The Stiff-Person Syndrome: An Autoimmune Disorder Affecting Neurotransmission of γ-Aminobutyric Acid

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The stiff-person syndrome, a rare and disabling disorder, is characterized by muscle rigidity and episodic spasms that involve axial and limb musculature. Continuous contraction of agonist and antagonist muscles caused by involuntary motor-unit firing at rest are the hallmark clinical and electrophysiologic signs of the disease. Except for global muscle stiffness, results of neurologic examination are usually normal. Results of conventional computed tomography and magnetic resonance imaging of the brain are also normal.

The cause of the stiff-person syndrome is unknown; however, an autoimmune pathogenesis is suspected because of 1) the presence of antibodies against glutamic acid decarboxylase (GAD), the rate-limiting enzyme for the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid (GABA); 2) the association of the disease with other autoimmune conditions; 3) the presence of various autoantibodies; and 4) a strong immunogenetic association. Anti-GAD antibodies, which are found in high titers in most patients, seem to be directed against conformational forms of GAD. New evidence suggests that these antibodies may be pathogenic because they interfere with the synthesis of GABA. In addition, a reduction in brain levels of GABA, which is prominent in the motor cortex, has been demonstrated with magnetic resonance spectroscopy in patients with the stiff-person syndrome.

The stiff-person syndrome is clinically elusive but potentially treatable and should be considered in patients with unexplained stiffness and spasms. Drugs that enhance GABA neurotransmission, such as diazepam, vigabatrin, and baclofen, provide mild to modest relief of clinical symptoms. Immunomodulatory agents, such as steroids, plasmapheresis, and intravenous immunoglobulin, seem to offer substantial improvement. Results of an ongoing controlled trial will elucidate the role of these agents in the treatment of the disease.

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Dr. Dalakas (Neuromuscular Diseases Section, National Institutes of Neurological Diseases and Stroke [NINDS], National Institutes of Health [NIH], Bethesda, Maryland): In 1956, Moersh and Woltman (1) reported a series of 14 patients with unexplained fluctuating rigidity and spasms who had visited the Mayo Clinic over a 32-year period. These authors called this entity the *stiff-man syndrome* because the patients did not have extrapyramidal disease, pyramidal tract dysfunction, or any other known neurologic disorder that could explain the stiffness. Since that report was published, several cases of this rare disorder—which is preferably called the *stiff-person syndrome*—have been reported in both men and women, and new cases are increasingly being recognized. The stiff-person syndrome causes substantial disability and is therefore of interest to various specialists, including neurologists, internists, rheumatologists, diabetologists, immunologists, and rehabilitation physicians (1–6). During the past 2 years, we studied the stiff-person syndrome to better define the disease, explore its pathogenetic mechanisms, and apply specific therapies.

It may seem that the stiff-person syndrome is elusive and requires a high degree of suspicion for diagnosis; however, in a typical presentation, the stiff-person syndrome is not difficult to identify. In our series, 20 consecutive patients—12 of whom have participated in a controlled trial—presented with two sets of symptoms: muscular rigidity and episodic spasms superimposed on the rigidity. The rigidity, which is characterized by tightness and stiffness, begins insidiously, over several months, at the axial muscles—especially the thoracic and lumbar spine—and spreads to the legs. The hallmark sign is the continuous contraction of the agonist and antagonist muscles; in the trunk, this produces a boardlike appearance. Hyperlordosis is caused by co-contraction of the abdominal and thoracolumbar paraspinal muscles.

In our series, 9 of 12 patients had an asymmetric presentation: One leg was affected more than the other (*stiff-limb syndrome*) (7), and the stiffness eventually spread to other areas of the body, includ-

ing the trunk. If the stiffness spreads to the respiratory and thoracic musculature, patients may have difficulty breathing. Eight of 12 patients experienced breathing problems caused by chest restriction and thoracic muscle stiffness (which was aggravated by anxiety and fear).

Previous reports have stated that the muscles of the face are not involved in this disorder (1–6); however, we observed stiffness in the facial muscles in 10 of 12 patients. At times, the patients' faces had the appearance of emotionless masks. In the stiff-person syndrome, rigidity fluctuates at first but gradually becomes fixed, affecting both the agonist and antagonist muscle groups and resulting in rigidity of the abdominal wall, hyperlordosis, difficulty walking or bending, and frequent falls. On palpation, the muscles feel similar to rocks, particularly in the lumbar spine, which is rigid. In almost all of our patients, we had to perform lumbar puncture under fluoroscopy. Except for global stiffness in the extremities, results of neurologic examination were normal; patients had normal muscle strength and no evidence of extrapyramidal or pyramidal tract signs. The tendon reflexes were normal or sometimes brisk but without the Babinski sign.

The second set of symptoms, episodic spasms, are sudden and may cause falls; patients may fall 3 to 4 times per month. Unexpected noises or tactile stimuli and emotional upset or fear precipitate the spasms, which are sometimes painful. In patients with the stiff-limb syndrome, the spasms are superimposed on the stiff leg and cause limping or difficulty walking. The gait is stiff, deliberate, and slow. Some of our patients did not want to walk unassisted because they were afraid of falling; other patients could not initiate gait. In some patients, unexpected stimuli caused a sudden freeze or fall. Although our 12 patients exhibited normal strength, 8 needed a cane to walk and 5 needed a walker because of truncal stiffness and sudden falls en bloc.

Howard (8) found that the spasms usually improve with use of diazepam. The response to high-dose diazepam has been used to help confirm the clinical diagnosis of the stiff-person syndrome, although it is not always a reliable sign. The diagnosis of the stiff-person syndrome remains clinical and one of exclusion. Patients should have the above-described symptoms, normal strength, no abnormal movements or dystonia, and no extrapyramidal or pyramidal tract signs. The blood chemistry is usually normal, but we noted a mildly elevated creatine kinase level in 4 of 12 patients.

Diseases that should be differentiated from the stiff-person syndrome include chronic tetanus, which is extremely rare; various types of dystonia and extrapyramidal disease, which are easily excluded on the basis of the clinical examination; psychogenic disease; and neuromyotonia, a rare peripheral nerve disease characterized by rippling painful muscle spasms (which, contrary to those seen in the stiff-person syndrome, persist after nerve block, anesthesia, and sleep and have typical electromyographic findings) (1–6). Several of our patients initially received a tentative diagnosis of a conversion syndrome or some kind of psychogenic process because their presentation was dominated by task-specific phobias and their stiffness was precipitated by unexpected noises or mental anticipation. A good response of the stiffness to diazepam, which is given to control the phobias, is often thought to confirm phobic neurosis rather than the stiff-person syndrome. When overwhelming anxiety and fear overshadow the stiffness from the time of disease onset, it may be difficult to distinguish the stiff-person syndrome from a psychogenic disorder.

The origin of the stiff-person syndrome is central. Approximately 10% of patients have seizures, the stiffness improves or disappears during sleep or anesthesia, and the symptoms improve with drugs that enhance brain levels of γ-aminobutyric acid (GABA), such as diazepam or valproic acid. Malfunction of the inhibitory networks in the central nervous system mediated by GABA or glycine—the two main neurotransmitters that facilitate inhibition—seems to play a major role in the manifestation of the stiffness. A proposed mechanism for the development of stiffness and spasms through the involvement of the main inhibitory network is depicted in **Figure 1**.

Inhibitory Pathways Defined by Electrophysiology

Dr. Mary Kay Floeter (Electromyography Section, NINDS, NIH, Bethesda, Maryland): Electromyography is a useful technique that detects firing of motor-unit action potentials in muscles. Motor-unit action potentials have a characteristic appearance and discharge rate that can be readily distinguished from other abnormal discharges associated with muscle stiffness, such as myotonia. In healthy persons, motor units do not fire when the muscles are at rest; firing occurs only during voluntary contraction. In patients with the stiff-person syndrome, a continuous background of motor-unit firing occurs despite the patient's attempts at muscle relaxation. This continuous, involuntary motor-unit firing at rest is the physiologic hallmark of the stiff-person syndrome.

Another abnormality in the stiff-person syndrome is co-contraction: When the patient attempts to contract a muscle to move in one direction, muscles that pull in the opposite direction are involuntarily

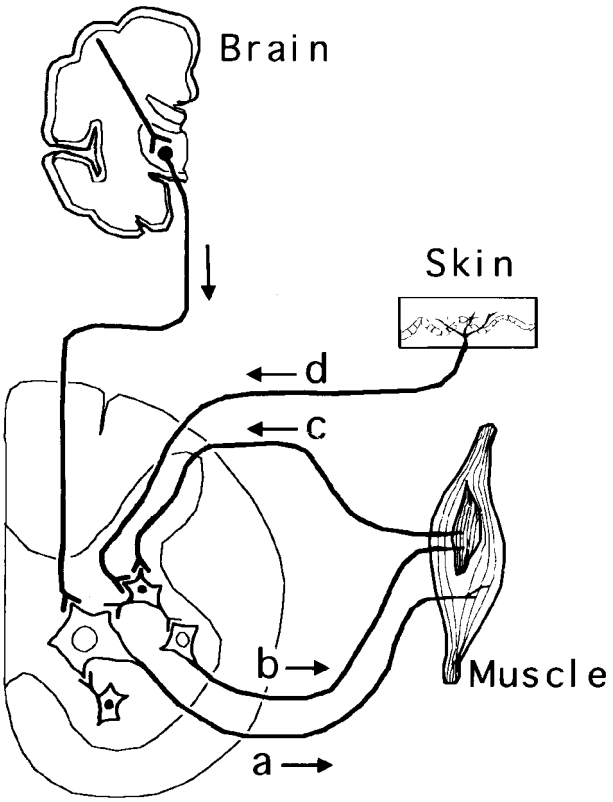

Figure 1. Proposed mechanism of development of stiffness in the stiff-person syndrome. Impairment of intracortical inhibitory neurons causes corticospinal neurons in the motor cortex to discharge heavily to the alpha motor neurons. The increased excitation to the spinal cord causes excessive firing by alpha motoneurons (*a*). The loss of spinal inhibitory circuits, represented by two inhibitory motor neurons (illustrated with solid dots in center), enhances the motoneuron hyperexcitability and may increase discharges from γ motor neurons to the muscle spindles (*b*). Excessive responses to afferent impulses from muscle spindles (*c*) and skin afferents (*d*), caused by impaired inhibitory interneurons, may explain the increased stiffness after sudden tactile stimuli.

activated (9). Normally, the timing of the contraction of a muscle that moves the limb in one direction and the contraction of the antagonist muscle that moves it in the opposite direction have a reciprocal relation. The nervous system is usually wired so that contraction of the prime mover muscle is coupled with relaxation in the antagonist muscle. Several circuits in the brain and spinal cord mediate this reciprocal inhibition, including two spinal circuits that use different inhibitory transmitters. One spinal circuit uses a glycinergic inhibitory interneuron that synapses on the motoneurons to produce direct, postsynaptic inhibition; the other circuit relays through a GABAergic interneuron that synapses on the presynaptic terminals of certain sensory inputs.

The loss of GABAergic input into motor neurons is thought to produce the tonic firing of motor neurons at rest and lead to their excessive excitation in response to sensory stimulation. To determine whether GABAergic inputs are hypoactive, Floeter and colleagues (10) measured the strength of reciprocal inhibition between pairs of antagonist muscles. Other inhibitory reflexes mediated by glycinergic neurons through spinal cord circuits were also tested. Although certain GABAergic inhibitory reflexes were impaired, the spinal circuits mediating reciprocal inhibition were normal; this finding suggests that the impaired reciprocal inhibition in the stiff-person syndrome is located in supraspinal circuits.

Sandbrink and coworkers (11) tested the excitability of the motor cortex by using transcranial magnetic stimulation, a noninvasive technique that uses a coil on the scalp to produce a transient magnetic field within the motor cortex. The magnetic field induces a brief discharge of corticospinal neurons, which evokes a muscle contraction—the motor-evoked potential. A paired-pulse method was used to test intracortical circuits. The first pulse has a very small intensity that is below the threshold for producing a motor-evoked potential but is strong enough to activate intracortical circuits. When this pulse is followed by a second pulse strong enough to cause a motor-evoked potential when received alone, the motor-evoked potential is inhibited at short intervals and facilitated at longer intervals. These changes are thought to reflect the balance between inhibitory and excitatory intracortical circuits. Patients with the stiff-person syndrome had a significantly greater facilitation: Motor-evoked potentials were 2 to 2.5 times greater than those of controls (11), indicating hyperexcitability of the motor cortex that was probably caused by a loss of intracortical inhibition by GABAergic neurons of the cerebral cortex.

These studies have shown that although the functioning of some GABAergic inhibitory circuits in the brain and spinal cord are impaired in the stiff-person syndrome, others may be spared. One explanation for such apparent selectivity may be the presence of additional inhibitory transmitters in some populations of GABAergic neurons that compensate for the loss of GABA. This possibility is supported by recent experimental observations that some classes of spinal interneurons contain both GABA and glycine in the same synaptic vesicle (12); it may also be explained by differences in the antigenic determinants among GABAergic neurons and their accessibility to or recognition by antibodies against glutamic acid decarboxylase (GAD).

Autoantibodies and Immunopathogenesis of the Stiff-Person Syndrome

Dr. Dalakas (Neuromuscular Diseases Section, NINDS, NIH, Bethesda, Maryland): In 1988, it was found that patients with the stiff-person syndrome have antibodies against GAD-65, which is the rate-

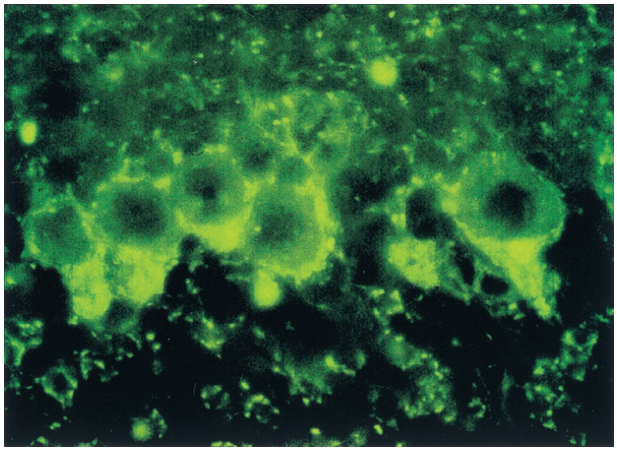

Figure 2. Cross-section of rat cerebellum immunostained with serum from a patient who has the stiff-person syndrome and with fluorescence-conjugated antihuman IgG. Intense and specific staining of the Purkinje cells and γ-aminobutyric acidergic synapses can be seen.

limiting enzyme for the synthesis of GABA at the GABAergic nerve terminals (13). Up to 65% of patients may have antibodies against the two isoforms of GAD, GAD-65 and GAD-67 (13–20). Because GAD is also present in the pancreatic cells, serum specimens from patients with the stiff-person syndrome who are positive for anti-GAD antibodies also stain the β cells of the pancreas (14). Low titers of anti-GAD antibodies are detected in patients with type 1 diabetes, and up to 30% of patients with the stiff-person syndrome also have diabetes (13–20).

Nature of Autoantibodies

The serum of patients with the stiff-person syndrome binds to GABAergic neurons and synapses in both human and rat brains (5, 14, 15), as shown in **Figure 2**. On Western blot assay of homogenates from a rat brain, serum from a patient with the stiff-person syndrome recognizes a 65-kDa protein, which corresponds to GAD-65 (as confirmed by the presence of monoclonal antibodies against GAD). The serum samples from our patients with type 1 diabetes did not immunostain GAD-65 on Western blot assay. The anti-GAD antibody titers can be quantified by using enzyme-linked immunosorbent assay. In our series, all 12 patients, whose serum immunostained the GABAergic neurons in the rat brain, had very high anti-GAD antibody titers (range, >32 μg/mL; optical density, 0.3 to 0.8). In contrast, patients with type 1 diabetes had anti-GAD antibody titers 50 times lower than those in patients with the stiff-person syndrome. Among the 47 patients with other autoimmune neuromuscular diseases that we examined, only 4 patients (3 with myasthenia gravis and 1 with dermatomyositis) had anti-GAD antibodies; however, these antibodies were present at very low titers (range, 100 to 1000 ng/mL; optical density, 0.3). The remaining 43 patients with other neuromuscular diseases had titers from 0 to 32 ng/mL (optical density, 0.1).

The epitope of the GAD antigen may also differ between patients with type 1 diabetes and those with the stiff-person syndrome (19, 20). In contrast to patients with type 1 diabetes, the antibodies in patients with the stiff-person syndrome seem to be against the conformational forms of GAD-65 and GAD-67 and recognize the denatured GAD-65 on Western blot assay. Differences in epitope specificity may explain why incidence of the stiff-person syndrome in persons with diabetes is low (about 1 in 10 000 persons). Other immunologic differences may also be important and require further study. For example, in patients with type 1 diabetes, a Th-1 response is seen with upregulation of interleukin-1 and interferon-γ and generation of cytotoxic T cells against the GAD of the pancreatic β cells. In patients with the stiff-person syndrome, however, the very high anti-GAD titers may be consistent with a Th-2 response, in which relevant cytokines, such as interleukin-6 and interleukin-4, suppress a T-cell–mediated cytotoxicity (20).

Possible Pathogenesis of Antibodies to Glutamic Acid Decarboxylase

The possibility of pathogenesis anti-GAD antibodies has been considered (20, 21) because 1) GAD

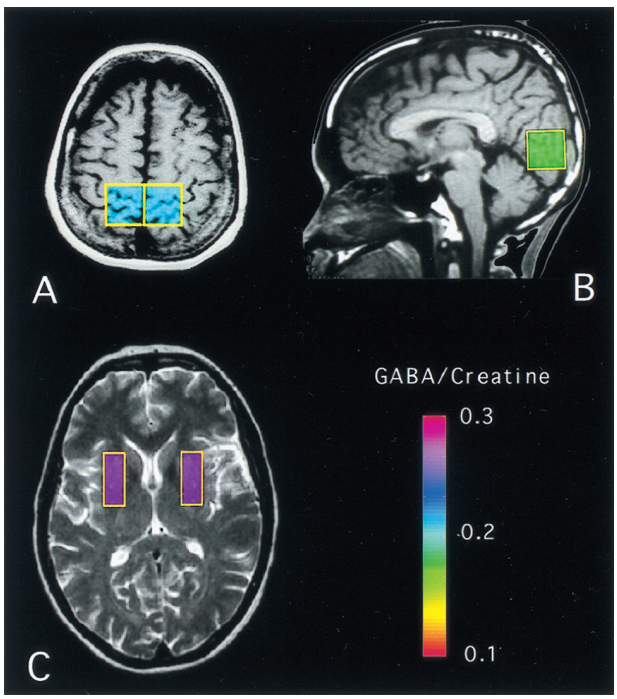

Figure 3. Conventional axial and sagittal magnetic resonance images of an unaffected person's brain. A. Placement of selected regions of interest in motor cortex. **B.** Placement of selected regions of interest in posterior occipital cortex. **C.** Additional regions of interest in the putamen. Average γ-aminobutyric acid (*GABA*) levels (expressed as ratios to creatine), obtained by magnetic resonance spectroscopy in unaffected persons, are displayed by using a color scale.

is a cytoplasmic antigen that may not be recognized by the immune system, 2) the stiff-person syndrome does not induce specific histopathologic changes in the brain, and 3) the pathogenic significance of anti-GAD antibodies is unknown. Recent data suggest that anti-GAD antibodies can be pathogenic. First, certain peptide fragments of GAD can be expressed at the cell surface during exocytosis of GABA and be presented to T-cell receptors by the antigen-presenting cells. Second, anti-GAD antibodies may block the function on still-intact cells rather than cause structural changes in GABAergic neurons. Improvement in patients who received various types of immunotherapy (22–25), lack of abnormal neurologic signs other than increased muscle tone, and reduction of GABA in the cerebrospinal fluid and the brain (as demonstrated by cerebrospinal fluid examination and magnetic resonance spectroscopy, in the absence of structural lesions seen on magnetic resonance imaging) support the view that the stiff-person syndrome is a functional disorder rather than a structural one. Third, it has now been shown that the IgG anti-GAD antibodies in the serum and cerebrospinal fluid of patients with the stiff-person syndrome inhibit GAD activity and affect the in vitro synthesis of GABA in crude extracts of rat cerebellum; IgG from patients without anti-GAD antibodies, however, does not have this effect (26). Although the effect of anti-GAD antibodies in vivo has not yet been established, the data on their in vitro effect suggest that these antibodies cause a functional impairment in the synthesis of GABA in persons with the stiff-person syndrome; therefore, anti-GAD antibodies should be considered to play a pathogenic role in the disease. Changes in the antibody titers after improvement with immunotherapy will be useful to support this view. Transmission of the disease in animal models, characterization of the GAD epitope, and a search for the presence of GAD-specific T cells are needed to establish the autoimmune hypothesis of the stiff-person syndrome.

Immunogenetics and Other Concurrent Autoimmune Diseases

We looked at the immunogenetic background of 13 antibody-positive patients with the stiff-person syndrome and found that all of them had alleles in the HLA-DR or DQ haplotypes; this finding confirms previous reports on a small series of patients (27). The stiff-person syndrome was associated with high frequency (up to 100%) of alleles in the DRβ_1 locus (0301, 0101, 03, 04, 13, 4) and the DQβ_1 locus (0202, 03, 05, 06). In contrast, the frequency of these alleles in the general population is 0% to 15% for the DRβ_1 locus and 1% to 28% for the DQβ_1 locus. The strong immunogenetic background of a patient with the stiff-person syndrome who is anti-GAD–positive is also consistent with the noted frequent association of the disorder with various autoantibodies and other autoimmune diseases. Five of our 12 patients with the stiff-person syndrome had type 1 diabetes, 3 had thyroiditis, 2 had a mild inflammation on muscle biopsy that was similar to polymyositis, and 2 had pernicious anemia. Four patients had antiparietal cell antibodies, 4 had antinuclear antibody titers ranging from 1:80 to 1:1280, 3 had antithyroidal antibodies, 1 had antibodies against Jo-1 antigen, 1 had antibodies against ribonucleoprotein, and 1 had antibodies against intrinsic factor.

Spinal Fluid Studies

Spinal fluid is abnormal in patients with the stiff-person syndrome. Among the 12 patients we examined, 8 had oligoclonal bands and 5 had increased IgG synthesis. Anti-GAD antibodies were also present in the spinal fluid in 80% of the samples we tested.

The Stiff-Person Syndrome as a Paraneoplastic Disease

In a subgroup of patients, the stiff-person syndrome is a paraneoplastic disease (17, 28–30). In these patients, the stiffness is mostly in the proximal muscles and precedes the detection of the tumor. The most common tumor seems to be breast cancer. Patients with paraneoplastic cases of the stiff-person syndrome do not have antibodies against GAD but against amphiphysin, another neuronal protein (molecular weight, 128 kDa) that is localized in neurons and synaptic vesicles (28–30). Amphiphysin antibodies may not be solely associated with paraneoplastic cases of the stiff-person syndrome; we have seen them in two patients who had myasthenia gravis without cancer (31). However, these antibodies are so rare in other conditions that their presence should trigger suspicion of an underlying neoplasm.

γ-Aminobutyric Acidergic Pathways Visualized by Multimetabolite Magnetic Resonance Spectroscopy

Dr. Lucien M. Levy (Neuroimaging Branch, NINDS, NIH, Bethesda, Maryland): Conventional magnetic resonance spectroscopic techniques can assess only a small number of metabolites in the human brain with a good degree of reliability. Alterations of cerebral metabolite levels have already been related to the pathophysiology of several neurologic disorders, including epilepsy, stroke, tumors, movement disorders, Alzheimer disease, trauma, neurometabolic diseases, mood disorders, migraine,

neuroendocrine diseases, alcoholism, and drug abuse. Conventional imaging methods, such as computed tomography or magnetic resonance imaging, have not proven fully adequate in the evaluation of these disorders. The primary information obtained from magnetic resonance imaging has usually been limited to the levels of the few largest metabolite peaks: creatine, choline, *N*-acetylaspartate, and lactate. More recently, various technical modifications have been introduced to recognize additional metabolites, such as myo-inositol, GABA, glutamine, glutamate, and glucose (32, 33). These attempts have not always been successful because of difficulties in extracting this type of information from the conventional one-dimensional spectra, which have overlapping resonant peaks. Spectral editing sequences have been used to detect additional metabolites; however, only one metabolite at a time can be selected (32, 33). Recently, two-dimensional J-resolved proton multimetabolite magnetic resonance spectroscopy has shown the possibility of obtaining all of the major cerebral metabolites in vivo in a single localized acquisition (34, 35). Further advances in the analytical processing of spectra have also helped researchers to extract information about the levels of various metabolites by the use of automated algorithms (36, 37).

Magnetic Resonance Spectroscopy

The first nuclear magnetic resonance experiments were performed in 1945 by Bloch and Purcell, who were subsequently awarded the 1952 Nobel Prize in physics. In their approach, a regular slow radiofrequency sweep was used to detect the characteristic resonant frequency of a compound. A significant advance occurred in 1966 when Ernst (who received the Nobel Prize in 1991) discovered that the sensitivity of spectra could be increased by a factor of 10 to 100 if radiofrequency pulses were used instead of a slow sweep. This finding, which made it possible for modern nuclear magnetic resonance spectroscopy to study small amounts of material, is the basis of conventional one-dimensional nuclear magnetic resonance. In 1975, the discovery of two-dimensional nuclear magnetic resonance spectroscopy resulted in a dramatic increase in resolution for the identification of larger, more complex molecules.

The conventional one-dimensional and two-dimensional nuclear magnetic resonance techniques differ in their time courses. In two-dimensional nuclear magnetic resonance, radiofrequency sequences are used instead of single pulses; this creates a second dimension of frequency spectrum. Introduction of this second dimension provides spectra of greater resolution, as if a mountain range were visualized from above (a two-dimensional view) rather than solely from its skyline (a conventional one-dimensional view).

Cerebral Metabolites

Spectroscopy is usually used to characterize metabolites in terms of total or relative concentration within each region of interest, or imaged volume element (voxel). Other characteristics (for example, flux rates) are also sometimes obtained. The in vivo concentrations of the various metabolites, including the relative sensitivity for detection by proton magnetic resonance spectroscopy (38), have been described in the literature. *N*-acetylaspartate is a compound localized exclusively in neurons (39, 40), and its changes in levels may reflect focal neuronal loss (41) or neuronal injury (42–44). Creatine reflects the total amount of creatine and phosphocreatine and is involved in energy metabolism (45). A higher concentration of creatine is seen in the gray matter than in the white matter, which indicates increased metabolic activity in the cortex compared with the white matter (46).

Ratios of various metabolites to creatine have been used in spectroscopy studies for normalization purposes (47). The concentration of choline reflects cellular density and total membrane content (48, 49) and varies with the relative amounts of gray to white matter and of glial cells to neurons (48). In the human brain, GABA is the main inhibitory neurotransmitter (50). Because the GABAergic system has certain anatomically defined projections in the brain, GABA concentration can vary substantially across different regions of the brain (51, 52). Glutamate is the main excitatory neurotransmitter in the brain and is a substrate of GABA metabolism. Glutamic acid decarboxylase produces GABA from the glutamate pool (50). In patients with the stiff-person syndrome, changes in GABA levels are thought to be related to anti-GAD antibodies. However, levels of GABA in the brains of these patients are unknown.

Evaluation of γ-Aminobutyric Acid with Magnetic Resonance Spectroscopy

We performed magnetic resonance examinations on a GE 1.5 Tesla Magnetic Resonance Unit (General Electric Medical Systems, Milwaukee, Wisconsin) in 17 normal volunteer controls and 8 patients with the stiff-person syndrome. All participants had high titers of circulating GAD antibodies and low levels of GABA in the cerebrospinal fluid. Conventional magnetic resonance images were obtained in all participants, and magnetic resonance spectra were acquired by using two-dimensional J-resolved spectroscopy (34, 35). Regions of interest, measuring 12 cm^3, were selected in regions of the motor cortex that corresponded to the lower extremities

and trunk both bilaterally and in the posterior occipital cortex (**Figure 3**). Acquisition time for each region was approximately 6 minutes. Spectroscopic data were analyzed by using software developed at the NIH that was designed to analyze the metabolite peaks of GABA, glutamate, *N*-acetylaspartate, choline, and creatine. Metabolite intensities were measured by using peaks that occurred at the characteristic chemical shifts (**Figure 4**) assigned to the largest resonances (34). Study of phantoms (template solutions of GABA) demonstrated adequate signal-to-noise ratios at physiologic GABA concentrations and good correlation between the actual GABA concentration in the phantoms and the GABA peak intensities, as measured with magnetic resonance spectroscopy ($R^2 = 0.995$). Ratios of metabolite levels to creatine levels were obtained in controls and patients and were compared by using the Student *t*-test.

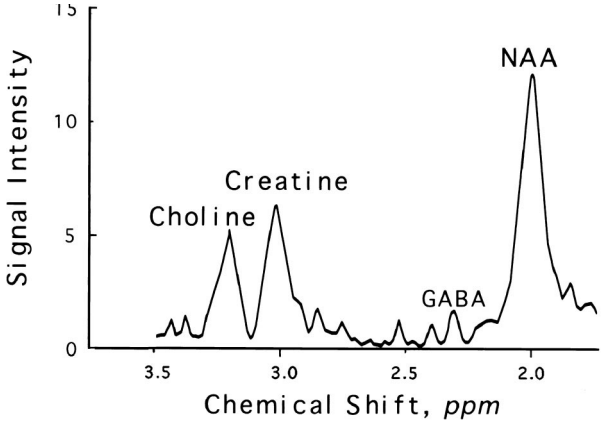

Figure 4. Two-dimensional J-resolved spectroscopy plot of the sensorimotor cortex of a patient with the stiff-person syndrome. The signal profile represents the magnitude of the metabolite peaks occurring in a two-dimensional J-resolved spectrum along the J = 0 axis, where J is the decoupling dimension variable. Decoupling of peaks by introduction of a second dimension improves separation and identification of metabolite peaks. GABA = γ-aminobutyric acid; NAA = *N*-acetylaspartate.

Regional Levels of γ-Aminobutyric Acid in the Brain

Results of conventional magnetic resonance imaging were unremarkable except for occasional nonspecific changes in the patient group. Ratios of *N*-acetylaspartate, choline, and glutamate to creatine did not show any significant abnormalities in the different brain regions of patients compared with controls. However, decreased GABA levels in the motor cortex and posterior occipital cortex were observed in patients with the stiff-person syndrome. Ratios of GABA to creatine in the motor cortices of patients (0.169 ± 0.010 for the right sensorimotor cortex and 0.133 ± 0.010 for the left sensorimotor cortex [mean ± SE]) were significantly lower than those in healthy participants (0.241 ± 0.032 for right sensorimotor cortex and 0.221 ± 0.026 for left sensorimotor cortex, corresponding to a 30% to 40% decrease; $P < 0.01$). A smaller decrease in ratios of GABA to creatine was also observed in the posterior occipital region (0.153 ± 0.008 in patients and 0.187 ± 0.010 in controls, corresponding to an 18% decrease; $P < 0.05$). The impaired GABA levels suggest that in the stiff-person syndrome, anti-GAD antibodies may interfere with the synthesis of GABA and play a major role in the clinical symptoms of stiffness. Magnetic resonance spectroscopy can be useful in evaluating patients with the stiff-person syndrome and in monitoring therapy.

Clinical Utility of Magnetic Resonance Spectroscopy

The fundamental roles of various metabolite levels and actions in mediating central nervous system function and dysfunction have been extensively discussed in the literature. Clinically, the ability to obtain cerebral metabolic information provides clinicians with a powerful, rapid, painless, and noninvasive tool to evaluate or serially follow up diseases. Present measurements of certain cerebral metabolites, such as GABA, are usually limited to measurements of concentration levels in the blood and cerebrospinal fluid. Because these measurements are not obtained directly from the brain, they only indirectly reflect general brain levels of metabolites. Furthermore, they cannot be localized to a particular anatomic region of the brain to assess localized metabolism or regional pathologic characteristics. In terms of clinical utility, direct magnetic resonance spectroscopy of the brain circumvents many of these problems and easily permits serial temporal quantitative assessment of disease progression and drug-mediated effects.

The dramatic increase in the number of metabolites simultaneously observable with magnetic resonance spectroscopy (compared with the number that can be seen with conventional spectroscopic techniques) creates a new and valuable opportunity to evaluate many important and previously unobservable metabolites. Spectroscopy can be applied in many ways, especially two-dimensional spectroscopy, which can be used in such areas as brain development and redevelopment, dementia, demyelinating diseases, depression, drug abuse, epilepsy, metabolic disorders, movement disorders, neuroendocrine diseases, schizophrenia, stroke, trauma, and tumors. Magnetic resonance spectroscopy can be used to investigate noninvasive regional intracerebral changes of particular metabolite and neurotransmitter levels and may enhance our understanding and management of certain neurologic disorders.

Therapeutic Considerations in Patients with the Stiff-Person Syndrome

Dr. Dalakas (NINDS, NIH, Bethesda, Maryland): On the basis of the pathogenesis of the stiff-person syndrome, two types of therapy can be rationally applied: 1) drugs that enhance GABA activity and 2) immunomodulators or immunosuppressants.

γ-Aminobutyric Acidergic Agents

If the reduced level of GABA, probably caused by anti-GAD antibodies, is responsible for patient stiffness, drugs that enhance GABA activity should alleviate the symptoms of the stiff-person syndrome. Howard (8) observed that patients with the stiff-person syndrome respond to high doses of diazepam. Although no controlled trials have been done, this drug (at dosages of up to 100 mg/d) has been the initial treatment of choice (53). Most patients with the stiff-person syndrome respond to diazepam to some degree and for some period of time; in fact, some clinicians have considered a dramatic clinical response to this drug as a confirmation of the diagnosis of the stiff-person syndrome. The required doses of diazepam, however, are so high that the drug is not easily tolerated and other agents are needed. Drugs affecting GABA transmission, such as vigabatrin (which decreases catabolism of GABA [33, 54]) or tiagabin (which interferes with uptake of GABA [55]), may also be helpful. Baclofen may help patients with the stiff-person syndrome by increasing GABA activity. In a double-blind, placebo-controlled trial performed in three patients, 50 μg of intrathecal baclofen improved the electrophysiologic findings of the disease more than intrathecal placebo; however, baclofen improved the physical symptoms of only one patient, and the improvement was minor (56–59).

Immunomodulators

Some reports have stated that prednisone may alleviate symptoms of the stiff-person syndrome. Plasmapheresis (60, 61) and high-dose intravenous immunoglobulin (an immunomodulating agent) (22–25, 62) have also been beneficial, but no controlled trials have been done. We are conducting a controlled trial of intravenous immunoglobulin in patients with the stiff-person syndrome, using the protocol we reported elsewhere (63). We recognize that it is difficult to objectively document stiffness because of disease fluctuations and the many variables involved. In our trial, we have been looking for changes in 1) degree of bending forward or sideways; 2) chest expansion during inhalation and exhalation; 3) sensitivity to stimuli; 4) timed activities (that is, the amount of time it takes for the patient to rise from a chair, walk 30 feet, turn, or go up and down four steps); 5) gait, which we analyze by using mathematical models of walking; 6) level of GABA in the cerebrospinal fluid and the brain, measured by using magnetic resonance spectroscopy; 7) anti-GAD antibody titers; and 8) electrophysiologic variables. We believe that the results may help us to understand the pathogenesis of the disease, clarify the role of the autoantibodies, and offer a rationale for applying immunotherapy.

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