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Serial electrophysiology in Guillain-Barré syndrome: a retrospective cohort and case-by-case multicentre analysis

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Abstract.

Objectives: To assess the usefulness of serial electrophysiology in Guillain-Barré syndrome (GBS) in a multicenter setting and the reasons for change in electrodiagnostic subtypes with serial studies.

Methods: We retrospectively analyzed serial electrophysiology of 51 patients with GBS from 4 European centers. Proportions of subtypes were determined at each timing. Individual case analyses were also performed where diagnostic changes occurred with either criteria, to ascertain if changes were due to disease progression or criteria inadequacy.

Results: At first study, comparing old versus new criteria, Acute Inflammatory Demyelinating Polyneuropathy (AIDP) was diagnosed in 70.6% vs. 51%, axonal GBS in 15.7% vs. 39.2%, equivocal forms in 11.8% vs. 7.8%. At second study, AIDP was diagnosed in 72.5% vs. 52.9%, axonal GBS in 9.8% vs. 33.3%, equivocal forms in 15.7% vs. 11.7%. Subtype proportions were unchanged for indicating serial studies did not, in the cohort, alter diagnostic rates for each subtype irrespective of criteria used. Individual review of cases where subtype electrodiagnosis changed indicated suboptimal specificity for AIDP/sensitivity for axonal GBS as main cause of diagnostic shifts with old criteria, whereas disease progression explained most changes with new criteria (55.6% vs. 81.8%; $p=0.039$).

Conclusions: Serial electrophysiology is unhelpful in GBS. Repeat studies cannot represent the gold-standard as electrodiagnosis may alter due to disease progression. Changes in electrodiagnosis relate more often to disease progression with new criteria but are more frequently due to suboptimal sensitivity/specificity with old criteria. A single electrophysiological study using the most accurate available criteria appears sufficient in GBS.

Introduction.

Various electrophysiological criteria have been published for subtype diagnosis in Guillain-Barré syndrome (GBS). Old criteria have been found of poor specificity for demyelination and of low sensitivity for axonal forms (1). Serial studies have been advocated for establishing actual subtype diagnosis (2, 3), particularly in relation to correcting early misdiagnosis of axonal GBS for AIDP with old criteria. On the other hand, new criteria have more recently been proposed for use with a single early study, using demyelinating cut-offs of greater specificity and introducing additional relevant parameters for proper identification of axonal forms (4).

We have previously demonstrated the absence of substantial effects of variable study timing in 2 GBS patient groups studied at different times from one of our centers (5). However the effects of serial evaluations on the same patients have not been examined in a heterogeneous multi-center cohort with pre-determined study timings. One report from a single center described diagnostic subtype fulfilment retrospectively with new and old criteria (6). This analysis importantly utilized the most informative serial study, which was repeated at highly variable times, ranging between very early at 7 days and very late at 70 days after disease-onset, rather than at a set interval. It is possible this methodology altered the final results and subsequent conclusions on the utility of serial electrophysiology, in creating a bias towards the benefit of such repeat studies, in selecting of the ones felt to be the most informative. Otherwise, how serial studies may actually impact on eventual diagnostic subtype changes with different criteria, as well as the possible reasons of such changes, remain uncertain.

The main objective of this current study was to ascertain the effects of serial electrophysiology in GBS in a multicenter cohort. We planned to establish the initial subtype classification using existing published criteria as well as the subsequent result obtained by the

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3 repeat study, in each patient individually. Proportions of diagnostic changes were determined.
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5 The electrophysiological characteristics and nature of these changes were analyzed for each
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7 subtype with each set of criteria. We aimed to compare our results with previously published
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9 studies and to establish similarities and/or differences, and possible explanations. Finally we
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11 planned to ascertain, in each individual case of classification change, what type of variations
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13 were encountered with serial studies with both criteria and what may have been the reasons
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15 for this. We believe the electrophysiological picture in GBS is dynamic as are clinical
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17 features. How this natural disease evolution may impact on findings of serial
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19 electrophysiology and on their interpretation, irrespective of criteria used, has not been
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21 studied. We attempted to separate what may be due to genuine criteria deficiencies from
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23 disease progression-related changes.
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Materials and Methods.

We retrospectively analyzed serial electrophysiologic data of consecutive patients with GBS from 4 European institutions, including University Hospitals of Birmingham, Birmingham, U.K., Newcross Hospital, Wolverhampton, U.K., Centre Hospitalier La Timone, Marseille, France, and Cliniques Universitaires Saint-Luc, Brussels, Belgium. Initial electrophysiological data were initially obtained within 3 weeks after disease onset and a second study subsequently performed, 3 to 10 weeks post-onset. First and second studies were separated by at least 7 days. Available motor conduction results were analyzed with normative values from our individual respective participating laboratories. We applied the criteria of Hadden et al. (1998) (defined here as “old criteria”) (1) and those of Rajabally et al. (2015) (defined here as “new criteria”) (4), to the data obtained.

The diagnosis of GBS was made in each case in accordance with established clinical criteria (7). Patients included had initially undergone electrophysiological testing of at least 3 motor and 2 sensory nerves. All had undergone a second study, within the timeframes specified above, when at least 2 motor nerves and 2 sensory nerves were tested. Electrophysiology was performed according to standard identical methods at all 4 institutions by a qualified senior physician trained and experienced in electromyography, using routine procedures and standard neurophysiological equipment. Tests had mostly, but not always been repeated by the same physician within each institution. The compound muscle action potentials (CMAPs) were evoked from the median nerve (stimulating at wrist and elbow, and recording at the *Abductor Pollicis Brevis* muscle), ulnar nerve (stimulating at wrist and below elbow, and recording at the *Abductor Digiti Minimi* muscle), common peroneal nerve (stimulating at ankle and fibular neck and recording at the *Extensor Digitorum Brevis* muscle) and tibial nerve (stimulating at ankle only or ankle and popliteal fossa and recording at the *Abductor Hallucis* muscle). Measured parameters were motor conduction velocity (MCV), distal motor

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3 latency (DML), minimum F-wave latency, distal CMAP amplitude and presence of
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5 conduction block (CB) as defined within the criteria considered. Results were analyzed with
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7 normal values for each participating laboratory.
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10 Fulfilment of old and new electrodiagnostic criteria was ascertained in each case. We
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12 classified patients with AIDP, axonal GBS, equivocal electrophysiology or with normal
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14 studies and established diagnostic rates. We compared the 2 electrophysiologic studies
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16 performed for diagnostic rates for each GBS subtype, using each one of the 2 sets of criteria.
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18 Findings were also compared with published literature using serial studies using most
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20 informative studies (6).
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24 We in addition established the numbers of diagnostic shifts for each set of criteria, as a result
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26 of serial studies. Further detail was then obtained on the nature of each diagnostic shift and
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28 the possible and likely precise reason(s) causing them to occur in each individual case. We
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30 thereby distinguished classification errors due to the criteria used (demyelination missed by
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32 new criteria due to low sensitivity and axonopathy misdiagnosed as demyelination by old
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34 criteria due to poorly-specific cut-offs for demyelination and/or low sensitivity for axonal
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36 GBS), from changes in electrodiagnosis which resulted from disease progression and
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38 therefore unrelated to the criteria *per se*. The proportions of diagnostic errors vs. changes due
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40 to disease progression, was established for each set of criteria, and compared.
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45 Comparison of proportions were performed using Fisher Exact Tests and comparison of
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47 means by T-tests. Significance level was set at p values <0.05. This retrospective work was
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49 registered and approved by our relevant, respective institutional review boards.
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Results.

We included 51 consecutive patients with a clinical diagnosis of GBS, admitted between 2005 and 2016 at our 4 institutions. Fifteen patients were included from Birmingham, 14 from Wolverhampton, 18 from Marseille and 4 from Brussels.

Patients were excluded on the basis of incomplete clinical details, delayed initial study performed >3 weeks after disease onset, delayed serial electrophysiology performed >10 weeks after disease onset, interval between the 2 studies of less than 7 days, insufficiently exhaustive electrophysiology for either examination, a diagnosis of Miller Fisher syndrome or a subsequently confirmed diagnosis of acute-onset CIDP.

There were 33 males and 18 females. Mean age was 52.5 years (S.D: 19.02). Mean interval from disease onset to the first nerve conduction study was 9.1 days (S.D.: 4.9). The mean timing interval of the second study was 39.2 days post-disease onset (S.D.: 12.4). The second study was performed a mean of 31.2 days after the first (S.D.: 12.6). Mean number of motor nerves tested was 6.4 (range: 3-8) at first study, and 5.8 (range: 2-8) at second study.

The main results obtained with the 2 sets of criteria are summarized in Table 1. At first study, with old criteria, 36/51 (70.6%) had AIDP, 8/51 (15.7%) had axonal GBS and 6/51 (11.8%) had an equivocal form. With new criteria, the first study produced 26 diagnoses of AIDP (51%), 20 of axonal GBS (39.2%) and 4 (7.8%) of an equivocal form. At second study, application of old criteria gave a diagnosis of AIDP in 37 (72.5%), of axonal GBS in 5 (9.8%) and of an equivocal form in 8 (15.7%), whereas new criteria produced diagnoses of AIDP in 27 (52.9%), axonal GBS in 17 (33.3%) and of an equivocal form in 6 (11.8%). Both sets of criteria produced one normal (2%) result at each study. Consequently, there were similar proportions of AIDP ($p=1$), axonal GBS ($p=0.55$) and equivocal forms ($p=0.77$) with old criteria for the 2 studies. Likewise, there were similar proportions of AIDP ($p=1$), axonal

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3 GBS ($p=0.68$) and equivocal forms ($p=0.74$), comparing the 2 study timings with new
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5 criteria.

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8 Table 2. shows the comparative analyses performed with initial studies reported in the recent
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10 literature using both sets of criteria (6). The findings of our current analysis are similar to
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12 those previously published, using old criteria, for the first study. They are also similar for
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14 both studies with new criteria. However, old criteria failed to produce with the second study
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16 the previously described diagnostic shift from AIDP to axonal GBS (3), with proportions of
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18 each subtype remaining unchanged, except for the significantly lower proportion of axonal
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20 GBS ($p=0.0007$) and higher proportion of equivocal forms ($p=0.047$), with the serial study, in
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22 our analysis compared to the previously published study, which used the most informative
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24 data.
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28 Table 3. details the diagnostic shifts observed and their nature, with both criteria as a result of
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30 the serial studies. The total number of changes occurred in comparable numbers with old
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32 versus new criteria (18 vs. 16; $p=0.83$), in diverse ways and directions.
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36 For each criteria, we detail below the shifts that occurred with serial studies towards (i)
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38 AIDP, (ii) axonal GBS or (iii) normalization, respectively. We also analyse the reasons for
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40 each and their frequency.
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43 **A. Old Criteria (Hadden et al., 1998)**

44 (i) Towards AIDP:

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47 Eight of 18 shifts occurred in a direction of demyelination. These were from
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49 an initial diagnosis of axonal GBS in 4 and of an equivocal form in the
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51 remaining 4. However 5 of these 8 subjects evolving towards demyelination
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53 with old criteria had an axonal GBS diagnosis at both studies with new
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3 criteria. We considered these 5 were therefore all incorrect diagnoses, as
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5 missed by old criteria due to their low sensitivity for axonal GBS. The other 3
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7 demonstrated delayed demyelination leading to an AIDP diagnosis on serial
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9 study with both criteria.
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12 (ii) Towards Axonal GBS:
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15 Four of 18 diagnostic shifts occurred towards axonal GBS, with 2 from an
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17 initial diagnosis of AIDP. We considered these 2 were both initially incorrect
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19 classifications due to poor specificity for AIDP and low sensitivity for axonal
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21 GBS. The remaining 2, initially equivocal and normal respectively, evolved as
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23 a result of delayed appearance of axonal features.
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27 (iii) Towards normalization:
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30 In 6/18, the shift was towards normalization, in 4 cases with an initial AIDP
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32 classification and of axonal GBS in 2. Of the 4 with an AIDP diagnosis, 3 had a
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34 classification of axonal GBS with new criteria on initial study, with only one
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36 having AIDP. We considered these represented 3 incorrect classifications as a
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38 result of poor specificity of old criteria for AIDP. The 2 axonal GBS cases
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40 were on the other hand also labeled axonal with new criteria and normalized
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42 with serial studies with these criteria as well.
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47 **B. New Criteria (Rajabally et al., 2015)**
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49 (i) Towards AIDP
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52 With new criteria, 6/16 shifts occurred in a direction of demyelination, 4 of
53
54 which with an initial diagnosis of axonal GBS and 2 with that of an equivocal
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56 form. Three were incorrect diagnoses, due to insensitivity of new criteria for
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3 demyelination, already picked up as having AIDP at first study with old
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5 criteria. In one case the initial diagnosis was one of an equivocal form with
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7 both criteria, and the shift to AIDP was therefore due to disease progression
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9 and delayed appearance of demyelination.
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12 (ii) Towards Axonal GBS:
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15 Five of 16 of shifts were in an axonal direction, of which 2 had a previous
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17 AIDP diagnosis, 2 had a previous equivocal diagnosis and one was normal.
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19 None had a correct early diagnosis through application of old criteria and
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21 changes could be explained in all cases by disease progression due to axonal
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23 loss.
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27 (iii) Towards Normalization:
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30 Five of 16 shifts demonstrated signs of normalization with serial study.
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32 Amongst those, 3 had an initial diagnosis of AIDP and 2 of axonal GBS.
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34 Again, none had a different early diagnosis by use of old criteria and all shifts
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36 could be explained by electrophysiological improvement concurrent to disease
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38 evolution.
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42 Hence, the calculated true initial misdiagnosis rate for shifts observed, purely due to the
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44 criteria insufficiencies and that could not be explained by disease progression, was
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46 significantly higher with old criteria vs. new criteria (10/18 [55.6%] vs. 3/16 [18.8%];
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48 $p=0.039$).
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Discussion.

Electrophysiology is a useful diagnostic test in GBS particularly in the presence of possible differentials. Although frequently advocated as essential for determining precise diagnostic subtype and often performed in many neuromuscular/neurology units in routine clinical practice in recent years, serial studies have little if no impact on clinical management.

Electrophysiology, although sometimes considered a prognostic marker, is unreliable for that purpose as significant variability may be observed, including in forms with apparent initial profound axonal loss which may turn out to instead correspond to rapidly reversible distal conduction blocks (8). Interventions available including repeat treatment by intravenous immunoglobulins (IVIg) or plasma exchanges (PE) and intensive rehabilitation therapy are offered in an attempt to improve prognosis, although electrophysiology cannot be used to justify either, this being an exclusively clinically-driven decision.

There has been a suggestion in a post-hoc analysis of a prospective therapeutic study that IVIg may be preferable to PE in pure motor GBS (9). This combined with retrospective data that anti-GM1 positive pure motor GBS patients may do better with IVIg (10), and in the context of analogy with multifocal motor neuropathy for which IVIg but not PE is recommended, may make early diagnosis of axonal GBS potentially more important than that of AIDP in practice. More sensitive criteria for axonal GBS such as the new criteria proposed may be useful for that purpose. There is however currently still no evidence that electrophysiology should be used in clinical management decisions in relation to treatment.

Review of the individual diagnostic shifts in our current study shows that changes globally occurred in several directions and were varied. Firstly, on the whole, proportions of different subtypes were unchanged with both criteria. This contradicts earlier reports of a diagnostic

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3 shift from AIDP to axonal GBS in up to 20% of cases with old criteria (3), as we only saw
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5 2/36 AIDP diagnoses (5.6%) behave in this way with serial study.
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8 Detailed additional review of individual cases provided useful information which allowed
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10 further interpretation. In separating shifts due to initial misclassification caused by the
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12 limitations of the criteria themselves, from shifts instead due to disease progression, our
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14 analysis enabled us to determine which criteria were least inaccurate with serial studies in
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16 cases taken individually. The significantly higher erroneous diagnosis rate of old criteria vs.
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18 new criteria (55.6% vs. 18.8%) further confirms their inadequacy and demonstrates the
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20 reasons for this in terms of poor specificity for AIDP and low sensitivity for axonal GBS.
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22 Shifts due to disease progression, although occurring with both criteria were more common
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24 with new criteria, found in >80% of cases with these. This indicates the natural disease
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26 progression explains most electrodiagnostic subtype changes that may occur during the
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28 course of GBS, demonstrating unequivocally that serial studies are inadequate as gold-
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30 standard.
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36 In conclusion, our current retrospective multicenter analysis of 51 GBS patients having
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38 undergone serial electrophysiology, at pre-established time-frames, firstly indicates that such
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40 studies do not alter globally proportions of different GBS subtypes, irrespective of criteria
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42 used. The classification shifts may be explained in most cases by disease progression with
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44 new criteria, highlighting the issue of the dynamic nature of electrophysiologic changes in
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46 GBS including demyelination, remyelination, reversible conduction failure, and wallerian
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48 degeneration. Serial studies at set times, as done in practice, can clearly not in these
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50 circumstances, systematically override the initial diagnosis and cannot as a result, provide the
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52 gold-standard for subtype classification in GBS. Our study of individual shifts otherwise
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54 demonstrates the greater inaccuracy of old criteria both in terms of low specificity for
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56 demyelination but also poor sensitivity for axonal forms. These findings indicate higher
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3 accuracy and reliability of new criteria in earlier disease stages, i.e. when most diagnostically
4 useful. This may be explained by use of more adequate cut-offs for demyelination (11), as
5 demonstrated in CIDP previously (12), and of the novel use of additional adequate
6 parameters for detection of nodo-paranodopathy (4).
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12 This analysis is limited by its retrospective nature as well as the lack of standardized nerve
13 conduction study protocols and of immunological and serological correlates using
14 antiganglioside antibody and *Campylobacter jejuni* status. The number of patients studied
15 was limited as most patients with GBS seen in our units could not be included as has not had
16 serial studies within the pre-specified timeframe. Prospective confirmation of our findings as
17 well as future emphasis on the sensitivity and specificity of electrophysiology as a whole,
18 irrespective of subtype, may consequently be desirable. Furthermore, consideration of the
19 integration of other parameters including F-wave abnormalities (13), as well as sensory
20 abnormality patterns (14), in new criteria, may be useful to optimize GBS electrodiagnosis in
21 future. Dispersion in particular, both at distal levels (15) but also proximally, may be an
22 important feature to distinguish subtypes. This may similarly benefit from future study.
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Table 1. Comparison of diagnostic subtype proportions with early studies versus serial studies in 51 consecutive patients with Guillain-Barré syndrome from Birmingham, U.K., Wolverhampton, U.K., Marseille, France and Brussels, Belgium (2005-16).

	Early Electrophysiology (days 0-21 post- disease-onset)	Serial Electrophysiology (days 22-70 post- disease-onset)	Comparison of Early Electrophysiology vs. Serial Electrophysiology p values (Fisher Exact Test)
Proportion of AIDP (by new criteria, (4))	51%	52.9%	p=1
Proportion of Axonal GBS (by new criteria, (4))	39.2%	33.3%	p=0.68
Proportion of Equivocal Cases (by new criteria, (4))	7.8%	11.8%	p=0.74
Proportion of AIDP (by old criteria, (1))	70.6%	72.5%	p=1
Proportion of Axonal GBS (by old criteria, (1))	15.7%	9.8%	p=0.55
Proportion of Equivocal Cases (by old criteria, (1))	11.8%	15.7%	p=0.77

Table 2. Comparison of diagnostic subtype proportions with early studies and serial studies in 51 consecutive patients with Guillain-Barré syndrome (from Birmingham, U.K., Wolverhampton, U.K., Marseille, France and Brussels, Belgium [2005-16]) with serial studies reported in the literature using same criteria (6)

	Current Study	Previous literature (6)	Comparison p values (Fisher Exact Test)
Proportion of AIDP at 1 st Study (by new criteria, Rajabally et al., 2015)	51%	45%	p=0.70
Proportion of AIDP at Serial Study (by new criteria, Rajabally et al., 2015)	52.9%	58%	p=0.70
Proportion of Axonal GBS at 1 st Study (by new criteria, Rajabally et al., 2015)	39.2%	35%	p=0.69
Proportion of Axonal GBS at Serial Study (by new criteria, Rajabally et al., 2015)	33.3%	38%	p=0.69
Proportion of Equivocal Cases at 1 st Study (by new criteria, Rajabally et al., 2015)	7.8%	20%	p=0.10
Proportion of Equivocal Cases at Serial Study (by new criteria, Rajabally et al., 2015)	11.8%	4%	p=0.15
Proportion of AIDP at 1 st Study (by old criteria, Hadden et al., 1998)	70.6%	67%	p=0.83
Proportion of AIDP at Serial Study (by old criteria, Hadden et al., 1998)	72.5%	58%	p=0.15
Proportion of Axonal GBS at 1 st Study (by old criteria, Hadden et al., 1998)	15.7%	18%	p=1
Proportion of Axonal GBS at Serial Study (by old criteria, Hadden et al., 1998)	9.8%	38%	<i>p=0.0007</i>
Proportion of Equivocal Cases at 1 st Study (by old criteria, Hadden et al., 1998)	11.8%	15%	p=0.78
Proportion of Equivocal Cases at Serial Study (by old criteria, Hadden et al., 1998)	15.7%	4%	<i>p=0.047</i>

Table 3. Diagnostic shifts with serial studies in 51 consecutive patients with Guillain-Barré syndrome (from Birmingham, U.K., Wolverhampton, U.K., Marseille, France and Brussels, Belgium [2005-16])

Diagnostic Shift	OLD CRITERIA	NEW CRITERIA
	Hadden et al., 1998 (1)	Rajabally et al., 2015 (4)
Equivocal → Axonal GBS	1	2
AIDP → Axonal GBS	2	2
Equivocal → AIDP	4	2
Equivocal → Normal	0	0
AIDP → Equivocal	4	3
Axonal GBS → AIDP	4	4
Normal → Equivocal	1	1
Normal → AIDP	0	0
Normal → Axonal	0	0
Axonal GBS → Equivocal	1	1
AIDP → Normal	1	0
Axonal GBS → Normal	0	1
TOTAL	18	16

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