STATIC AND WHOLE-BODY IMAGES *VS*. SPECT: TOGETHER OR SEPARATE FOR AN ACCURATE DETECTION OF TRANSTHYRETIN CARDIAC AMYLOIDOSIS

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STATIC AND WHOLE-BODY IMAGES VS. SPECT: TOGETHER OR SEPARATE FOR AN ACCURATE DETECTION OF TRANSTHYRETIN CARDIAC AMYLOIDOSIS (Abstract): Transthyretin cardiac amyloidosis (ATTR-CA) is a protein deposition disease that represents a challenge to be diagnosed by the practicing physician. As the gold standard method is not widely available correlations between biomarkers, electrocardiography, echocardiography, bone scintigraphy and free light chain dosage has proven to be a reliable alternative. Bone scintigraphy represents the corner stone for ATTR-CA detection; however, some patients cannot undergo all the required images for an easy and accurate diagnosis. Therefore, the aim of this study is to determine the bare minimum images that can be performed for an accurate diagnosis. **Materials and methods:** 80 patients that met the inclusion criteria were evaluated throw bone scintigraphy. Acquired images included: whole body bone scan (early and delayed), static followed by Single Photon Emission Computed Tomography (SPECT), if possible, centered on the thorax. Images were interpreted by visual scoring and semiquantitative methods. **Results**: 20 patients were diagnosed with ATTR cardiac amyloidosis by visual scoring, however not all of them underwent all the necessary images. Semiquantitative methods results were above the established threshold and therefore sustained the visual score. Nevertheless, ratio results differed between static and SPECT images. **Conclusions**: Ideally all type of images should be acquired for this type of patients, however, we determined that a minimum of whole-body ± static centered on the thorax images interpreted throw visual scoring and semiquantitative analysis can be enough if SPECT is not possible for a reliable diagnosis. **Keywords**: WHOLE-BODY, STATIC, SPECT, ATTR-CA, VISUAL SCORING, SEMIQUANTITATIVE ANALYSIS.

Transthyretin cardiac amyloidosis (ATTR-CA) is a rare disease characterized by continuous and progressive deposition of amyloid at the myocardium level resulting in a thickening of both ventricles and inter-atrial-ventricular septum. Undiagnosed and therefore untreated, can be fatal to the patient. The mechanism behind it is based on misfolding the transthyretin protein (a plasma transport protein that circulates as a stable tetramer and transport thyroxin and retinol). ATTR-CA can be

classified as wild-type (ATTRwt) and hereditary or with mutation (ATTRm or ATTRh) (1, 2).

Diagnosing this rare disease has always represented a challenge for the practicing physician. The gold standard method, endomyocardial biopsy, has proven to be invasive and not widely available. Therefore, the European Society of Cardiology (ESC), has presented and alternative to this method, by correlating the electrocardiography, ultrasonography and bone scintigraphy characteristics. Nevertheless, screening for these patients, before reaching the actual methods for detection, is based on the so called "red flags" that offer a possible profile for the most likely ATTR-CA candidate (3). The final diagnosis for ATTR-CA is represented by bone scintigraphy, an imaging investigation technique that studies the biodistribution of a radiotracer at the skeletal level using bisphosphonates such as HDP (hydroxyethylene diphosphonate) which is mainly indicated in oncology, rheumatology, bone and joint infections, orthopedics, sports and traumatology, metabolic bone disease and pediatrics. Nevertheless, it is also indicated for detecting ATTR-CA Standard uptake mechanism for bone scan is based on the absorption to the surface of hydroxyapatite crystals and it is dependent on local bone vascularization and osteoblastic activity. However, in case of ATTR-CA the exact uptake mechanism is not completely elucidated and therefore a few theories that try to explain it have emerged that are based on the calcium level, microcalcification, the amount and type of fibrils involved (3-10).

The acquisition protocol according to the American Society of Nuclear Cardiology (ASNC) and European Association of Nuclear Medicine (EANM) practice points guideline is based on acquiring planar centered on the thorax (anterior, lateral and left anterior oblique) or whole body (WB) images, followed by SPECT centered on the thorax at 1 hour with optional acquisition at 3 hours after the iv administration of the radiotracer. Image processing and interpretation is based on the Perugini visual score that analysis the uptake of the myocardium and a semiquantitative analysis based on comparing the heart uptake with the uptake contralateral side (H/CL) and the rib (H/R). According to the ASNC practice points guide the threshold for H/CL ratio for ATTR positive patients should be over 1.5 on SPECT images at one hour. However, for comparing the heart to the rib uptake, the guide suggests a visual evaluation (11-13).

Therefore, a correct assessment of heart uptake using visual score and semiquantitative methods may represent a solution for a better and more accurate detection. Nevertheless, basing the ratio result only on SPECT images obtained at one hour may prove to be useful in patients that have a referral diagnosis of possible cardiac amyloidosis. For patients that have been accidentally diagnosed (different referral diagnosis), most likely the SPECT at one hour step was missed. As a result, the diagnosis was most likely based on the static images. The aim of this paper is to compare the visual score and the semiquantitative method of both static and SPECT centered on the thorax images in order to determine the bare minimum of images that can be acquired for an accurate diagnosis.

MATERIALS AND METHODS

The lot was comprised of patients from the Nuclear Medicine Laboratory of "Sf. Spiridon" County Clinical Emergency

Hospital Iasi archive (2015-2023) and was based on the following criteria: patients with a referral diagnosis of possible cardiac amyloidosis, ATTR positive patients after bone scintigraphy regardless of the referral diagnosis, ATTR positive patients that underwent both static and SPECT centered on the thorax images. The analysis was focused especially on the patients that had underwent both static and SPECT images.

The patients were required to sign an informed consent. All the protocols were approved by the Ethics Committee of both the "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania and "Sf. Spiridon" County Clinical Emergency Hospital of Iasi.

Bone scintigraphy acquisition protocol include early and delayed whole body (WB) images, static centered on the thorax images early (WB unavailable) and delayed followed by SPECT centered in the thorax.

Images processing and interpretation relied on the Perugini visual score and a semiquantitative method based on ratios between different regions of interest (ROI). The ROI for the static images was made initial on the highest uptake region (from a visual point of view) of the heart muscle, without including the ribs and by using the "mirror" function it was projected on the contralateral side and placed consecutively first over one of the ribs and then between the ribs (contralateral). The ROIs made on the SPECT images were made in a similar fashion, with the initial ROI made over the heart and using the "mirror" function it was projected on the contralateral side. The ROIs in this case include the whole left ventricle and was made on the transverse and coronal incidences. However, the initial ROI over the heart was made on the slice which presented the maximum dimension of the heart and was maintained for all of the other slices. The ratio results were analyzed based on the following parameters (tab. I):

TABLE I.
Semiquantitative method results and interpretation (H=heart; R=rib; CL=contralateral)

Ratio	Result	Interpretation
H/R	> 1	Myocardial uptake greater than rib uptake
	< 1	Myocardial uptake lower than rib uptake
	1	Myocardial uptake similar to rib capture
H/CL	0 - 1.49	Absence/slight uptake of the radiopharmaceutical in the myocardium
	1.5 - 3	Moderate/increased uptake of the radiopharmaceutical in the myocardium

RESULTS

Out of 80 patients with referral diagnosis of possible cardiac amyloidosis only 20 were determined to be ATTR positive after bone scintigraphy. Due to the fact that the other patients presented visual scores and ratio result underneath the threshold they were classified as non-ATTR (n-ATTR) and required further investigations. Not all of the patients were able to undergo SPECT imaging, however, almost all underwent static centered on the thorax images and all of them made WB images. The patients that were accidentally diagnosed, presented only with WB images. Nevertheless, H/CL and H/R, were obtained regardless of the acquired images.

Visual Score

Visual score was determined on early and delayed images. Most of the early images were acquired only in patients that

presented a referral diagnosis of cardiac amyloidosis. Therefore, for patients that were accidentally diagnosed, this type of images was not acquired.

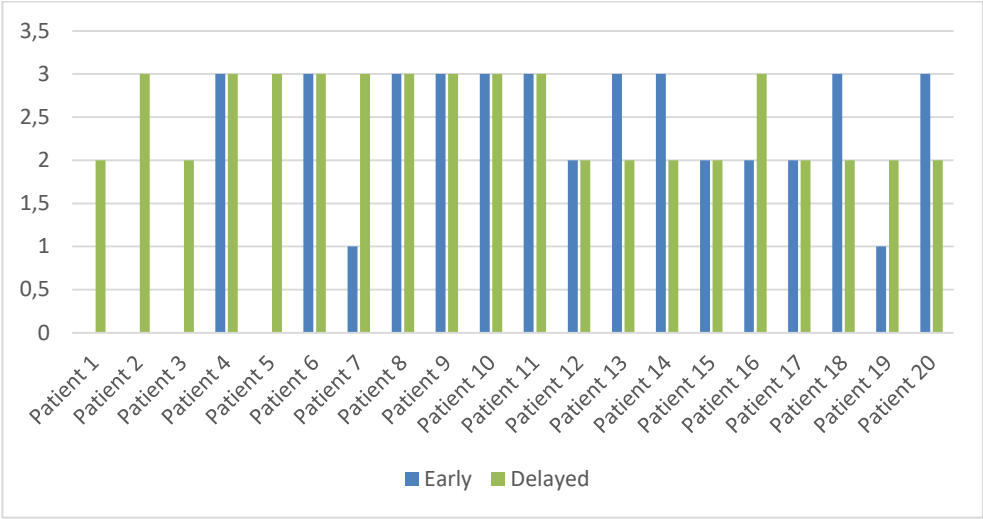
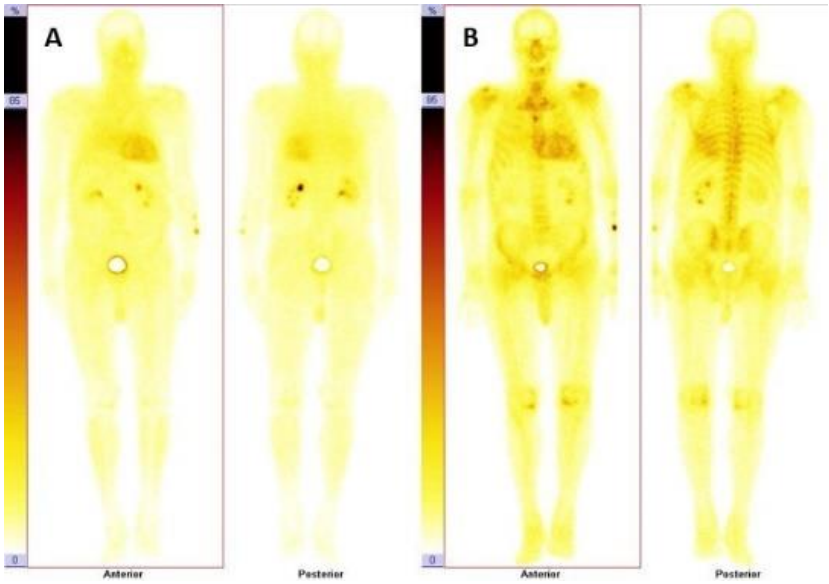
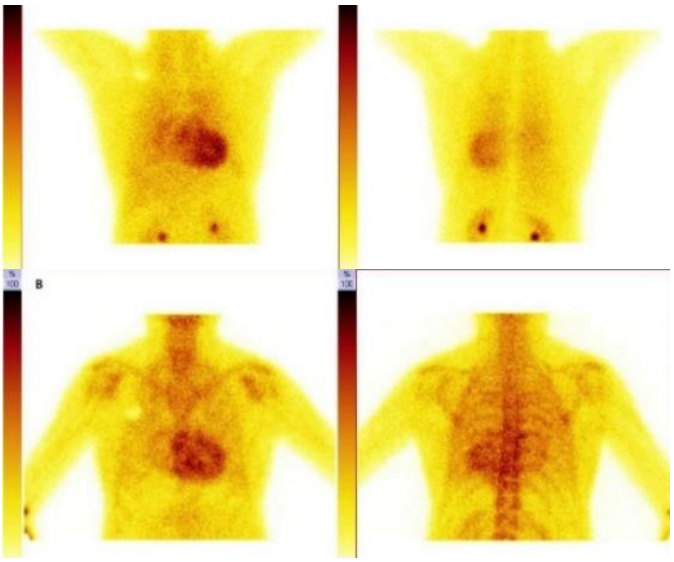


Fig 1. Visual Score of early and delayed images regarding for all 20 patients

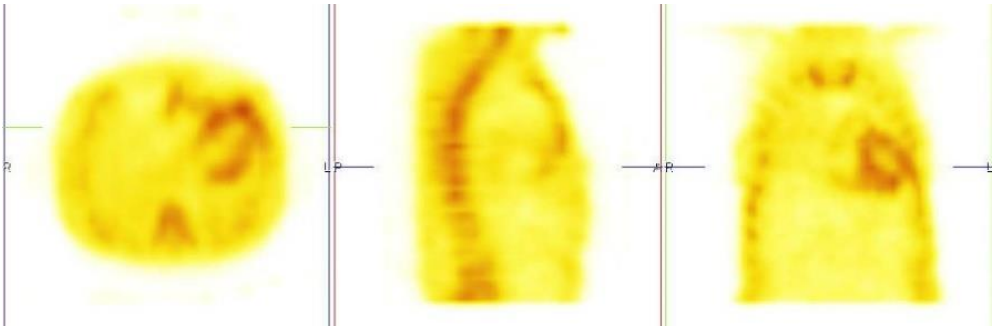
Visual scoring varied on early images, however, the aim of these images was to determine the location and dimension of the heart. Delayed images presented visual scoring typical for ATTR-CA (scores of 2 or 3).



CASE 1: 81 years old patient suspected of cardiac amyloidosis:
A. early WB images - visual score = 3; **B.** delayed WB images - visual score = 3



CASE 2: 52 years old patient suspected of cardiac amyloidosis: **A.** early static centered on the thorax - visual score = 3; **B.** delayed static centered on the thorax - visual score = 3



CASE 3: 82 years old patient suspected of cardiac amyloidosis: SPECT imaging reveals high visual uptake of the myocardium resulting in ATTR-CA

Fig 2. 3 Cases from our database - ATTR-CA positive patients determined by visual scoring Visual Scoring and Semiquantitative method

ATTR positive patients only with WB or Static images

The H/R and H/Cl ratios were performed on all of the patients that underwent bone scintigraphy and the visual score revealed a possible myocardium uptake. In accidental diagnosis in which only WB images were acquired, the ratios were performed only on those images, as static centered on the thorax were not acquired. Ratio results varied as follows: H/R: 0.9-2.08; H/Cl: 1.20-2.71. Nevertheless, in both cases, the ratio results were over the threshold and sustained the visual score.

The average of these ratio, demonstrated that the threshold of 1 for the H/R ratio and 1.5 for the H/Cl ratio represent, in association with the visual score as the bare mini-

mum for a possible diagnosis of ATTR-CA.

ATTR positive patients with WB/static and SPECT centered on the thorax images

The patients that underwent both WB/static and SPECT centered on the thorax, the ratio results differed slightly, but not to significant. In both image types, the H/R and H/Cl ratio results were over the determined threshold, therefore sustaining the visual score.

TABLE II.

Correlation between Delayed Visual Scoring and Semiquantitative Analysis on patients with WB/static and SPECT centered on the thorax images

	Visual scoring	H/R	H/CL		
	Delayed images	Static or WB	Static or WB	SPECT	
				Transvers	Coronal
Patient 4	3	1.68	2.09	2.13	2.50
Patient 6	3	1.56	1.75	1.82	1.82
Patient 7	3	2.06	2.41	2.97	2.98
Patient 11	3	1.67	1.60	2.37	2.98
Patient 13	2	1.64	1.81	2.11	1.79
Patient 14	2	1.88	2.07	2.80	2.94
Patient 15	2	1.66	1.72	1.88	1.57
Patient 16	3	1.77	2.08	2.71	2.25
Patient 17	2	1.42	2.12	1.61	1.75
Patient 18	2	1.08	1.54	2.90	2.11
Patient 19	2	1.19	1.65	2.30	1.80
Patient 20	2	1.18	1.63	1.81	2.06
AVERAGE Semiquantitative method results		1.57	1.87	2.28	2.19

By comparing the two semiquantitative methods it can be surmised that at least one ratio exceeds the established threshold. It can also be stated, that by comparing the H/CL made on the static images to those obtained on SPECT, the ratio results differ, in some cases. An explanation for this difference in the ratio result can be due to the type of images that were acquired. Static images are acquired in 2D, presenting the possibility of overlay, while SPECT presents a 3D image, reducing considerably the overlay factor. H/R ratio can only be made on static (2D) images therefore and therefore the ratio results are much lower compared to H/CL, but over the threshold in almost all of the patients. Furthermore, SPECT images offer a much clearer and with decreased background noise compared to static images. As a result, the ratios made on the SPECT images will present a higher result compared to those obtained on the static images.

Relying only on one ratio to sustain the visual score may prove to be inefficient (e.g. patients 18 - 20), as it can offer an equivocal result at best. By correlating both ratios made on static and SPECT images the additional information can offer a more accurate diagnosis.

DISCUSSION

ATTR-CA is a protein deposition disease located mainly in the myocardium. Diagnosing this rare pathology has proven to be difficult as, the gold standard method (endomyocardial biopsy) is not widely available. Therefore, alternative diagnostic

algorithms based on correlating different investigations have been utilized. As a result, nowadays, the main investigation used for ATTR-CA detection is bone scintigraphy, which has proven to be invaluable for this type of disease. The evaluation is based on myocardium uptake of the radiotracer. Standard acquired images include planar and SPECT centered on the thorax (WB images being considered only as an option) followed by visual evaluation of the uptake.

Our study aimed to determine if ATTR-CA diagnosis can be made on planar or WB images without necessarily using SPECT images even though it is recommended by the guidelines. Interpretation wise, we used visual scoring and semiquantitative methods based on H/CL made on both planar ± WB and SPECT and H/R made on planar ± WB. Due to the fact that some patients were discovered accidentally. As such, we compared the H/CL ratio result made on planar ± WB images to those obtained on SPECT images. In almost all of the cases the threshold on both image types was overcome. Due to the fact that planar images offer a 2D image of the patient, the problem of overlay should be taken into consideration and therefore, the ratio results could be lower than those obtained on SPECT, but still over the threshold. We also recorded cases in which the ratio result was close to the threshold, but didn't pass it on planar images compared to SPECT. In cases such as these, the H/R ration offered an additional parameter to the equation, that presented the possibility, along with the visual score, of ATTR-CA but in an early stage. In cases such as this, SPECT imaging could prove to be invaluable if the additional parameter didn't offer sufficient evidence to determine the diagnosis.

SPECT images offer a 3D image of the patient. The main advantage in these cases is the fact that the H/CL ratio result is much clearer in determining the presence of ATTR-CA than those obtained on planar images. However, in this type of images, H/R cannot be performed and as a consequence the result can be based only on visual scoring and H/CL region. Therefore, an additional parameter that could lighten the decision cannot be obtained on this type of image. Another disadvantage of this images refers to the dimension and position of the myocardium. If the myocardium is too large or if it's located to medial, it may be difficult to determine the H/CL region as the ROI made on the heart cannot be accurately mirrored to another region big enough or that doesn't include the myocardium to obtain a good result. In such cases, planar images may prove invaluable.

Ideally for ATTR-CA planar/WB and SPECT images should be performed and evaluated in the clinical context, visual scoring and semiquantitative analysis as each of them present different advantages and disadvantages. Therefore, in accidental diagnosed cases, if SPECT is unavailable, the ATTR-CA diagnosis can be determined by correlating the visual score, with the H/CL and H/R ratios.

CONCLUSIONS

In an ideal situation for diagnosing ATTR-CA, standard protocol should be followed regardless. Therefore, acquired images should be planar/WB followed by SPECT between 2-4 hours. Early planar/WB images, if acquired, present an approximation of the myocardium size and position, but cannot ascertain the presence of ATTR-CA. If SPECT images cannot be acquired, planar images should be enough to make a correct diagnosis, by analyzing them throw visual scoring and semiquanti-

tative analysis (H/CL and H/R).

To conclude, planar/WB vs SPECT, ideally together, if not possible, at least planar/WB for a correct diagnosis of ATTR-CA.

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