ORIGINAL ARTICLE

ASSOCIATION OF DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS AND AORTIC VALVE SCLEROSIS

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Abstract   The principal objective of this investigation was to analyze the association between diffuse idiopathic skeletal hyperostosis (DISH) and the presence of aortic valve sclerosis (AVS). For this study we used results from 1000 consecutive outpatients (473 males), older than 50 years of age (average 67.6 years), that had been examined with Doppler echocardiogram and anterior and lateral chest radiographs. Overall, 195 patients (19.5%) were diagnosed with DISH and 283 (28.3%) with AVS. DISH was more prevalent than AVS in males (66.7% vs. 42.6%, p< 0.0001) and in older patients (73.6 ± 9 years vs. 66.1 ± 9 years, p < 0.0001). Furthermore, 55.4% of patients with dorsal DISH presented aortic sclerosis calcification vs. 21.7% of patients free of DISH (OR = 4.47; 95% CI = 3.22-6.21). The adjusted odds ratio (OR) was calculated by sex and age resulting in 3.04 (95% CI = 2.12-4.36; p < .0001). A statistically significant association was found between DISH and AVS in accordance to age and sex. The biological plausibility of this association is based on similar risk factors, pathogenic mechanisms and vascular complications.

Key words: diffuse idiopathic skeletal hyperostosis, aortic valve sclerosis

Resumen   ***Asociación de hiperostosis esquelética idiopática difusa y esclerosis valvular aórtica.*** El objetivo principal fue analizar la asociación entre la hiperostosis esquelética idiopática difusa (DISH) y la presencia de esclerosis valvular aórtica (AVS). Se evaluaron los resultados de 1000 pacientes ambulatorios consecutivos (473 varones), mayores de 50 años (promedio, 67.6 años), que habían sido examinados con un ecocardiograma Doppler y radiología torácica anterior y lateral. Globalmente, 195 pacientes (19.5%) tuvieron diagnóstico de DISH y 283 (28.3%) de AVS. DISH fue más prevalente que AVS en varones (66.7% *vs.* 42.6%, p < 0.0001) y en pacientes de mayor edad (73.6 ± 9 años *vs.* 66.1 ± 9 años, p < 0.0001). Además, 55.4% de los pacientes con DISH dorsal presentaron AVS *vs.* 21.7% de los pacientes sin DISH (OR = 4.47; 95% CI = 3.22-6.21). El *odds ratio* (OR) ajustado por sexo y edad fue 3.04 (95% CI = 2.12-4.36; p < 0.0001). Se encontró una asociación estadísticamente significativa entre DISH y AVS, que se mantuvo después de ajustar por sexo y edad. La plausibilidad biológica de esta asociación se basa en los factores de riesgo, mecanismos patogénicos y complicaciones vasculares compartidos.

Palabras clave: hiperostosis esquelética idiopática difusa, esclerosis valvular aórtica

Diffuse idiopathic skeletal hyperostosis (DISH; also known as Forestier and Rotés-Querol disease) is a condition characterized by the calcification or ossification of soft tissues, mainly entheses, ligaments and joint capsules. The classical site of this condition is the spine, of which the lower thoracic segment is the most affected. Soft tissue ossification is the most characteristic feature (Fig. 1). However, DISH is not limited to the spine and can independently involve multiple peripheral sites. Extra-spinal

enthesis ossifications are frequent, and the presence of these can lead to a diagnosis of DISH[1, 2].

Bone proliferation (exostoses) and vascular calcifications are common in elderly patients, but it is not clear if these phenomena have a shared etiology. A derivative study from the Framingham Heart Study showed that osteophytes from the lumbar spine and calcifications of the abdominal aorta were present in the same patients, even after adjusting for age and other co-variables. The inclusion of subjects with DISH (7.0% of the sample) did not affect the analysis[3].

The cause of DISH is unknown, but several risk factors are involved; these are based on the frequency of association with different metabolic diseases, including
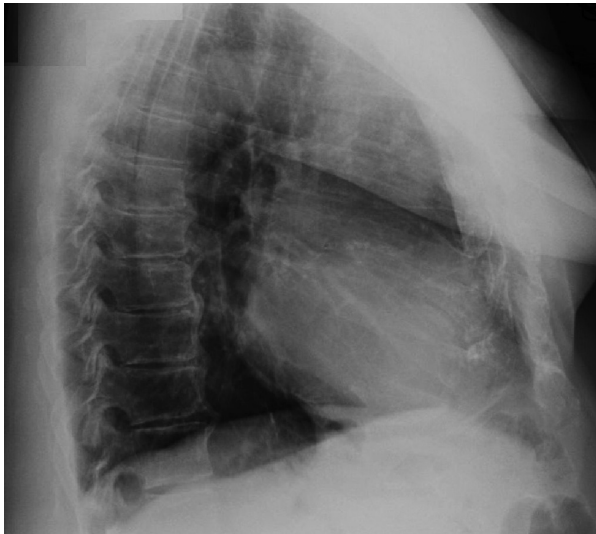
Fig.1.– Dorsal DISH.

hyperinsulinemia with or without diabetes mellitus, obesity, hyperuricemia, dyslipidemia, hypertension and long-term isoretinol use[4-6]. DISH is associated with an increased incidence of coronary and cerebrovascular disease risk factors, and patients with DISH are significantly more likely to present with metabolic syndrome than are non-DISH patients[7]. These reports are common but not uniform in all studies[6, 8, 9].

Aortic valve stenosis (AS) due to calcification is the main indication for replacement surgery in Europe and the United States of America. Valve calcification occurs in a wide range of diseases from aortic sclerosis (AVS), defined as a focal thickening with increased echogenicity of the aortic valve surfaces and returning velocities of < 2.5 m/s, to severe stenosis with thickening and calcification, leading to ventricular outflow obstruction with returning velocities of > 4 m/s[10, 11].

Several studies have shown that AVS risk factors, which include dyslipidemia, hypertension and diabetes, are also common to atherosclerosis. These disorders share pathological characteristics such as endothelial damage, lipid deposition, and inflammatory infiltration, which is why early aortic valve lesions appear similar to atheromata. Scleral calcification is an active biological process, similar to vascular calcification, and it is supported by mechanical tension and inflammation. It is associated with the synthesis of extracellular matrix proteins such as metalloproteinases, tenascin-C, osteopontin and bone sialoprotein. The coexistence of neoangiogenesis, T lymphocyte infiltration, adhesion molecules and HSP60 gene expression indicate an active immunomediated process[12].

DISH and AVS share risk factors, comorbidities and pathogenic mechanisms[1, 2, 4-9, 11-23]. Clinical observations of aortic valve involvement in DISH patients led to the aim of the present study: to analyze, in outpatients, the association between DISH that is diagnosed with conventional dorsal chest radiography and the presence of aortic valve involvement according to Doppler echocardiography.

Materials and Methods

Outpatients over 50 years of age underwent a bidimensional Doppler echocardiogram. Anterior and lateral chest radiograph for any clinical indication (i.e., arterial hypertension) were included.

Patients with prosthetic heart valves were excluded, as well as those previously diagnosed with ankylosing spondylitis or sacroiliitis.

The echocardiograms were performed with a Vivid I echocardiograph (General Electric, Fairfield, CT, USA), and sclerosis and valve calcification were determined according to the recommendations of the EAE/ASE[14]. The echocardiographers were unaware of the radiographic results.

The radiographs were taken with CR technology (digital radiography) and GE Legacy equipment. The radiographic technique was as follows: the patient was positioned at a 1.70 m distance, after which the anterior thorax was imaged at 70 kV/400 mA/0.004 s and the lateral thorax at 80 kV/400 mA/0.08 s. The images were stored for later availability in the Carestream PACS package, v 11.3 (Carestream Health Inc./Vue Solutions, Rochester, NY, USA).

DISH was diagnosed according to Resnick's criteria[24]. Three independent observers performed the diagnoses without knowing the echocardiographic results.

For the statistical analysis, the data are shown as means ± standard deviations for numerical variables and as percentages for categories. The Chi-square test was applied to compare proportions, and Student's t-test to compare means. Logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals (CI). Age and sex were adjusted in a multiple logistic regression analysis. A value of $p < 0.05$ was considered significant. The analysis was performed with the Stata 11.0 program (StataCorp LP, College Station, TX, USA).

The study was approved by the Ethics and Teaching-Research Committees of the participating institutions.

Results

Doppler echocardiogram and anterior and lateral chest radiograph results of 1000 patients over 50 years of age were analyzed. Demographic data (age and sex), aortic and mitral valve echocardiographic data (normality, scleral calcification, stenosis and insufficiency) and the presence or absence of DISH was recorded.

A description of the sample is presented in Table 1. Table 2 shows the comparison between the DISH and Non-DISH groups.

TABLE 1.– *Sample description*

	Study patients (n = 1000)
Average age (yrs)	67.6 ± 9
Males	473 (47.3%)
Aortic sclerosis	283 (28.3%)
Mitral sclerosis	125 (12.5%)
DISH	195 (19.5%)

TABLE 2.– *Comparison of DISH and Non-DISH groups*

	DISH (n = 195)	Non-DISH (n = 805)	Significance
Average age (yrs)	73.6 ± 9	66.1 ± 9	$p < 0.0001$
Males	130 (66.7%)	343 (42.6%)	$p < 0.0001$
Aortic sclerosis	108 (55.4%)	175 (21.7%)	$p < 0.0001$
Mitral sclerosis	28 (14.4%)	97 (12.1%)	$p = 0.38$

Overall, 55.4% of the patients with dorsal DISH had AVS, versus 21.7% of the patients without DISH (OR = 4.47, 95% CI = 3.22-6.21). The adjusted OR (for age and sex) was 3.04 (95% CI = 2.12-4.36; $p < 0.0001$).

To avoid statistical biases when comparing groups of different sizes, random samples of 395 patients without DISH and 195 patients with DISH were taken (Non-DISH:DISH ratio = 2:1). The AVS frequency in the Non-DISH group was 20.2% (n = 78) vs. 55.4% in the DISH group. The OR was 4.90 (95% CI = 3.36-7.14; $p < 0.0001$). The adjusted OR (for age and sex) was 3.48 (95% CI = 2.31-5.24: $p < 0.0001$).

Discussion

In 1950, Forestier and Rotés-Querol published a study about a condition named "senile vertebral ankylosing hyperostosis", which was distinguished as a different disease entity from spondyloarthropathy and ankylosing spondylitis[25]. In 1975, Resnick published an extensive study of the extraspinal locations of the condition, showing its high prevalence and suggesting its current name, "Diffuse Idiopathic Skeletal Hyperostosis (DISH)"[26].

Posterior longitudinal ligament ossification (OPLL) of the spine is most frequent in Japanese and other Asian populations; it was present in 50% of studied cases and considered as a DISH variant[27, 28].

Initially, Forestier and Rotés-Querol considered DISH a "spectacular but innocuous radiographic alteration" (Fig. 1)[29]. Progressively, spinal rigidity of varying degrees, dynamic overload of the mobile segment and space occupation syndromes (esophageal, tracheal or laryngeal compression, or medullar compromise with or without spinal fractures) were described[30-34]. Finally, hyperostosis was shown to be caused by manifestations in peripheral structures such as the shoulders, hips and feet[29].

The global prevalence, according to studies of different populations and countries (including Finland, Budapest, Israel, Korea, Naples, The Netherlands, South Africa and the USA), varies from 3.6% to 28%, depending on the diagnostic criteria and study population. This condition has been observed in 2.4 to 5.4% of patients older than 40 years of age and in 11.2% of patients above 70 years of age in radiological studies; these findings have been confirmed in necropsy series. DISH prevalence increases with age. Accordingly, the condition is present in 10% of men between 50 and 54 years of age and 36% of men above 75 years of age, and in 1.9% of women between 50 and 54 years of age and 26% of women above 75 years of age. The male/female prevalence ratio is 2:1 and decreases with age[15, 34-42].

The DISH classification criteria have not been fully defined, but classification requires at least 2 (according to Forestier) or 3 (according to Resnick) criteria in the presence of disk preservation and the absence of spondylitis and sacroiliitis. Utsinger considered 3 bridges to indicate a definitive diagnosis, with or without other involved entheses[16, 17, 24, 26, 43]. A recent attempt at consensus was positive only for exuberant new bone formation and the presence of intervertebral bridges. There was a perfect consensus with regard to the spine. There was no consensus on the constitutional, demographic and metabolic factors required for the definition of DISH[18].

In recent years, there has been a dramatic change in the understanding of aortic valve calcification mechanisms that led to acknowledgment of this disease as an active process similar to atherosclerosis[10-12].

Population studies such as the Helsinki Ageing Study, which included subjects between 55 and 71 years of age, and the Cardiovascular Health Study, a prospective study of subjects over 65 years of age in the United States, showed AVS prevalence rates between 21% and 26% in adults over 65 years of age and aortic stenosis prevalence rates of 2% to 7%, depending on the exact definition of outflow obstruction[10-12].

Extracellular matrix mineralization or calcification is regulated under physiological conditions and is generally limited to bone tissues. In pathological conditions, ectopic calcification can occur[1] when calcium and phosphate concentrations in the extracellular fluid exceed the saturation point (metastastic calcification)[2], consequent to the substitution or transition of damaged, degenerated or necrotic tissues due to mineral deposition or[3] due to mesenchymal cell transdifferentiation in bone tissues (ectopic calcification)[19].

The initiation process and the relationship between the metabolic conditions and new bone formation in DISH are unknown. Neoformation is believed to be the result

of abnormal osteoblastic growth activation. This increase in growth continues beyond bone function, due to several growth factors. Insulin-like growth factor I stimulates alkaline phosphate and type II collagen activity in osteoblasts, while growth hormones can induce the local production of insulin-like growth factor I and insulin-like growth factor binding proteins in chondrocytes and osteoblasts[20, 21]. Because ossification begins at certain sites, El Miedany et al. suggested that hypervascularization might indicate the process[1].

Several systemic hormones such as 1,25-dihydroxy-vitamin D, parathyroid hormone (PTH), insulin and leptin and local growth factors such as transforming growth factor-β (TGF-β) and bone morphogenic protein (BMP) have been studied. These might participate in the initiation and evolution of the ossification of the spine ligament (OSL) [13, 16, 19, 27].

The underlying mechanism of aortic stenosis calcification has been investigated in clinicopathological studies; these have shown that calcified deposits are associated with the mineralization of devitalized cells and subcellular vesicles, as well as with protein deposition in the extracellular matrix of the bone (ECM). These proteins, including osteocalcin, osteopontin, osteonectin, matrix Gla protein, bone morphogenic protein, matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), are present in cardiovascular calcification, including calcified valves, but are not present in normal cardiovascular tissue[23].

Although the results were adjusted for age and sex, the study had limitations. Prospective studies that register hypertension, diabetes and metabolic syndrome are required to rule out any bias in the studied association between DISH and AVS and to reinforce this hypothesis. The instability of the statistical results in comparisons of different groups (case/control ratio over 4) is another limitation. A second analysis with a control sample was used to demonstrate a closer relationship between the groups; this resulted in non-significant modifications.

In summary, the present study shows a statistically significant association between DISH and AVS, even after adjusting for age and sex. The biological plausibility of this association is based on the previously exposed risk factors, co-morbidities and physiopathological mechanisms. This finding encourages the performance of other studies in which variables that could reinforce the validity of this association are controlled, and basic studies that explore existing biological mechanisms behind the probable shared genesis of these manifestations.

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"La *falsedad* se refiere directamente a las cosas, en la medida en que el concepto de la mente no corresponde a ellas; la *mentira*, a las palabras, en la medida en que no corresponden al alma; la *impostura*, a los hechos, en la medida en que las palabras, los actos y el silencio buscan engañar al otro, es decir, hacerle creer lo falso en beneficio del que engaña y con el objeto de satisfacer alguna pasión innoble de éste". Definiciones hechas por Tommaseo*.

Citadas por Leonardo Sciascia en: Puertas Abiertas. Barcelona: Tusquets Editores, 2005; p 36

* Niccolò Tommaseo (1802-1874), escritor y lingüista italiano.