Sequence of demyelination-remyelination in Guillain-Barré disease

IRA WEXLER

From the Department of Neurology, St Agnes Hospital, Baltimore, Maryland, USA

SUMMARY A detailed investigation of nerve conduction was made in a patient with Guillain-Barré disease. Conduction velocity and configuration of the compound action potential in distal (median), intermediate (tibial) and central (sciatic) nerve segments were studied serially as the patient weakened and then recovered. Demyelination was found to follow a centripetal pattern, occurring first in the most distal portion of nerve and progressing, as the patient weakened, to the spinal root level. Motor and sensory fibres were equally affected although clinically motor weakness predominated. During recovery, central conduction was the first to improve. The pattern of demyelination-remyelination in Guillain-Barré disease appears to be one in which clinical recovery follows remyelination at the spinal root level and in which the first nerve segments to be demyelinated are the last to be remyelinated.

Electrophysiological studies of patients with Guillain-Barré disease began in the early 1960's, yet despite a considerable accumulation of data on this subject, important questions remain unanswered regarding the extent of proximal versus distal nerve involvement, and the time course of demyelination of motor and sensory fibres. In an attempt to shed further light on these questions, serial measurement of proximal and distal sensory and motor conduction was done in a patient with Guillain-Barré disease, throughout the initial phase of motor weakness and during subsequent recovery.

Methods

The patient was a 23-year-old female who was in excellent health until two weeks prior to hospitalisation, when, subsequent to a mild upper respiratory infection, she experienced a "warm" sensation from her navel to her toes. This sensation alternated with feelings of chills or "numbness" in the same distribution. Pain in the lumbar portion of her back subsequently developed but no bladder or bowel incontinence occurred. A feeling of "heaviness" developed in her legs and her gait became slow and unsteady. Weakness in the arms, tingling of the face, of the tongue and of the fingertips then developed. At the time of her admission she was still able to walk, albeit with a clumsy, slow gait. Considerable pelvic, hip and thigh weakness was present. The left arm was weaker than the right but bilateral abduction overhead was still possible. No objective sensory loss could be demonstrated; the deep tendon reflexes were absent. Two days after admission (19 days from onset) she developed right peripheral facial weakness. The arms when outstretched drooped considerably and left wrist drop was present; independent ambulation was no longer possible. By the 28th day of her illness she was virtually quadriplegic; only weak flexion at the hips remained in the lower extremities; in the upper extremities only the right arm could barely overcome gravity. Mild improvement became noticeable on the 34th day after onset of her symptoms; her left arm became stronger and could briefly overcome gravity. She was able to flex hips and knees fairly well although it was impossible for her to raise either leg completely from the bed. There was continued slow improvement thereafter. By the time of her discharge, 50 days after onset, she was able to take small shuffling steps while holding on to the wall. Her arms could easily raise overhead but she was clumsy with fine control in both upper and lower extremities. The facial paresis had disappeared but mild tingling paraesthesias remained around her mouth, in her fingertips and in her toes. No deep tendon reflexes were obtainable. When seen as an outpatient 95 days after the onset of her symptoms, and approximately 60 days after improvement was first noticed, she walked quickly and easily with only a slight residual pelvic weakness. Strength in arms and legs was excellent but no deep tendon reflexes could be elicited. She still had mild tingling paraesthesias at the tips of her fingers and toes.

Laboratory studies throughout her illness were within normal limits. These included complete blood count, sedimentation rate, preparatons for LE cells, liver and muscle enzyme studies, electrolytes, protein albumin/globulin ratio, serology, serum protein electro- and immuno-phoresis, urine analysis, chest radiography, Holter monitor, ECG, and pulmonary function studies. Although the patient underwent repeated needle electrode testing in the lower thoracic portion of her back she refused throughout her illness to have a lumbar puncture.

Nerve conduction

Nerve conduction studies were performed on the 17th, 21st,
28th, 38th, 45th, 52nd and 95th day of her illness. The first three studies were done as she became progressively weaker; after the 28th day a clinical plateau was reached and all succeeding measurements were done during her recovery phase. Nerve potentials were recorded from the median (digit-wrist; sensory) and tibial (ankle-knee; mixed) nerves. and from the region of the conus medullaris via the sciatic nerve stimulating the latter at the popliteal fossa. Details of needle electrode placement in the T12–L1 epidural interspace for conus potential measurements have been described previously. At each recording session, median (sensory and motor), tibial (mixed) and "sciatic" (mixed) nerve conduction velocity was determined. Standard monopolar needle electrode techniques for sensory and mixed nerve recording and surface electrodes for motor nerve recording were used in this study. It has been found that surface electrodes, when used for sensory or mixed nerve recording, tend to "smooth out" the compound nerve potential, minimising or even obliterating low level irregularly peaked potentials (unpublished observations). For this reason, given the low amplitude of potentials from demyelinated nerves, needle electrode recording with signal averaging was employed throughout. Small amplitude dispersed compound potentials from demyelinated nerves show ragged contours; signal averaging was used, not to smooth out such contours but rather to enhance them for subsequent analysis.

Results

Weakening Phase

Figures 1–3 show the median sensory (top), right and left tibial (middle) and right and left sciatic-conus medullaris (bottom) mixed nerve potentials; all measured as the patient progressively weakened. Figure 1 shows the potentials obtained 17 days after onset of symptoms while the patient was in a moderately weak condition. Motor and mixed motor-sensory conduction velocity had by this time decreased to below normal values (table). Irregularity and temporal dispersion was evident in the median and tibial potentials while the conus medullaris potentials remained normal. As the patient continued to weaken (figs 2, 3), median and tibial potentials all but disappeared while dispersion, low amplitude and disorganisation became apparent in the conus potentials. Despite the slowing, or perhaps in association with it, rapidly conducting low amplitude potentials occasionally appeared in the records (left and right tibial, 17th day; left tibial 21st and 28th days; left and right conus 21st day; right conus 38th day; see inset fig 3).

Recovery Phase

Figures 4–6 show the median, tibial and conus potentials as the patient slowly recovered strength. Clinically, recovery had begun by the 38th day but median and tibial potentials remained undetectable. Median motor and sciatic mixed nerve conduction velocity showed slow improvement but still remained below normal by the 52nd day after onset of symptoms. The conus potentials improved in parallel with the patients clinical recovery; beginning on day 38 and continuing thereafter, amplitude, velocity and configuration of the conus potentials all showed steady improvement.

By the 95th day the configuration of the conus potentials looked normal, with conduction velocity improved but still somewhat below normal. Median and tibial potentials were by now detectable, although their velocity was quite slow. Despite almost complete clinical recovery and excellent proximal and distal muscle strength, motor conduction in the median still remained very slow and the distal latency was considerably prolonged.

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<td>Days</td>
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<td>17</td>
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<td>52</td>
<td>7</td>
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<td>95</td>
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* = Estimated, due to irregular takeoff from baseline.
Fig 1  Median (top), right and left tibial (middle) and right and left sciatic-conus medullaris (bottom) potentials from the patient with Guillain-Barré disease, 17th day of illness. Inset shows comparable median, tibial and conus potentials from normal patients. Disorganisation in median and tibial, but not in the conus potentials is evident. Calibration in this and all subsequent figures = 5 microvolts; 1 millisecond.

Fig 2  21st day of illness. Patient is clinically worse; there is further slowing and disorganisation in median and tibial potentials with some early disorganisation of conus potentials. Order of tracings as in fig 1.
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Fig 3  28th day of illness. Plateau of clinical illness reached; there is almost total disorganisation of all potentials. Inset shows small, rapidly conducting potentials recorded from the left tibial nerve at higher sensitivity. Order of tracings as in fig 1.

Fig 4  Beginning clinical recovery. 38th day of illness. Improvement is seen proximally in the conus potentials while tibial and median potentials remain undetectable. Order of tracings as in fig 1.
Clinical recovery continues, 45th (left group) and 52nd (right group) day of illness. Improved conduction is seen in the conus potentials, the tibial and median potentials remain undetectable. Order of tracings as in fig 1.

95th day of illness. Virtually “complete” clinical recovery. Median and tibial potentials now detectable, although conduction in both is very slow. Conus potentials appear normal. Order of tracings as in fig 1.
Discussion

The present study details an electrophysiological investigation carried out over months on one patient with Guillain-Barré disease. It may invite the criticism—how “typical” are these results since only one patient was studied? To the extent that certain features of the disease are “typical”10 this patient, clinically, was typical of one so afflicted. The antecedent mild respiratory infection, the ascending symmetrical flaccid paralysis, lack of prominent sensory signs, areflexia, absence of prior metabolic, toxic or hereditary factors, good clinical recovery and so on all conform to the criteria for diagnosis. These data, therefore, may not be applicable to all patients with Guillain-Barré syndrome but, it can reasonably be argued, may be quite applicable to other patients with this disease who show a similar constellation of signs and symptoms.

The pathology of Guillain-Barré disease has been described as segmental demyelination with oedema and cellular infiltration throughout the longitudinal extent of peripheral nerves.1112 Despite the predominance of motor over sensory signs, the few pathology studies that have been done show no especial involvement of motor versus sensory fibres, nor do roots seem more severely involved than more distal portions of the peripheral nerve.12 With regard to electrophysiologic studies, these are acknowledged to be useful, indeed may be critical, in the diagnosis of this condition, but review of the literature shows surprisingly poor correlation between conduction change and the evolution of clinical signs. In fact, a considerable proportion (14%–41%) of patients may have normal motor conduction irrespective of the degree of their clinical impairment.51315

A few studies have been made of serial measurement of nerve conduction in Guillain-Barré patients,371415 but even in these it is difficult to correlate the results or to reach firm conclusions based on the data obtained; viz, the degree of slowing may show no correlation with the clinical disability of the patient or with the duration of illness14; motor and sensory conduction may continue to deteriorate in spite of improving clinical status67 and, in many patients, normal conduction throughout the illness may be found.561415

Perhaps technical factors, at least in part, are responsible for this apparent lack of correlation. It would seem that data reported exclusively in terms of motor conduction perform focuses on conduction in the unblocked fibres while conduction remaining in partially demyelinated or fully blocked fibres tends to be minimised by this procedure. In some studies, moreover, data have been reported in terms of only a single conduction value; since conduction does change with time in this dynamic neurologic illness, such single measurements may miss significant shifts in conduction values. Finally, the majority of investigations have employed surface electrodes in conduction measurements. This technique tends to smooth out compound action potentials making the detection of slower conducting “peaks”, early reduction in amplitude, and temporal dispersion rather difficult.816 Bergamini, and associates,9 were among the first to do serial studies on patients with Guillain-Barré disease, using needle electrodes and clearly showed the change in sensory potentials early on in this disease.

Normal peripheral nerve conduction throughout a patient’s illness has led to the inference that conduction may be blocked at more proximal root or spinal nerve levels and the suggestion put forth14 that F-wave measurements might prove useful in detecting this. King and Ashby4 used F-wave techniques in Guillain-Barré patients but found, however, that conduction was reduced to the same extent in proximal and distal portions of nerves in nine out of 11 patients. Kimura5 measured F-wave velocity and did find statistical evidence for greater slowing in proximal nerve segments but more sophisticated F-wave ratios of conduction in proximal versus distal segments remained about the same in the majority of affected nerves.

Given these discrepancies, the present study was therefore undertaken with the aim of assessing proximal versus distal conduction directly in a Guillain-Barré patient, using needle electrodes to record potentials from the peripheral (wrist, knee) and central (conus medullaris) portions of nerve, and to do so serially as the patient’s clinical state changed in order to correlate conduction with such changes.

It was found that, as the patient weakened, conduction in the distal-most sensory and motor fibres deteriorated first. Conduction in more proximal portions of nerve in turn became affected as the disease process continued. By the time demyelination had reached the root level, sensory potentials distally had virtually disappeared. Although the patient complained of (minor) paraesthesias, overt sensory loss, clinically, was not present. At this point in the illness uniform involvement of all fibres contributing to the compound action potential seemed to have occurred; its amplitude had decreased, temporal dispersion had become evident and fragmentation into slower conducting subgroups had taken place. Remaining nerve potentials on the order of 0.5 microvolts were still detectable, which meant that only about 50 nerve fibres, 10 micra or more in diameter, were still conducting.16

Potentials at the spinal root level “disappeared” at a time when the patient became virtually quadriplegic and reappeared when clinical signs of motor improvement first became evident. This clinical improvement occurred despite continued severe block of conduction in intermediate and distal nerve segments.7 Clearly, clinical improvement was most correlatable with remyelination at the root level and, in this patient, the first portions of nerve demyelinated were the last to be remyelinated.

...
whereas proximal root fibres, the last to be demyelinated, were the first to undergo remyelination.

The slow march of demyelination proximally may explain the reported late rise in cerebrospinal fluid protein which typically does not occur in this illness until days or weeks after the onset of symptoms. Ashbury et al. suggested that CSF protein increased when demyelination reached the level of the spinal roots, at which time protein passed from the roots themselves into the CSF. In our patient one would therefore have expected the CSF protein to be highest three weeks after the onset of initial symptoms when the roots, electrophysiologically, were most demyelinated; unfortunately, direct access to this patient's CSF was denied us.

Controversy still exists over whether demyelination in Guillain-Barré syndrome can begin exclusively in distal nerve segments. Eisen and Humphreys were inclined to doubt it, although their own data and the data of others cited by them seemed to indicate it could. Early changes in distal motor conduction and in the configuration of the sensory action potential were found, in the present study, at a time when conduction at the spinal root level still appeared quite normal; hence, demyelination in the Guillain-Barré syndrome can most certainly involve distal nerve before invading more proximal segments.

As the patient's illness evolved, and conduction slowed, rapidly conducting low amplitude deflections consistently appeared in the records. This suggested normal or even greater than normal conduction in partially demyelinated nerves. Can a form of ephaptic conduction occur in such partially demyelinated nerve? Older work utilising unmyelinated squid axon fibres suggested it could, or at least could affect the excitability and rate of firing of contiguous axons. In dystrophic mice with myelinated fibres undergoing demyelination, impulses can be transmitted transversely from fibre to fibre ("cross-talk"). Rasminsky and Sear20 demonstrated, in single rat fibres, that conduction remains saltatory in demyelinated internodes to the point at which conduction is blocked. Associated with this is an increase in internodal conduction time, an increased relative and absolute refractory period and a failure to conduct trains of impulses; all of which, it should be pointed out, would tend to slow, rather than increase conduction velocity. Conceptually, therefore, weak interaction between partially blocked demyelinated fibres via extrinsic current flow might give rise to sensory paraesthesias as has been proposed by Waxman et al., but it is difficult to see how such interaction could lead to above normal or apparently above normal fibre conduction such as suggested in the present study.

References