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Analysis of patterns of three-phase bone scintigraphy for patients with complex regional pain syndrome diagnosed using the proposed research criteria (the 'Budapest Criteria')

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Editor's key points

- Complex regional pain syndrome (CRPS) can be difficult to diagnose.
- This study investigates the role of three-phase bone scintigraphy (TPBS) in the management of CRPS.
- Some clinical signs such as skin colour and oedema were associated with a positive TPBS.
- Particular patterns in the three phases of TPBS may be associated with a diagnosis of CRPS.

Background. Three-phase bone scintigraphy (TPBS) is an established objective diagnostic method for complex regional pain syndrome (CRPS), but its validity remains controversial. The aims of this study were: (i) to re-evaluate the diagnostic performance of TPBS, and (ii) to suggest new TPBS criteria based on the proposed research criteria for CPRS in Budapest (the 2003 Budapest research criteria).

Methods. The medical records of 228 consecutive patients, evaluated using the Budapest research criteria, were retrospectively analysed. Of these, 116 patients were included in the present study, and 69 of 116 were diagnosed to have CRPS based on these criteria. The diagnostic performance of TPBS was assessed by determining its sensitivity, specificity, and positive and negative likelihood ratios, and new criteria for TPBS were identified by pattern analysis using the Budapest research criteria.

Results. The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of TPBS for the diagnosis of CRPS according to the Budapest research criteria were 40.0, 76.5, 1.73, and 0.78, respectively. Furthermore, D–D–D, D–D–S, and D–D–I patterns [i.e. according to decreased (D), symmetrical (S), or increased (I) tracer uptake during Phases I, II, and III] of TPBS were found to be positively predictive for CRPS.

Conclusions. The diagnostic value of a positive TPBS for CRPS is low from the view point of the Budapest research criteria. Our findings suggest that a diagnosis of CRPS using the Budapest research criteria should be considered when decreased patterns of TPBS are observed during Phases I and II.

Keywords: bone; complex regional pain syndromes; diagnosis; radionuclide imaging

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Complex regional pain syndrome (CRPS) has been defined as a neuropathic pain condition since the publication of consensus-based criteria by the International Association for the Study of Pain (IASP).[1] However, the lack of specificity (0.41)[2] and diagnostic consistency (0.43–0.66)[3] of the IASP criteria for CRPS led to a proposal to adopt modified criteria in Budapest in 2003 (the 'Budapest Criteria').[3–6] A unique feature of the Budapest Criteria is the provision of two sets of decision rules—one for clinical diagnoses and the other for research purposes. Clinical diagnosis for CRPS according to the Budapest Criteria is performed when the patient has at least three symptoms in the following four categories: sensory, vasomotor, sudomotor/oedema, and motor/trophic, and at least two signs from the same four categories. Otherwise, according to the Budapest research criteria, patients should have at least one symptom from all four categories and at least two signs from the same four categories for diagnosing CRPS.[7] Among the existing sets of criteria, the Budapest research criteria have been reported to have highest specificity (0.79).[2]

The diagnosis of CRPS using the Budapest Criteria is performed on purely clinical grounds and is based on practical ways of ruling out other conditions.[8 9] Several tests can be used to assist the differential diagnosis, and these include three-phase bone scintigraphy (TPBS).[1 8 10] Unlike a conventional bone scan, TPBS is performed after the injection of a

radioactive substance during Phase I (the blood-flow phase). Approximately 3 min later, during Phase II (the blood-pool phase), another scan is performed and this is followed by an additional scan after 2–4 h during Phase III (the delayed phase).[11] We use the terms 'Increased,' 'Decreased,' and 'Symmetric' to describe the uptake of the affected side with respect to the contralateral unaffected side during each phase. Symmetric uptake during Phase III is usually considered a normal finding in conventional bone scans.

The role of TPBS in the diagnosis of CRPS is to support or even confirm a diagnosis, given its various presentations, and to exclude other diagnoses.[12] Positivity of TPBS for CRPS during Phases I and II must be concordant, and it requires increased uptake in the affected extremity during Phase III.[13 14] Typically, the TPBS pattern in CRPS patients shows increased activity in the affected extremity during all three phases.[11 14] However, the sensitivity (54–100%), specificity (85–98%), positive predictive value (67–95%), and negative predictive value (61–100%) of TPBS for a diagnosis of CRPS vary widely,[13 14] and furthermore, no general consensus has been reached regarding the TPBS criteria that must be met for a diagnosis of CRPS. In a previous study, the positive findings of TPBS were based on reflex sympathetic dystrophy in response to sympathetic blockade,[15] which had been suggested earlier when the concept of the sympathetic independent pain was included in the diagnostic criteria of CRPS.[1] As far as we are aware, no report has been issued on the diagnostic performance of TPBS for CRPS based on the Budapest Criteria, and thus, it is questionable whether current criteria for a positive TPBS finding could be applied to the Budapest Criteria. Furthermore, blood flow differences dependent on clinical stage of CRPS would impact on the likelihood of a positive TPBS.[11 12] If so, a positive TPBS finding should be related to some objective sign of the diagnostic criteria for CRPS related to pain duration.

Accordingly, the aims of this study were: (i) to re-evaluate the diagnostic performance of TPBS, (ii) to investigate the relationship between a positive TPBS finding and the objective signs of CRPS, and finally, (iii) to suggest a new TPBS diagnostic criteria for CRPS based on the Budapest research criteria.[4–6]

Methods

After obtaining approval from the Institute Review Board of Seoul National University Hospital (no. 0908-030-290), we reviewed the medical records of 228 consecutive patients evaluated for CRPS using the Budapest research criteria[4 5] that underwent TPBS at our university-based Pain Management Centre between January 1, 2007 and December 31, 2009.

The exclusion criteria were: (i) bilateral symptoms based on medical history or the physical examination, (ii) an implanted device, such as, a prosthesis[16] or a spinal cord stimulator,[17] and (iii) a history of sympathetic blockade within a month of TPBS.[18]

To evaluate the relationship between objective clinical signs and TPBS results, we selected patients who underwent TPBS within 3 weeks of physical examination.

Procedures used to diagnose CRPS

We used a standardized assessment protocol to evaluate and diagnose CRPS, which included the CRPS database checklist of signs and symptoms (as described by the Budapest research criteria), TPBS, standard radiographs of the affected region and of the contralateral region, electromyography/nerve conduction velocity tests, and psychological assessments. As is required by the Budapest research criteria, patients reported more than one symptom in each of the following four categories: sensory, vasomotor, sudomotor/oedema, and motor/trophic. In addition, the patients were required to have at least two signs from the same four categories. These signs were identified during initial evaluations.

During quantitative sensory testing (QST)[19] using a CASE IV device (CASE IV, WR Medical Electronics Co., Stillwater, MN, USA), vibration and cooling perception thresholds were formally documented. Thresholds for vibration and cooling sensation were calculated for affected and contralateral extremities. Results were given in JND units (empirically derived 'just noticeable difference' values for the vibration and cooling perception thresholds), displacement units (the maximum amplitude of the vibrating stimulator waveform measured in micrometre for the vibration perception threshold), and temperature units (measured in degree-Celsius for the cooling perception threshold). Any discrepancies between an affected and a contralateral extremity were noted.

For the objective evaluation of temperature asymmetry, we applied digital infrared thermography (IRIS® 5000, MEDICORE Inc., Seoul, Korea) and determined temperatures in the affected region of interest and in the contralateral region[20] after a minimum period of acclimatization of 30 min in a room temperature environment. A difference in temperature greater than 1°C between the two parts was considered as a positive sign.

Signs of trophic changes, skin colour asymmetry, and asymmetric oedema were recorded by attaching photographs to the patient's electronic chart. Furthermore, a 11-point Numerical Rating Scale (NRS) was used to assess the overall pain intensity during every visit made to our Pain Management Centre.

Three-phase bone scintigraphy

TPBS was performed using large field-of-view gamma cameras equipped with low-energy general purpose collimators (E.CAM, Siemens Medical Solutions, PA, USA or SKYLight, Philips Medical Systems, Best, The Netherlands). I.V. cannulation was secured in an arm antecubital vein. Patients complaining of upper limb pain were cannulated in a pedal vein. With the patient positioned symmetrically, radiopharmacological isotope was injected at least 3–5 min after releasing the tourniquet. The dynamic scan for Phase I was obtained at 1 frame s^{-1} after an i.v. bolus injection of 740 MBq of ^{99m}Tc-methylene diphosphonate, and a static scan for Phase II was acquired over 3 min from injecting the radiotracer. The static Phase III scan was performed 4 h after injecting the radiotracer. The results of TPBS were interpreted by at least three nuclear medical physicians at our institute.