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ORIGINAL ARTICLE

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# Calcineurin-inhibitor induced pain syndrome (CIPS): a severe disabling complication after organ transplantation

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**Abstract** Bone pain after transplantation is a frequent complication that can be caused by several diseases. Treatment strategies depend on the correct diagnosis of the pain. Nine patients with severe pain in their feet, which was registered after transplantation, were investigated. Bone scans showed an increased tracer uptake of the foot bones. Magnetic resonance imaging demonstrated bone marrow oedema in the painful bones. Pain was not explained by other diseases causing foot pain, like reflex sympathetic dystrophy, polyneuropathy, Morton's neuralgia, gout, osteoporosis, avascular necrosis, intermittent claudication, orthopaedic foot deformities, stress fractures, and hyperparathyroidism. The reduction of cyclosporine- or tacrolimus trough levels and the administration of calcium channel blockers led to relief of pain. The Calcineurin-inhibitor Induced Pain Syndrome (CIPS) is a rare but severe side effect of cyclosporine or tacrolimus and is accurately diagnosed by its typical presentation, magnetic resonance imaging and bone scans. Incorrect diagnosis of the syndrome will lead to a significant reduction of life quality in patients suffering from CIPS.

**Keywords** Cyclosporine · Tacrolimus · Pain · Transplantation · Reflex sympathetic dystrophy · Avascular necrosis

**Abbrevations** *CIPS* Calcineurin-inhibitor induced pain syndrome

## Introduction

The aim of organ transplantation in endstage diseases is not only to prolong the individual's life but also to improve the quality of life. However, several complications can occur after transplantation which might influence the overall outcome. One of these complications is musculoskeletal pain which occurs in one third of the patients after kidney transplantation [21] and heart transplantation [18]. Several diseases, like hyperparathyroidism, polyneuropathy, bone deformities and gout can cause musculoskeletal pain after transplantation [14]. However, pain after transplantation is most frequently caused by osteoporosis due to immunosuppressive therapy with corticosteroids. Corticosteroids can also cause pain by osteonecrosis. Calcineurin-inhibitors like cyclosporine and tacrolimus are another class of immunosuppressive drugs which have an impact on bone metabolism. We report here a pain syndrome that causes significant disability in the patients after organ transplantation and that could occur in connection with high trough levels of calcineurin-inhibitors, the Calcineurin-inhibitor Induced Pain Syndrome (CIPS). The definition of this disorder, the diagnostic criteria, differential diagnosis, and therapy recommendations are presented.

## Materials and methods

Nine allograft recipients (8 of 637 renal transplant recipients, and 1 of 39 heart transplant recipients) were admitted to our outpatient clinic between 1991 and 1998 for severe bone pain in their lower limbs after transplantation. Characteristically, the pain was described as severe and disabling, and it was not attributable to a common diagnosis. These patients were consequently investigated, and their charts were retrospectively evaluated for diagnosis leading to organ failure, complications, and immunosuppressive therapy. Cyclosporine- and tacrolimus trough levels were measured by the TDX monoclonal test and by the immunoassay IMX tacrolimus II (Abbott, USA). Magnetic resonance imaging was performed on a 1,5 Tesla system (Siemens Vision, Erlangen, Germany). The T1- and T2-weighted images were obtained in the coronal and sagittal plane. Bone scintigraphies of the whole body were performed in all patients 10 min and 3 h after the injection of the tracer (700 MBq Technetium 99m DPD). In addition, planar spot views of both feet were obtained immediately, 10 min, and 3 h after injection of the tracer (Cameras: Bodyscan and Orbiter, Siemens, Erlangen, Germany). All patients were interviewed with a standardised questionnaire about the onset, duration, description, and localisation of their pain (Table 1). The pain was characterised with the "Hamburg Pain Adjective List" which allows a reliable and reproducible quantification of chronic pain syndromes [8, 9, 22]. The patients were asked to judge which of 37 different qualities as represented by 37 adjectives on the list, were typical characteristics of their pain. Each property was rated by the patient with 0 points if it was not applicable, and with 6 if the description was accurate. The maximum number of points was 222. The analysis provides assessment of 4 different qualities of pain: intensity; characteristics (hammering, knocking); affective components (like anxiety); and degree of individual suffering.

## Results

All patients developed an unusual pain syndrome of the lower limbs after transplantation. The onset of pain ranged from 3 weeks to 14 months after transplantation and improved after a duration of 3–18 months. The pain was always located symmetrically in both feet, sometimes spreading out into the ankles and knees (Table 1). It was characterised as a deeply aching, severe pain that was aggravated by walking and weight-bearing. Most of the patients had to use crutches or a wheel-chair. They felt relief at physical rest, especially when feet were elevated. Patients' life quality was considerably impaired by the pain: The mean total value of the "Hamburg Pain Adjective List" score was 119 ± 11 of maximally possible 222 points (52 ± 5 %). The 4 qualities of pain were assessed in relation to the maximum score of each subgroup as follows: 37.7 ± 14.2 % were given for adverse characteristics, 40 ± 15 % for intensity of pain, 61 ± 17 % for associated anxiety, and 71 ± 18 % for suffering from CIPS.

Clinical examination was mostly unremarkable. X-rays of the feet were performed in all patients and excluded exostosis or fractures. Three phase bone scintigraphy was performed in all the patients and showed an increased tracer uptake of joints and bones in all three phases accentuated at the tarsus, indicating hyperperfusion, hypervascularity, and hypermetabolism (Figure 1). In six patients, magnetic resonance imaging was performed and revealed fluid in the talotibial joint and soft tissue oedema. Four patients additionally showed a diffuse bone marrow oedema in the painful areas such as the foot bones and the distal tibia (Table 2). The bone marrow oedema was limited sharply at the epiphysis of the distal tibia in patient 2 (Figure 2) and declined significantly with the relief of pain, as was documented in further magnetic resonance investigations. Angiographies (patients 2 and 7) and neurological investigations (patients 1, 2, 6, 8 and 9) were performed to exclude polyneuropathy, reflex sympathetic dystrophy, and atherosclerosis (Table 2).

Laboratory investigations showed normal values of inflammatory and rheumatic parameters. However, trough levels of cyclosporine and tacrolimus were elevated in all patients (cyclosporine 201–330 ng/ml and tacrolimus 11 ng/ml). The desired therapeutic window is usually between 120 and 180 ng/ml for cyclosporine and between 4–8 ng/ml for tacrolimus. Especially patient 3 described a strong connection between the intensity of pain and elevated cyclosporine trough levels. Pain relief was experienced in all cases after reduction of cyclosporine or tacrolimus doses (Table 1). The pain syndrome was terminated within 2 weeks after withdrawal of cyclosporine therapy (patients 3, 8, 9).

Patients tried to reduce their pain with analgesic drugs (Table 2). Only one patient described a transient

**Table 1** Characteristics and immunosuppressive therapy of patients with CIPS (Calcineurin inhibitor Induced Pain Syndrome). **Abbrevations**: *GN* glomerulonephritis, *HD* haemodialysis, *CAPD* continuous ambulatory peritoneal dialysis, *CsA* cyclosporine, *MMF* mycophenolate, *FK* tacrolimus, *Aza* azathioprine, *Pred* prednisone, *ATG* anti lymphocyte globuline, *Tx* transplantation, *M* male, *F* female

| Patient Age[1], Sex | Donated organ (date of Tx) | Diagnosis leading to organ failure | Pretreatment of organ failure | Onset of pain after Tx/duration of pain | Immunosuppression/treatment of rejection | CsA (FK) trough levels at onset of pain / after reduction of CsA-dosage |
|---|---|---|---|---|---|---|
| 1<br>26, F | Kidney<br>(3/96) | IgA-nephropa thy | 4 Years CAPD | 2 Months/<br>3 Months | CsA, Aza, Pred<br>6th day post Tx:<br>Pred 3 × 500 mg,<br>ATG | CsA 201 ng/ml/<br>107–169 ng/ml |
| 2<br>52, M | Kidney<br>(5/96) | Nail-patella-syndrome | 11 Years HD | 14 Months/<br>10 Months | FK, Aza, Pred | FK 11 ng/ml/<br>3,6–7,8 ng/ml |
| 3<br>44, M | Kidney<br>(6/93) | Mesangio-proliferative GN | 14 Years HD | 6 Weeks/<br>12 Months | CsA, Aza, Pred | CsA 252 ng/ml/<br>withdrawn |
| 4<br>32, M | Kidney<br>(2/96) | Adult polycystic kidney disease | 7 months HD | 3 Weeks/<br>6 Months | CsA, Aza, Pred | CsA 229 ng/ml/<br>120–150 ng/ml |
| 5<br>47, M | Kidney<br>(5/91) | Membrano-proliferative GN | 10 Years HD | 6 Months/<br>18 Months | CsA, Aza, Pred | CsA 222 ng/ml/<br>122–169 ng/ml |
| 6<br>32, F | Kidney<br>(12/93) | Reflux nephro-pathy | 3 Years CAPD | 6 Weeks/<br>3 Months | CsA, Aza, Pred | CsA 280 ng/ml/<br>134–164 ng/ml |
| 7<br>47, M | Heart<br>(12/93) | Ischemic cardiomyopathy | conservative | 10 Months/<br>12 Months | CsA, Aza, Pred<br>10 months post Tx:<br>Pred 10 × 100 mg | CsA 330 ng/ml/<br>183–241 ng/ml |
| 8<br>52, M | Kidney<br>(7/97) | Glomerulo-sclerosis | 7 Years HD | 10 Months/<br>10 Months | CsA, MMF, Pred | CsA 240 ng/ml/<br>withdrawn |
| 9<br>48, M | Kidney<br>(4/97) | Glomerulo-sclerosis | 6 Years HD | 4 Weeks/<br>10 Months | CsA, MMF, Pred | CsA 221 ng/ml/<br>withdrawn |

[1] Age at time of transplantation

relief of pain after application of antiphlogistic drugs (ibuprofen, patient 5) and two patients (patient 3) after intake of a morphine derivate (tilidin). Other therapeutic attempts with alpha-lipoic acid, bisphosphonates (ibandronate 2 mg), and carbamazepine did not induce pain relief. Most of the patients had already been treated with calcium channel blockers because of hypertension. Two of them (patient 1 and 6) observed a relief of pain 30 min after intake of the calcium blocker (Table 2).

## Discussion

After solid organ transplantation, one third of patients develop musculosceletal pain of different origins [18, 21]. Mostly, this pain is not severe and self limiting. Here we report on nine patients who suffered from an unusual pain syndrome of the lower limbs. In our series it was a rare condition with an incidence of 1%. However, the pain caused a significant disability in these patients, which is demonstrated by a mean pain score of 71% of the highest possible level of suffering.

A similar pain syndrome in correlation with cyclosporine therapy was first described by Lucas *et al* in 1991 [13]. Three years later, Gauthier *et al* published an unexplained bone pain in patients after organ transplantations (liver, lung, pancreas, kidney) that improved after administration of calcium channel blockers [5]. Thereafter a "Post-Renal Transplant Distal Limb Bone Pain" was described showing increased tracer uptake in bone scintigraphy [20]. In accordance with our findings, bone marrow oedema were detected with the help of magnetic resonance imaging in cyclosporine treated renal transplant recipients with bone pain [10].

Despite consultation of orthopedic, neurologic, and rheumatologic experts, the pain of our patients could not be attributed to a common cause. It was recognized as a disease entity as such which could occur as an adverse event of immunosuppressive therapy after transplantation. Since, in our patients, the occurrence of pain corresponded with high levels of cyclosporine or tacrolimus, and the pain stopped after withdrawal of these drugs, we called it Calcineurin-inhibitor Induced Pain Syndrome (CIPS). Differential diagnosis includes many other disorders causing foot pain. Their differentiation is important because therapy varies considerably

**Table 2** Results of laboratory, radiological and further investigations

| Pat. | MR of feet | Bone scintigraphy | Additional investigations | Effect of pharmacological drugs |
|---|---|---|---|---|
| 1 | Bone marrow oedema of foot bones, fluid in talotibial joint | Symmetrical increased tracer uptake of foot bones and knees, and less intense of almost all remaining joints (Fig. 1) | | Nitrendipin: relief within 30 min |
| 2 | Bone marrow oedema limited at the epiphysis of tibia, fluid in talotibial joint, (Fig. 2) | Symmetrical increased tracer uptake of foot bones and less intense knees, elbows, shoulders | Sympatholytic therapy: no effect<br>Galvanic skin response: normal<br>Angiography: normal | Diclofenac: no effect<br>Diphosphonates: no effect |
| 3 | Not done | Symmetrical increased tracer uptake of foot bones | | Tilidin: slight effect<br>Alpha-lipoic acid: no effect<br>Carbamacepine: no effect |
| 4 | Not done | Symmetrical increased tracer uptake of foot bones and less intense of all remaining joints | | |
| 5 | Not done | Increased tracer uptake of foot bones | | Ibuprofen: slight effect |
| 6 | Soft tissue oedema, fluid in talotibial joint | Symmetrical increased tracer uptake of foot bones and less intense of all remaining joints | Nerve conduction studies: normal<br>Galvanic skin response: normal | Nitrendipin: relief within 30 min |
| 7 | Fluid in talotibial joint, soft tissue oedema | Increased uptake of foot bones | Angiography: normal | Nifedipine: no effect |
| 8 | Bone marrow oedema of distal tibia and talus, fluid in talotibial joint | Symmetrically increased uptake of foot bones and right knee | Histology of right femur: high bone turn over | Tilidin: slight effect |
| 9 | Bone marrow oedema of distal femur, tibia, foot bones fluid in talotibial joint | Symmetrical increased uptake of foot bones and knees | | Ibuprofen: no effect |

from treatment of CIPS (Figure 3). Differential diagnosis is most easily assessed by distinction in unilateral and bilateral foot pain.

Unilateral foot pain can be induced by fractures, foot deformities, exostosis, gout, and Morton's neuralgia. Symptoms caused by orthopaedic foot deformities are diagnosed by typical clinical signs of the missing longitudinal or diagonal arch. Exostosis of bones and fractures can easily be excluded or detected by x-ray. The diagnosis of gout is supported by repeated arthritis attacks on the metacarpophalangeal joint of the first toe or other small joints with calor, rubor, dolor, and swelling in combination with elevated uric acid levels and inflammatory parameters [15]. The pain induced by Morton's neuralgia is localised between the distal metatarsal bones 3 and 4 or 4 and 5, can be provoked by compression of the heads of these bones, and neurological investigation shows a loss of sensibility of the interdigital nerve [2]. Peripheral atherosclerosis [19] can also mimic weight dependent foot pain of CIPS, but can be excluded by angiography.

The bilateral symmetrical character of foot pain of CIPS can be difficult to distinguish from polyneuropathy, osteoporosis, and hyperparathyroidism. Polyneuropathy can be caused by cyclosporine, which is known to affect peripheral nerve fibres. In particular, if small-diameter myelinated and unmyelinated fibres are involved, specific evaluation with thermal stimulation and sudomotor testing must be performed. The damage of large diameter nerves can be quantified with nerve conduction studies [3]. Osteoporosis is the most common cause of bone pain after transplantation. It is induced by a rapid loss of bone mass during the first months after transplantation when glucocorticoid dosages are high [6]. Although most patients suffering from CIPS simultaneously had low bone mineral density at the lumbar spine, none of them suffered from back pain, the typical sign of posttransplant osteoporosis. Al-

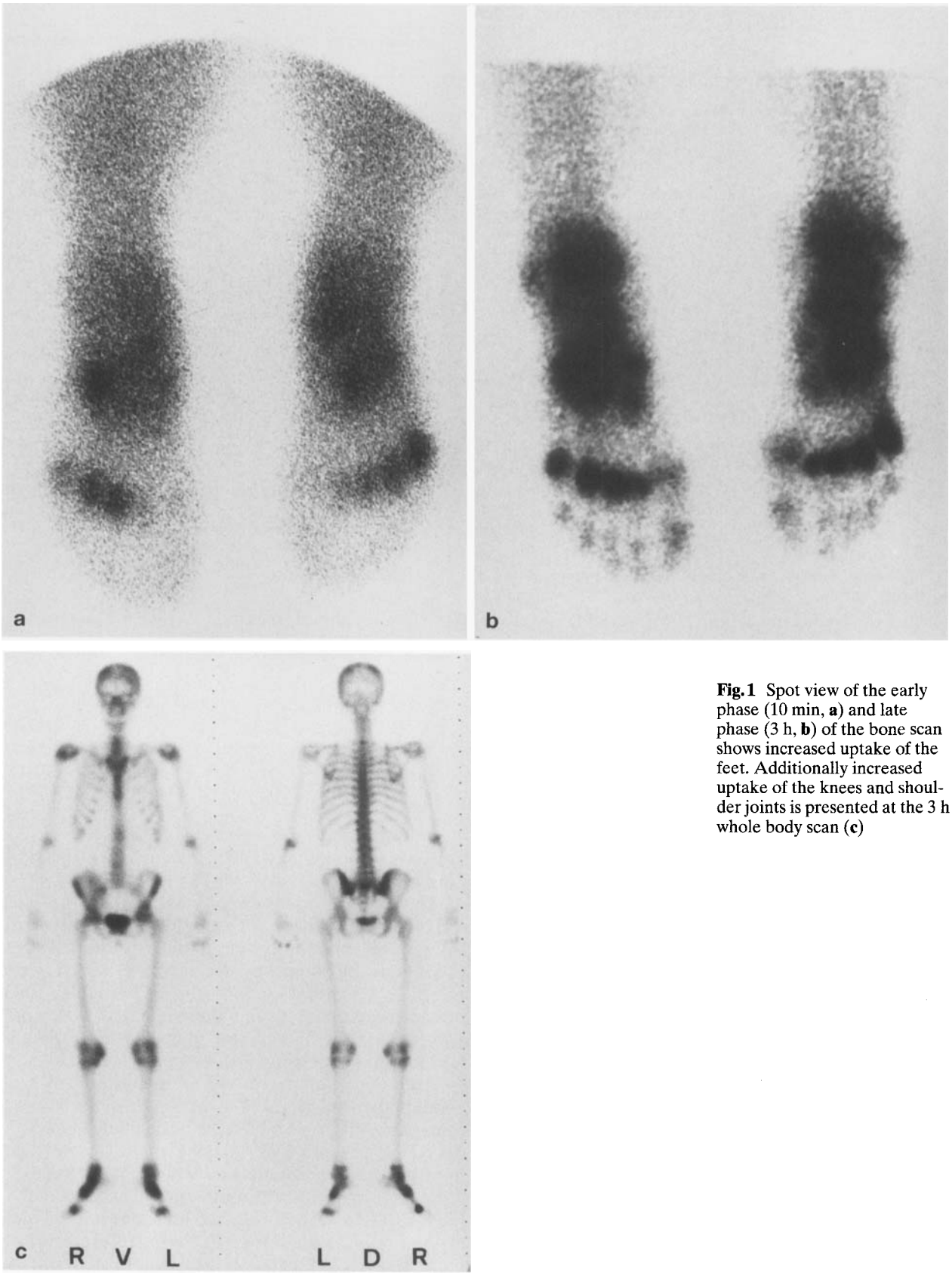



**Fig. 1** Spot view of the early phase (10 min, **a**) and late phase (3 h, **b**) of the bone scan shows increased uptake of the feet. Additionally increased uptake of the knees and shoulder joints is presented at the 3 h whole body scan (**c**)

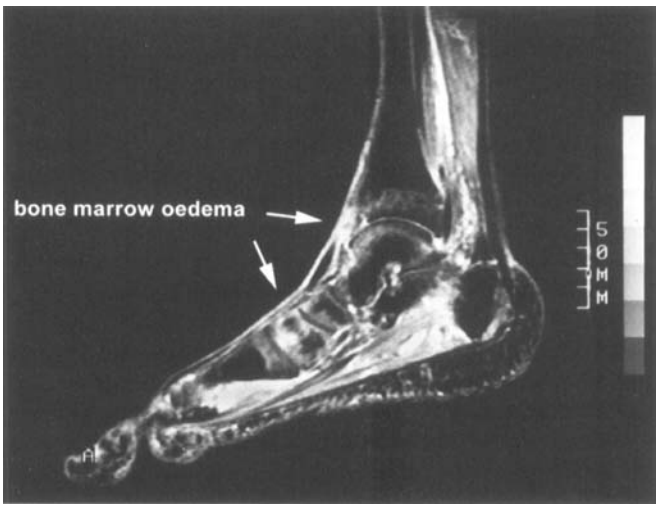


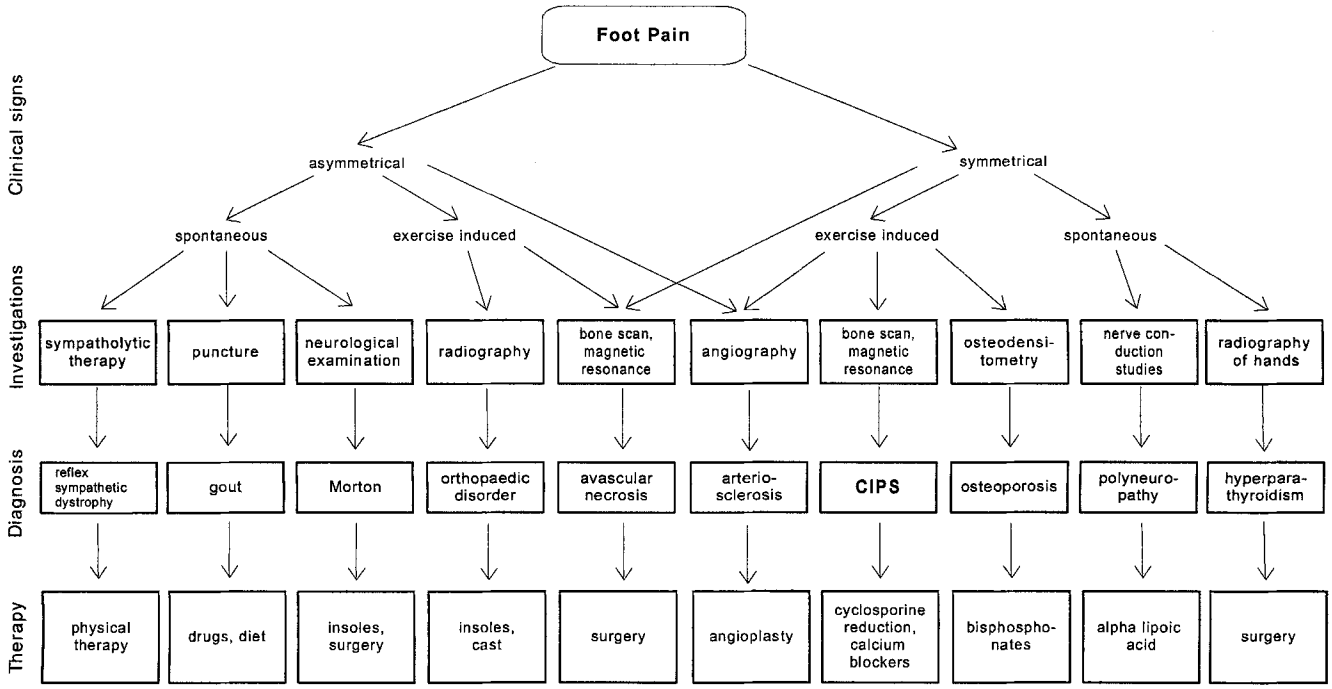

**Fig. 2** In the T2-weighted fat suppressed MR normal bone marrow appears dark due to low signal intensity. The bone marrow oedema is shown by a high T2 signal intensity (*bright areas*) in talus, navicular and medial cuneiform bones (marked with *arrows*)

though persisting raised parathyroid hormone levels are a frequent finding in patients after kidney transplantation, patients with CIPS did not show the characteristic x-ray findings of hyperparathyroidism, like subperiostal resorption or acroosteolysis [16]. In addition, the distribution of the tracer uptake of bone scans allows the distinction between hyperparathyroidism and CIPS. The uptake in hyperparathyroidism is located in several joints and in the tips of the ribs, whereas uptake in CIPS is most prominent in foot bones.

The three typical radiological signs (normal initial x-ray, positive bone scan, and bone marrow oedema in magnetic resonance) may also be caused by two further diseases: reflex sympathetic dystrophy, and avascular bone necrosis. However, reflex sympathetic dystrophy is typically asymmetrical [17] and shows the combination of allodynia, dysaesthesia, swelling, motor symptoms, and signs of vasomotor or sudomotor instability. Also, the pattern of tracer uptake is different: Reflex sympathetic dystrophy shows an increased uptake in all bones of the affected foot, predominantly in the periarticular areas of the toes and tarsal bones in all three phases [7], whereas in CIPS some joints can be spared (Fig. 1). Furthermore, sympatholytic intervention with guanethidin intravenously, or blockage of the paravertebral sympathic ganglia can help to distinguish the two conditions from each other.

Avascular bone necrosis is a further complication after transplantation that shows bone marrow oedema. However, it is associated with permanent, weight dependent pain, mostly localised at the hip. It is corticosteroid related and irreversible after impression fracture [4]. Its incidence as a complication of transplantation has decreased since cyclosporine has been introduced to the immunosuppressive regimen and since the dosage of corticosteroids could be reduced [12]. In contrast, CIPS is reversible and its onset is often associated with high cyclosporine trough levels.

**Fig. 3** Diagnosis and treatment of CIPS and other pain syndromes



The pathogenesis of CIPS is unknown. Several factors imply that CIPS is associated with, or even caused by, calcineurin-inhibitor therapy. i) The onset of pain is often associated with high calcineurin-inhibitor trough levels. ii) Reduction of calcineurin-inhibitor doses resolves symptoms. iii) Up to now, the syndrome has only been observed in the context of immunosuppression with cyclosporine or the other calcineurin-inhibitor, tacrolimus, but not with azathioprine [13]. CIPS was only observed in the setting of transplantation, but not in autoimmune disorders like rheumatoid arthritis, uveitis, psoriasis and glomerulonephritis, probably because of higher doses of calcineurin-inhibitors after transplantation. We support a hypothesis which stresses a calcineurin-inhibitor induced vascular disturbance [11] of bone perfusion and of permeability causing a bone marrow oedema. Such a vascular origin of CIPS is supported by imaging techniques: Bone scintigraphies show an increased tracer uptake by the foot bones, indicating hyperperfusion, hypervascularity, and hypermetabolism. Magnetic resonance imaging demonstrates a bone marrow oedema [10] sharply limited at the epiphysis of the distal tibia, the border of different vascular supply territories (Figure 2). At this stage it is unclear whether the oedema is only an epiphenomena or an important causative factor for the pathogenesis of CIPS. Its importance is underlined by the parallel decrease of bone marrow oedema and pain relief. Foot bones seem to be preferentially affected because of the high venous pressure resulting from the upright position. Conversely, venous pressure, bone marrow oedema, and pain are lessened when the legs are elevated. Furthermore, the effect of calcium channel blockers [5] can be explained by their ability to antagonise cyclosporine- or tacrolimus related vasoconstriction [1] and to intramedullary pressure which has been detected in patients with bone marrow oedema caused by avascular necrosis [23]. However, pathogenesis is still hypothetical, and further investigations are necessary to prove the pathogenesis of a calcineurin-inhibitor induced bone marrow oedema.

Therapy of CIPS is in accordance with the assumed etiology: The greatest relief of pain is achieved by reduction of the cyclosporine- or tacrolimus trough levels. Less immunosuppression has to be compensated by higher doses of other immunosuppressive drugs with a combination therapy. Furthermore, calcium channel blockers should be applied, preferentially nifedipine or nitrendipine, which do not inhibit the cyclosporine- or tacrolimus degrading cyctochrome p450. In addition, patients can be advised to elevate their legs as long as they are symptomatic. Non-steroidal antiphlogistic drugs should be avoided because of their minor benefit in CIPS and their harmful action on kidney function, especially in the setting of renal transplantation and high calcineurin-inhibitor levels.

In conclusion, CIPS should be suspected if the patient complains of a deep aching pain occurring symmetrically in the lower limbs during walking, especially in the early phase after transplantation, when cyclosporine- or tacrolimus trough levels are high. The final diagnosis is supported by bone scans showing the characteristic tracer uptake of the foot bones in all three phases, and by magnetic resonance imaging, which can demonstrate bone marrow oedema. It is a rare but severe complication following transplantation that deters patients from walking and markedly reduces their quality of life.

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