J Neurol (2003) 250 : 962 – 966
DOI 10.1007/s00415-003-1128-7

ORIGINAL COMMUNICATION

Alexander J. Radziwill
Andreas J. Steck
Susanne Renaud
Peter Fuhr

Distal motor latency and residual latency as sensitive markers of anti-MAG polyneuropathy

Received: 25 September 2002
Received in revised form: 3 March 2003
Accepted: 20 March 2003

A. J. Radziwill
Dept. of Neurology
University Hospital
Lausanne, Switzerland

A. J. Radziwill · A. J. Steck · S. Renaud · P. Fuhr
Dept. of Neurology
University Hospital
Basel, Switzerland

A. J. Radziwill (✉)
26 av. de Rumine
1005 Lausanne, Switzerland
Tel.: +41-21/311-9464
Fax: +41-21/311-9459
E-Mail: aradziwill@gntmed.ch

Abstract There is debate whether the terminal latency index (TLI) is a sensitive marker for polyneuropathy with anti-myelin-associated-glycoprotein antibodies (anti-MAGP). We examined 6 patients with an anti-MAGP and 6 patients with a chronic inflammatory demyelinating polyneuropathy (CIDP). The electroneurographic features studied were: distal compound motor action potential (CMAP), distal motor latency (DML), motor conduction velocity (MCV) elbow to wrist (distal MCV), MCV axilla to elbow (proximal MCV), MCV distal/proximal, terminal latency index (TLI), residual latency (RL), F-wave, and modified F ratio. We found significant differences between anti-MAGP and CIDP for DML and for RL. No significant differences were found for TLI and the other measures. The TLI values were not significant probably because our patients had a longer duration of disease, which supports the hypothesis of a distal to proximal progression of conduction slowing over time. We propose that a residual latency > 4.0 and a distal motor latency > 7.0 are strongly suggestive for an anti-MAGP.

Key words chronic inflammatory demyelinating polyneuropathy · anti-myelin-associated glycoprotein polyneuropathy · distal motor latency · terminal latency index · residual latency

Introduction

There is some controversy in the literature concerning the usefulness of electroneurographic parameters such as distal motor latency (DML), terminal latency index (TLI), or motor conduction velocities (MCV) for the distinction between chronic inflammatory demyelinating polyneuropathies (CIDP) and chronic demyelinating polyneuropathy with anti-myelin-associated-glycoprotein (anti-MAG) antibodies. Standard electrophysiological testing may not discriminate between CIDP and anti-MAG polyneuropathy (anti-MAGP), Charcot-Marie-Tooth disease (CMT1A) or hereditary neuropathy with liability to pressure palsy (HNPP). In addition, there is no specific biological marker for CIDP, and results for anti-MAG antibody or genetic testing for deletion or duplication in chromosome 17p11.2 are often not immediately available. There is efficacious treatment for CIDP including intravenous immunoglobulin (IVIg), corticosteroid, plasma exchange and immunosuppressive drug therapy that should be given as early as possible and there are different therapeutic options with inconsistent results for the treatment of anti-MAGP [11–13].

Kaku et al. described 4 patients with anti-MAGP and found in 76 % of the studied nerves a TLI ≤ 0.25, but only in 6 % of the studied nerves in a CIDP control group [8]. Similar results were also reported by Trojaborg et al. [17]. Recently, Katz et al. described a new variant of CIDP, a distal acquired demyelinating symmetric neuropathy (DADS) and found in 67 % of DADS a mono-

JON 1128

clonal gammopathy (20 of 30 patients). They could not find any significant differences between electrophysiological features, including TLI, among "classic" CIDP with proximal and distal pattern of sensory or sensorimotor involvement and DADS with monoclonal gammopathies and anti-MAG antibodies (in 10/20 confirmed cases) and a more distal pattern of sensory or sensorimotor involvement [9].

With the knowledge of these conflicting reports in the literature, we performed this study to search for the best electrophysiological parameter that might help to distinguish anti-MAGP from CIDP.

Methods

Patients

We studied 6 patients with the clinical and electrodiagnostic features of a chronic demyelinating polyneuropathy with anti-MAG antibodies who were selected for a therapeutic open-label study with rituximab [13]. The mean age was 61 (range 52–71) years and the mean disease duration was 7 (range 1–14) years. Six patients with a mean age of 52 (range 40–65) years and a mean disease duration of 4.5 (range 0.25–10) years met the clinical and electrodiagnostic research criteria of the American Academy of Neurology for idiopathic CIDP [3]. Patients with multiple myeloma or plasmocytoma, POEMS syndrome or a motor multifocal neuropathy with a persistent conduction block were not included.

Electrodiagnostic studies

We performed standard motor nerve conduction studies on the ulnar nerve using a Viking IV EMG machine (Nicolet) at skin temperatures of 34°C. The study was performed with data from the ulnar nerve, as it represents the best choice of a single nerve for longitudinal comparisons in a severe, diffuse demyelinating neuropathy for the following reasons: 1. the ulnar nerve innervates hand muscles and, therefore, is easily and reproducibly measurable; 2. prolongation of its distal latency is less likely to be confounded with an entrapment-neuropathy than in the median nerve; 3. Owing to its superficial location, supramaximal stimulation can always be achieved as opposed to the tibial nerve, which in the popliteal fossa is relatively deeply located; 4. it remains measurable even in severely affected patients as opposed to the peroneal nerve, from which in our 6 patients with anti-MAG neuropathy no CMAP was elicitable. The distal compound motor action potential (CMAP), distal motor nerve conduction velocity (MCV) between elbow and wrist, proximal MCV between axilla and elbow and distal motor latency (DML) were determined. At least 16 consecutive distal F waves were elicited, and the minimum F-wave latency was measured. The TLI was used to compare the wrist-to-thenar muscle (distal segment) with the elbow-to wrist conduction velocity. We used the formula developed by Shahani et al. [15]: TLI = Distal conduction distance (mm)/[distal MCV(m/s) x DML (ms)]. The TLI is the ratio between the calculated latency (distance/MCV) and the measured latency (DML). The residual latency (RL) is a subtraction of the calculated latency from the measured latency and was determined following the formula RL = DML – [distal conduction distance/distal MCV] [5]. We calculated a ratio of distal and proximal MCV and the modified F ratio (MFR) as recently described by Attarian et al.: MFR = (F + DML – 2 x PML – 1)/(2 x DML) where PML is the proximal motor latency in ms between elbow and hypothenar muscle [1].

Laboratory studies

All patients underwent a complete blood count, routine chemistries, sedimentation rate, vitamin B12, antinuclear antibody, thyroid function tests, serum protein and immunofixation electrophoresis. HIV and hepatitis panels were ordered in selected patients. Anti-MAG antibodies were measured by a commercially available ELISA test (Bühlmann Laboratories, Schönenbuch, Switzerland). In addition bone-marrow biopsy and computed tomography of abdomen and thorax were performed in anti-MAG positive patients. Nerve biopsies were performed in 5 of the 6 CIDP patients revealing characteristic findings of chronic inflammatory demyelination and in one patient with anti-MAGP showing typical deposits of IgM in the myelin sheath.

Statistical analysis

Electrodiagnostic measures of patients with anti-MAG polyneuropathy and CIDP were compared using nonparametric Mann-Whitney U test. In the case of 2 tested ulnar nerves in the same patient we used the mean value of both sides to achieve independence of the groups. Owing to the small sample size and the unbalanced design, we left out an analysis of variance. All tests are performed at a level of $\alpha = 0.05$. Because of the multiple interdependencies of the variables, we did not correct the p-values of these calculations. These results therefore have to be considered as exploratory.

Results

Comparisons between the anti-MAGP group and the CIDP group showed significant differences between the mean DML and RL, but not between the mean TLI (Table 1; Figs. 1–3). The DML has a median of 7.5 ms (range 4.7–13.2) in the anti-MAGP group and 3.7 ms (range 2.6–6.2) in the CIDP group ($p = 0.025$) and the median of the RL in the anti-MAGP group is 4.3 ms (range 3.0–9.3) versus 2.1 ms (range 1.33–4.14) in the CIDP group ($p = 0.025$). The median of the TLI in the anti-MAGP group is 0.31 (range 0.21–0.51) versus 0.41 (range

Table 1 Comparison of electrodiagnostic findings

	Anti-MAGP (n = 6 pat.)	CIDP (n = 6 pat.)	p value
DML[a]	7.5 (4.7–13.2)	3.7 (2.6–6.2)	0.025
TLI	0.31 (0.21–0.51)	0.41 (0.33–0.51)	n. s.
RL[a]	4.3 (3.0–9.3)	2.1 (1.3–4.1)	0.025
prox. MCV[b]	41 (28–57)	52 (23–70)	n. s.
dist. MCV[b]	27 (17–54)	39 (25–57)	n. s.
MCV dist./prox.	0.74 (0.47–1.03)	0.77 (0.56–1.69)	n. s.
CMAP[c]	3.7 (0.6–5.9)	6.9 (1.0–33.8)	n. s.
F wave[a]	53.3 (39.4–1000[d])	32.6 (28.5–55.5)	n. s.
MFR	2.6 (1.5–65.9[d])	3.1 (1.3–4.1)	n. s.

Median values of electrodiagnostic parameters in ulnar nerves (range)
[a] DML, RL, and F wave in ms
[b] MCV in m/s
[c] CMAP in mV
[d] F wave = 1000 ms: Test performed, but F wave not measurable

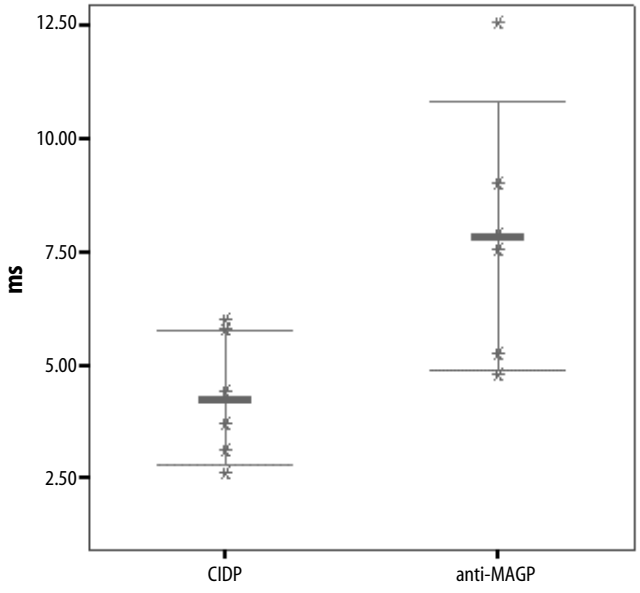

Fig. 1 Distal motor latency (p = 0.025; mean in the anti-MAGP group 7.8 ms, in the CIDP group 4.1 ms)

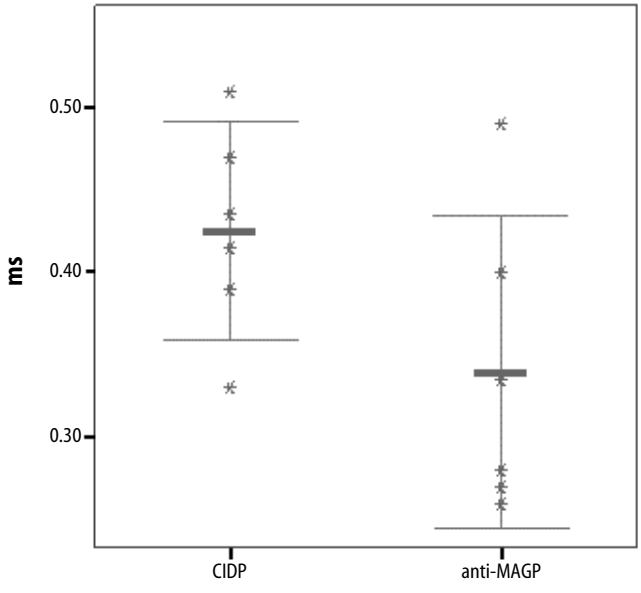

Fig. 2 Terminal latency index (p = 0.13; mean in the anti-MAGP group 0.33, in the CIDP group 0.41)

0.33–0.51) in the CIDP group (p = n. s.). TLI ≤ 0.25 was only met in 2 of 12 tested ulnar nerves in the anti-MAGP group (16.7 %). Statistical comparison only of the right ulnar nerves showed also significant differences for the mean DML (p = 0.023) and the mean RL (p = 0.032). There were no significant differences between the distal MCV, the proximal MCV, the ratio proximal/distal MCV, the CMAP, the F-wave and the modified F ratio between these two groups. We found no asymmetry between the

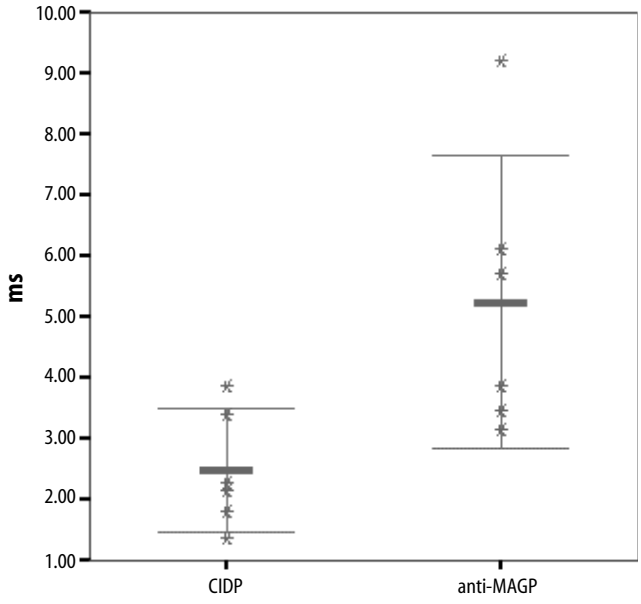

Fig. 3 Residual latency (p = 0.025; mean in the anti-MAGP group 5.2 ms, in the CIDP group 2.4 ms)

Fig. 1–3 shows mean values and 95 % confidence intervals of CIDP and anti-MAGP for DML, TLI and RL. Each star represents the mean value of one patient. In the anti-MAGP group (n = 6) ulnar nerves were examined on both sides (12 nerves or 6 mean values), in the CIDP group (n = 6) ulnar nerves were examined on both sides in 3 patients (6 nerves or 3 mean values) and only on one side in 3 patients (3 nerves or 3 values)

6 right-sided ulnar nerves and the 6 left-sided ulnar nerves in our anti-MAGP patients. We examined also 12 anti-MAGP peroneal nerves, but no CMAP was elicitable.

Discussion

CIDP and anti-MAGP are both demyelinating neuropathies that differ in their pathogenesis. There are effective treatments for CIDP that should be given as early as possible and there are different therapeutic options for anti-MAGP with inconsistent results [11, 12]. The pathogenesis of CIDP is still poorly understood: antibodies to peripheral myelin proteins such as P0 and P2 as well to gangliosides such as GM1 can be detected in some patients [10]. These anti-GM1 antibodies are not specific, but high titers are most often seen with multifocal motor neuropathy or axonal GBS [7]. The presence of T cells and macrophages in the biopsy specimens confirms the inflammatory nature of this immune-mediated neuropathy [14]. An enhanced synthesis of T-helper 1 cytokines resulting in damage to the blood-nerve barrier and peripheral nerve myelin has been described [4].

Anti-MAGP is a chronic slowly progressive neuropathy caused by monoclonal IgM-antibody against

myelin-associated glycoprotein (MAG) in the context of an IgM paraproteinemia [16]. Pathological studies on nerve biopsy specimens show segmental demyelination with deposits of IgM M-Protein and complement (C3 d, terminal complement complex) on nerve myelin. Previous studies have shown that a reduction of anti-MAG antibodies usually leads to an improvement of the neuropathy (reviewed in 11).

CIDP has no specific biological marker, such as anti-MAG antibody or DNA testing for CMT1A or HNPP. Although these tests are diagnostic, the results are often not readily available. Electrophysiological testing can be helpful in the distinction between CIDP and anti-MAGP. There is some controversy in the literature concerning the best electrodiagnostic feature for the distinction of CIDP from anti-MAGP and other demyelinating neuropathies. Our study of the ulnar nerves showed that the median DML and RL differed significantly between the patients with CIDP and those with anti-MAGP as in the study of Trojaborg et al., but not the TLI [17]. Our findings show that a RL > 4.0 and a DML > 7.0 are suggestive for an anti-MAGP although the small number of patients in our study does not permit a firm conclusion. We have no good explanation why TLI as another measure of distal involvement was not concordant with RL and DML. TLI is an index and RL and DML are time parameters. Unlike the study of Kaku et al. where 76 % of the tested nerves (median, ulnar, peroneal and tibial nerves) in anti-MAGP had a TLI ≤ 0.25 or the study of Attarian where 68 % of the tested nerves (median and ulnar nerves) had a TLI ≤ 0.25 we found only in 16.7 % of the studied ulnar nerves a TLI ≤ 0.25 [1, 8]. The 75 percentile of the anti-MAGP TLI in our study was 0.4. Considering only the ulnar nerves Attarian et al. found a TLI ≤ 0.25 in 43 % of the cases with anti-MAGP and Kaku et al. in 50 % of the cases. Both studies found a similar mean TLI in the ulnar nerve (Table 2).

There was no significant difference for TLI probably because our patients had a longer duration of disease which supports the hypothesis of a distal to proximal progression of conduction slowing over time. Also in the study of Cocito et al. patients with CIDP had a shorter duration of disease which may explain their significant lower TLIs in anti-MAGP with longer duration of disease (2, Table 2). Our anti-MAGP patients (Table 2) had the longest duration of disease (mean duration of 84 months) compared with the published cases of Kaku et al., Trojaborg et al., Attarian et al. and Cocito et al. (mean duration between 34 and 60 months) [1, 2, 8, 17].

We examined also the peroneal nerves, but no CMAP was elicitable in all anti-MAGP patients. This fact is probably also due to the lengthy duration of disease in our patients.

The pattern of involvement in anti-MAGP is also considered as a reflection of a length dependent process. But the length of the ulnar nerve could not be a sufficient explanation for the lack of a difference in the measured parameters between anti-MAGP and CIDP. The lack of difference in proximal conduction, F waves and modified F ratio between anti-MAGP and CIDP is probably also due to the duration of disease. Furthermore, the usefulness of TLI probably depends on the clinical pattern of CIDP. This may explain why Katz et al. found no electrodiagnostic differences between the distal pattern of CIDP, the DADS variant, and the anti-MAGP with also a more distal pattern of sensory or sensorimotor involvement [9]. In accordance with Katz et al. with an inhomogeneous group of patients with DADS and monoclonal gammopathy we also found with our defined anti-MAGP group no difference of TLI between CIDP and anti-MAGP [9]. Dyck and Dyck recently questioned the suggestion that the DADS variant should be separated from CIDP as a specific clinical entity. They instead argued that it is more important to distinguish patients with neuropathy by pathophysiological processes [6]. The course of the anti-MAGP is that of a chronic, slowly progressive disease whereas CIDP can show a fluctuating or chronic progressive course or even remission. This may explain differences from other studies. In this respect our results may help to distinguish two types of demyelinating neuropathies that differ in their pathogenetic mechanisms and treatments.

Table 2 DML, TLI and RL of ulnar nerve in anti-MAGP and CIDP

Ulnar nerve[a]	n	age (years)	duration (months)	DML (ms)	TLI	RL (ms)
Kaku et al. 1994						
CIDP	13	?	?	?	?	?
anti-MAGP	4	67	34	6.5	0.27	4.8
Trojaborg et al. 1995						
CIDP	25	63	?	?	0.51[b]	6.3[b]
anti-MAGP	15	62	?	?	0.34[b]	9.6[b]
Attarian et al. 2001						
CIDP	19	47	47	4.2	0.49	?
anti-MAGP	25	65	43	5.6	0.27	?
Cocito et al. 2001						
CIDP	18	53	29	?	0.44	?
anti-MAGP	11	70	60	?	0.36	?
Radziwill et al. (present study)						
CIDP	6	52	54	4.1	0.41	2.4
anti-MAGP	6	61	84	7.8	0.33	5.2

[a] Mean values of ulnar nerves
[b] Trojaborg et al. used a slightly modified definition of TLI and RL and their results were described as a mean of the sum of median and ulnar nerve

References

1. Attarian S, Azulay JP, Boucraut J, Escande N, Pouget J (2001) Terminal latency index and modified F ration in distinction of chronic demyelinating neuropathies. Clin Neurophysiol 112: 457–463
2. Cocito D, Isoardo G, Ciaramitaro P, Migliaretti G, Pipieri A, Barbero P, Cucci A, and Durelli L (2001) Terminal latency index in polyneuropathy with IgM paraproteinemia and anti-MAG antibody. Muscle Nerve 24:1278–1282
3. Cornblath DR, Asbury AK, Albers JW, Feasby TE, Hahn AF, McLeod JG, Mendell JR, Parry GJ, Pollard JD, Thomas PK (1991) Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Neurology 41:616–618
4. Creange A, Lefaucheur JP, Authier FJ, Gherardi RK (1998) Cytokines and peripheral neuropathies. Rev Neurol (Paris) 154:208–216
5. Daube JR (1996) Compound muscle action potentials. In: Daube JR (ed) Clinical Neurophysiology. FA Davis Company, Philadelphia, pp 199–324
6. Dyck PJ, Dyck PJ (2000) Atypical varieties of chronic inflammatory demyelinating neuropathies. Lancet 355(9212):1293–1294
7. Hadden RD, Cornblath DR, Hughes RA, Zielasek J, Hartung HP, Toyka KV, Swan AV (1998) Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Ann Neurol 44:780–788
8. Kaku DA, England JD, Sumner AJ (1994) Distal accentuation of conduction slowing in polyneuropathy associated with antibodies to myelin-associated glycoprotein and sulphated glucuronyl-paragloboside. Brain 117: 941–947
9. Katz JS, Saperstein DS, Gronseth G, Amato AA, Barohn RJ (2000) Distal acquired demyelinating symmetric neuropathy. Neurology 54:615–620
10. Melendez-Vasquez C, Redford J, Choudhary PP, Gray IA, Maitland P, Gregson NA, Smith KJ, Hughes RA (1997) Immunological investigation of chronic inflammatory demyelinating polyradiculoneuropathy. J Neuroimmunol 73:124–134
11. Nobile-Orazio E, Meucci N, Baldini L, Di Troia A, Scarlato G (2000) Long-term prognosis of neuropathy associated with anti-MAG IgM M-proteins and its relationship to immune therapies. Brain 123:710–717
12. Radziwill AJ, Kuntzer T, Steck AJ (2002) Immunopathology and treatment of Guillain-Barré syndrome and of chronic inflammatory demyelinating polyneuropathy. Rev Neurol (Paris) 158 :301–310
13. Renaud S, Gregor M, Fuhr P, Lorenz D, Deuschl G, Gratwohl A, Steck AJ (2001) Rituximab and anti-MAG-associated polyneuropathy: A pilot study. Neurology 56(8):A396–A396 (Suppl. 3)
14. Rizzuto N, Morbin M, Cavallaro T, Ferrari S, Fallahi M, Galiazzo-Rizzuto S (1998) Focal lesions area feature of chronic inflammatory demyelinating polyneuropathy (CIDP). Acta Neuropathol (Berl) 96:603–609
15. Shahani BT, Young RR, Potts F, Maccabee P (1979) Terminal latency index (TLI) and late response studies in motor neuron disease (MND), peripheral neuropathies and entrapment syndromes (abstract). Acta Neurol Scand (Supp. 73):118
16. Steck AJ, Murray N, Meier C, Page N, Perruisseau G (1983) Demyelinating neuropathy and monoclonal IgM antibody to myelin-associated glycoprotein. Neurology 33:19–23
17. Trojaborg W, Hays AP, Vandenberg L, Younger DS, Latov N (1995) Motor conduction parameters in neuropathies associated with anti-MAG antibodies and other types of demyelinating and axonal neuropathies. Muscle Nerve 18:730–735