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Chapter 3

Current Practise of Testing for Inherited Thrombophilia

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SUMMARY

Background:
The usefulness of testing for inherited thrombophilia is subject to debate and it is unknown how contradicting opinions influence the daily practice.

Methods:
We have performed a survey among physicians that ordered 2000 consecutive thrombophilia tests in the Netherlands.

Results:
Thrombophilia tests were ordered for numerous indications by medical doctors from various disciplines. Venous thromboembolism was the reason for testing in 58% of all ordered tests; other indications were arterial thrombotic disease (23%) and pregnancy related vascular complications (17%). The physicians who ordered the tests admitted that a large proportion (77%) of the tests had not led to management decisions in that particular patient.

Discussion:
The absence of management studies for individuals with thrombophilia has probably led to widespread testing in numerous clinical settings, in which a large proportion of these costly tests have no management consequences.
INTRODUCTION

About half of all episodes of venous thromboembolism (VTE; i.e. deep-vein thrombosis and pulmonary embolism) is elicited by an acquired clinical risk factor, such as recent surgery, immobilisation or pregnancy. Before the discovery of antithrombin deficiency in 1965, the other half remained unexplained. In the decades thereafter, we have witnessed the emergence of numerous mainly inherited coagulation abnormalities, such as deficiencies of protein S and protein C, the factor V Leiden mutation (APC resistance), the prothrombin 20210A mutation and elevated levels of clotting factor VIII. These thrombophilias can be identified in at least 50% of cases with idiopathic VTE, thereby providing an explanation for a previously poorly explained disease. However, despite strong associations between thrombophilia and a first VTE, thrombophilia is, at best, a weak predictor for recurrent VTE.

Probably encouraged by the high prevalence in VTE, testing for inherited thrombophilia was also performed in many studies on arterial thrombosis such as myocardial infarction and ischemic stroke. Although some studies have found associations between thrombophilia and arterial events at younger age, thrombophilia was not associated with these diseases in unselected patient groups.

Finally, the hypercoagulable state induced by inherited thrombophilia, has been linked to an increased risk of unexplained recurrent miscarriage, stillbirth and other pregnancy related vascular complications such as preeclampsia and the HELLP syndrome.

At present, there are no clinical trials that compare different management strategies for patients with thrombophilia and vascular events or an estimated high risk of vascular events. Therefore, management recommendations for patients with inherited thrombophilia, such as in the 7th ACCP Guideline for Antithrombotic Therapy for Venous Thromboembolic Disease, are usually graded level 2, meaning that individual patients’ (or physicians’) values may lead to different choices. This can lead to different and, not rarely, contradicting hospital guidelines on who to test and on the management consequences of the test results. In this study, we have investigated the current practise of testing for inherited thrombophilia in the Netherlands; in particular, who orders the tests, what are the reasons for testing, and what are the management decisions made on the basis of the test results?

METHODS

Two thousand consecutive patients were identified in whom tests for APC resistance, factor V Leiden, prothrombin 20210A mutation, antithrombin, protein C or protein...
S activity were ordered between November 2003 and March 2004. These tests were performed in the laboratory of a non-profit organisation that provides nationwide specialised diagnostic facilities for regional or hospital laboratories (Sanquin Diagnostic Services, Amsterdam, The Netherlands). The tests of the selected patients originated from 61 mainly non-academic hospitals or regional diagnostic centres throughout the Netherlands. For each patient, a short multiple-choice questionnaire was sent to the ordering physicians that included questions regarding their medical specialty, reasons for testing and presence and nature of management decisions made in that particular individual. The study was approved by the institutional Medical Ethics Committee.

RESULTS

Of a total of 2000 sent questionnaires, 63% was returned. One hundred thirty-five returned questionnaires could not be analysed, because it was unclear which physician had actually ordered the tests or because only antithrombin was determined as a measure of liver synthesis capacity. Of the remaining 1134 tested patients, 64% were women (median age 38 years, inter-quartile range (IQR) 30-50) and 36% were men (median age 51 years, IQR 41-59).

Venous thromboembolism was the reason for testing in 42% of patients; 20% had had a single episode of deep-vein thrombosis or pulmonary embolism, 4% had had a single episode in combination with a familial thrombotic predisposition and 8% had had recurrent venous thromboembolism (Table). Twenty-three percent of patients were tested because of a history of arterial thrombotic disease. Of those, 46% were aged over 50 years at time of testing. Pregnancy related vascular events and a familial predisposition for VTE in asymptomatic patients was the reason for testing in 17 and 16%, respectively. The table provides further details on the reasons for testing.

Internists requested testing in 37% of the patients, followed by gynaecologists (20%), neurologists (15%) and general practitioners (13%). In the group of asymptomatic patients with a familial predisposition, 65% of tests were ordered by general practitioners. Neurologists requested 58% of tests in the group with arterial thrombotic disease, while 95% of the tests in patients with obstetrical complications were ordered by obstetricians.

The physicians that ordered the tests responded that in 23% of patients, the tests had directly altered patient management (Table). In another 48% of patients, the tests would have influenced patient management if thrombophilia would have been present. The tests had had no influence in 24% of patients and in 5% it was uncertain whether or not the test would have altered the physician’s policy if thrombophilia would have been present. The observed and intended management decisions are specified in the Table.
In this survey, 60% of the tests for inherited thrombophilia were performed because of venous thromboembolism, either in the tested patient (42%) or in a relative of the tested patient (16%). The remainder of tests were performed in patients with other...
vascular conditions in which the association with inherited thrombophilia is either weaker or questionable. More striking is the finding that in 77% of tested patients, the thrombophilia tests did not alter management of that particular patient, which raises concern regarding the necessity of these costly tests. We cannot exclude the possibility that physicians felt inclined to justify the testing by expanding the consequences further than they originally had. If so, the proportion of tests that would not alter management would probably have been even larger.

A limitation of this survey is its retrospective nature. Even though we sent out the questionnaires within 6 months after the tests were performed, some recall bias may have been present. The tests originated mainly from general (non-academic) hospitals and general practitioners throughout all parts of The Netherlands. As academic hospitals perform these tests in their own laboratories, our findings do not reflect academic testing practise. However, since only 8 out of 104 Dutch hospitals are academic hospitals, we believe that the present study provides an accurate insight into the current practise of testing for inherited thrombophilia and it is plausible that these results can be extrapolated to many other countries.

Even when thrombophilia tests do change patient management, it is debatable whether or not these decisions are rational. Ideally, diagnostic and management strategies should be tested in randomised controlled trials in order to ascertain their validity. Unfortunately, in the field of inherited thrombophilia no such trials exist. Therefore, management guidelines are generally based on decision models that extrapolate estimated risks and risk-benefit ratios of various interventions 10, and therefore, management and testing guidelines will remain open to debate.

How this debate influences physicians that are confronted with patients in whom they consider to test is uncertain. We feel that the results of this survey indicate that testing for inherited thrombophilia is widespread, is performed in numerous different clinical settings and remains without consequences in a large proportion of tested patients. At present, we believe that when thrombophilia testing is considered in a patient, management decisions based on the results of the test should at least be clear before the tests are performed.

REFERENCES


