CLINICAL AND LABORATORY FEATURES OF NEUROPATHIES WITH SERUM IgM BINDING TO TS-HDS

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ABSTRACT: *Introduction:* In this investigation we studied clinical and laboratory features of polyneuropathies in patients with serum IgM binding to the trisulfated disaccharide IdoA2S-GlcNS-6S (TS-HDS). *Methods:* We retrospectively compared 58 patients with selective IgM binding to TS-HDS to 41 consecutive patients with polyneuropathies without TS-HDS binding. *Results:* Patients with IgM vs. TS-HDS commonly had distal, sensory, axonal neuropathies. Weakness was associated with IgM M-proteins. Hand pain and serum IgM M-proteins were more common than in control neuropathy patients. TS-HDS antibody binding was often selectively κ class. Biopsies showed capillary pathology with thickened basal lamina and C5b9 complement deposition. IgM in sera with TS-HDS antibodies often bound to capillaries. *Conclusions:* Serum IgM binding to TS-HDS is associated with painful, sensory > motor, polyneuropathies with an increased frequency of persistent hand discomfort, serum IgM M-proteins, and capillary pathology. Serum IgM binding to TS-HDS suggests a possible immune etiology underlying some otherwise idiopathic sensory polyneuropathies.

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Serum IgM antibody binding to carbohydrate moieties on proteins and glycolipids is a marker for several chronic polyneuropathy syndromes. Well-defined clinical associations include IgM binding to myelin-associated glycoprotein (MAG) with demyelinating sensory–motor polyneuropathies[1,2] and to GM1 ganglioside with motor neuropathies.[3,4] We previously reported a small series of patients with serum IgM binding to IdoA2S-GlcNS-6S, a trisulfated heparin disaccharide (TS-HDS), who had a painful, predominantly sensory, polyneuropathy syndrome with axonal loss and serum IgM M-proteins.[5] In this study we document clinical and pathological features in 58 consecutive patients with selective high titers of serum IgM binding to TS-HDS and compare the results with 41 consecutive antibody-negative patients evaluated in our clinic within the same time period.

METHODS

To examine the associations of IgM binding to TS-HDS we measured titers in 2342 consecutive sera referred to our neuromuscular clinical laboratory over a period of 14 months. We reviewed charts of the 71 patients with high titers of serum IgM binding to TS-HDS ($\geq$10,000), and 41 controls, who had extensive clinical, electrodiagnostic, and laboratory evaluation in our neuromuscular center at Washington University, St. Louis. The 71 patients with IgM binding to TS-HDS were divided into 3 groups: 10 with concurrent serum IgM binding to MAG; 3 with asymmetric chronic motor neuropathies; and 58 with sensory or sensory–motor polyneuropathies. The 58 patients with sensory or sensory–motor polyneuropathies had evaluations for a possible etiology that included history of involvement of other family members or exposure to neurotoxic drugs or agents and laboratory testing for M-proteins (serum immunofixation methodology), neuropathy-related serum antibodies, hemoglobin A_{1C}, vitamin deficiencies, vitamins B_{12} and E, cryoglobulins, anti-nuclear antibody (ANA) and extractable nuclear antibody (ENA) evaluations, and hepatitis. Cerebrospinal fluid (CSF) was not evaluated. The 41 consecutive control neuropathy patients were tested in the same manner at the beginning of the same period and had sensory or sensory–motor polyneuropathies but no IgM binding to TS-HDS. Strength was reported according to the 5-point Medical Research Council (MRC) scale with 4/5 or less defining weakness. Qualitative evaluations of pin-prick and vibration sense were recorded. Vibration sense was quantitated using a Rydel–Seiffer tuning fork. Any demyelinating features on electrodiagnostic testing were categorized according to the presence of slowed nerve conduction velocities, conduction block, abnormal F-waves, or prolonged distal latencies.[4] Six patients with serum IgM binding to TS-HDS had nerve and muscle biopsies for evaluation of causes of neuropathy. Eight additional patients had muscle biopsies (deltoid or quadriceps), usually for the evaluation of discomfort or fatigue. None had weakness. One biopsied patient had diabetes, and another had treatment with intravenous immunoglobulin 6 months before the biopsy.

Standard Protocol Approval, Registration, and Patient Consent. The human studies committee of Washington University approved all procedures. Informed consent was not required.

Abbreviations: ANA, anti-nuclear antibody; CIDP, chronic inflammatory demyelinating neuropathy; CRP, C-reactive protein; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunoassay; ENA, extractable nuclear antibody; MAG, myelin-associated glycoprotein; MRC, Medical Research Council; SNAP, sensory nerve action potential; TS-HDS, trisulfated heparin disaccharide; UEA-1, *Ulex europaeus* agglutinin-1

Key words: heparin disaccharide, IgM antibody, M-protein, neuropathic, pain, sensory neuropathy

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Assay for IgM Binding to TS-HDS. Serum IgM binding to TS-HDS (IdoA-2S-GlcNS-6S; Sigma H9267) was assayed using an enzyme-linked immunosorbent assay (ELISA) method, as previously described, with covalent antigen linkage to Costar microwell ELISA plates (Nuclepore; Fisher Scientific).[4] To measure serum IgM binding to TS-HDS we used 0.5 μg of TS-HDS dissolved in 50 μl of 0.05% *N*-hydroxysuccinamide per well. Levels of selective binding to TS-HDS were calculated by subtracting levels of IgM binding to GD1a ganglioside, an antigen used in our laboratory to calculate background IgM binding for many carbohydrate-containing antigens, and histone H3.[6] High titers of selective IgM binding to TS-HDS ($\geq$10,000) were >4 standard deviations above the mean of a separate initial series of tests in sera from 20 control subjects. Serum IgM binding to MAG was carried out using Immulon II ELISA plates (Fisher 14-245-61).[7]

Antibodies, Pathology, and Immune Staining. Antibodies used in this study were to C5b9 complement (1:25; M0777; Dako, Carpinteria, California), collagen IV (1:40, polyclonal AB748; Chemicon, Billerica, Massachusetts), human kappa light-chain–peroxidase conjugate (1:1300; Sigma A-7164), human lambda light-chain–peroxidase conjugate (1:35,000; Sigma A-5175), and human IgM (1:1000, goat polyclonal IgG anti-human; MP Biomedicals, Solon, Ohio). Antibody binding was visualized using secondary antibodies conjugated to fluorescent markers (anti-mouse Alexa Fluor 488, 1:200, A11029; anti-goat Alexa Fluor 488, 1:200, A11055; and anti-rabbit Alexa Fluor 594, 1:200, A11037; all from Invitrogen, Carlsbad, California). For TS-HDS blocking experiments, patient sera, diluted to 1:2500 in polynorbonene (NEL701A; Perkin Elmer), were incubated for 2 hours at 37°C and then overnight at 4°C with TS-HDS at 10 mg/ml. For ultrastructure, tissues were processed as described elsewhere.[8]

Statistics. Fisher exact tests were used to calculate significance of differences between diagnostic groups. Statistical analysis was performed by one investigator (A.P.). Results are expressed as mean $\pm$ standard error. To correct for multiple comparisons only differences with $P < 0.01$ were considered significant.

Representative Patient. A 47-year-old woman developed burning and tingling sensations in her legs bilaterally, left more than right. Several years later similar symptoms began in the hands and arms. Muscle discomfort, which was worse at night and improved during physical activity, was diagnosed as fibromyalgia. The overall degree of discomfort became slowly worse. No weakness, gait impairment, or autonomic symptoms were noted. Pain was managed with acetaminophen and hydrocodone. Symptomatic treatments over 15 years with multiple other medications and two carpal tunnel release surgeries provided no benefit. Medical history included diagnoses of hypertension, hypothyroidism, arthritis, and gout. On examination, cranial nerves, strength, tendon reflexes, and cerebellar testing were normal. Sensation was decreased to pin-prick and scratch distally in a symmetric stocking-glove distribution. Vibration and proprioception sense were normal. Motor and sensory nerve conduction studies were normal in the arms and legs. Skin biopsy in the leg showed a reduced number of axons. Serum IgM binding to TS-HDS was present at a titer of 25,000 with κ but not λ light-chain reactivity. Immunofixation studies showed no M-protein. Extensive evaluations at several centers for possible other causes of neuropathy were negative, including family history, toxin exposure, ANA and ENA, sedimentation rate, C-reactive protein (CRP), vitamins B_{12} and E, diabetes, lipid disorders, copper, hepatitis, and cryoglobulins.

RESULTS

Features of 58 Sensory or Sensory–Motor Polyneuropathy Patients with Selective Serum IgM Binding to TS-HDS. The onset age of neuropathic symptoms, usually pain or numbness, in the 58 TS-HDS–positive polyneuropathy patients ranged from 16 to 83 years (mean 60 years) (Table 1). Thirty-one patients were women, and 27 were men. The symptom course was usually reported as slowly progressive. Symptom duration at presentation to our clinic ranged from 6 months to 21 years (mean 4.8 years). TS-HDS antibody–positive neuropathy patients had distal-predominant, symmetric sensory loss that involved the legs (100%) and often the arms (48%). Vibration sense at the toes was measured as reduced ($\leq$2) in 57% and absent in 17% of patients. Absent vibration sensation at the toes was more common ($P = 0.009$) in patients with an IgM M-protein (43%) than in those without (9%). Pain or persistent paresthesias were noted in 66% of patients, involving both the hands and legs in 40%. Weakness, usually confined to the feet or toes, was present in 22% and was more common ($P = 0.00009$) in TS-HDS patients with serum IgM M-proteins (64%; 9 of 14) than in those without (9%; 4 of 44). Sural sensory nerve action potential (SNAP) amplitudes were reduced in 55% of patients and were absent in 41%. No patient had electrodiagnostic evidence of nerve entrapment or focal nerve damage that could explain the hand pain or distribution of sensory loss. At least one demyelinating feature on nerve conduction studies was present in 16% of the patients. Demyelinating features were more common ($P = 0.0003$) in

Table 1. Clinical and laboratory features of sensory or sensory-motor polyneuropathy patients..

	TS-HDS Ab^+			
	MAG Ab^+	MAG Ab^-	TS-HDS Ab^- control	*P*–value: TS-HDS Ab^+ and MAG Ab^- vs. TS-HDS Ab^-
Total no. of patients	10	58	41	
Age (mean ± SE)	62.3 ± 3.6	59.8 ± 1.8	56.4 ± 2.4	0.3
Sensory loss				
Legs	10	58	41	1.0
Arms	8	28	15	0.31
Vibration loss (quant)	10	33	30	0.14
Discomfort				
Legs	8	38	21	0.21
Arms	4	23	3	0.0004
Weakness (distal)				
Legs	5	13	11	0.64
Arms	5	7	4	1.0
Symmetric	10	52	40	0.23
Diabetes	1	7	12	0.04
Sural SNAPs (abnormal)	10	32	22	1.0
Demyelination	9	9	3	0.3
IgM M-protein	10	14	1	0.003

Sensory loss: reduced vibratory or pin-prick sense in distal extremities on examination. Vibration loss (quant): reduced vibration sense at toes measured with a Rydel-Seiffer tuning fork. Discomfort: pain or other discomfort reported as present at the time of initial evaluation. Sural SNAPs (abnormal): sural sensory nerve action potential amplitudes abnormal. TS-HDS: trisulfated heparin disaccharide. Ab^+: antibody present at high titer in serum; Ab^-: antibody not present at high titer in serum. MAG: myelin-associated glycoprotein. Demyelination: presence of slowed nerve conduction velocities, conduction block, or prolonged distal latencies.

patients with IgM M-proteins (50%; 7 of 14) than in those without (5%; 2 of 44). The specific demyelinating features in individual patients were variable and often mild. Five of the 9 patients with demyelinating features had prolonged distal motor latencies. Two of these patients had prominent distal demyelination with generally abnormal terminal latency indices, slowed nerve conduction velocities, and no conduction block; this is the pattern typically seen in patients with IgM binding to MAG.[9,10] Other demyelinating features included focal motor conduction block (4 patients), variably slowed conduction velocities (3 patients), and selectively prolonged F-wave latencies (1 patient). Other positive results from evaluations for possible etiologies underlying the neuropathies were diabetes (7 patients) and a positive ANA (6 patients) or SSA (3 patients).

ELISA and Serum Testing. Titers of IgM binding to TS-HDS in positive sera ranged from 10,000 to 800,000. TS-HDS titers averaged fivefold higher ($P < 0.000001$) in patients with IgM M-proteins (131,500 ± 55,428) than in those without (25,591 ± 4642). There was no relation between TS-HDS titers and the severity of vibratory loss. TS-HDS titers averaged higher in patients with weakness (123,923 ± 59,815) than in those without (33,391 ± 5866), but the difference was not significant ($P = 0.08$). Serum IgM M-proteins were κ in 9 patients and λ in 5. In 9 patients with κ IgM M-proteins, TS-HDS binding was selectively κ in 8 and both κ and λ in 1. In 5 patients with λ IgM M-proteins, TS-HDS binding was all κ in 3, both κ and λ in 1, and all λ in 1. In 32 TS-HDS sera with no M-proteins detected by immunofixation TS-HDS, binding was all κ in 26, both κ and λ in 5, and all λ in 1.

Comparison of Features of Sensory–Motor Neuropathies in Patients with Selective IgM Binding to TS-HDS to Antibody-Negative Controls. We compared the 58 sensory–motor neuropathy patients with selective serum IgM binding to TS-HDS to the 41 consecutive control neuropathy patients with no IgM binding to TS-HDS (Table 1). A history of persistent hand pain or paresthesias was fivefold more common ($P = 0.0004$) in patients with IgM binding to TS-HDS (40%) than in the antibody-negative polyneuropathy controls (7%). Serum immunofixation showed IgM M-proteins tenfold more frequently ($P = 0.003$) in patients with IgM binding to TS-HDS (24%) than in the antibody-negative neuropathy controls (2%). Demyelinating features on electrodiagnostic studies were more common ($P = 0.001$) in the subgroup of 14 patients with both selective serum TS-HDS binding and serum IgM M-proteins (50%) compared with the 41 controls (2%). There was a trend toward less frequent diabetes ($P = 0.04$) identified in patients with selective IgM binding to TS-HDS. The ages and frequency of distal weakness and discomfort in the legs were similar in TS-HDS patients and antibody-negative neuropathy controls (Table 1). Other similarities between the TS-HDS and control groups included disease duration; frequency and severity of weakness and vibratory

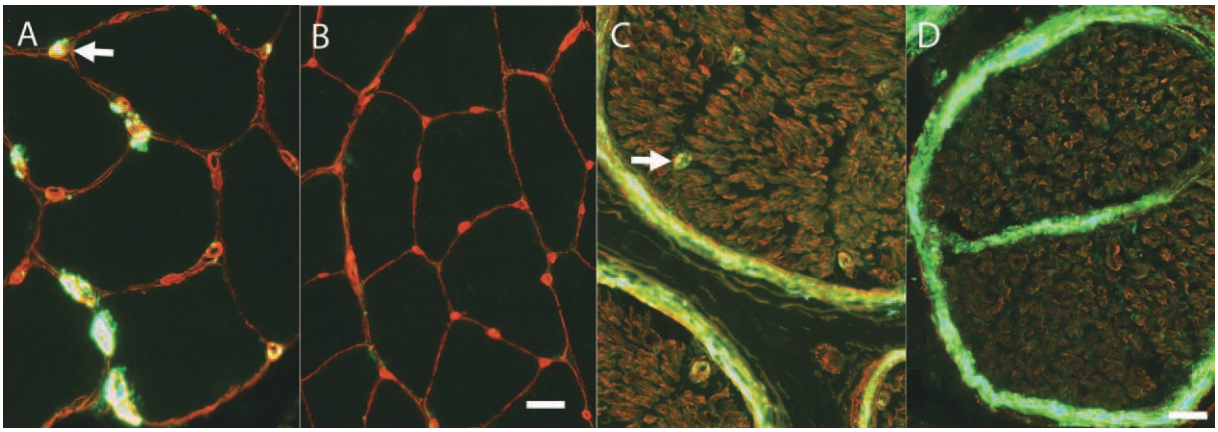

FIGURE 1. C5b9 complement deposits on capillaries in patients with IgM vs. TS-HDS. Staining of muscle and nerve is shown: C5b9 (green) and collagen IV (red). Overlap in the distribution of C5b9 and collagen IV is yellow. (**A**) Muscle from a patient with serum IgM binding to TS-HDS shows prominent C5b9 complement deposits on some endomysial capillaries (arrow and yellow). (**B**) Control muscle with no C5b9 complement deposits on endomysial capillaries. (**C**) Nerve from patient with serum IgM binding to TS-HDS showing prominent C5b9 complement deposits on endoneurial capillaries (arrow and yellow). (**D**) Control nerve with no C5b9 complement deposits on endoneurial capillaries. Perineurium normally stains for C5b9 (**C**, **D**). Bar = 25 μm for (**A**) and (**B**); bar = 38 μm for (**C**) and (**D**).

sense loss; frequency of foot pain; associated neoplasms (other than M-proteins); laboratory changes, including ANA and ENA; vitamin deficiencies (not found in either group); and electrodiagnostic results, such as normal nerve conduction studies, absent or abnormal SNAPs, demyelination, and evidence of entrapment syndromes.

Features of 13 Other Patients with Serum IgM Binding to TS-HDS. Ten patients had serum IgM binding to both TS-HDS and MAG. All had sensory loss in the legs. Hand discomfort was present in 50% (5 of 10) of the patients. Vibration sense was absent in the toes in 80% compared with 43% of patients with IgM M-proteins and selective serum IgM binding to TS-HDS but not to MAG ($P = 0.10$). All had serum IgM M-proteins. Most (90%; 9 of 10) had demyelinating polyneuropathies with typical features associated with anti-MAG antibodies with prolonged distal latencies in multiple nerves, uniformly slowed conduction velocities, and no conduction block.[9,10] Patients with IgM binding to both TS-HDS and MAG were more likely to have at least 1 demyelinating feature of their neuropathies (90%) than those with selective IgM binding to TS-HDS alone (16%) ($P = 0.000009$). An abnormal (prolonged) distal latency index in 2 or more nerves was more common in patients with M-proteins and IgM binding to both TS-HDS and MAG (80%) than in those with M-proteins and selective IgM binding to TS-HDS (17%) ($P = 0.003$). Three patients with IgM binding to TS-HDS (but not to MAG) had motor neuropathies with asymmetric arm predominant weakness. One of these patients had motor conduction block at several sites on nerve conduction testing.

Nerve and Muscle Pathology in Patients with Serum IgM Binding to TS-HDS. All 6 nerve biopsies showed axon loss, 2 with variability among fascicles, but none showed evidence of demyelination. One nerve had abnormal alkaline phosphatase staining of the epineurium. None had inflammation or active Wallerian degeneration. Endoneurial capillary morphology in most nerves was unremarkable. One nerve had scattered, enlarged endoneurial capillaries with diameters of up to 45 μm (normal <25 μm) and abundant endothelial cells but normal vessel wall thickness. Five of the 6 nerves had abnormal C5b9 complement deposited on endoneurial capillaries (Fig. 1). Eleven of the 14 muscles had abnormal C5b9 complement deposited on endomysial capillaries (Fig. 1). One of 9 disease control biopsies showed this pathology ($P = 0.003$). Collagen IV staining often showed thickened endomysial capillary wall basal lamina. *Ulex europaeus* agglutinin-1 (UEA-1) lectin staining showed qualitatively normal numbers of capillaries with all muscle fibers having at least 1 adjacent capillary. Ultrastructural examination showed endomysial capillaries in the quadriceps with consistently thickened basal lamina walls (Fig. 2) that often contained normal pericyte processes. Capillary endothelial cells and lumens appeared normal. There was no inflammatory cellularity surrounding capillaries. Seven of the 14 muscle biopsies showed chronic denervation with fiber type grouping. Histochemical features in other biopsies included varied fiber size (2), increased numbers of alkaline phosphatase–positive capillaries (2), targets (1), and severe atrophy with end-stage features (1). No biopsy showed amyloid deposition. Six of 9 TS-HDS–positive sera tested showed selective

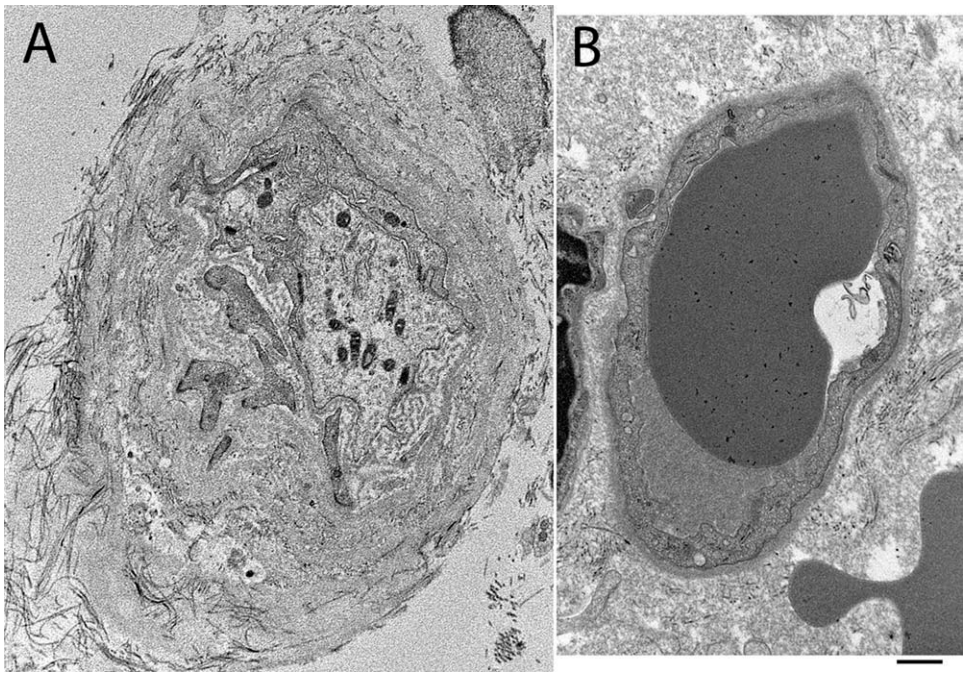

FIGURE 2. Thickened capillary walls in patients with IgM vs. TS-HDS. (**A**) A capillary in muscle from a patient with serum IgM binding to TS-HDS shows a markedly thickened wall. Endothelium is normally present. (**B**) A capillary in muscle from a control patient has normal wall thickness and endothelium. Bar = 1 μm.

binding of IgM to endomysial capillaries of normal control muscles. None of 7 control sera showed this pattern of capillary binding ($P = 0.01$) (Fig. 3). Preincubation of sera with TS-HDS reduced IgM binding to capillaries in 3 of the 4 samples tested (Fig. 3).

DISCUSSION

Our results show that TS-HDS is a target of IgM antibodies in some patients with distal, predominantly sensory polyneuropathies[5] that were otherwise idiopathic. We found serum IgM binding to TS-HDS in 71 of the patients evaluated in our neuromuscular clinic for neuropathic disorders over a period of 14 months. Ninety-six percent (68 of 71) of antibody-positive patients had sensory or sensory–motor polyneuropathies. Persistent hand discomfort was the most distinctive sensory feature in TS-HDS antibody-associated polyneuropathies compared with the control polyneuropathy group ($P < 0.0004$). Hand discomfort was present in 41% (28 of 68) of patients with sensory disorders and IgM binding to TS-HDS and in 40% of the subgroup with selective serum IgM binding to TS-HDS, compared with 7% of those with control neuropathies. Early involvement of the hands during the progression of a neuropathy suggests that the axonal pathology is not entirely length-dependent and has a short differential diagnosis that includes chronic inflammatory demyelinating polyneuropathy (CIDP), vincristine toxicity, amyloidosis, and entrapment and immune vasculopathies.[11,12] In the absence of hand pain, there was often little to clinically distinguish patients with TS-HDS antibodies from others with painful sensory neuropathies.

Some clinical and electrodiagnostic features differed when patients had serum findings in addition to IgM binding to TS-HDS. The degree of large-fiber modality sensory loss was worse, and weakness was more common in the presence of IgM M-proteins. Demyelinating features had increased frequency in the presence of IgM M-proteins. Some of these associations could be attributed partially to additional reactivity of some TS-HDS–positive sera with MAG. However, an increased association of IgM M-proteins and TS-HDS antibodies with sensory loss and demyelinating features was also present in the subgroup of patients with IgM M-proteins but no MAG binding. Two patients with IgM M-proteins and IgM binding to TS-HDS but not MAG fit into the group with distal acquired demyelinating polyneuropathy without anti-MAG antibodies.[13] Defining the causes of the associations of IgM binding to TS-HDS with axonal loss or different patterns of demyelination may require further clarification of the antigenic targets of the antibodies in nerve tissue, which are not known at present.

The finding that serum IgM M-proteins were more frequent in patients with selective IgM binding to TS-HDS compared with the sensory neuropathy controls is consistent with our initial report.[5] A correlate of that finding is the observation that IgM binding to TS-HDS was monoclonal (especially κ class) in a majority of patients. The finding that some patients had monoclonal TS-HDS antibodies

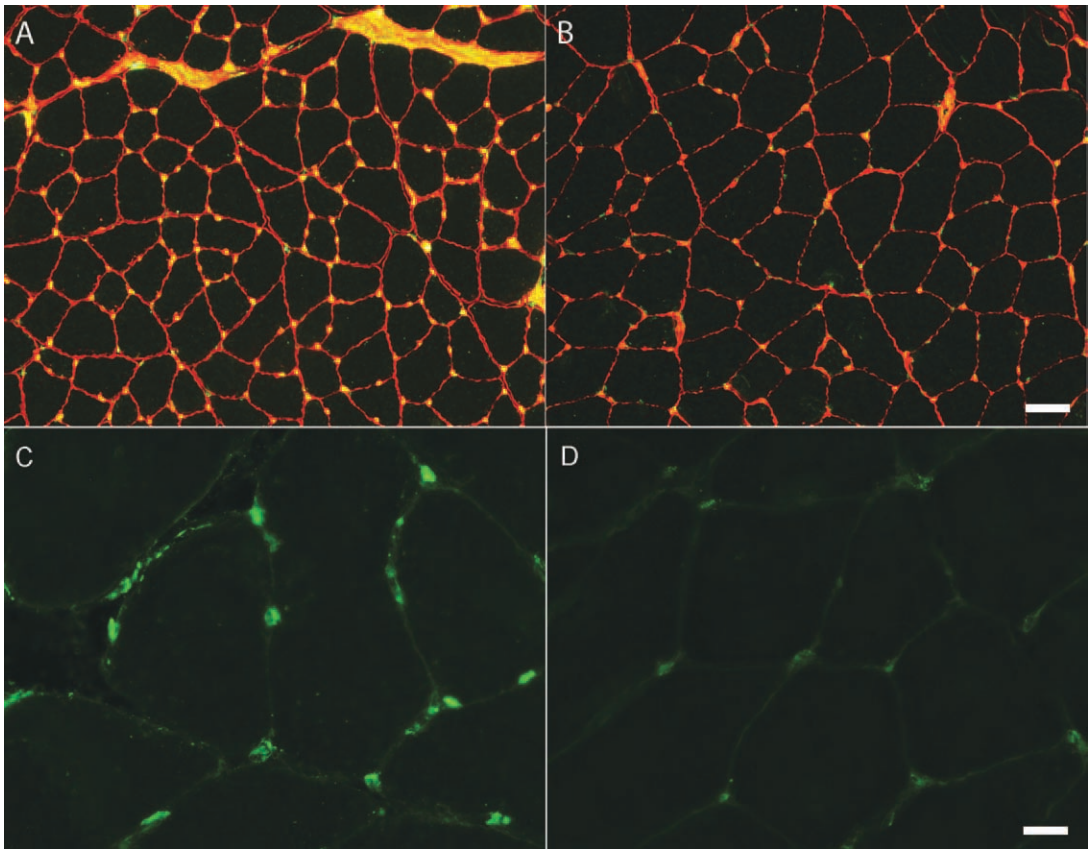

FIGURE 3. Serum with IgM vs. TS-HDS shows IgM binding to endomysial capillaries. Staining of normal muscle by IgM (green) from TS-HDS and control patient serum. Collagen IV is stained red. Overlap in the distribution of serum IgM binding and collagen IV is yellow. (**A**) Serum IgM from a patient with TS-HDS antibodies binds to endomysial capillaries (yellow). (**B**) Serum IgM from a control patient does not bind to endomysial capillaries. IgM is normally present in the center of some capillaries. Bar = 50 μm for (**A**) and (**B**). (**C**) Serum IgM from a patient with TS-HDS antibodies binds to endomysial capillaries (green). (**D**) Binding to capillaries of serum IgM from the same patient is reduced by TS-HDS. Bar = 18 μm for (**C**) and (**D**).

with a class that was different from their M-protein suggests that, for an unknown reason, there was a hematologic tendency to produce several monoclonal antibodies, some of which occurred at levels too low to be detected by immunofixation methods. Our data suggest that TS-HDS may be the most common antigenic target in sera with IgM M-proteins in patients with polyneuropathy. During the study period, IgM binding to TS-HDS was found in 24 patient sera with M-proteins, whereas MAG binding was found in 11. Ten of the 11 sera found with MAG binding also bound to TS-HDS, often in higher titers.

The muscle and nerve biopsies in our patients with TS-HDS antibodies showed that capillary pathology is common. The capillary involvement in muscle includes thickened walls (Fig. 2), circumferential enlargement, and C5b9 complement deposits, especially on the collagen IV–containing basal lamina (Fig. 1). C5b9 complement deposits were also noted in capillaries in endoneurium. Capillary pathology in muscle endomysium has also been documented extensively in dermatomyositis.[8,14,15] Endomysial capillary pathology in TS-HDS neuropathy patients differs from the microvascular changes found in dermatomyositis. In dermatomyositis the pathologic capillaries are typically small, have reduced or absent endothelium, and are distributed selectively in some regions of muscle but not others. In TS-HDS neuropathy patients, capillary pathology was more diffusely distributed with preservation of numbers, normal to large size, thickened walls, and retention of endothelium and lumens.

IgM binding to TS-HDS, or similar disaccharides, could play a role in the pathogenesis of the associated neuropathy. The roles of other IgM anti-carbohydrate antibodies in the pathogenesis of their associated neuropathies have been incompletely defined. There is some evidence that IgM anti-MAG antibodies, which can cross-react with sulfated glucuronyl epitopes or TS-HDS, play a role in the pathogenesis of its distinctive associated demyelinating polyneuropathy.[1,16] We did not find evidence of direct binding of serum IgM to axons or myelin in our patients with IgM binding to TS-HDS. The specific vascular (or neural) antigenic molecules containing the TS-HDS disaccharide

epitope have not been identified. Serum IgM from some patients with TS-HDS binding labeled endomysial capillaries in normal muscle (Fig. 3), suggesting that antibodies could play a role in the capillary pathology. Pre-incubation with TS-HDS markedly reduced IgM binding to capillaries for 3 of the 4 sera tested. Possible causes of a neuropathy associated with capillary pathology include ischemia due to reduced blood flow or leakage of pathologic factors through capillary walls that have reduced integrity of their blood–nerve barrier. TS-HDS capillary pathology is present in muscle as well as nerve. The involvement of endomysial capillaries was clinically silent in our patients who had no edema or myopathic features on clinical or electrodiagnostic testing and a normal creatine kinase. Further studies are required to define any physiological or pathologic consequences of the capillary pathology in muscle and nerve in patients with IgM binding to TS-HDS.

Whether or not the specific binding of IgM to TS-HDS is pathogenic, the association of neuropathy syndromes with a serum autoantibody suggests that they could be humoral immune-mediated disorders. In 43 of 58 (74%) patients in our series the association with serum IgM binding to TS-HDS was the only clue to the pathogenesis underlying the neuropathy syndromes. Other neuropathy syndromes associated with IgM autoantibodies are difficult to treat with immunomodulating agents. In anti-MAG antibody–related neuropathies there is incomplete evidence that they may respond best to agents that reduce the IgM autoantibody titers for prolonged periods, such as rituximab and cyclophosphamide. It remains to be seen whether immune therapies can alter the course of neuropathies with serum IgM binding to TS-HDS.

One limitation of this study is its retrospective design. Patient data and estimates of the sensitivity of antibody testing may reflect referral bias to a large tertiary academic center with an interest in neuropathies. Further study of acquired sensory neuropathies is necessary to define whether serum IgM anti–TS-HDS antibodies are associated with any other different or specific clinical or laboratory features or treatment responses, or any pathogenic role in producing the disorders. However, it is unlikely that these limitations would alter the main conclusions of our study. Serum IgM binding to TS-HDS is associated with painful, predominantly distal and sensory polyneuropathies with capillary pathology. Neuropathies with IgM binding to TS-HDS carry with them an increased frequency of persistent discomfort in the hands and presence of IgM M-proteins, as identified by immunofixation. Serum IgM binding to TS-HDS may be the only clue to the etiology underlying otherwise idiopathic sensory polyneuropathies.

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