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The Spectrum of IgM-Associated Peripheral Neuropathies – A Cohort Study from the Neurohaematology Clinic at Queen Square and UCLH

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Background

The IgM-associated peripheral neuropathies (IgM-PN) are a heterogenous collection of disorders, with a causal association with IgM monoclonal gammopathy of undetermined significance (MGUS) or Waldenstrom's Macroglobulinaemia (WM) via different mechanisms. We describe the distribution, clinical features and treatment outcomes of IgM-PN at our specialist centre.

Methods

A retrospective cohort analysis was undertaken using the UCLH WM patient registry. All patients with a confirmed diagnosis of IgM-PN as deemed by expert assessment, following examination, serological testing and neurophysiological assessment, were included.

Results

A total of 667 patients with IgM gammopathy were reviewed, 98 with IgM MGUS and 569 with WM. IgM-PN was diagnosed in 125 (18.7%) patients, of whom 112 had adequate data available. Baseline clinicopathological details are given in table 1. Patients were diagnosed between years 1997 and 2024, with median follow up of 83 months (3-835m). The underlying disorder was IgM MGUS in 56 (50%), WM in 53 (47.3%), CLL 2 (1.6%) and IgM POEMS 1 (0.8%). No systemic disease was detected in 14/112 cases; isolated flow cytometric disease in 5, and isolated $MYD88^{L265P}$ PCR in 3 cases and 1 case of isolated $CXCR4^{WHIM}$ likely due to a non-L265P MYD88 mutation. Nerve biopsy was done in 22/112 (19.6%) patients.

Frontline treatment (1L) was given in 84/112 (75%), and an additional 2/4 patients with MMN-CB* received intravenous immunoglobulin (IVIg). Median lines of treatment received was 1 (range 1-5). Frontline regimen was rituximab monotherapy (R) in 46, dexamethasone-rituximab-cyclophosphamide (DRC) 22, R-CHOP/CVP in 5, R-bendamustine 3, R-chlorambucil 3, Bortezomib-dexamethasone 2, ibrutinib 1, R-methotrexate-cytarabine 1 (BNS), and lenalidomide-dexamethasone 1 (POEMS).

Progression despite 1L therapy occurred in 19/70 (27.1%) assessable patients, stabilisation in 25/70 (35.7%), and improvement in 26/70 (37.1%). Second-line therapy has been given in 34 cases, including 14 cases of R-retreatment following an initial period of response to 1L therapy. Bruton's Tyrosine Kinase inhibitors (BTKis) were employed in 12 patients, including ibrutinib (n=7), zanubrutinib (n=4) and pirtobrutinib (n=1).

Of patients with anti-MAG neuropathy, 61/80 (76.3%) required therapy, including frontline R in 37 and DRC in 17 cases. Improvement occurred in 22 (41.5%), stabilisation in 20 (37.7%) and progression in 11/53 (20.8%) assessable cases.

On univariate analysis, progressive disease following frontline therapy was significantly more common in patients who do not attain a partial response (p 0.05), AL amyloid (p 0.04) and PN-BNS (p 0.001); AL amyloid remained significant (p 0.039) on multivariate analysis.

Up to date survival information was available in 95 patients; 16/95 (16.8%) are deceased. Median OS for anti-MAG PN 835m (225-NR), with 3- and 5-year OS 100% and 94.8% (89-100%); AL amyloid 162m (144-NR), 3- and 5-year OS 100%.

Conclusion

The incidence of IgM-PN in our cohort was 18.7%, with anti-MAG representing most cases (71%). Clonal burden in the bone marrow is typically small and several patients have disease only on immunophenotyping (n=5) or PCR (n=4). A significant majority of IgM-PN cases is associated with a $MYD88^{L265P}$ mutation. Approximately 73% of patients experienced stabilisation or improvement in PN with frontline therapy.

Table 1 – Clinicopathological Characteristics of Patients with IgM-PN	
Demographics	n = 112
Age, median (range)	66 (30-86)
Male	82 (73.2%)
Underlying Disorder	n = 112
IgM MGUS	56 (50%)
Waldenstrom's Macroglobulinaemia	53 (47.3%)
CLL	2 (1.6%)
IgM POEMS	1 (0.8%)
Pathology	
Paraprotein concentration, median (range) (g/L)	5 (too faint to quantify – 55)
Kappa	98 (87.5%)
Lambda	14 (12.5%)
$MYD88^{L265P}$	36/47 (76.6%)
MYD88 not detected	11/47 (23.4%)
IgM-PN Diagnosis	n = 112
Anti-MAG	80 (71.4%)
AL amyloid	8 (7.1%)
Multifocal motor neuropathy with conduction block* (MMN-CB)	4
Cryoglobulinaemic vasculitis	3
PN Bing-Neel syndrome (BNS)	2
Light chain deposition disease	1
Neurolymphomatosis, high grade transformed	1
CANOMAD	1
IgM POEMS	1
Other, putative IgM-associated	11