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Original Article

Variation in Cardiac Screening and Management of Carcinoid Heart Disease in the UK and Republic of Ireland

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Abstract

Aims: Screening for carcinoid heart disease is an important, yet frequently neglected aspect of the management of patients with neuroendocrine tumours (NETs). Screening is advocated in international guidelines, although recommendations on the modality and frequency are poorly defined. We mapped current practice for the screening and management of carcinoid heart disease in specialist NET centres throughout the UK and Republic of Ireland.
Materials and methods: Thirty-five NET centres were invited to complete an online questionnaire outlining the size of NET service, patient selection criteria for carcinoid heart disease screening and the modality and frequency of screening.
Results: Twenty-eight centres responded (80%), representing over 5500 patients. Eleven per cent of centres screen all patients with any NET, 14% screen only patients with midgut NETs, 32% screen all patients with liver metastases and/or carcinoid syndrome and 43% screen all patients with evidence of syndrome or raised urinary/serum/plasma 5-hydroxyindoleacetic acid (5HIAA). The mode of screening included clinical examination, echocardiography and biomarker measurement: 89% of centres carry out echocardiography, ranging from at initial presentation only (24%), periodically without clearly defined intervals (28%), annually (36%) or less than annually (12%); three centres use a scoring system to report their echocardiograms. Fifty per cent of centres utilise biomarkers for screening (chromogranins, plasma/urinary 5HIAA or most commonly N-terminal pro-brain natriuretic peptide) at varying time intervals.
Conclusion: There is considerable heterogeneity across the UK and Ireland in multiple aspects of screening and management of carcinoid heart disease.

Key words: Carcinoid heart disease; management; neuroendocrine; screening

Introduction

Carcinoid heart disease is a complication of metastatic neuroendocrine disease and occurs in 20–50% of patients with the carcinoid syndrome [1,2]. The cardiac manifestations of neuroendocrine tumours (NETs) are a consequence of tumour secretion of vasoactive substances such as serotonin, prostaglandins, tachykinins and histamine [3,4]. Hepatic metastases enable these substances to reach the right heart without being inactivated [5]. Rarely, carcinoid heart disease may occur in the absence of liver metastases, for example, in primary ovarian NETs, when the ovarian venous drainage bypasses the portal venous system [6,7].

Carcinoid heart disease can be clinically silent, with no symptoms or signs of disease, even in patients with advanced pathology [8,9]. However, cardiac involvement has significant prognostic implications; a 3 year survival for patients with carcinoid heart disease of 31% compared with 68% for those with no cardiac involvement [10]. The prognosis has improved in recent years, with the median survival about 4 years from diagnosis [11], but this is still significantly shorter than the median survival duration of 10 years of patients with grade 1 NETs [12]. As moderate to severe right ventricular dilatation and New York Heart Association Class III–IV symptoms are associated with

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increased mortality [11], screening for carcinoid heart disease is an important component of disease monitoring in patients with NETs.

UK and Ireland Neuroendocrine Tumour Society (UKINETS) guidelines recommend that indications for screening for carcinoid heart disease include the presence of a midgut NET, with or without hepatic metastasis, or the presence of carcinoid syndrome [13]. Measurement of serum N-terminal pro-brain natriuretic peptide (NT-proBNP), a surrogate marker of carcinoid heart disease [14], is advised, with echocardiography reserved for those with a serum NT-proBNP concentration >260 pg/ml. By contrast, the 2012 European Neuroendocrine Tumor Society (ENETS) guidelines advocate biochemical criteria rather than clinical or radiological criteria as the trigger to initiate cardiac screening [15]. The authors recommend the use of chromogranin A and urinary 5-hydroxyindoleacetic acid (5HIAA) and advise screening on a regular basis, but do not state the optimum frequency. The North America Neuroendocrine Tumor Society (NANETS) also recommend using biochemical criteria, but use NT-proBNP as an adjunct to determine who requires echocardiography for carcinoid heart disease screening without stating screening frequency [16].

Considering the discordance between guidelines regarding 'who, when and how' for cardiac screening, we sought to map current UK and Republic of Ireland practice for carcinoid heart disease screening and management in specialist NET centres. Further to this, we propose that an algorithm for the screening of carcinoid heart disease should be developed and introduced.

Materials and Methods

Thirty-five specialist NET centres in the UK and Republic of Ireland were invited by email to complete an online questionnaire (www.surveymonkey.com) between August and September 2013. Centres were identified from UKINETS committee members and the NET Patient Foundation Website (http://www.netpatientfoundation.org/net-expertise/net-centers/). The questionnaire consisted of 10 questions relating to respondent demographics, population screened for carcinoid heart disease, mode and frequency of screening, access to cardiology expertise and criteria for consideration of valve surgery. The questions required a mixture of multiple choice and short answer responses (Figure 1). Questionnaires were completed by consultants working within the NET specialist service. All responses were kept confidential.

Results

Twenty-eight centres (80%) completed the survey, representing a total caseload of over 5500 patients. The experience of each centre varied from less than 5 years to more than 20 years, reflecting more than 300 centre years of clinical experience with NETs. The NET patient caseload of each centre ranged from less than 50 patients to greater than 300, with 50% of centres managing in excess of 200 patients (Figure 2).

Screening for carcinoid heart disease occurred in all responding centres, although the clinical characteristics of the population screened differed significantly between centres. Twelve centres screen only NET patients with carcinoid syndrome, nine centres screen patients with radiological evidence of liver metastases or symptoms of carcinoid syndrome, four centres screen all patients with midgut NETs irrespective of the presence/absence of carcinoid syndrome/liver metastases and three centres screen all NET patients (Figure 3).

The method used to screen for carcinoid heart disease also varied enormously between centres. Sixty-eight per cent ($n = 19$) of centres use clinical examination as part of their screening process for carcinoid heart disease. Eighty-nine per cent of centres ($n = 25$) carry out transthoracic echocardiography to screen patients for carcinoid heart disease with wide variation in the frequency of scans; 21% at baseline, 32% annually, 25% on an ad hoc basis and 11% less than annually. All centres receive a standard clinical echocardiogram report with the exception of three centres, which use an echocardiographic scoring system to quantify carcinoid heart disease. The use of biomarkers for the screening of carcinoid heart disease varies between centres, with one centre using it as the sole method of screening and others using it as an adjunct to clinical examination and/or echocardiography. In the 50% of centres ($n = 14$) that routinely measure biomarkers, 50% ($n = 7$) measure NT-proBNP, 14% ($n = 2$) measure 5HIAA, 7% ($n = 1$) measure chromogranins and 21% ($n = 3$) measure a combination of the above. The frequency of biomarker measurement varies from biannually to once every 2 years. See Table 1 for more details.

A cardiology service with expertise in carcinoid heart disease is not available at all centres, with 50% of centres ($n = 14$) lacking cardiology input to their multidisciplinary team and 32% of centres ($n = 9$) referring patients to their local general cardiology service. Eighty-six per cent of centres ($n = 24$) refer all patients with evidence of carcinoid heart disease to a cardiologist, with the remainder referring only those who are symptomatic, have moderate to severe valvular dysfunction, right ventricular failure or cardiac metastases. Patients with established carcinoid heart disease are scanned at varying frequencies ranging from less than annually (35%), annually (48%), every 6 months (13%) and more frequently than every 6 months (4%).

Criteria for referral for valve surgery varied widely, with some centres never referring patients (expressing the view that 'surgery is not helpful in these patients') and others referring all patients with carcinoid heart disease with a prognosis greater than 1 year. There was a general feeling among respondents that decisions regarding valve surgery are difficult and must be made in a multidisciplinary setting.

Discussion

This study shows that currently there is wide variation in clinical practice with respect to screening methods for