Diagnostic Performance of Doppler-Echocardiography in the Follow-Up of Patients With Toxic Oil Syndrome

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Introduction and objectives. Toxic oil syndrome is an epidemic, multisystemic disease that appeared in Spain in 1981, and was caused by the consumption of rapeseed oil denatured with 2% aniline. The disease is similar to eosinophilia-myalgia syndrome. One of the cardiovascular disorders caused by this syndrome is pulmonary hypertension. We conducted a study to assess the validity of our indications for echocardiography in the follow-up of cardiovascular disorders in patients with this disease.

Patients and method. These patients are followed at our center with a standardized protocol for annual check-ups. From December 1997 through July 2002, a total of 1993 patients were examined. In this period we performed a total of 487 echocardiographic studies in 424 patients. The clinical records were reviewed to assess the indications for echocardiography according to the most recent guidelines for the clinical application of echocardiography of the American College of Cardiology and American Heart Association, and the indications were grouped into several categories. The diagnosis was recorded from the cardiologist's reports at the hospital where echocardiography was done. We calculated the sensitivity, specificity and positive likelihood ratio.

Results. 67% of the echocardiographic examinations were indicated to investigate possible pulmonary hypertension. About one-tenth of the studies (476 studies, 9.9%) led to a diagnosis of pulmonary hypertension. Sensitivity was highest (83%) for suspected pulmonary hypertension. Specificity was very high for most of the other indications.

Conclusions. This study does not allow us to draw general conclusions about the cardiovascular disorders associated with toxic oil syndrome. However, echocardiography appears to be a good follow-up technique to diagnose complications such as pulmonary hypertension in these patients.

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Rendimiento diagnóstico de la indicación de ecocardiografía en el seguimiento de los pacientes con «síndrome del aceite tóxico»

Introducción y objetivos. El «síndrome del aceite tóxico» es una enfermedad multisistémica, aparecida en España en 1981, debida al consumo de aceite de colza desnaturalizado con un 2% de anilina. Tiene similitudes con enfermedades como el síndrome eosinofilia-mialgia. La hipertensión pulmonar es una de las alteraciones cardiovasculares secundarias a este síndrome. Nuestro objetivo era conocer la validez de nuestras indicaciones de ecocardiografía para el seguimiento de las afecciones cardiovasculares en esta enfermedad.

Pacientes y método. Nuestro centro realiza el seguimiento de estos enfermos con visitas anuales protocolizadas. Entre diciembre de 1997 y julio de 2002 se examinó a 1.993 pacientes. En este período se realizaron 487 ecocardiogramas a 424 pacientes. Las indicaciones se recogieron de las historias clínicas y se utilizaron las últimas guías de práctica clínica (American College of Cardiology/American Heart Association) para agruparlas en varias categorías. Los diagnósticos se obtenían del informe de cardiología del hospital donde se realizaron dichas pruebas. Se calcularon la sensibilidad, la especificidad y la razón de probabilidades diagnósticas.

Resultados. El 67% de los ecocardiogramas fue solicitado por sospecha de hipertensión pulmonar, que fue diagnosticada en el 9,9% de las pruebas realizadas (n = 476). La sensibilidad más alta (83%) fue la referida a sospecha de hipertensión pulmonar. La especificidad fue muy alta para la mayor parte de las indicaciones.

Conclusiones. Aunque este estudio no permite extraer conclusiones generales sobre las enfermedades cardiovasculares asociadas al síndrome tóxico, la ecocardiografía aparece como una técnica adecuada para el seguimiento de estos pacientes y para la detección de complicaciones como la hipertensión pulmonar.

ABBREVIATIONS

TOS: toxic oil syndrome.
PHT: pulmonary hypertension.
HT: arterial hypertension.
ACC/AHA: American College of Cardiology/ American Heart Association.
CD_{CO}: pulmonary diffusion coefficient.

Palabras clave: *Síndrome del aceite tóxico. Ecocardiografía. Hipertensión pulmonar.*

INTRODUCTION

Toxic oil syndrome (TOS) is a new multisystemic disease that appeared in Spain in 1981, caused by the consumption of rapeseed oil denatured for industrial use with 2% aniline but then fraudulently sold as cooking oil. The disease acquired epidemic proportions and affected more than 20 000 people, leading to over 300 deaths in the first years.[1,2] The pathogenesis of TOS remains unclear, although evidence exists to suggest an underlying autoimmune mechanism.[3] However, some patients with TOS have been found to have a genetic susceptibility due to a particular metabolic profile in N-acetyltransferase-2.[4]

Toxic oil syndrome presented in three clinical phases: acute, intermediate and chronic. The acute phase lasted 2 months and was characterized by eosinophilia, pulmonary edema, myalgias, fever and rash. The intermediate phase was characterized by weight loss, edema, abnormal liver function, sicca syndrome, pulmonary hypertension (PHT), arterial hypertension (HT), thromboembolism and persistent myalgia. The chronic phase (after 4 months) was characterized by peripheral neuropathy, abnormal liver function, scleroderma and pulmonary hypertension.[5,6]

The clinical course of TOS resembles that of other autoimmune diseases such as progressive systemic sclerosis, Sjögren syndrome, graft-versus-host disease and eosinophilia-myalgia syndrome.[7]

Histologic alterations in the coronary parenchyma were found in the most seriously affected patients. These changes included endothelial injury in coronary arteries (proliferative myointimal degeneration), ischemia, myocardial lesions (secondary fibrosis and inflammation) and conduction disturbances (e.g. fibrinoid degeneration of the sinus node). In some patients these alterations produced mechanical or electric destabilization of heart activity. Patients have presented with syncope, heart failure, angina or electrocardiographic alterations (sinus tachycardia, left or right bundle branch block, atrial dilation, and repolarization abnormalities).[8-11]

Pulmonary hypertension is of particular interest as it occurred in 20% of patients with TOS when the epidemic began,[12-14] whereas the incidence of PHT in the general population is 1-2 cases per million.[15,16] In some patients, PHT symptoms disappeared spontaneously. Some patients died, and in others PHT developed slowly into a chronic illness.[12-14] Research into this particular clinical manifestation of PHT shows it is clinically and anatomopathologically indistinguishable from primary PHT.[10,17]

Our center (the Centro de Investigación para el Síndrome del Aceite Tóxico) is the only one in the world devoted to TOS research. The present report describes work carried out as part of the care and research roles of the center's clinical unit at the Hospital Carlos III (Madrid, Spain) since 1997, when an on-going clinical follow-up study began. Patients are assigned to a protocol for annual clinical examinations that includes medical history, physical examination and basic complementary tests (laboratory tests, electrocardiography, respiratory function tests and chest x-ray). Further diagnostic tests such as echocardiography are considered after the clinical evaluation and test results are reviewed. The Center strives to improve the care and management of patients with TOS, and to contribute to the knowledge of TOS and its natural history so that this information can be used for patients with TOS or other similar diseases.

The objective of this study was to evaluate the validity of our indications for echocardiography for patients with TOS and suspected PHT or heart disease, and to assess their role in follow-up for TOS.

PATIENTS AND METHODS

Population and cohort

Of the 1993 patients with TOS seen at our unit between December 1997 and July 2002, 424 who had undergone at least one echocardiographic examination were recruited. Women accounted for 74.3% of the cohort and average ages were 51.8 years for women and 48.1 years for men. A total of 487 echocardiographic examinations were performed during the study period.

Variables

Indications for echocardiography were recorded from the patients' clinical records. We used American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the clinical application of electrocardiography[18] (Table 1) to classify indications as follows: PHT study (subcategories: annual PHT follow-up; suspected PHT due to hypoxemia and/or reduction in pulmonary diffusion coefficient (DL_{CO}) in the absence

of a respiratory pathology;[19,20] PHT episode during the acute phase of TOS that was not followed up; suspected PHT due to chronic hyperventilation in the absence of any other infection; suspected PHT due to dilation of the pulmonary arteries; suspected PHT due to right bundle branch block; suspected PHT due to dilation of the right heart chambers), pericardial disease, unexplained heart murmurs, valvular heart disease, functional evaluation of heart failure, chest pain study following inconclusive initial examination, functional evaluation of ischemic heart disease, functional evaluation of hypertensive cardiomyopathy, cardiomegaly, unexplained recurrent syncope and collagen vascular disease related to suspected heart disease.

The hospital echocardiography service diagnostic report was used as the «gold standard.» Two-dimensional transthoracic echo-Doppler examinations were performed on patients using an ATL-PHILIPS HDI-5000 unit. To compare indications with diagnoses, the diagnoses were categorized as: absence of alterations, hypertensive cardiomyopathy, pulmonary hypertension, valvular heart disease, ischemic heart disease, pericardial effusion, dilation of the chambers, diastolic dysfunction, left ventricular hypertrophy.

Pulmonary hypertension was diagnosed according to the criteria of the World Symposium on Primary Pulmonary Hypertension, held in France in 1998.[21] Diagnoses were made by evaluating the right ventricle-right atrium gradient using continuous wave Doppler, then adding 10 mm Hg to this figure. One patient needed contrast enhancers (LEVOVIST®, Schering) due to a poor signal of tricuspid valve failure and suspected hypertension.

Both the classified indications and diagnoses were made by different, blinded operators

Indications were contrasted with our established «gold standard» (diagnosis by echocardiography) using 2 2 contingency tables. We calculated:

– Sensitivity: the probability that a patient with the disease (diagnosed by echocardiography) would be classified appropriately with a positive result; i.e., that the patient would be referred for echocardiographic examination on the grounds of a possible positive diagnosis.[22]

– Specificity: the probability that a patient without the disease (diagnosed by echocardiography) would be classified appropriately with a negative result; i.e., that the patient would be referred for echocardiographic examination on the grounds of a possible negative diagnosis.[22]

– Positive likelihood ratio, with a 95% confidence interval: this is an index of the value of a diagnostic test that, as opposed to the positive or negative predictive values, does not depend on the proportion of patients in the sample studied. The coefficient is obtained by dividing the rate of true positive results by the rate of false positives. The higher the value of the coefficient (>1), the better the test is able to diagnose the presence of the disease,[23] or in our study, to indicate echocardiographic examination for possible diagnosis.

Statistical data were analyzed with SPSS software and the Two By Two Analyzer program.

TABLE 1. **Published ACC/AHA guidelines for the application of echocardiography18**

I	Heart murmurs and valvular heart disease
II	Chest pain
III	Ischemic heart disease
IV	Cardiomyopathy and left ventricular function evaluation
V	Pericardial diseases
VI	Mass and tumor of the heart
VII	Diseases of large vessels
VIII	Pulmonary disease
IX	Systemic hypertension
X	Neurological disorders and other cardioembolic conditions
XI	Arrhythmia and palpitations
XII	Echocardiography of the critically ill patient
XIII	Echocardiography in the adult patient with congenital heart disease
XIV	Echocardiography of the pediatric patient

ACC/AHA indicates American College of Cardiology/American Heart Association.

RESULTS

Only 476 of the 487 echocardiograms performed were included in the study. The remaining 11 were excluded because the patient's clinical record was not available.

More than one echocardiogram was done in 38 patients, further reducing the total number of patients to 424. Furthermore, 55 patients were examined for more than one indication and 34 patients were diagnosed with conditions classified in more than one category. Consequently, the number of indications was 534 and the number of diagnoses was 528 (Tables 2 and 3).

The distribution of the number of echocardiograms performed during the study period follows a downward curve. Follow-up began in December 1997, when three tests were performed. In 1998 and 1999, most of the patients attended for the first time and the number of echocardiograms requested (138 and 124, respectively) was greater in an initial effort to identify cases of PHT. Later, the number of new patients decreased and annual protocol check-ups increased. This led to a further decrease in the number of echocardiograms requested (88 in 2000 and 2001, and 35 in 2002).

More than half of the echocardiograms (67%) were requested for suspected PHT. Suspicion of PHT was based on the categories shown in Table 4. The most frequent category was suspected PHT due to hypoxemia and/or reduction of the DL_{CO} (in the absence of another pulmonary condition that might account for the

TABLE 2. **Toxic oil syndrome (TOS): categories of indications for echocardiography 1997-2002**

Indications for echocardiography TOS population	No. indications (% echocardiographic in theexaminations)[b]	AHA categories[a]
Pulmonary hypertension study	319 (67)	VIII
Pericardial disease	9 (1.9)	III
Unexplained heart murmurs	54 (11.3)	I
Valvular heart disease study	29 (6.1)	I
Functional evaluation of heart failure	12 (2.5)	IV
Chest pain study	11 (2.3)	II
Functional evaluation of ischemic heart disease	15 (3.2)	III
Functional evaluation of arterial hypertension	57 (11.9)	IX
Peripheral ischemia of suspected cardiac origin	1 (0.2)	X
Illnesses of large vessels	9 (1.9)	VII
Other	7 (1.5)	
Marfan syndrome	1 (0.2)	I-VII
Ventricular septal defect	1 (0.2)	XIII
Syncope	3 (0.6)	XI
Obstructive cardiomyopathy	1 (0.2)	IV
History of myopericarditis (acute phase TOS)	1 (0.2)	IV
Total indications	523	
Total echocardiographic examinations	476	

AHA indicates American Heart Association.
[a]Table 1. [b]Percentage of echocardiographic examinations requested for each of the indications. Any one echocardiography may have been requested for more than one indication.

TABLE 3. **Toxic oil syndrome: classification of cardiovascular diseases diagnoses, 1997-2000**

Diagnosis	No. diagnoses (% echocardiographic examinations)[a]
Normal	270 (54.5)
Hypertensive cardiomyopathy	98 (19.8)
Valvular heart disease	68 (13.7)
Pulmonary hypertension	49 (9.9)
Pericardial effusion	13 (2.6)
Left ventricular hypertrophy	10 (2)
Dilatation of cavities	9 (1.8)
Ischemic heart disease	2 (0.4)
Other diagnoses	19 (3.8)
Atrial septum aneurysm	1 (0.2)
Primary diastolic dysfunction	8 (1.6)
Total diagnoses	528
Total echocardiographic examinations	476

[a]Percentage of echocardiographic examinations in which each diagnosis appears. Any one echocardiography may be associated with more than one diagnosis.

findings). The second most frequent indications were for functional evaluation of patients with hypertension and for unexplained heart murmurs. Each of these indications accounted for nearly 11% of the patients. Valvular heart disease was the indication in 6%, and ischemic heart disease in 3% of the patients. Other indications accounted for less than 3% of the echocardiograms (Table 2).

More than half of the echocardiographic reports recorded were normal (54.5%). Diagnoses of hypertensive and valvular heart disease accounted for 18.8% and 13.5%, respectively. Pulmonary hypertension was diagnosed in 49 patients (9.9%) of the tests (Table 3) and was mild in 54.2% of patients.

Table 4 presents data on sensitivity, specificity and diagnostic probability together with the 95% confidence intervals for indications when compared to diagnoses. The highest level of sensitivity (83%) was associated with an indication for echocardiogram for suspected PHT (for any of the causes listed in Table 1). Sensitivity of this indication was analyzed for the period 1998-2002; the resulting values ranged from 75% to 100%, and confidence intervals ranged from 39% to 100%. However, it was found that for some years, some of the values used to calculate sensitivity were low, therefore caution is needed in interpreting these results on a year-by-year basis.

Specificity was very high for most of the indications (Table 4). Annual PHT follow-up, valvular heart disease study, and suspected hypertensive cardiomyopathy, were prominent among indications for which the confidence interval of the coefficient of probabilities did not include the null value (Table 4).

DISCUSSION

Toxic oil syndrome is a new disease that appeared in 1981, and its course and natural history are unknown. Pulmonary hypertension and heart conditions are still present in patients with TOS after 22 years' evolution. Consequently, follow-up of these patients continues to be relevant.

We have only studied part (21.3%) of the total TOS cohort. Although severity of illness was not an inclusion criterion, we recognize that bias may have been introduced due to selection of patients' experience an adverse clinical course. However, this did not occur in other studies (with the same group of patients), nor do we believe it would affect our objectives. Analysis of the distribution of the number of echocardiograms requested during the study period shows that this was greatest in the first year, and gradually decreased thereafter. This is because the initial phase of follow-up concentrated on distinguishing between patients, making a larger number of tests essential. Echocardiograms ordered in later years were to follow up on earlier illnesses, to evaluate patients included in the study at a later date, or to evaluate patients whose clinical situations had changed. The criteria used to request echocardiographic studies (whether in the initial examination or on subsequent

TABLE 4. **Validity of the indications for echocardiography in Toxic oil syndrome. Sensitivity, specificity and positive likelihood ratio**

Indication/diagnosis	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)
PHT study/PHT	83 (69-92)[a]	35 (30-40)[a]	1.3 (1.1-1.4)[a]
Annual follow-up for PHT	54 (39-68)[a]	98 (96-99)[a]	23.2 (12-44.5)[a]
Hypoxemia and/or reduced DL_{CO}	19 (9-33)	64 (59-69)	0.5 (0.3-0.9)
PHT in acute phase without follow-up	10 (4-23)	79 (75-83)	0.5 (0.2-1.1)
Chronic hyperventilation	0 (0-7)	96 (94-98)	0 (0.3-2.6)
Dilation of pulmonary arteries	0 (0-7)	96 (96-99)	0 (0-4.2)
Right bundle branch block	2 (0-12)	98 (96-99)	0.9 (0.2-5.7)
Dilation of right cavities	0 (0-7)	98 (97-99)	0 (0.1-6.1)
Pericardial disease/pericardial effusion	7 (0-38)	98 (96-99)	7.9 (4.9-12.9)
Unexplained heart murmurs/valvular heart disease	14 (7-26)	89 (86-92)	1.3 (0.7-2.5)
Valvular heart disease study/valvular heart disease	25 (16-38)	97 (95-98)	8 (4.1-15.6)
Heart failure evaluation/dilation of cavities	0 (0-33)	97 (95-98)	0 (0.2-14.9)
Suspected ischemic heart disease/ischemic heart disease	0 (0-84)	94 (92-96)	0 (0.5-16.6)
Evaluation HT/hypertensive cardiomyopathy	41 (31-52)	95 (92-97)	7.9 (4.8-12.9)

LR+ indicates positive likelihood ratio; DL_{CO}, pulmonary diffusion coefficient; HT, arterial hypertension; PHT, pulmonary hypertension; CI, confidence interval.
[a]95% CI>1.

visits) have not changed during the study, which means that these numerical differences are unlikely to affect the results.

To avoid any possible bias due to the application of non-standardized diagnostic criteria, we adopted the ACC/AHA clinical application of echocardiography categories[18] (Tables 1 and 2). The most frequent indication was suspected PHT, present in 67% of the echocardiograms requested. This fully met our expectations for four reasons: *a)* the incidence of PHT in acute phase TOS was 20%, versus 1-2 cases per million in the general population; *b)* the evolution of these patients was heterogeneous: prevalence decreased to 3.5% in 1983,[12] decreased to 1.5% in 1985[24,25] and rose again to 2.4% in 1998.[26] The initial decrease in prevalence was due to the spontaneous disappearance of symptoms, or the death of some patients. However, the increased prevalence in 1998 may be explained by our improved ability to diagnose PHT since the follow-up study began in 1997; *c)* there are no symptoms in the early stage of PHT, which is usually marked by a form of progressive dyspnea. When PHT becomes observable it is already advanced;[15,16]and *d)* PHT is a severe condition and therapeutic interventions modify the prognosis.[15,16] Given these circumstances, and the fact that patients with TOS are affected by a new syndrome whose course is unknown, this complication was extensively investigated in the patients in our cohort.

The second most frequent indication was for unexplained heart murmurs, present in 11.3% of the echocardiograms. Unexplained heart murmurs, and the study of previously diagnosed valvular heart disease, cardiomegaly and recurrent syncope, were the indications that were probably most directly related to this syndrome. In TOS, conditions such as endomyocardial fibrosis, which can lead to valvular lesions and heart murmurs, have been found. Although few cases of clinical myocardial disease have been found, histologic abnormalities of the myocardium were a constant finding in the pathology reports of patients who died of TOS.[8-10] This has led to greater efforts in the diagnosis of cardiomegaly. Finally, syncope might be due to fibrosis and necrosis of the conduction system which has been found in the heart tissue of some patients who have died of TOS.[8,9]

The diagnoses made by the Hospital Carlos III cardiology-echocardiography service were adopted as the «gold standard.» Analysis of the distribution of diagnoses by year (unpublished data) does not reveal any trends or possible bias. The risk of classification errors arising from the echocardiograms was accepted, but it was decided to use these as «gold standard» because of the quality of the cardiology-echocardiography service.

Pericardial effusion has not been established as a complication characteristic of TOS, and the 6 echocardiograms requested for this indication were performed as part of the follow-up of previously recognized episodes of effusion. The percentage of patients diagnosed as having pericardial effusion was higher than expected (2.6% of the echocardiograms). Twelve of these were discovered by chance, and all were mild cases.

Several cardiovascular risk factors (obesity, dyslipidemia, smoking and diabetes) are highly prevalent in patients with TOS.[26] However, the prevalence of essential HT in 1998 was 34%,[26] almost exactly that found in the Spanish population in 1999 (33%).[27] Hypertensive cardiomyopathy was diagnosed in 19% of the echocardiograms.

Finally, our results for sensitivity, specificity and the likelihood ratio (Table 4) show that PHT was the

indication with the greatest sensitivity (83 which demonstrates that the number of patients with suspected PHT who in fact developed this complication was high. Moreover, the positive likelihood ratio was 1.3 and the confidence interval did not include the null value. This means that a patient in our cohort with suspected PHT, for any of the pre-established causes (Table 2), has a >30% probability of developing PHT (true positive) than of not developing it (false positive).

Analysis of indications for follow-up examinations to detect PHT during the study period shows that sensitivity remained high (75%-100%) and that the confidence interval remained stable. This demonstrates that the policy of requesting tests had been applied consistently throughout the study period.

Those illnesses for which the echocardiogram gave a positive likelihood ratio with a confidence interval that did not include the null value were: PHT follow-up, valvular heart disease, pericardial effusion and suspected hypertensive cardiomyopath.

The low level of sensitivity of echocardiography to evaluate heart failure, suspected ischemic heart disease and suspected PHT in cases of chronic hyperventilation, dilation of the pulmonary arteries or dilation of the right cavities, is surprising. This may be due to the low number of tests requested for these indications. Subsequent studies will be needed in order to confirm these data.

CONCLUSIONS

The natural history of this disease is unknown, therefore we cannot draw conclusions as to the future evolution of patients with TOS with or without cardiovascular disease. Consequently, we must continue our follow-up of these patients in order to improve their care and to detect and prevent any new complications as early as possible.

Even though we are unable to draw general conclusions about the range of cardiovascular diseases that affect patients with TOS, this study is a first step and establishes a solid foundation for future research.

Echocardiographic examinations would appear to be appropriate for this purpose, and except in isolated cases, we will continue to perform them as they have proved their value in the diagnosis of the more severe complications associated with TOS, such as PHT. These results confirm our initial policy decision to screen carefully for and follow up patients with PHT or suspected PHT. Although comparative studies of echocardiography versus catheterization for the diagnosis of PHT in this cohort do not exist, unlike the case for other diseases such as scleroderma,[28] it seems reasonable to adopt a non-invasive technique in the follow-up of TOS. Future studies may evaluate other diagnostic techniques.

Similarities between TOS and other diseases such as eosinophilia-myalgia syndrome increase the value of any conclusions we might reach through the study and follow-up of patients with toxic oil syndrome.

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