THREE-PHASE BONE SCAN AND DYNAMIC VASCULAR SCINTIGRAPHY IN ALGONEURODYSTROPHY OF THE UPPER EXTREMITY

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Algoneurodystrophy (AND) is a complex disorder with a wide spectrum of clinical presentations. Patients referred for a work-up of unilateral upper extremity AND were reviewed, and 50 patients were enrolled with sufficient documentation on history, causal event, clinical stage, and final outcome. There were 27 females, 23 males, mean age 44 years. The affected area was : shoulder 5, arm 3, elbow 3, wrist 26 and hand 13. Main precipitating events were fracture, contusion, or prior surgery. Three-phase bone scintigraphy was performed followed by a 2-phase vascular scintigraphy on another day. Typical periarticular uptake on the delayed bone scan was used to diagnose AND. Staging was done with the dynamic phase of the vascular scan. The clinicians diagnosed 30 patients positive for AND, 14 negative, and 6 equivocal. Bone scintigraphy yielded 25 positive, 20 negative, and 5 equivocal scans, i.e. sensitivity 73% and specificity 86%. Of the positive bone scans, 21 had all 3 phases positive, and 16 were concordant on vascular scintigraphy. The remaining 5 vascular scans classified 3 patients in transition (stage I → II) and 2 in stage II. In other words, in 24% of patients vascular scintigraphy indicated restaging. Conclusion : dynamic bone scintigraphy is an accurate method to diagnose AND. Vascular scintigraphy changed AND stage in one quarter of the patients. Therefore, a combination of both studies is indicated in the work-up and treatment monitoring of AND.

Keywords : Sudeck's atrophy ; algoneurodystrophy ; bone scan ; Tc-99m MDP ; vascular scintigraphy ; Tc-99m HSA.

Mots-clés : syndrome de Sudeck ; algoneurodystrophie ; scintigraphie osseuse ; TC-99m MDP ; scintigraphie vasculaire ; TC-99m HSA.

INTRODUCTION

Algoneurodystrophy (AND) or reflex sympathetic dystrophy syndrome (RSDS) is a complex disorder with pain as the predominant feature but widely varying clinical symptoms and signs (3, 5, 6). The pathophysiology is not completely understood, but many investigators consider it an exaggerated response to injury due to an abnormal sympathetic reflex (3, 6). It is important to treat early and effectively ; otherwise the prognosis is guarded leading to significant disability with lasting socioeconomic consequences (7).

In this study, we evaluated the utility of dynamic scintigraphy, i.e. 3-phase bone scan and two-phase vascular scan, in the diagnosis and staging of AND in the upper extremity. Also, the relationship between clinical and scintigraphic staging was investigated. Correct staging is of paramount importance since different therapies are employed. In our institution calcitonin is used in stage I and vasodilatation therapy in stage II. Vasomotor disturbances are prominent in stage I, characterized by hyperemia on scintigraphy, i.e. increased flow to the affected area and increased blood pool.

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In stage II, the flow is decreased whereas the blood pool changes are less pronounced. In stage III, pseudo-normalization occurs or a mild chronic hypoperfusion may persist. In addition, irreversible signs of *functio laesa* characterize the end stage of this syndrome.

MATERIALS AND METHODS

Patient Population

We reviewed all patients referred to nuclear medicine from April 1989 through December 1992 for a work-up of upper limb AND and enrolled 72. Fifty patients could be selected with sufficient documentation on history, causal event, clinical stage, imaging procedures and final outcome. There were 27 females and 23 males, mean age 44 years, range 19 to 77 years.

The affected areas were : shoulder 5, arm 3, elbow 3, wrist 26 and hand 13. Main precipitating events were : fracture 22, contusion 9, prior surgery 7, crush trauma 4, stroke 2, tendinitis 2, and in the remaining 4 the causative event was unclear.

Imaging

Three-phase bone scintigraphy was performed after intravenous administration of 740 MBq (1 Mega-Becquerel = 1 million disintegrations per second) Tc-99m methylene-diphosphonate (MDP) followed by dynamic vascular scintigraphy with 740 MBq Tc-99m human serum albumin (HSA) one or two days later. The acquisition protocols were adaptations of those proposed by Driessens (2). Briefly, for the bone scintigraphy the first or flow phase consisted of 24 frames of 4 sec duration (total 1.67 min.). Hereafter the second phase was acquired, 1 frame of 2 min. duration. The third or delayed phase was acquired 2.5 - 3 hr. after tracer administration, and comprised a spot view of the hands as well as a whole body scan. For the vascular scintigraphy, phase 1 had 25 frames of 3 sec (total 1.25 min.), and phase 2 had 55 frames of 15 sec (total 14 min.). The scintigraphic procedures were performed while the patient was off vasoconstrictive or vasodilatory medications. The affected area and the contralateral control side were positioned carefully on the gamma camera to ensure symmetry. The tracer was injected in a dorsal vein of the foot to avoid the application of a tourniquet or other constrictive device in the upper extremity.

Analysis

A large region-of-interest (ROI) was drawn over the affected area. This ROI was mirrored to the contralateral control side. Time-activity curves were generated from which the affected-to-control ratio was calculated. For phase 1 the summed activity over the first 25 frames was used (see above).

For the second phase, summation of activity over 2 min. (bone) or 14 min. (vascular) was performed. A ratio of the uptake in the affected area to the control side smaller than 0.89 or greater than 1.11 was considered abnormal. Driessens (2) adopted this criterion for the vascular scan and we arbitrarily assigned the same values to the first and second phase of the bone scan.

Interpretation

The final diagnosis of AND and the clinical staging was performed by the referring physicians, e.g. surgeons, anesthesiologists of the pain clinic or rheumatologists. This strategy was used, since there is no generally accepted test or 'gold standard' to assess presence or absence of AND. The scintigraphic criterion for diagnosing AND was diffusely increased periarticular uptake on the delayed (or third) phase of the bone scan, a typical pattern easily recognized by nuclear medicine specialists. Scintigraphic staging was done based on the uptake ratios of the dynamic vascular scan in phase 1 and 2. The diagnostic controversies, lack of a pathological standard and biochemical markers, and the value of imaging in AND were recently reviewed by Fournier and Holder (3).

RESULTS

The clinicians diagnosed 30 patients positive for AND, 14 negative, and 6 equivocal. Bone scintigraphy yielded 25 positive, 20 negative, and 5 equivocal scans (Table I). Of the 23 positive bone scans with a definite clinical diagnosis, 22 were true positive and 1 false positive.

An uptake ratio of 0.89 to 1.11 of the affected to the control area in phase 1 and 2 was considered normal (2). All 3 phases were positive in 21 of the true positive bone scans, 16 of which had a concordant pattern on vascular scintigraphy. The other 5 HSA scans were discordant and classified

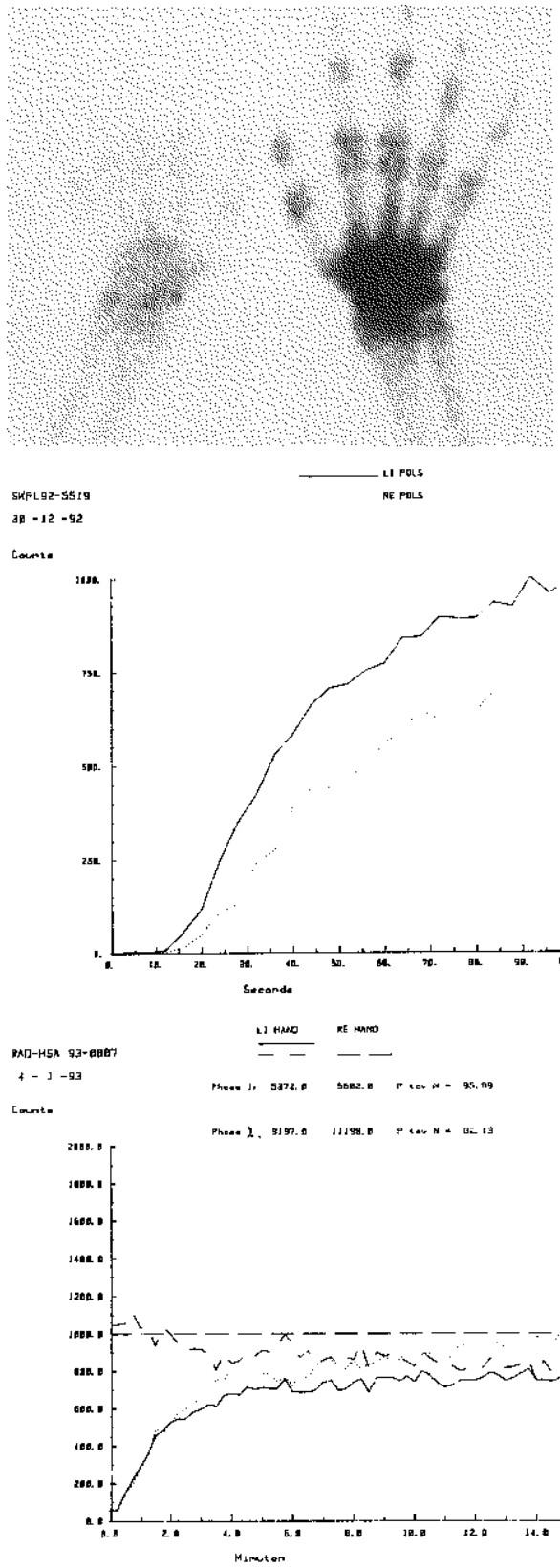

Table I. — Delayed-phase bone scintigraphy vs final clinical diagnosis

Bone scintigraphy		+	−	?
Clinic	+	22	5	3
	−	1	12	1
	?	2	3	1
Sensitivity 73%			PPV 88%	
Specificity 86%			NPV 60%	

3 patients in transition (stage I → II) and two in stage II. Overall, in 5/21 (24%) of AND patients vascular scintigraphy indicated restaging. In figure 1 a representative patient is shown.

In Table II the average uptake ratio and standard deviation is given for the clinically positive and negative AND patients. For positive AND patients Table II reveals abnormal values for both phases, with higher ratios for the bone than vascular scintigraphy. However, for clinically negative patients the average ratio of the vascular scintigraphy is abnormal in phase 1 (normal range 0.89 - 1.11) and borderline normal in phase 2. The bone scan indices are well within normal limits.

Table II. — Average uptake ratios ± 1 s.d. — Affected to control side mean (normal range : 0.89 - 1.11)

Scintigraphy	phase 1	phase 2
Clinical positives	N = 30	
Bone	1.53 ± 0.75	1.71 ± 0.83
Vascular	1.33 ± 0.40	1.31 ± 0.35
Clinical negatives	N = 14	
Bone	1.06 ± 0.33	1.08 ± 0.25
Vascular	1.12 ± 0.24	1.10 ± 0.23

Fig. 1. — Typical delayed-phase bone scan in algoneurodystrophy. This 30 year-old male attempted suicide by cutting his left wrist, 6 months before the bone scintigraphy. In this palmar view of the hands, diffusely increased uptake in the periarticular areas is seen on the left (upper panel).
Phase 1 of the bone scintigraphy shows increased uptake on the left (middle panel, solid line).
Phase 1 and 2 of the vascular scan show decreased uptake on the left (solid line) compared to the right hand (dotted line), and the ratios are 0.96 and 0.82, respectively (lower panel). This indicated restaging and change of therapy. The dashed line in the lower panel represents the uptake ratio in function of time.

Table III. — Average uptake ratios ± 1 s.d. — Affected to control side mean (normal range : 0.89 - 1.11) p — significance level paired t-test : Bone vs Vascular uptake ratios

Scintigraphy	phase 1	p	phase 2	p
All true positives	N = 22			
Bone	1.75 ± 0.76	0.02	1.96 ± 0.83	0.001
Vascular	1.42 ± 0.42		1.38 ± 0.38	
Stage I	N = 16			
Bone	1.93 ± 0.82	0.07	2.19 ± 0.88	0.001
Vascular	1.59 ± 0.37		1.54 ± 0.31	
Stage II	N = 6			
Bone	1.26 ± 0.17	0.02	1.37 ± 0.17	0.01
Vascular	0.98 ± 0.12		0.96 ± 0.12	
All true negatives	N = 12			
Bone	1.09 ± 0.31	0.63	1.11 ± 0.25	0.91
Vascular	1.13 ± 0.26		1.11 ± 0.27	

This suggests that there is a significant vascular asymmetry in most patients suspected of having AND, not only in the true positives as expected, but also in the true negatives.

Subgroup analysis is shown in Table III. In general, bone uptake ratios are higher than those of the vascular scan in corresponding phases. In stage II AND, the bone uptake ratios are still elevated whereas the vascular ratios have dropped just below 1 ($p < 0.05$). Again seen is the high, on average abnormal, ratio of the vascular scintigraphy in patients negative for AND. However, there is no significant difference between bone and vascular scans, both in phase 1 and 2 of these true negatives.

For true positive AND patients, the ratios were statistically different between bone and vascular scintigraphy, except for phase 1 in stage I ($p = 0.07$).

Comparison of true positive vs true negative patients revealed highly significant differences ($p = 0.001$) both for the bone and vascular scintigraphy in phase 1 and 2. For stage II, however, the uptake ratios are statistically not different from negative patients, for both phases of the bone ($p = 0.5$) or vascular scintigraphy ($p = 0.3$).

DISCUSSION

In the present investigation we were able to demonstrate the effectiveness of three-phase bone scintigraphy in the diagnosis of AND. The accuracy of the dynamic bone scan was 68% (Table I), which is relatively low because of the number of equivocal cases, both on the delayed bone scan and final clinical diagnosis. In our hands, bone scintigraphy appeared an excellent test to exclude AND.

The sensitivity and specificity are lower than in other reported series. Holder *et al.* (4) used carefully selected patients ($n = 40$) with RSDS of the hands to get values over 90%. We studied patients from routine referrals from surgery, orthopedics, rheumatology and anesthesiology who were not preselected. Removal of the selection bias decreased the sensitivity more than the specificity. The relatively high specificity of the bone scan is very useful to rule out suspected RSDS. As has been shown by Greco *et al.* (4) and Holder *et al.* (5), the second phase of the bone scan is very reliable in diagnosing stage I RSDS (average ratio of 2.2, see Table III). The increased uptake in the blood-pool phase is caused by vascular stasis and

edema (3). Table III suggests that this condition is sometimes present in negative patients. An explanation may be other coexisting (inflammatory ?) disease (3). Further investigations are needed to elucidate this phenomenon.

Still, there were 6 patients (12%) who could not be classified as having definite AND by our clinicians, again emphasizing the difficulty to diagnose this syndrome in clinical practice. The accuracy of the delayed bone scan was 68% overall. Eliminating the equivocal clinical cases yields an accuracy of 77%, a PPV of 96% and NPV of 80%, values close to those reported by other authors (2, 3, 4, 5).

In our study the various stages of AND could be distinguished by the uptake ratios. In general, the bone ratios were higher than those of the vascular scan. In stage II AND the vascular ratios are within normal limits or decreased, as has also been demonstrated by Blockx *et al.* (1). Surprisingly, both bone and vascular ratios in stage II do not differ significantly from patients negative for AND.

These findings of different ratios in stage I and II are in sharp contrast to the University of Nijmegen experience (8). In a large prospective clinical study, they could not confirm the commonly accepted staging of RSDS. In addition, they emphasized the exaggerated inflammatory response in RSDS. As has been shown by other authors (1, 2, 3, 4, 5), we were able to document clear-cut scintigraphic differences in the various stages of algoneurodystrophy.

The vascular scan indices of phase 1 turned out to be abnormal in negative patients (using Driessens' normal range of 0.89 - 1.11). Although superior to Tc-99m MDP, Tc-99m HSA is not a true vascular tracer. HSA will leave the vascular compartment and accumulate in the extracellular fluid. Driessens chose Tc-99m HSA as vascular tracer because of the close correspondence of this radiopharmaceutical to blood pool imaging with labeled red blood cells. Indeed, under normal circumstances 80-90% of HSA is still in the vascular space after 15 minutes, but AND causes local disturbances which affect permeability (3, 4).

The finding of 'increased vascularity' in the affected limb of negative patients necessitates strict adherence to the imaging sequence that has to be followed. The three-phase bone scan should be performed first. If the bone scan is negative, there is no need to proceed with HSA. The only indication for vascular scintigraphy is to stage a previously documented or diagnosed AND. This staging is important to select the correct therapeutic approach (1, 7). In this series, restaging based on the vascular scan was necessary in 24% of patients.

CONCLUSION

Dynamic bone scintigraphy is an accurate method to diagnose or exclude algoneurodystrophy. Vascular scintigraphy changed AND stage in one quarter of patients. Therefore, a combination of both studies is indicated in the work-up and treatment monitoring of algoneurodystrophy.

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SAMENVATTING

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Algoneurodystrofie (AND) is een complex syndroom met een zeer varierend ziektebeeld. Patienten verwezen voor onderzoek van een unilaterale AND van de bovenste extremiteit werden nagekeken. Vijftig patiënten hadden voldoende informatie betreffende ziektegeschiedenis, oorzaak, klinisch stadium, en uiteindelijke diagnose. Er waren 27 vrouwen, 23 mannen, gemiddelde leeftijd 44 jaar. Het aangedane gebied was : schouder 5, arm 3, elleboog 3, pols 26 en hand 13. De voornaamste causale factoren waren : fractuur, contusie of voorafgaande heelkunde. 3-fasen skelet scintigrafie werd verricht, gevolgd door 2-fasen vasculaire scintigrafie op een andere dag. Het typische peri-articulaire stapelings patroon op de laattijdige bot scan werd gebruikt als scintigrafisch criterium om AND te diagnostiseren. Stadiering werd gedaan met de dynamische fase van het vasculair onderzoek. De clinici diagnostiseerden 30 patienten positief, 14 negatief and 6 twijfelachtig voor de aanwezigheid van AND. Bot scintigrafie gaf 25 positieve, 20 negatieve and 5 twijfelachtige resultaten, dwz. een sensitiviteit van 73% and specificiteit van 86%. Van de positieve botscans, waren er 21 met alle drie fasen positief, waarvan 16 concordant met de vasculaire scintigrafie. De overblijvende 5 klassificeerden 3 patienten in transitie van stadium I → II en 2 in stadium II. M.a.w. in 24% der patiënten veranderde de vasculaire scintigrafie de stadium indeling.
Conclusie : dynamische skelet scintigrafie is een nauwkeurige methode om AND te diagnostiseren. De vasculaire scintigrafie veranderde het stadium in een kwart van de patiënten. Daarom is een combinatie van beide studies aangewezen voor de diagnose en opvolging van AND.

RÉSUMÉ

C. SCHIEPERS, I. BORMANS, M. DE ROO. Intérêt de la scintigraphie osseuse en trois phases et de la scintigraphie vasculaire dynamique dans l'algoneurodystrophie du membre supérieur.

L'algoneurodystrophie (AND) est un syndrome complexe dont la présentation clinique est très variable. Nous avons étudié un groupe de 50 malades envoyés pour une AND unilatérale du bras. Nous disposions de données suffisantes concernant l'évolution clinique, la cause de l'affection, le stade clinique et le diagnostic final. Parmi ces 50 malades on comptait 27 femmes et 23 hommes avec un âge moyen de 44 ans. La région atteinte était l'épaule (5 cas), le bras (3 cas), le coude (3 cas), le poignet (26 cas) et la main (13 cas). Chez la plupart des malades, des fractures, des contusions ou des interventions chirurgicales étaient à l'origine des symptômes. Une scintigraphie en trois phases a été effectuée, suivie, après quelques jours, d'une scintigraphie vasculaire en deux temps. L'image tardive typique avec hypercaptation péri-articulaire du traceur osseux nous a permis de poser le diagnostic. Le staging de l'AND a été effectué en tenant compte des données dynamiques de la scintigraphie vasculaire. Le diagnostic clinique a permis d'identifier 30 malades avec une AND, 14 cas étaient négatifs et 6 cas douteux. La scintigraphie osseuse était positive chez 25 malades, négative dans 20 cas et douteuse dans 6 cas. La sensibilité était donc de 73% et la spécificité de 86%. Parmi les cas avec scintigraphie osseuse positive, 21 patients présentaient un tableau complet avec trois phases positives, avec dans 16 cas des données concordantes avec le résultat de l'examen vasculaire. Les cinq autres scintigraphies vasculaires classaient 3 cas dans le stade de transition (entre stades I et II) et 2 cas dans le stade II. On peut donc conclure que chez 24% des malades la scintigraphie vasculaire a modifié le staging de la maladie. La scintigraphie osseuse dynamique est une méthode fiable pour le diagnostic d'algoneurodystrophie. La scintigraphie vasculaire a changé le stade de la maladie dans environ un quart des cas. De ces données on peut conclure que la combination des deux explorations est indiquée dans l'évaluation diagnostique et le monitoring thérapeutique de l'algoneurodystrophie.