Reflex sympathetic dystrophy (RSD) is a condition characterized by localized or diffuse pain, usually with associated swelling, trophic changes and vasomotor disturbance [1]. Alldynia, hyperhidrosis, and nail or hair growth changes may also occur. Motor abnormalities have been reported [2], in particular, tremor, involuntary movement and muscle spasm. Contractures may occur in the later stages. Involvement may be either unilateral or bilateral. Most commonly recognized is peripheral disease [3], although RSD may affect any region of the trunk or limbs. There is often a history of trauma, occasionally of such low significance that it may be overlooked by the patient. Symptoms may occur up to 6 months after injury [4]. Other triggering factors have been reported. Several drugs have been implicated, for example, phenobarbitone, phenytoin, isoniazid [5], and the immunosuppressive agents cyclosporin [6] and tacrolimus [7], as has surgery or a neurological event, particularly with peripheral manifestations. Rapamycin is currently under investigation as an immunosuppressive agent administered after solid organ transplantation. A recent report associated this drug with bone pain, osteolysis on plain radiographs and high uptake of tracer on isotope bone scanning. Resolution of symptoms occurred on withdrawal or reduction of rapamycin, or following administration of the bisphosphonate pamidronate [8]. Concurrent medical conditions may predispose to RSD, and diabetes mellitus, hyperthyroidism, hyperparathyroidism and type IV hyperlipidaemia have all been associated. RSD may occur at any age, and is well recognized in children, where vasomotor changes may be particularly marked [9–11]. Chronic pain in a poorly understood condition may cause depression and isolation, and although a higher rate of psychological abnormalities has been reported, this appears to be little different from other patient groups who suffer chronic pain [12, 13].

The natural history of RSD is still unclear as it would appear not all cases progress unremittingly, and resolution may occur during any stage. Some cases seem to respond rapidly to treatment while others may be resistant. Three stages are recognized, with clinical and
radiographic features utilized in the staging [5, 14]. Stage 1 is characterized by the onset of pain, with swelling and oedema and evidence of patchy bone loss on plain radiographs. Stage 2 recognizes more established disease, with continuing pain, atrophy of the skin and tissues and contracture of the joint. Diffuse bone loss is seen on plain radiographs. In stage 3, pain is less prominent, and as there is little active movement, the pain is most marked during passive movement. Those patients who develop a trophic, cold limb may be less responsive to treatment and the longer the duration of the disease, the less favourable the outcome. However, no studies have compared treatments or outcomes between the three stages. In some, the intractable pain is sufficient for amputation to be considered and undertaken. In others, there may be resolution of signs and symptoms, either spontaneously or following treatment. Recurrence may occur subsequently at the original or at a completely separate anatomical site.

The diagnosis can often be made on clinical grounds alone. However, a range of diagnostic tools is available. Plain radiographs may show evidence of osteopenia in the affected area, indicating bone loss of at least 30%. The pattern of bone loss depends on the stage of the syndrome, with patchy loss occurring early and diffuse loss seen in the later stages [15–18]. Another diagnostic and validated method is thermography. An infra-red camera semi-quantifies heat emission from the skin, and vasomotor instability may be monitored [19–21]. Three-phase bone scintigraphy typically demonstrates increased local blood flow and increased soft tissue uptake immediately following administration of the radioactive isotope. Delayed images, at 3–4 h, indicate increased uptake within the bone, and if these strict criteria are met, the sensitivity and specificity of this technique are high [17, 18, 22]. The changes seen in stage 3 disease are difficult to interpret and are often indistinguishable from a disuse syndrome. More recently, magnetic resonance imaging (MRI) has been used with success and has the advantage of excluding other pathologies, for example stress fracture [23].

Despite a wealth of literature and discussion the pathophysiology remains unclear. Several hypotheses have been offered, including a central mechanism involving the substantia nigra [24]; a peripheral mechanism involving a primary synapse dysfunction; or altered response to neurotransmitters [25]. Sympathetic overactivity has been traditionally considered to be the underlying mechanism. However, plasma concentrations of adrenaline, noradrenaline and metabolites are lower than in controls [26], and attempts to quantify the sympathetic skin response have been statistically insignificant [27, 28]. One study which attempted to identify abnormalities specific to RSD did not find any consistent histological findings in peripheral nerve or muscle [29]. Abnormalities of local mediator release, for example, of substance P and vasoactive polypeptides, have been postulated. No clear culprit has been identified to date.

There is evident localized bone loss which cannot be solely attributed to immobility. The pain is often most severe during stages 1 and 2 when the rate of bone loss is most rapid. Similarities exist between RSD and Charcot’s neuroarthropathy of diabetes. Pain may occur in each condition, although Charcot’s joints are classically painless. Histologically, there is bone loss with a normal underlying bone architecture in RSD, with predominantly trabecular bone resorption [30], whereas a destructive pattern of bone loss is seen in the Charcot’s joint. The Charcot’s joint is typically hyperaemic whereas the limb involved by RSD, especially in the later stages, is cooler. The pathogenesis of both conditions remains elusive, but a common pathway towards rapid bone loss does not seem unreasonable. A painful limb is not subjected to normal weight bearing, and immobility must be considered as a mechanism of bone loss. However, the bone loss which occurs in the post-operative period is not associated with the severe burning pain that characterizes RSD, and the rate of bone loss due to immobility does not match the speed of bone loss that must occur in RSD to cause osteopenia on plain radiographs [31].

A variety of treatments has been used with anecdotal success, and there is a great need for randomized controlled studies. Physiotherapy remains the cornerstone of treatment, and the value of rehabilitation of the affected area—starting with light touch and slowly moving on to passive, then active movements with weight-bearing exercises—may be underestimated in the quest for pharmacological virtuosity. Sympathetic blockade, either as a single or repeated procedure has been beneficial in reducing pain. The use of regional intravenous guanethidine, a favoured agent for this technique, is no more effective than placebo [32, 33]. Historically, oral prednisolone was prescribed with little success, often in conjunction with calcium channel antagonists, to reduce the presumed inflammatory response and to increase local blood flow [34–36]. Gabapentin has been used to treat the pain of RSD with anecdotal benefit [37]. Randomized controlled studies are required to evaluate this further.

Calcitonin and the bisphosphonates have also been used with some success. Calcitonin is administered subcutaneously, and there may therefore be compliance implications. However, several papers report success with this treatment in the management of RSD [5, 38], although only one was a randomized controlled study. Calcitonin is believed to have an analgesic as well as an anti-resorptive effect [39, 40]. The role of bisphosphonates is being explored as a treatment for RSD. Administration can be oral or intravenous although there are no published data on the role of oral therapy. Intravenous pamidronate is well established in the treatment of Paget’s disease and hypercalcaemia associated with malignancy, and has an analgesic and perhaps therapeutic role in patients with metastatic bone disease [41]. The analgesic effect of bisphosphonates may have an important role in RSD. Both calcitonin and the bisphosphonates are established treatments for osteoporosis, and their use in RSD where there is localized bone loss is reasonable. No controlled trials exist to
assess the effects of the bisphosphonates, and the evidence of calcitonin’s efficacy is conflicting [5, 38, 42], lacking long-term studies. Whether generalized osteopenia or osteoporosis is an independent risk factor for RSD has yet to be resolved. One study of 19 patients indicated lumbar bone density was lower than expected, although this was not a significant finding [42]. Individuals with lower than average bone density may therefore be at risk of developing RSD following what would have otherwise been a relatively minor traumatic incident.

RSD of the ankle and foot may be a distinct subset of RSD that could be looked at more closely. The vasomotor changes are most marked in the periphery, which aids diagnosis, the clinical signs being more marked than in the knee or hip. A correct diagnosis may be made earlier, enabling prompt treatment with a better prognosis, although most studies make no attempt to stage the disease, and the natural history remains unclear. No studies have compared outcome of RSD affecting different anatomical sites, although our own experience suggests that RSD of the ankle and foot may have a better prognosis than RSD at other sites. Ultrasound of the calcaneum is becoming increasingly accepted in the assessment of bone density, although dual energy X-ray absorptiometry (DEXA) remains the gold standard. A recent study has looked closely at the role of quantitative ultrasound of the calcaneum in patients with unilateral RSD of the foot [42]. Two measurable quantities, namely broadband ultrasound attenuation and ‘stiffness’, a term used to quantify bone quality, were reduced and improved with calcitonin therapy and a reduction in reported pain levels. Ultrasound may therefore be more useful than DEXA in this group of patients, although other causes of unilateral bone loss are not excluded [43]. One of the difficulties in assessing the efficacy of treatments has been the lack of objective evidence and quantification of the response to treatment. Attempts have been made to quantify the sympathetic response [27, 28], but this is unlikely to be very useful as RSD is characterized by vasomotor instability. Bone loss appears to start early in the disease and patchy osteoporosis is evident in cases with a short history. Quantification of this bone resorption may be an indirect measure of disease progression and resolution. In cases where there is unilateral involvement, the unaffected foot acts as a control, as reported variation between two normal feet is minimal and reproducibility is 0.9% [43].

Our experience of RSD of the ankle and foot extends to 29 patients over a period of 9 yr. Of these, 23 recalled a history of trauma, which ranged from fracture to prolonged vibration from a wheel arch on a bus. Of those who had no history of trauma, one had a history of low back pain with nerve root irritation, another underwent spinal fusion surgery 2 weeks prior to the onset of RSD symptoms, and a third had a hemiparesis 4 yr before she developed pain, swelling and hyperaesthesia in her spastic foot. Almost all patients had stage 1 or 2 disease at presentation. In those who had stage 3 disease and who were wheelchair bound at presentation, a poorer response to treatment and outcome was seen. Treatment was usually a single pamidronate infusion (90 mg), with, or more recently without, calcitonin administration, and 2 weeks of in-patient physiotherapy and rehabilitation. Only four patients failed to report improvement by 3 months. Two of these suffered severe trauma and comminuted fractures, one had established stage 3 disease, and the fourth did not improve with pamidronate and calcitonin but did improve with regional blockade.

It is apparent that there is much work to be done to understand the pathogenesis of RSD, so that therapy can be targeted more effectively. Very few randomized controlled studies have been undertaken to confirm reported anecdotal successes in treatment. However, treatments aimed at reducing localized bone loss may be important and should be assessed further. The chief failure of published research is the lack of quantification of outcome measures. Few studies utilize a simple functional assessment or quality of life assessment. Quantitative ultrasound needs further assessment with regard to the natural history of RSD and then in assessing response to therapy. Patients with RSD of the ankle and foot, who present early with characteristic clinical findings, would be the most appropriate group to target. The relevance of classification of the different stages of RSD both at the time of diagnosis and in assessing outcome could fuel the need for early treatment and raise awareness of this poorly understood condition.

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References

8. Crosbie O, Collier J, Bateman E et al. A pilot study of sirolimus (rapamycin) as primary immunosuppression...