Journal of Neurology (2019) 266:1973–1979
https://doi.org/10.1007/s00415-019-09367-0

ORIGINAL COMMUNICATION

Relevance of anti-HNK1 antibodies in the management of anti-MAG neuropathies

Emilien Delmont[1] · Shahram Attarian[1] · Jean-Christophe Antoine[2] · Stephane Paul[3] · Jean Philippe Camdessanché[2] · Aude-Marie Grapperon[1] · Alexandre Brodovich[1,4] · Jose Boucraut[4]

Received: 23 March 2019 / Revised: 5 May 2019 / Accepted: 7 May 2019 / Published online: 14 May 2019

Abstract

Introduction In peripheral neuropathies with antibodies against Myelin Associated Glycoprotein (MAG), an IgM monoclonal gammopathy recognizes a specific epitope called Human Natural Killer 1 (HNK1) shared by NK lymphocytes and several components of the peripheral nerve myelin. Recently an ELISA test has been developed to detect antibodies against HNK1 epitope. Objectives were to determine the usefulness of this assay in the management of anti-MAG neuropathy.

Methods Anti-HNK1 antibodies were assessed with the GanglioCombi™ MAG ELISA test (Buhlmann) in 41 anti-MAG neuropathies and in 118 controls: 34 chronic inflammatory demyelinating polyradiculoneuropathies, 3 Miller Fisher syndromes, 12 sensory neuronopathies, 63 length-dependent axonal sensory polyneuropathies, 6 healthy controls. Anti-HNK1 antibody was tested before and 1 year after rituximab therapy in seven patients with anti-MAG neuropathy.

Results Anti-HNK1 antibodies were positive in 40/41 anti-MAG neuropathies, and in 1/118 controls (sensitivity 98%, specificity 99%). Only considering controls with IgM paraprotein, specificity was 96% (23/24). In anti-MAG neuropathies, anti-HNK1 titre was correlated with sensory deficiency evaluated with the INCAT sensory sum score ($r=0.4$, $p=0.01$) and with disability evaluated with the Rasch-built Overall Disability Scale ($r=-0.4$, $p=0.01$) and Overall Neuropathy Limitation Scale ($r=0.4$, $p=0.02$). Anti-HNK1 titres were not related to age, disease duration, atypical clinical features and anti-MAG antibodies titres. Anti-MAG titres were not associated with disease severity. Anti-HNK1 titres were decreased by 18% 1 year after rituximab treatment.

Conclusions Anti-HNK1 antibodies have good sensitivity and specificity for the diagnosis of anti-MAG neuropathy. Interestingly, anti-HNK1 titres are related to the disease severity and decrease after rituximab infusions.

Keywords Anti-MAG antibodies · Anti-HNK1 antibodies · Peripheral neuropathy · Biomarker

Introduction

Peripheral neuropathies with antibodies against Myelin Associated Glycoprotein (anti-MAG neuropathies) are chronic sensory neuropathies characterized by the presence of an IgM monoclonal gammopathy and high titres of anti-MAG antibodies [1]. Typical clinical features are foot paraesthesia, sensory gait ataxia and postural tremor. Muscle weakness is rare and when existent, it involves mainly the distal part of the legs [2]. Up to 24% of the patients may have atypical clinical features as proximal weakness, upper limbs' involvement and subacute progression [2–4]. The range of disability is wide, but most of the patients can walk independently [5, 6]. Nerve conduction studies usually show distal demyelination [7]. Nerve biopsy, when performed, reveals IgM deposits and widening of the peripheral myelin sheathes. There is no definitely recognized treatment but Rituximab (RTX) is often used for disabled patients [8, 9].

The diagnosis of anti-MAG neuropathy relies on the detection of anti-MAG antibodies in the patients 'serum. Western blot technique using bovine or human MAG

✉ Emilien Delmont
emilien.delmont@ap-hm.fr

1 Referral Centre for ALS and Neuromuscular Diseases, Hospital La Timone 264 rue Saint Pierre, 13005 Marseille, France

2 Department of Neurology and Referral Centre for Neuromuscular Diseases, Saint Etienne, France

3 Immunology Laboratory, Saint Etienne, France

4 Immunology Laboratory, Marseille, France

preparation was historically first used for antibody detection but it was less convenient and less sensitive than ELISA (enzyme-linked immunosorbent assay) kits [10]. The main issue with the ELISA technique is a loss of specificity with low titres of anti-MAG antibodies and the absence of correlation between anti-MAG titres and disease severity [2, 11].

The antigenic region of MAG is a specific carbohydrate epitope called Human Natural Killer 1 (HNK1), which comprises three sugar residues with sulphated modifications (sulfate-3-glucuronyl paragloboside) [12, 13]. This epitope is borne by natural killer (NK) lymphocytes and shared with several glycoproteins and glycolipids of the peripheral nerve myelin sheath (MAG, P0, PMP22, SGPG, SGLPG, and phosphocan) [14, 15]. The injection of a glycopolymer mimicking the natural HNK1 epitope led to the removal of the pathological antibodies in a mouse model of anti-MAG neuropathy [16].

In the classic ELISA assay the entire MAG protein is coated in the wells of the plates. A new assay has been developed using a synthetic HNK1 carbohydrate moiety. This test detects antibodies only directed against the HNK1 epitope of the MAG protein. The diagnostic accuracy of this test has not been evaluated in a large cohort yet. Our objective is, thus, to determine sensitivity and specificity of anti-HNK1 antibodies in the diagnosis of anti-MAG neuropathy and to know if their titres are correlated with disease severity.

Methods

Patients were followed in the Referral Centres for Neuromuscular diseases of Marseille or Saint Etienne in France. All patients gave informed consent. Clinical assessment and blood samples were part of their routine evaluation. Biological samples were provided by the Marseille Conception hospital immunology Bio-bank (authorisation number DC-2012-1704).

Patients with anti-MAG neuropathy fulfilled the EFNS/PNS diagnostic criteria [1]. They all have IgM monoclonal gammopathy and positive anti-MAG antibodies. The following data were collected: age, gender, duration of the disease, presence of IgM MGUS (monoclonal gammopathy of undetermined significance) or lympho-proliferative disease, 80-point Medical Research Council (MRC) sum score [6], Jamar grip dynamometry, 9 holes peg test, 10-meter timed walk, Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sum Score (ISS) [17], Overall Neuropathy Limitation Score (ONLS) [18], Rasch-built Overall Disability Score (RODS) [19], ataxia score [20], anti-MAG titres, dosage of the IgM monoclonal peak. Nerve conduction studies were performed on the median, ulnar, tibial, peroneal and sural nerves. Distal demyelination was considered as predominant if more than 2 nerves had a terminal latency index (TLI) above 0.25 [7].

Seven patients with anti-MAG neuropathy received two infusions of 1 g of rituximab (RTX) with a 15-days interval. Improvement was defined by a decrease of at least one point of the ONLS disability scale [9]. Anti-MAG and anti-HNK1 antibody titres were determined before treatment, and 6 months (M6) and 12 months (M12) after RTX therapy.

One hundred and eighteen controls were included in this study: 34 chronic inflammatory demyelinating polyradiculoneuropathies (CIDP), three Miller Fisher syndromes, 12 sensory neuronopathies, 63 length-dependent axonal sensory polyneuropathies and six healthy controls. Among CIDP patients, one patient had antibodies against nodal isoform of neurofascin [21], five patients had IgM isotype antibodies against GD1b ganglioside, one patient against GM1 ganglioside, one patient against GD1a ganglioside and three patients had an IgM monoclonal gammopathy and antibodies against disialylated gangliosides responding to the diagnosis of CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins and disialosyl antibodies) [22]. The patients with Miller Fisher syndrome had IgG isotype antibodies against GQ1b antibodies. Aetiologies of sensory neuronopathies were Sjogren syndrome (3), paraneoplatic (3), metabolic (1) and idiopathic (5). Healthy controls were blood donors. Among the controls, 24 patients had an IgM monoclonal gammopathy (four lymphoma and 20 MGUS) without anti-MAG antibodies: 12 CIDP, three CANOMAD, eight length-dependent axonal sensory polyneuropathies and 1 sensory neuronopathy.

Anti-HNK1 antibodies were measured with the GanglioCombi™ MAG ELISA test (Buhlmann) according to the manufacturer instructions. In brief, 100 microlitres of patient's serum diluted at 1/50 was incubated at 4 °C during 2 h in wells coated with synthetic HNK1 carbohydrate. After washing, peroxidase-labelled anti-human IgM antibody was applied for 2 h at 4 °C. Detection was performed using tetramethylbenzidine. Optical density was measured at 450 nm with a plate reader (Infinite F200, Tecan). The antibody titres were expressed as the percentage ratio of the absorbance of samples and the absorbance of the calibrator.

Anti-MAG antibodies were assessed with the Buhlmann ELISA test (Buhlmann Company). Anti-MAG antibodies were considered positive if the titre was above 4000 Buhlmann titre units (BTU). When the result of anti-MAG test was > 70,000 BTU, end-point dilution was performed to obtain the final antibody titre.

Quantitative data were expressed as mean with standard deviation and were compared using a Student's *T* test. Linear regression, Spearman correlation coefficient, and Receiver Operator Characteristic (ROC) analysis were performed using GraphPad Prism 5 (GraphpadInc, California,

USA) and IBM SPSS statistics (version 20). A two-sided p value < 0.05 was considered as significant.

Results

Forty-one patients with anti-MAG neuropathies were included (14 females and 27 males). Data are summarized in the Table 1. Thirty-five patients had a typical clinical phenotype and six patients had an atypical clinical phenotype: two patients with proximal muscle weakness in the lower limbs (MRC 4/5), three patients with distal muscle weakness of both upper and lower limbs, one patient with subacute onset. Nerve conduction studies results were available for 36 patients. One patient had an axonal neuropathy and 35 had a demyelinating neuropathy. Demyelination was predominant in the distal parts of the nerves in 25 patients. Seventeen patients received a chemotherapy prior to anti-HNK1 dosage (rituximab alone for 13 patients). All the patients had an IgM monoclonal gammopathy, eight with lambda light chain and 33 with kappa light chain. Twenty-nine patients had an MGUS and 12 a non-Hodgkin lymphoma or a Waldenstrom's macroglobulinemia. Mean anti-MAG titre was 132,000 BTU (184,000) and median 66,000 BTU, ranging from 4000 to 900,000 BTU.

Mean anti-HNK1 antibody titre was 105% (34) in anti-MAG neuropathies and 13% (13) in controls ($p < 0.0001$). According to the ROC analysis, a threshold of 50% gave the best balance of sensitivity and specificity (Fig. 1) for the diagnosis of anti-MAG neuropathy. Using a threshold of 50%, anti-HNK1 antibodies assay had a 98% sensitivity (40/41) and a 99% specificity (117/118), with only one false negative and one false positive results. Only considering the controls with an IgM monoclonal gammopathy and a neuropathy, the specificity was 96% (23/24).

The inappropriate negative result with the anti-HNK1 antibody test concerned an 82 years-old man with a 14-years history of sensory ataxia and mild distal motor weakness of the four limbs. Initial explorations revealed an IgM kappa MGUS, a positive Western blot against human MAG and a

Table 1 Characteristics of the 42 patients with anti-MAG neuropathy and correlation with anti-MAG and anti-HNK1 antibodies titres

		Correlation with anti-HNK1 titres	Correlation with anti-MAG titres
Clinical assessment			
Age	72 years (10)	NS	NS
Disease duration	7 years (6)	NS	NS
ONLS	2 (2)	$r=0.36$, $p=0.02$	NS
RODS	70/100 (13)	$r=-0.43$, $p=0.01$	NS
ISS	4 (2)	$r=0.43$, $p=0.01$	NS
Ataxia score	1/3 (0.6)	NS	NS
9 holes peg test	33 s (26)	NS	NS
10 metres walk	10 s (3)	NS	NS
Grip test	29 kg (15)	NS	NS
MRC sum score	76/80 (6)	NS	NS
Biological assessment			
Anti-MAG titres	132,000 BTU (184,000)	NS	NS
Anti-HNK1 titres	105 (34)	–	NS
IgM peak quantification	2.4 g/l (2.8)	NS	–
Electrophysiological assessment			
CMAP sum score	24 mV (14)	NS	NS
SNAP sum score	19 microV (17)	NS	NS
Mean median motor conduction velocity	37 m/s (10)	NS	NS
Mean ulnar motor conduction velocity	42 m/s (12)	NS	$r=0.41$, $p=0.02$
Mean median distal latency	8 ms (1.9)	NS	NS
Mean ulnar distal latency	4.9 ms (1.9)	NS	NS
Mean median TLI	0.19 (0.1)	NS	NS
Mean ulnar TLI	0.3 (0.06)	NS	NS

NS non-significant, *ONLS* overall neuropathy limitations scale, *RODS* rasch-built overall disability scale, *ISS* INCAT sensory scale, *r* Spearman's correlation coefficient, *pp* value, *HNK1* human natural killer 1, *MAG* myelin-associated glycoprotein, *TLI* terminal latency index, *CMAP* sum score, addition of distal motor amplitude of the median, ulnar, tibial and fibular nerves, *SNAP* sum score, addition of distal sensory amplitude of the median, ulnar and sural nerves, *ms* milliseconds

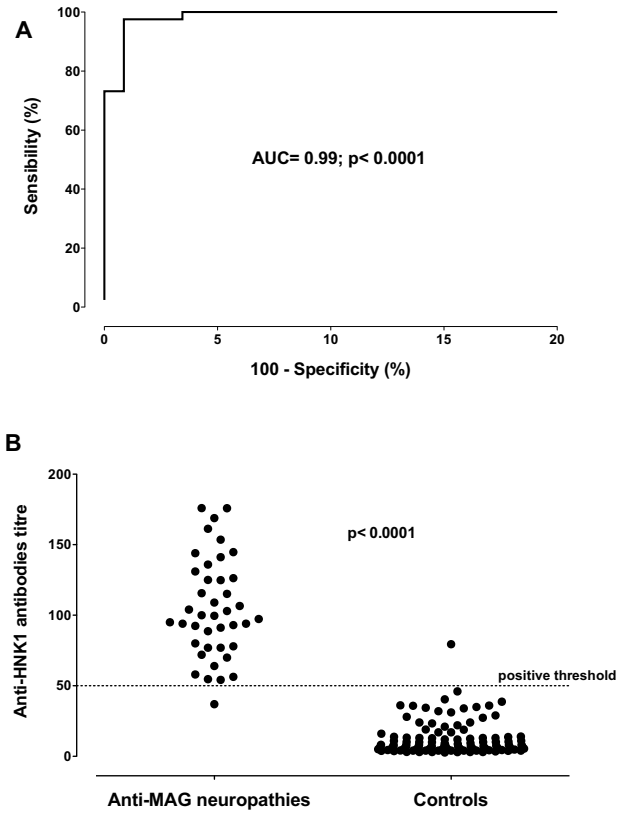

Fig. 1 **a** ROC curve for diagnostic accuracy of anti-HNK1 antibodies in anti-MAG neuropathies. **b** comparison of anti-HNK1 antibodies titres in anti-MAG neuropathies and controls. The dotted line represents the positive threshold of 50%. *ROC* receiver operating characteristic, *AUC* area under the curve, *HNK1* human natural killer 1, *MAG* myelin-associated glycoprotein

distal demyelinating sensory and motor neuropathy on nerve conduction studies. The patient never received any chemotherapy nor intravenous immunoglobulins. Nowadays, the patient has a severe sensory and motor neuropathy with distal muscle atrophy of the four limbs. Nerve conduction study shows a sensory and motor axonal loss. Current analysis displays positive anti-MAG antibodies (titre 119,000 BTU). Anti-HNK1 antibodies are negative (titre 37%) on the first analysed sample and slightly positive (titre 54%) on a control sample (positive if > 50%). The monoclonal IgM dosage is 1.7 g/l without evidence of haematological malignancy. This patient has an uncommon anti-MAG neuropathy because of the early motor involvement and the severity of the axonal loss.

The inappropriate positive result with the anti-HNK1 antibody test corresponded to a 74 years-old woman suffering from CANO34MAD [22]. Clinical examination showed sensory gait ataxia, Achilles tendon areflexia and foot hypoesthesia. Nerve conduction study displayed conduction blocks and reduced sensory and motor action potential amplitudes. Biological analysis revealed an IgM kappa MGUS and positive anti-ganglioside antibodies against both GD1b and GQ1b. Anti-HNK1 antibodies titre was 80% and anti-MAG antibodies were equivocal with a titre of 1,420 BTU [10].

There was no correlation between the titres of anti-MAG and anti-HNK1 antibodies (Table 1 and Fig. 2). Anti-MAG antibody titre was only related to mean ulnar motor conduction velocity at the forehand ($r = 0.41$, $p = 0.02$). There was no correlation between the anti-MAG titre and any of the clinical scores or other biological data (Table 1). The anti-MAG antibody titre was similar in patients with typical and atypical clinical features (152,000 vs 151,000 BTU, p = 1).

In patients with anti-MAG neuropathies (Table 1 and Fig. 2), the anti-HNK1 antibody titre was correlated with the sensory deficit evaluated with the ISS score ($r = 0.43$, $p = 0.01$) and with disability measured with the ONLS score ($r = 0.36$, $p = 0.02$) and the RODS score ($r = -0.43$, $p = 0.01$). The anti-HNK1 antibody titre was not related to age, disease duration, presence of a MGUS or a lymphoma, prior administration or not of a chemotherapy, 9 holes peg test, 10-m walk test, grip test, ataxia score, MRC testing, level of the IgM monoclonal peak and electrophysiological analysis. The anti-HNK1 antibody titre was similar in patients with typical and atypical clinical features (94% vs 100%, $p = 0.69$).

Seven patients with anti-MAG neuropathy received RTX (Fig. 3). Four patients improved at 1 year of follow-up. The Mean ONLS score was decreased by 34%, the mean anti-HNK1 titres decreased by 18% and anti-MAG titre remained relatively stable (increase of 3%) one year after RTX therapy.

Discussion

The objective of this study was to evaluate the sensitivity and specificity of anti-HNK1 antibodies in the diagnosis of anti-MAG neuropathy and to search if the anti-HNK1 titres were related to the severity of the neuropathy.

In the anti-MAG ELISA assay, the entire MAG protein is coated in the well of the ELISA plates, meanwhile only a synthetic HNK1 component is coated in the well of the anti-HNK1 ELISA plates. As the HNK1 epitope is shared by several structures of the peripheral nerves [15], the major issue of anti-HNK1 antibody detection could have been a loss of specificity with sera containing antibodies against other myelin components as P0, PMP22 or SGPG [23, 24]. To evaluate the accuracy of this test, we included a large cohort of controls who can be misdiagnosed with anti-MAG neuropathy: sensory neuropathies or neuropathies associated with IgM monoclonal gammopathy or with anti-ganglioside antibodies. Controls without paraproteins were included because a recent study demonstrated that the prevalence of the anti-MAG antibody in chronic demyelinating neuropathy

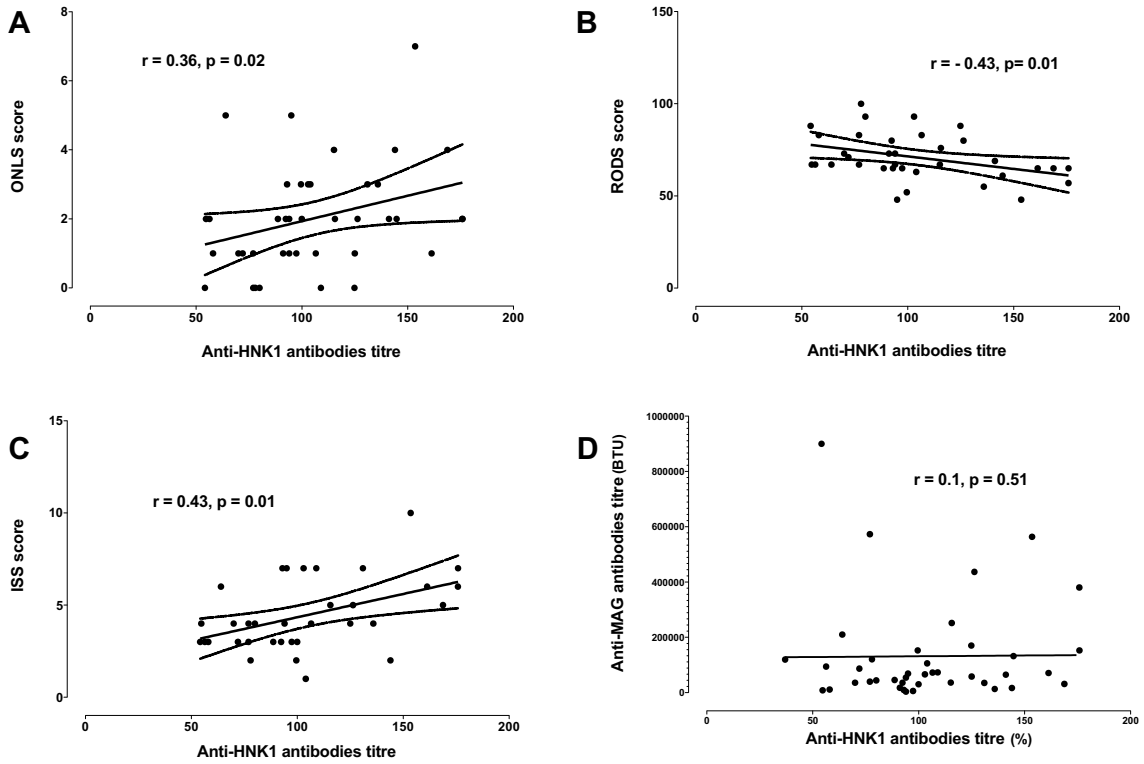

Fig. 2 Linear regression between anti-HNK1 antibodies titres and ONLS score (**a**), RODS score (**b**), ISS (**c**) and anti-MAG antibodies titres (**d**). Graphs show best-fit line and 95% confidence band of best-fit line (dotted line). *ONLS* overall neuropathy limitations scale, *RODS* rasch-built overall disability scale, *ISS* INCAT sensory scale, *r* Spearman's correlation coefficient, *pp* value, *HNK1* human natural killer 1, *MAG* myelin-associated glycoprotein

without any detectable M-protein was 5.6%, and concluded that anti-MAG antibody might be detectable earlier than the M-protein [25].

All but one control were negative for anti-HNK1 antibodies, which led to an excellent specificity of 99% (117/118) considering all the controls and 96% (23/24) only considering the controls with a neuropathy and an IgM paraprotein. The inappropriate positive anti-HNK1 result was in a patient suffering from CANOMAD syndrome with an IgM monoclonal gammopathy, anti GD1b and GQ1b antibodies. The anti-MAG ELISA assay was also equivocal with this sample in this patient. It has been demonstrated that for titre below 10,000 BTU, the anti-MAG ELISA assay can similarly give false-positive results, mainly due to a cross reaction with antibodies against GM1 and disialylated gangliosides [11]. The most specific test to detect anti-MAG antibody is a Western blot using human MAG, but this assay was less sensitive and less convenient as a routine test in a study which compared Western blot and ELISA techniques [10]. Nowadays, the anti-MAG ELISA assay is more often used to detect anti-MAG antibodies. For example the diagnosis of anti-MAG neuropathy was based on this technique in the recent report of 202 anti-MAG neuropathies [2] and in the last therapeutic trials with rituximab [20].

Anti-HNK1 ELISA assay had a good sensitivity of 98% (40/41). Only one patient with anti-MAG neuropathy was not positive with this technique. The assay was negative on a frozen sample and was slightly positive on a fresh sample, suggesting that conservation of the sera may be an issue in the detection of these antibodies. Another hypothesis is that this patient's anti-MAG antibody is directed against a peptide epitope of the MAG and not the HNK1 carbohydrate moiety. Actually, immunisation of animals with human MAG leads to generation of different anti-MAG antibodies which react either with the protein or the carbohydrate epitope of the MAG [26].

The structure of the HNK1 epitope depends on the carrier glycoprotein. It can be a N-glycan structure as on GluA2 (subunit of AMPA receptor), a O-mannose-linked glycan structure as on phosphocan or a specific structure as in aggrecan [15]. Antibodies of anti-MAG neuropathy patients exhibit differential affinity against the different HNK1 epitopes as illustrated in one study which compares the affinity against phosphocan and MAG [12]. This difference of immunogenicity may explain why the titres of anti-MAG and anti-HNK1 antibodies are not correlated in our study.

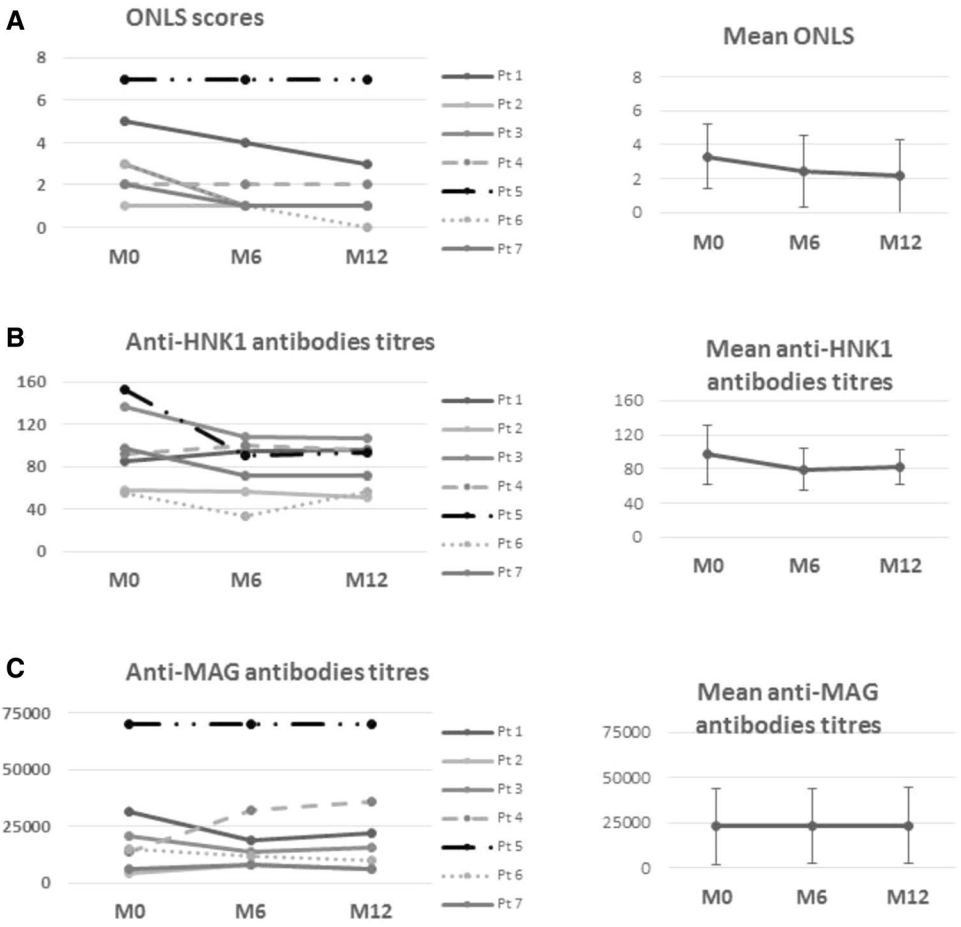

Fig. 3 Evaluation of 7 patients with anti-MAG neuropathy after rituximab therapy during a 12 months follow-up. ONLS (**a**), anti-HNK1 (**b**) and anti-MAG (**c**) titres were determined before treatment, 6 months (M6) and 12 months (M12) after RTX therapy. *ONLS* overall neuropathy limitations scale, *HNK1* human natural killer 1, *MAG* myelin-associated glycoprotein

Anti-HNK1 titres are correlated with sensory deficiency and disability whereas anti-MAG antibody titres have never been associated with the severity of the disease neither in previous studies nor in this one [2, 6]. Only one study [12] showed that the patients with anti-MAG antibodies more reactive to phosphocan than to MAG had a more severe disease. Titres of anti-HNK1 and anti-MAG antibodies were similar in patients with typical and atypical clinical features.

Anti-MAG neuropathies are usually treated with rituximab [8], which decreases the titres of anti-MAG antibodies [9, 20, 27, 28]. In this study, rituximab also induced a decrease of anti-HNK1 antibodies titres in 7 treated patients. Relation between the rituximab therapy and the initial titre of anti-MAG antibodies is not obvious: efficacy had been associated with a high titre of anti-MAG antibodies in two studies [2, 27], with low titres of anti-MAG antibodies in another study [29] and we did not find any correlation in a retrospective analysis performed in our department [9]. The present study was not designed to assess if the anti-HNK1 antibody titre was correlated with the efficacy of the rituximab therapy.

This study provides evidence that anti-HNK1 antibodies have high sensitivity and specificity in the diagnosis of anti-MAG neuropathy. We suggest that anti-HNK1 assays may be used to diagnose anti-MAG neuropathy instead of ELISA or Western blot using human MAG substrate. As anti-HNK1 antibody titres are correlated with disease severity, we hypothesize that they may be tested for the monitoring of patients in routine or as secondary outcomes measures in clinical trials. However, these results need to be confirmed in a larger prospective cohort.

Compliance with ethical standards

Conflicts of interest The author declares that there is no competing interest.

Ethical standards This study was in compliance with the ethical principles of the conference of Helsinki.

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