Neural Autoantibodies and Neurophysiologic Abnormalities in Patients Exposed to Molds in Water-Damaged Buildings

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ABSTRACT. Adverse health effects of fungal bioaerosols on occupants of water-damaged homes and other buildings have been reported. Recently, it has been suggested that mold exposure causes neurological injury. The authors investigated neurological antibodies and neurophysiological abnormalities in patients exposed to molds at home who developed symptoms of peripheral neuropathy (i.e., numbness, tingling, tremors, and muscle weakness in the extremities). Serum samples were collected and analyzed with the enzyme-linked immunosorbent assay (ELISA) technique for antibodies to myelin basic protein, myelin-associated glycoprotein, ganglioside GM_1, sulfatide, myelin oligodendrocyte glycoprotein, α-B-crystallin, chondroitin sulfate, tubulin, and neurofilament. Antibodies to molds and mycotoxins were also determined with ELISA, as reported previously. Neurophysiologic evaluations for latency, amplitude, and velocity were performed on 4 motor nerves (median, ulnar, peroneal, and tibial), and for latency and amplitude on 3 sensory nerves (median, ulnar, and sural). Patients with documented, measured exposure to molds had elevated titers of antibodies (immunoglobulin [Ig]A, IgM, and IgG) to neural-specific antigens. Nerve conduction studies revealed 4 patient groupings: (1) mixed sensory–motor polyneuropathy (n = 55, abnormal), (2) motor neuropathy (n = 17, abnormal), (3) sensory neuropathy (n = 27, abnormal), and (4) those with symptoms but no neurophysiological abnormalities (n = 20, normal controls). All groups showed significantly increased autoantibody titers for all isotypes (IgA, IgM, and IgG) of antibodies to neural antigens when compared with 500 healthy controls. Groups 1 through 3 also exhibited abnormal neurophysiologic findings. The authors concluded that exposure to molds in water-damaged buildings increased the risk for development of neural autoantibodies, peripheral neuropathy, and neurophysiologic abnormalities in exposed individuals.
<Key words: mold exposure, mycotoxins, neural antibodies, neuropathy, neurophysiology>

WATER INTRUSION into houses and office buildings leads to the growth of molds and bacteria, which are known to produce toxic byproducts that include endotoxins (lipopolysaccharides), β-D-glucans, and mycotoxins (e.g., trichothecenes, ochratoxins, and aflatoxins, tremorgens), as well as volatile organic compounds.[1–8] These compounds have been found in water-damaged buildings and homes, and in artificially infested building materials.[7–11] Indoor air can be contaminated with mold spores and hyphae fragments.[12] In addition, mycotoxins have been identified in ventilation duct particulate matter or dust, and in the air of buildings in which occupants and pets have experienced adverse health effects related to mold exposure.[13–23]

Molds and mycotoxins affect the respiratory tract, kidneys, liver, and skin, as well as the immune and nervous systems.[24–45] Neurotoxic mycotoxins include ergot alkaloids, trichothecenes, citreovirdin, patulin, fumonisins, and tremorgens.[46–54] Tremorgens affect the brainstem[46] and stellate ganglion, and the basket and Pur-

kinje cells of the cerebellum.[47] Mycotoxins affect neuroreceptor sites (e.g., gamma-aminobutyric acid [GABA] receptor site[48] and inositol 1,4,5-trisphophate receptor[49]), inhibit acetylcholinesterase,[50] release excitatory neurotransmitters (e.g., glutamate, aspartate, GABA, and serotonin),[51,52] and block biosynthesis of complex sphingolipids through inhibition of ceramide synthase.[53,54] They are also mitochondrial toxins and apoptotic agents.[43,44,53]

The symptoms and health problems associated with mold-infested, water-damaged buildings involve multiple organs, including the upper and lower respiratory tracts, gastrointestinal tract, circulatory system, and the central nervous system (CNS) and peripheral nervous system (PNS).[2,5,24-37] Recent studies have shown that mold exposure has adverse effects on the nervous system. Some mycotoxins have been shown to be tremorgenic and are suspected as causative agents in woodtrimmer's disease[20] and tremorgenic encephalopathy;[21] mycotoxins present in household environments have been found to affect dogs.[22,23]

Two patterns of neurobehavioral impairment attributable to mold exposure have been described. Kilburn[26] reported on 10 individuals who had impaired balance, reaction time, color discrimination, visual fields, cognition, verbal recall, and trail making. A different group of 10 subjects exhibited impairments in all but measures of color discrimination and visual fields. Abnormalities in electroencephalograph (EEG) theta and delta activity, visual evoked potentials, and brainstem evoked potentials have been reported in children exposed to molds.[27] The EEG changes in the children were specific to the frontotemporal area of the brain, suggesting a metabolic encephalopathy. Six individuals had abnormal nerve conduction. In addition, abnormal brainstem auditory evoked potentials have been described in 4 children with suspected mycotic neuromas who were exposed to mixed molds, including *Stachybotrys chartarum* and *Aspergillus species*.[57] Moreover, both neurobehavioral[31,57] and correlated quantitative EEG[31] changes indicative of right frontal lobe involvement have been reported in patients with chronic exposure to mold in water-damaged buildings. Mold exposure has also been implicated in optic neuritis[57] and multifocal choroiditis.[58] Finally, demyelination of the CNS has been reported following exposure to ibotenic acid,[59] abuse of "magic mushrooms" (Psilocybe),[60] and gliotoxin.[61] Because stachylysin has been found in human serum following exposure to *S. chartarum*,[62] and mycotoxins are present in indoor air and bioaerosols,[13-19] it is imperative that health complaints of occupants exposed to molds in water-damaged buildings be taken seriously and be investigated with appropriate diagnostic testing.

This communication describes 119 mold-exposed patients who had multiorgan symptoms and peripheral neuropathy. Complaints included severe fatigue, decreased muscle strength, sleep disturbances, numbness and tingling of extremities (with and without tremors of the fingers and hands), and severe headache. Patients had abnormal neurological examinations. Ninety-nine of these individuals had abnormal nerve conduction velocities (NCVs) in association with autoantibodies against 9 neural antigens, whereas 20 had normal test results. We present data on motor neuropathy, sensory neuropathy, and mixed sensory–motor polyneuropathy, as well as increased antibodies to neural antigens.

Materials and Method

Patients. The study population consisted of 119 patients (79 females and 40 males; mean age ± standard deviation [*SD*] = 41.3 ± 12.9 yr). The patients had health complaints and proven environmental exposure to molds in their homes and/or workplaces. Mold exposure was documented by Aerotech Laboratories (Phoenix, Arizona). All patients were interviewed one-on-one by the principal author (AWC) regarding exposure history, as well as health problems and symptoms for each organ system (e.g., CNS, PNS, respiratory, skin, musculoskeletal). Mold-specific serum antibody tests for *S. chartarum, Penicillium, Aspergillus, Cladosporium, Alternaria,* and *Chaetomium,* performed on each patient by Immunosciences Lab., Inc. (Beverly Hills, California), verified exposure to molds. Some of these data have been reported previously.[63-65]

We studied patients who had symptoms of peripheral neuropathy (e.g., tingling, tremors, loss of sensation in extremities). Blood was drawn for serology testing for neural antigens. NCV tests were performed at or near the time of initial presentation as follows: all 119 patients were tested at 10.8 ± 41 days; patients with abnormal NCVs (n = 99) were tested at 11.5 ± 44 days; and patients with normal NCVs (n = 20, controls) were tested at 7.5 ± 18 days.

Blood samples. Peripheral venous blood was collected and shipped at ambient temperature to Immunosciences Lab., Inc. (Beverly Hills, California). Autoantibodies (immunoglobulin IgG, IgM, and IgA) against 9 neural antigens were assessed for each patient.

Neural antigens. Myelin basic protein (MBP), myelin-associated glycoprotein (MAG), ganglioside (GM_1), chondroitin sulfate ($CONSO_4$), α-B-crystallin (crystallin), and tubulin were purchased from Sigma-Aldrich (St. Louis, Missouri). Neurofilament antigen (NAF) was purchased from Boehringer Mannheim Roche (Indianapolis, Indiana). MBP peptides 87-206 and myelin oligodendroctye glycoprotein (MOG) peptides 21-4-, 61-80 were synthesized by Research Genetics (Huntsville, Alabama).

Controls for neural antigens. The controls for determination of the mean ± *SD* and 95% confidence intervals (CIs) for the neural antigens consisted of 500

healthy adult blood donor volunteers. The controls were of similar age and sex distribution as the 119 patients.

ELISA testing. We used enzyme-linked immunosorbent assay (ELISA) to test for antibodies against 9 different neural-specific antigens, as reported previously.[66–68] Briefly, antigens were dissolved in methanol at a concentration of 1.0 mg/ml and then diluted 1:100 in 0.1 M carbonate-bicarbonate buffer (pH 9.5). Then, 50 µl of the mixture was added to each well of a polystyrene flat-bottom ELISA plate. Plates were incubated overnight at 4 °C and then washed 3 times with 20 mM Tris-buffered saline (TBS) containing 0.05% Tween 20 (pH 7.4). The nonspecific binding of immunoglobulins was prevented by adding a mixture of 1.5% bovine serum albumin (BSA) and 1.5% gelatin in TBS and then incubating for 2 hr at room temperature, followed by incubation overnight at 4 °C. Plates were washed as described above, and serum samples diluted 1:100 in 1% BSA-TBS were added to duplicate wells and incubated for 2 hr at room temperature. Sera from patients with multiple sclerosis (MS), polyneuropathies, and other neurological disorders with known high titers of IgG, IgM, and IgA against different neurological antigens were used to rule out nonspecific antibody activities of inter-assay and intra-assay variability. Plates were washed, and peroxidase-conjugated goat antihuman IgG, IgM, or IgA antiserum (KPI [Gaithersburg, Maryland]), diluted 1:400 in 1% BSA-TBS, was added to each well. The plates were incubated for an additional 2 hr at room temperature. After washing 5 times with TBS-Tween buffer, the enzyme reaction was started by the addition of 100 µl of *o*-phenylenediamine in citrate-phosphate buffer containing hydrogen peroxide diluted to 1:10,000 (pH 5.0). After 45 min, the reaction was stopped with 50 µl of 2N sulfuric acid. The optical density was read at 492 nm with a microtiter reader (Dynex Laboratories [Chantilly, Virginia]). Several control wells containing all reagents except human serum were used to detect nonspecific binding.

We calculated coefficients of intra-assay variation by running 5 samples 8 times in 1 assay. Coefficients of inter-assay variation were determined by measuring the same samples in 6 consecutive assays. This replicate testing established the validity of the ELISAs, determined the appropriate dilutions with minimal background, and detected IgG, IgM, and IgA against different antigens. Sera from 500 asymptomatic blood donors in southern California were used to calculate expected ranges at 95% CI.

Neurophysiological tests. Bilateral peripheral nerve studies involving nerve conduction and central response (F wave) were performed on the 119 patients in accordance with accepted techniques of the American Society of Electroneurodiagnostic Technologists (Kansas City, Missouri) and the American Neurological Association (Minneapolis, Minnesota).[69–71] The testing was performed under the direct supervision of, and interpreted by, a board-certified neurologist. Onset latency (ms), amplitude (µV), and velocity (m/sec) were recorded for 4 motor nerves (median, ulnar, peroneal, and tibial). The peak latency (ms) and amplitude (µV) were recorded for 3 sensory nerves (median, ulnar, and sural). F wave and H reflex were recorded for the median, ulnar, peroneal, and tibial nerves. The studies were conducted with a TECA Synergy Multimedia Electromyograph with multisync color SVGA monitor and Delux stimulator probe (TECASyngery, Synergy Version 8.2 [Oxford Instruments {Surry, U.K.}]). The motor axons of peripheral nerves that innervate somatic muscle were evaluated by recording the response following electrical stimulation.

Statistical analysis. We performed critical 2-tailed *t* tests on neural autoantibodies. Odds ratios (ORs) were calculated for the data to determine the percentage of individuals with antibody titers that exceeded the maximum expected laboratory range (95% CI) for each neural autoantibody. For this calculation, data for patients with abnormal and normal NCVs were combined.

Results

Neural autoantibodies. The mean ± *SD* of autoantibodies for each isotype (IgA, IgM, and IgG) against each neural antigen for patients with abnormal NCVs (n = 99), normal NCVs (n = 20), and asymptomatic blood donor controls (n = 500) are given in Table 1. Rather than repeating the data for each antineural antigen isotype, the salient features will be outlined briefly. In general, the highest isotype titers detected were MBP, MAG, tubulin, and NAF. These were followed by the other 5 neural antigens: GM_1, sulfatide, MOG, crystallin, and $CONSO_4$.

We performed critical 2-tailed *t* tests for each isotype titer against neural antigens, comparing abnormal vs. normal patients, abnormal patients vs. controls, and normal patients vs. controls for each isotype (statistical data not shown). With respect to IgG titers, the only significant difference between abnormal and normal patients was NAF ($p < 0.01$). IgG titers for all isotypes for abnormal and normal patients differed significantly from controls ($p < 0.001$). IgM titers for neural antigens were significantly different between abnormal and normal patients for glutamate receptor ($p < 0.01$), tubulin ($p < 0.01$), NAF ($p < 0.01$), and $CONSO_4$ ($p < 0.05$). IgM titers against each neural antigen for abnormal patients vs. controls ($p < 0.001$) and for normal patients vs. controls ($p < 0.001$) were significantly different. The only significant difference between patients with abnormal vs. normal IgA titers was NAF ($p < 0.05$). Comparison of abnormal and normal patients vs. controls revealed IgA titers for each neural antigen which were

significantly different ($p < 0.01$), except for normal crystallin titers ($p < 0.05$).

The percentages of individuals with autoantibodies for each isotype that exceeded the laboratory expected range at 95% CI against the neural antigens are presented in Table 2. IgG titers for abnormal patients exceeded the 95% CI for sulfatide (17.2%), MOG (10.1%), crystallin (10.1%), glutamate receptor (11.1%), tubulin (57.6%), $CONSO_4$ (27.3%), and NAF (6.1%); MBP (4%), MAG (4%), and GM_1 (0%) did not exceed their expected ranges. Similar observations for normal patients were made for sulfatide (20%), MOG (20%), crystallin (20%), tubulin (30%), and $CONSO_4$ (20%), except for MBP (0%), GM_1 (0%), glutamate receptor (0%), and NAF (0%). IgM titers for abnormal patients exceeded those of controls for all neural antigens (range = 17.2%–42.4%) except GM_1 (0%). In normal patients, IgM titers did not exceed control values for GM_1 (0%), sulfatide (5%), MOG (5%), glutamate receptor (0%), and tubulin (5%), whereas MBP (20%), MAG (30%), crystallin (25%), $CONSO_4$ (20%), and NAF (20%) exceeded control values. IgA autoantibodies in abnormal patients for each neural antigen exceeded control values for MBP (20.3%), MAG (23.2%), crystallin (8.1%), glutamate receptor (7.1%), tubulin (8.1%), $CONSO_4$ (10.5%), and NAF (10%). With respect to normal patients, only MAG (15%), tubulin (10%), and NAF (10%) exceeded values for controls.

The percentage of patients who had ORs that exceeded the 95% CI are given in Table 3. The ORs for IgG were not significant for MBP (0.66) and MAG (1.05), whereas those for all other neural autoantibodies were significant as follows: sulfatide (3.36), crystallin (6.53), glutamate receptor (10.08), tubulin (55.1),

Table 1.—Autoantibody Titers against 9 Neural Antigens in Patients with Abnormal Nerve Conduction Velocities (NCVs) (n = 119) and Those with Normal NCVs (n = 20), vs. Asymptomatic Controls (N = 500), for Each Isotype

	IgG						IgM						IgA					
	Abnormal		Normal		Controls		Abnormal		Normal		Controls		Abnormal		Normal		Controls	
Neural autoantibody	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*
MBP	63.3	21.6	54.7	18.3	27.0	12.2	50.8	24.3	47.0	9.2	25.1	13.2	18.5	6.0	16.8	4.7	7.2	3.7
MAG	63.6	18.8	69.0	18.2	26.0	7.3	51.0	16.1	48.1	12.4	24.5	8.1	19.4	7.6	17.5	7.4	8.3	2.4
GM_1	15.8	6.7	16.4	7.0	11.1	2.8	16.4	6.3	15.6	4.5	10.4	3.3	12.3	6.2	12.6	4.4	11.5	3.6
Sulfatide	16.7	6.2	17.5	6.7	12.2	3.4	17.2	6.3	15.1	4.3	11.3	3.7	13.3	9.1	12.4	4.0	9.4	3.1
MOG	15.9	5.9	17.5	6.6	8.9	5.5	18.2	6.3	16.8	4.7	8.4	5.5	12.0	3.5	11.4	2.3	7.9	4.6
Crystallin	16.1	5.8	16.5	6.7	11.9	2.5	18.7	6.9	19.0	8.2	12.1	2.9	13.6	7.5	13.2	4.7	11.1	4.3
Glutamate	10.2	3.4	9.2	1.5	7.0	2.8	10.6	3.7	9.3	1.2	7.6	2.0	9.5	3.7	8.5	2.1	8.1	2.1
Tubulin	64.1	16.8	58.7	11.9	23.7	9.2	41.9	18.5	33.0	7.8	18.1	7.9	17.9	16.1	14.7	3.7	9.8	2.6
$CONSO_4$	11.5	4.7	10.2	2.1	7.7	2.2	11.8	4.9	10.4	2.0	5.6	2.1	11.0	7.7	9.2	1.4	7.0	2.7
NAF	61.6	23.9	53.3	10.7	26.4	11.3	53.1	20.7	44.1	12.0	24.7	10.3	18.2	8.2	16.4	5.4	8.7	3.4

Notes: Ig = immunoglobulin, $\bar{x}$ = mean, *SD* = standard deviation, MBP = myelin basic protein, MAG = myelin-associated glycoprotein, GM_1 = ganglioside, MOG = myelin oligodendroctye glycoprotein, $CONSO_4$ = chondroitin sulfate, and NAF = neurofilament antigen.

Table 2.—Percentages of Individuals with Autoantibody Titers that Exceeded Expected Ranges (95% Confidence Intervals), for Patients with Abnormal Nerve Conduction Velocities (NCVs) and Those with Normal NCVs, vs. Asymptomatic Controls, for Each Isotype

	IgG			IgM			IgA		
Neural autoantibody	Abnormal (%)	Normal (%)	Controls (%)	Abnormal (%)	Normal (%)	Controls (%)	Abnormal (%)	Normal (%)	Controls (%)
MBP	4.0	0	5	34.3	20	2	20.2	5	1
MAG	4.0	5	4	42.4	30	3	23.2	15	2
GM_1	0.0	0	2	0.0	0	4	4.0	5	5
Sulfatide	17.2	20	6	17.2	5	5	3.0	5	2
MOG	10.1	20	5	25.3	5	4	1,0	0	3
Crystallin	10.1	20	2	27.3	25	4	8.1	5	3
Glutamate	11.1	0	1	15.2	0	0	7.1	0	2
Tubulin	57.6	30	2	39.4	5	2	8.1	10	1
$CONSO_4$	27.3	20	2	33.3	20	1	10.5	5	2
NAF	6.1	0	3	41.4	20	2	18.2	10	1

Notes: Ig = immunoglobulin, MBP = myelin basic protein, MAG = myelin-associated glycoprotein, GM_1 = ganglioside, MOG = myelin oligodendroctye glycoprotein, $CONSO_4$ = chondroitin sulfate, and NAF = neurofilament antigen.

$CONSO_4$ (17.26), and NAF (5.15). The OR for GM_1 could not be calculated because of the 0 value for the patients. The ORs for IgM neural autoantibodies were significant for all antigens, and ranged from 3.39 to 44.6. The ORs for GM_1 and glutamate receptor were not calculated because of 0 values for the controls. With respect to IgA autoantibodies, the ORs for sulfatide (1.7) and MOG (0.82) were not significant, whereas those for the other neural antigens were significant as follows: MBP (21.2), MAG (13.7), crystallin (2.65), glutamate receptor (3.03), tubulin (9.08), $CONSO_4$ (4.99), and NAF (2). GM_1 could not be calculated because of 0 values; the 95% CI for MOG was not calculated because of the value of 1 in controls.

The percentages of individuals with autoantibody titers that exceeded the maximum 95% CI for expected laboratory ranges, along with ORs, are presented in Table 4. We calculated these data for abnormal, normal, and control patients as follows: If an individual had only 1 isotype against a neural antigen (i.e., IgG), that person was given the same score as an individual with 2 or more isotypes (i.e., IgG + IgM + IgA). The percentages of individuals with autoantibodies against each neural antigen were highest among the abnormal

Table 3.—Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Autoantibodies for Each Isotype Presented in Table 1

	IgG		IgM		IgA	
Neural autoantibody	OR	95% CI	OR	95% CI	OR	95% CI
MBP	0.66	1.92, 0.22	22.98	47.9, 11.0	21.2	57.4, 7.8
MAG	1.05	3.86, 0.39	21.86	40.9,11.59	13.7	6.2,28.8
GM_1	—*		—*		—*	
Sulfatide	3.36	6.1,1.84	3.39	5.6, 2.05	1.7	0.52, 5.5
MOG	2.53	4.95, 1.25	6.7	12.2, 3.5	0.82	—†
Crystallin	6.53	15.2, 2.83	8.83	16.4, 4.9	2.65	1.13, 6.17
Glutamate	10.08	29.4, 3.3	—*		3.06	8.17, 1.14
Tubulin	55.1	112.4, 27.1	24.8	50.9, 11.8	9.08	38.02,26.8
$CONSO_4$	17.26	36.6, 8.2	44.6	116.7, 16.4	4.99	2.05, 11.9
NAF	5.15	13.06, 1.88	29.8	62.2, 14.9	20.0	7.26, 54.6

Notes: Ig = immunoglobulin, MBP = myelin basic protein, MAG = myelin-associated glycoprotein, GM_1 = ganglioside, MOG = myelin oligodendroctye glycoprotein, $CONSO_4$ = chondroitin sulfate, and NAF = neurofilament antigen. For these calculations, patients with abnormal nerve conduction velocities (NCVs) were grouped with those with normal NCVs and compared vs. controls.
*Not calculated because of zero values (refer to Table 2).
†Not calculated because of the value of 1 in a cell (refer to Table 2).

Table 4.—Percentages of Individuals with 1 or More Isotypes for Each Neural Antigen that Exceeded the Maximum 95% Confidence Interval (CI) Titer

Neural autoantibody	Abnormal (n = 119) (%)	Normal (n = 20) (%)	Controls (n = 500) (%)	OR	95% CI
MBP	47.5	20	8	8.63	11.5,6.4
MAG	54.5	45	9	11.4	16.4,7.8
GM_1	4.0	5	11	0.91	1.7,0.48
Sulfatide	30.3	25	13	2.8	4.4,1.7
MOG	32.3	25	12	3.3	4.85,2.2
Crystallin	35.4	35	9	5.5	8.0,2.7
Glutamate	26.3	0	3	9.0	17.6,4.6
Tubulin	69.7	35	5	33.58	56.8,19.1
$CONSO_4$	46.5	30	5	14.75	25.3,8.58
NAF	50.5	25	5	16.3	16.3,12.4

Notes: MBP = myelin basic protein, MAG = myelin-associated glycoprotein, GM_1 = ganglioside, MOG = myelin oligodendroctye glycoprotein, $CONSO_4$ = chondroitin sulfate, and NAF = neurofilament antigen. The percentages were determined as follows: If a patient had 1 isotype (e.g., immunoglobulin [Ig]G, IgM, or IgA), that patient was given the same score as a patient with 2 or more isotypes. Thus, the total percentages for patients with abnormal nerve conduction velocities (NCVs), normal NCVs, and controls were less than the totals for each isotype as presented in Table 1. For simplicity, the data for patients with abnormal and normal NCVs were combined to obtain the odds ratios (ORs).

patients (range = 26.3%–69.0%) when compared with controls (range = 3%–13%), with the exception of GM_1 (4%). Similarly, the normal patients had an increased percentage of individuals with higher titers (range = 20%–45%) when compared with the controls, with the exception of GM_1 (5%) and glutamate receptor (0%). The ORs were significant (95% CI) for all neural antigens, except for GM_1 (0.91). The ORs were highest for tubulin (33.58) and decreased, in descending order, for NAF (16.3), $CONSO_4$ (14.75), MAG (11.4), glutamate receptor (9.0), MBP (8.63), crystallin (5.5), MOG (3.3), and sulfatide (3.3).

NCV testing. No changes or abnormalities were observed for F and H waves in the abnormal or normal patients (data not shown).

The data obtained from the NCV studies for motor nerves and sensory nerves are summarized in Tables 5 and 6. Patients with abnormal findings comprised 3 groups, as follows: (1) mixed sensory–motor polyneuropathy (n = 55), (2) motor neuropathy (n = 17), and (3) sensory neuropathy (n = 27). There were 20 patients with no abnormalities (controls). We compared the data obtained for the 20 controls with data for the 3 groups of abnormal patients (mixed, motor, and sensory neuropathies), for statistical purposes.

Results for the mixed polyneuropathy group differed significantly from controls. Latencies for the median (4.2 ± 1.2 ms, $p < 0.001$), ulnar (3.13 ± 1.1 ms, $p < 0.05$), peroneal (5.1 ± 1.4 ms, $p < 0.001$), and tibial motor nerves (5.5 ± 2.9 ms, $p < 0.001$) were signifi-

Table 5.—Neuropathies Experienced by Patients with Abnormal Nerve Conduction Velocity (NCV) Measurements (n = 119), vs. Controls with Normal Values (n = 20), by NCV Parameter Tested

	Neuropathy with abnormal NCV							
	Mixed (n = 55)		Motor (n = 17)		Sensory (n = 27)		Controls (n = 20)	
NCV parameter	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Median latency (ms)	4.2	1.2*	3.6	1.1	3.4	0.36	3.3	0.4
Median amplitude (μV)	9.5	4.3	7.6	3.3†	10.8	2.6	10	3.3
Median velocity (m/sec)	56.5	7.8‡	55.9	5.3‡	58.1	7.4	61.5	7.1
Ulnar latency (ms)	3.13	1.1†	3.7	2.05‡	2.7	0.38	2.56	0.53
Ulnar amplitude (μV)	9.9	3.7	9.9	2	9.9	1.8	10	3.13
Ulnar velocity (m/sec)	60.9	9.9§	60.4	7.4‡	65.1	6.6	66.2	5.4
Peroneal latency (ms)	5.1 (n = 54)	1.4*	5.5	1.2*	4.7 (n = 26)	0.52*	3.9	0.86
Peroneal amplitude (μV)	5.6 (n = 54)	3.2	4.2	1.9§	6.05 (n = 26)	2.2	6.6	3
Peroneal velocity (m/sec)	52.5 (n = 54)	12.7	47.5	13.3†	52.2 (n = 26)	5.8	58.2	13.8
Tibial latency (ms)	5.5 (n = 53)	2.9*	6.3	3§	4.2	0.55	4	1
Tibial amplitude (μV)	9.8 (n = 53)	6	8.1	4.8†	13.6	4.8	12.7	6.8
Tibial velocity (m/sec)	46.6 (n = 53)	11.3†	47.3	5.5†	46.6	4.4§	52.3	8.3
Median latency (ms)	4.2 (n = 54)	1.3*	3 (n = 16)	0.16	4.2	1.5*	3.08	0.17
Median amplitude (μV)	27.1 (n = 54)	15.9	40.3 (n = 16)	15.2	32.4	20.5	35.1	15.6
Ulnar latency (ms)	3.7 (n = 54)	1.41*	2.7 (n = 16)	0.2	4.6	2.3*	2.54	0.25
Ulnar amplitude (μV)	27 (n = 54)	18.5†	31.9 (n = 16)	14.9	28.1	18.6	35	15.3
Sural latency (ms)	4.9 (n = 44)	3.2‡	3.8 (n = 11)	0.28	4.4 (n = 24)	1.4†	3.8 (n = 17)	0.32
Sural amplitude (m/sec)	11 (n = 44)	8.4†	14.2 (n = 11)	5.9	11.2 (n = 24)	10.5†	21.7 (n = 17)	19.2

Notes: With respect to the 20 normal patients, no abnormal values were observed for each measurement except for the tibial motor nerve measurements, in which the velocity was slightly reduced (41 ms), with the cutoff for normal being > 41 ms. For cases in which the number of patients was not the same as that shown in the column heading, the actual number (n) is given within the table.

*$p < 0.001$.
†$p < 0.05$.
‡$p < 0.02$.
§$p < 0.01$.

Table 6.—Percentages of Individuals with Various Numbers (0–7) of Nerves Showing Abnormal Nerve Conduction Measurements (Latency Onset, Amplitude, or Velocity), for Mixed (Motor and Sensory), Motor, and Sensory Neuropathies

No. of nerves with abnormal measurements	Neuropathy		
	Mixed (n = 55) (%)	Motor (n = 17) (%)	Sensory (n = 27) (%)
0	0.0	0.0	11.1
1	1.8	41.2	33.3
2	38.2	47.1	33.7
3	23.6	5.9	18.5
4	21.8	5.9	—
5	10.9	—	—
6	1.8	—	—
7	1.8	—	—

Notes: Among the 20 controls, 1 individual had an abnormal measurement for the tibial motor nerve (velocity = 41 ms), resulting in an abnormal rate of 0.4% for all motor nerve measurements. No abnormalities were seen among the controls for the other 4 motor nerves or the 3 sensory nerves.

cantly increased vs. controls. Amplitudes for all motor nerves were not significantly different from controls. Velocities for the median (56.5 ± 7.8 m/sec, $p < 0.02$), ulnar (60.9 ± 9.9 m/sec, $p < 0.01$), and tibial (46.6 ± 11.3 m/sec, $p < 0.05$) motor nerves were significantly decreased vs. controls. Latencies for the median (4.2 ± 1.3 ms, $p < 0.001$), ulnar (3.7 ± 1.41 ms, $p < 0.02$), and sural (4.9 ± 3.2 ms, $p < 0.02$) sensory nerves were significantly increased vs. controls. Amplitudes for the ulnar (27 ± 18.5 μV, $p < 0.05$) and sural (11 ± 8.4 μV, $p < 0.5$) sensory nerves were significantly decreased compared with controls.

In patients with only motor nerve neuropathy, latencies for ulnar (3.7 ± 2.05 ms, $p < 0.02$), peroneal (5.5 ± 1.2 ms, $p < 0.001$), and tibial (6.2 ± 3 ms, $p < 0.01$) nerves were significantly increased; amplitudes for the median (7.6 ± 3.3 μV, $p < 0.05$), peroneal (4.2 ± 1.9 μV, $p < 0.01$), and tibial (8.1 ± 4.8 μV, $p < 0.5$) nerves were significantly decreased; and velocities for the median (55.9 ± 5.3 m/sec, $p < 0.01$), ulnar (60.4 ± 7.4 m/sec, $p < 0.02$), peroneal (47.5 ± 13.3 m/sec, $p < 0.05$), and tibial (47.3 ± 5.5 m/sec, $p < 0.05$) nerves were significantly slower than the controls. Latencies and amplitudes for the sensory nerves (median, ulnar, and tibial) were not significantly different from control values.

In patients with only sensory neuropathy, latencies for the median (4.2 ± 1.5 ms, $p < 0.001$), ulnar (4.6 ± 2.3 ms, $p < 0.001$), and sural (4.4 ± 1.4 ms, $p < 0.05$) nerves were significantly increased vs. controls; amplitudes of the sural nerve (11.2 ± 10.5 μV, $p < 0.05$) were significantly decreased; and all neurophysiological measurements tended to differ from the control values. None of the measurements for motor nerves in this group—except for peroneal latency ($p < 0.001$) and amplitude ($p < 0.01$)—were different from the controls.

Table 6 summarizes the data for the percentages of patients with various numbers of nerves that demonstrated abnormal conduction. In those patients with mixed neuropathy, all nerves had abnormal measurements with a distribution as follows: 1 involved nerve (5.5%), 2 involved nerves (38.2%), 3 involved nerves (23.6%), 4 involved nerves (21.8%), and 5 or more involved nerves (14.5%). Of those patients who exhibited motor neuropathy, 41.2% had only 1 involved nerve, whereas 58.9% had 2 or more involved nerves. Patients with sensory neuropathy had the following distribution: 11.1% had nerves with no abnormal findings, 33.3% had only 1 nerve with abnormal measurements, and 52.2% had 2 or more nerves with abnormal measurements.

Discussion

All patients in this study had documented exposure to molds in their homes and/or workplaces. They also had significantly elevated antibodies to molds and to mycotoxins, which confirmed exposure.[63–65] In addition, multiple organ symptoms were present, as reported previously.[63] In this particular group of patients, additional health complaints consisted of symptoms of peripheral neuropathy (i.e., tingling, numbness, tremors, and muscle weakness in the extremities). Thus, we evaluated these patients for the presence of antibodies to 9 neural antigens, as well as for evidence of abnormalities in peripheral nerve conduction. All patients had significant increases in autoantibodies against neural antigens (Tables 1–4). Abnormalities in latencies, amplitudes, and velocities of selected peripheral nerves (Tables 5 and 6), and peripheral neuropathy, were observed in 99 patients, whereas 20 symptomatic patients had normal NCV measurements.

Examination of the patients' antibody titers revealed that IgG antibody titers to the neural antigens between patients with abnormal vs. normal NCVs were not significantly different, with the exception of NAF ($p < 0.01$). However, when compared with healthy controls, the difference between IgG titers for abnormal vs. normal patients was highly significant ($p < 0.001$). In contrast, IgM titers in abnormal patients were consistently elevated when compared with normal patients, with significant differences for $CONSO_4$ ($p < 0.05$), glutamate receptor ($p < 0.01$), tubulin ($p < 0.01$), and NAF ($p < 0.01$). Autoantibodies in both abnormal and normal patients showed significant elevations compared with controls ($p < 0.001$). With respect to IgA antibodies, NAF titers were significantly elevated in abnormal vs. normal patients. The titers for both abnormal and normal patients were significantly elevated compared with controls, with the exception of GM_1 and glutamate receptor. Thus, we concluded that exposure to molds,

and symptoms of peripheral neuropathy, are associated with autoantibodies to 9 different neural antigens. These data support and extend the observations of Gray et al.,[30] who demonstrated increased antibodies to myelin and NAF in mold-exposed individuals.

Autoantibodies to neural antigens have been reported for several neurological conditions.[66,72] Pestronk et al.[66] confirmed that elevated titers of MAG antibodies in patients are relatively specific for sensory and motor polyneuropathy syndromes with demyelination. NCVs were used to confirm the demyelinating changes in these patients. Of the patients studied, 92% with IgM antibodies to MAG had physiologic evidence of demyelination.[66] MS patients have shown antibodies to myelin, MOG, MBP, α-B-crystallin, and complement-mediated demyelination.[68,73] Anti-ganglioside, anti-glycolipid, anti-sulfatide, anti-MAG, anti-tubulin, and anti-$CONSO_4$ antibodies have been demonstrated in motor, sensory, and polyneuropathies with demyelination.[72–86] IgM isotypes to sulfatide,[74,75,77] ganglioside,[78] and MAG[83] are correlated with electrophysiological peripheral nerve abnormalities. Moreover, antigangliosides and galactocerebroside antibodies are associated with infections from *Campylobacter jejuni* and *Mycoplasma pneumoniae* in patients with Guillain-Barre syndrome.[81] In addition, IgM, anti-MAG, anti-glycolipids, and anti-NAF antibodies are present in individuals with chronic demyelinating conditions of the nervous system.[67,73,83,86] Thus, we suggest that the presence of autoantibodies to neural antigens in our patients is the result of exposure to toxic metabolites[13–23,60,61] of molds, or may result from an infectious process. The presence of abnormal T and B cell function of the immune system[30] in nasal,[41] pulmonary,[39,40] and neurologic[87,88] infections by molds supports this conclusion. Finally, we have observed increased T cell activation; C3 and C4 complements; and IgA, IgM, and IgG immune complexes in 33 patients who had chronic exposure to molds in a water-damaged building, which suggests an inflammatory process (manuscript forthcoming).

The ORs in Table 3 are also revealing. IgM isotypes against the neural antigens had ORs consistently greater (range = 3.39–44.6) than those for IgG isotypes (range = 0.66–17.26), with the exception of antitubulin (55.1 vs. 24.8). The ORs indicate an increased risk of developing antineural antibodies, but also may suggest that IgM isotypes are more consistent with symptomatic active or progressive neuropathy than are IgG isotypes, and may represent an ongoing acute or subacute process. As mentioned earlier, IgM antibodies to various neural antigens have been associated with neurophysiological and pathological changes characteristic of various neuropathies. Finally, the ORs in Table 4 for the percentages of individuals with 1 or more isotypes against the neural antigens show a relative increased risk (range = 2.8–33.58) of developing autoantibodies. The only exception was GM_1 autoantibodies (OR = 0.91). Thus, we concluded that individuals exposed to molds in a water-damaged building have an increased risk of developing antineural antibodies. Additional work is needed to determine at what point these processes become irreversible.

Our neurophysiological data revealed 3 different types of peripheral neuropathies: mixed sensory–motor polyneuropathy (55 abnormal patients), motor neuropathy (17 abnormal patients), and sensory neuropathy (27 abnormal patients), as well as patients who exhibited symptoms but had no abnormal electrophysiological findings (20 normal controls) (Table 5). The differences between the 20 normal patients and the 99 abnormal patients are likely attributable to the significant increase in IgG and IgM autoantibodies to NAF, tubulin, glutamate receptor, and $CONSO_4$ observed in the abnormal patients. The role that IgA antibodies play is unclear at this time. Additional observations are needed to clarify the role of each isotype (IgA, IgM, and IgG) and to determine which neural autoantibodies contribute to the observed neuropathies.

The increased latencies for motor and sensory nerves observed in the 55 patients with mixed neuropathy suggest a demyelinating process.[83] The increased latencies were accompanied by a decrease in velocities for the median, ulnar, peroneal, and tibial nerves. All three sensory nerves (median, ulnar, and sural) exhibited increased latencies and decreased amplitudes. Thus, the polyneuropathy observed in these patients appears to be a demyelinating process with decreased number and size of fibers (decreased amplitudes) and chronic involvement of the nerve (decreased velocities).[72,83] Those with motor neuropathies (17 patients) had decreases in latencies (ulnar, peroneal, and tibial nerves), decreased amplitudes (median, peroneal, and tibial nerves), and decreased velocities (median, ulnar, peroneal, and tibial nerves). This appears to be a diffuse neuropathy and may involve some demyelination.[89] Finally, those with sensory neuropathies (27 patients) had increased latencies for all 3 nerves, whereas the sural nerve had a decreased amplitude. The increased latencies and decreased amplitude of the these nerves suggest that demyelination is occurring.[90]

The severity of the neuropathies experienced by the patients in our study is implicit as a result of the involvement of several nerves (Table 6). With respect to the mixed-neuropathy patients, only 1.8% had abnormalities in only 1 nerve, whereas 38.2% had at least 2 nerves involved. The remaining patients (59.5%) had 3 or more nerves with abnormal neurophysiological recordings. Impairments in the patients with motor neuropathy were slightly less dramatic, with 41.2% having a single nerve involvement, and the remainder having 2 or more nerves involved. Finally, in those patients with sensory neuropathy, 33.3% had 1 nerve and 52.2% had

2 or more nerves involved. Thus, we concluded that the neuropathies in these patients were severe and in many cases involved several nerves.

In summary, 119 individuals exposed to mold colonies in water-damaged buildings were found to have autoantibodies directed against 9 different neural antigens. Neurophysiological recordings for latencies, amplitudes, and velocities on 4 motor nerves and 3 sensory nerves revealed peripheral neuropathies in 99 patients (83%). Three abnormal conditions were found: mixed sensory–motor polyneuropathy, motor neuropathy, and sensory neuropathy. We recommend that mold-exposed individuals with symptoms of neuropathy be evaluated for antibodies against neural antigens and for neurophysiological abnormalities. Additional work is needed to correlate and clarify the extent of the peripheral nerve pathology and demyelination, as well as the role of neural autoantibodies in this process.

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