Original Article

Usefulness of asymmetry score on quantitative three-phase bone scintigraphy in the evaluation of complex regional pain syndrome

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ABSTRACT

Introduction: Complex regional pain syndrome (CRPS) is primarily a clinical diagnosis. Diagnostic imaging in CRPS can be used, especially to exclude other disorders. The sensitivity and specificity of three phase bone scintigraphy (TPBS) for the diagnosis of CRPS is variable throughout the literature. **Aim**: To establish a simple and effective quantitative approach to help in the diagnosis of CRPS by TPBS. **Materials and Methods**: TPBS done in patients ($n = 68$) with suspected CRPS was analyzed retrospectively. They were classified into bone scan positive group (BSP), bone scan negative group (BSN) and non-CRPS group based on diffusely increased periarticular uptake, symmetrical uptake, and focal uptake respectively. Asymmetry score (AS) was also measured between the affected and unaffected side. **Results:** 16 patients showed focal uptake, 37 were in BSP group with mean AS score of 1.57 ± 0.5 and 15 were in BSN group with mean AS score of 1.01 ± 0.05. The mean AS was significantly different ($P < 0.0001$). AS of 1.06 had sensitivity and specificity of 96.43% and 100% respectively ($P = 0.0001$). There was a trend of negative correlation between the AS and the duration, $r = -0.21$; however, it was not statistically significant ($P = 0.28$). **Conclusion:** TPBS should be considered in the evaluation of CRPS to rule out patients who have focal involvement, not diagnostic of CRPS ($\sim$24% in this study). Quantitative AS of 1.06 can be included to support visual interpretation in the delayed phase.

Keywords: Asymmetry score, complex regional pain syndrome, Tc99m methylene diphosphonate, three phase bone scan

INTRODUCTION

Complex regional pain syndrome (CRPS) is primarily a clinical diagnosis and manifests itself in the form of pain, skin, and subcutaneous changes, and musculoskeletal symptoms. It is a neuropathic pain disorder, evolving after limb trauma either without (CRPS I), or with definable nerve lesion (CRPS II).[1] Lankford described CRPS in three different clinical stages.[2] The first stage (within 3 months of onset) is characterized by much greater pain and swelling than expected following injury or surgery. The pain gradually peaks near the end of this stage. In the second stage (3-12 months after onset), intense pain persists, especially on motion. The edema becomes hard, brawny, and fixed, predisposing to marked joint stiffness. The third stage (more than 1 year after onset) is characterized by diminished pain, gradual decrease in swelling, and fibrosis of the joints and ligaments. In this stage, atrophy of the skin and subcutaneous tissue are pronounced with osteoporosis and allodynia in extreme cases.[2] The International Association for the Study of Pain (IASP) had issued a set of diagnostic criteria for CRPS.[3] However, uncertainty exists in accurately diagnosing CRPS clinically. The signs and physical abnormalities seen in the various stages of CRPS can be confirmed by certain diagnostic testing; however, there is no single measurement or interpretation that establishes the overall diagnosis. Imaging can be used in the diagnosis of CRPS, especially to exclude other disorders. The classic finding on three phase bone scintigraphy (TPBS) is diffuse increased periarticular activity in the affected extremity[4] and is more sensitive than plain X-rays.[5] Very few studies have attempted the quantitative approach in the evaluation of CRPS by TPBS. The technique used for quantitation

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Table 1: Proposed modified research diagnostic criteria for CRPS as per International Association for the Study of Pain

Criteria
Continuing pain, which is disproportionate to any inciting event
Must report at least one symptom in three of the four following categories
Sensory: Reports of hyperesthesia and/or allodynia
Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
Sudomotor/edema: Reports of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
Must display at least one sign* at time of evaluation in two or more of the following categories:
Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia
Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
Sudomotor/edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic: Evidence of decreased range of motion and/or motor dysfunction
There is no other diagnosis that better explains the signs and symptoms

CRPS: Complex regional pain syndrome

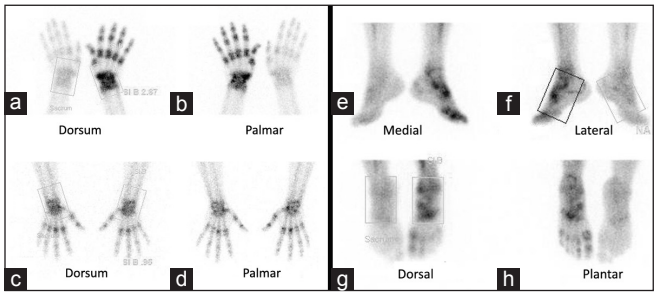

Figure 1: Tc 99m methylene diphosphonate scintigraphic images of the hand in the delayed phase (a) dorsumand (b) palmar views showing diffusely increased periarticular tracer uptake in the wrist joint, carpal bones and metacarpal and interphalangeal joints of right hand indicating bone scan positive (BSP) complex regional pain syndrome. Images (c and d) represent images of a patient with negative bone scan. Bone scan images of the foot (e) medial, (f) lateral, (g) dorsal and (h) plantar also show diffusely increased periarticular tracer uptake in the distal tibia, tarsal bones and metatarso-phalangeal and interphalangeal joints on left siderepresenting BSP foot

and the sensitivity and specificity of TPBS for the diagnosis of CRPS is variable throughout the literature.[6-11] The primary aim of our study was to evaluate if a simple and effective quantitative approach on TPBS can help in the diagnosis of CRPS and secondarily to identify if there is any relation between the duration of illness and the scan findings.

MATERIALS AND METHODS

A retrospective analysis of clinical and scintigraphic records of 68 patients (males = 30; females = 38; mean age 43 + 16 years) who underwent TPBS for suspected CRPS, was done. CRPS was suspected in all patients based on the proposed diagnostic criteria by the IASP given in Table 1. A history of trauma to the affected limb was found in 11 patients, paraparesis in one and hemiparesis in one patient, whereas no predisposing cause was noted in the rest of the patients.

All TPBS were performed using Technetium99m labeled methylene diphosphonate (Tc99m-MDP) under a dual-head gamma camera equipped with a low-energy high resolution collimator (E. Cam, Siemens, Erlangen, Germany). Palmar and dorsal views of the bilateral distal forearm and hand were acquired in patients with suspected CRPS of the hand (n = 57) while plantar and dorsum views of the bilateral distal legs and feet were acquired in suspected CRPS of the foot (n = 11).

Approximately, 740 MBq of Tc99m-MDP was injected into the dorsal vein of the foot in patients with hand involvement and the antecubital vein in patients with foot involvement. This was carried out to allow uniform comparison of the affected and unaffected sides. An initial dynamic imaging of the perfusion phase (phase 1), 20 frames of 4 s each in 64 × 64 matrix, was started after visualization of the tracer activity in the limb after radiotracer injection. Following the perfusion phase, static blood pool imaging was acquired for 2 min in 256 × 256 matrix (phase 2). A delayed static image was taken at 3-4 h after injection for 5 min in 256 × 256 matrix (phase 3).

All the cases were visually assessed for any asymmetry of tracer uptake in the affected limb. Diffusely increased periarticular uptake in the affected limb in phase 3 was considered as positive for CRPS (bone scan positive group [BSP]), while symmetrical uptake in all the phases was considered as negative for CRPS (bone scan negative group [BSN]). An alternative diagnosis was considered whenever there was focal/multifocal uptake in the blood pool/delayed phase (Non-CRPS group). The non-CRPS group was excluded from further analysis. Quantitative analysis, to measure the asymmetry score (AS) between the affected and unaffected side, was done in the BSP and negative groups. The standard region of interest (ROI) of sacro-iliac (SI) index was placed in the carpal bones, wrist, and distal forearm, or else in the tarsal bones, ankle and distal leg in CRPS of hand and foot cases respectively [Figure 1a and b]. The sacral ROI was placed on the unaffected side while the SI ROI was placed on the affected side. This gives the AS, which was measured on both the views and then, a geometric mean of the two AS was calculated. These cases were also divided into three stages based on the duration of symptoms as described by Demangeat *et al.*[12] They were as follows, stage-I: 0-20 weeks, stage-II: more than 20-60 weeks, stage-III: more than 60 weeks. Based on the stage wise analysis, 22 patients were in stage-I, 18 in stage-II, and 12 in stage-III.

Statistical analysis

Descriptive statistics were used for the variables as needed. Pearson correlation was used to calculate the correlation between the AS and the duration of symptom. Receiver-operating curve (ROC) analysis was done to find out the cut-off value of AS in differentiating BSP from negative cases. The significance level was set up at $P < 0.05$.

RESULTS

Focal or multifocal uptake in the blood pool/delayed phase was noted in 16/68 (23.5%) of the patients suggesting alternate diagnoses (non-CRPS). This included 14 hand and 2 foot cases respectively. The diagnoses in these patients were as follows, psoriatric arthritis = 1, osteoarthritis = 3, rheumatoid arthritis = 2, nonspecific inter-phalangeal joint arthritis = 2, limited scleroderma = 1, focal inflammation in the distal end of ulna/radius = 3, focal inflammation in the carpal bones = 4. They were excluded from further analysis. Of the remaining 52 patients, 37 (71%) patients (30 hands, 7 foot) showed diffusely increased peri-articular tracer uptake in the phase 3 of bone scan making it as BSP group. The representative bone scan of hand and foot involvement is depicted in Figure 1a and b and Figure 1e-h respectively. Quantitation was possible in 28 patients and the mean AS score was 1.57 ± 0.5. Symmetrical tracer uptake in all the three phases (BSN) was noted in 15 (29%) patients, which included 13 hand [Figure 1c and d] and 2 foot cases. Quantitation was possible in 10 patients and the mean AS score was 1.01 ± 0.05.

The geometric mean of the AS in the BSP group ranged from 1.04 to a maximum of 2.80; whereas, geometric mean of AS in the BSN group ranged from 0.89-1.06. Thus, AS > 1.06 had a sensitivity of 96.43% and specificity of 100% for the characteristic pattern of CRPS. 100% sensitivity could not be achieved because one patient with CRPS of the hand had AS of 1.04, though visual asymmetry could be appreciated.

The details of BSP and BSN patients are depicted in Table 2. The mean AS of the BSP and BSN groups were significantly different ($P < 0.0001$). ROC analysis of BSP and BSN groups yielded a cut-off AS of 1.06 with sensitivity and specificity of 96.43% and 100% respectively ($P = 0.0001$), [Figure 2a]. In the BSP and BSN group, only 56% (29/52) were women in our series. It is less than that reported in literature, which is 60-81%.[13] The mean age of the patients was 43 years, and there were no pediatric cases except for a 14 year old boy.

Based on the stage wise analysis, 15out of the 22 (68%) in stage-I, 14 out of 18 (78%) in stage-II, and 8 out of 12 (67%) in stage-III showed delayed periarticular uptake. A higher proportion of patients in stage-II were positive for CRPS by bone scan. The distribution of patients who showed perfusion and blood pool positivity is shown in Table 3. In stage-III, significantly less number of patients showed positive finding in perfusion and blood pool phases. There was a trend of negative correlation between the AS in BSP group and the duration, $r = -0.21$ [Figure 2b]; however, it was not statistically significant ($P = 0.28$).

Table 2: List of BSP and BSN patients

No	Age	Sex	Side	Site^	Duration (weeks)	Disease stage	Asymmetry score		
							Dorsal	Palmar*	GM
1	49	M	R	Hand	2	I	0.87	0.91	0.89
2	48	F	R	Hand	312	III	0.98	0.95	0.96
3	58	M	B	Hand	104	III	0.95	0.98	0.96
4	32	F	R	Hand	468	III	1.02	0.98	1.00
5	24	F	R	Hand	4	I	1.01	1.00	1.00
6	32	M	L	Hand	20	I	1.04	1.03	1.03
7	35	F	R	Hand	52	II	1.09	0.99	1.04
8	50	M	B	Foot	13	I	1.08	1.01	1.04
9	15	F	R	Hand	6	I	1.05	1.07	1.06
10	41	F	R	Hand	4	I	1.09	1.04	1.06
11	33	M	R	Hand	61	III	–	–	–
12	45	F	L	Hand	8	I	–	–	–
13	22	F	L	Foot	52	II	–	–	–
14	30	F	B	Hand	43	II	–	–	–
15	30	F	R	Hand	34	II	–	–	–
16	24	F	B	Hand	104	III	1.06	1.03	1.04
17	42	F	B	Foot	130	III	1.1	1.1	1.10
18	58	M	B	Hand	26	II	1.2	1.15	1.17
19	49	M	R	Foot	12	I	1.16	1.2	1.18
20	56	F	R	Hand	4	I	1.23	1.16	1.19
21	69	M	R	Hand	208	III	1.21	1.21	1.21
22	65	F	R	Hand	312	III	1.22	1.22	1.22
23	45	F	L	Hand	52	II	1.25	1.21	1.23
24	40	F	L	Hand	8	I	1.28	1.27	1.27
25	50	M	R	Hand	65	III	1.3	1.29	1.29
26	57	M	L	Hand	12	I	1.27	1.36	1.31
27	62	F	R	Foot	13	I	1.4	1.29	1.34
28	75	M	L	Hand	22	II	1.32	1.38	1.35
29	38	M	L	Foot	13	I	1.4	1.36	1.38
30	27	F	R	Hand	52	II	1.46	1.36	1.41
31	63	M	L	3rd Finger	21	II	1.34	1.49	1.41
32	60	F	L	Hand	8	I	1.43	1.42	1.42
33	14	M	R	Hand	8	I	1.42	1.47	1.44
34	39	M	B	Hand	52	II	1.53	1.51	1.52
35	23	F	R	Hand	78	III	1.54	1.55	1.54
36	36	F	L	Foot	8	I	1.56	1.54	1.55
37	72	F	R	Hand	104	III	1.57	1.67	1.62
38	42	F	R	Hand	52	II	1.82	1.83	1.82
39	43	M	R	Hand	8	I	1.91	1.92	1.91
40	30	F	R	Foot	52	II	2.18	1.98	2.08
41	52	M	R	Hand	20	I	2.11	2.13	2.12
42	66	M	R	Hand	12	I	2.67	2.78	2.72
43	65	M	L	Hand	35	II	2.85	2.76	2.80
44	21	F	L	Hand	52	II	2.85	2.76	2.80
45	60	F	R	Hand	52	II	–	–	–
46	45	F	R	Hand	78	III	–	–	–
47	50	M	L	Hand	4	I	–	–	–
48	23	M	R	Hand	26	II	–	–	–
49	49	F	B	Hand	26	II	–	–	–
50	19	M	R	Foot	52	II	–	–	–
51	40	F	B	Hand	4	I	–	–	–
52	45	M	R	Hand	8	I	–	–	–

BSP: Bone scan positive group, BSN: Bone scan negative group, Site^: Site of suspicion at referral, *Plantar in case of foot, GM: Geometric mean, R: Right, L: Left, B: Both, Patient no: 1-15–BSN group, Patient no: 16-52–BSP group

DISCUSSION

Out of the 68 patients referred for the evaluation of CRPS, 16 patients showed focal or multifocal uptake not characteristic of CRPS. In the remaining 52 patients, TPBS was positive for CRPS 37 patients (71%) and negative in 15 patients. CRPS was suspected in all patients based on the proposed diagnostic criteria by the IASP.[3] The natural history of CRPS can be divided into three stages as described by Lankford[2] In accordance with TPBS,

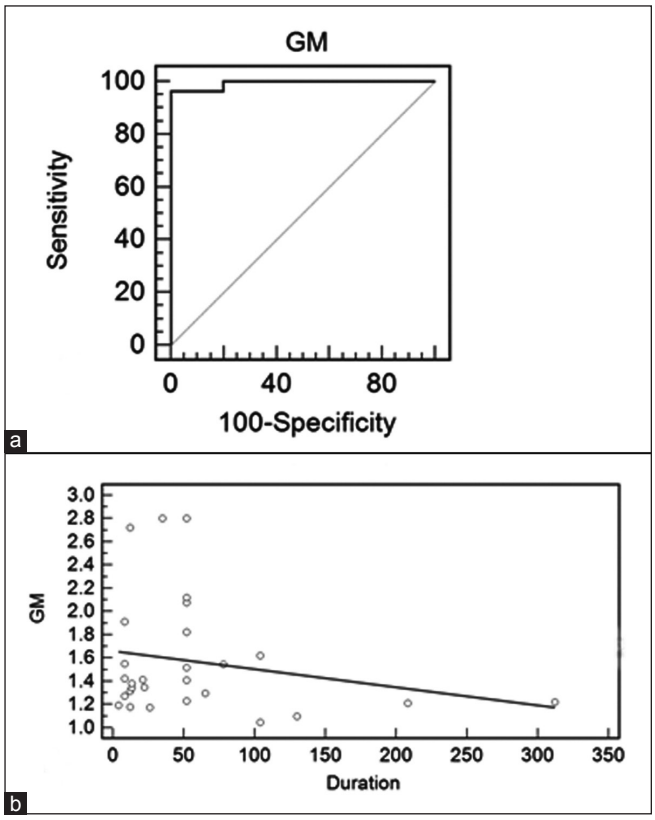

Figure 2: Receiver-operating curve (a) depicting 96.43% sensitivity and 100% specificity for a cut-off asymmetry score (AS) of 1.06 (P = 0.0001). Linear regression (b) showing a trend of negative correlation (r = −0.21) between the AS and the duration in bone scan positive group group (P = 0.28)

Demangeat *et al.* have classified the TPBS findings into three stages.[12] The scintigraphic stages of reflex sympathetic dystrophy (RSD) by Demangeat *et al.*, roughly correlate with Lankford's clinical stages of RSD.[11] Hence, the same classification has been used in our study. TPBS is usually done to support the diagnosis in CRPS and to exclude other diagnoses such as arthritis. Though CRPS diagnosis is essentially clinical, clinical evaluation is somewhat subjective with poor inter-observer reliability.[14] In a recent analysis of inter-observer variability in reporting CRPS, 96% of the participants considered that focal hyperactivity in bone scan was not suggestive of CRPS.[15] In our study, focal or multifocal uptake was noted in ~ 24% of the patients, in whom CRPS was suspected. An alternate diagnosis was observed in them as described previously.

Sensitivity and specificity of TPBS for diagnosing CRPS has been quoted in many studies based on the clinical diagnosis.[6-11] Many inflammatory conditions other than CRPS can produce similar clinical features and TPBS may be negative in few cases of CRPS. Hence, we did not calculate the sensitivity and specificity in diagnosing CRPS, and only the number of cases in whom TPBS was characteristic for CRPS was assessed. We injected Tc99m-MDP into the dorsal vein of the foot in upper limb cases and the antecubital vein in lower limb cases. This approach may increase the asymmetry of the affected side and thus increases the sensitivity of the TPBS in detecting CRPS. Since an injection in the unaffected side may increase the perfusion and bone uptake in that side, there is a chance that asymmetry may be reduced.

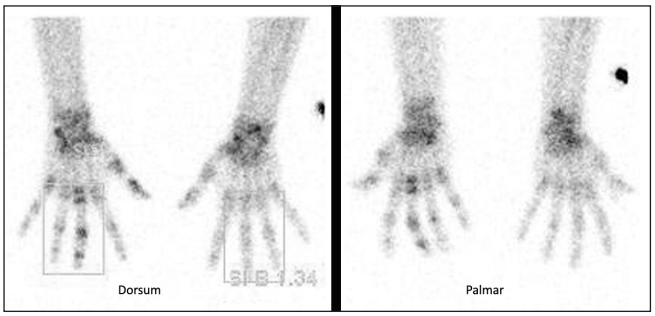

Figure 3: Complex regional pain syndrome in the middle finger of left hand showing placement of a standard sized region of interest around the left middle finger in the dorsum and palmar views

Table 3: Distribution of positivity of perfusion and blood pool phases in the BSP group

Phase	Stage-I (%) N = 15	Stage-II (%) N = 14	Stage-III (%) N = 8
Perfusion	13 (87)	11 (79)	4 (50)
Blood pool	14 (93)	12 (86)	5 (62.5)

BSP: Bone scan positive group

Atkins *et al.* suggested that the region immediately around a fracture site should not be considered when recognizing CRPS on a scintigram.[7] This includes the carpal area in cases in which CRPS follows a fracture of the distal radius. Increased tracer uptake in CRPS is not confined to the periarticular area but occurs throughout the bone of the affected regions.[7] Pertaining to this, ROI of the metacarpal bones has been argued as better for the quantitation purposes.[6,8] However, in our study none of the patients had distal radius fractures, and also only few patients in BSP group had increased tracer uptake in the metacarpal region. Hence, we included the carpal and tarsal bones in the hand and foot respectively for ROI analysis as described. ROC analysis of BSP and BSN groups yielded a cut-off AS of 1.06 with sensitivity and specificity of 96.43% and 100% respectively. Using the ROI-based evaluation, a sensitivity of 69% and specificity of 75% for a score of 1.32 in phase 3 was shown by Wüppenhorst *et al.*[8] In their study, the ROI was manually drawn only over the metacarpophalangeal joints (MCP). The low sensitivity and specificity could be likely due to the equivocal involvement of MCP in CRPS and normal patients. We used the standard vendor provided SI index software for drawing ROI. The dimension of the ROI was not changed in any patient and a similar ROI was used in the hand, foot cases and in one patient with CRPS of the middle finger with the ROI centered over the middle finger [Figure 3]. By this way, standardization could be achieved such that uniform area will be covered in all patients, irrespective of the site of involvement. In the previous studies, ROI score was established by dividing the counts obtained from the ROI of the affected and unaffected side.[6-10] However, the SI index directly

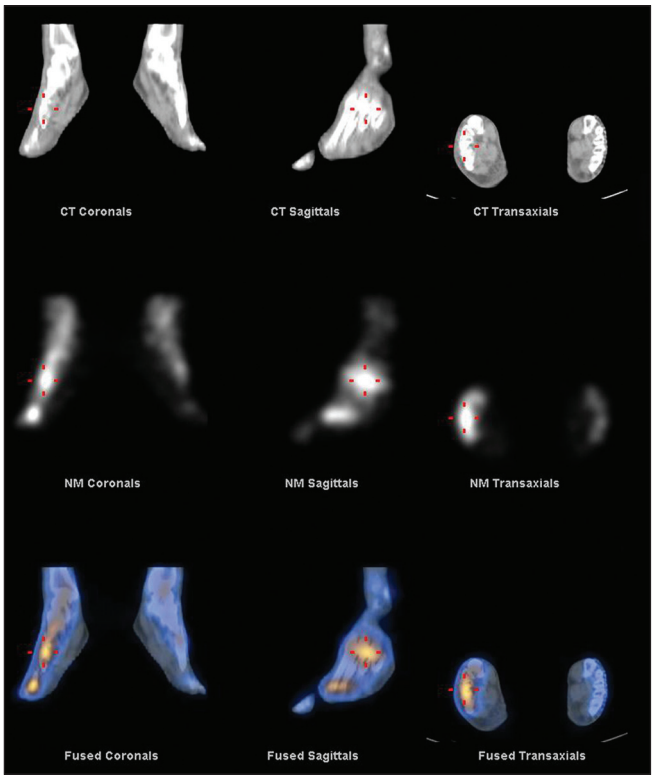

Figure 4: SPECT/computed tomography images of complex regional pain syndrome in right foot. Increased tracer uptake is clearly localized to the proximal and distal metatarsal bones

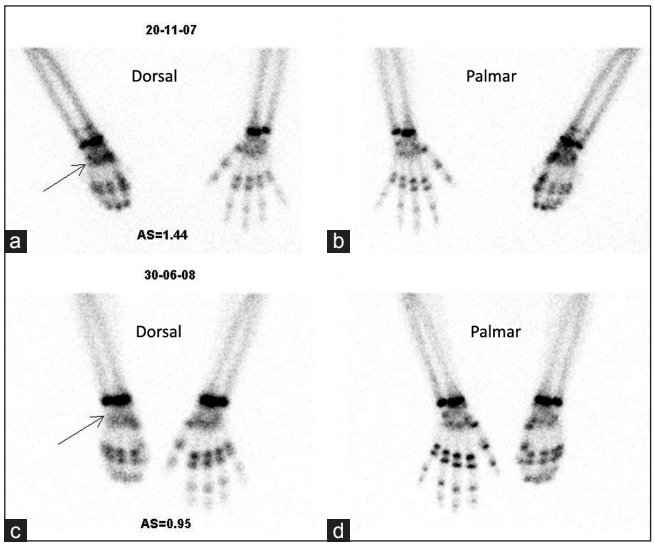

Figure 5: Pre (a and b) and post (c and d) treatment of complex regional pain syndrome of the right hand. Decrease in tracer uptake in the carpal bones is shown by arrow. Conversely, the increased tracer uptake in the left metacarpo-phalangeal joint (d) depicts the actively growing physes of the unaffected side

provides the AS on screen without the need to do a second step process of calculation and it simplifies the methodology.

In stage-III, significantly less number of patients showed positive finding in perfusion and blood pool phases [Table 2]. Similar finding has also been reported previously.[16] This reinforces the fact that delayed phase is the most sensitive for CRPS. Few authors have demonstrated that the duration of CRPS had a significant effect on the uptake ratios in each phase and ROI of the bone scan.[6-8,12] Though not statistically significant, there was a trend of negative correlation ($r = -0.21$) between the AS in BSP group and the duration, in our study. Of the 11/68 patients investigated for suspicion of CRPS of the foot, 2 showed focal uptake. TPBS was positive in 7 of remaining nine (78%) patients and negative in 2 patients. Thus, TPBS can be used to detect CRPS with high sensitivity even in the case of foot. In one patient with suspicion of CRPS in the right foot (AS-1.34), single photon emission tomography/computed tomography (SPECT/CT) was also carried out, which clearly showed the involvement of individual bones on the affected side [Figure 4].

We could perform the follow-up study in two patients only. A 45-year-old female patient presented with clinical features of CRPS of the left hand of 8 weeks duration; TPBS was however negative at that time. Because of persistent symptoms, a follow-up scan was carried out after 1 year, by then all the three phases showed increased tracer activity in the left hand, characteristic of CRPS. Such a sequential change in TPBS findings during the time course for the CRPS group has previously been described.[17] Furthermore, in our study significantly higher number of patients in stage-II (~80%) showed positive TPBS characteristic for CRPS, compared to stages I and III (67%). Thus, in patients with high clinical suspicion of CRPS, a follow-up bone scan can always be carried out to confirm the diagnosis. The second patient was a 14-year-old male who presented with skin changes and musculoskeletal deformity in the right hand. TPBS was positive for all phases (AS = 1.44). After 7 months of multimodality treatment, he had significant clinical improvement, when delayed phase of TPBS was normal (AS = 0.95); however, increased perfusion and blood pool persisted till then. This documents the decrease in bone metabolism and turn over. Zyluk and Birkenfeld suggested that treatment does not affect the rate of reduction of uptake.[9] However, reduction in bone uptake had been documented in our patient, after treatment with improvement in clinical outcome [Figure 5]. The management of CRPS is a multidisciplinary approach that involves analgesia, physiotherapy and psychotherapy; oral bisphoponates have also been implicated to reduce pain, edema, and improve range of motion.[18] TPBS may be used in the treatment monitoring of patients with CRPS.

The limitations of the study include retrospective analysis; since there is no other established investigation to compare our results, the IASP criteria and TPBS were considered as a combined gold-standard for the diagnosis of CRPS; we were able to do follow-up scintigraphy in only two patients.

CONCLUSION

Quantitative AS of 1.06 can be included to support visual interpretation in the delayed phase. At > 20 weeks and < 60 weeks duration, approximately 80% of the TPBS are likely to be positive

for CRPS excluding the focal cases and delayed phase is the most sensitive for CRPS in all stages. Furthermore, TPBS should be considered in the evaluation of CRPS to find out patients having focal involvement, not diagnostic of CRPS (~24% in this study).

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