The use of three-phase radionuclide bone scanning in the diagnosis of reflex sympathetic dystrophy

One hundred forty-five consecutive three-phase radionuclide bone scans were reviewed. One hundred two of these were performed to evaluate pain in the hand. Of these, 23 patients clinically had reflex sympathetic dystrophy (RSD). The hand scans were performed by the three-phase technique. Phase I is a radionuclide angiogram. Phase II is the blood pool or tissue phase. Phase III consists of delayed images obtained 3 to 4 hours after radionuclide injection. Detailed analysis of the 145 three-phase radionuclide bone scans of the hand demonstrated that the diffuse increased tracer uptake in the delayed image (phase III) is diagnostic for RSD, with a sensitivity of 96% and a specificity of 98%. The two early phases (radionuclide angiogram and blood pool) were positive in only 45% and 52% of the RSD patients, respectively. The strictly interpreted delayed radionuclide image is extremely sensitive in the diagnosis of RSD and will facilitate the early diagnosis and subsequent treatment of this syndrome. (J HAND SURG 9A:556-63, 1984.)

Susan E. Mackinnon, M.D., F.R.C.S.(C), and Lawrence E. Holder, M.D.,
Toronto, Ontario, Canada, and Baltimore, Md.

The clinical syndrome of reflex sympathetic dystrophy (RSD) presents a major diagnostic and therapeutic problem for the hand surgeon. The terms used to describe this syndrome are numerous, the criteria for diagnosis are varied, and the treatment methods meet with only partial success.1–3 Although the classic description of RSD was made more than a century ago,4 a generally accepted definition of this clinical entity is still lacking. We have established our own strict criteria for the diagnosis of RSD and in this report describe the use of the three-phase radionuclide bone scan (TPBS) in its diagnosis. We have found that the strictly interpreted delayed radionuclide images are extremely sensitive in the diagnosis of RSD.

Material and methods

Patient selection. All of the 145 TPBSs of the hand performed at the Union Memorial Hospital* from July 1, 1981, to June 9, 1982, were reviewed. In 102 patients the prime complaint was pain in the hand. For the purposes of our study, four clinical groups were defined (Table I).

Group I consisted of 23 postsurgical or posttraumatic patients with pain who had definite RSD according to our clinical definition of this syndrome (Table II). Symptoms compatible with this syndrome were present for an average of 7 months with a range from 1 month to 4 years. There were 12 women and 11 men in this group ranging in age from 18 years to 78 years with a mean of 43 years. While most of these patients had received some standard method of treatment for RSD, all patients were still being followed for ongoing problems with RSD.

Group II consisted of 26 patients who complained of diffuse hand pain but did not demonstrate any of the other established criteria for RSD. These included patients who had been referred to hand surgeons by other physicians to “rule out” RSD. In the cases placed in

*The Raymond M. Curtis Hand Centre, Union Memorial Hospital, Baltimore, Md.
Table I. Clinical groups

<table>
<thead>
<tr>
<th>Clinical group</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Definite RSD</td>
<td>23</td>
</tr>
<tr>
<td>II. Diffuse hand pain (not RSD)</td>
<td>26</td>
</tr>
<tr>
<td>III. Focal pain</td>
<td>51</td>
</tr>
<tr>
<td>IV. Other</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>145</td>
</tr>
</tbody>
</table>

In this category, the hand surgeon did not feel that the patient had RSD. TPBS was performed largely to look for other potential causes of hand pain.

The third group consisted of 51 patients who complained of focal hand pain. None had diffuse hand pain as the chief complaint and none had any of the signs suggestive of RSD (Table II). The fourth group included 43 patients referred for TPBS of the hand for reasons other than pain, including fracture diagnosis, tumor evaluation, and a variety of vascular problems.

The clinical aspects of each case were reviewed with the referring hand surgeon, and it was this surgeon who determined whether the clinical diagnosis of RSD was valid in their patients.

Scintigraphic studies. Hand scans were performed according to the three-phase technique, which has recently been described in detail. Phase I is the radionuclide angiogram (RNA), which consists of sequential 5-second images obtained for 40 seconds with a γ scintillation camera, following rapid, bolus injections of 20 mCi of technetium 99m-labeled methylene diphosphonate. Immediately after the RNA, phase II (blood pool or tissue phase) images are obtained for 500 K counts with the high-sensitivity, low-energy all-purpose collimator. Phase III consists of delayed (metabolic) images obtained with a high-resolution parallel-hole collimator 3 to 4 hours after the injection. These scans were then evaluated by a nuclear radiologist (L. E. H.) who did not know the patients' clinical histories. The images were graded as normal (Fig. 1), focally or multifocally abnormal (Fig. 2), or diffusely abnormal (Fig. 3). To be considered diffusely positive, RNA perfusion had to be increased in all portions of the wrist and hand. The phase II blood pool and phase III delayed images had to demonstrate increased activity in the areas of the radial and ulnocarpal, intercarpal, carpectacarpal, metacarpophalangeal and the juxta-articular regions of the digits to be considered diffusely positive.

Results

The results of the evaluation of the delayed images are seen in Table III. Twenty-two of 23 patients with clinical RSD (group I) had diffusely positive scans. The
Table III. Findings on delayed image of TPBS of the hands

<table>
<thead>
<tr>
<th>Clinical groups</th>
<th>Normal</th>
<th>Focal changes</th>
<th>Diffuse RSD pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. RSD</td>
<td>1/23</td>
<td>6/23</td>
<td>22/23</td>
</tr>
<tr>
<td>2. Diffuse pain</td>
<td>13/26</td>
<td>12/26</td>
<td>1/26</td>
</tr>
<tr>
<td>3. Focal pain</td>
<td>20/51</td>
<td>29/51</td>
<td>2/51</td>
</tr>
<tr>
<td>4. Other</td>
<td>16/45</td>
<td>24/45</td>
<td>0/45*</td>
</tr>
</tbody>
</table>

*Two patients with vascular lesions had diffusely decreased scan active delayed scanning was not performed in three patients.

31 patients demonstrated very minimal diffuse increased activity on the delayed scan and the results were interpreted as questionably positive and considered false positive. In both patients the RNA and blood pool images were normal. Both patients had longstanding posttraumatic wrist pain.

A number of patients in group IV had vascular problems. Consequently, decreased activity was noted on some of the scans in this group. Five of the scans showing focal changes showed focal decrease. Two other patients had diffuse decreases; none had diffuse increases. Three patients with vascular disease were taken directly to the operating room after the early studies were completed, and delayed images were not obtained in these patients.

In this study, 10 diffusely positive RNAs and 12 diffusely positive blood pool images were noted. All of these results were found in group I patients who also demonstrated diffusely positive phase III images (Table IV). Thus the RNA was positive in 45% of the group I patients (10/23) and the blood pool image was positive in 52% (12/23). These RNA and blood pool images were variably related. Eight of the 10 patients who had positive RNAs demonstrated positive blood pools; four patients with positive blood pools had negative RNAs.

In the detection of RSD by use of the delayed images alone, the sensitivity was 96%, the specificity was 98%, the positive predictive value was 88%, and the negative predictive value was 99% (Table V). Roentgenograms of the hands were available in 17 of the 23 patients with clinical RSD. These were "positive" for RSD, showing diffuse and patchy osteoporosis in 11 of the 17 cases.

Discussion

Radiographic changes associated with RSD have been documented by many authors. Early reports emphasized the osteoporosis that occurred. This patchy
Fig. 2A. Focally abnormal TPBS. RNA, dorsal view. Focal increased perfusion to the area of the third metacarpophalangeal joint is noted on the left side (arrow). Note the symmetry of activity of the radial and ulnar arteries and digits when compared with the normal right hand.

Table IV. TPBS analysis in patients with clinical RSD

<table>
<thead>
<tr>
<th>Scan</th>
<th>Phase I (RNA)</th>
<th>Phase II (blood pool)</th>
<th>Phase III (delayed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSD positive</td>
<td>10</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>Normal</td>
<td>12*</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

*No one patient RNA was not performed.

Semirenalization was not specific for RSD and was variably present, being reported as a positive finding in 30% to 70% of cases.7, 8 Sixty-five percent of our patients (11/17) had positive radiographs. According to our strict criteria for both the clinical and the scintigraphic diagnosis of RSD, we were able to confirm recent work that has suggested that bone scintigraphy is both sensitive and specific for the diagnosis of this syndrome.8–15

Although Swezey16 is attributed with having first used bone imaging in a patient with RSD, it is more recent reports by Kozin et al.,8, 10, 11 Genant et al.,9 and Beckerman et al.12 that have emphasized the usefulness of scintigraphy in this syndrome.

Our report presents considerable difference from the work of Kozin et al., both in patient selection and in scan interpretation. Only two thirds of their patients had upper extremity involvement, while all patients in our study were evaluated for problems involving the hand. Like other authors, Kozin et al.11 noted the “lack of clear diagnostic criteria” for this syndrome and subsequently defined their own set of four clinical groups of RSD. The patients in our series represent a unique group in that their care was monitored by surgeons specially trained in surgery of the hand. Well versed in the subtleties of examining the hand, these physicians determined if their patients had RSD based on clinical criteria (Table II). Thus the “probable, possible, and doubtful” RSD categories of Kozin et al. were eliminated. Accepting that this is a difficult and somewhat controversial diagnosis to make, we believe that our RSD group represents as pure as possible a population of patients with the clinical entity of RSD as recognized by practicing hand surgeons.

While RNA has been used for a number of years, its use in the evaluation of diseases of the hand is still being defined.17–20 Strict criteria for the interpretation of the normal TPBS of the hand have recently been reported, but diagnostic findings in RSD have yet to be clearly outlined. We have defined very specific criteria for the diagnosis of “abnormal” or positive RSD scans. While others11 have considered flow studies

Table V. Correlation between the clinical and RNA diagnosis of RSD

<table>
<thead>
<tr>
<th>Scan</th>
<th>RSD negative</th>
<th>RSD positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>119</td>
<td>1</td>
</tr>
<tr>
<td>RSD positive</td>
<td>3</td>
<td>22</td>
</tr>
</tbody>
</table>

*Sensitivity = \( \frac{22}{22 + 1} = 98\% \); specificity = \( \frac{119}{119 + 3} = 98\% \); positive predictive value = \( \frac{119}{119 + 1} = 99\% \).
for the RSD syndrome as the delayed phase III images (Table IV). In patients with RSD, the RNA and the blood pool images were positive 45% and 52% of the time, respectively. The delayed scan was considered positive in all but one patient in the RSD group (96%).

In 145 patients we had three false positive delayed images. One patient had had clinical evidence of RSD 12 months prior to the TPBS. This patient’s positive scan may offer supportive evidence for the assertion that it may take up to 18 months for a positive scan to revert to normal after symptoms resolve. Alternatively, one could postulate that subclinical disease was still present. Both of the other two patients had focal symptoms, and the delayed images demonstrated minimally positive diffuse uptake superimposed on more focal changes. Our scans were interpreted by purely qualitative criteria; perhaps a quantitative computer-assisted analysis would help resolve these false positive delayed scans. Conversely, these two patients may have had minimal problems with RSD.

With strict criteria for scan evaluation, we find that TPBS of the hand, and in particular the delayed images, is both sensitive (96%) and specific (98%) for the diagnosis of RSD.

The neurophysiologic events associated with the syndrome of RSD are not well understood. Theories from the 1930s and 1940s of abnormalities in the ‘interunical pool’ of the spinal cord and peripheral ‘short-circuiting’ between somatic (afferent sensory) and autonomic (efferent sympathetic) fibers are still quoted as likely abnormalities in this syndrome. Recent advances in the neurophysiology of the nociceptive (pain) system may help us to expand on these early theories and explain the findings on TPBS. Some of the previously unknown factors in the classic reflex arc or “nociceptive loop” are now well documented. Primary afferent pain impulses are conducted to the spinal cord (spinothalamic neurons in the dorsal horn) by way of the dorsal root ganglion. Substance P is a neurotransmitter for noxious stimuli at this level and is also located in the sensory terminals in the skin. Substance P has also been shown to induce plasma extravasation in the skin and is a likely candidate for neurogenically induced increased capillary permeability in the skin. This extravasation may result in the release into the tissue of agents that have been shown to facilitate pain (prostaglandins) or to increase the activity in the pain fiber system (bradykinin, serotonin, histamine). Murray has observed that localized pain in the hand (local causalgia) has frequently been associated with the flushed and rubious area that is clearly demarcated and corresponds almost exactly with the

Fig. 2, B-C, B, Blood pool image, palmar view. Poorly margined increased activity in the area of the head of the third metacarpal and base of the third proximal phalanx is noted (arrow). The thenar and digital vascularity is normal and similar to that in the right hand. C, Delayed image, palmar view. More intense abnormal increased tracer accumulation (arrow) is noted in the distal half of the third metacarpal and proximal half of the third phalanx. Slight increased activity is noted at the base of the third metacarpal. Activity in the wrist and digits is normal and similar to that in the normal hand. (Clinical diagnosis: synovitis of the metacarpophalangeal joint.)

‘positive’ when there was asymmetric appearance of radionuclide in the affected extremity, we do not consider focal increases in perfusion positive but require diffuse increased perfusion to be present.

Similarly, for the blood pool images and certainly for the delayed (phase III) images, increased juxta-articular activity in multiple joints is not acceptable. All joints must be involved before the diagnosis of RSD can be entertained. Based on such criteria, it is apparent that neither the early blood flow (RNA) nor the blood pool images (tissue phase) are as diagnostically important
Three-phase radionuclide bone scanning in diagnosis

Fig. 3A. Diffusely abnormal TPBS. RNA, dorsal view. On the right, more perfusion is via the radial artery (arrow). Increased perfusion to the wrist and digits is noted in the right hand as compared with the normal left side. Previous traumatic amputation of the thumb and parts of the second and third digits is noted on the left hand.

can postulate that after the release of prostaglandins, the relatively increased bone turnover in juxta-articular regions, with associated increased extraction ratio of the radiotracer, is at such a level in many patients that the summed active accretion into the hydration shell of the bone crystal is visualized on the delayed scan. The minimal, if any, increased blood flow (phase I) or increased passive diffusion of tracer (phase II) may be insufficient to be visualized by current techniques. With the use of both experimental studies and computer perturbation analysis, Charkes and Vidya et al. have suggested that in the normal situation bone behaves as if it is saturated with the tracer and that an increase in the velocity of blood flow is in itself not sufficient to cause an increase in tracer deposition. They have postulated a recruitment phenomenon, consisting of a sympathetic nervous system effect on the microvasculature within the bone such that closed vessels open, perfusing more osteons and hence increasing tracer uptake.

Although a clear understanding of the pathogenesis of RSD and of the mechanisms of tracer uptake is still lacking, the TPBS remains useful as a diagnostic indicator for patients suspected of having RSD and thus may help facilitate both the early diagnosis and the treatment of this significant problem.

Summary

While controversy still surrounds the pathogenesis, diagnosis, and management of RSD, it is generally agreed that early diagnosis and treatment offers the best
modalities for RSD. While the etiology of this syndrome remains hypothetical, it is hoped that studies such as this will bring us closer to understanding of the pathophysiology and management of this difficult clinical syndrome.

The authors gratefully acknowledge the assistance of Drs. G. L. Clarke, A. Lee Dellow, M. A. McClinton, and E. F. Shaw Wigram for their documentation and helpful discussion.

REFERENCES