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RESEARCH REPORT

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Limitations in daily activities and general perception of quality of life: Long term follow-up in patients with anti-myelin-glycoprotein antibody polyneuropathy

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Abstract

In this study, we assessed the modifications over time of daily activities and quality of life (QoL) in 32 subjects with anti-myelin-glycoprotein (MAG) antibody neuropathy. A widespread panel including clinical scores and patient-reported questionnaires, in compliance of the terms by the International Classification of Functioning, Disability, and Health (ICF) of the World Health Organization (WHO), was employed at enrollment (T0) and at follow-up evaluation (T1) after a mean interval of 15.4 ± 5.7 months. The Sensory Modality Sum score (SMS) at four limbs showed a significant worsening over time (mean score 27.2 ± 3.9 at T0 vs 25.7 ± 3 at T1 at upper limbs, $P = .03$; 20.5 ± 4.8 at T0 vs 18.6 ± 5.9 at T1 at lower limbs, $P = .04$). The Visual Analogue Scale (VAS) for pain significantly worsened at upper limbs at T1 (mean values 0.84 ± 1.95 at T0 vs 1.78 ± 2.6 at T1, $P = .03$). All the other tests did not show significant differences between T0 and T1. In the subgroup who underwent rituximab (15/32 treated before T0, 3/32 patients treated between T0 and T1 with median interval of 1 year), no significant differences were observed between T0 and T1. Despite the quite long follow-up, statistical significance was not achieved either for the limited number of patients or for the lack of sensitive outcome measures. In our cohort, the significant worsening of the SMS and VAS after a median of 14 months can be considered as a reliable expression of the natural history of the disease, and suggest that these scales might represent possible outcome measures in anti-MAG antibody neuropathy.

KEYWORDS

anti-MAG antibodies, follow-up, International Classification of Functioning, Disability and Health (ICF), peripheral neuropathy, quality of life (QoL)

1 | INTRODUCTION

The neuropathy associated with anti-myelin-glycoprotein (MAG) antibodies is a sensory-motor IgM paraproteinemic demyelinating neuropathy characterized by sensory ataxia and upper limbs tremor.[1] Sensory disturbances may heavily impact both on walking (instability secondary to sensitive ataxia with risk of falls and the need of support even for short lengths) and on fine motor skills (manual dexterity), due to hypoesthesia, paresthesias, and upper limbs tremor. The natural history of the neuropathy is characterized by a slow progression,[2] but severe limitations in health-related quality of life (HRQoL) may occur especially with long disease duration or when axonal damage and motor impairment occur. However, evidence-based data and sensitive outcome measures to detect disease progression are still lacking[3] and only a few studies focused on the natural history and long-term prognosis of the disease[4,5] or on possible risk factors of disability.[6]

To date, several scales and measures have been suggested as general functionality parameters in anti-MAG antibody neuropathy, such as the ability to walk[7] or quantitative gait analysis,[8] but neither of them have shown adequate sensitivity when considered alone, requiring to be employed in combination with other validated tools to fully reflect the impact of the disease on quality of life (QoL). Recently, a correlation between the objective evaluation of muscular strength with the vigorimeter and the patient's reported scale Inflammatory-RODS (I-RODS) has been observed in immune-mediated neuropathies including anti-MAG antibody neuropathies.[9] These findings have been confirmed by another recent study,[10] that, besides the I-RODS questionnaire, observed the Fatigue Severity Scale (FSS) as another reliable tool to quantify the impact of the disease on daily activities. The International Classification of Functioning, Disability, and Health (ICF) of the World Health Organization has recently suggested a new definition of "functioning," that includes impairment in different functions, limitations in daily activities and general perception of the QoL, together with other parameters such as age and environment.[11] In light of these findings, a standardized and sensitive evaluation and quantification of the impact of anti-MAG neuropathy on the QoL of patients becomes crucial, in order to detect early in the course of the disease signs of a possible clinical worsening or amelioration after treatment.

In a recently published multicenter cross-sectional study[12] we evaluated the functioning and HRQoL determinants in 67 patients with anti-MAG antibody neuropathy in compliance of the terms defined by the ICF. In our cohort we observed that walking ability and fatigue were the most reliable predictors of physical and mental aspects of QoL, respectively.

The aim of this follow-up study was to examine the long-term functioning and QoL in patients with anti-MAG antibody neuropathy.

2 | PATIENTS AND METHODS

Thirty-two patients of the original study (24 men, mean age 67.5 ± 8.7 years, mean disease duration 5.4 ± 3.3 years) underwent a second follow-up evaluation (T1), after the baseline neurological evaluation (T0), with a mean interval of 15.4 ± 5.7 months.

Inclusion criteria for the study were the same as those of the original study: age 18-80 years, IgM monoclonal gammopathy of undetermined significance[13] or Waldenström's macroglobulinemia[14] and anti-MAG neuropathy diagnosed according to European Federation of Neurological Societies/Peripheral Nerve Society diagnostic criteria[15] (anti-MAG antibodies cut-off value on enzyme-linked immunosorbent assay >1.000 Buhlmann Titer Unit, BTU).[16]

Patients with other conditions with the potential of influencing the general performance were excluded.

Patients' evaluation was performed, after informed consent, by a single examiner with clinical experience in peripheral neuropathies.

The following assessments were performed in all patients:

- MRC (Medical Research Council) Sum Score to test muscle strength (12 muscle for each side)[17,18]
- Sensory Modality Sum score (SMS)[19]
- Visual Analogue Scale (VAS) to evaluate pain[20,21]
- self-reported Rasch built 7 item modified FSS to investigate fatigue[22]
- Berg Balance Scale to evaluate balance[19,23]
- Nine-hole peg test (9-HPT) to investigate hand dexterity, with the score calculated by averaging three attempts in the dominant hand[24,25]
- 6-minute walk distance to test the walking performance of the patient[26,27]
- Impact on Participation and Autonomy questionnaire (IPA), divided in two different subscales for indoor and outdoor activities[28-31]
- self-reported Medical Outcome Study 36-item short-form health status scale (SF-36) for quality of life, with the 36 items divided in eight subscales.[32,33]

3 | STATISTICAL ANALYSIS

Significance between groups was checked by using the *t* test for normally distributed variables or the Mann-Whitney *U* test for ordinal variables. In case of repeated measure (T0 vs T1) the paired *t* test or the Wilcoxon test were used for respectively normal or ordinal variables. The significance level was set at $P < .05$.

4 | RESULTS

Clinical and demographic data were recorded for each patient (Table 1).

Median anti-MAG antibodies titers were 56 804 BTU (range 3900-70 000 BTU).

The SMS values at both upper and lower limbs showed a significant deterioration at the follow-up evaluation (T1) when compared with baseline (T0) (mean score 27.2 ± 3.9 at T0 vs 25.7 ± 3 at T1 at upper limbs, $P = .03$; 20.5 ± 4.8 at T0 vs 18.6 ± 5.9 at T1 at lower limbs, $P = .04$).

The VAS for pain disclosed significant worsening at T1 at upper limbs (mean values 0.8 ± 1.9 at T0 vs 1.8 ± 2.6 at T1, $P = .03$). All the

TABLE 1 Demographics and clinical characteristics of patients with neuropathy

Patients	Sex	Age (yrs)	Hematological disease	Disease duration (yrs)	Interval T0-T1 (months)	Therapy
1	F	70	MGUS	14	9	Yes
2	M	65	MGUS	4	16	Yes
3	F	64	MGUS	7	17	Yes
4	F	72	MGUS	4	13	No
5	M	68	MGUS	2	9	No
6	M	74	MGUS	6	15	Yes
7	M	56	MGUS	10	12	Yes
8	M	72	MGUS	2	16	No
9	M	61	MGUS	2	9	No
10	M	64	MGUS	4	19	Yes
11	M	83	WM	4	26	Yes
12	M	44	MGUS	3	27	Yes
13	M	76	MGUS	2	14	No
14	M	64	MGUS	5	16	Yes
15	F	70	MGUS	5	16	No
16	M	53	MGUS	4	15	No
17	M	70	MGUS	9	15	Yes
18	M	72	MGUS	6	16	No
19	M	73	MGUS	5	6	Yes
20	F	53	MGUS	6	15	No
21	M	66	MGUS	11	13	No
22	M	65	MGUS	6	13	No
23	M	73	MGUS	7	13	No
24	M	71	MGUS	12	13	No
25	M	76	MGUS	4	10	Yes
26	F	69	MGUS	1	10	No
27	F	83	MGUS	2	13	Yes
28	M	64	MGUS	1	17	Yes
29	M	76	MGUS	11	15	Yes
30	M	61	MGUS	5	12	Yes
31	F	54	MGUS	5	16	Yes
32	F	52	MGUS	3	13	Yes

Note: T0 baseline visit; T1 follow-up visit.
Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; WM, Waldenström's macroglobulinemia.

other clinical tests, including MRC Sum Score, FSS, Berg Balance Scale, 9-HPT, and 6-minute walk distance did not show significant difference between T0 and T1.

Regarding the SF-36 questionnaire for the QoL, most of the subscales at baseline evaluation were similar to the Italian normative sample, with the exception of PF (Physical Functioning) and GH (General Health), that presented a significant reduction in our patients' population (PF $P = .0001$; GH $P = .0005$) (Figure 1). The comparison between T0 and T1 evaluations showed stability of the majority of SF-36 subscales (Figure 2), despite a significant worsening ($P = .04$) in the SMS over time, especially at lower limbs.

IPA questionnaire scores did not disclose significant differences between T0 and T1 (Table 2).

We further subdivided our study population accordingly to therapy: 14/32 (10 men, mean age 67.2 ± 6.8 years, mean disease duration 5 ± 3.2 years) at T0 were therapy-naïve, 15/32 (11 men, mean age 65.7 ± 10.2, mean disease duration 5.5 ± 3.4 years) had undergone therapy with rituximab before T0, and 3/32 (3 men, mean age 75.6 ± 5.4, mean disease duration 6.3 ± 2 years) underwent rituximab between T0 and T1. No significant difference in age at onset, disease duration, antibody titers, severity, and impairment of autonomy and QoL quantified with clinical scales and patient-reported questionnaires were observed between the therapy naive and rituximab-treated patients.

In the therapy-naive subgroup, the follow-up evaluation was performed after a median time of 13.5 months, with significant worsening in

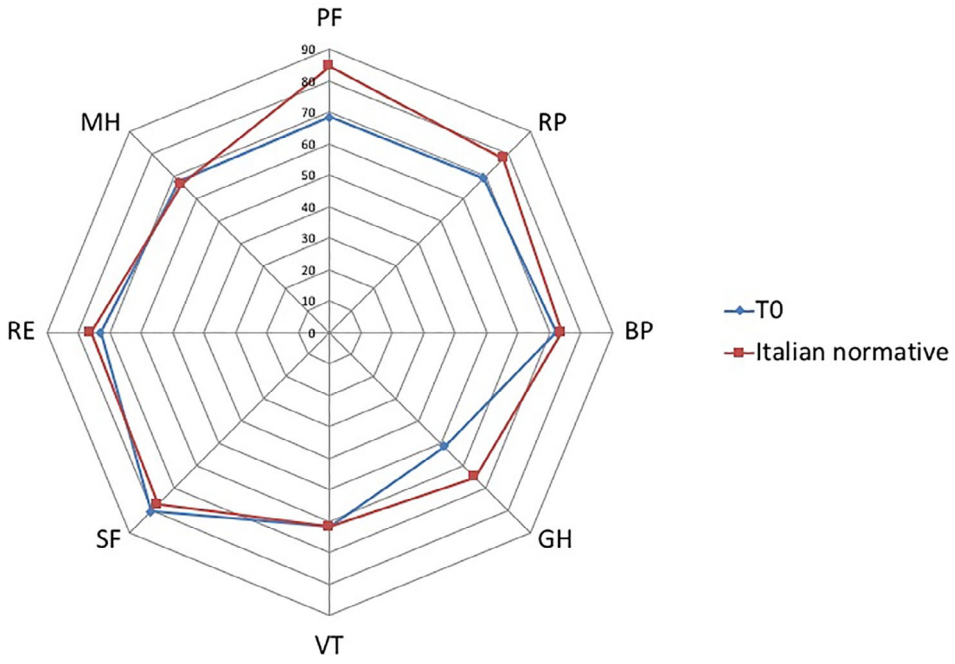

FIGURE 1 Comparison between SF-36 subscales in normative Italian sample (red line) and our patients with anti-MAG neuropathy (blue line) [Color figure can be viewed at wileyonlinelibrary.com]

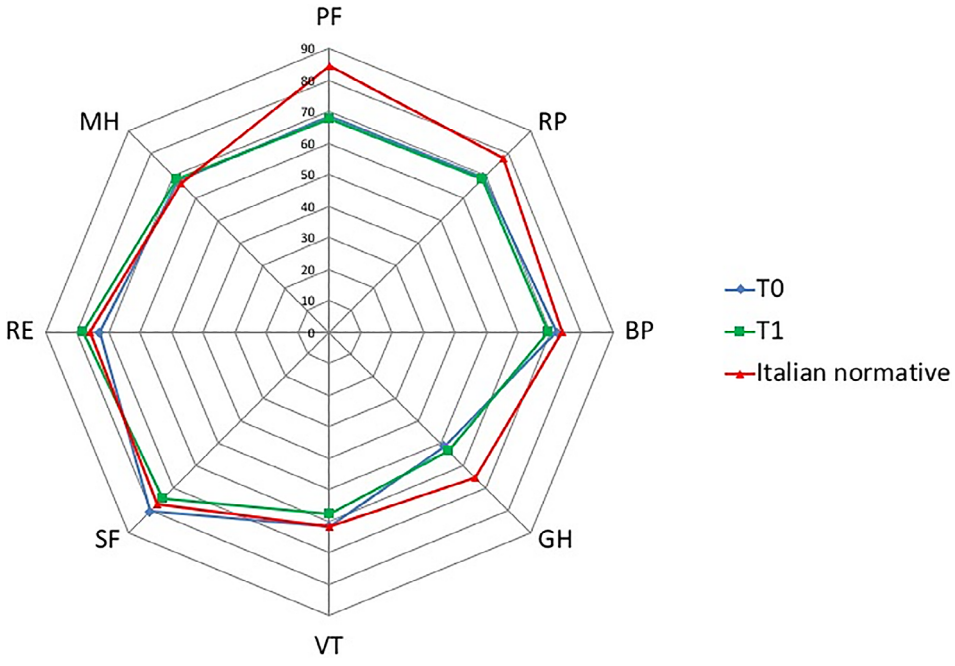

FIGURE 2 SF-36 subscales at baseline (blue line) and follow-up evaluation (green line) [Color figure can be viewed at wileyonlinelibrary.com]

the SMS total score (mean score 48.6 ± 3.5 at T0 vs 42.7 ± 8.3 at T1, P = .009) and in the VAS total score (mean score 1.8 ± 2.3 at T0 vs 4.3 ± 3.2 at T1, P = .01), and no significant differences in all the other tests performed (Table 3).

In the 15 patients treated with rituximab before T0 (median interval between treatment and T0 2 years, range 0.2-10 years); a follow-up evaluation was performed after a median time of 14 months (range 7-25). Three patients underwent rituximab between T0 and T1, with median interval between T0 and therapy of 12 months (range 3-12 months), and with T1 performed after a median time of 15 months (range 15-28). The first patient was a 74-year-old man with 6 years disease duration, treated with rituximab 8 months after the first visit, and evaluated at follow-up 15 months after T0. The second patient was a 83-year-old man with 4 years disease duration, treated with rituximab 12 months after T0 and evaluated at follow-up 28 months after T0. The last patient, a 70-year-old man with 9 years disease duration, underwent rituximab 3 months after T0, and follow-up evaluation 15 months after T0. In the treated cohort as a whole, no significant changes were observed in all the scores over time, neither in the subgroup treated before T0 nor in the group treated between T0 and T1 (with T1 performed after a median time of 14 and

TABLE 2 Outcome measures in the total population T0 vs T1

Scale		T0		T1		
		Mean	SD	Mean	SD	*P* value
MRC Sum Score	*UL*	68.1	2.8	67.7	3.9	.44
	LL	46.3	5.7	45.9	6.8	.61
Sensory Modality Sum score	*UL*	27.2	3.9	25.7	3.03	***.03***
	LL	20.4	4.7	18.6	5.8	***.04***
Visual Analogue Scale	*UL*	0.8	1.9	1.8	2.5	***.03***
	LL	2.1	2.8	2.8	2.6	.16
Fatigue Severity Scale		8.12	6.7	11.09	12.1	.25
Berg Balance Scale		45.2	17	49.3	6.8	.60
6-minute walking distance		410	121.4	400.4	123.5	.46
9-HPT		26.5	11.3	26.2	10.9	.61
IPA questionnaire total score		4.1	4.5	3.9	5	.83
SF-36 questionnaire	*Physical*	64.8	21.6	64.4	19.7	.84
	Mental	68.9	19	68.2	19.8	.71

Note: Bold italics are the statistically significant *P* values. T0 baseline visit; T1 follow-up visit.
Abbreviations: 9-HPT, Nine-hole peg test; IPA, Impact on Participation and Autonomy questionnaire; LL, lower limbs; MRC, (Medical Research Council) Sum Score; SF-36 questionnaire, 36-item short form health status scale; UL, upper limbs.

TABLE 3 Therapy naive and rituximab treated patients T0 vs T1

Scale			T0		T1		
			Mean	SD	Mean	SD	*P* value
MRC Sum Score	Therapy naive		115.2	5.7	115.7	4.7	.59
	Rituximab		113.8	9.1	112	11.1	.08
Sensory Modality Sum score	Therapy naive		48.6	3.5	42.7	8.3	***.009***
	Rituximab		46.9	9.1	45.7	7.2	.55
Visual Analogue Scale	Therapy naive		1.8	2.3	4.3	3.2	***.01***
	Rituximab		3.8	4.8	4.7	5	.28
Fatigue Severity Scale	Therapy naive		8.6	6.4	10	12.7	.62
	Rituximab		7.7	6.7	11.9	11.1	.09
Berg Balance Scale	Therapy naive		48.9	13.9	50.6	4.2	.68
	Rituximab		42.3	18.2	48.2	8.1	.21
6 minute walking distance	Therapy naive		424	112.2	430.7	99.6	.73
	Rituximab		398.5	123.9	375.4	131.8	.22
9-Hole Peg	Therapy naive		24	5.3	25.3	5.8	.24
	Rituximab		29.7	14.2	29.3	12.3	.68
IPA questionnaire	Therapy naive	*Indoors*	3.7	3.8	2.8	4.6	.29
	Rituximab		4.5	4.7	4.8	5.1	.67
	Therapy naive	*Outdoors*	4.5	4.1	4.2	4.2	.76
	Rituximab		5.5	5.4	5.6	5.3	.92
SF-36 questionnaire	Therapy naive	*Physical*	71.8	20	69.1	18.7	.35
	Rituximab		59.3	18.2	60	12.5	.87
	Therapy naive	*Mental*	66.7	21.8	68.6	18.6	.52
	Rituximab		70.7	13.3	69.4	10.7	.60

Note: Bold italics are the statistically significant *P* values. T0 baseline visit; T1 follow-up visit.
Abbreviations: 9-HPT, Nine-hole peg test; IPA, Impact on Participation and Autonomy questionnaire; LL, lower limbs; MRC, (Medical Research Council) Sum Score; SF-36 questionnaire, 36-item short form health status scale; UL, upper limbs.

15 months, respectively) (Table 3). Despite the quite long follow-up, statistical significance was not achieved either for the limited number of patients or for the lack of sensitive outcome measures.

5 | DISCUSSION

In our cohort of patients with anti-MAG antibody neuropathy, the clinical and functional evaluations confirmed a predominant involvement of sensory modalities at four limbs, with potential impact on daily activities and on the global perception of autonomy and QoL. Moreover, in patients with follow-up evaluation, the SMS scores at upper and lower limbs showed a significant impairment when compared with baseline confirming that, although slowly, the predominant sensory involvement of the neuropathy tends to worsen over time. In our cohort, high scores in the VAS scale for pain at upper limbs have been observed, with worsening values over time. In a previous study by Pazzaglia et al[34] on 93 patients with immune-mediated neuropathies, pain, mainly defined as paresthesias/dysesthesias and spontaneous superficial pain, was described in up to 50% of the cohort, with the small subgroup with anti-MAG antibody neuropathy (6%) presenting high scores in all questionnaires. In another cohort of 55 patients with anti-MAG antibody neuropathy from France and the United Kingdom studied by Delmont et al,[35] 80% complained of pain with different characteristics (burning or pressing spontaneous pain, paroxysmal pain, evoked pain, and paresthesias), and 64% had muscle cramps. Moreover, in a recent cross-sectional study performed on 55 patients with anti-MAG antibody neuropathy, Rajabally et al showed that pain of any type was reported in 80% of the subjects, with sensory positive symptoms such as paresthesias and dysethesias representing the most common complaint. Muscle cramps were also frequent (>60% of patients) and had a major impact on daily activities, exercise, and sleep.[36] These findings suggest that although this condition is thought to be painless and pain is excluded from the clinical diagnostic criteria, it may represent a major complaint and affect QoL.[37] Moreover, other concomitant symptoms such as tremor and fatigue are often reported in patients with anti-MAG antibody neuropathy, and can impair autonomy. Regarding QoL, the values from our cohort were compared with those from a normative Italian sample[38]: at enrollment only PF and GH scores disclosed significant differences whereas the remaining items showed similar scores. Follow-up evaluations evidenced stability in the majority of SF-36 subscales, suggesting the development of compensatory mechanisms and adaptation to the slow evolution of clinical deficits. This explanation has already been proposed also in other slowly progressive conditions such as hereditary neuropathies.[39] In therapy-naive and untreated patients, the significant worsening of the SMS and VAS total score after a median interval of 14 months (range 8-28) can be considered as a reliable expression of the natural course of the disease. All previous clinical trials had 8 or 12 months follow-up periods, that, together with the unavailability of adequate and sensitive outcome measures, may not be sufficient to detect modifications in the clinical condition, thus explaining some limitations of these studies. Among patients who underwent rituximab, no significant change was observed in all the scores over time, neither in the subgroup treated before T0 nor in that treated between T0 and T1 (with T1 performed after a median time of 14 and 15 months, respectively). In our cohort, the significant worsening of the SMS and VAS after a median interval of 14 months can be considered as a reliable expression of the natural history of the disease, and suggest that these scales might represent reliable outcome measures in anti-MAG antibody neuropathy.

CONFLICT OF INETREST

The authors declare that they have no conflict of interest.

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