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Immunostaining of skin biopsy adds no diagnostic value in MGUS-associated peripheral neuropathy

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ABSTRACT

Background and purpose: For several decades an association between MGUS, IgM-MGUS in particular, and peripheral neuropathy has been suspected. Several histopathology studies have shown binding of IgM to myelin and a secondary widening of myelin lamellae in cutaneous nerves and in the sural nerve of patients with IgM-MGUS, or Waldenström's Macroglobulinaemia (WM), and peripheral neuropathy.
In this retrospective study we investigated the value of skin biopsy examination in the diagnosis of MGUS- and WM-associated peripheral neuropathy.
Methods: A total of 117 patients, who were examined for an M-component in serum with associated nerve symptoms, had a skin biopsy taken and examined for immunoglobulin deposition in cutaneous nerves. Thirty-five patients were diagnosed with MGUS or WM and peripheral neuropathy with no other cause of neuropathy. Nineteen patients had MGUS but no peripheral neuropathy.
Results: Of the 35 patients with MGUS or WM and peripheral neuropathy, four had immunoglobulin deposition in the skin biopsy, all of whom had an IgM gammopathy. In the control group of 19 without peripheral neuropathy, three had immunoglobulin deposition in the skin biopsy, all of whom had IgM-MGUS. In both groups, there was a trend towards higher IgM blood levels in patients with immunoglobulin deposition. Half of the patients with IgM gammopathy in the neuropathy group had anti-MAG reactivity, whereas only one in the control group had weak anti-MAG reactivity.
Conclusion: Our study indicates that examination of skin biopsies for immunoglobulin deposition does not add significant diagnostic value in the evaluation of neuropathies suspected to be caused by MGUS or WM. IgM immunoglobulin deposition in skin biopsy might merely be an epiphenomenon secondary to high IgM blood levels.

1. Introduction

Monoclonal gammopathies are a heterogeneous group of disorders caused by accumulation of monoclonal plasma cells or mature B-lineage cells. They range from Monoclonal Gammopathy of Unknown Significance (MGUS), to malignant disorders such as Multiple Myeloma, Amyloid Light-chain Amyloidosis, and Waldenström's Macroglobulinaemia. MGUS is the most common monoclonal gammopathy [1–3]. The prevalence of monoclonal gammopathy rises with age reaching 3–10% among those over 70 years of age [4,5], while MGUS has a prevalence of 3% in subjects over 50 years of age [3].

For several decades an association between monoclonal gammopathy and peripheral neuropathy has been suspected, especially between MGUS and peripheral neuropathy [1,2]. This is due to the fact that the prevalence of peripheral neuropathy is 5–8% among people over the age of 50 [6,7], whereas the prevalence of peripheral neuropathy in monoclonal gammopathies, including MGUS, has been reported to be 10–50% [8–10].

The association between the different monoclonal gammopathies and peripheral neuropathy is thought to be different. For Multiple Myeloma, the peripheral neuropathy is often due to treatment-related toxicity, or advanced disease [2]. The neuropathy associated to Amyloid Light-chain Amyloidosis is thought to be secondary to either vascular insufficiency or to direct toxic effect of amyloid deposition [11]. In Waldenström's Macroglobulinaemia the associated neuropathy is thought to be caused, at least in part, by the characteristics of the IgM-type M-protein which may or may not have reactivity against myelin-associated glycoprotein (MAG). Consequently, the neuropathy clinically, electrophysiologically, and pathologically

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resembles that of IgM-MGUS-associated peripheral neuropathy, which is a demyelinating, primarily sensory distal neuropathy [12–14].

The co-existence of MGUS and peripheral neuropathy differs among studies [8,10]. The strongest association is by far that of IgM-MGUS and peripheral neuropathy [1,8,9,15–17]. Most studies find that IgM gammopathy makes up around 50% of the gammopathies observed among patients with peripheral neuropathy and gammopathy [1,8,9,15–17] with the majority of patients with IgM gammopathy having MGUS [9,18]. Around 50% of patients with IgM gammopathy and peripheral neuropathy have elevated anti-MAG titer [2,19]. Patients with IgM-MGUS and peripheral neuropathy typically have a predominantly sensory chronic demyelinating symmetric peripheral neuropathy, though it can also be axonal [20]. Several pathological studies have shown binding of IgM to nerve myelin and a secondary widening of myelin lamellae in cutaneous nerves and in the sural nerve of patients with IgM-MGUS and peripheral neuropathy [8,14,17,21].

The association of IgG/IgA-MGUS and peripheral neuropathy is more equivocal. Thus, IgG-MGUS is underrepresented among patients with MGUS and peripheral neuropathy [1,2]. Moreover the clinical presentation of IgG- and IgA-MGUS is variable and the associated neuropathies electrophysiologically often show axonal degeneration [2,8,16]. However, demyelinating variants are also seen [20] and may clinically be indistinguishable from chronic inflammatory demyelinating polyneuropathy [22]. Furthermore, widening of myelin lamellae has been reported in a case of IgG-MGUS and peripheral neuropathy [23].

From 2006 we decided to incorporate skin biopsies in the diagnostic work-up of patients with monoclonal gammopathy and suspected peripheral neuropathy at Odense University Hospital and Vejle Hospital, since the relation between monoclonal gammopathy and peripheral neuropathy may be obscure and there is a need for better identifying patients with a causal relationship. In this retrospective study, we investigated the value of performing skin biopsy analysis in the diagnosis of MGUS-associated peripheral neuropathy and Waldenström's Macroglobulinaemia-associated peripheral neuropathy. We aimed at testing if immunoglobulin binding to nerve structures in the dermis could be a marker of MGUS-associated neuropathy. Waldenström's Macroglobulinaemia-associated peripheral neuropathy was included in the study because of the clinical, electrophysiological, and pathological resemblance with IgM-MGUS-associated peripheral neuropathy.

2. Material and methods

2.1. Patients

From 2006 to 2012 patients with a monoclonal gammopathy and neurological symptoms from one of four departments in two hospitals (Departments of Neurology and Hematology, Odense University Hospital and Departments of Neurology and Hematology, Vejle Hospital) had routinely taken a skin biopsy for examination for immunoglobulin deposition in cutaneous nerves. All the skin biopsies were examined at the Department of Pathology, Odense University Hospital, and most of the patients had a thorough examination at the neurological department, including clinical and electrophysiological examination as well as extensive blood testing and other laboratory work-up as needed. Some few patients were not systematically examined in the neurological department because their symptoms early proved to be of a non-neurological origin. A total of 117 patients had a skin biopsy taken and examined for immunoglobulin deposition in cutaneous nerves.

For the present retrospective study the complete neurological and hematological patient medical records, blood samples, skin biopsies, bone marrow biopsies, and other information such as CSF analysis, were reviewed. The study was registered at the Danish data registration authorities according to regional practice and the patients gave informed consent for participation in the study.

Study flow diagram for the 117 patients with skin biopsies is shown in Fig. 1. For our cases, the following patients were excluded: Patients with no peripheral neuropathy, patients with M-protein secondary to other hematological diseases, patients with other possible causes of peripheral neuropathy, patients with only a transient M-protein, patients that underwent a sural nerve biopsy, and patients with insufficient data.

Thus, of the initial 117 patients with M-protein and possible peripheral neuropathy, 35 patients had MGUS (27) or Waldenström's Macroglobulinaemia (8) and definite peripheral neuropathy with no

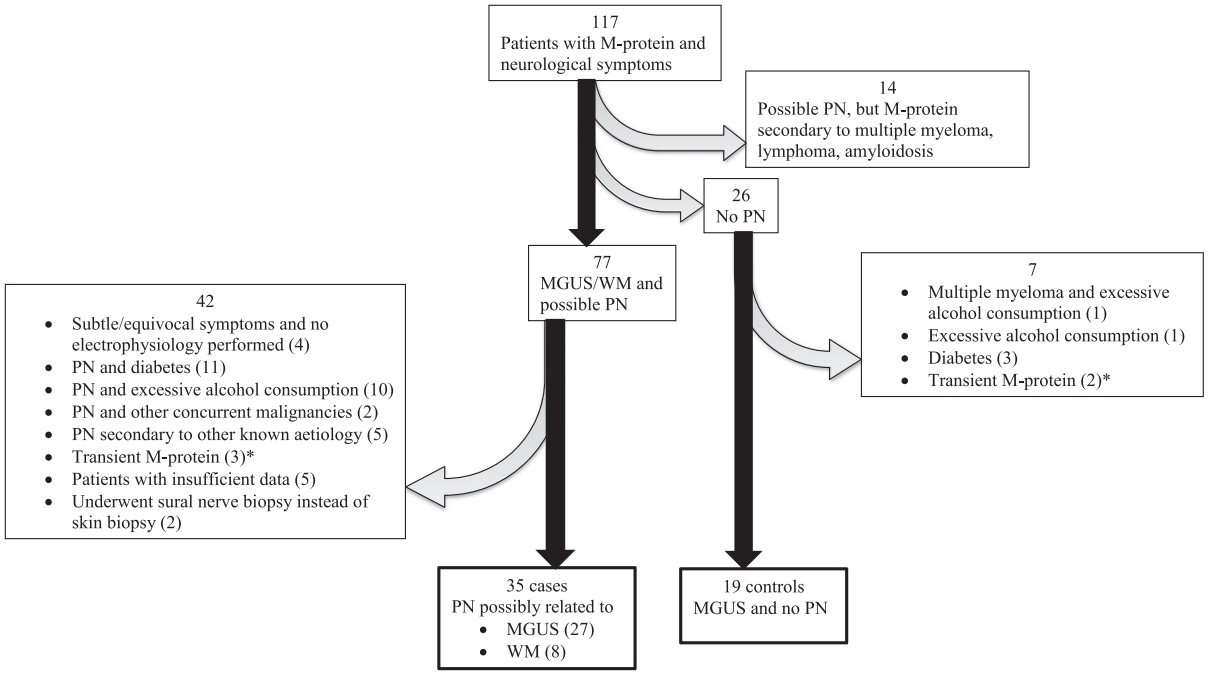

Fig. 1. Study flow diagram. PN: peripheral neuropathy. *: Only low-level M-protein on one occasion before skin biopsy was taken. Upon re-testing after skin biopsy was performed, no M-protein was found.