waves, having relatively constant shape and latencies, some did not (Fig. 1A, 1B, 1C). Those non-overlapping discharges or the discharges appearing and disappearing on consecutive stimulations gave a relatively changing appearance to the consecutive recordings presented in raster and superimposition modes (Fig. 1A′, 1B′, 1C′). With stimulation of the tibial nerves at the knee level (1 ms duration submaximal stimuli), no H reflexes could be recorded from both soleus muscles, but similar 'discharges following CMAPs' were clearly noticeable with each stimulus (Fig. 1D, 1D′). Needle EMG revealed no abnormal spontaneous activity and motor unite potentials with normal size and shapes were observed.

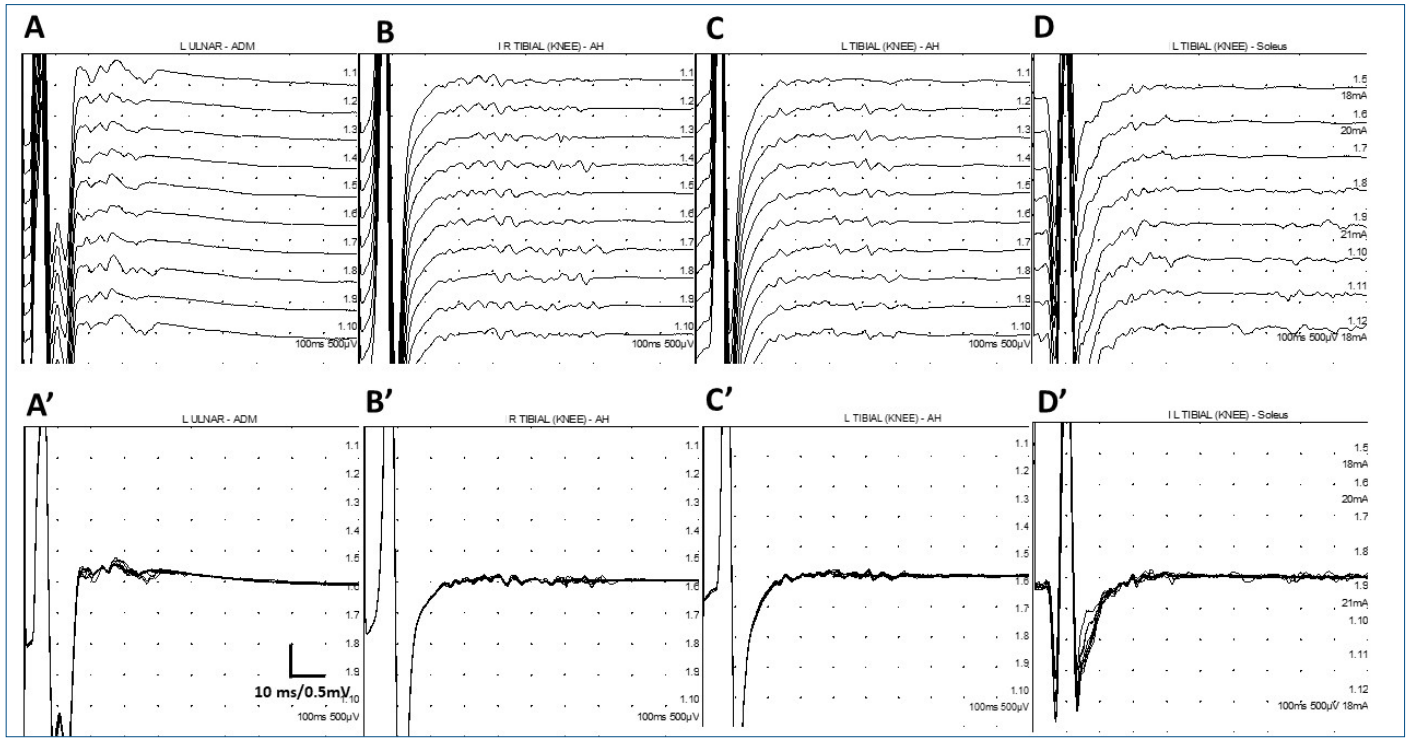

Figure 1. Discharges following CMAPs in left ulnar and bilateral tibial F-wave studies recorded at admission (A, B, C) as well as in left tibial H-reflex study (D). The superimposed traces are shown below (A′, B′, C′, D′). Note that some of the discharges do overlap while some do not

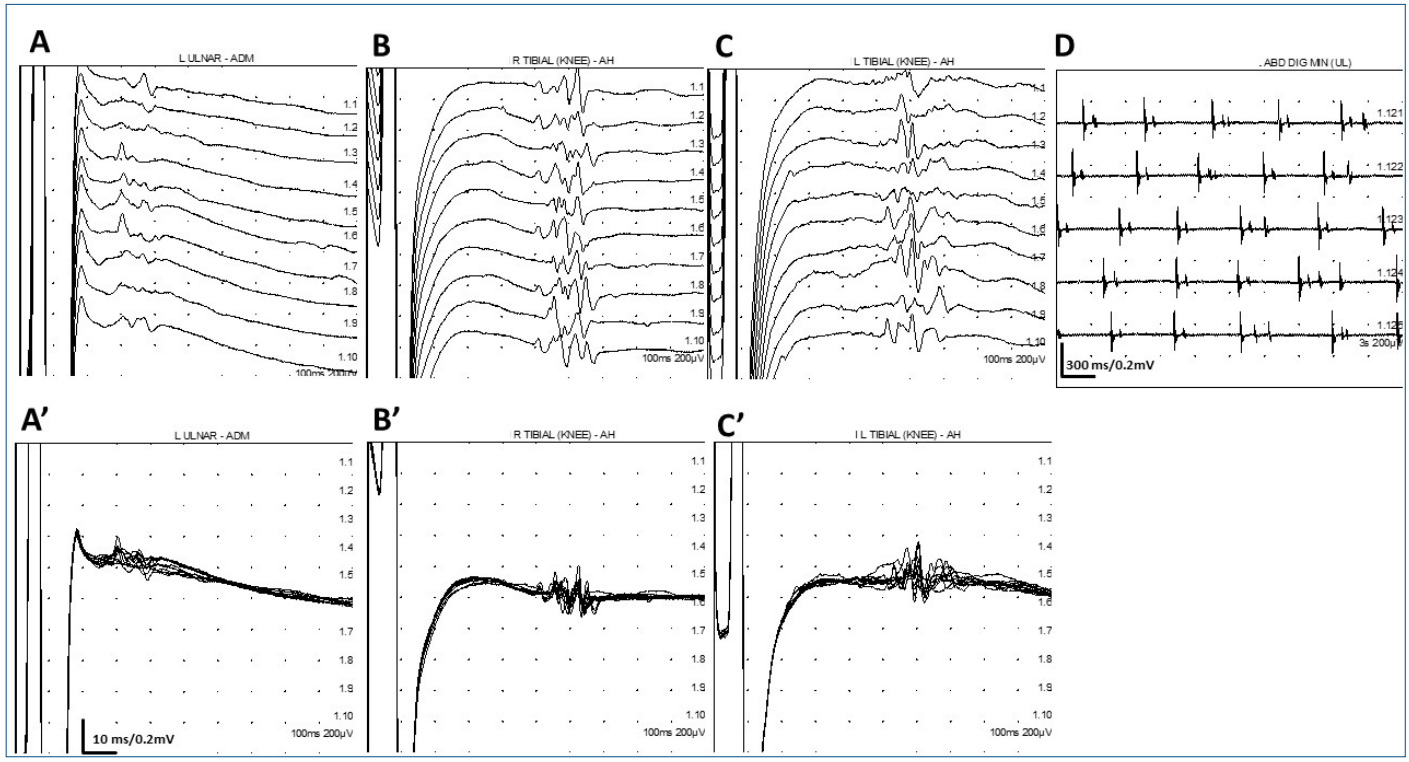

Figure 2. F-waves recorded by left ulnar and bilateral tibial nerve stimulation at first month visit after treatment (A, B, C). The superimposed traces are shown below (A′, B′, C′). Note that the discharges following CMAPs were disappeared and myokymia-like spontaneous discharges recorded from left abductor dijiti minimi muscle with surface electrodes (D).

Cerebrospinal fluid (CSF) was acellular and protein concentration was 120 mg/dl. With the diagnosis of GBS, IVIg treatment (0.4 mg/kg/day for 5 days) was given.

Following IVIg treatment, a month after her initial complaints, she declared hundred percent resolution of her symptoms. The neurological examination was normal. Electrophysiological findings were also getting better in parallel to the clinical findings. Prolonged distal CMAP negative peak durations were recorded in a lesser number of nerves (10.35 ms for the right peroneal and 7.2 ms for the right median nerve). The other motor and sensory nerve conduction studies were normal as well as the F-waves. The 'discharges following CMAPs' were disappeared (Figs. 2A, 2A', 2B, 2B', 2C, 2C'). Some myokymia-like spontaneous discharges were recorded from left abductor digiti minimi muscle with surface electrodes as the patient did not allow to have needle electromyography (Fig. 2D).

CASE 2

A 72-year-old man began experiencing severe back pain interfering his sleep twenty days before his admission. Cardiac work-up for aortic dissection and acute coronary syndrome were negative. Physiotherapy and dry needle treatment were applied. In nearly ten days, his back pain got better but numbness in his hands emerged. He states that, those sensory complaints were actually started from the very beginning but became more noticeable after back pain resolved. Afterwards, he suffered from an acute onset left-sided peripheral facial nerve palsy a week ago and was in remission at the time of referral. His medical history revealed diarrhea and upper respiratory tract infection nearly a month before the onset of his complaints.

His muscle strength was normal except for the mild weakness in left side eye closure. His deep tendon reflexes were globally decreased. No superficial sensory deficits were noted. Vibration sensation was absent on the big toes, knees and fingertips bilaterally. No pyramidal sign was detected and he did not describe any symptoms indicating a sphincter disturbance.

In electrophysiological examination performed on the 10th day of his initial complaints, SNAP amplitudes of median and ulnar nerves were decreased with a slight asymmetry and the superficial peroneal and sural nerve sensory conductions were normal leading to the pattern of 'sural sparing' . Distal latencies of median and tibial nerves on both sides were slightly prolonged and the amplitudes of median distal motor responses were decreased with a slight asymmetry. The tibial motor responses were dispersed on both sides showing the obvious 'discharges following CMAPs' elicited with both ankle and popliteal fossa stimulations (Figs. 3A, 3A', 3B, 3B'). In F-wave studies of the tibial nerves 'discharges following CMAPs' constituting of multiple A-waves and accompanying non-overlapping discharges were seen. In needle examination, no pathological spontaneous activity was observed and voluntary activity was normal except for the slightly increased ratio of polyphasic motor unit potentials. Facial motor response recorded from left sided orbicularis oculi was dispersed and the latency of left R1 response recorded from this muscle was prolonged in blink reflex studies.

The cranial, cervical and thoracal spinal CT examinations were normal. Among antiganglioside antibodies, Anti GD1a and anti GM1 IgG were positive. On his second visit, after 10 days of his first referral, he was still getting well with normal mobility and minimal sensory complaints.

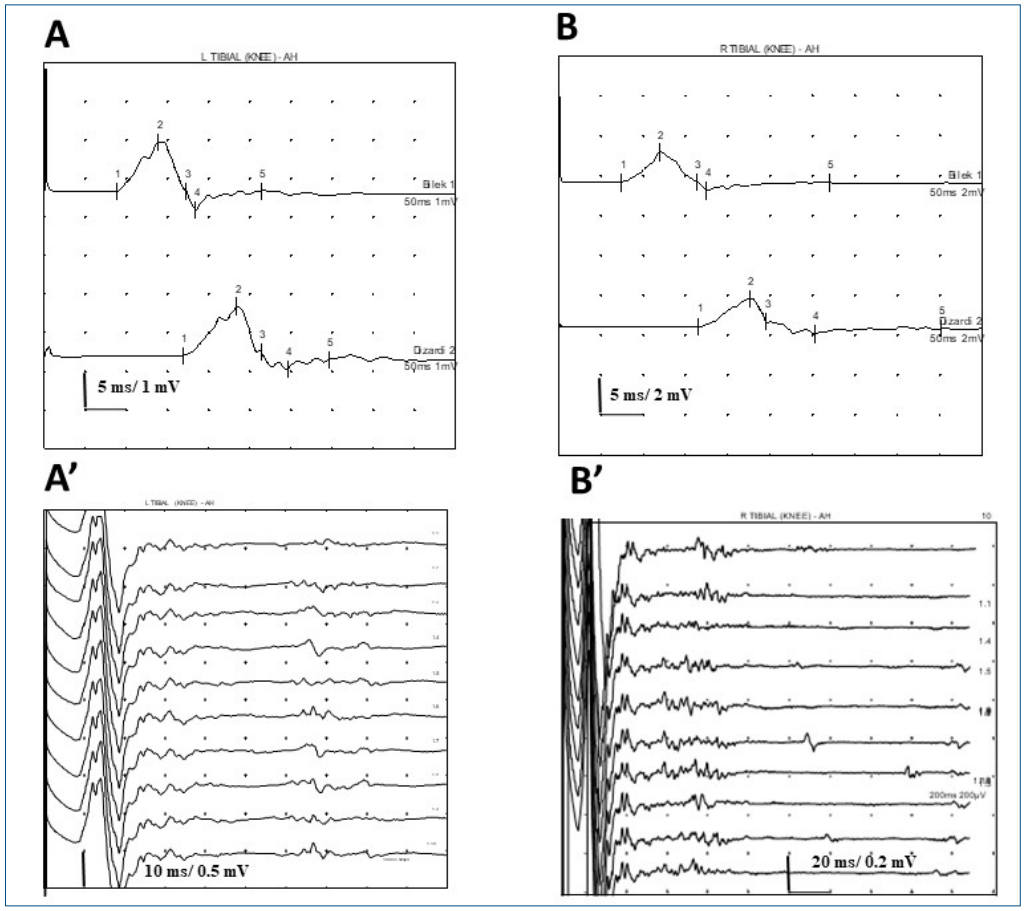

Figure 3. CMAPs recorded following left tibial (A) and right tibial nerve stimulations. Discharges following CMAPs with left tibial (A') and right tibial (B') nerve stimulations in F-wave studies.

DISCUSSION

We report two patients with GBS in whom the initial diagnosis was made by clinical features with the support of CSF findings and electrophysiology. Their clinical course and prognosis were quite favorable. However, the early electrophysiology was fairly challenging. 'Discharges following CMAPs' were remarkable in addition to prolonged distal CMAP durations, sural sparing, M dispersion and A-waves.

The commonly encountered form of A-waves is recorded during routine F-wave studies with supramaximal stimuli. They usually have lower amplitude and shorter duration than F-waves, with relatively constant latencies (less than 1.5 ms latency change in consecutive stimulations) and shapes. The amplitude does not change by increasing stimulus intensity in contrast to axon reflex. The exact localization of the generator of A-waves has not been clearly demonstrated yet. Some A-waves were thought to be recorded as extra discharges of an axon called 'auto-excitation' (3–5); while some to be generated via ephaptic transmission, either from one axon to another or through a myo-axonal ephapse (6).

A-waves have been recorded in different peripheral nerve disorders; such as polyneuropathies, entrapment neuropathies and radiculopathies. They can also be recorded from the intrinsic foot muscles of healthy subjects with tibial nerve stimulation, but multiple A-waves always reflect peripheral nerve dysfunction. A-waves were also thought as a sensitive sign of GBS, and one study reported abundant A-waves as a novel reliable marker of demyelination (7). Recently, EAN/PNS guideline on diagnosis of GBS described the 'indirect discharges' , often multiple and resembling A-waves and distinct from F-waves as an electrodiagnostic abnormality of GBS with low to moderate sensitivity but high specificity (8). As the guideline have been mentioned, these indirect discharges are known to be common in AIDP (sensitivity 59–100%, specificity 73%)(1,2), but they have also been reported in AMAN (9).

By stimulating ulnar and tibial nerves, we recorded some 'discharges following CMAPs' better recognized while studying F responses and H reflexes in our very early stage GBS patients. These discharges were closely related to CMAPs in time scale axis, yet the first deflection of these discharges was observable while CMAPs were returning to the baseline. They had obviously lower amplitudes than the expected F-waves or H reflexes. Some of these discharges had constant latency and shape, which we accepted as A-waves or M dispersion, but some were not. The discharges following CMAPs with inconstant latency and shape gave a changing appearance through consecutive recordings which led us to give a more general term covering all changing and constant discharges that followed the CMAP.

The discharges with inconstant latency and shapes were quite resembling the afterdischarges recorded in hyperexcitability syndromes (10,11). Those afterdischarges were defined as repetitive late potentials following the CMAPs after each stimulus. They reflect the hyperexcitability of nerve membrane mostly related to voltage gated potassium channel (VGKC) dysfunction which causes suppression of outward K current, and prevents termination of the action potential. Contactin-associated protein-like 2 (CASPR2) is expressed at juxtaparanodes of Ranvier nodes and is essential for clustering of VGKC. One might hypothesize that juxtaparanode and VGKC (either with or without CASPR2 association) might be affected in GBS as in peripheral nerve hyperexcitability (PNH) syndromes and afterdischarges could be recorded following CMAPs. Benatar et al. reported the specificity and sensitivity of afterdischarges in identifying PNH as 79% and 88%, respectively, with 10 Hz repetitive supramaximal stimulation of peripheral nerves (12). Niu et al. presented 6 PNH patients and suggested afterdischarges in motor nerve conduction studies to be quite sensitive to peripheral nerve hyperexcitability in patients with VGKC antibodies, even more sensitive than needle EMG findings. In other words, afterdischarges recorded during motor nerve conduction studies might reflect a mild subclinical peripheral nerve hyperexcitability, as presented in our patients (13).

A focal demyelination in a peripheral nerve may decrease the threshold of nerve excitability and a locus on this neuron, apart from its natural synapse, may generate impulses. This locus with ectopic excitation may cause auto-excitation following a conditioning impulse (14). Discharges following CMAPs recorded in early GBS, with or without A-waves, might also be explained with abnormal auto-excitation of motor axons, reminiscent of a merely electrophysiologic and reversible analogue of hemifacial spasm. The myokymia-like discharges in the convalescent phase of our first presented case could be another sign of hyperexcitability or ephaptic excitation of the peripheral nerve terminals akin to the speculated pathophysiology (15–17).

It is important to keep in mind that a meticulous neurophysiological examination is important to recognize discharges following CMAPs because they are very small in amplitude and may be overlooked in routine motor nerve conduction studies. F-wave recordings or H reflex studies without the split screen mode, in order to see the terminal phases of CMAP with high sensitivity (100–500 μV/div), may help to recognize them more easily.

As a result although electrophysiologic studies support the diagnosis of GBS, nerve conduction studies may not be conclusive at the very early stages of the disease. Studying late responses may give additional information. 'Discharges following CMAPs' , with or without A-waves, can be another early sign of GBS and may reflect peripheral nerve demyelination and/or hyperexcitability.

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Conflict of Interest: The authors declared that there is no conflict of interest.

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