

Multimodality Predictive Diagnostic Characterization of Chronic Regional Pain Syndrome an Observational Study with Clinical and Imaging Correlation

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Abstract

Complex Regional Pain Syndrome or CRPS, its subtypes CRPS I: No nerve injury, CRPS II: Definitive nerve injury, characterized clinically by pain, vasomotor disturbances, trophic skin changes, and radiographically by regional osteoporosis and bone resorption poses diagnostic challenges. Objective: Multimodality imaging characterization of CRPS, and clinical and imaging phenotypes. Materials & Methods: Fifty-seven patients in the age range of 33-65, the mean age of 49 men, 35 men (61.40%), 22 Women (38.60%) underwent this observational diagnostic accuracy study at Prathima Institute of Medical Sciences (Karimnagar Telangana, India). The multimodality imaging protocol on Radiography (Diagnox 302, Philips), Ultrasound Doppler (Infinity Philips), Low dose Multi-slice CT (Ingenuity), MRI (1.5 T Achieva, PHILIPS Health care) for characterization of CRPS phenotypes after IRB approval. The imaging findings from all the modalities were analyzed using descriptive statistics. Results: Patients with upper limb involvement (n=18), lower limb involvement (n=32), Pelvic involvement (6). CRPs Type 1:- 27, CRPS Type 2 :- 23, Mixed pattern: 7, 1. Juxta regional osteopenia (n=17) 2. Patterns of bone resorption on radiography and CT :Pattern A: Mild (n=31), B: Aggressive (19) Pattern C- No significant radiological changes (7); Locations of bone loss on radiography/CT. Periarticular: 18, Sub Periosteal: 8, subchondral/endosteal: 11-Intracortical : 7-Mixed pattern: 12, Bone marrow edema: 32, Soft tissue edema: 31, Pattern A: Positive Predictive Value (PPV) of 91%, a concordance rate of 94% with clinical diagnosis of CRPS. Pattern B: PPV of 98%, a concordance rate of 97%. Conclusion: The multimodality imaging approach predicts the accurate diagnosis of CRPS evolving from early acute to late atrophic stages.

Keywords: Complex regional pain syndrome; Computed tomography; Ultrasonography; Magnetic resonance imaging

Introduction

Reflex Sympathetic Dystrophy Syndrome (RSDS) or CRPS manifests with pain, vasospasm or vaso-dilatation, and trophic skin and nail changes as clinical characteristics with radiographic of regional osteoporosis in the affected area, being the vital radiographic characteristics. (Synonyms: causalgia, Sudeck's atrophy, post-traumatic osteoporosis, post infarctional sclerodactyly, shoulder-hand syndrome, and reflex neurovascular dystrophy).

Currently, the preferred term is RSDS (Reflex Sympathetic Dystrophy) or CRPS I. The onset of pain is immediate or a few weeks after inciting event and manifests as burning, lancinating, throbbing in character. CRPS frequently involves the upper limb than lower limbs, and Truncal or facial CRPS is very uncommon. An initiating event to the affected part, such as a fracture, sprain, or surgical procedure, precedes the onset of CRPS.

To formulate a predictive characterization framework based on Multimodality Imaging (Radiography, USG with doppler, CT, MRI, and) features and clinical scenarios associated with RSD (Reflex sympathetic Dystrophy) or CRPS (Chronic Regional Pain Syndrome for accurate detection of Chronic Regional Pain syndrome) [Figures 1-5].



Figure 1A: Radiograph of the wrist in plaster cast showing distal radius Colles' fracture with per articular osteopenia soft tissue swelling presenting as CRPS I, downstream osteopenia in proximal and distal row of carpal.

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How to Cite this Article: Vadapalli R, et al. Multimodality Predictive Diagnostic Characterization of Chronic Regional Pain Syndrome an Observational Study with Clinical and Imaging Correlation. *Ann Med Health Sci Res.* 2021;11:S2-45-51.

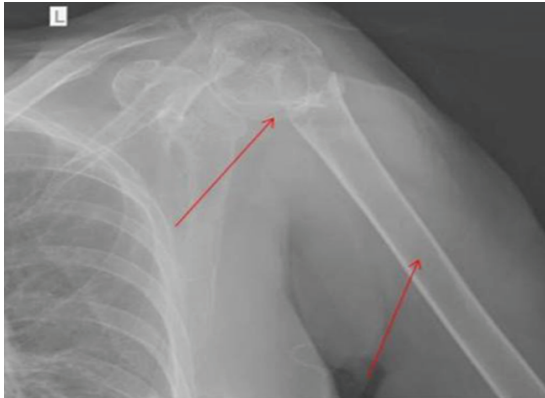


Figure 1B: Radiograph of left shoulder joint fracture dislocation in proximal humeral neck with upstream periarticular osteopenia and subchondral and subperiosteal bone resorption in the head neck and downstream osteopenia proximal diaphysis of humerus.

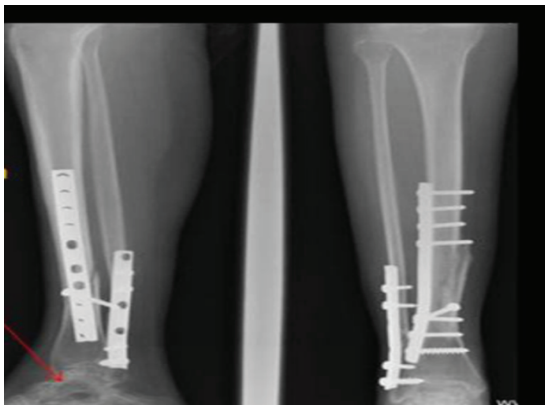


Figure 2: Radiographs of leg showing comminute fractures with internal fixations involving distal tibia and fibula with downstream osteopenia peri articular subchondral endosteal; bone resorption in the ankle joint -CLI.



Figure 3: Radiograph of left hip joint and proximal and mid leg for fracture neck of the femur with intra medullary metallic prosthesis. Evidence of diffuse peri articular osteopenia of the left hip joint with subchondral periarticular and endosteal bone loss. CRPS I in the atrophic stage.

Materials and Methods

Fifty-seven patients in the age range of 33-65 with a mean age of 49 years with 35 men (61.40%) and 22 Women (38.60%) who matched inclusion criteria were recruited for the study performed at Pratima institute of Medical Sciences, Karimnagar, India during 2020-2021. A multimodality imaging protocol imaged all patients by radiography system (Diagnox 302), Ultrasound doppler* (Infinity, Philips), multi-slice CT (Ingenuity), MRI (1.5

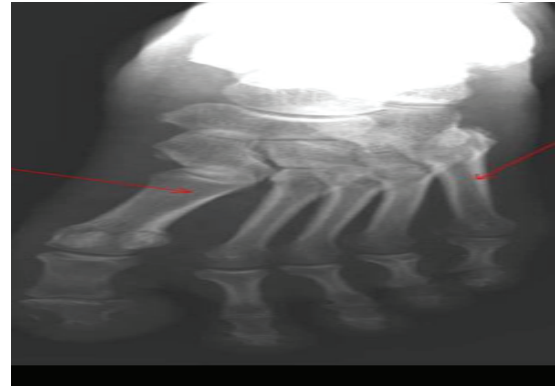


Figure 4: Radiograph of ankle and foot diffuse osteopenia in tarsals and metatarsals with subperiosteal subchondral and endosteal and periarticular bone resorption.

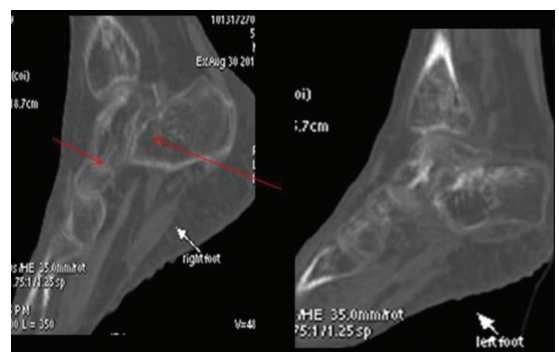


Figure 5: Low dose CT of the right ankle and foot with multiplanar sagittal reconstruction showing diffuse osteopenia, multifocal periarticular subchondral and subperiosteal bone resorption of the distal tibia, calcaneum talus and navicular bones - CRPS type II due to proximal peroneal nerve injury.

T Achieva -PHILIPS Health care) after informed consent and IRB approval.

Patients with clinical profiles matching the Diagnostic criteria proposed by the international consensus conference, Budapest, 2004 represent the inclusion criteria.

The radiography region of interest images of upper limb lower limb pelvis and followed by region-specific ultrasound with color-flow doppler and limited field of view low dose CT with multiplanar reconstructions MRI as follows:

Patients with upper limb involvement: Radiographs from the elbow till the wrist and hand with limited FOV low dose CT and loco-regional ultrasound with colour-doppler followed by MRI.

Patients with lower limb involvement: Radiographs from the hip joint till the wrist and hand followed by lower limb MRI including thigh legs.

Patients with pelvic bone involvement: Radiographs of pelvis followed by pelvic MRI

MRI: Protocol on 1.5 T included T1 coronals, T2 STIR Coronals axials, DWIBS (Diffusion-Weighted Imaging With Background Suppression) for upper and lower limbs, T1 coronals STIR coronals of pelvis until the greater trochanter level either side.

Three-phase radionuclide bone imaging and F18 bone scans were performed in an outside institution in 7 patients and hence not included in the analysis.

Parameters for T1 coronals and axials are as follows: TR 500 ms TE 10 ms Flip angle; 90 degrees, TSE factor: 4, Slice thickness: 4 mm.

Parameters for STIR coronals are as follows: Acq mode: TSE IR Multi shot TR shortest TE 60 ms TSE factor: 15 (Echo train length), Slice thickness; 4 mm.

Parameters for DWIBS axials with coronal reformats: TR 8650 TE 85 TI 260 slices: 90 EPI factor-47, FOV 400, B value 800, SENSE factor-2, slice orientation: axials, voxel size-3.5 mm × 3.5 mm × 3.5 mm. Analysis of Ultrasound Doppler images was performed for increased blood flow and soft-tissue edema. Radiography, CT, MR images were evaluated for bone loss and osteopenia in the affected region to detect the following patterns:

1. Juxta regional osteopenia, 2. Patterns of bone resorption

Pattern A: Mild radiological changes with Positive Ultrasound Doppler changes

Pattern B: Aggressive and severe.

The inclusion criteria

An Inciting event: Trauma, fracture, nerve injury as CRPS cardinally manifests as continuing pain disproportionate to any inciting event. The features should be the following categories. Hyperaesthesia, temperature asymmetry and skin color changes. Sudomotor/edema: Edema, sweating changes with asymmetry. Motor/trophic: or motor dysfunction (weakness, tremor, dystonia) and trophic changes (hair, nail, skin).

Exclusion criteria

Patients with external fixation devices for fractures. Patients with absolute contraindications to MRI.

Statistical analysis

After confirming the homogeneity of data, all continuous variables are reported as mean and standard deviation; whereas all categorical variables are reported as frequencies/percentage. Based on clinical history and presence of inciting event and presence or absence of nerve injury, the study population consists of two groups *viz.* nerve injury group those with no evidence of nerve injury [Figures 6-9]. The differences between the groups for continuous variables were assessed using independent student t-test and differences for categorical variables were evaluated using chi-square test. Association between study variables was evaluated using Spearman rank correlations. A $p \leq 0.05$ is reported as significant difference/finding. Statistical Package for Social Sciences (SPSS) for Windows Version 22.0, IBM Computers, New York, USA is.

Results: Patients with upper limb involvement (n=18), Patients with lower limb involvement (n=32), Patients with Pelvic involvement (n=6).

CRP 1-Pattern in 22 patients and CRPS 2 -Pattern is seen in 28 patients. Mixed pattern in 6.

Image analysis

1. Juxta regional osteopenia (n=17)

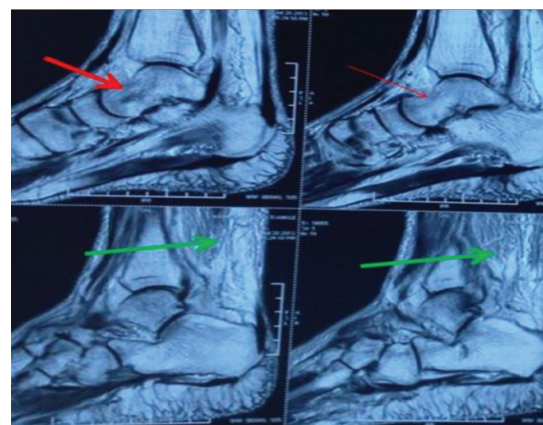


Figure 6: MRI T1 non fat sat sagittal of the left ankle and foot: Downstream bone loss with osteopenia with regional hyperaemia seen as patchy areas of T1 hypo intensity. Note the soft tissue oedema in kager' fat pad. Subchondral and subperiosteal bone resorption at talar neck and dome –sequelae of proximal fracture of mid tibial fracture-CRPS Type I.

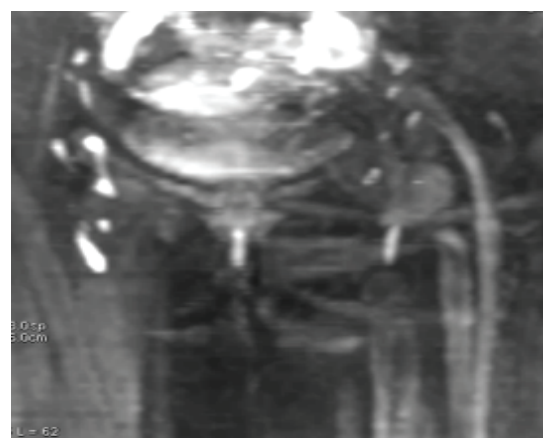


Figure 7: MR neurography using dwibs sequence with 3d mip sequences showing axonotmesis of right lumbosacral trunk with a post traumatic neuroma and underlying sacral fracture. Downstream distal CRPS Type II followed in the right lower extremity in the calf and ankle.

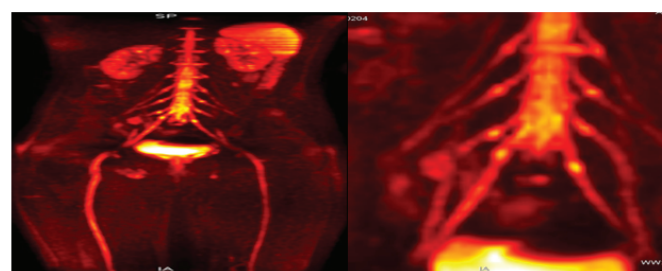


Figure 8: STIR coronal MRI of both knee joints and proximal and mid calf muscles show denervation oedema which was followed by CRPS TYPE II followed in the left calf and leg and left ankle with pain vasomotor symptoms and soft tissue oedema. Early stages: MRI may show no or subtle marrow edema may be essentially normal. Late stages: The progressive development of marrow edema with subchondral, intramedullary, and peri, juxta-articular locations reflecting the regional hyperaemia.

2. Patterns of bone resorption:

Pattern A: Mild radiological changes (n=31)

Pattern B: Aggressive and severe (n=18)

Pattern C: No significant radiological change (n=7)

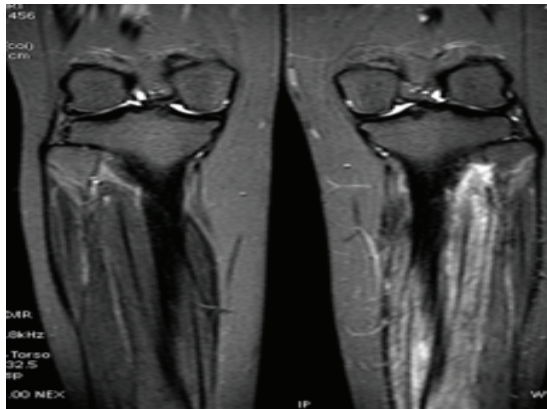


Figure 9: STIR coronal MRI of the Left Knee and proximal leg in a patient with common peroneal nerve injury with denervation edema in Tibialis anterior muscle.

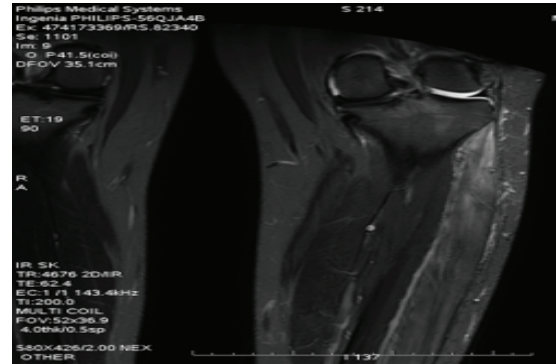


Figure 10: STIR coronal MRI of the mid and distal leg in a patient with common peroneal nerve injury with denervation oedema in tibialis anterior muscle with associated soft tissue oedema and skin and trophic changes due to CRPS Type II.

Locations of bone loss on radiography and CT.

- Periarticular L: 18
 - Sub-Periosteal: 8
 - Subchondral/Endosteal: 11
 - Intra-cortical:7
 - Mixed pattern: 12
3. Bone marrow edema: 32
4. Soft tissue edema: 31

Ultrasound and Doppler showed a sensitivity of specificity, the overall diagnostic accuracy of 65%, 56%, 58% respectively for soft tissue edema and increased blood flow. Ultrasound showed a concordance rate of 72% for CRPS type I and 55% for CRPS II. The positive predictive value of ultrasound alone for CRPS I is 70%, and RPS II is 44%.

Radiography showed a sensitivity of specificity, the overall diagnostic accuracy of 52%, 48%, 50% respectively for osteopenia and bone loss with a concordance rate of 40% for CRPS I and 62% for CRPS II. The positive predictive value of Radiography alone was 48.4%. [1-5]

CT: showed a sensitivity of 5% specificity 54%, the overall diagnostic accuracy of 52% respectively for osteopenia and bone loss. A concordance rates of 41% for CRPS I and 52% for CRPS II. The positive predictive value of CT alone was 54%.

MRI: showed a sensitivity of 62% specificity 68%, the overall diagnostic accuracy of 62% respectively for osteopenia and bone loss and bone marrow edema. A concordance rates of 65% for CRPS I and 89% for CRPS II. MRI with Diffusion MR neurography sequence demonstrated Peripheral nerve injury with associated denervation edema with a sensitivity of 89% for CRPS type II [Figures 10-12]. Positive predictive value of MRI for CRPS II was 81.6%.

The multimodality approach with ultrasound, radiography, low dose CT and MRI as a comprehensive protocol showed an overall sensitivity of 87% and specificity of 79%. Overall diagnostic accuracy of 86%. The positive predictive value with the multimodality approach was 88%.

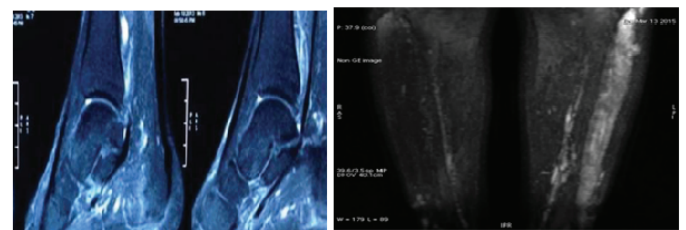


Figure 11: Technetium MDP bone scan: Diffuse peri articular uptake in the ankle joint and proximal foot. showing CRPS pattern II due to an inciting proximal nerve injury. F18 PET CT showing diffuse periarticular uptake IN Left foot and ankle. Showing CRPS pattern II due to an inciting proximal nerve injury.

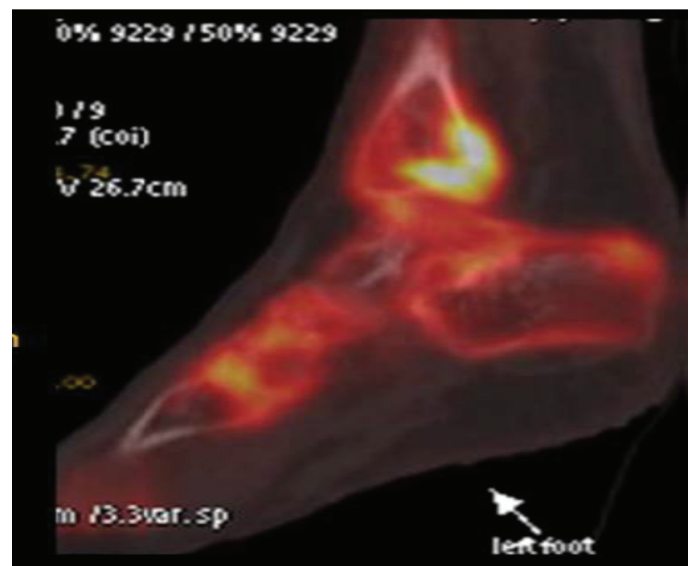


Figure 12: CRPS II due to proximal Sciatic nerve injury with patchy soft tissue oedema in the ankle and foot with associated foci of bone marrow oedema and regional hyperaemia.

Diagnostic Utility (Concordance rates)-Multimodality approach.

Discussion

Complex regional pain syndrome manifests with pain, vasospasm or dilatation, skin changes with atrophy and hyperhidrosis, and nail changes clinically and with regional osteopenia in the affected segments.

Synonyms include causalgia, acute bony atrophy, Sudeck's

atrophy, shoulder-hand syndrome, and reflex neurovascular dystrophy.

The diagnostic criteria For CRPS include Orlando Criteria and The Budapest Clinical Diagnostic Criteria.

CRPS is classified into two types, viz CRPS types I and II, based on identifiable nerve injury. CRPS type I develops after an inciting noxious episode, being disproportionate to it and not restricted to a specific peripheral nerve territory. It is associated with edema, skin blood flow changes, abnormal sudomotor activity in the region of the pain, allodynia and hyperalgesia. CRPS type I commonly involves the distal aspect of the affected limb distal to the proximal gradient. CRPS type II manifests with burning pain, allodynia, and hyperpathia in the limb area after partial nerve injury with denervation edema [Tables 1-4].

The preferred term currently is RSDS (Reflex Sympathetic Dystrophy) or CRPS I, which occurs after a harmful event to the affected anatomical region like a sprain, fracture, or surgical procedure. The Cardinal symptom is pain sharp and burning in nature which commences immediately or within a few days to weeks involving the extremities. In Our present study on CRPS, the lower extremity was more frequently affected, unlike the literature reports where the upper limb was more often affected than the lower limb. Truncal or facial CRPS is very rare. Even in our study, we did not encounter a single case of truncal or facial CRPS, The evolution of CRPS clinically involved three stages, viz, Acute (0-3 months), Dystrophic (3-6 months), atrophic (>6 months, long-standing). Acute (three to six months (n=): Burning, flushing, blanching, sweating, swelling, pain, and tenderness. Imaging changes at this stage showed subtle radiographic evidence of bone loss with patchy bone thinning

Table 1: Demographics.

| Variable | Mean/Average | Range/Percentage |
|-------------|--------------------|------------------|
| Age (years) | 25.35 (SD =3) | 3 to 53 |
| Women (%) | 22 (22/57) =38.60% | 52.80% |
| Men (%) | 35 (35/57) =61.40% | 76.40% |

Table 2: Diagnostic utility (sensitivities & specificities)-ultrasound doppler.

| | | |
|-------------------------------|-------|----------------|
| Sensitivity (%) | 54% | 48 to 60% |
| Specificity (%) | 50 | 11.81 to 78.19 |
| Positive predictive value (%) | 67.37 | 64.32 to 78.80 |
| Negative predictive value (%) | 30 | 15 to 58% |
| Accuracy (%) | 61.94 | 55 to 72% |

Table 3: Diagnostic utility (sensitivities & specificities)-radiography.

| | | |
|-------------------------------|-------|----------------|
| Sensitivity (%) | 58 | 55%-63% |
| Specificity (%) | 40 | 24% to 56% |
| Positive predictive value (%) | 57.3 | 44.32 to 68.20 |
| Negative predictive value (%) | 30 | 12.64 to 48.42 |
| Accuracy (%) | 51.14 | 55.67 to 76.06 |

Table 4: Diagnostic utility (sensitivities & specificities)-low dose CT.

| | | |
|-------------------------------|----|----------------|
| Sensitivity (%) | 54 | 40.00 to 68 |
| Specificity (%) | 51 | 42.11 to 60.32 |
| Positive predictive value (%) | 52 | 54.32 to 78.20 |
| Negative predictive value (%) | 30 | 12.64 to 48.42 |
| Accuracy (%) | 52 | 63.37 to 74.08 |

with the subperiosteal distribution. Ultrasound and Color Doppler demonstrated soft-tissue edema and increased blood flow in the region affected.

Dystrophic (3-6 months): Early skin changes of shiny, thickened skin and contracture with persistent pain with reduced blood flow. MRI shows soft tissue signal changes, marrow edema due to hyperaemia. Atrophic (may be long-standing): Loss of motion and function of the involved hand or foot with contracture (flexed scarring process) and thinning of the fatty layers under the skin.

Radiography and Low dose CT can show significant osteoporosis or bone resorption

Investigations

CRPS is principally a clinical diagnosis, and no single investigation is highly specific for the diagnosis of CRPS. This was the primary motivation of this study.

Hence it is worthwhile to perform a multimodality imaging approach with radiography, Ultrasound doppler, loco-regional low dose multi-slice CT with multiplanar reconstruction, and MRI with various image contrast DWIBS, T1, STIR yielding diagnostic imaging biomarkers.

The multimodality approach helps for a dynamically evolving CRPS in its acute, dystrophic and atrophic stages and its tissue correlates. The method also facilitates confirmation of the diagnosis and rules out other differentials.

MRI specifically identifies Type II CRPS with nerve injury by demonstrating the neurography of the affected region and nerve status, grading the nerve injury, and detecting denervation edema.

EMG or nerve conduction studies may play an adjunct role to exclude a diffuse or focal peripheral neuropathy in the affected area or for indirect confirmation of nerve injury. Nerve conduction studies cannot offer any specific evidence for the diagnosis of CRPS as nerve conduction tests only interrogate large myelinated fibers but not small A delta and C fibers, which are primarily affected in CRPS. [6-8]

Punch skin biopsy visualizes the defects in small axonal fibers, which is not specific to CRPS. Thermography and Laser Doppler flow metry help assess the cutaneous blood flow patterns and vasoconstrictor reflexes with no specific diagnostic characterization for CRPS. Sweat axon reflex testing: can determine small axonal fibers, but this is not specific to CRPS. The key radiographic findings are soft tissue swelling and regional osteoporosis, bone loss.

Osteoporosis

Aggressive and severe (Trabecular, subperiosteal, intracortical, endosteal, or subchondral bone. Significant juxta-articular osteoporosis mimicking inflammatory arthritis such as rheumatoid arthritis. The critical diagnostic point is the absence of significant intra-articular erosions or joint space loss, which usually allows the differentiation of CRPS from inflammatory arthropathies like rheumatoid arthritis.

CRPS of the ankle and foot may be a distinct subset. It

demonstrates all the cardinal manifestations of CRPS, with vasomotor changes being more marked in the periphery, which aids in diagnosis. [9-11]

Radiography

Osteoporosis has been reported in 60% of patients with upper>lower extremity CRPS, which is not specific, often due to disuse secondary to the pain associated with CRPS.

Soft tissue swelling or diffuse soft tissue atrophy may be seen in acute or atrophic stages, respectively, as CRPS evolves overtime of 3-6 months after an inciting event [Tables 5-7].

Plain radiographs of the affected region show regional or diffuse osteopenia or bone loss evolving from a patchy focal pattern of early stages to diffuse osteopenia in later stages.

Ultrasound and color Doppler: play a role in detecting CRPS type I in early acute stages loco-regional soft tissue swelling, regional hyperaemia, and increased blood flow by using color flow or power doppler visualization. Ultrasound is an acceptable non-invasive adjunct and also rules out other causes of incidental coexisting pathologies in the soft tissues.

Low dose CT with multiplanar reconstructions: plays a definitive role in evaluating bone trauma, fractures and pre- and post-surgical assessment, before and after instrumentation or prosthetic surgery. Contrary to Previous reports (5-8), Low dose CT can enhance bone loss visualization and its location within the bone, showing bone resorption pattern.

Magnetic Resonance Imaging (MRI): The role of MRI is evolving in CRPS towards an established technique in the diagnostic evaluation of CRPS. Regional hyperaemia is reflected by the foci of T1 hypo intensity, usually in talar dome and body and head of Talus and Medial cuneiform and other tarsal bones. Soft tissue changes like swelling edema, however,

| Parameter | Sensitivity (%) | Specificity (%) |
|-------------------------------|-----------------|-----------------|
| Sensitivity (%) | 54 | 40.00 to 68 |
| Specificity (%) | 51 | 42.11 to 60.32 |
| Positive predictive value (%) | 52 | 54.32 to 78.20 |
| Negative predictive value (%) | 30 | 12.64 to 48.42 |
| Accuracy (%) | 52 | 63.37 to 74.08 |

| Parameter | Sensitivity (%) | Specificity (%) |
|-------------------------------|-----------------|-----------------|
| Sensitivity (%) | 62 | 55 to 70.58 |
| Specificity (%) | 68 | 66 to 70.32 |
| Positive predictive value (%) | 65 | 44.32 to 78.20 |
| Negative predictive value (%) | 34 | 20 to 48.45 |
| Accuracy (%) | 62 | 55.67 to 76.06 |

| Imaging Modality | CRPS I | CRPS II |
|------------------------|--------|---------|
| Ultrasound and Doppler | 72% | 55% |
| Radiography | 40% | 62% |
| Low dose CT | 41% | 52% |
| MRI | 65% | 69% |
| MR Neurography | 65% | 71.60% |
| Multimodality protocol | 72% | 78% |

are present as MRI offers excellent soft-tissue contrast and, with the aid of fluid sensitive sequences can detect and differentiate CRPS from other infective and inflammatory conditions which mimic this entity.

Three-phase radionuclide bone imaging yields an early angiogram perfusion phase followed by a blood pool phase and delayed phases showing diffuse uptake of the isotope in the periarticular locations. There is a diffuse accumulation of tracer in blood pool or tissue phases in about 40%-50% of patients with CRPS, which is different from that of extremities' infections and inflammatory conditions. These Radio nucleotide scan findings may often predate the clinical and radiographic findings. The scenario includes CRPS 1: If the patient had a previous hip fracture: Pain syndrome characterized by diffuse non-anatomic unremitting pain with autonomic-vasomotor signs (warm or cool skin temperatures and moist-sweaty dry-scaly skin) and scenario 2 if Post-traumatic nerve injury is present.

Our study shows that the temporally evolving phases of complex regional pain syndrome could be effectively diagnosed by multimodality Approach with each modality contributing to detect the underlying pathological substrate like soft-tissue edema, regional hyperaemia osteopenia, region-specific bone resorption, bone marrow edema, The underlying inciting event of nerve injury can be seen by DWIBS MR neurography sequence in MR Imaging protocol definitively separating the CRPS I and CRPS II.

Limitations

Radionuclide bone scan using F18 at an outside institute shows for 7 cases where the diagnosis of CRPS type I was equivocal, which confirmed the diagnosis by showing diffuse periarticular uptake of the tracer in a region of ankle joint and. However, this was not included in the analysis and was not part of our study.

Our sample size is relatively small with no analysis on Gender predilection and clinical phenotypes of CRPS II.

The ground truth for confirmation was the inciting event followed by the onset of clinical features. The follow up was clinically without any other imaging evidence for a longitudinal period of one year.

Conclusion

Multimodality imaging approach for diagnostic characterization of CRPS shows optimal sensitivity and specificity and positive predictive values in early and late-stage subtypes of Complex regional pain syndrome.

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