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C. Stayer, MD; V. Tronnier, MD; J. Dressnandt, MD; E. Mauch, MD; G. Marquardt, MD; K. Rieke, MD; G. Müller-Schwefe, MD; F. Schumm, MD; and H.-M. Meinck, MD

Article abstract—We report on eight patients with stiff-man syndrome (SMS) or its "plus" variant, progressive encephalomyelopathy with rigidity and myoclonus (PERM) receiving intrathecal baclofen via pump. In six of the patients, follow-ups continued for approximately 2.5 to 6.5 years after pump implantation. Intrathecal baclofen was an effective last-resort alternative for patients who responded poorly to or did not tolerate oral antispasticity medications. General mobility increased, and spasms and rigidity were reduced; however, no complete remissions were observed either before or after pump implantation. PERM patients showed more severe and rapid progression of symptoms and more attacks of autonomic dysregulation than SMS patients. They also required higher doses and more rapid dosage increases. Complications of intrathecal baclofen therapy included spasm-induced rupture of the catheter, catheter dislocation causing radicular symptoms, and pump malfunction resulting in inaccurate dosage administration. Patients suffered fewer side effects with intrathecal baclofen than with oral medication, but overdose resulted in a transient, comalike state in one patient and sudden dosage reduction due to pump failure was fatal in another.

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Stiff-man syndrome (SMS) is a rare neurologic disorder with progressive and fluctuating muscle rigidity combined with paroxysms of painful spasms. Both rigidity and spasms can be severe enough to cause joint ankylosis, dislocations, and even fractures.[1-3] Spasms are characteristically provoked by unexpected acoustic or sensory stimuli and passive movements. They generally disappear during sleep or administration of neuromuscular blocks and can be abolished completely with diazepam.[1-3] With the exception of brisk reflexes, the neurologic examination is usually normal. Some patients, however, show additional neurologic symptoms such as ocular motor or sensory disturbances, vertigo, ataxia, or neuropsychological deficits. These symptoms most likely represent a "plus" variant of SMS—called progressive encephalomyelopathy with rigidity and myoclonus (PERM).[3] Current studies support the notion of an autoimmune pathogenesis. At least 60% of all SMS/PERM patients have autoantibodies against glutamic acid decarboxylase (GAD), known to catalyze the conversion of glutamate to gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter of the CNS.[4]

Attempts at treating the disease with immunosuppression[3] and plasmapheresis[3,5-8] have yielded conflicting results. The standard therapy for patients with SMS/PERM has been the GABA neuromodulator diazepam. Initial results are usually good but adaptation and disease progression make increased doses (up to 200 mg/day) necessary.[2,3] The subsequent side effects (sedation, dysarthria, vertigo, or ataxia) as well as the risk of addiction limit the applicability of high-dose oral therapy. Clinical trials with intrathecal baclofen, a GABA-B agonist, have recently been reported on patients with spasticity refractory to oral medications.[9-11] Intrathecal administration enables fourfold increases in CSF levels with only 1/100 the usual oral dosage,[12] thereby increasing efficacy while reducing the incidence of side effects. Preliminary reports on SMS patients receiving intrathecal baclofen have been controversial, but few such patients have been reported in the literature.[13-17] We have been following eight patients receiving intrathecal baclofen over the span of up to 6.5 years and report them here.

Patient reports. *Patient 6.*[18] Patient 6 (D.H.) was born in 1959. His symptoms began at the age of 25 years with stiffness of the paravertebral muscles and gait unsteadiness leading to frequent falls. Painful spasms gradually

From the Departments of Neurology (Drs. Stayer, Rieke, and Meinck) and Neurosurgery (Dr. Tronnier), University of Heidelberg; Department of Neurology (Dr. Dressnandt), Technical University of Munich; Fachklinik für Neurologie (Dr. Mauch), Ulm-Dietenbronn; Department of Neurosurgery (Dr. Marquardt), University of Frankfurt; the Pain-Clinic (Dr. Müller-Schwefe), Göppingen; and the Department of Neurology (Dr. Schumm), Christophsbad, Göppingen, Germany. Supported by grants from the Volkswagen Stiftung (VW) and the medical faculty of the University of Heidelberg.

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Address correspondence and reprint requests to Dr. Hans-Michael Meinck, Department of Neurology, University of Heidelberg, Im Neuenheimerfeld 400, D-69120 Heidelberg, Germany.

Table 1 *Survey of SMS/PERM patients receiving intrathecal baclofen*

					Before baclofen		Baclofen dosage		
Patient*	Sex	Age (y)	Diagnosis	GAD	SMS duration	Oral drugs	Bolus (μg)	Start (μg)	End (μg)
1/H.C.	M	64	PERM	−	3 mo	Diazepam Clonazepam Baclofen Tizanidine	100	150	400
2/M.K.	F	65	PERM	+	2 y	Diazepam Baclofen Tizanidine Valproate	50 100 150	240	1,440
3/G.W.	M	36	PERM	+	1.5 y	Diazepam (iv) Baclofen Tizanidine	150 200	200	200
4/K.P.	F	69	SMS	+	1.5 y	Clonazepam Tizanidine Carbamazepine Tetrazepam	40	50	58.5
5/C.B.	F	26	SMS	−	1.5 y	Diazepam Baclofen Tizanidine	50 75	120	925
6/D.H.	M	33	SMS	−	4 y	Diazepam Clonazepam Baclofen Tizanidine Valproate	150	200	530
7/L.K.	M	63	PERM	+	4 mo	Diazepam Baclofen Tizanidine	50 75	200	1,500
8/V.H.	M	27	PERM	+	9 y	Clonazepam Baclofen Tizanidine Valproate	150	200	220
A	M	42	SMS	?	7 y	Diazepam	75	120	1,200
B	F	63	SMS	+	4 y	Narcotics Diazepam	75	120	120
C	F	61	SMS	+	1.5 y	Diazepam (iv) Clonazepam Baclofen	75 100 1,000	260	260
D	F	64	SMS	+	?	Baclofen Diazepam Valproate	50 75 100	—	—
3/patients	?	?	SMS	+	Range, 4–10 y	Diazepam Clonazepam Baclofen Valproate Prednisone	50	—	—

* Our patients are Patients 1 through 8. Patients from the literature are indicated by letters A through D

GAD = glutamic acid decarboxylase; SMS = stiff-man syndrome; M = male; F = female; PERM = progressive encephalomyelopathy with rigidity and myoclonus, + = presence of anti-GAD antibodies; − = absence of anti-GAD antibodies.

developed in the legs and lower back. They appeared at rest, during movement, and in response to unexpected acoustic and sensory stimuli. Ambulation deteriorated as the symptoms progressed and by the age of 33 years he was confined to a wheelchair. In the examination, scoliosis of the lumbar vertebrae, and boardlike rigidity in the neck, shoulder, and upper back muscles were noted. Passive hip flexion was limited to 45 degrees in the right leg and 10 degrees in the left; dorsal and plantar flexion of the feet was nearly impossible. Even the slightest passive abduction or rotation of the legs induced extremely painful spasms. With the exception of exaggerated deep tendon

Table 1 Continued

Comedication	Duration baclofen	Pump type	Outcome	Comments	Source
Methotrexate, Prednisolone	3 y	Infusaid	Control of spasms, wheel chair, death due to cancer	Automatic dysregulation, lower limb ankylosis	Meinck et al.[3]
Clonazepam, Diazepam, Azathioprine	4 y	Medtronic	Satisfactory, bedridden, death due to pump failure	Autonomic dysregulation, lower limb ankylosis	Meinck et al.[3,16]
None	10 mo	Medtronic	Initially good, walks with crutches, catheter obstruction	Disk protrusion L 3/4	—
Clonazepam, Tizanidine	6 y	Medtronic	Prompt improvement, walks with crutches	Lower limb ankylosis	—
Morphine	6.5 y	Infusaid, Therex	Initially bedridden, walks with crutches, hip and back pain	Congenital hip dysplasia	—
Clonidine patch	5 y	Medtronic	Improved mobility, can walk without crutches, persisting cramps	—	—
None	4.5 y	Medtronic	Can walk with crutches, wheelchair	Autonomic dysregulation lower limb ankylosis	Dressnandt et al.[17]
Clonazepam	6 mo	Medtronic Infusaid	Walks without crutches	—	Meinck et al.[3]
Diazepam (20 mg)	2.5 y	Medtronic	Spasms completely controlled	—	Penn and Mangieri[14]
?	9 mo	?	Bedridden, good control of spasms and pain	Lower limb ankylosis and atrophy	Penn and Mangieri[14]
Azathioprine	2 y	Infusaid	Bedridden, remission, complete mobility	—	Seitz et al.[13]
—	—	—	No response, short-term observation	—	Ford and Fahn[15]
Diazepam, clonazepam, baclofen, valproate, prednisone	One-time test dose	—	Reduced stiffness in all patients, clinical improvement in one, increased gait unsteadiness in two	Decrease in total EMG activity	Silbert et al.[20]

reflexes in the lower extremities, the remaining neurologic examination was normal. Cranial CT and MRI, and CSF and laboratory results were normal, as were EEG and nerve conduction studies. His EMG showed signs of involuntary motor unit firing. In the EMG-polygraphy, typical signs of spasmodic reflex myoclonus[3,5,19] were noted in the paravertebral and abdominal muscles in response to median nerve stimulation, confirming the diagnosis of SMS. Various oral medications were administered, but the patient invariably responded with severe side effects (e.g., sedation and gastrointestinal disturbances) (table 1). Treatment with cortisol, plasma exchange, and intravenous immunoglobulins led to only temporary improvement. A test bolus of intrathecal baclofen resulted in marked reduction of stiffness, enabling him to walk short distances without crutches. In 1992 a pump was installed, and long-term reduction in both the severity and frequency of spasms was achieved. Hip flexion increased to 85 de-

grees in the right leg and 50 degrees in the left. His condition has remained relatively stable over the past 5 years, but spasms still occur occasionally. Although he relies primarily on crutches, it is possible for him to walk short distances without crutches.

Patient 7.[17] Within the span of a few days, Patient 7 (L.K.), a 63-year-old farmer (born in 1929), suddenly developed stiffness of the legs and axial musculature. Stiffness gradually spread to the arms, and general mobility was drastically impaired. Hip and knee flexion was limited to 10 degrees and leg abduction was impossible. Both tactile and acoustic stimuli induced severe spasmodic jerks. His past history and neurologic examination were unremarkable. Oligoclonal bands were found in the CSF. Cranial and spinal MRI and myelography were normal. Slow waves and, prior to phenytoin therapy, spike waves were noted in the EEG, but no seizures were reported. An EMG showed increased, nonsuppressible motor activity in response to acoustic and tactile stimuli. Muscle spasms were abolished by diazepam, but stiffness persisted. Neither oral drugs nor intravenous cortisol (see table 1) showed a significant effect on muscle relaxation. After PERM was diagnosed, test boluses of intrathecal baclofen were administered and spasms ceased completely. However, as mobility did not improve, a pump was not initially implanted. Some 2 months after onset of symptoms, gradual progression led to near immobility, autonomic dysregulation (with fluid loss of 8 L/day), and respiratory failure. The patient required 3 months of intensive care therapy until trials with intrathecal baclofen began. Within a week, vegetative symptoms resolved completely and mobility improved considerably. A pump was subsequently installed. Within a year, leg abduction increased to 10 degrees and hip flexion to 30 degrees. The patient remained clinically stable for about 4.5 years until the pump battery failed. Symptoms of severe autonomic dysregulation and paroxysmal spasms of the axial musculature reappeared, but could be eliminated completely once baclofen therapy was reinstated. He can now walk short distances with crutches, but due to ankylosis of the lower extremities he still remains primarily confined to a wheelchair.

Results. We have been following roughly 40 SMS/PERM patients at various centers throughout Germany. Eight of these patients—three with SMS and five with PERM—are presently receiving intrathecal baclofen. This represents an unusual cohort, as our experience shows the incidence of SMS to be about twice that of the more complicated PERM. Although the sample size is small, patients with PERM differed in several respects from those with SMS (see table 1). Firstly, PERM patients showed a more rapid disease progression than patients with SMS. Three of the five PERM patients became confined to a wheelchair (Patients 1 and 7) or bedridden (Patient 2) within a few years. Only one patient with SMS (Patient 5) was bedridden before the onset of intrathecal baclofen (table 1). Secondly, patients with PERM were more likely to suffer attacks of autonomic dysregulation. Three of the five patients (Patients 1, 2, and 7) required emergency intensive care, but none of the patients with SMS suffered such attacks. Thirdly, patients with PERM responded less well to both long-term oral and intrathecal therapy. Average intrathecal dosages were higher and increases were more frequent (figure).

Table 2 *Clinical status before and after intrathecal baclofen therapy*

Clinical status	Before	After
Spasms		
Satisfactory to good control	0	8
Mobility		
Ambulation without crutches	0	1
Ambulation with crutches	0	5
Wheelchair bound	4	1
Bedridden	4	1
Orthopedic status		
Ankylosis of lower legs	4	4
Congenital hip dysplasia	1	1

The duration of symptoms before onset of intrathecal therapy ranged from 3 months to 4 years. In all patients prior attempts with oral medications proved unsatisfactory. Either side effects were prohibitive (Patients 1, 2, 4, and 6) or long-term therapeutic response was inadequate (Patients 1, 2, 3, 5 through 8). In four of the eight patients (Patients 1, 2, 6, and 8), initial response to oral medication was good, but adaptation occurred quickly. Some patients received corticosteroids (Patients 1 and 4 through 8), plasmapheresis (Patients 1, 2, 4, 6, and 8), or intravenous immunoglobulins (Patients 4, 6, and 8), but no long-lasting improvement was achieved under any of these therapies. Prior to pump implantation, one or more test boluses (40 to 200 μg) were administered. Responses varied. Pain was alleviated (Patients 3 and 4), frequency of spasms (Patients 1, 2, 4, 5, 7, and 8) and stiffness (Patients 1, 2, 3, 5, 6, and 8) were reduced, and general mobility was increased (Patients 5, 6, and 8).

Six of the eight patients were followed over an extended period of time (about 2.5 to 6.5 years) after implantation. With the exception of two patients (Patients 1 and 5), all were initially implanted with the SynchroMed (Medtronic Inc.,) pump system (see table 1). Starting doses ranged from 50 to 240 μg/day, but within the span of a few months most patients required increasing amounts (see figure). The dosage was based on both clinical response and suppression of tendon jerks in the lower extremities. No reflex changes were noted in the upper extremities. Maintenance doses varied considerably among patients (from 58.5 to 1,600 μg/day). In two patients with the "plus" variant of SMS (Patients 2 and 7), PERM, requirements increased drastically within the first year (from approximately 200 μg/day to about 1,500 μg/day), and the dosage would have increased even more (in Patients 1 and 7) had complaints of sedation not limited applicability. Only one SMS patient (Patient 5) required such high amounts (from 120 to 1,000 μg/day), but the increases occurred over a longer time span. Doses in the remaining SMS patients were kept low. In Patient 4 an increase beyond 58.5 μg/day resulted in severe sedation (she is also reported to have suffered a comalike state of short duration after a test bolus of 40 μg), whereas in Patient 6 the dosage was intentionally maintained at about 530 μg/day to avoid the consequences of reaching the therapeutic maximum (i.e., fewer medication alternatives and increased danger of accidental with-

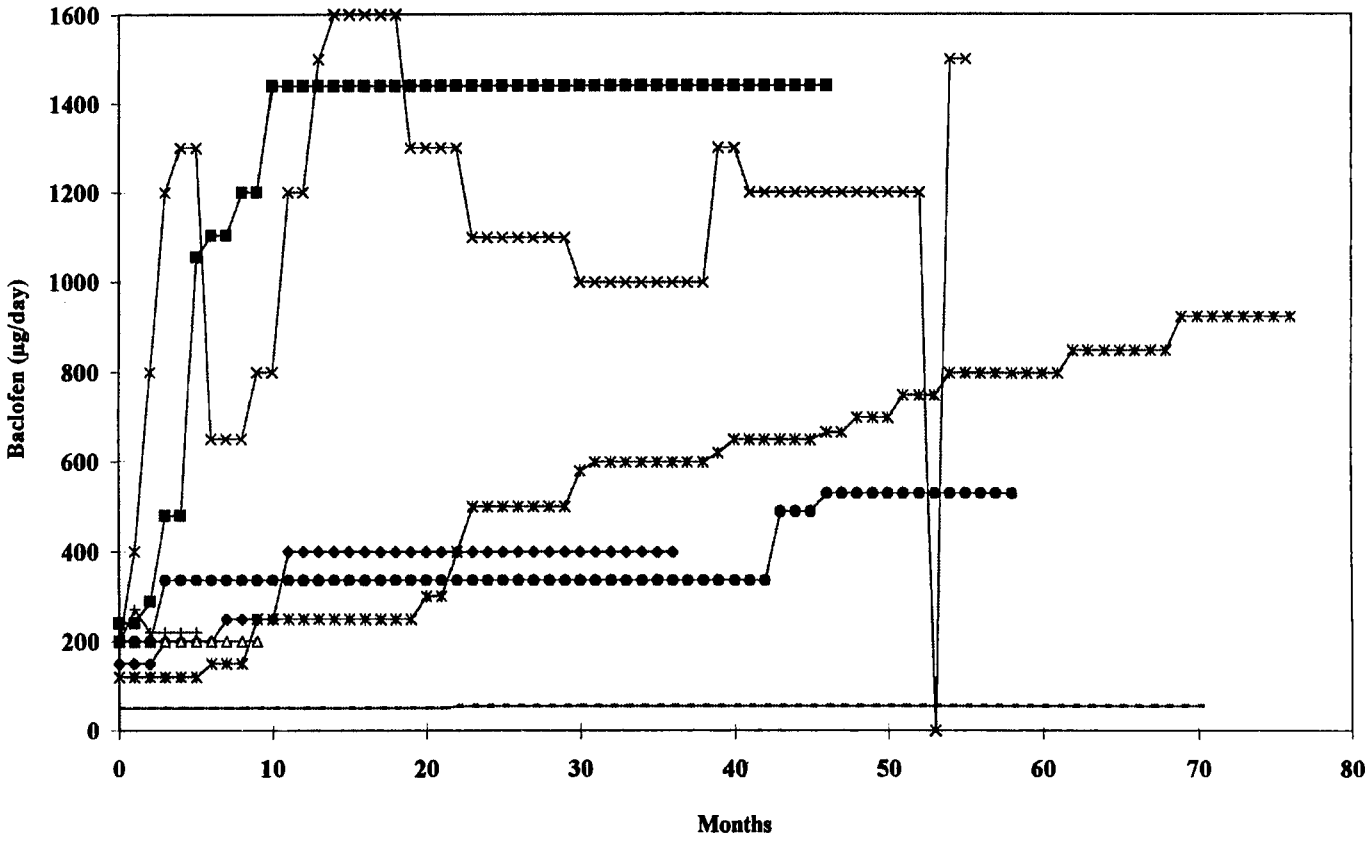

*Figure. Dosage over time in patients receiving intrathecal baclofen. ♦ = Patient 1 (H.C.); ■ = 2 (M.K.); △ = 3 (G.W.); ▬ = 4 (K.P.); * = 5 (C.B.); ● = 6 (D.H.); x = 7 (L.K.); + = 8 (V.H.).*

drawal). A reduction in dosage (from 1,000 to 925 μg/day) was possible in only one patient (Patient 5, SMS).

Although orthopedic problems in most patients made clinical assessment difficult (see table 1), intrathecal baclofen therapy resulted in long-lasting improvement of symptoms. Muscle stiffness was significantly reduced (especially in Patients 1, 6, and 8), as were frequency and severity of spasms (especially in Patients 1, 5, and 8). General mobility improved significantly. Prior to intrathecal baclofen, all patients were either confined to a wheelchair (Patients 3, 4, 6, and 8) or bedridden (Patients 1, 2, 5, and 7). Under therapy, only two patients remained in this condition (Patients 1 and 2). Five patients can now walk with crutches, while one patient (Patient 8) no longer requires them (see table 2). Symptoms of autonomic dysfunction, occurring either spontaneously (Patient 7) or after acute withdrawal (Patients 2 and 7), were also alleviated after administration of intrathecal baclofen. Nearly all patients, however, required comedication either to facilitate the therapeutic effect (Patients 2, 5, and 8) or to avoid side effects (Patients 4 and 6) (see table 1).

The side effects (vertigo, nausea, and sedation) were similar but generally milder than those observed with oral medication. Severe complications, however, occasionally interfered with the therapeutic success of intrathecal baclofen. In Patient 5, postoperative infection required several wound revisions, and improper fitting of the pump (Infusaid) later necessitated replacement with a smaller model (Therex). Catheter obstruction and pump malfunction (Medtronic) resulted in long delays in Patient 3's therapy. Patient 8 was recently implanted with a pump but initially showed no response to therapy. Radiographs revealed a complete rupture of the catheter, which was presumably caused by a severe spasm shortly after implantation. Particularly dangerous were the complications resulting from sudden cessation of intrathecal baclofen. In Patient 7 this occurred on two occasions—once after forgetting his refill appointment and recently after pump battery failure (1,200 μg/day). Severe, prolonged spasms and vegetative symptoms (diaphoresis, tachycardia, tachypnea, and hyperthermia) developed only hours after drug administration had stopped.[17] Fortunately, readministration of intrathecal baclofen led to prompt improvement, circumventing the need for intensive care therapy. Similarly, Patient 2's pump was inadvertently filled with one-quarter the usual concentration (1,100 μg/day), resulting in the same symptoms. She was admitted to the intensive care unit and was successfully treated with intrathecal baclofen, but 3 years later erroneous pump programming led to a similar attack. Despite intensive therapy, symptoms could not be alleviated. She died of autonomic failure 2 days after the pump was reprogrammed.[16]

Discussion. Our findings indicate that patients with SMS and its "plus" variant, PERM, who are refractory to oral antispasticity medications and immunosuppression respond well to intrathecal baclofen. Although orthopedic disabilities made quantification of clinical improvement difficult, we observed an increase in overall mobility as well as a reduction of

both muscle stiffness and severity of spasms. As only verum was administered in this nonblind, retrospective study, we can not exclude the possibility that results were in part due to the placebo effect. However, in contrast to prior forms of therapy, all patients responded favorably to intrathecal baclofen and even those prone to drastic side effects tolerated intrathecal baclofen relatively well. When side effects did occur, they were usually transient and milder than when the patient was under oral medication. Complete remission was not achieved in any of our patients. Symptoms progressed despite therapy.

As with our patients, both patients reported by Penn and Mangieri[14] showed good control of spasms and pain under intrathecal baclofen. In their first patient (Patient A; see table 1) the dosage was increased from 120 to 1,200 μg/day over 2.5 years and 20 mg/day of diazepam was coadministered. Their second patient (Patient B; see table 1) remained stable on 120 μg/day, although ankylosis made ambulation impossible. Seitz et al.[13] recently reported on a 61-year-old bedridden woman (Patient C; see table 1) who regained complete mobility and remained stable on 260 μg/day for more than 2 years. In contrast, Ford and Fahn[15] found no clinical improvement in their patient (Patient D; see table 1) after several test boluses of intrathecal baclofen (up to 100 μg), but ankylosis of hips and legs may have prevented notable changes in mobility and patients were only observed for about 8 hours. In a double-blind, placebo-controlled study, Silbert et al.[20] observed the clinical and electrophysiologic responses of three SMS patients receiving a one-time bolus of 50 μg of baclofen. Although stiffness was reduced in all three patients, only one was reported to show significant clinical improvement. Again, patients were observed only briefly (approximately 2 to 2.5 hours) after injection and, according to our experience (see table 1), the dosage may have been too low to elicit a pronounced clinical response. Nevertheless, Silbert et al.[20] found a decrease of 72% in reflex EMG activity (as compared with 18% with placebo).

In contrast to patients with spasticity, there are certain caveats to intrathecal baclofen therapy for patients with SMS/PERM. Whereas spasticity patients are usually clinically stable at doses well below 500 μg/day[9-11,21] and show only moderate adaptation in the first year, much higher dosages were required in three of the eight SMS/PERM patients (Patients 2, 5, and 7). Furthermore, spasticity patients tend to show more mild and transient side effects (somnolence, weakness, nausea, and blurry vision).[10,11,21] Although overdoses have been known to cause short periods of coma, they usually remit spontaneously and can be reversed with physostigmine (2 mg iv). In contrast, even those SMS/PERM patients requiring comparably low doses (Patients 1, 4, and 6) suffered more frequently from side effects. Complications with the pump or catheter can occur in both cohorts. The system may leak, become dislocated (Patients 3 and 5), or even rupture (Patient 8). More serious, however, is the danger of acute withdrawal due to sudden cessation of intrathecal baclofen. Although otherwise rare in spasticity,[22,23] this life-threatening complication occurred in two of our patients (Patients 2 and 7). Symptoms were characterized by massive, prolonged spasms; respiratory cyanosis; and signs of acute autonomic dysregulation (hyperthermia, tachypnea, tachycardia, severe diaphoresis, mydriasis, etc.). Despite intensive care therapy, one patient died.[16] There is increasing evidence that acute autonomic failure may be a common danger in SMS/PERM patients[24,25] and this must be borne in mind when administering baclofen via pump. Provided the situation is quickly assessed, symptoms can be promptly alleviated with intravenous diazepam and readministration of intrathecal baclofen. We recommend that patients carry a pass informing others of the action necessary in such an event.

As the myorelaxant effect of intrathecal baclofen on spasms and rigidity in SMS/PERM resembles that of spasticity from spinal lesions, one could infer a spinal etiology in the upregulation of muscle tone in SMS/PERM. Indeed, we observed attenuated tendon reflexes in the legs but not arms of patients optimally treated with intrathecal baclofen. Despite rostral flow of CSF in the subarachnoid space,[26] baclofen distribution is four times higher in the lumbar than cervical region[11] and higher doses are necessary when the catheter tip is located more rostrally.[27,28] However, it is unlikely that the site of action is limited strictly to the spinal cord. Baclofen activates primarily presynaptic inhibition via GABA receptors[29] known to be densely located in the gray matter of both the spinal cord and brain. Anatomic and electrophysiologic evidence lends support to the theory that the etiology of SMS/PERM may also lie in the brain stem.[19,30-33] As most SMS/PERM patients have antibodies to GAD,[4] a dysfunction of GABAergic mechanisms is likely to be involved. It remains to be seen whether spinal or bulbar[34] GABAergic neurons or the spinal terminals of descending GABAergic projections (e.g., from the ventromedial medullary reticular formation)[35] could be the site of the suspected autoimmune attack.

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