

Articles

Complex regional pain syndrome type I (RSD)

Pathology of skeletal muscle and peripheral nerve

L. van der Laan, MD; H.J. ter Laak, PhD; A. Gabreëls-Festen, PhD; F. Gabreëls, PhD; and R.J.A. Goris, PhD

Article abstract—*Background:* Reflex sympathetic dystrophy (RSD) (recently reclassified as complex regional pain syndrome type I) is a syndrome occurring in extremities and, when chronic, results in severe disability and untractable pain. RSD may be accompanied by neurologic symptoms even when there is no previous neurologic lesion. There is no consensus as to the pathogenic mechanism involved in RSD. To gain insight into the pathophysiology of RSD, we studied histopathology of skeletal muscle and peripheral nerve from patients with chronic RSD in a lower extremity. *Methods:* In eight patients with chronic RSD, an above-the-knee amputation was performed because of a nonfunctional limb. Specimens of sural nerves, tibial nerves, common peroneal nerves, gastrocnemius muscles, and soleus muscles were obtained from the amputated legs and analyzed by light and electron microscopy. *Results:* In all patients, the affected leg showed similar neurologic symptoms such as spontaneous pain, hyperpathy, allodynia, paresis, and anesthesia dolorosa. The nerves showed no consistent abnormalities of myelinated fibers. In four patients, the C-fibers showed electron microscopic pathology. In all patients, the gastrocnemius and soleus muscle specimens showed a decrease of type I fibers, an increase of lipofuscin pigment, atrophic fibers, and severely thickened basal membrane layers of the capillaries. *Conclusion:* In chronic RSD, efferent nerve fibers were histologically unaffected; from afferent fibers, only C-fibers showed histopathologic abnormalities. Skeletal muscle showed a variety of histopathologic findings, which are similar to the histologic abnormalities found in muscles of patients with diabetes.

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Minor trauma to or operation of an extremity may evoke reflex sympathetic dystrophy (RSD) in the hand or foot of the injured limb. The syndrome is characterized by vasomotor changes, edema, decreased limited range of motion, and pain (with allodynia and hyperpathy). Various neurologic symptoms may also be present, such as paresis, incoordination, tremor, myoclonus, and dystonia. An increased efferent sympathetic response after the initiating injury was until recently the generally accepted hypothesis for the pathogenesis of RSD. The equal outcome of a placebo versus guanethidine blockade study¹ and the finding of diminished concentrations of norepinephrine in RSD extremities versus the unaffected side² refutes the hyperactive sympathetic theory of RSD. Currently, the hyperactive efferent sympathetic theory has been replaced by the hypothesis that an upregulated sensitivity of α -adrenoreceptors for catecholamines in the affected

extremity may induce RSD.³ Another hypothesis for the pathogenesis of RSD is based on the assumption of an exaggerated regional inflammatory response⁴ after the initiating injury provoked by oxygen-derived free radicals⁵ or neuropeptides.⁶ To be neutral with respect to the various hypotheses of the pathogenesis of RSD, this syndrome has been renamed complex regional pain syndrome (CRPS) with two subgroups: type I, which occurs without a definable nerve lesion; and type II, which occurs with a definable nerve lesion.⁷ In this report, the term RSD is used because the term CRPS is not yet generally used.

Not only is the pathogenesis of RSD unclear, but so is the origin (central or peripheral) of the neurologic symptoms. Reports concerning histologic analysis of skeletal muscle tissue and nerves in RSD which could give more insight into the presence of the described factors, are scarce. Folkerts et al.⁸ re

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From the Departments of Surgery (Drs. van der Laan and Goris) and Neurology (Drs. ter Laak, Gabreëls-Festen, and Gabreëls), University Hospital Nijmegen, Nijmegen, The Netherlands.

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Address correspondence and reprint requests to Dr. L. van der Laan, Department of Surgery, University Hospital Nijmegen, PO Box 9101, 6500 H Nijmegen, The Netherlands.

Table 1 The reflex sympathetic dystrophy population (eight patients) from whom nerves and skeletal muscles were histologically analyzed

Patient no.	Age, y	Sex	Etiology	Skin temperature	Duration, y	Special remarks
1	46	Male	Arthrodesis	Cold	6	Atrophy
2	41	Male	Sprain	Cold	1	Atrophy
3	40	Female	Fracture os metatarsalia	Cold	2.5	Atrophy, dystonia
4	32	Male	Spontaneous	Cold	3	Chronic edema, atrophy
5	43	Male	Contusion foot	Cold	2.5	Chronic edema
6	24	Female	Contusion knee	Normal	4	Chronic edema, atrophy
7	54	Female	Contusion foot	Cold	10	Atrophy, dystonia, ulcer
8	40	Male	Contusion knee	Cold	5	Dystonia, ulcer

ported pathologic motor end-plates and atrophic fibers in histologically analyzed muscles from three patients with RSD in whom, in addition to the RSD, a neurologic deficit was present in the affected skeletal muscle tissue. Also in the muscle, edema with degeneration was observed in one patient with stage II RSD⁹; in seven patients with chronic RSD, ultrastructural abnormalities of myofibrils, swelling, and vesiculation of mitochondria were found.¹⁰ Kurvers et al.¹¹ reported that the subcutaneous arteries of two patients with chronic RSD had a decreased density of sympathetic nerve fibers as compared to the unaffected side. Other abnormal findings concern synovial biopsy tissue from four patients with RSD¹² and bone tissue biopsies from seven patients with RSD who were in the acute phase. The biopsies revealed extensive zones of irregular tissue showing increased osteoclastic resorption and thickened arteriols.¹³

The first aim of this study was to investigate, by light and electron microscopic analysis, skeletal muscle tissue, efferent mixed motor-sensory nerves, and afferent sensory nerves of patients with chronic RSD. Subsequently, the main goal of this study was to interpret the histologic findings to obtain more insight into the role of afferent and efferent nerve fibers and skeletal muscle tissue in the pathophysiology of RSD.

Methods. Patients. The patients (n = 8) included in this study had chronic RSD in the lower extremity according to established diagnostic criteria.^{4,7} These patients visited the outpatient clinic of the Department of Surgery (University Hospital Nijmegen) for a second opinion or advice because they had therapeutic-resistant, severe, chronic RSD. Amputation of the affected extremity was advised to these patients¹⁴ because they had RSD with severe hyperpathy in combination with a nonfunctional limb, or recurrent severe infections in this limb. The earlier mentioned criteria were derived from a previous study of patients with RSD in which amputation of the affected limb was performed.¹⁴ After the decision to amputate was made, the patients were asked for permission to perform histologic analyses of the amputated limb. All patients gave their consent for extensive histologic analysis of the amputated leg.

Preoperatively, patients were treated with epidural anesthesia over 5 days. In all patients, the amputation level was chosen above the knee because the sensibility of the skin was disturbed to that level. Three amputations were performed at the Nijmegen University Hospital, the Netherlands; five were performed in other hospitals in the presence of the first author. The eight successive patients were operated during the period of February 1996 to February 1997. None of the eight patients had diabetes or other signs or symptoms of a central or peripheral nervous system disorder.

Protocol. Immediately after amputation, the investigated tissues were dissected out by the first author, resulting in a maximal ischemia duration of 20 minutes.

First, the sural nerve was dissected 5 cm above the ankle, followed by dissection of the tibial nerve and common peroneal nerve just distally of the sciatic nerve. A 2-cm long specimen was obtained from all nerves. These specimens were then used for the various histologic procedures. Skeletal muscle specimens (20 × 40 mm) were obtained from the middle of the gastrocnemius muscle and soleus muscle.

Specimens of sural nerves, tibial nerves, and common peroneal nerves were prepared for light microscopic examination using standard techniques, including 1 μm Epon embedded cross sections. In addition, sural nerves were prepared for electron microscopic analysis, morphometry, and teased fiber studies, using previously described techniques.¹⁵

The skeletal muscle specimens were divided into two pieces: one specimen for light microscopic investigations and the second for ultrastructural research. A standard batch of staining techniques was carried out on freshly frozen transversely cut (8 μm) sections; these included a hematoxylin and phloxin stain and various enzyme histochemical reaction techniques for the demonstration of myofibrillar ATPase (preincubation at pH 4.3), succinic dehydrogenase, cytochrome oxidase, and acid phosphatase. Specimens for ultrastructural research were fixed in glutaraldehyde, postfixated in osmium tetroxide, embedded in Epon, cut, and stained with uranylacetate and leadcitrate.

Results. The population of patients with RSD in this study consisted of three women and five men (table 1). The age at operation varied from 24 to 54 years (median, 40.5 years). The duration of the RSD symptoms varied from 1 to 10 years (median, 3.5 years). The RSD followed an arthro-

desis, contusion, fracture, or sprain (see table 1). In one patient (Patient 4), RSD developed in the right leg after an arthroscopy. Because of recurrent infections, this leg was amputated 3 years earlier. In the left leg, signs and symptoms of RSD were present for 3 years. These complaints developed without a precipitating factor. All patients showed in the affected extremity: discoloration of the skin (red or blue), limited range of motion, paresis, anesthesia dolorosa (sensitivity to touch absent while severe pain present in the anesthetic area) up to the thigh, and atrophy of the skin, subcutaneous tissue, and muscles. In seven patients, the leg had a cold skin temperature up to the thigh, whereas in Patient 6 the leg had a normal skin temperature. Spontaneous pain, hyperpathy, and allodynia was present in all patients. In Patients 3, 7, and 8, dystonia was present with an equinus varus position of the foot, accompanied by an ulcer of the foot in Patients 7 and 8. Chronic edema of the lower part of the leg was present in Patients 4, 5, and 6. Before the decision to amputate, all patients were extensively, but unsuccessfully, treated by sympathetic blockade, free radical scavengers, and pain-relieving drugs. In all patients, the indication for amputation was a limb without any residual function and unbearable pain. Besides these criteria, recurrent infection of the limb was an additional reason for amputation in Patients 4 and 6. In Patient 6, no infection was present at the time of amputation. Patient 4 had various periods of erysipelas caused by *Streptococcus haemolyticus* group β , which were controlled successfully by penicillin. At the time of amputation, Patient 4 had no signs of erysipelas.

Histologic analysis. All skeletal muscle specimens were reviewed by the second author; all nerve specimens were reviewed by the third author. These authors are researchers at the Center for Investigation of Neuromuscular Disorders of the University of Nijmegen, The Netherlands, both with years of experience in human nerve and muscle pathology. The fourth author, a neurologist specialized in neuromuscular disorders, reviewed the findings of both researchers. The slides were not reviewed blindly.

On light microscopy of the motor and sensory nerves, no abnormality was found in four patients (Patients 2, 3, 6, and 7). Morphometric data of the sural nerves (density and diameter distribution of myelinated fibers) were within the range of values of age-matched controls. Age-matched control values were obtained from sural nerve biopsy specimens from patients with diffuse cerebral degenerative disorders or system degenerations but without clinical, electrophysiologic, or morphologic signs of neuropathy in whom a sural nerve biopsy was indicated for diagnostic purposes. Teased fibers studies showed no or little abnormal fiber type. Electron microscopy revealed normal myelinated and unmyelinated fibers except in Patient 2, in whom a marked thickening of Schwann cell basal membranes was observed around unmyelinated fibers and, to a lesser degree, around myelinated fibers. In four patients (Patients 1, 4, 5, and 8), the sural nerves showed a slight decrease in myelinated fiber density ranging from 68 to 83% of age-matched controls, which could partly be attributed to (subperineural) edema in Patient 4. Sporadically axonal degeneration and few regenerative clusters were observed. In addition, in these four patients, electron microscopic examination revealed unmyelinated fiber pathol-

ogy evidenced by denervated parallel Schwann cell stacks, miniature axon sprouts, and an obvious increase of collagen pockets. Blood vessels in epineurium, perineurium, and endoneurium showed a normal structure. In Patients 1, 4, 5, and 8, the small endoneurial vessels were surrounded by multiple basal membranes. A small epineurial infiltrate was present in Patients 2, 6, and 8.

The most frequent morphologic abnormalities in the muscle specimens are summarized in table 2. The most consistent pathologic changes concern a clear decrease of type I fibers, an increase of lipofuscin pigment, atrophic fibers with a slight angular appearance, and the presence of abnormal capillaries (figure). Almost all capillaries showed a multiplication of the basal membrane or a severely thickened basal membrane. Frequently, debris resulting from pericytes was present between the basal membrane layers. Furthermore, endothelial cells often showed a shrunken appearance and capillaries with only endothelial cell debris in the lumina were observed. Occasionally, the former location of a capillary could be traced by the thickened basal membrane only, without the presence of other cellular remnants (see figure).

Discussion. Light and electron microscopic analysis of skeletal muscle tissue and peripheral nerves of an extremity affected by RSD in the chronic phase as performed in the current study showed various histopathologic abnormalities in the muscle specimens but no consistent pathology of the peripheral nerves. To our knowledge, this is the first combined histologic investigation of skeletal muscle tissue and peripheral nerves in eight patients with chronic RSD. An explanation for this lack of histologic research in RSD may be that an additional injury, namely by taking biopsies, may trigger an increase of severity or recurrence of RSD. For this reason, in this study only tissue obtained by amputation was investigated. Consequently, the investigated tissue belonged to an extremity with chronic severe RSD with unbearable pain and limited function or recurrent infections.¹⁴ The presence of unbearable pain within the RSD extremity is not a good indicator for the necessity of amputation because in most amputated patients with RSD, pain relief will not be achieved. In addition, in most amputated patients with RSD, a recurrence of RSD occurs in the stump.¹⁴ Recurrence of RSD in the stump could be explained by the hypothesis that the level of tissue affected by RSD is higher than the level of amputation.

In chronic RSD (existence of RSD for more than 1 year), neurologic symptoms within the affected extremity are common. In this phase, Veldman et al.⁴ reported hypoesthesia in 85% of the patients, hyperpathy in 81%, incoordination in 61%, tremor in 50%, involuntary movements in 50%, muscle spasms in 42%, and paresis in 97%. In the acute phase of RSD (existence of RSD for less than 2 months), Veldman et al. also reported neurologic symptoms, but in a lower frequency than in the chronic phase. Hypoesthesia was found in 69%, hyperpathy in 75%, incoordination in 53%, tremor in 54%, involuntary movements in 19%, muscle spasms in 11%, and pare-

Table 2 Morphologic data from 16 muscle specimens (eight reflex sympathetic dystrophy patients)

Patient no.	Normal		1		2		3		4		5		6		7		8	
Sex			M		M		F		M		M		F		F		M	
Age, y			46		41		40		32		43		24		54		40	
Muscle specimen from	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G
% Fibers with internal nuclei	0-3		2	7	5	4	1	9	1	0	2	5	6	3	1	2	20	19
% Type I fibers	74-98	46-56	31	10	26	29	26	12	29	38	55	45	26	16	13	12	12	20
% Type IIC fibers	0-5		5	2	31	14	26	62	7	1	0	0	26	29	5	3	4	4
Lipofuscin	-		++	+	+	++	++	++	+	+	+	++	+	++	++	+	++	++
Ring fibers	-		++	+++	-	+	-	-	-	-	-	-	-	-	-	-	+	++
Basophilic fibers	-		+	-	-	+	+	+	-	-	-	-	+	+	+	+	-	+
Atrophic fibers with pyknotic nuclei	-		-	-	+	+	+	+	-	-	-	-	+	+	++	++	-	+
Fibers with SDH-negative zones	-		-	-	+	+	-	-	-	-	-	-	-	-	-	-	+	+
Necrosis of muscle fibers	-		-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-
% Area with fat cells	0		0	0	0	0	0	0	0	0	0	0	20	5	10	15	0	0
Muscle fiber diameters:																		
Variability	-		+	+	+	+	++	++	+	-	-	-	++	++	++	++	++	++
Atrophy	-		+	+	+	+	++	++	+	+	-	+	++	++	+++	+++	++	++
Hypertrophy	-		-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
Ultrastructural changes:																		
Capillary BM thickness	-		++	++	++	++	++	++	++	++	++	++	++	++	++	++	+	++
Necrotic capillaries	-		++	+	++	++	++	++	+	+	+	++	+	++	-	-	++	++

Generally accepted normal values and findings for the soleus and gastrocnemius muscle are shown in the column entitled "Normal."

S = soleus muscle; G = gastrocnemius muscle; - = not present or normal; + = increased; ++ = marked; +++ = extensive; SDH = succinic dehydrogenase; BM = basal membrane.

sis in 98%.⁴ The major difference between the neurologic signs of acute and chronic RSD is the presence of the movement disorders dystonia and myoclonus,^{16,17} which appear in some of the patients with

chronic RSD. The pathogenesis of movement disorders in an extremity affected by RSD may be explained by a peripheral nervous origin, reorganization of the CNS, or psychological factors.^{16,17}

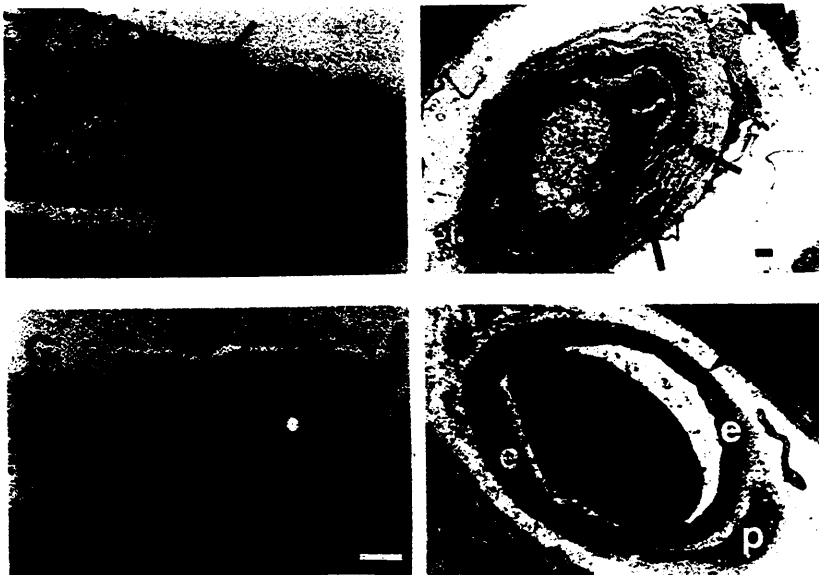


Figure. (A) Accumulations of lipofuscin (arrows) in muscle fiber. (B) Capillary with multiple basal membrane layering. Cell debris from pericytes between the laminae (arrows). (C) Necrotic capillary consisting of layered basal membrane and endothelial cell debris only. (D) Normal muscle capillary with a red blood cell (e = endothelial cell, p = pericyte) surrounded by a thin BM (arrow). A and C: Patient 1 (soleus muscle); E: Patient 5 (gastrocnemius muscle); D: capillary of a 41-year-old female control. Bar: 1 μ m (all figures).

The spontaneous pain sensation and mechanical/thermal allodynia and hyperpathy may be explained by the antidromical effect of neuropeptides,⁶ increased sensitivity of the nociceptors, upregulation of the α -adrenergic receptors for catecholamines,¹⁸ alterations in the afferent sensory fibers of the large myelinated fibers¹⁹ or the small myelinated A- δ fibers and unmyelinated C-fibers,²⁰ or increased efferent sympathetic nervous system.²¹

We chose to analyze the sural nerve in an area just above the ankle, because biopsies of this nerve are usually obtained at this level and control values are available. A loss of the C-fibers in the sural nerve was the only pathologic feature, observed in four patients. This finding shows similarities to the sural nerve pathology in patients with peripheral nerve disease and cold hyperalgesia, cold hypaesthesia, and cold skin.²² These authors explain the cold skin by a partial sympathetic denervation supersensitivity, which also could be present in patients with RSD.²³ The intact population of large myelinated fibers (A- β fibers) of the investigated nerves may explain why in electromyography²⁴ normal conduction velocity was registered in patients with RSD.

In the animal model, based on ligation of the sciatic nerve,²⁵ currently used as representation of RSD, axonopathy is described. However, in contrast to our histologic findings of human RSD nerves, in the animal model the number of small fibers increase, whereas the large fibers diminish.²⁶ The discrepancy in this finding could be because in the animal model a chronic primary lesion of the nerve is the main cause of the various pain sensations, whereas in the investigated patients with RSD no primary nerve lesion is present.

The role of the sympathetic fibers in patients with RSD has not been investigated in this study, but the axonal degeneration of the small C-fibers and the thickened basal membrane of the capillaries of the skeletal muscles support the hypothesis that the main histopathologic conditions are located in the skeletal muscle tissue and afferent nervous system.

The morphologic changes in the soleus muscle and gastrocnemius muscle are similar and concern decreased numbers of type I fibers, increase of lipofuscin, atrophic fibers, and impressive capillary changes ranging from severely thickened basal membrane to necrosis. The capillary changes resemble those observed in muscle biopsies from patients with diabetes. Layering and extremely thickened basal membranes are general findings in diabetes and are suggested to be results of repeated episodes of cell death and cell regeneration.²⁷ Furthermore, loss of pericytes and necrosis of capillaries were also observed in diabetes. Our findings with respect to the presence of atrophic fibers and the predominance of type II fibers may be related to an existing microangiopathy because in dermatomyositis defective capillaries give rise to atrophic fibers and loss of myosin ATPase activity. Furthermore, type II muscle fiber

predominance was also reported in non-insulin-dependent diabetic microangiopathy.

The finding of increased amounts of lipofuscin in muscle fibers is nonspecific. Lipofuscin results from oxidation of unsaturated membrane lipids by free radicals and increases with age.

Thus, the earlier mentioned consistent changes in the various muscle specimens seem to be related to ischemic conditions and point to a microangiopathy, but with a different etiology as compared with diabetes and dermatomyositis. In dermatomyositis, the first changes are observed in endothelial cells, and the resulting microangiopathy gives rise to multiple thrombus formation and infarction of the muscle. In diabetes, according to the hemodynamic hypothesis, microvascular flow and pressure are increased early, giving rise to an injury response resulting in basal membrane thickening of capillaries. The underlying defect may be the increase of oxygen-derived free radicals in vascular cells caused by an accumulation of advanced glycation products and resulting in a disturbed autoregulation of vascular tone. The hemodynamic hypothesis may also be applied to our cases; the underlying cause is unknown, but in the RSD extremity, the oxygen consumption is diminished as compared to the unaffected side.²⁸ Treatment with free radical scavengers of patients with RSD improved the oxygen consumption²⁹ and decreased the complaints of the RSD extremity.⁵ The healing effect of local treatment with the free radical scavenger dimethylsulfoxide (DMSO) in the RSD extremity⁵ is also reported in diabetic perforating ulcers. We hypothesize, founded on the current histopathologic findings of the skeletal muscle of patients with chronic RSD and the findings in the literature described earlier, that oxygen-derived free radicals are involved in the pathophysiology of RSD.

In the chronic phase of RSD, the mixed motor-sensory nerves were largely unaffected, as revealed by light and electron microscopic examination. From sensory afferent nerves, only the C-fibers showed pathologic abnormalities. The skeletal muscles of chronic RSD extremities consistently showed a variety of histopathologic findings that are similar to the histologic abnormalities found in skeletal muscles of patients with diabetes. In our view, the earlier mentioned histopathologic findings argue for an organic origin in the pathophysiologic mechanism of severe chronic RSD and negate the hypothesis of a primary psychological mechanism in the pathophysiology of severe chronic RSD.

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