Central and peripheral neurological involvement in monoclonal gammopathies of undetermined significance

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Received 8 May 2013; revised 8 July 2013; accepted 8 August 2013

ABSTRACT

Several studies have suggested a pathogenetic role of paraproteinaemias in PNS damage. Over the few last years, the presence of symptomatic or subclinical PNS lesions in CNS diseases like multiple sclerosis has been described. On the other hand, CNS demyelinating lesions and cervical atrophy have been reported in patients affected by chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Very few cases of MGUS associated with CNS disease alone or with both CNS and PNS disease have been reported. Since 1999, we have been studying 16 patients (8 M, 8 F), with a mean age 60.2 ± 13.4, affected by MGUS associated with symptomatic neurological central and/or peripheral diseases. Patients affected with lymphomas, lupus eritematosus and other immunological diseases were excluded. Involvement of both PNS and CNS was not associated to a particular type of paraproteinemia: monoclonal IgM were found in 8 patients; monoclonal IgG in 6 patients and monoclonal IgA in 1 patient and Igλ in 1 patient. High anti-nervous system autoantibodies were found in 10/16 patients and anti-MAG antibodies were detected in patients with paraproteinemiec demyelinating neuropathy (PDN). High reactivity anti-nervous system might support the hypothesis of a pathogenetic role of MGUS in these neurological diseases. Nevertheless, at present, we cannot exclude that there is only a circumstantial association between MGUS and neurological damages, particularly concerning CNS.

Keywords: Multiple Sclerosis (MS); Monoclonal Gammopathies of Undetermined Significance (MGUS); Peripheral Nervous System (PNS) Involvement; Central Nervous System (CNS) Involvement

1. INTRODUCTION

While the association of monoclonal gammopathies of undetermined significance (MGUS) with peripheral nervous system (PNS) involvement has been widely documented [1-8], the involvement of the central nervous system (CNS) in the presence of MGUS has seldom been described [9-13].

Several studies have suggested a pathogenetic role of paraproteinemia in PNS damage; 10% of patients with an idiopathic neuropathy have an associated monoclonal gammopathy, while 8%-37% of patients with MGUS have symptomatic neuropathy where often it is the only clinical manifestation of an underlying hematologic disorder [3,7,14]. The monoclonal antibodies reacting with neural antigens in MGUS are more likely to belong to the IgM class although IgG is the most common class of paraproteins in patients with MGUS [4]. Very few cases of CNS disease associated with MGUS and of the coexistence of CNS and PNS involvement in patients with a paraproteinemia are described [14,15]. For this reason, we have studied these particular cases of patients who have referred to our institution over the last ten years, with the aim to evaluate a possible causal relation between MGUS and CNS involvement.

2. MATERIALS AND METHODS

A retrospective chart review was carried out on 40 patients who were under our care from 1999 to September 2009, affected with peripheral neuropathy of unknown pathogenesis (patients with diabetes, neurotoxicity, hypovitaminosis, haematological diseases were excluded) and 71 patients with suspected demyelinating disease. We evaluated those affected by MGUS.
We identified 16 patients (8 males and 8 females) with a mean age 60.2 ± 13.4 and affected by MGUS. Fifteen patients underwent haematological analysis (basic haematological exams, immunoelectrophoresis, neurological autoantibodies such as ANA, anti-Yo, anti-Ri, anti-Hu, anti-MAG, anti-GM1, anti-GQ1b, GD1b), and cerebrospinal fluid (CSF) examination (cytochemical, intrathecal production of IgG, oligoclonal bands-OB) research, Link Index); one patient only had haematological screening and not a CSF exam. All patients underwent X-Ray skeletal surveys, and neurophysiological and neuroradiological investigations: electroneuromyography (ENMG), Magnetic Resonance Imaging (MRI) of the brain and spinal cord. Each patient visited our Institute at different times, and had their serial examinations at different times, each according to their disease, their symptomatology and their responses to therapy. Patients affected by lymphomas, myeloma, amyloidosis, systemic lupus erythematosus and other immunological diseases were excluded. The follow-up varies between 2 and 12 years.

3. RESULTS

Patient charts were divided into two groups. Group one—Central Nervous System damage (Total 5 patients): 4 Multiple Sclerosis (MS) and 1 cerebellar atrophy. Second group—Neuroperipheric Damage (Total 11 patients with): 8 paraproteinemic demyelinating neuropathy (PDN) and 3 axonal neuropathy. This group was then divided into 2 subgroups (first: group IIa with only PNS damage (7 patients) and group IIb with PNS and CSN damage (4 patients: 2 with PDN + Parkinson diseases (PD) and 2 with PDN + Multisystemic Atrophy (MSA) (Tables 1-3).

In group I: 2 patients had MGUS type IgM and 3 patients MGUS type IgG. All of them had CSF alteration while ANA and anti-GM1 seric positivity was found in 4 patients.

In group IIa e IIb: 6 patients had MGUS type IgM, 3 MGUS type IgG, 1 MGUS type IgA and 1 Igλ. Anti-MAG seric positivity was detected in 4 cases, all of them had been affected by PDN and with MGUS type IgM; anti-GM1 autoantibodies were present in 2 cases: 1 MGUS type IgG and 1 MGUS type IgA. CSF was abnormal in 9 cases, 3 of them had also CNS involvement (2MSA e 1 PD).

Patients with PD and MSA had a typical symptomatology, that began at the same time or after the onset of the peripheral neuropathy.

4. DISCUSSION AND CONCLUSIONS

Several data suggest a pathogenetic role of paraproteinæmias in PNS damage. A demyelinating neuropathy can be induced in animals after systemic administration of serum or intraneuronal injection of IgM taken from patients with a demyelinating neuropathy and MGUS. Fur-
thermore, anti-nerve autoantibodies in the serum of patients with IgM paraproteinemiac neuropathy were detected and the deposition of immunoglobulin and complement in endoneurium was demonstrated by immunofluorescent staining [7]. One-half of patients with IgM-MGUS neuropathy have an illness that is associated with antibodies against a specific myelin associated glycoprotein (anti-MAG) [14,16]. Fluri et al. [17] demonstrated that, in patients with neuropathy associated with IgM paraproteinaemia and anti-MAG antibodies, the IgM binding strength to MAG was higher for CNS myelin than for PNS myelin, even in the absence of any clinical CNS involvement. Over the last few years, the presence of symptomatic or subclinical PNS lesions in CNS diseases like multiple sclerosis has been described [18-25]. On the other hand, CNS demyelinating lesions and cervical cord atrophy have been reported in patients affected by acute or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [26-28].

In group 2 (PNS disease), a higher frequency of IgM was confirmed (53%), and in more than half of the cases it was found to be associated to anti-MAG. In the 3 cases of axonal damage, there was no IgM MGUS. Regarding the 4 cases in which damage of the CNS was associated to PNS disease, we emphasize that the distinctive involvement of the extrapiramidal system and the high prevalence of this co-occurrence (36%, that is 4/11 patients), compared to the prevalence of parkinsonism in the general population (1% over 60 years of age) [29], might support the hypothesis of a link between MGUS and such disorders. However the sample size is too small to permit a true statistical conclusion.

In group 1, 4 patients met the diagnostic criteria of late onset MS, prevalent in 30% (over 13 of our cases). This prevalence is much higher than the risk in the association between MGUS and MS (0.0065/100) [14]. These data and the research of Fluri et al. [17] may suggest a pathogenetic link between MGUS and MS of late onset.

The case of the young man with cerebellar atrophy shows that he suffered progressive cerebellar syndrome, first unilaterally, then bilaterally. A serial MRI showed only cerebellar vermis atrophy. A CSF exam showed oligoclonal bands and elevated IgG monoclonal gammapathy, but no autoantibodies. Genetic analysis for SCA was negative and seric value of vitamin E, vitamin B12 and folic acid were normal. Nerve conduction studies were normal [7,30]. Far from being demonstrated, we think that a pathogenetic role of IgG MGUS in this patient could be an intriguing hypothesis.

MGUS is found in approximately 1% - 3% [31] of people above 50 years of age and in 3% - 5% above 70 years.

They evolve into malignant disorders at a rate of only 1% per year. Quality of life may be compromised by an associated disease.

It is known that a bigger sample size is needed if a true statistical association exists, however, we have reported the coexistence of MGUS in particular types of CNS disease. We think that it would be useful to test the presence of MGUS in these selected patients considering that MGUS may be the precursor of more serious diseases, such as multiple myeloma, primary amyloidosis and Waldenström macroglobulinemia. More importantly, if larger studies confirm the association between MGUS and these diseases, further knowledge in the pathogenetic mechanism of these complex CNS diseases will be obtained.

Our data seem to confirm the pathogenetic role of MGUS (especially IgM) in some polyneuropathies, as shown by Bida et al. [32] for CIDP. Meanwhile, a pathogenetic link, and not only a chance occurrence, may be hypothesized between MGUS and late onset MS and any extrapiramidal disorders.

5. ACKNOWLEDGEMENTS

We thank Ms Tania Merlino for reviewing the English of this paper.

REFERENCES


