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Distal acquired demyelinating symmetric neuropathy associated with anti-GM1 and anti-GD1b antibodies

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Distal acquired demyelinating symmetric (DADS) neuropathy is a variant form of chronic inflammatory demyelinating polyradiculoneuropathy. A 54-year-old man presented with gait disturbance owing to weakness in both legs. Nerve conduction studies showed demyelinating sensorimotor polyneuropathy, and laboratory studies demonstrated anti-GM1 and anti-GD1b IgG antibodies, but no anti-myelin associated glycoprotein activity. We suggest that an antiganglioside antibodies assay needs to be applied when DADS neuropathy is suspected in order to improve the classification of dysimmune neuropathies.

Key words: Gangliosides; Antibodies; Demyelination; Neuropathy

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The clinical hallmark of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is the presence of both proximal and distal weakness. Patients with both proximal and distal motor involvement are highly likely to respond to corticosteroids, irrespective of the presence or absence of a serum paraprotein.[1] Another well-documented group of patients with symmetric, acquired, demyelinating polyneuropathies predominantly presents with sensory involvement. When weakness is present, it is limited to distal muscle groups in a length-dependent fashion. Distal acquired demyelinating symmetric (DADS) neuropathy is an acquired demyelinating polyneuropathy that presents with distal, symmetric, and predominantly sensory or sensorimotor involvement.[2] DADS neuropathy is usually most strongly associated with IgM anti-myelin associated glycoprotein (MAG) antibody at significant titers.[3] The role of antiglycolipid antibodies in the pathophysiology of peripheral neuropathy and their association with particular clinical phenotypes continues to be a source of informative case reports, clinical-serological studies and basic research. Antibodies to a wide range of gangliosides, including GM1 and GD1b, have been reported for Guillain-Barré syndrome and chronic inflammatory neuropathies.[4] To our knowledge, there are few case reports on the presence of anti-ganglioside antibodies in DADS neuropathy.[5,6]

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CASE

A 54-year-old man presented with gait disturbance owing to weakness in both distal legs. He had first noticed weakness about 3 years previously and his symptoms had progressed insidiously to foot drop. Motor symptoms were preceded by both foot hypoesthesia and a tingling sensation, although the patient was not aware of the exact time of onset. For several months preceding admission, the patient had complained of clumsiness and numbness in both hands. His family history was unremarkable. Symmetric weakness of ankle dorsiflexion, eversion (Medical Research Council [MRC] grade 3) and plantar flexion (MRC grade 4) were observed, but the proximal muscle power strength was normal, including of the knees and hips. Muscle atrophy was evident in both anterior compartments of the lower leg, and was equivocally present in the first inter-digital web space of both hands. Mild motor weakness was observed in finger spreading and hand grip power (MRC grade 4). A sensory examination revealed hypoesthesia of touch and vibration senses below the knee and elbow, but the pain sense was preserved. Deep tendon reflexes were absent in both ankles, and were hypoactive in both biceps brachii and quadriceps. The cranial nerve function was normal.

Nerve conduction studies showed demyelinating sensorimotor polyneuropathy (Table 1). The findings of blood tests for serum antinuclear antibody titer, anti-Ro/La antibody, anti- double strand-DNA antibody, and fluorescent antinuclear antibody were all negative. Examination of the cerebrospinal fluid revealed typical albuminocytological dissociation and a protein level of 85 mg/dL, but no inflammatory cells. Other laboratory data, including protein and immunofixation electrophoresis, revealed no abnormal patterns. A well-established enzyme-linked immunosorbent assay was applied for the qualitative determination of IgG and IgM antibodies against angliosides. We determined the presence of antibodies against GM1, asialo-GM1, GD1a, GD1b, GT1a, and GQ1b gangliosides, using 96-well microtiter plates coated with individual gangliosides. Serial dilutions were made (from 1:50 to 1:200) and each sample was analyzed in duplicate. A positive and a negative control consisting of a serum sample, produced by the manufacturer, were included in the assay. Anti-MAG antibody was negative, but serum anti-GM1 IgG antibody (31 EU/mL), and anti-GD1b IgG antibody (43 EU/mL) were positive. Genetic analyses of peripheral myelin protein 22 and myelin protein zero mutations produced normal findings. We conducted nerve conduction studies in family members of the patient including two sons and one daughter. The results were unremarkable.

The patient was treated with intravenous IgG at 0.4 g/kg for 5 days. There was no improvement in motor weakness or sensory symptoms for 3 months after IgG therapy. After that, oral prednisolone was administered at an initial dosage of 1 mg/kg per day. However, the electrophysiological results, sensory symptoms, and weakness did not show any improvement even after 6 months of steroid therapy.

DISCUSSION

Previous studies have categorized DADS neuropathy primarily on the basis of the presence of an IgM M-protein or antibodies reactive to MAG; most patients with a DADS neuropathy phenotype will have a monoclonal gammopathy of unidentified significance, which is almost exclusively IgM.[2] Two-thirds of the patients with the DADS neuropathy phenotype can have an IgM-kappa paraprotein (DADS-M).[7] Although one-half to two-thirds of patients with DADS-M neuropathy carry anti-MAG antibodies,[8] the clinical differences with regard to management, prognosis, and pathophysiology between MAG-positive and MAG-negative DADS-M neuropathy remain unclear. The remaining one-third of patients with the DADS phenotype do not have M-protein; this group is referred as idiopathic DADS neuropathy (DADS-I).[7] According to these criteria, our patient would be classified as DADA-I. Individuals classified as DADS-I are heterogeneous and show a response to treatment that is intermediate between DADS-M and CIDP. The DADS-I neuropathy group may also include individuals with untreatable disorders, such as hereditary neuropathies. We differentiated our patient from hereditary neuropathy through genetic and family studies.

Our patient exhibited unequivocal motor weakness and sensory symptoms in the distal extremities, and did not respond to treatment with immunoglobulin and steroids. The more striking laboratory features of our patient were the presence of serum anti-GM1 IgG and anti-GD1b IgG antibod-

Table 1. Data obtained in the nerve conduction studies of the patient

Motor nerve conduction studies						
Nerve	**Latency (ms)**	**Amplitude (mV)**	**CV (m/s)**	**Latency (ms)**	**Amplitude (mV)**	**CV (m/s)**
Median, Rt/Lt						
Wrist	7.97 (< 3.60)	10.07 (> 5)		5.63	8.33	
Elbow		9.34	28.83 (> 49.96)		7.41	30.16
Axilla		9.11	41.35 (> 55.96)		7.21	42.87
Ulnar, Rt/Lt						
Wrist	6.41 (< 2.51)	12.04 (> 5)		5.94	13.05	
Elbow		10.33	29.28 (> 50.61)		11.04	30.39
Axilla		9.30	34.38 (> 52.69)		9.15	41.26
Tibial, Rt/Lt						
Ankle	10.16 (< 5.11)	3.04 (> 5)		10.94	4.80	
Knee		2.3	33.82 (> 40.63)		3.56	27.32
Peroneal, Rt/Lt						
Ankle	NR			NR		
Knee	NR			NR		
Sensory nerve conduction studies						
Nerve		**Amplitude (μV)**	**CV (m/s)**		**Amplitude (μV)**	**CV (m/s)**
Median, Rt/Lt						
Third digit		9.51 (> 10)	24.87 (> 41.26)		7.62	29.34
Wrist		23.65	35.71 (> 49.39)		13.11	35.54
Elbow		62.32	44.53 (> 53.90)		50.37	42.90
Ulnar, Rt/Lt						
Fifth digit		12.40 (> 10)	26.46 (> 39.26)		11.57	27.58
Wrist		24.35	34.32 (> 47.46)		21.50	35.16
Elbow		40.35	27.92 (> 48.18)		36.61	36.59
Sural, Rt/Lt						
Lateral malleolus, 14 cm		5.36 (> 6)	21.57 (> 34.68)		4.75	20.45

CV, conduction velocity; Lt, left; NR, no response; Rt, right; ( ), normal range.

ies. The scarcity of the reported cases may explain why little is known about the clinical, electrophysiological, and laboratory features of patients with DADS neuropathy without anti-MAG antibodies. Most commonly, anti-GM1 antibodies recognize the Galβ1-3GalNAc determinant and cross- react with GD1b ganglioside, asialo-GM1, and certain glycoproteins. Since GM1 is the only common glycolipid antigen that reacts with all of the anti-GM1 antibodies found in motor nerve disorders, it is likely to be the relevant target antigen in neural tissue.[9] Another known correlation between neurological symptoms and antibody specificity in patients with IgM monoclonal gammopathy is a sensory ataxic neuropathy being associated with antibodies that react with GD1b and other gangliosides having disialosyl moieties such as GD3, GD2, GT1b, and GQ1b. Despite anti-GM1 and anti-GD1b antibodies being associated with purely motor and purely sensory syndromes, respectively, these two gangliosides appear in remarkably similar proportions in motor and sensory nerves. Perhaps complex formation specific to the different nerve types might explain this apparent discrepancy. Furthermore, it is possible that potential antigenic targets have been overlooked due to the investigations focusing on assessing single

molecules, rather than considering their multifarious interactions in vivo.[10] In addition, study evidence and case reports supporting the aforementioned presumption are scarce. We could not convince whether the presence of anti-GM1 and anti-GD1b antibody has pathogenic role or not. Although these findings might be incidental, we think that the present case might play a role in broadening the spectrum of DADS.

We find the concept of DADS helpful, because it emphasizes the greater degree of uncertainty regarding treatment response as well as the need to consider a broader differential diagnosis in these patients, compared with those having a proximal and distal weakness phenotype. We report a DADS neuropathy, which is devoid of M-protein and anti-MAG antibodies, but positive for anti-GM1 and anti-GD1b IgG antibodies. We suggest that DADS neuropathy without anti-MAG antibodies, although sharing common features with anti-MAG DADS neuropathy, should be considered a variant of CIDP.

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REFERENCES

1. Barohn RJ, Kissel JT, Warmolts JR, Mendell JR. Chronic inflammatory demyelinating polyradiculoneuropathy. Clinical characteristics, course, and recommendations for diagnostic criteria. Arch Neurol 1989;46:878-884.
2. Katz JS, Saperstein DS, Gronseth G, Amato AA, Barohn RJ. Distal acquired demyelinating symmetric neuropathy. Neurology 2000;54:615-620.
3. Dimachkie MM, Barohn RJ, Katz J. Multifocal motor neuropathy, multifocal acquired demyelinating sensory and motor neuropathy, and other chronic acquired demyelinating polyneuropathy variants. Neurol Clin 2013;31:533-555.
4. O'Leary CP, Willison HJ. The role of antiglycolipid antibodies in peripheral neuropathies. Curr Opin Neurol 2000;13:583-588.
5. Larue S, Bombelli F, Viala K, Neil J, Maisonobe T, Bouche P, et al. Non-anti-MAG DADS neuropathy as a variant of CIDP: clinical, electrophysiological, laboratory features and response to treatment in 10 cases. Eur J Neurol 2011;18:899-905.
6. Remiche G, Kentos A, Mavroudakis N. Distal acquired demyelinating symmetric neuropathy associated with anti-GM1 antibodies: is this a CIDP variant? Acta Neurol Belg 2010;110:103-106.
7. Saperstein DS, Katz JS, Amato AA, Barohn RJ. Clinical spectrum of chronic acquired demyelinating polyneuropathies. Muscle Nerve 2001;24:311-324.
8. Nobile-Orazio E, Manfredini E, Carpo M, Meucci N, Monaco S, Ferrari S, et al. Frequency and clinical correlates of anti-neuronal IgM antibodies in neuropathy associated with IgM monoclonal gammopathy. Ann Neurol 1994;36:416-424.
9. Quarles RH, Weiss MD. Autoantibodies associated with peripheral neuropathy. Muscle Nerve 1999;22:800-822.
10. Rinaldi S, Willison HJ. Ganglioside antibodies and neuropathies. Curr Opin Neurol 2008;21:540-546.