PAPER

The effect of treatment upon temporal dispersion in IvIg responsive multifocal motor neuropathy

A Ghosh, A Virgincar, R Kennett, M Busby, M Donaghy

J Neurol Neurosurg Psychiatry 2005;76:1269–1272. doi: 10.1136/jnnp.2004.050252

See end of article for authors' affiliations

Correspondence to:
Dr Michael Donaghy,
Department of Clinical
Neurology, Radcliffe
Infirmary, Oxford OX2
6HE, UK;
joanna.wilkinson@
cneuro.ox.ac.uk

Received 22 July 2004
Revised version received
24 February 2005
Accepted 28 March 2005

Background: Multifocal motor neuropathy with conduction block (MMN) is a treatable disorder that can be mistaken for other lower motor neurone syndromes. Existing electrophysiological diagnostic criteria for MMN are restrictive. In particular, many are cautious about diagnosing conduction block (CB) in the presence of abnormal temporal dispersion (TD).

Objective: To study the significance of TD in MMN, its relationship to CB in intravenous immunoglobulin (IvIg) responsive patients, and its utility in detecting a treatment response.

Methods: We compared pre- and post-treatment changes in CB and TD in nine patients who satisfied clinical and electrophysiological criteria for MMN and responded to IvIg.

Results: TD improved in one or more nerve segments in eight of nine patients tested. There was marked improvement in 65% of all nerve segments, and 60% of those segments with CB. By comparison, significant improvement in CB occurred in only 33% of segments. Of segments with significantly better CB after treatment, all but one showed similar improvements in TD. Such changes were not related to the degree of TD before treatment, being seen in segments with abnormal as well as normal TD. There was no correlation between improvements seen in TD and CB.

Conclusion: We believe that TD should be considered an inherent feature of MMN. Improvement in TD is an independent marker of electrophysiological improvement in this disorder and is likely to be more useful than CB. When MMN is clinically suspected, the use of stringent criteria for CB in the presence of TD should be avoided.

Multifocal motor neuropathy with conduction block (MMN) is a relatively rare disorder characterised by slowly progressive, asymmetrical, lower motor neurone weakness usually starting in the arms with minimal or no sensory symptoms.¹ Treatment with intravenous immunoglobulin (IvIg)^{2–7} or cyclophosphamide^{8–10} or both^{5 11} results in clinical improvement. Correct differentiation of this treatable condition from other motor neurone diseases is crucial. The electrophysiological hallmark of MMN is conduction block (CB).^{6 9 12–20} A major obstacle to the satisfactory definition of CB has been the presence of temporal dispersion (TD). This can produce an apparent, but misleading, drop in the proximal CMAP (compound motor action potential) amplitude through a process of interphase cancellation.¹³ Most definitions of CB either do not accommodate TD or demand even more stringent criteria in its presence. Potentially this reduces the value of nerve conduction studies in detecting this potentially treatable disorder.²¹ The occurrence of TD has been noted in MMN patients.^{14 16 22 23} Whilst a variety of alterations in CB have been documented in MMN following IvIg,^{7 11 14 22 24–26} there are no systematic studies of changes in TD, and their correlation with clinical benefit, following effective treatment with IvIg.

METHODS

This study looked at pre- and post-IvIg changes in TD in patients who satisfied clinical and electrophysiological criteria for MMN and who responded clinically to IvIg. All patients had chronic, progressive, asymmetric motor neuropathy, no upper motor neurone signs, and CB at one or more motor nerve segments separate from common sites of nerve compression. A neurologist with experience in assessing peripheral nerve disorders (MD or AG) performed the clinical observations. An improvement of the MRC score by at least

one grade in one or more affected muscle groups or a self assessed functional performance score by at least one grade (normal>independent but with difficulty>performs with help>cannot perform) in $\geq 30\%$ of affected tasks was taken as a positive clinical outcome following treatment. Post-IvIg clinical and electrophysiological assessments were made between 2 and 4 weeks after treatment.

Much of the neurophysiological data was analysed retrospectively and the nerves tested post-IvIg tended to be those with known CB (fig 1). CB, in the context of MMN, was defined as a distal to proximal reduction in negative peak CMAP area $>23\%$ across the distal segment and $>29\%$ across the proximal segment or in negative peak amplitude $>32\%$ for the distal segment and $>33\%$ for the proximal segment.²¹ Abnormal TD is an inappropriate increase in duration of CMAP following proximal stimulation of a nerve when compared to distal stimulation. For our study, abnormal TD was defined as an increase in negative peak duration of CMAP $>37\%$ (mean ± 3 SD over healthy controls), although the definition of CB was not affected by TD.²¹ Percentage changes in CB following treatment were calculated according to the formula (CB before treatment–CB after treatment)/CB before treatment $\times 100\%$.¹⁴ Changes in TD were also calculated using a similar formula, that is (TD before treatment–TD after treatment)/TD before treatment $\times 100\%$.

Although there is uncertainty regarding what constitutes clinically meaningful change in pre- and post-treatment values in CB and TD, we considered a $>20\%$ improvement to be significant for both.¹⁴

Abbreviations: CB, conduction block; CMAP, compound motor action potential; IvIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy with conduction block; TD, temporal dispersion

Figure 1 Compound muscle action potential amplitudes recorded from abductor pollicis brevis before and 2 weeks after IVlg treatment. Changes in amplitude and duration are shown following median nerve stimulation at the wrist, elbow, and axilla.

Statistics

We used non-parametric statistical methods. Spearman correlation coefficient was used to assess correlation between the improvement of TD and of CB.

RESULTS

Pre- and post-treatment data on TD were available in nine patients (seven male and two female; age of onset 27–67 years; median 40 years). Thirteen nerves with CB in at least one segment were studied. Data on TD were available from 15 nerve segments with CB but also from five other segments without CB (table 1).

TD lessened in one or more nerve segments in eight of nine patients tested. This occurred irrespective of whether the pre-treatment TD was prolonged or within the normal range. In all, 15 of the 20 segments showed some improvement in TD; 11 of these were in regions showing CB. TD improved by >20% of the pre-treatment values in 13 segments (65%). The actual improvements were >30% in all these segments. Nine of the 13 segments were in areas of pre-treatment CB and four of the nine segments showed a significant, that is >20%, improvement in CB.¹⁴

We assessed separately the effect of treatment on abnormal TD. We tested response using three different values for abnormal TD, namely >37%,²¹ >30%,^{27, 28} and >15%.^{14, 29} Abnormal TD at most sites either disappeared or improved by at least 30% of its pre-treatment value, whichever criterion was used (table 2). Only one segment showed an increase in TD following treatment.

Of the 15 segments with CB, only five segments showed a >20% improvement in the block. Four out of the five segments also showed >30% reductions in TD including one segment with a pre-treatment TD value in the normal range. CB disappeared in two nerves.

Six segments with pre-treatment CB showed neither significant reduction nor worsening of TD following IVlg. Significant improvement in CB was seen in only one of these six segments.

Distal CMAP amplitudes improved by 30% or more after treatment in three out of the 13 segments studied, and worsened by a similar degree in one patient.

DISCUSSION

Most of the electrophysiological interest in MMN has focussed upon CB, with the significance of TD largely unexplored. This study emphasises the occurrence of TD in MMN patients and demonstrates that successful treatment of MMN produces more widespread improvements in TD than in CB.

The relation between TD of a CMAP and a drop in CMAP area is complex. Interphase cancellation, compounded by polyphasic motor units, is a recognised mechanism by which TD can reduce CMAP area and hence mimic CB.¹³ Consequently, many have been cautious about diagnosing CB when there is abnormal TD in the same segment.^{13, 14, 20, 27, 29} In reality, the changes seen in CMAPs are likely to depend, among other factors, upon the relative balance between delay and block of axonal conduction among the faster and slower conducting fibres. Thus, disproportionate slowing along the slower conducting fibres could contribute to TD but produce little change in amplitude. Blocking axonal conduction predominantly through smaller fibres as opposed to the faster conducting fibres could produce lesser reduction in CMAP amplitude and a shorter CMAP duration. On the other hand, a non-uniform slowing of conduction (without actual block of axonal conduction) through the faster conducting fibres could lead to increased interphase cancellation and therefore pseudo-CB with or without TD,¹³ while complete block through these same fibres would produce true CB. As it is not known which subpopulations of nerve fibres are affected by each process, and as non-uniform slowing and CB are likely to occur simultaneously, it may be difficult to quantify the true degree of CB from CMAP recordings. These complex interactions may explain why the degree of measurable CB often does not improve despite obvious clinical benefit following IVlg treatment. We believe TD is just as much an inherent electrophysiological feature of MMN as CB, and that its measurement may avoid these complex uncertainties in quantifying CB.

Previous studies have investigated improvement in CB as a possible electrophysiological marker of clinical improvement in MMN and found inconsistent results.^{2, 7, 22–30} In our study, changes in TD were independent of any change in CB

Table 1 Pre- and post-treatment changes in conduction block (CB) and temporal dispersion (TD)

Patient No.	Nerve	Segment	Distal CMAP amplitude		TD			CB		
			Pre-Ivlg (mV)	Post-Ivlg (mV)	Pre-Ivlg (%)	Post-Ivlg (%)	Better (%)	Pre-Ivlg (%)	Post-Ivlg (%)	Better (%)
1	RU	D	4.9	16.3	12	11	8	41	35	15
	LU	D	13.4	4.9	13	-18	238	32	41	-43
2	RM	D	18.3	18.5	4.6	-8.8	291	No	-	-
		P			81.2	24.8	69	78.7	49.4	37
3	RU	D	8.0	7.4	12	7.9	34	60.7	13.9	77
4	RM	D	12.1	9.7	28.6	40	-40	73.9	70.6	4
		P			23.7	7.1	70	No	-	-
5	RM	D	10.5	15.5	171	99	42	52.3	56.7	-8
	RU	D	14.0	13.5	180	115	36	78.6	69.6	11
6	LU	D	7.0	7.0	48.4	31	36	37	26	30
		P			6.3	0	100	No	-	-
7	RM	D	8.9	11.9	11.6	4	65	60.7	54.6	10
	RM	D	11.5	8.3	16.4	-5.4	132	26	21.9	16
8	RU	D	5.5	4.6	6.2	11.5	-85	No	-	-
		P			96.7	90	7	64.3	63	2
9	RM	D	13.8	13.0	0.1	-12.7	128	No	-	-
		P			-8.4	6.4	-176	81.4	65.8	19
9	LM	D	7.3	7.7	97.4	2.4	98	44.8	25.7	43
					-32	9.1	-128	65.7	59.7	9

D, distal; L, left; M, median; P, proximal; R, right; U, ulnar.

(correlation coefficient = 0.103, $p = 0.72$) and occurred twice as frequently. Marked improvements in TD were seen in 65% of all nerve segments and 60% of those segments with CB. This compares to only 33% of segments showing significantly better CB, or 23% with increased CMAP amplitudes, after Ivlg. On the other hand, all but one segment with significantly better CB after treatment also showed similar improvements in TD. Such reductions were not related to the degree of TD before treatment, being seen in segments with abnormal as well as normal TD. Changes in TD or CB in the distal segment did not correlate with changes in the distal CMAP amplitudes.

Successful treatment of MMN is likely to produce alterations in conduction through the various subpopulations of axons leading to a spectrum of changes, as was seen in our study. TD depends on slowing of conduction across a segment. Improved conduction either through faster or slower conducting fibres could improve TD. An improvement in CB, on the other hand, is largely dependent on the response of fast conducting fibres. Also, unlike pseudo-CB, pseudo-TD does not occur as long as the distal CMAP amplitude is not too small. Out of the 15 segments with CB, six showed neither improvement nor worsening of TD despite clinical improvement. This too can be explained by differential recovery among axons, including the phenomenon of newly unblocked axons still conducting slowly. That five out of these six segments also showed no significant improvement in the CB may reflect new interphase cancellations.

An improvement in muscle strength reflects reduced CB rather than increased conduction velocity in those slow conducting fibres particularly contributing to TD. Our

findings imply that whilst treatment reverses CB in some fibres, detection of this is masked by the complex contribution made to the CMAP profile by individual subgroups of motor fibres. From this retrospective study we conclude that TD is an important and independent part of the electrophysiological definition of MMN. When MMN is suspected clinically, the use of stringent criteria for CB in the presence of TD should be avoided. Improvement in TD seems to be a more sensitive marker of electrophysiological improvement than CB.

Authors' affiliations

A Ghosh, M Busby, M Donaghy, Department of Clinical Neurology, University of Oxford, Radcliffe Infirmary, Oxford OX2 6HE, UK

A Virgincar, R Kennett, Department of Clinical Neurophysiology, Radcliffe Infirmary, Oxford OX2 6HE, UK

Competing interests: none declared

REFERENCES

- Roth G, Rohr J, Magistris MR, et al. Motor neuropathy with proximal multifocal persistent conduction block, fasciculations and myokymia. Evolution to tetraplegia. *Eur Neurol* 1986;25:416-23.
- Kaji R, Shibasaki H, Kimura J. Multifocal demyelinating motor neuropathy: cranial nerve involvement and immunoglobulin therapy. *Neurology* 1992;42:506-9.
- Chaudhry V, Corse AM, Cornblath DR, et al. Multifocal motor neuropathy: response to human immune globulin. *Ann Neurol* 1993;33:237-42.
- Donaghy M, Mills KR, Boniface SJ, et al. Pure motor demyelinating neuropathy: deterioration after steroid treatment and improvement with intravenous immunoglobulin. *J Neurol Neurosurg Psychiatry* 1994;57:778-83.
- Van den Berg LH, Kerkhoff H, Oey PL, et al. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995;59:248-52.
- Van den Berg-Vos RM, Franssen H, Wokke JH, et al. Multifocal motor neuropathy: diagnostic criteria that predict the response to immunoglobulin treatment. *Ann Neurol* 2000;48:919-26.
- Federico P, Zochodne DW, Hahn AF, et al. Multifocal motor neuropathy improved by IVlg: randomized, double-blind, placebo-controlled study. *Neurology* 2000;55:1256-62.
- Pestronk A, Cornblath DR, Ilyas AA, et al. A treatable multifocal motor neuropathy with antibodies to GM1 ganglioside. *Ann Neurol* 1988;24:73-8.
- Krarp C, Stewart JD, Sumner AJ, et al. A syndrome of asymmetric limb weakness with motor conduction block. *Neurology* 1990;40:118-27.
- Feldman EL, Bromberg MB, Albers JW, et al. Immunosuppressive treatment in multifocal motor neuropathy. *Ann Neurol* 1991;30:397-401.
- Nobile-Orazio E, Meucci N, Barbieri S, et al. High-dose intravenous immunoglobulin therapy in multifocal motor neuropathy. *Neurology* 1993;43:537-44.

Table 2 Post-treatment changes in segments with abnormal TD only (by using different criteria)

	ΔTD>37%	ΔTD>30%	ΔTD>15%
Abnormal TD	6	6	9
TD disappeared	3	2	3
TD still abnormal but better by >30%	2	3	4
TD worse post-IVIG	1	1	1

- 12 Cornblath DR, Sumner AJ, Daube J, et al. Conduction block in clinical practice. *Muscle Nerve* 1991;**14**:869-71; discussion 867-8.
- 13 Rhee EK, England JD, Sumner AJ. A computer simulation of conduction block: effects produced by actual block versus interphase cancellation. *Ann Neurol* 1990;**28**:146-56.
- 14 Chaudhry V, Corse AM, Cornblath DR, et al. Multifocal motor neuropathy: electrodiagnostic features. *Muscle Nerve* 1994;**17**:198-205.
- 15 Oh SJ, Kim DE, Kuruoglu HR. What is the best diagnostic index of conduction block and temporal dispersion? *Muscle Nerve* 1994;**17**:489-93.
- 16 Katz JS, Wolfe GI, Bryan WW, et al. Electrophysiologic findings in multifocal motor neuropathy. *Neurology* 1997;**48**:700-7.
- 17 Cappellari A, Nobile-Orazio E, Meucci N, et al. Criteria for early detection of conduction block in multifocal motor neuropathy (MMN): a study based on control populations and follow-up of MMN patients. *J Neurol* 1997;**244**:625-30.
- 18 Sumner AJ. Consensus criteria for the diagnosis of partial conduction block and multifocal motor neuropathy. In: Kimura J, Kaji R, eds. *Physiology of ALS and related diseases*. Amsterdam: Elsevier, 1997:221-7.
- 19 Olney R. Consensus criteria for the diagnosis of partial conduction block. *Muscle Nerve* 1999;**22**:S225-9.
- 20 Taylor BV, Wright RA, Harper CM, et al. Natural history of 46 patients with multifocal motor neuropathy with conduction block. *Muscle Nerve* 2000;**23**:900-8.
- 21 Ghosh A, Busby M, Kennett R, et al. A practical definition of conduction block in IgG responsive multifocal motor neuropathy. *J Neurol Neurosurg Psychiatry* 2005;**76**:1264-8.
- 22 Comi G, Amadio S, Galardi G, et al. Clinical and neurophysiological assessment of immunoglobulin therapy in five patients with multifocal motor neuropathy. *J Neurol Neurosurg Psychiatry* 1994;**57**(Suppl):35-7.
- 23 Saperstein DS, Katz JS, Amato AA, et al. Clinical spectrum of chronic acquired demyelinating polyneuropathies. *Muscle Nerve* 2001;**24**:311-24.
- 24 Meucci N, Cappellari A, Barbieri S, et al. Long term effect of intravenous immunoglobulins and oral cyclophosphamide in multifocal motor neuropathy. *J Neurol Neurosurg Psychiatry* 1997;**63**:765-9.
- 25 Vucic S, Black KR, Chong PS, et al. Multifocal motor neuropathy: decrease in conduction blocks and reinnervation with long-term IVIg. *Neurology* 2004;**63**:1264-9.
- 26 Van den Berg-Vos RM, Franssen H, Wokke JH, et al. Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment. *Brain* 2002;**125**:1875-86.
- 27 Lange DJ, Trojaborg W, Latov N, et al. Multifocal motor neuropathy with conduction block: is it a distinct clinical entity? *Neurology* 1992;**42**:497-505.
- 28 Bouche P, Moulouguet A, Younes-Chennoufi AB, et al. Multifocal motor neuropathy with conduction block: a study of 24 patients. *J Neurol Neurosurg Psychiatry* 1995;**59**:38-44.
- 29 Brown WF, Feasby TE. Conduction block and denervation in Guillain-Barre polyneuropathy. *Brain* 1984;**107**:219-39.
- 30 Azulay JP, Blin O, Pouget J, et al. Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: a double-blind, placebo-controlled study. *Neurology* 1994;**44**:429-32.