

Distal Acquired Demyelinating Symmetric Neuropathy Is the Predominant Phenotype of IgM-Related Neuropathy and Identifies Patients with a Favorable Outcome

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Background. Neuropathy affects up to 15-30% of patients with IgM monoclonal gammopathies. The clinical spectrum, biological characteristics and therapeutic outcomes remain incompletely defined.

Aim. We aimed to characterize the clinical spectrum of IgM-related neuropathies, describe the pattern of treatment and outcome of Distal Acquired Demyelinating Symmetric (DADS) neuropathies.

Methods. We reviewed a prospectively maintained database including 116 patients, diagnosed and followed in three University Hospitals from 1994 to 2026. Inclusion criteria were the presence of an IgM monoclonal protein and of neuropathy. The severity of neuropathy was assessed clinically and classified in mild, moderate and severe, based on the burden of the neurological symptoms. Neuropathy response to treatment was classified as resolved, improved, stable and worsened. A response was obtained with at least an improvement of symptoms.

Results. Overall, we analyzed 116 patients, including 60 Waldenstrom Macroglobulinemia (WM), 51 Monoclonal Gammopathies of Clinical Significance (MGCS), 2 IgM-Monoclonal Gammopathies of Undetermined Significance (MGUS) and 1 asymptomatic WM were included in the analysis. Two patients were grouped in "Other" category because they had Marginal Zone Lymphoma (MZL, n=1) or IgM Multiple Myeloma (MM, n=1). Their baseline characteristics are presented in Table 1. Peripheral neuropathy was classified as DADS polyneuropathy in 79/116 patients (68.1%) of which 64 (81.0%) had anti-Myelin Associated Glycoprotein (anti-MAG) antibodies, amyloidotic neuropathy in 14/116 (12.1%), CIDP 6/116 (5.2%), cryoglobulinemic neuropathy in 4/116 (3.4%), Bing-Neel Syndrome in 3/116 (2.6%), POEMS in 1/116 (0.9%) and CANOMAD in 1/116 (0.9%) (Figure 1). In 8/116 (6.9%) neuropathies were classified as "Other" because after diagnostic work-up their etiology was not related to the IgM paraprotein. Polyneuropathy severity was mild, moderate or severe in 26 (22.6%), 51 (44.3%) and 38 cases (33%) respectively. Of 79 patients with DADS neuropathy, 51 (64.6%) were treated. Clinical characteristics and treatment details of patients with IgM and DADS polyneuropathy are summarized in Table 2. Twenty-five of 51 (49%) were treated with Rituximab (R), 30 (58.8%) with chemo-immunotherapy (CIT), 9 (17.6%) with Bruton Tyrosine Kinase Inhibitors (BTKis). A resolution or improvement of neuropathy was observed in 8/25 (32.3%) of patients treated with R, 12/30 (41.4%) of patients treated with CIT and 2/9 (22.2%) treated with BTKis, respectively (Fish $\chi^2=1.27$, $p=0.53$). With a median follow-up of 8.6 years (IQR: 3.8–14.1), the median overall survival (OS) was not reached; estimated 5-year and 10-year OS were 90.5% and 81.9%, respectively (Figure 2). A survival advantage was observed in patients with DADS neuropathies as compared with other neurological phenotypes (10-year OS 89.4%, 95%CI: 81.2-97.6% vs 67.7%, CI: 51.8-83.6%, Greenwood Formula log-rank $p<0.001$) (Figure 2). Comparison of OS between anti-MAG positive versus anti-MAG negative DADS showed no significant difference (10-year OS 90.9%, 95%CI: 91.9-100% vs 85.1%, 95%CI: 66.0-100%, log-rank $p=0.55$).

Conclusions. DADS neuropathy was the predominant phenotype and was associated with better OS. Response to treatment were similar among the patterns of therapy.

Table 1. Baseline patients' characteristics

Variable	Value
Number of patients	116
Demographics	
Sex, male	80 (69.0%)
Age at diagnosis, years, median (IQR)	63.8 (54.7–73.4)
Diagnosis	
Waldenström macroglobulinemia (WM)	60 (51.7%)
Monoclonal gammopathy of clinical significance (MGCS)	51 (44.0%)
Other	2 (1.7%)
IgM-MGUS, NOS	2 (1.7%)
Asymptomatic/smoldering WM (aWM)	1 (0.9%)
Genetics	
MYD88 mutated	60 (88.2% of 68 tested)
MYD88 VAF, %, median (IQR), mutated only (n=28)	2.9 (0.3–14.1)
Monoclonal component	
Isotype IgMκ	83 (72.2%)
Isotype IgMλ	23 (20.0%)
Other/biclonal isotypes	9 (7.8%)
Monoclonal component, g/dL, median (IQR)	0.70 (0.49–1.20)
Serum IgM, mg/dL, median (IQR)	698 (360–1180)
FLC ratio, median (IQR)	1.79 (1.00–4.36)
Amyloidosis	
AL-Amyloidosis	16 (13.8%)
Polyneuropathy type (N=116)	
DADS anti-MAG+	63 (54.3%)
DADS anti-MAG–	15 (12.9%)
Amyloidotic neuropathy	14 (12.1%)
Other	8 (6.9%)
CIDP	6 (5.2%)
Cryoglobulinemic neuropathy	4 (3.4%)
Bing–Neel syndrome	3 (2.6%)
DADS anti-MAG+ / Bing–Neel syndrome	1 (0.9%)
POEMS	1 (0.9%)
CANOMAD	1 (0.9%)
Severity at diagnosis (N=115)	
Mild	26 (22.6%)
Moderate	51 (44.3%)
Severe	38 (33.0%)

Variable	Value
Presenting symptoms (N=114)	
Paresthesia	113 (99.1%)
Hypoesthesia	72 (63.2%)
Neuropathic pain	61 (53.5%)
Motor symptoms	55 (48.2%)
Ataxia	42 (36.8%)
Cramps	22 (19.3%)
Tremor	14 (12.3%)
Follow-up	
Follow-up, years, median (IQR)	8.58 (3.80–14.11)

Table 2. Baseline clinical characteristics of patients with DADS antiMAG (positive or negative)

Variable	Value (n=79)
Sex, male	52 (65.8%)
Age at diagnosis, years, median (IQR)	65.5 (54.4–73.6)
Diagnosis	
WM	39 (49.4%)
MGCS	38 (48.1%)
Other	2 (2.5%)
Genetics / laboratory	
MYD88 mutated	45 (88.2% of 51 tested)
MYD88 VAF, %, median (IQR)	5.4 (0.8–15.3)
Isotype IgMκ	60 (76.9%)
Isotype IgMλ	10 (12.8%)
Monoclonal component, g/dL, median (IQR)	0.70 (0.49–1.31)
Serum IgM, mg/dL, median (IQR)	709 (414–1190)
FLC ratio, median (IQR)	1.90 (1.25–3.50)
Hemoglobin, g/dL, median (IQR)	14.1 (13.3–14.8)
Leukocytes, /mmc, median (IQR)	6810 (6180–8680)
Neutrophils, /mmc, median (IQR)	4065 (3208–5074)
Lymphocytes, /mmc, median (IQR)	1870 (1627–2500)
Platelets, /mmc, median (IQR)	243,000 (198,000–279,000)
LDH, U/L, median (IQR)	188 (168–213)
Anti-MAG antibodies positive	67/77 (87.0% tested)
Anti-MAG titer, BTU, median (IQR) — anti-MAG+ patients only (n=64)	46,598 (25,825–73,750)

Variable	Value (n=79)
Systemic involvement / severity	
Lymphadenopathy	4 (5.1%)
Splenomegaly	1 (1.3%)
Severity: mild / moderate / severe	21.5% / 48.1% / 30.4%
Presenting symptoms	
Paresthesia	79 (100%)
Hypoesthesia	48 (60.8%)
Neuropathic pain	40 (50.6%)
Motor symptoms	35 (44.3%)
Ataxia	29 (36.7%)
Treatment and outcome	
Rituximab, any line	25/51 evaluable (49.0%)
Immunochemotherapy, any line	30/51 evaluable (58.8%)
Target therapy, any line	9/51 evaluable (17.6%)
Deceased	9 (11.4%)

Figure 1. Distribution of polyneuropathy phenotypes across the whole cohort

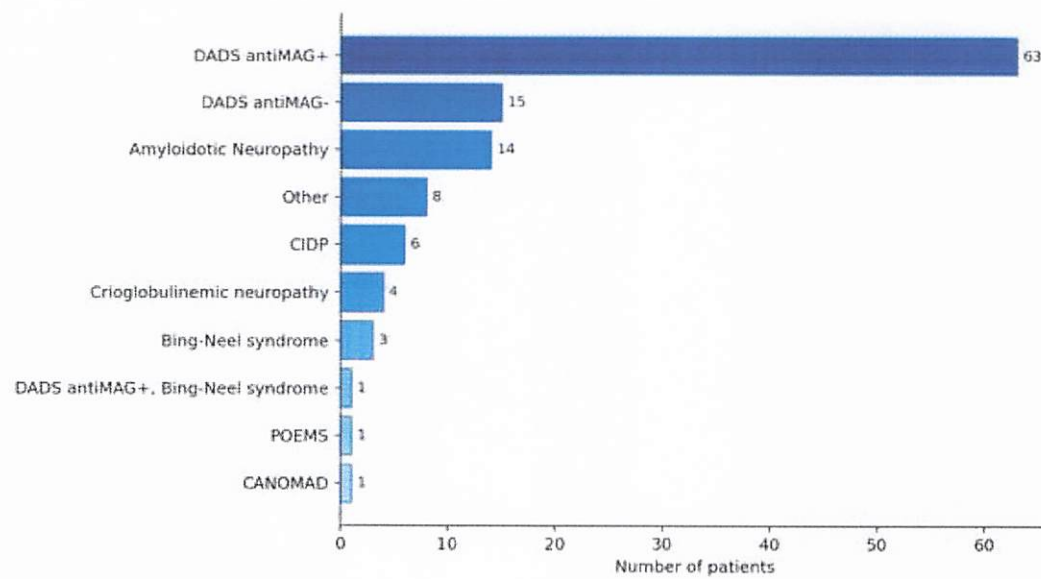
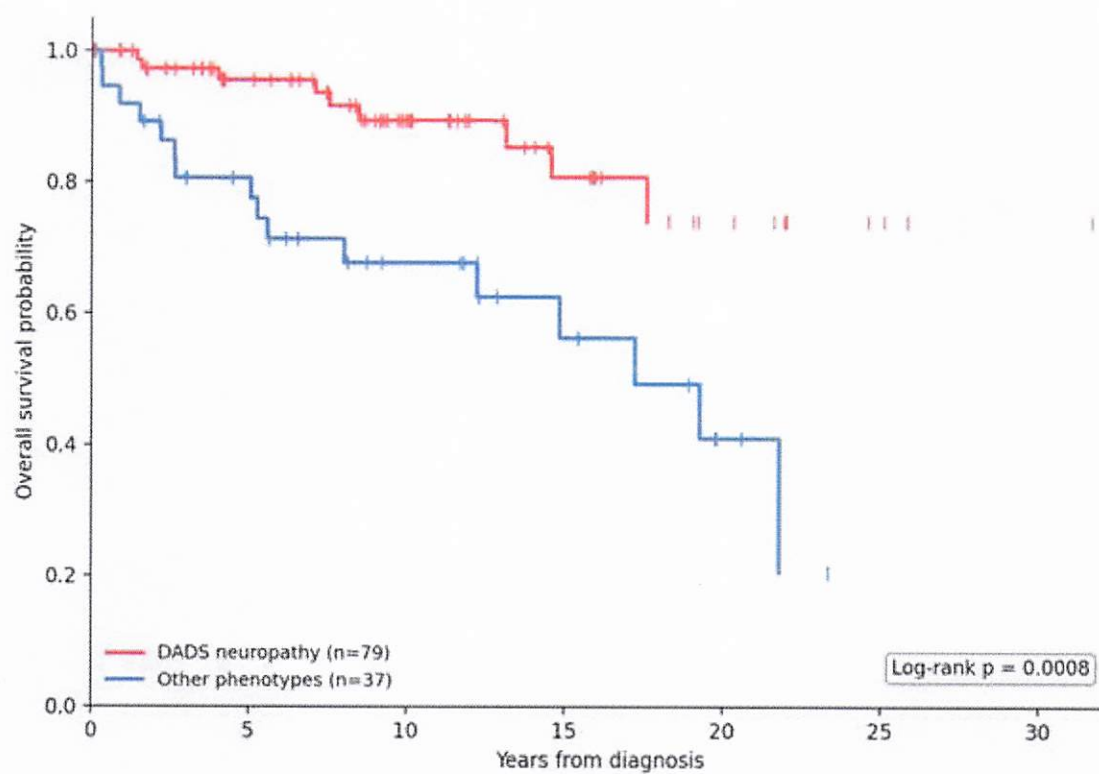


Figure 2. OS in patients with DADS polyneuropathy or with non-DADS neuropathies



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