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Neuropathy of the phrenic nerve associated with antiganglioside antibodies

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Abbreviations

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ANCA: anti-neutrophil cytoplasmic antibodies; ANA: Antinuclear Antibodies; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; CMAP: Compound Motor Action Potential; CSF: Cerebrospinal Fluid; EMG: Electromyography; FVC: Functional Vital Capacity; GBS: Guillain-Barré syndrome MMN: Multifocal Motor Neuropathy; MR: Medical Resonance; NIV: Non-Invasive Ventilation; PE: Plasma Exchange;

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Abstract

Background: Antiganglioside antibodies have been implicated in several auto-immune mediated neuropathies and binding of these antibodies can result in inflammatory changes of the nerves. Diaphragmatic paralysis is a rare condition, mostly arising from diseases affecting the phrenic nerve, neuromuscular junction or skeletal muscle.

Objectives: In this case series, we identified five patients with diaphragmatic paralysis due to unilateral or bilateral neuropathy of the phrenic nerve associated with the presence of antiganglioside antibodies (IgG anti-*GT1a* antibodies and IgM anti-*GM1* antibodies).

Discussion: The combination of an isolated phrenic nerve palsy with anti-*GM1* antibodies has only once been described. On the other hand, the association of anti-*GT1a* antibodies with a phrenic nerve palsy has never been reported before.

Conclusions: We report an association between phrenic nerve palsy and the presence of antiganglioside antibodies, but it remains unclear if there is a causal relationship. Further studies are needed to explore this matter.

Introduction

Gangliosides are glycosphingolipids that are present in large quantity in the nervous system and play a role in proper cell signaling and neuroplasticity. Binding of antibodies to gangliosides may elicit inflammatory changes resulting in nerve conduction blocks and axonal degeneration.¹ Antiganglioside antibodies have been implicated in several auto-immune mediated neuropathies such as Guillain-Barré syndrome (GBS), multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). This field of research is rapidly developing and numerous antibody-phenotype associations have been described.²

Diaphragmatic paralysis is a rare condition, mostly arising from diseases affecting the phrenic nerve, neuromuscular junction or skeletal muscle. Phrenic nerve palsy is a common feature of GBS, but has been only rarely reported in association with CIDP or brachial plexopathy. A few case series reported patients with CIDP and phrenic nerve palsies, but none of these patients were reported to have positive antiganglioside antibodies.³

In this case series, we identified five patients with diaphragmatic paralysis due to unilateral or bilateral neuropathy of the phrenic nerve associated with the presence of antiganglioside antibodies (*Table 1 and Supplementary table 1*).

Cases

Case 1

This currently 65-year old patient progressively developed dyspnea and orthopnea over a period of one year at the age of 45 years. He had no other neurological signs or symptoms. His medical history was unremarkable (in particular no cervical spine injury or cardiothoracic surgery). Electrodiagnostic studies (with nerve conduction studies of the bilateral phrenic nerve) confirmed the clinically and radiologically suspected bilateral neuropathy of the phrenic nerve and ruled out a generalized neuropathy. Biochemically we detected antiganglioside antibodies against *Gt1a* (IgG, 1/1000). Antinuclear antibodies (ANA) were negative and MR imaging of the cervical spine was normal. Cerebrospinal fluid (CSF) analysis was not performed. He was treated with nocturnal non-invasive ventilation (NIV) since the age of 61 years with a stable further clinical course.

Case 2

This 60-year-old man progressively developed dyspnea and episodes of loss of consciousness over a period of less than two years. He concomitantly suffered from Parkinson's disease, with no other medical or surgical history. On examination we found areflexia and a loss of vibration in the lower limbs. Electrodiagnostic studies showed a right phrenic nerve palsy and a mild sensorimotor axonal polyneuropathy. Serum antiganglioside antibodies against *GM1* (IgM 1/200) and *GM4* (IgG 1/1000) were identified. CSF analysis showed no pleocytosis, nor other abnormalities. MR imaging of the cervical spine was not performed. He received five sessions of plasma exchange (PE), without any improvement on follow-up.

Case 3

The third patient first developed a left recurrent nerve palsy at the age of 35 years, a left phrenic nerve palsy three years later and a right recurrent nerve palsy another three years later. At 44 years of age he developed a brachial plexopathy. Antiganglioside antibodies in serum against *GT1a* (IgG 1/2000) were found, the titer remained stable at follow-up 4 months later. In addition, *GQ1b* (IgG 1/500) were identified but only at follow-up after 4 months. MR imaging of the cervical spine, CSF analysis and imaging of the thorax excluded other causes of the phrenic nerve palsy. Additionally he had no other relevant medical history. He received PE without any effect. He died at the age of 48 years of an unknown cause.

Case 4

Over a period of seven years this female patient gradually developed a right peripheral facial palsy, a left peroneal neuropathy and dyspnea due to a left phrenic nerve palsy since the age of 47 years. In her medical history she suffered from degenerative changes in the cervical spine, without evidence for C3-C5 root compression. Antiganglioside antibodies against *GT1a* (IgG 1/5000) were positive. ANA and anti-neutrophil cytoplasmic antibodies (ANCA) were negative and CSF finding were normal. Electrodiagnostic studies showed no signs of a diffuse polyneuropathy. A treatment with PE was tried, without any clinical benefit.

Case 5

This 75-year-old man suffered from mild dyspnea since several years, but experienced a subacute increase in dyspnea over one month. He had no relevant medical history. On examination there were no other neurological signs. Radiologically a left diaphragmatic paralysis was suspected, which later was confirmed

on electrodiagnostic studies. Imaging of the thorax and immunological parameters revealed no alternative cause. CSF analysis and imaging of the cervical spine were not performed. We detected antiganglioside antibodies against *GM1* (IgM, 1/1000). He received respiratory muscle training with a good clinical benefit.

Discussion

We present three cases with a phrenic nerve palsy with IgG anti-*GT1a* antibodies (of which one with also anti-*GQ1b* antibodies) and two cases with IgM anti-*GM1* antibodies (of which one with also anti-*GM4* antibodies). Three patients received PE without any clinical benefit. Remarkably, three cases presented with an isolated phrenic nerve palsy without any other neurological abnormalities. All patients had a slow clinical progression of the diaphragmatic paralysis, not compatible with GBS or with a paraneoplastic disorder. Hence, antineuronal antibodies were not checked in these cases.

The laboratory used an antiganglioside dot immunoassay (GA Generic Assays GmbH, Berlin, Germany) The purpose of this immunoassay is the multiparametric detection of antiganglioside autoantibodies. In patient 1-4 the dots were evaluated visually, in patient 5 automatically.

The presence of selective IgG anti-*GM1* antibodies is rare, but when present it is strongly associated with acute axonal motor neuropathies or chronic lower motor neuron syndromes.⁴ Anti-*GT1a* IgG antibodies frequently are described in association with the pharyngeal-cervical-brachial variant of GBS.⁵ The presence of antiganglioside antibodies in the healthy population has thus far not been thoroughly studied. Several studies however state that these antibodies can be detected in 1-9% of healthy volunteers. Sometimes after bacterial infections IgM anti-*GM1* antibodies can be found without any neurological complaints.⁶

The combination of an isolated phrenic nerve palsy with anti-*GM1* antibodies has only once been described.⁷ On the other hand, the association of anti-*GT1a* antibodies with a phrenic nerve palsy has never been reported before. Although low or moderately elevated antibody titers are not specific, high titers (as we observed in the patients with anti-*GT1a* antibodies) usually suggest a dysimmune mechanism.⁴ However, at present it is still unclear if there is any causal relationship between the neuropathy of the phrenic nerve and the presence of the antiganglioside antibodies in the blood. Further studies are needed to explore this possible causal relationship.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Statement on ethics approval

The case series was approved by the ethics committee of the university hospitals Leuven (S50354).

Table 1

	Age of onset (year)	Clinical features	Elevation of hemidiaphragm on Chest X-ray	FVC seated / supine	Antibodies (with titer)	Treatment
Case 1	45	Bilateral phrenic nerve palsy	L > R	2,13 l (48%) / 1,3 l (29%)	Anti-Gt1a (IgG, 1/1000)	NIV
Case 2	60	Right phrenic nerve palsy and mild sensorimotor axonal polyneuropathy	R	2,58 l (63%)/ 2,06 l (50%)	Anti-GM1 (IgM 1/200) Anti-GM4 (IgG 1/1000)	Plasma exchange
Case 3	35	Bilateral recurrent nerve palsy, left phrenic nerve palsy and brachial plexopathy	L	3,33 l (76%) / -	Anti-GT1a (IgG 1/2000) Anti-GQ1b (IgG 1/500)	Plasma exchange
Case 4	47	Left peripheral facial palsy, left peroneal palsy and right phrenic nerve palsy	L	3,97 l (119%)/ 3,55 l (108%)	Anti-GT1a (IgG 1/5000)	Plasma exchange
Case 5	75	Left phrenic nerve palsy	L	2,42 l (67%)/ 2,07 l (57%)	Anti-GM1 (IgM, 1/1000)	Respiratory muscle training