Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients

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Summary

The pathogenesis of reflex sympathetic dystrophy—variously known as Sudeck's atrophy, causalgia, algodystrophy, and peripheral trophoneurosis—is not yet understood, and diagnosing and treating patients is difficult.

We have prospectively studied 829 patients, paying particular attention to early signs and symptoms. In its early phase, reflex sympathetic dystrophy is characterised by regional inflammation, which increases after muscular exercise. Pain was present in 93% of patients, and hypoaesthesia and hyperpathy were present in 69% and 75% respectively. With time, tissue atrophy may occur as well as involuntary movements, muscle spasms, or pseudoparalysis. Tremor was found in 49% and muscular incoordination in 54% of patients. Sympathetic signs such as hyperhidrosis are infrequent and therefore have no diagnostic value. We found no evidence consistent with the presence of three consecutive phases of the disease. Early symptoms are those of an inflammatory reaction and not of a disturbance of the sympathetic nervous system.

These data support the concept of an exaggerated regional inflammatory response to injury or operation in reflex sympathetic dystrophy.

Lancet 1993; **342:** 1012–16

Introduction

Reflex sympathetic dystrophy (RSD) is a complication occurring after even minor injury or operation to a limb. It is a major cause of disability as only one in five patients is able fully to resume prior activities.[1] The reported incidence of RSD is 1–2% after various fractures,[2] from 2–5% after peripheral nerve injury,[3] and 7–35% in prospective studies of Colles fracture.[4] Furthermore, changes similar to RSD may appear in 5% of the patients with a myocardial infarction (shoulder hand syndrome),[5] after local cold injury (trench foot), and after revascularisation of an ischaemic extremity (reperfusion syndrome). In 10–26% of cases no precipitating factor can be found.[6]

RSD has been given various names, depending on the precipitating factor, the country concerned, or the specialty treating the patient: reflex sympathetic dystrophy in English-speaking, Sudeck's atrophy in German-speaking, and algodystrophy in French-speaking countries; causalgia after nerve injury; postinfarction sclerodactyly by cardiologists; Pourfour du Petit syndrome by anaesthetists; and peripheral trophoneurosis, or Babinsky-Froment sympathetic paralysis by neurologists. The pathophysiology of RSD is unknown. It has not been reproduced in an experimental model and there is no corollary in veterinary medicine. At present there is some agreement that RSD is caused by an abnormal sympathetic nervous reflex. However, local blockade of the sympathetic system or sympathectomy, has not been found to be invariably effective.[7]

In 1990, Sudeck[8,9] considered the syndrome to be due to an exaggerated inflammatory response to injury or operation but, as he pointed out in his last article in 1942, this view has not found many adherents. Though his name has been given to the osteoporosis occurring in RSD, Sudeck himself regarded osteoporosis as only one of many late consequences. RSD has been considered to occur in patients who are emotionally unstable, depressive, manic, insecure, anxious,[10] or pathological malingerers.[11,12] These opinions, although never proven, have done patients a lot of harm, because their complaints are often not taken seriously. In contrast to the many opinions and prejudices, only scanty scientific information is available about RSD. Reported signs and symptoms concern mostly patients with severe illness and at a late stage, and have been described only in case reports. We therefore prospectively studied all patients with RSD coming to our attention. Special attention was given to early signs and symptoms as these might provide more information about the cause than the more-often reported late changes.

Patients and methods

All new patients presenting at the outpatient clinic of the Department of Surgery, Nijmegen University Hospital, were examined for signs and symptoms of RSD. As RSD has never been clearly defined, the following criteria for admission were used.

1. 4 or 5 of:
   Unexplained diffuse pain
   Difference in skin colour relative to other limb
   Diffuse oedema
   Difference in skin temperature relative to other limb
   Limited active range of motion
2. Occurrence or increase of above signs and symptoms after use
3. Above signs and symptoms present in an area larger than the area of primary injury or operation and including the area distal to the primary injury

Only signs and symptoms definitely present at the time of the first examination were noted, and were related to the duration of RSD. Statistical analysis was by chi-square and Kruskal-Wallis tests. When two groups were compared, the Wilcoxon test was used.

Results

Age, sex, and onset

From November 1984 to June 1992, 829 consecutive patients fulfilling the criteria were studied (if 3 instead of 4 signs of inflammation had been used, 942 patients would have entered the study). Of the 829, 615 (74%) were referred from other departments or hospitals because of

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Age (yr)	Male		Female		Total	
	n	%	n	%	n	%
0–9	—	—	1	—	1	—
10–19	8	4	43	7	51	6
20–29	29	14	118	19	147	18
30–39	50	25	98	15	148	18
40–49	57	29	135	21	192	23
50–59	37	18	108	17	145	18
60–69	14	7	94	15	108	13
>69	6	3	31	5	37	4
Total	201	100	628	100	829	100

Table 1: **829 patients with RSD**

RSD. 628 were female (76%) and 201 male (24%). Age varied between 9 and 85 (median 42 years) (table 1). 12 patients were younger than 14. In 487 patients (59%) RSD affected the upper extremity, in 342 patients (41%) the lower extremity. In 545 (65%), RSD followed trauma (mostly a fracture), in 155 (19%) operation, in 15 (2%) an inflammatory process, and in 34 (4%) after various other precipitants, such as injection or intravenous infusion (11), or cerebrovascular accident (2). In 80 (10%) no precipitant could be identified. Complaints started within 1 day in 75% of the patients; in 7 > 1 yr elapsed, making a relationship between the precipitant and onset of RSD in these cases questionable. The time between the start of RSD and clinic attendance varied from several days to 20 years (mean 405 days, median 156 days).

678 patients could remember which difference in skin temperature existed between the affected and unaffected limb at the time complaints started (primary temperature). In 58% the diseased extremity was warmer, in 39% colder, and in 3% there was no apparent difference in temperature. Of patients we examined within 2 months after onset of RSD, 35/156 (22%) were characterised by a primarily cold RSD. Primarily cold RSD occurred in 108/403 in the upper limb and 154/275 in the lower limb ($p < 0.001$). In those patients seen first by the authors, objective assessment of temperature showed a primarily cold RSD in 13%.

Treatment before presentation

489 patients received physiotherapy before examination and in 322 (66%) complaints temporarily increased in the hours following treatment. In 273, treatment was directed towards the sympathetic nervous system: operative or chemical sympathectomy (29), guanethidine blockades (191), lumbar, axillary, or stellate ganglion blockades (53). In 19 (7%) results were good and lasting, in 66 moderate and temporary, in 157 no change was found, while in 21 complaints became more severe. In 10, results were unknown.

Signs and symptoms

Pain was present in 93% (table 2), 91% had discolouraton of skin; 92% had altered skin temperature; oedema was present in 69%, and limited active range of movement in 88%. In 96% the above signs and symptoms appeared or increased in severity after exercising the affected limb, while 4% were unable to exercise at all. The longer the interval between the beginning of RSD and the first examination, the more patients were found with a cold limb. In most, exercising the limb resulted in a rapid increase in skin temperature, while the skin became hyperaemic and the pain increased. On the other hand, a warm limb was also found in patients with RSD present for up to 12 years. The vasomotor lability classically described in RSD, was regularly seen but was invariably related to exercise or painful stimuli.

Neurological symptoms included sensory changes, typically with a glove- or stocking-like distribution. In the first 2 months of RSD, hypoaesthesia was found in 69%, hyperpathy (exaggerated response to painful stimuli) in 75%. In many patients we found hypothermaesthesia; proprioception was also sometimes affected. In advanced

Sign, symptom	Duration of RSD														
	0–2 months n=156			2–6 months n=242			6–12 months n=200			>12 months n=231			Total n=829		
	Ev	+ve	%	Ev	+ve	%	Ev	+ve	%	Ev	+ve	%	Ev	+ve	%
Inflammatory															
Pain	155	142	92	242	213	88	199	192	97	230	222	97	826	769	93
Colour difference	154	149	97	241	231	96	200	179	90	229	194	84	824	753	92
Oedema	152	131	86	155	76	80	200	121	61	231	127	55	824	571	69
Temperature difference	153	149	98	240	218	91	197	175	89	231	211	91	821	753	92
Limited movement	152	137	90	237	213	90	196	173	88	225	186	83	810	709	88
Increase of complaints after exercise	136	133		218	208	95	184	176	96	216	210	97	754	727	96
Neurological															
Hyperaesthesia	136	94	69	219	164	75	192	139	72	218	185	85	765	582	76
Hyperpathy	132	94	69	204	162	79	187	148	79	221	179	81	744	588	79
Incoordination	101	53	53	172	80	47	173	95	55	184	112	61	630	340	54
Tremor	117	63	54	200	88	44	178	86	48	218	109	50	713	346	49
Involuntary movements	90	17	19	164	39	24	157	69	44	186	88	47	597	213	36
Muscle spasm	120	13	11	204	27	13	184	50	27	129	92	42	728	182	25
Paresis	94	92	98	145	135	93	134	122	91	156	151	97	529	500	95
Pseudoparalysis	129	21	16	212	15	7	188	28	15	216	57	26	745	121	16
Atrophy															
Skin	123	47	38	204	76	37	190	74	39	220	97	44	737	294	40
Nails	115	17	15	184	42	23	183	52	28	214	77	36	696	188	27
Muscle	117	47	40	194	97	50	174	98	56	205	137	67	690	379	55
Bone*	41	3	7	54	22	41	48	23	48	48	25	52	191	73	38
Sympathetic															
Hyperhidrosis	104	59	57	174	98	56	171	71	42	209	83	40	658	311	47
Changed growth hair	80	43	54	126	89	71	89	29	53	83	29	35	378	208	55
Changed growth nails	82	56	68	113	68	60	85	50	59	96	50	52	376	224	60

*Spotty or diffuse osteoporosis seen on X-ray.
Ev = patients in whom signs and symptoms were evaluable. +ve = signs of symptoms present.

Table 2: **Signs and symptoms at time of first visit related to duration of RSD**

disease we sometimes found anaesthesia dolorosa—sensibility to touch absent while severe pain present in the anaesthetic area. The severe pain present in later cases was different from the pain in the acute phase, as it was invariably present at rest and often resistant to treatment. Tremor of affected limb was found in 49% and muscular incoordination in 54%. In RSD of longer duration, severe muscular spasms were present in 25% of the patients. Localised muscle spasms mainly after exercise were seen in only 49 patients. Weakness was found in 95%. Finally, in 121 patients weakness became so severe that no active movements of the limb were possible. Electromyographic stimulation always produced normal contractions. Single fibre electromyographic examination was done in 6 of these patients which showed no definite abnormalities. Several patients with this pseudoparalysis had been dismissed from treatment in other hospitals as malingerers, while others, for the same reason, had been admitted to a psychiatric clinic.

Tissue dystrophy and atrophy were present in skin, subcutaneous tissue, muscles, and bone. However, the oedema present in the acute phase of RSD prevented assessment of subcutaneous tissue and muscle atrophy, resulting in higher incidences of atrophy reported in later stages. Tissue atrophy was more severe and occurred earlier in primarily cold RSD. As a number of patients with less severe RSD improved and as late referrals to our department were more severe, the higher incidence of dystrophic and atrophic changes in longstanding RSD may partly be due to negative selection. On the other hand, more than half of the later cases did not show signs of tissue dystrophy or atrophy. Nodular fasciitis of the palmar or plantar skin was found in 167 patients.

Hyperhidrosis was seen in 57% of early cases. When present, temperature of the skin was warm in 47%, cold in 47%, and no difference in temperature was found in 6%. Changes in the growth pattern of hair or nails on the affected limb were seen in 55% and 60% respectively. In 377 patients (45%), one or more triggerpoints were found. These included localised pain at the ulnar styloid process after Colles fracture and of the lateral malleolus after a sprain. In 103 patients, RSD in the hand was accompanied by complaints of the shoulder. In 6 of them we found a frozen shoulder and in 97, tendinitis of the biceps. In 19 with chronic lymphoedema due to RSD, we found chronic relapsing infections resistant to treatment. This severe complication required amputation in 5 cases. 19 patients had recurrent unexplained spontaneous haematomas, localised to the affected limb. A high proportion of patients had brown-grey scaly pigmentations of the skin in the diseased limb. We noted clubbing of fingers or toes in 30 patients and hourglass nails in 65 patients, in both affected and unaffected limbs. In 39 RSD was present in more than one limb. In 34 in two, in 4 in three, and in 1 patient in all four limbs. In 18 patients RSD recurred in the same limb after a period of no or few complaints. In 30 of these 57 patients (53%) no evident cause preceded the relapse. 5 patients told us one or more blood relatives suffered from RSD.

Discussion

In the present series, RSD appeared equally frequently in every age group, except in children under 10 as widely reported.[13-16] The lower prevalence in children may be an artifact because children are not usually referred to adult outpatient clinics. The higher prevalence found in women and in the upper limb conform to previous reports. Sympathetic blockade or sympathectomy, before referral was a lasting success in only 7% of patients. Though the group of referred patients is highly selected (cured patients are not referred), the results clearly show that interruption of the sympathetic system is not a panacea in RSD.

This study indicates that RSD affects all systems and in 95% the acute phase is characterised by the classic signs and symptoms of inflammation—pain, oedema, discoloration, changes in temperature, and decreased function. The signs and symptoms may be present at rest or elicited by exercise. In 32% of our cases RSD was primarily cold while other signs and symptoms were the same as primarily warm RSD. This high percentage may not represent the true incidence because more patients with cold RSD have late complaints.[18] In patients from our own clinic—not referred to us—we found a primarily cold RSD in only 13%. The division into primarily warm and primarily cold RSD is important, but to our knowledge has not been made before. In early cases, inflammatory signs were present in an area larger than the primary site of injury, and invariably symptoms were caused or increased in severity by exercise. Muscular paresis and rapid fatiguability were almost invariably present. Tissue dystrophy and atrophy were mainly late findings and only so in a small percentage of the popualtion studied.

Diagnosis

The above findings may be related to the selection criteria used for the study. However, no uniformly accepted criteria have been formulated for RSD, and no special investigation has been proven sensitive and specific enough for diagnosing RSD. In some studies the criterion was that the clinical entity of RSD was recognised by practising hand surgeons[19] or responded favourably to sympathetic ganglionic blockade.[20,21] Our criteria were similar to other studies of large numbers of patients.[22,23] Requiring the presence of diffuse osteoporosis in the affected extremity as an entry criterium would have resulted in the rejection of 70% of all cases from the present study; of severe pain in the rejection of 8%; of a warm, red extremity in rejection of 31% of early cases, and of hyperhidrosis in rejection of 43% of early cases. Also, in our view, the diagnosis of RSD should not be reserved for late stages when tissue atrophy is present. To see if our criteria would yield a similar incidence of RSD as in other series, we examined the incidence of RSD in our hospital population of Colles-fracture patients. The incidence was 8%, as in most other studies.[4,24]

Differentiation of RSD from other clinical conditions may be difficult. In chronic arterial insufficiency, pulses are absent, while present in RSD. Complaints in RSD may be precipitated by cold as in Raynaud's disease, though RSD complaints are specifically aggravated by exercise. Phlebothrombosis is not associated with neurological disturbances and can be diagnosed by echography or phlebography. RSD is not associated with increased sedimentation rates or the presence of specific antigens or auto-immune antibodies in blood or tissue as in rheumatologic disorders. Differentiation from infectious disorders may be difficult. Several patients in this study had incision and drainage because of presumed infection. However, in RSD no leucocytosis or fever is present. Because most authors agree that treatment should be started at an early stage, establishing early signs and symptoms is essential. In the present series, the

characteristic early findings were the appearance of, or the increase in inflammatory signs with use of exercise of, the affected limb, and the muscular paresis with easy fatiguability. Increase of complaints with exercise was noticed by others[5,20,25,26] though its importance was not emphasised.

Pain is almost invariable: 7% of our patients did not complain of pain though all other signs and symptoms of RSD were present. Sensory changes in RSD are diverse. Sensibility for tactile and thermal stimuli is decreased—hypoaesthesia and hypothermaesthesia. Also proprioception may be limited. This is often combined with hyperpathy. In severe cases all sensibility for touch is gone while pain is still present in the anaesthetic area—anaesthesia dolorosa. Loss of proprioception and anaesthesia dolorosa have not been previously reported in RSD, as far as we know. The sensory changes are typically of a stocking or glove type; they do not conform to a specific dermatome or to peripheral nerve distribution, as reported by others.[25,27] Muscular hypertony has been reported previously by Miller,[25] Steinbrocker,[28] and Bonnet;[29] sustained muscle spasms, myoclonies and muscle-jerks by Mitchell[30] and Marsden et al.[31] Paresis and incoordination may progress until the patient is unable to move at all. This entity has been reported only once before by Babinsky et al.[32] We call this pseudoparalysis, because during careful examination, discrete muscle contractions could regularly be felt and because we found no changes on electromyography. The latter finding fits in with previous observations.[31,33] The neurological signs and symptoms of RSD are best thought of as a unilateral peripheral polyneuropathy.

Sympathetic signs and symptoms (hyperhidrosis, hypertrichosis, and altered nailgrowth) are often required for diagnosis, but we found them unreliable indicators of RSD. Intriguing as they are, they seem to be irrelevant to establishing a diagnosis, and are of little if any concern to the patient. When hyperhidrosis was present, skin temperature was warm or cold in equal percentages of patients, indicating that there is no specific sympathetic nervous defect in RSD.

Less frequently we found nodular fasciitis, nail-clubbing, and hourglass nails, the latter never having been reported before in RSD, and clubbing only in one case report.[34] Also, intractable or relapsing skin infections, spontaneous haematomas and increased pigmentation have by our knowledge, not been reported in RSD. RSD in the hand is sometimes accompanied by shoulder complaints. We found this association in 103 patients. In 94%, the apparent 'shoulder-hand syndrome'[28] was caused by RSD of the hand and tendinitis of the scapular insertion of the biceps tendon. In all patients with tendinitis, shoulder pain disappeared or improved after a single local infiltration with local anesthetics and many patients were permanently relieved by corticosteroids. Bilateral RSD has been reported before,[5,28,35] but we found no report of a localisation in three or four extremities as seen in 5 of our patients. Because of intractable pain and incapacity, one of these patients committed suicide. In 53% of patients with relapsing or multiple RSD no precipitating event could be found, indicating that these patients may be predisposed to RSD.

Staging

Classically, RSD is subdivided in three phases:[14,28] a warm phase of 2–3 months, a phase of vasomotor instability for several months, and a cold end-phase. No prospective studies are available in which this staging is confirmed. We could not confirm this subdivision: in 13% of our patients, RSD started with a cold extremity, in some patients the extremity was still warm 8 and 12 years after the complaints started; and vasomotor instability was related to muscular exercise or painful stimuli. We suggest that a subdivision into a primarily warm and cold form, as related to the skin temperature at onset, gives a more realistic description of RSD.

Pathogenesis

Our findings do not support the generally accepted idea of a sympathetic nervous cause for RSD; they support Sudeck's concept of an exaggerated regional inflammatory response. This inflammatory concept is supported by new data. In patients with acute RSD, immunoglobulin G labelled with ^{111}Indium is concentrated in the affected extremity,[36] proving an increased microvascular permeability for high molecular weight proteins. This finding was present in patients with primarily warm as well as primarily cold RSD. A study with ^{31}P NMR spectroscopy showed an impairment of high energy phosphate metabolism,[37] which explains why these patients are unable, rather than unwilling to exercise. Electronmicroscopic studies of skeletal muscle biopsies showed reduced mitochondrial enzyme activity, vesiculation of mitochondria, disintegration of myofibrils, abnormal depositions of lipofuschin, swelling of endothelial layers, and thickening of the basal membrane—all signs of oxidative stress.[38] Also, oxygen consumption is reduced in limbs affected by RSD,[39] and treatment with oral vasodilatators reduces or abolishes pain.[40,41] Regrouping signs and symptoms of RSD in terms of inflammation proved suitable for establishing the diagnosis in this study. With evolving time, all functions and structures of the affected extremity may be damaged. We hope this observation incites physicians to develop new forms of treatment for this disabling disease.

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Evidence for a dopaminergic deficit in sporadic amyotrophic lateral sclerosis on positron emission scanning

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Summary

Although rare, the chronic neurodegenerative disorders amyotrophic lateral sclerosis (ALS) and idiopathic parkinsonism coexist to a greater degree than expected by chance. This suggests that patients with ALS may have subclinical lesions of the nigrostriatal dopaminergic pathway. To study this hypothesis, we did positron emission tomography with 6-fluorodopa on 16 patients with sporadic ALS and without extrapyramidal disease, and compared the results with age-matched controls. We found a significant progressive fall in 6-fluorodopa uptake with time since diagnosis, and reduced dopaminergic function in 3 patients with ALS of long duration. This supports the hypothesis that ALS and IP may share pathogenesis and, perhaps, aetiology.

Lancet 1993; **342:** 1016–18

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Introduction

The chronic neurodegenerative conditions, amyotrophic lateral sclerosis (ALS) and idiopathic parkinsonism (IP) share features that suggest a common pathogenesis and perhaps even a similar cause:[1,2] ALS and IP occur in the same individual more frequently than expected by chance;[2] models of both disorders may be produced by toxins and viruses;[1] and plasma concentrations of cysteine sulphate are abnormal in both.[3] Moreover, there is morphological similarity between ALS and IP; both are characterised by the accumulation of intracytoplasmic, eosinophilic, neurofilamentous material in areas of maximal neuronal loss.[4] In addition, the incidence of these disorders increases with age and both have an insidious onset followed by progression without remission. The ALS-parkinsonism-dementia complex (known in Guam as Lytico-Bodig) is a further example of the association between syndromes of the major neurodegenerative disorders.[5] Taken together, these observations suggest that ALS may be associated with a subclinical dopaminergic deficit. We have previously demonstrated dopaminergic deficits in Guamanians with Lytico-Bodig expressed as ALS without parkinsonism.[6] To explore the hypothesis that patients with ALS have subclinical dopaminergic deficits, we did positron emission