chapter
3
SIGNS AND SYMPTOMS OF REFLEX SYMPATHETIC DYSTROPHY: prospective study of 829 patients.

Peter H.J.M.Veldman, M.D.
Han M.Reynen, M.D., Ph.D.
Ivo E.Arntz, M.D.
R.Jan A.Goris, M.D., Ph.D.

Department of Surgery, University Hospital Nimegen, The Netherlands

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ABSTRACT

The pathogenesis of reflex sympathetic dystrophy (RSD) - 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, RSD is characterized by regional inflammation, which increases after muscular exercise. Pain was present in 93% of patients, and hypesthesia 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 RSD.
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.

The reported incidence of RSD is 1 or 2% after various fractures, from 2 to 5% after peripheral nerve injury and 7-35% in prospective studies of Colles fracture. Furthermore, changes similar to RSD may appear in 5% of the patients with a myocardial infarction (shoulder hand syndrome), after local cold injury (trench foot) and after revascularisation of an ischemic extremity (reperfusion syndrome). In 10-26% of cases no precipitating factor can be found.

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 anesthetists; 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.

In 1900, Sudeck 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, or pathologic malingerers. 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 not been clearly defined, the following criteria were used.

1. 4 or 5 of:
   - Unexplained diffuse pain
   - Difference in skin color 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 much 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-test and the Kruskal-Wallis test. 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 in stead 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 RSD. 628 were female (76%) and 201 male (24%). Age varied between 9 and 85 years (median 42 years) (table 3.1). 12 patients were younger than 14.

In 487 (59%) RSD affected the upper extremity, in 342 patients (41%) the lower extremity. In 545 patients (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).
Table 3.1 829 patients with RSD

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>male n</th>
<th>male %</th>
<th>female n</th>
<th>female %</th>
<th>Total n</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10-19</td>
<td>8</td>
<td>4</td>
<td>43</td>
<td>7</td>
<td>51</td>
<td>6</td>
</tr>
<tr>
<td>20-29</td>
<td>29</td>
<td>14</td>
<td>118</td>
<td>19</td>
<td>147</td>
<td>18</td>
</tr>
<tr>
<td>30-39</td>
<td>50</td>
<td>25</td>
<td>98</td>
<td>15</td>
<td>148</td>
<td>18</td>
</tr>
<tr>
<td>40-49</td>
<td>57</td>
<td>29</td>
<td>135</td>
<td>21</td>
<td>192</td>
<td>23</td>
</tr>
<tr>
<td>50-59</td>
<td>37</td>
<td>18</td>
<td>108</td>
<td>17</td>
<td>145</td>
<td>18</td>
</tr>
<tr>
<td>50-69</td>
<td>14</td>
<td>7</td>
<td>94</td>
<td>15</td>
<td>108</td>
<td>13</td>
</tr>
<tr>
<td>&gt;69</td>
<td>6</td>
<td>3</td>
<td>31</td>
<td>5</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>201</td>
<td>100</td>
<td>628</td>
<td>100</td>
<td>829</td>
<td>100</td>
</tr>
</tbody>
</table>

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 two months after onset of RSD, 35/156 (22%) were characterized 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 physical therapy 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 3.2). 91% had discoloration 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 et al. 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 hyperemic 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, hypesthesia was found in 69%, hyperpathy (exaggerated response to painful stimuli) in 75%. In many patients we found hypothermesthesia; proprioception was also sometimes affected. In advanced disease we sometimes found anesthesia dolorosa - sensibility to touch absent while severe pain present in the anesthetic 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. Localized 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.

Table 3.2 Signs and symptoms at time of first visit related to duration of RSD

<table>
<thead>
<tr>
<th>Sign, symptom</th>
<th>0-2 months</th>
<th>2-6 months</th>
<th>6-12 months</th>
<th>&gt;12 months</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=156</td>
<td>n=242</td>
<td>n=200</td>
<td>n~231</td>
<td>n=829</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>142/155</th>
<th>213/242</th>
<th>192/199</th>
<th>222/230</th>
<th>769/826</th>
</tr>
</thead>
<tbody>
<tr>
<td>pain</td>
<td>92%</td>
<td>88%</td>
<td>97%</td>
<td>97%</td>
<td>93%</td>
</tr>
<tr>
<td>difference color</td>
<td>149/154</td>
<td>231/241</td>
<td>179/200</td>
<td>194/229</td>
<td>753/824</td>
</tr>
<tr>
<td>edema</td>
<td>131/152</td>
<td>192/241</td>
<td>121/200</td>
<td>127/231</td>
<td>571/824</td>
</tr>
<tr>
<td>difference temperature</td>
<td>149/1153</td>
<td>218/240</td>
<td>175/197</td>
<td>211/231</td>
<td>753/821</td>
</tr>
<tr>
<td>temperature</td>
<td>98%</td>
<td>91%</td>
<td>89%</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>Limited Range of Motion</td>
<td>Increase of Complaints after Exercise</td>
<td>Neurological</td>
<td>Atrophy</td>
<td>Sympathetic</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------------------------</td>
<td>--------------</td>
<td>---------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>137/152 90%</td>
<td>133/136 98%</td>
<td>Hypalgesia 94/136 69%</td>
<td>47/123 38%</td>
<td>Hyperhidrosis 59/104 57%</td>
<td></td>
</tr>
<tr>
<td>213/237 90%</td>
<td>208/218 95%</td>
<td>Hyperpathy 94/132 75%</td>
<td>76/204 37%</td>
<td>Changed Growth Hair 43/80 54%</td>
<td></td>
</tr>
<tr>
<td>173/196 88%</td>
<td>176/184 96%</td>
<td>Incoordination 53/101 53%</td>
<td>74/190 39%</td>
<td>Changed Growth Nails 56/82 68%</td>
<td></td>
</tr>
<tr>
<td>186/225 83%</td>
<td>210/216 97%</td>
<td>Tremor 63/117 54%</td>
<td>97/220 44%</td>
<td>98/174 56%</td>
<td></td>
</tr>
<tr>
<td>709/810 88%</td>
<td>727/754 96%</td>
<td>Involuntary Movements 17/90 19%</td>
<td>97/220 44%</td>
<td>71/171 42%</td>
<td></td>
</tr>
</tbody>
</table>

*Spotty or diffuse osteoporosis seen on X-Ray*
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 fascitis 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 trigger points were found. These included localized 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 lymphedema 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 hematomas, localized to the affected limb. A high proportion of patients had brown-grey scaly pigmentation 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 in literature. The lower prevalence in children may be an artefact, 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), 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 characterized by the classic signs and symptoms of inflammation- pain, oedema, discoloration, changes in temperature, and decreased function.

The signs and symptoms maybe 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. In patients from our own clinic - not referred to us - we found a primarily cold temperature 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 population 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 criterium was that the clinical entity of RSD was recognized by practicing hand surgeons or responded favorably to sympathetic ganglionic blockade. Our criteria were similar to other studies of large numbers of patients. 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. 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 luxated by cold as in Raynaud disease, though RSD complaints specifically are aggravated by exercise. Phlebothrombosis is not associated with neurologic disturbances and can be
diagnosed with echography or phlebography. RSD is not associated with increased sedimentation rates or the presence of specific antigens or autoimmune-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\textsuperscript{5, 20, 25, 26} though its importance was not emphasized.

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 - hypesthesia and hypothermesthesia. 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 anesthetic area -anesthesia dolorosa. Loss of proprioception and anesthesia dolorosa have not been previously reported in RSD, as far as we know. The sensory changes are typically of a stocking of glove type: they do not conform to a specific dermatome or to peripheral nerve distribution, as reported by others\textsuperscript{25-27}Muscular hypertony has been reported previously by Miller \textsuperscript{25}, Steinbrocker \textsuperscript{28} and Bonnet \textsuperscript{29}; sustained muscle spasms, myoclonies and muscle-jerks by Mitchell \textsuperscript{30} and Marsden et al \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 nail growth) are often required for diagnosis, but we found them unreliable indicators of RSD, intriguing as they are, they seem to be irrelevant as 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 sympathetic nervous defect in RSD.

Less frequently we found nodular fascitis, clubbing, and hourglass nails, the latter never having been reported before in RSD and clubbing only in one case report \textsuperscript{34}. Also, intractable or relapsing skin infections, spontaneous hematomas 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" was caused by RSD of the hand and tendinitis of the scapular insertion of the biceps tendon.

In all patients with a 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, but we found no report of a localization 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 for RSD.

**Staging**
Classically, RSD is subdivided in three phases, 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 labeled with Indium is concentrated in the affected extremity, 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 31P-NMR-spectroscopy showed an impairment of high energy phosphate metabolism, which explains why these patients are unable, rather than unwilling to exercise. EM studies of skeletal muscle biopsies showed reduced mitochondrial enzyme activity, vesiculation of mitochondria, disintegration of myofibrils, abnormal depositions of lipofuscin, swelling of endothelial layers and thickening of the basal membrane - all signs of oxidative stress. Also, oxygen consumption is reduced in limbs affected by RSD and treatment with oral vasodilatators reduces or abolishes pain. 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.
REFERENCES


