Guillain-Barré syndrome: a model of random conduction block

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SUMMARY In the Guillain-Barré syndrome clinical deficit is caused by failure of conduction in nerve fibres. Immunological mechanisms are generally held responsible, but the mechanism has not yet been elucidated. A recent longitudinal analysis of the distribution of lesions along the nerve trunks suggested two main patterns. In one of them, motor conduction block dispersed over the length of the nerve trunk was found, whereas sensory fibres were usually spared. For further pathogenetic studies of this subgroup, it is important to know whether conduction block occurs randomly or at preferred sites. As a tool to establish this, a model for conduction block is presented, based on a random distribution of lesions in the peripheral nerves. It is applicable to compound muscle action potentials (CMAP) obtained in routine EMG studies. Comparison of predicted and measured CMAPs in a first group of seven Guillain-Barré patients with evidence of conduction block supports the concept of a random distribution of lesions in this subgroup.

The main clinical features of the Guillain-Barré syndrome are progressive symmetrical paresis and depression of reflexes.¹ Diagnostically, slowing of conduction has always been an important characteristic but this is not related to the severity of the disease.²

Paresis can only be understood as the result of conduction failure known to occur early in Guillain-Barré syndrome.³⁻⁸ In another study⁹ we investigated the pattern of conduction failure longitudinally by repeated measurement of compound muscle action potentials (CMAP) and sensory nerve action potentials (SNAP). One group of patients showed "simple reduction" of the CMAP and SNAP; that is, the amplitude was the same after stimulation at several levels of the nerve, but decreased during clinical deterioration; this has been ascribed to distal conduction failure (fig 1B for schematic illustration). The other group showed "length-dependent reduction" of the CMAP, that is, in a single investigation, the CMAP-amplitude decreased with stimulation at more proximal levels of the nerve; this could be ascribed to conduction block. In this subgroup the sensory fibres were spared in the majority of the patients (fig 1A for schematic illustration). To understand the patho-

Fig 1 Typical patterns of conduction failure in Guillain-Barré syndrome as suggested from a former EMG study.⁹ Crosses indicate observed conduction failure. Pattern A is characterised by a decrease of the CMAP with more proximal stimulation. Often the sensory system is spared. In pattern B conduction failure is predominantly distal and the CMAPs vary little with more proximal stimulation. The sensory system was always involved in this pattern.

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genesis of the disease in this subgroup, it is important to know whether the lesions occur at preferential sites or randomly along the motorfibres. Waxman *et al*¹⁰ have introduced a model predicting conduction failure in single nerve fibres based on a random distribution of lesions. That model has now been further developed to make it applicable to the results of routine electromyographic (EMG) studies. The adapted model can predict the CMAP after stimulation at any level of the nerve during clinical deterioration. The predictions can be compared with actual measurements obtained from standard EMG tests, thereby supporting or refuting the assumption of a random distribution of lesions. This model has been applied to seven Guillain-Barré syndrome patients with "length-dependent reduction of the CMAP". A short report has already been published elsewhere.⁷

The model

If a process affects a nerve randomly, a fixed proportion of nerve fibres will be blocked per unit of length. Therefore with increasing nerve length conduction block will increase exponentially. Based on this concept, a general formula will be derived applicable in routine EMG studies.

The first step is to determine the chance of conduction (P_c) occurring in a single nerve fibre. This step is complementary to the work of Waxman *et al*¹⁰ who discussed the chance of conduction block occurring in single fibres.

Chance of conduction (P_c) occurring in a single fibre:

$$P_c = (1 - p)^L \quad (1)$$

p = chance of conduction failure per unit of length

L = number of units of length (in all the following cm).

For a large group of motoraxons one can suppose the proportion of conducting axons in a nerve is equal to P_c . These conducting axons determine the size of the CMAP. Since the contribution of individual motor units depends on several unrelated factors such as their size and their position with respect to the recording electrode,¹¹ it has been assumed that the relationship between the CMAP and the number of conducting axons is linear. Therefore, it can also be assumed that the CMAP is proportional to P_c .

After substitution in formula (1):

$$CMAP_L = (1 - p)^L \times CMAP_{max} \quad (2a)$$

$CMAP_L$ = the observed CMAP after stimulation at distance L from the recording electrode

$CMAP_{max}$ = the original CMAP prior to disease onset; for simplicity, assumed to be equal for stimulation at all levels of the healthy nerve.

This formula is not directly applicable to patient data since $CMAP_{max}$ and p are both unknown. It can be used, however, to predict the relationship between the amplitudes after stimulation at different levels of a nerve, for example the CMAPs in abductor pollicis brevis muscle (APB) after stimulation of the median nerve at wrist and elbow; substitution of formula 2 gives:

$$CMAP_{wrist} = (1 - p)^{L-wrist} \times CMAP_{max} \quad (2b)$$

$$CMAP_{elbow} = (1 - p)^{L-elbow} \times CMAP_{max} \quad (2c)$$

by combining 2b and 2c, p can be eliminated:

$$CMAP_{elbow} = \left(\frac{CMAP_{wrist}}{CMAP_{max}} \right)^{\frac{L-elbow}{L-wrist}} \times CMAP_{max} \quad (3a)$$

or more generally:

$$CMAP_{proximal} = \left(\frac{CMAP_{distal}}{CMAP_{max}} \right)^{\frac{L-proximal}{L-distal}} \times CMAP_{max} \quad (3b)$$

This function describes the relationship between the CMAPs evoked at two levels of the nerve in relation to the original normal CMAP prior to disease onset ($CMAP_{max}$).

Proportional to $CMAP_{max}$, the formula is further generalised and simplified:

$$CMAP_{proximal} = CMAP_{distal}^{\frac{L-proximal}{L-distal}} \quad (3c)$$

or alternatively:

$$CMAP_{distal} = CMAP_{proximal}^{\frac{L-distal}{L-proximal}} \quad (3d)$$

Application of the model

1. By using the simplified formulas 3c and 3d general predictions can be made concerning the findings in single and longitudinal EMG studies. In the case of a single study, the model can illustrate how the CMAP varies after stimulation

Fig 2 Calculated CMAPs as a function of distance between muscle and stimulation site (proportional to $CMAP_{max}$) in a single EMG study. Random distribution of lesions has been assumed with total conduction block along the nerve of 25, 50, 75 and 90% (right ordinate). This corresponds to 75, 50, 25 and 10% of the original CMAP ($CMAP_{max}$) if stimulation is performed at the level of the root (left ordinate; root at 80 cm on the abscissa). The distances for standard stimulation sites are indicated by arrows. See text for further discussion.

Table Measured and calculated compound muscle action potentials in relation to clinical deficit.

Patient	Muscle function (MRC)	Measurements					Calculations			
		Grasp force* (kPa)	CMAP† wrist (mV)	CMAP elbow (mV)	CMAP axilla (mV)	Differential dispersion‡	CMAP max (mV)	CMAP axilla (mV)	CMAP root (mV)	Block %
1	APB 3	0	17.5	14.0		+	18.8		8.7	54
2	APB 4	11	7.2	4.7		—	8.0		2.4	70
3	APB 2	0	8.0	4.0	2.2	—	9.6	2.7	0.9	91
	ADV 1		11.1	5.2	4.2	—	12.8	3.9	1.3	90
4	APB 2	0	7.6	2.0	0.95	+	12.3	0.9	0.07	99
5	APB 4	0	12.0	8.0		+	13.6		2.9	79
6	APB 2	0	8.2	0.9	0.3	—	16.0	0.4	0.01	99
7	APB 4	14	8.4	6.8		—	9.0		3.7	60

Abbreviations: APB, abductor pollicis brevis muscle; ADV, abductor digiti quinti muscle.

*Measured with a hand held dynamometer; lower limit of normal: 75 kPa.

†Recorded with surface clip electrodes; peak-peak measurements.

‡Defined as a more than 8% increase in the duration of the negative phase in the forearm segment.

at different levels of the nerve. As an example, fig 2 has been constructed for APB with formula 3d; after substitution:

$$\text{CMAP}_{\text{distal}} = \text{CMAP}_{\text{root}} \frac{L - \text{distal}}{L - \text{root}}$$

Four curves are calculated based on 25, 50, 75 and 90% conduction block respectively along the whole length of the nerve (right ordinate). This corresponds to CMAPs obtained after root stimulation of 75, 50, 25 and 10% of the original CMAP_{max} (left ordinate). These values have been substituted for $\text{CMAP}_{\text{root}}$ in the formula.

Total length of the nerve from root to APB is 80 cm (abscissa) and is substituted for L-root. The curves have been calculated by varying L-distal between 0 and 80 cm. For

Fig 3 The calculated relationship between the CMAPs evoked in abductor pollicis brevis after wrist and elbow stimulation in a longitudinal EMG study. Given a random distribution of lesions (inset) the relation during the progressive phase of the disease can be calculated with the given formula. L-elbow: 33 cm; L-wrist: 7.5 cm. Note: onset of the disease in the right top corner.

convenience the distances for standard stimulation sites have been indicated by arrows. The curves illustrate the non-linearity of the CMAP-decrease despite an even distribution of lesions. CMAP decrease is most pronounced in the distal part of the nerve. Therefore, it should be easier to detect a random conduction block in long distal segments of nerves; for example, in the lower arm segment of the median nerve. Measurements made in patients are in accordance with this prediction; CMAP decrease between wrist and elbow is more substantial than between elbow and axilla (table). Furthermore, it is clear from these curves that the CMAP after wrist stimulation could easily be within normal limits, whereas conduction block along the entire nerve is pronounced. If the CMAP over the entire nerve is decreased by 90%, it can be read from the lowest curve in fig 2, that only a 16% decrease in CMAP will be found after wrist stimulation. A random distribution of lesions could, therefore, explain the relatively normal CMAPs obtained on distal stimulation in severely paretic patients (table).

Longitudinal studies during clinical deterioration are helpful in studying the pattern of conduction failure in Guillain-Barré syndrome patients. In such studies, CMAPs are obtained from stimulation at standard levels of the nerve. The relationship between CMAP_{APB} evoked at the wrist and the elbow during deterioration can be deduced from fig 1 by moving down from the top to the bottom curve at the level of the respective arrows. More explicitly, the relationship is given by formula 3c; after substitution:

$$\text{CMAP}_{\text{elbow}} = \text{CMAP}_{\text{wrist}} \frac{L - \text{elbow}}{L - \text{wrist}}$$

L-elbow and L-wrist are measurable values. Figure 3 has been calculated by varying $\text{CMAP}_{\text{wrist}}$ from 0–100%. Again, one can see that the decrease of $\text{CMAP}_{\text{wrist}}$ is relatively small compared to that of $\text{CMAP}_{\text{elbow}}$. In the next section a patient example will be given, not in relative, but in absolute values to show that actual measurements can fit the theoretical curves surprisingly well (fig 5).

2. By using formula 3b predictions can be made in absolute values (mV). The first step is to calculate the original CMAP before the disease (CMAP_{max}). By rewriting formula 3b:

$$\text{CMAP}_{\text{max}} = \left(\frac{\text{CMAP}_{\text{wrist}}}{\text{CMAP}_{\text{elbow}}} \right) \frac{L - \text{elbow}}{L - \text{wrist}} \frac{1}{\frac{L - \text{elbow}}{L - \text{wrist}} - 1} \quad (4)$$

Fig 4 Comparison of CMAP-axilla obtained in a single EMG study with the predicted curve after stimulation of the ulnar nerve to ADV (upper curve, closed circles) and median nerve to APB (lower curve, triangles), respectively. The CMAPs obtained after wrist and elbow stimulation are used to construct the curves with formulae 4 and 5 and therefore fit the curve precisely (see text). Note that the measured CMAP-axilla is in both instances close to the predicted values.

All variables on the right are obtained in a routine EMG study. Using this formula CMAP_{max} has been calculated for the seven patients (table).

With the value of CMAP_{max} it is possible to predict the absolute value of the CMAP after stimulation at any level of the nerve by substituting the distance for L-proximal in the substituted formula 3b:

$$\text{CMAP}_{\text{proximal}} = \left(\frac{\text{CMAP}_{\text{wrist}}}{\text{CMAP}_{\text{max}}} \right)^{\frac{L-\text{proximal}}{L-\text{wrist}}} \times \text{CMAP}_{\text{max}} \quad (5)$$

All values at the right can be measured or calculated (CMAP_{max}).

For patient 3 two curves have been calculated for the median (APB) and ulnar (ADV) nerves, respectively, by varying L-proximal (fig 4). It can be seen that the CMAP value obtained with axilla stimulation has approximately the value predicted. Further quantitative comparisons of predicted and measured values of CMAP_{axilla} are given in the table. They suggest that in these patients the distribution of lesions might well be random.

The absolute value of the CMAPs obtained in longitudinal studies can also be compared with predicted curves. Comparison of the measured values and the calculated curves in fig 5 suggests also in this patient a more or less random distribution of the lesions.

Finally it is possible to estimate total conduction block along the nerve and to compare this with the clinical function. Therefore L-root, the measured distance from C₇ to the muscle has been substituted for L-proximal in formula 5 and

Fig 5 Comparison of the predicted relation (curves) with the measured relations (symbols) between the CMAPs obtained after proximal and distal stimulation of median (APB) and peroneal nerve (EDB), respectively, in patient 1. All measurements were obtained during clinical deterioration. Median nerve has been stimulated at wrist and elbow, peroneal nerve at ankle and knee. The curves have been calculated using formula 3b. CMAP_{max}, necessary for formula 3b, has been calculated from the first EMG study using formula 4 (see text). Note: onset of the disease at the top of the curves.

CMAP_{root} calculated (table).

Conduction block has been calculated as follows:

$$\text{Conduction block} = \frac{\text{CMAP}_{\text{max}} - \text{CMAP}_{\text{root}}}{\text{CMAP}_{\text{max}}} \times 100\% \quad (6)$$

Calculated conduction block roughly fits clinical deficit (table) but it is not such a reliable measure for testing the random distribution of lesions as the other options described above.

Limitations of the model

In the foregoing description it has been implicitly assumed that CMAP-reduction is caused by conduction block. Phase cancellation between individual motor unit action potentials, however, is a second cause of CMAP reduction. This is due to differential decrease of conduction velocity between individual motor fibres leading to dispersion of the CMAP. In normal nerves it is measured as causing a CMAP area decrease⁶ of 24%/m or in other studies, 10% when CMAP area is compared after wrist and axilla¹² or Erbs point⁸ stimulation. These values will increase with lower conduction velocities.¹³ Therefore, it has been stated that CMAP reduction in excess of the

values given above can only be confidently attributed to conduction block, if the increase in duration of the negative phase of the CMAP does not exceed 15% when distal and proximal stimulation are compared.^{4,6} The model can be corrected easily for the CMAP reduction seen in normal nerve,⁷ but the influence of pathological dispersion cannot be quantitatively estimated. Therefore, if excessive dispersion of the CMAP is present, conduction block will be overestimated. Often, especially early in the course of the disease, CMAP reduction can be observed without abnormal dispersion.^{4,6} Experimental demyelination has also shown that conduction block is the early manifestation of demyelination; slow conduction is a characteristic of remyelinating fibres.¹⁴ The model is not only applicable for demyelination but for any type of lesion, as long as the distribution is random. Therefore, if axonal degeneration should occur at random along the nerve trunk the same formula can be applied. It should be realised, however, that, because of Wallerian degeneration, the lesions quickly spread down and evidence for a former random distribution disappears.

An experimental limitation might be the decreased electrical excitability of partly demyelinated nerve fibres. It is, however, our experience that early in the Guillain-Barré syndrome maximal amplitudes can be obtained with standard stimulation strengths (20 mA or less) and that only later in the disease care should be taken to adjust the stimulation parameters.

If one is aware of these three phenomena the model might be applicable in the majority of Guillain-Barré syndrome patients early in the disease and might yield important information for further pathogenetic studies.

Discussion

The model described is based on a random distribution of lesions. Comparison of calculations and measurements in Guillain-Barré syndrome patients with evidence of conduction block indicated that the lesions in this subgroup might well be randomly distributed. Further studies are necessary to confirm these findings. Transcutaneous spinal root stimulation, a new technical tool, will be very helpful in analysing CMAP decrease over the whole length of the nerves.^{6,15}

Some pathogenetic considerations concerning this subgroup might, however, be made. If in Guillain-Barré patients an attack occurs by either humoral or cellular immune mechanisms it might be assumed to occur preferentially there, where the blood nerve barrier is naturally deficient: in the distal nerve twigs, at the level of the dorsal root ganglia and possibly the roots themselves.¹⁶ This should result in low CMAPs

with distal stimulation, as indeed is seen in other patients.⁹ In the patients discussed here, however, the opposite has been observed: the distal part of the nerve was relatively spared and a marked decrease of the CMAP occurred over a nerve segment with normally an efficient blood nerve barrier.

These diffuse or possibly random changes in the nerves might be explained by at least two mechanisms: (1) the blood nerve barrier breaks down before the nerve fibres themselves are attacked; (2) the route of the agent is not direct from the blood vessels to the myelin, but indirect. Uptake by motor nerve terminals and retrograde transport is a known mechanism in several disease processes.¹⁷ Such a selective uptake by motor terminals might also explain the severe involvement of motor fibres with sparing of the adjacent sensory fibres in the majority of these patients.⁹ This mechanism is currently under experimental investigation.

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Babinski's Sign

Amongst the founders of the celebrated Société de Neurologie de Paris were, Pierre Marie, Dejerine, Brissaud and Babinski. Born on 17 November 1857 in the Boulevard Montparnasse, Josef Francois Babinski graduated in Paris, was an intern to Vulpian and became chef de clinique under Charcot in 1885. He failed to secure Charcot's post (largely as the result of an internecine dispute between Charcot and Bouchard), but from 1880 to 1927 he headed the neurological, strictly male clinic at the Hôpital de la Pitié where both Charcot and Vulpian had previously worked.

Babinski was a bachelor who shared an elegant flat with Henri his brother, a distinguished engineer and like Josef a devotee of opera and gastronomy. He was a loner, a rather dignified, statuesque figure, taciturn in manner and prone to rituals of austere silence.¹ Like Gordon Holmes, his history taking was brief, but examination was detailed, painstaking and repetitive. He persuaded Clovis Vincent to train with Cushing and later he sent de Martel to Victor Horsley; they were to become the principal French exponents of neurosurgery.

Cutaneous reflexes had been described by Gowers in 1888,² and Remak³ claims some priority by describing extension of the great toe in response to plantar stimulation in transverse myelitis in 1893. But it was Babinski who earns credit for systematically investigating the phenomenon. His report was to the Société de Biologie on 22 February 1896, entitled "le réflexe cutané plantaire dans certaines affections organiques de système nerveux central".⁴ His principal purpose was to find a sign with which to discriminate organic from hysterical paralysis. His description was both clear and concise:

"In a certain number of cases of hemiplegia or crural monoplegia secondary to organic involvement of the central nervous system I have observed an alteration of the cutaneous plantar reflex which I shall describe briefly. Pricking of the sole of the foot on the unaffected side causes flexion of the thigh on the pelvis, of the leg on the thigh, of the foot on the leg, and of the toes on the metatarsus. This is the ... normal state. A similar stimulus on the paralysed side also causes flexion of the thigh on the pelvis, of the leg on the thigh, and of the foot on the leg, but the toes show a movement of extension on the metatarsus instead of the usual flexion. I have had the opportunity to observe this phenomenon in cases of hemiplegia of only a few days duration as well as in cases of spastic hemiplegia of several months duration. I have verified its occurrence in patients who were incapable of voluntary motion of the toes and also in those who were still capable of performing such motion. I must add, however, that this phenomenon is not constant.

In many cases of paraplegia ... I have seen extension of the toes following pricking of the sole of the foot ... In summary, the reflex movement resulting from pricking the sole of the foot undergoes not only a modification of its intensity, as is well known, but also an alteration of its form in those cases of paralysis of the lower extremities resulting from an organic lesion of the central nervous system."

Many tried to jump onto the bandwagon of Babinski's clinical shibboleth: Chaddock, Gordon, Oppenheimer and Yoshimura each tendered their modifications, but in this context at least, they were "deuxième cru" in comparison to Babinski's discovery.

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