Excitability properties of motor axons in patients with spontaneous motor unit activity

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Abstract

Objectives—Measures of nerve excitability provide information about biophysical properties of peripheral axons in disease states. One measure, the strength duration time constant (τ_SD), was previously reported to be prolonged in motor axons of patients with acquired neuromyotonia. The present study used a new protocol that applies a more comprehensive and sensitive panel of measures of axonal excitability, to determine firstly whether changes in τ_SD were present in a group of patients with evidence of spontaneous motor unit activity; and secondly, if such changes in τ_SD were present, whether other parameters of axonal excitability were affected, to clarify the mechanism of the change in τ_SD.

Methods—Eleven patients with both symptoms and EMG evidence of spontaneous motor unit activity were studied. Eight patients had autoimmune associated acquired neuromyotonia (aNMT) and three had the cramp fasciculation syndrome. The protocol first measured stimulus-response behaviour using two stimulus durations (from which the distribution of strength-duration time constants was estimated), and then threshold tracking was used to determine threshold electronus to 100 ms polarising currents, a current-threshold relation (indicating inward and outward rectification), and the recovery of excitability after supramaximal activation.

Results—The results were compared with previously published normal data. The value for τ_SD of motor axons in the patient group was 0.43 (0.02) ms (mean (SEM)), identical with the control value. Most other indices of axonal excitability, including those dependent on fast potassium channels, were also found to be normal. When compared with age matched controls however, the patients with acquired neuromyotonia had significantly greater late subexcitability after an impulse, greater excitability overshoots after depolarisation or hyperpolarisation, and more accommodation.

Conclusions—No clear evidence for the mechanism of ectopic discharge in these patients was obtained, probably because the activity was generated focally, and more often at the motor nerve terminals. The unexpected finding of increased excitability overshoots and accommodation compared with age matched controls, suggests a relative up regulation of slow potassium conductance, possibly as a consequence of the continuous motor unit activity.

Keywords: excitability; spontaneous activity; fasciculation; cramp

Fasciculation and cramp are common manifestations of neurological disease and may be caused by peripheral nerve hyperexcitability. In a recent study on patients with acquired neuromyotonia (aNMT), a condition attributed to nerve hyperexcitability,1,2 it was reported that the strength-duration time constant (τ_SD) of motor axons was prolonged.3

Some of these patients expressed antibodies to neuronal voltage-gated potassium channels (VGKC), thought to be involved in the pathogenesis of this disease, and it was hypothesised that the increase in τ_SD was also caused by a functional blockade of VGKC by antibodies.

The mechanism whereby anti-VGKC antibodies might increase τ_SD is not clear.4 Strength-duration time constant is a membrane time constant inferred from the relation between threshold current and stimulus duration. It has been defined as the ratio between the minimum charge threshold and the rheobase.4,5 Studies of τ_SD have shown that it is a nodal property, depending partly on the passive membrane time constant (the product of nodal capacitance and resting resistance) and partly on voltage-dependent membrane properties, particularly a persistent Na+ conductance active at subthreshold potentials.6,8 Membrane depolarisation increases τ_SD as although the passive time constant is reduced by an increase in K+ conductance, this effect is outweighed by the activation of Na+ channels.8

Thus blocking nodal K+ channels active at the resting potential could increase τ_SD directly, by increasing nodal resistance, whereas blocking either nodal or internodal K+ channels would cause membrane depolarisation and increase τ_SD by activating Na+ channels.

However, the anti-VGKC antibodies in aNMT are thought to be directed against fast K+ channels,9 which contribute little to nodal conductance.10 These channels are found in their greatest number in the paranodal and juxtaparanodal regions,11 where they can contribute to the resting potential, but where access of antibodies is restricted. Further information about the mechanism of the increase in τ_SD should be obtainable from other excitability measurements sensitive to mem-
brane potential, and/or K⁺, or both conductances, such as the recovery cycle after an impulse and threshold electrotonus. Tomimoto et al have reported finding anti-VGKC antibodies capable of suppressing K⁺ currents not only in patients with aNMT, but also in patients with myokymia of unknown origin. The question therefore arose as to whether patients with such clinical syndromes associated with nerve hyperexcitability also demonstrated changes in axonal membrane properties. The current study was undertaken to determine whether changes in \( \tau_{50} \) were present in a group of patients with evidence of spontaneous motor unit activity, and if so, to determine how other parameters of axonal excitability were affected, to clarify the mechanism of the change in \( \tau_{50} \). In addition, the study was the first to assess the utility in the clinical setting of a newly described method designed to measure multiple measures of axonal excitability.

### Patients and methods

Studies were performed on 11 patients (eight men, three women, aged 37–67 years). All patients gave informed consent and the study was approved by the South Sefton research ethics committee (Walton Centre). No patients were taking immunosuppressive drugs. Patients stopped taking medication for symptomatic control of their cramp and muscle twitching 1 to 7 days before testing (carbamazepine five patients, sodium valproate two patients, phenytoin one patient, lamotrigine one patient, no therapy two patients).

Patients were recruited from a specialised neuromuscular outpatient clinic having presented with symptoms suggestive of continuous motor unit activity including muscle cramps, twitching, and stiffness, affecting both proximal and distal muscle groups in more than one limb. In each patient there was EMG evidence of nerve hyperexcitability in at least one affected muscle. Most (eight patients) demonstrated the characteristic EMG discharges present in aNMT—namely, doublet, triplet, or multiplet single motor unit discharges having a high intraburst frequency of between 40–400/s. An example is illustrated in fig 1 (lower plot). The remaining three patients had generalised fasciculation on EMG (six patients), extensive serum autoimmunity screens were normal.

Studies were performed using a recently described protocol designed to measure a number of different nerve excitability parameters rapidly. Compound muscle action potentials were recorded from thenar muscles using surface electrodes over the abductor pollicis brevis, with the active electrode at the motor point and the reference on the proximal phalanx. The EMG signal was amplified (gain 1000, bandwidth 1.6 Hz to 2 kHz) and digitised by computer (486 PC) with A/D board (DT2812, Data Translation Inc, 100 Locke Drive, Marlboro, MA 01752–1192, USA), using a sampling rate of 10 kHz. Stimulus waveforms generated by the computer were converted to current with a purpose built current stimulator (maximum output \( \pm 50 \) mA). The stimulus currents were applied via non-polarisable electrodes (Red Dot, 3M Health Care, D-46325 Borken, Germany), with the active electrode over the median nerve at the wrist, and the reference electrode about 10 cm proximal over muscle. Stimulation and recording were controlled by new software, written in BASIC (QTRAC version 4.3, copyright Institute of Neurology, London, UK with multiple excitability protocol TRONDH). Test current pulses of 0.2 ms or 1 ms were applied regularly at 1 s intervals, and combined with suprathreshold conditioning stimuli or subthreshold polarising currents as required. A complete recording sequence is illustrated in figure 1. The amplitude of the compound muscle action potential (CMAP) was measured from baseline to negative peak. For all tracking studies, the target CMAP was set to be 40% of the peak response. Skin temperature was monitored close to the stimulation site and was kept constant above 32°C.

Stimulus-response curves were recorded separately for test stimuli of durations 0.2 ms and 1 ms. The stimuli were increased in 6% steps, with two responses averaged for each step, until three averages were considered maximal (fig 1 A). The stimulus-response data were used for several purposes. Firstly, the 1-ms peak response was used to set the target submaximal response (40% of peak) for threshold tracking for the remainder of the study. Secondly, the slope of the 1 ms stimulus-response curve was used in conjunction with the tracking error (deviation from the target) to optimise the subsequent threshold tracking. Finally, when the data were analysed, the ratio between the 0.2 ms and 1 ms stimuli required to evoke the same responses were used to estimate the strength-duration time...
constants and rheobases of axons of different threshold.

Prolonged subthreshold currents were used to alter the potential difference across the internodal axonal membrane, a process referred to as electrotonus. The changes in threshold associated with electrotonus normally have a similar time course to the changes in membrane potential and are known as threshold electrotonus. In the present protocol, test stimuli of 1 ms duration were used to produce the target CMAP (40% of maximal). Threshold tracking was used to record the changes in threshold induced by subthreshold polarising currents, 100 ms in duration, set to be +40% (depolarising) and −40% (hyperpolarising) of the control threshold current. The three stimulus combinations were tested in turn: test stimulus alone (to measure the control threshold current), test stimulus+depolarising conditioning current, and test stimulus+hyperpolarising conditioning current. Threshold was tested at 26 time points (maximum separation 10 ms) before, during, and after the 100 ms conditioning currents. Each stimulus combination was repeated until three valid threshold estimates were recorded, as judged by the response being within 15% of the target response, or alternate responses being either side of the target (fig 1 B).

The current-threshold relation was tested with 1 ms pulses at the end of subthreshold polarising currents lasting 200 ms (fig 1 C). The polarising current was altered in a ramp fashion from +50% (depolarising) to −100%

![Figure 1](http://jnnp.bmj.com/)  Example of data recorded from each patient: upper three plots show amplitudes of stimuli, CMAP responses and delay between conditioning and test stimuli for four segments of recording A-D. The lowest plot illustrates one EMG trace in 14, during the prestimulus period, to show spontaneous motor unit activity, with the sweep separation corresponding to an amplitude measure of 30 µV. (A) Stimulus-response behaviour, stimulus duration 0.2 ms, then 1.0 ms. (B) Threshold electrotonus recording with 100 ms conditioning stimuli, 40% and −40% of threshold. (C) Current/threshold recording with 200 ms conditioning stimuli varied from 50% to −100% of threshold. (D) Recovery cycle, threshold changes 200 to 2 ms after single, supramaximal stimulus.
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(1.9) years, temperature 32.3 (0.2)

normal controls in the previous study (age 39.4

temperature (32.5 (0.5)

three patients with CFS were similar in age

whereas the 

However, some excitability properties change

threshold estimates were obtained.

The final part of the protocol recorded the 

recovery of excitability after a supramaximal

conditioning stimulus (fig 1 D). These changes 

were recorded at 18 conditioning test intervals, 

decreasing from 200 to 2 ms in roughly 

geometric progression. Three stimulus combi-

nations were tested in turn: (1) unconditioned 

stimulus (of 1 ms duration) tracking the 

control threshold, (2) supramaximal condi-

tioning stimulus (1 ms duration) alone, and (3) 

conditioning+test stimuli. The response to (2) 

was subtracted on line from the response to (3) 

before the test CMAP was measured, so that 

the conditioning maximal CMAP did not con-

taminate the measured response when the 

conditioning test interval was short. Each stimulus 

combination was repeated until four valid 

threshold estimates were obtained.

Rheobase current and \( \text{VR} \) were calculated off 

line from the stimulus-response data. The strength-duration curve for peripheral nerve 

axons is hyperbolic, not exponential, and the 

best curve fit for strength-duration data comes 

from Weiss’ equation. This empirical law 

relates stimulus charge (threshold current 

multiplied by its duration) to stimulus duration 

and may be estimated reliably from the thresh-

olds for just two pulse durations.\(^{15-20} \)

Values for the excitability parameters ob-

tained in the current study were compared with 

normative data established in a previous study 

where testing conditions were identical.\(^{14} \)

However, some excitability properties change 

with age and/or temperature. Whereas the 

three patients with CFS were similar in age 

(40.7 (1.9) years, mean (SEM)) and skin tem-

perature (32.5 (0.5)°C) to the full group of 

normal controls in the previous study (age 39.4 

(1.9) years, temperature 32.3 (0.2)°C, n=29), 

the patients with aNMT were significantly 

older (53.6 (2.6) years, n=8), and slightly 

warmer (33.8 (0.6)°C). To allow for these differ-

ences, a subset of age and temperature 

matched controls was constructed by selecting 

control subjects over 43 years old with skin 

temperatures above 31°C. This matched con-

trol subjects did not di-


V

ter significantly in age 

H.22

C)

from the patients with aNMT. Excit-

ability parameters were compared between the 

patient and both control groups (full and 

matched) using two tailed \( t \) tests. As multiple 

excitability parameters were compared, \( p \)

values>0.01 were not considered significant.

Results

As with studies using the new protocol in 

healthy subjects, no patient found the stimula-

tion sequence painful. The complete recording 

sequence took 8.5–11.8 minutes, mean 9.4 

minutes. All patients had continuing symptoms 

and signs of generalised spontaneous muscle 

overactivity on the day of the recording. During 

the recording three patients had evidence of 

spontaneous activity in the abductor pollicis 

brevis muscle. In one subject doublet dis-

charges were recorded throughout the study, 

illustrated in fig 1.

Primary data from all the patients are plotted 
in fig 2, and selected pairs of parameters are 

plotted as scatter plots in fig 3.\(^{14} \) Open circles 

differentiate the small CFS group in figs 2 A 

and 3, and the dotted lines in each figure indi-

cate the 95% confidence intervals for a normal 

subject, based on the 29 controls in the 

previous study.\(^{14} \)

The stimulus-response curves in fig 2 A are 

normal in shape, because the normalised traces 

in figure 2 B all fall within the normal limits, as 

do the stimulus-response slopes in figure 3 B.

There was therefore no evidence of axons being 

affected non-uniformly by the disease.\(^{21} \)

The peak CMAP amplitudes were smaller on aver-

age, than the normal controls (figs 2 A, 3 B), 

but this difference was not significant when the 

comparison was made with age matched 

controls. One patient with CFS had an abnor-

mally high threshold (fig 2 A) and rheobase (fig 

3 A), and there was a tendency for the patients 

to have higher thresholds on average than the 

controls (fig 2 A). However, the difference from 

age matched controls was not significant at the 

1% level, and was in the opposite direction 

from one which could account for the continu-

ous motor unit activity.

The current-threshold relations for each 

patient, calculated using the normalised 

threshold changes at the end of 200 ms current 

pulses, are plotted in fig 2 C. For each level of 

conditioning current, from +50% to −100% of 

the control threshold, the threshold change was 

measured, and the percentage threshold reduc-

tion plotted, depolarisation to the right and 

hyperpolarisation to the left. The current-

threshold relation reflects the rectifying proper-

ties of the axon (both nodal and internodal 

axolemma), and the slope of the curve can be 

used to provide an estimate of the threshold 

analogue of input conductance. The steepen-

ing of the curve towards the top right results 

from outward rectification, an accommodative 

response to the depolarising current, associated 

with the activation of fast and slow K+ 

channels, the steeper the plot the greater the 

accommodation (rectification). The less 

prominent steepening towards the bottom left 

of the figure represents accommodation to the 

hyperpolarising current due to inward recti-

fication, and thereby represents activation of the 

hyperpolarisation-activated conductance, \( \text{I} \).\(^{22} \)

Curves for each of the patients studied were 

within the normal range, as were the minimum 

and resting slopes of the current/threshold 

relationship (fig 3 C). This suggests that the 

rectifying properties of the nerves studied 

remained intact.\(^{14} \)

Strength-duration time constant was calcu-

lated from the thresholds measured using test 

pulses of two durations, 0.2 and 1.0 ms.\(^{14-20} \) Cal-

culations were performed for different axonal 

populations, using the normalised stimulus-

response data as in figure 2 B. Nine populations 

were used, starting from axons contributing to
the responses between 5%-15% of maximal, then 15%-25%, further increasing in 10% batches up to the maximum of 85%-95%. These nine \( \tau_{\text{SD}} \) values were plotted against their corresponding CMAP responses in fig 2 D, and all patient \( \tau_{\text{SD}} \) measurements fell well within the normal limits. This is also shown in fig 3 A, where \( \tau_{\text{SD}} \) are plotted against rheobase for responses 35%-45% of maximal. The value for \( \tau_{\text{SD}} \) of motor axons in the patient group was 0.43 (0.02) ms (mean (SEM)). This value is the same as that reported for the control group (0.43 (0.02) ms; mean (SEM)) and very similar to that reported elsewhere for normal nerve (0.46 (0.13) ms, mean (SD)).

Significantly, there was no evidence for the high \( \tau_{\text{SD}} \) reported by Maddison et al in some of their patients with aNMT. As with the thresholds for a 50% maximum CMAP in fig 2 A, the rheobases in fig 3 A were higher than normal on average, and well above the normal range in one patient with CFS. A technical explanation, perhaps related to the distance of the stimulating electrode from the underlying motor fascicles, may have been responsible, as nerve conduction studies were normal in this patient, as in the others.

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**Figure 2** Excitability data for all subjects superimposed on the 95% confidence intervals for a member of the control population taken from a previous study (broken ellipses). (A) Absolute stimulus-response relations indicated by plotting half maximal CMAP amplitude vs stimulus for half maximal response (log-log coordinates); (B) normalised stimulus-response relations; (C) current-threshold relation; (D) distribution of strength-duration time constants; (E) threshold electrotonus; (F) recovery cycle. Threshold tracking performed using a test pulse of 1 ms duration. In plot A, filled circles=patients with aNMT, open circles=patients with CFS.
The changes in excitability associated with threshold electrotonus are illustrated in fig 2 E. As in previous studies, the changes in threshold are plotted as threshold reductions, with responses to depolarising currents upwards, as is normal for electrotonus. The fast changes in threshold that occur at delays of 0 and 100 ms are due to the rapid (<1 ms) changes in potential occurring at the nodes of Ranvier at the onset and offset of the polarising currents. The slower excitability changes are caused by slower potential changes occurring passively on the internodal membrane, and by ion channels with slow kinetics, especially slow potassium channels at the nodes. The traces from the patients all fell within the normal limits, and conventional indices derived from the threshold electrotonus recordings, including the early depolarising response TEd (10–20 ms) which can reflect fast potassium channel activity, also fell within normal limits (fig 3 E).

To complete the protocol, the recovery cycle (the absolutely and relatively refractory periods, the supernormal period, and the late subnormal period) was recorded. In fig 2 F the threshold changes are plotted with a logarithmic time scale, to show more clearly the early events in the cycle. The traces from the patients mostly fell within the normal limits, but between 20 and 70 ms, the late subexcitability was greater than normal in one patient with aNMT and less than normal in a patient with CFS (fig 3 F). The remaining patients...
with aNMT had subexcitabilities in the upper half of the normal range, and the mean subexcitability of the aNMT group (19.4 (1.5)%, mean (SEM), n=8) was abnormally high, whether compared with the full control group (14.7 (0.7)%, n=29, p=0.006) or with age and temperature matched controls (12.2 (1.1)%, n=8, p=0.002). Even when the outlying patient was omitted, the aNMT group had significantly higher subexcitability (18.0 (0.8)%, n=7) than the matched controls (p=0.001). By contrast, although there was a tendency for the superexcitabilities of the patients with aNMT (−20.9 (1.3)%, n=8) to be less than in the full control group (−25.3 (1.0)%, n=29, p=0.04), they were not significantly different from the matched controls (−23.0 (1.7)%, n=8, p=0.35).

To obtain further information about the membrane properties underlying this abnormality in subexcitability, we tested another 10 excitability parameters (in addition to the 12 in fig 3), derived from the data in fig 2, to see if they were abnormal in the patients with aNMT. Statistically the most significantly abnormal parameter tested was the subexcitability of the aNMT group (19.4 (1.5)%, mean (SEM), n=8) for selected excitability parameters: (A) Late subexcitability, (B) threshold electrotonus depolarising undershoot; and (C) threshold electrotonus hyperpolarising overshoot. Results are expressed as mean (SEM) and marked by an asterisk where significant (2 tailed t test; *p<0.01; **p<0.001).

**Discussion**

The present study has established that a protocol recently developed to record multiple measures of axonal excitability can be used in the clinical setting, is tolerable to the patient, and can be employed in an efficient manner. Using this protocol, we have shown that patients with immune-associated aNMT, or CFS, who have active symptoms and signs of nerve hyperexcitability, and in some cases EMG findings of spontaneous motor unit activity during the recordings, had no clear evidence of axonal membrane hyperexcitability when compared with healthy control subjects.

It has been reported that $\tau_{SD}$, a measure of axonal excitability, can be prolonged in motor axons of patients with amyotrophic lateral sclerosis (ALS). More recently a similar finding was obtained in some patients with aNMT. Such an increase in $\tau_{SD}$ may indicate membrane depolarisation. Alternatively it may occur by means of an increase in a persistent sodium conductance, or by paranodal demyelination.

In the study on patients with ALS, it was suggested that a greater representation of a persistent Na$^+$ conductance may be responsible for both the prolongation of $\tau_{SD}$ and the development of fasciculation. In patients with aNMT, it was proposed that in addition to the above mechanisms, anti-VGKC antibodies may contribute to the prolongation of $\tau_{SD}$ recorded from motor axons by means of an indirect effect on axonal membrane properties. By contrast, the present study has found that in patients with similar clinical syndromes associated with spontaneous motor unit activity, no prolongation in the $\tau_{SD}$ of motor axons was evident.

Strength-duration time constant is a nodal property of the axonal membrane. Voltage gated K$^+$ channels are not uniformly distributed along the axonal membrane. In aNMT the antibodies are thought to act against fast K$^+$ channels, of which there are very few present in the nodal region. Their density is greatest in the paranodal region where, provided the myelin sheath is intact, they should be protected from circulating autoantibodies. Studies of the effects of 4-aminopyridine, a blocker of fast potassium channels, on the electrical properties of myelinated axons have shown that superexcitability is increased, as is the early depolarising electrotonus, and there is
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Whether or not patients are taking car-
a high density of slow K+ channels present at
control group. These changes, which suggest a
parameters that depend most on slow K+
accommodation that occurs with depolarisation
depolarisation during threshold
electrotonus, and the undershoot in excitability that
were within the normal range
and on average significantly greater in the
these patients, could not account for the
during a single, short period of recording while
weaker, there was no relation between the prolon-
was no evidence of any such changes among
By contrast with the fast K+ channels, there is a
high density of slow K+ channels present at
nodes of Ranvier, a site more accessible to
immune attack. However, the excitability
parameters that depend most on slow K+ channels—namely, the late subnormal phase in
the recovery cycle, the accommodation that
occurs with depolarisation during threshold
electrotonus, and the undershoot in excitability that
follows”—were within the normal range
and on average significantly greater in the
patients with aNMT than in the age matched
control group. These changes, which suggest a
relative up regulation of slow K+ channels in
these patients, could not account for the
ectopic discharges. They might, however, indicate
an adaptive response to the continuous
motor unit activity. Recently differences in the
same excitability parameters have been re-
ported between median and peroneal axons,
and the suggestion made that slow K+ conduct-
ance may depend on axonal discharge patterns
or peak firing rates.11

WHERE DO THE ECTOPTIC IMPULSES ORIGINATE?

These findings prompt questions about the
nature and origin of the generator producing the
ectopic motor activity that occurs in
patients with aNMT and related syndromes. In
aNMT, as in other immune mediated diseases,
symptom severity and EMG findings can vary
time often in an unpredictable pattern.
This may be one explanation why some previously
studied patients have a prolonged \(\tau_{SD}\)
during a single, short period of recording while
our and other similar patients do not.1 By
implication, it is possible that the results using
our protocol would be less uniform if testing
were repeated serially in individual patients.

In the patients studied, no evidence of axonal
hyperexcitability was detected, even when they
had spontaneous activity in the abductor polli-
cis brevis during the testing, and regardless of
their anti-VGKC antibody status or evidence of
a systemic autoimmune diathesis. It seems
unlikely that this lack of abnormality reflected
an ongoing effect of the patient’s drug therapy,
in most cases the anticonvulsant car-
bamazepine. All patients remained sympto-
matic, albeit to a lesser degree, even while tak-
ing medication. Furthermore, all patients
cessated their medication from 1 to 7 days before
testing, at which stage it was possible to record
spontaneous activity during testing (fig 1).
Finally, \(\tau_{SD}\) has been found to be similar
whether or not patients are taking car-
bamazepine.3

In the study by Maddison et al,3 some patients with aNMT had a prolonged \(\tau_{SD}\) while others had values in the normal range. More-
over, there was no relation between the prol-
gation in \(\tau_{SD}\) and the presence or absence of
serum anti-VGKC antibodies, or the presence
or absence of spontaneous motor unit activity
during the recordings. These findings, taken
together with our results, suggest that, as some
other immune mediated neurological diseases
(for example, myasthenia gravis, Guillain-
Barré syndrome, and multifocal motor neu-
ropathy) acquired autoimmune mediated neu-
romyotonia may be a focal or multifocal disorder.

Previous studies have shown that there is
variability in the site of origin for spontaneous
activity between patients with aNMT.36–42
When the present data are combined with pre-
vious studies on patients with aNMT, electro-
physiological heterogeneity becomes apparent,
suggesting that such patients are likely to
exhibit a focal or multifocal rather than gener-
alised excitatory axonopathy. The ectopic
activity present in our patients was not caused
by a generalised disturbance of CNS neurons
in an identical pattern to serum containing
anti-VGKC antibodies, may support this
view.33

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