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Increased cerebrospinal fluid protein and motor conduction studies as prognostic markers of outcome and nerve ultrasound changes in Guillain–Barré syndrome

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ABSTRACT

Objective: Our study examined the prognostic role of increased cerebrospinal fluid protein and motor conduction studies on outcome and nerve ultrasound changes in Guillain–Barré syndrome (GBS).
Methods: Fifty post-GBS patients underwent clinical and nerve ultrasound examination, with a mean of 3.4 years (SD = 2.8) after disease onset. Outcome was measured using the Medical Research Council Sum Score (MRC), the Rasch-built Overall Disability Scale (R-ODS) and the Rasch-built fatigue severity scale (R-FSS). In addition, the results of the motor conduction studies and cerebrospinal fluid (CSF) examination at disease onset were retrospectively evaluated.
Results: No significant changes in outcome were noted between patients with (p-CSF) and without increased CSF protein (n-CSF). The p-CSF group showed significant lower cross-sectional area (CSA) values of the radial nerve in spiral groove ($p < 0.001$) and higher values of the internerve-CSA variability ($p < 0.001$) compared to n-CSF patients. GBS patients with axonal affection in motor studies (GBS-a) showed significantly lower values of the R-ODS and MRC sum scores ($p > 0.001$), but not of the R-FSS Score ($p = 0.018$). Sonographically the GBS-a patients showed significant lower values of the median and ulnar nerve in the upper arm ($p < 0.001$).
Discussion: Axonal affection in motor studies, but not increased CSF protein at disease onset, seems to be an infavourable prognostic factor for outcome in GBS. Both axonal affection and increased CSF protein have a minor prognostic role in the development of nerve ultrasound changes.

1. Introduction

The incidence of Guillain–Barré Syndrome (GBS) is 0.6-4.0 per 100,000 worldwide and increases linearly with age, while men are about 1.5 times more likely to be affected than women [1–3]. The main features of GBS are a rapidly progressive bilateral and relatively symmetric weakness of the limbs with or without involvement of respiratory muscles or cranial nerve-innervated muscles and often an albuminocytologic dissociation in cerebrospinal fluid [4,5].

Various cerebrospinal fluid biomarkers, such as albumin, myelin basic protein, axonal damage markers (neurofilaments, tau and anti-ganglioside antibodies), glial and neuronal markers (neuron specific enolase, 14-3-3 proteins, S100B and hypocretin-1), have been proposed to act as a surrogate marker for disease process, prognostic accuracy and treatment response [6–8]. In addition, electrophysiological studies on GBS patients have highlighted the prognostic value of early motor conduction studies [9].

While nerve-conduction studies remain fundamental to confirm the diagnosis and to assess the severity of this type of polyradiculoneuropathy, the diagnostic role of neuromuscular ultrasound in clinical practice remains less well defined. Two ultrasound studies performed during the acute phase of GBS reported cross-sectional area (CSA) enlargements in various peripheral nerves [10,11]. In addition, the absence of significant correlation between pathological ultrasound changes, electrophysiology and functional disability in post-GBS patients has been recently reported in the literature [12].

The aim of this study was to examine the role of increased CSF protein and motor conduction studies as prognostic markers of outcome and nerve ultrasound changes in Guillain–Barré syndrome.

2. Materials and methods

2.1. Subjects and patients

The ethics committee of the Ruhr University in Bochum, Germany, approved our study protocol, and all GBS patients signed informed consent. Overall, 50 patients, aged over 18 years, fulfilling the diagnostic criteria of GBS published elsewhere [4], were recruited in the study a mean of 3.4 years (SD = 2.8) after onset of the disease (post-GBS patients). All patients had received intravenous immunoglobulins in the acute phase of the disease in a dosage of 1 g/kg body weight as therapy.

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2.2. Study protocol

The study was divided in two phases. On the first phase, all 50 post-GBS patients underwent a blinded ultrasound examination of their peripheral nerves from a neurologist of our department (A.K). In addition, a documentation of outcome was done blinded for ultrasound from an experienced neurologist (K.P.) using the Medical Research Council (MRC) sum score, the Rasch-built Overall Disability Scale (R-ODS) [13] and the modified Rasch-built fatigue severity scale [14]. A third neurologist (V.B.), blinded to ultrasound and clinical examination, retrospectively evaluated the results of the motor conduction studies and cerebrospinal fluid (CSF) examination. Both motor conduction studies and CSF examination were performed during the first week from disease onset.

On the second phase, the 50 post-GBS patients were divided from two neurologists (K.P., V.B.) into two groups, according to the presence of increased CSF protein [group with increased CSF protein (p-CSF) and group without increased CSF protein (n-CSF)] or the presence of axonal affection in the motor conduction studies [group with axonal affection (GBS-a) and group without axonal affection (GBS-d)] at disease onset. A statistical comparison of the acquired clinical and ultrasound data was performed in order to detect significant differences .

A CSF protein level of 450 mg/l was used as upper cutoff value of our lab. Axonal affection was defined as reduction of compound muscle action potential (cMAP) and denervation potentials (fibrillations and positive sharp waves), while demyelinating changes were defined as the increase of the distal motor latency (DML), the reduction of motor conduction velocity and the increase of F-wave latency.

2.3. Statistics

All study groups (p-CSF, a-CSF, GBS-a and GBS-d) showed a normal distribution according to the Anderson–Darling normality test ($p = 0.147$, $p = 0.203$, $p = 0.122$ and $p = 0.154$ respectively) so that statistical comparison and correlation analysis were performed with the help of Student's t test and Pearson's product–moment correlation coefficients for independent samples, using SPSS 17.0 for Windows. Due to the large number of sonographic measurements performed in the study, a Bonferroni correction was performed so that only $p < 0.001$ values were accepted as statistically significant.

2.4. Ultrasound examination

Ultrasonography was performed from a neurologist (A.K.) with more than 2 years of neuromuscular ultrasound experience. All ultrasound studies have been performed with the use of an Aplio® XG ultrasound system (Toshiba Medicals, Tochigi, Japan). For the superficial nerves of the body (median, ulnar, radial, brachial plexus, tibial at the ankle and sural) an 18-MHz linear array transducer was used, and for the deeper nerves (tibial and fibular in popliteal fossa), a 12-MHz linear array transducer was used. The transducer was always kept perpendicular to the nerves to avert anisotropy. No additional force was applied other than the weight of the transducer, and the extremities were kept in the neutral position to avoid causing any artificial nerve deformity. Cross-sectional area measurements were performed at the inner border of the thin hyperechoic epineural rim by the continuous tracing technique, and the average values were calculated after serially measuring three times.

All peripheral nerves and brachial plexus were measured bilaterally in all subjects and GBS patients at the following sites: median nerve at the entrance to carpal tunnel (retinaculum flexorum), forearm (15 cm proximal to retinaculum flexorum), axillary fossa, ulnar nerve at Guyon's canal, forearm (15 cm proximal to Guyon's canal), elbow (between medial epicondyle and olecranon), axillary fossa, radial nerve in the spiral groove, tibial nerve in the popliteal fossa and at the ankle and fibular nerve at the fibular head and in the popliteal fossa and sural nerve (between the lateral and medial head of the gastrocnemius muscle). The brachial plexus was also assessed in the supraclavicular (next to the subclavian artery) and interscalene space.

After obtaining the CSA values in each predefined site of clinical interest, we performed an ultrasound scan of the complete course of the median and ulnar nerve from proximal (axillary fossa) to distal (carpal tunnel for median nerve and Guyon's canal for ulnar nerve) in order to measure the maximal and minimal CSA of each nerve. Maximal CSA was defined as the site in the course of the nerve with the maximal area at the inner border of the thin hyperechoic epineural. Similarly, minimum CSA was defined as the site in the course of the nerve with the minimal area at the inner border of the thin hyperechoic epineural.

For each of the peripheral nerves and brachial plexus, we used the recently proposed measures in the literature [15–18] for the quantification of the ultrasound findings. According to the reference values of our lab, a CSA at a certain anatomic site was considered as pathological, when it exceeded the mean value + 2 SD [18]. Due to anatomical limitations in the imaging of the nerves of the lower extremities (short visualisable length of fibular and tibial nerve), we used the cross-sectional area values acquired from the predefined sites of interest for the calculation of the above measures. Concerning the radial and sural nerves, due to their short visualisable course, they were imaged at one site only, so that the above measures could not be calculated and are not included in this study. Due to the short visualisable length of the brachial plexus as a unique entity, we used the cross-sectional area values acquired from the supraclavicular and interscalene space for the calculation of the intraplexus cross-sectional area variability.

2.5. Electrophysiology

All electrophysiological studies of GBS were performed from a board certified neurologist (M.-S. Y.), with the use of a Medtronic 4 canal electromyography Device (Medtronic, Meerbusch, Germany). All testing was done while maintaining the skin temperature at 36 °C. Motor studies (distal motor latency, motor conduction velocity, F-wave and compound muscle action potential) were performed on both sides in the median, ulnar, tibial and fibular nerve. We used the ones already published in the literature as reference values for the motor conduction studies [19].

3. Results

A total of 50 post-GBS patients (mean age = 53.4, SD = 11.5, 21 women) underwent clinical and ultrasound examination of their peripheral nerves a mean of 3.4 years (SD = 2.8) after disease onset.

3.1. Outcome and ultrasound findings with respect to increased CSF protein

Overall, 28 p-CSF (mean age = 53.7, SD = 15.1, 11 women) and 22 n-CSF patients (mean age = 55.1, SD = 13.2, 10 women) were enrolled in the study. Both groups were matched for age ($p = 0.723$) and disease duration ($p = 0.517$). All patients had received at disease onset intravenous immunoglobulins in a dosage of 1 g/kg body weight as therapy.

3.1.1. Outcome

The p-CSF group showed no significant changes of the R-ODS ($p = 0.187$), R-FSS ($p = 0.274$) and MRC Sum score ($p = 0.062$) compared to n-CSF group (Table 1).

3.1.2. Cross-sectional area

The p-CSF group showed statistically significant lower CSA values of the radial nerve in spiral groove ($p < 0.001$) compared to n-CSF group. No other statistical significant changes of the CSA in peripheral nerves or brachial plexus were documented (Table 2, Fig. 1).