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Thrombophilia ad dies vitae

Cohn, D.M.

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Chapter 4

The psychological impact of testing for thrombophilia: a systematic review

Cohn DM, Vansenne F, Kaptein AA, De Borgie CA, Middeldorp S. The psychological impact of testing for thrombophilia: a systematic review. J Thromb Haemost 2008; 6:1099-104.

Abstract

Background

Large numbers of patients are tested for thrombophilia nowadays, even though the benefits are unclear. A potential disadvantage of this (mainly) genetic testing might be its psychological impact, such as fear, depression and worry.

Objectives

To systematically review studies that determined the nature and extent of psychological impact of testing for thrombophilia.

Methods

We searched the MEDLINE database (1966 to February 2008), the EMBASE database (1985 to 2008, week 5) and the PsychInfo database (1806 to February 2008) for relevant trials, without language restrictions. Bibliographies of relevant articles were scanned for additional articles. We reviewed all relevant studies that focused on the psychological impact of testing for thrombophilia. Only full papers of studies that included 15 patients or more were considered eligible for this review. Two reviewers independently extracted data and assessed quality.

Results

Six studies fulfilled the eligibility criteria. As these studies varied tremendously in methodology; pooling of the data was not possible. Studies of psychological impact of genetic testing for thrombophilia report few negative results, but most assessments are limited to the short term or lack methodological accuracy.

Conclusion

No valid conclusions can be drawn about the psychological impact of genetic testing in patients based on the current available literature. Given the large number of patients that are being exposed to thrombophilia testing, and the uncertain benefits, there is an urgent need for more uniformity in the measurement of psychological impact of thrombophilia testing.

Introduction

Venous thromboembolism (VTE) commonly manifests as deep vein thrombosis or pulmonary embolism, or a combination of both. VTE affects approximately 2-3/1000 persons each year.¹⁻³

It is a multifactorial disease, in which both exogenous and endogenous conditions are known to increase the risk.⁴ Established exogenous risk factors are cancer, pregnancy, puerperium, surgery, immobilisation and oral contraceptive use. The endogenous risk factors for VTE contribute to the term “thrombophilia”. Thrombophilia has gained interest since a growing number of ‘common’ abnormalities were discovered in the 1990’s, such as factor V Leiden and the prothrombin mutation.^{5,6} Due to the discovery of these more prevalent thrombophilias, in approximately 50-60% of patients with VTE at least one thrombophilic defect can be demonstrated nowadays.⁷ Thrombophilic abnormalities can be acquired or inherited. The most common *acquired* thrombophilic abnormality is the antiphospholipid antibody syndrome. *Inherited* forms of thrombophilia are deficiencies of the natural anticoagulants (antithrombin, protein C and protein S) and the more common mutations: factor V Leiden (FVL) and prothrombin 20210A. Moreover, persistently elevated levels of FVIII:c increase the risk of VTE; this condition is at least partially hereditary.⁸ Whether (mild) hyperhomocysteinaemia should be considered a risk factor for venous thrombosis remains controversial.^{9,10}

Thrombophilia tests are also being performed within the scope of other disorders with which it is associated, such as recurrent miscarriage and intra-uterine fetal death, but also for conditions for which no association has been established, such as arterial diseases including stroke. Finally, healthy individuals are often tested for thrombophilia, usually within the context of family testing after diagnosing thrombophilia in an affected proband.¹¹

The question whether testing for thrombophilia is justified is still a matter of debate and can not be answered unequivocally.¹²⁻¹⁴ Potential advantages of testing may be the possibility to take preventive measures or to avoid exposure to evitable risk factors. However, in accordance to other genetic tests, a potential drawback of testing for thrombophilia could be social consequences, such as problems with acquiring life or disability insurances.¹⁵ Moreover, results of genetic tests may have substantial psychological consequences, such as depression, anxiety, and persistent fear.^{16,17} Not all psychological consequences following genetic testing are negative; testing may also lead to relief and fear reduction.¹⁸ As the benefits and disadvantages of testing for thrombophilia are not fully clear, the

psychological consequences of testing for thrombophilia should also be considered in the decision whether testing for thrombophilia is indicated or can be justified.

Here we systematically review the studies on psychological consequences of testing for thrombophilia. Furthermore, we critically appraise the methods of assessment of psychological impact in the reviewed studies.

Methods

All full papers that reported the psychological impact of testing for thrombophilia were eligible. We considered all study designs and all indications for testing eligible, as long as at least 15 individuals were included. The primary outcome was the degree of psychological impact of testing for thrombophilia. Secondary outcome measures were descriptions of the degree of satisfaction after testing for thrombophilia and uptake of behavioural changes after disclosure. Potential eligible articles were systematically searched in the MEDLINE (1966 to February 2008), EMBASE (1985 to 2008, week 5) and PsychInfo databases (1806 to February 2008). The used search strategy was highly sensitive, without language restrictions. One restriction was made: “NOT hemophilia”, since there was considerable overlap between “Factor VIII” AND “hemophilia”. The used search terms (structured as PICO) are stated in table 1.

Table 1. Literature search terms

	search terms
Patients	no specific search terms
Intervention	thrombophilia; thrombophil*; prothrombin; hyperhomocysteinemia; homocystein; hyperhomocyst*; homocystein*; protein c deficiency; protein s deficiency; antithrombin deficiency; activated protein c resistance; “factor V/genetics” [MeSH]; hypercoagulabil*; “apc resistance”; “factor V”; “protein c”; “protein s”; antithrombin; “at III”; F VIII; factor VIII; thromboplastinogen
Comparison	no specific search terms
Outcomes	“psychology”[Subheading]; anxiety; anxieties[tw]; nervousness[tw]; stresses[tw]; distress[tw]; psycholog*[tw]; psychosocial[tw]; worry[tw]; worrying[tw]; “stress, psychological”[MeSH]; anguish*[tw]; “mental suffering”; distress*; emotion*[tw]; “Stress”[MeSH]; depressive[tw]; “Depression”[MeSH]; worries[tw], “risk perception”, “illness cognition”, “cognition”, “health beliefs”, “lay beliefs”, “treatment beliefs”, “emotion regulation” and “common sense model”

They were used both as MESH terms and free text (unless noted otherwise). Bibliographies of relevant articles were scanned for additional articles. In case more publications concerning the same participants suited the search terms, only the most relevant article was included. Two reviewers (DC, FV) independently screened the results of searches to identify potentially relevant papers, and independently extracted the data from each paper using the

same form. Data extraction was checked and discrepancies were resolved through discussion. If necessary, we contacted authors of selected papers to provide additional data. We aimed to pool the results in a meta-analysis in case of sufficient comparability of the used methods, or otherwise to assess the psychological consequences of testing for thrombophilia qualitatively.

Results

A search in Medline yielded 1823 potentially relevant studies. Given the substantial heterogeneity of interventions and methods across studies, it was not possible to pool the results for meta-analysis.

After screening for title and abstract, 6 relevant studies were identified.¹⁹⁻²⁴ Searches in the EMBASE and PsychInfo databases yielded 1301 and 387 hits, respectively, but after screening for title and abstract no additional relevant articles were found.

Table 2 summarises the included studies. Most participants reported to be satisfied with the knowledge of being carrier of (a) thrombophilia (respectively 97/110 (88%) and 202/215 (94%) and testing for thrombophilia was perceived as less harmful than a genetic test for breast cancer or a non-genetic test for diabetes.²⁴ However, a substantial number of participants reported to be more worried (respectively 47/110 (43%) and 58/215 (27%).^{19,20} Furthermore, thrombophilia testing might be associated with negative effects, as reported in a small, qualitative study: asymptomatic carriership of FVL can influence daily life by having concerns, stigmatisation and problems with insurance eligibility.²¹ It is of note that 43/110 (39%) of the participants in one study did not recall to have consented for their genetic test and that 14/110 (13%) of the participants were unaware of their abnormal test result.¹⁹

The number of participants ranged from 17 to 168 per study. Four-hundred of 692 participants were tested for research purposes in three studies.²⁰⁻²² The selected participants of two of these studies were a subset of a large group of individuals that were tested previously to assess the incidence and thrombotic risk of carriership of FVL.^{25,26} The participants of the third study had been tested for protein C deficiency to clarify the high frequency of VTE in their kindred.²⁷

The greater part (266/692; 38%) of all participants was apparently healthy and never experienced VTE. One third (227/692; 33%) were asymptomatic relatives of probands with VTE. Only 160/692 (23%) of the participants experienced a VTE. The VTE or thrombophilia history in the remaining 6% was unknown.

Table 2. Overview of the included studies

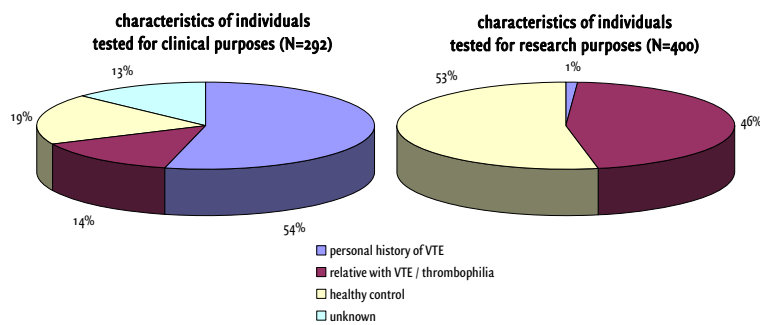
	participants	setting	thrombophilic defects	instruments	point in time	outcome
Hellmann 2003¹⁹	110 consecutive individuals 83 personal history of VTE 27 reason for testing unknown	clinical purposes	factor V Leiden	1 not validated questionnaire, based on previous publications concerning other genetic tests	mostly several years after disclosure of test results	knowledge of genetic status increased awareness of thrombotic risk, but the magnitude of the risk is often overestimated knowledge of factor V Leiden status increased worry in 43% of the participants, although 88% of all participants was glad to know the outcome
Lindqvist 2003²⁰	4 personal history of VTE* 211 healthy controls *reported in correspondence by the authors	research purposes: to assess the incidence of APC resistance amongst pregnant women	factor V Leiden* in case of altered test result of APC resistance *reported in correspondence by the authors	2 not validated questionnaires regarding satisfaction, the awareness and behaviour after receiving a positive test result	6-12 months after disclosure of test results	94% was satisfied with the awareness of being APC-resistant 27% declared to be more worried
Bank 2004²¹	17 asymptomatic relatives of individuals with factor V Leiden	research purposes: to assess the incidence of VTE in individuals with thrombophilia	factor V Leiden	qualitative, semi-structured interviews	4 to 7 years after disclosure of test results	asymptomatic carriership of factor V Leiden might influence daily life by concerns, stigmatisation and problems with insurance eligibility
Van Korlaar 2005²²	168 family members of one kindred with a high incidence of protein C deficiency	research purposes: to assess the heritability of a rare protein C deficiency	protein C deficiency	validated risk perception and worry scales and validated trait anxiety (STAI) questionnaire attitudes about testing	mostly ten years after disclosure of test results	risk perception and worry increased in individuals with protein C deficiency no significant differences in attitudes about genetic testing
Saukko 2006²³	42 participants 10 personal history of VTE or thrombophilia 20 family history of VTE or thrombophilia 12 other reason or unknown	clinical purposes	factor V Leiden prothrombin mutation* protein S deficiency* protein C deficiency* antithrombin deficiency* *self reported by the participants	qualitative, semi-structured interviews	at most two years after testing for thrombophilia	testing for thrombophilia was generally considered to be less serious than a genetic test for breast cancer or a non-genetic test for diabetes
Legnani 2006²⁴	140 participants 63 personal history of VTE or thrombophilia 55 apparently healthy individuals	clinical purposes	factor V Leiden prothrombin mutation protein S deficiency protein C deficiency antithrombin deficiency hyperhomocysteinaemia lupus anticoagulant	Perceived Health Score and validated CBA scale A&B questionnaire	prior to testing and 20 days after disclosure of test results	no (significant) harmful effects of genetic testing in individuals with thrombophilia a non-significant decrease of Perceived Health Score in the subjects without a personal history of VTE

The characteristics of individuals tested for clinical purposes differed from those tested for research purposes (Figure 1).

Almost all studies assessed the impact between 6 months and 10 years or more after testing.¹⁹⁻²³ One study (140 individuals) had a prospective design with a baseline measurement.²⁴

Two studies used qualitative, semi-structured interviews^{21,23}, two studies used validated questionnaires^{22,24} and two studies used non-validated questionnaires.^{19,20} The thrombophilic tests that participants had undergone varied: FVL¹⁹⁻²¹, protein C deficiency (without mutation analysis, but with awareness of its inheritable nature)²² and a set of thrombophilic defects.^{23,24}

Figure 1. Characteristics of individuals tested for clinical and research purposes



Discussion

Following a highly sensitive search strategy through the main literature databases, only 6 studies reporting the psychological impact of thrombophilia testing could be identified. As the applied methods varied considerably amongst these studies, it was impossible to pool the results for meta-analysis. Therefore, we described the results of the individual studies.

The large majority of participants reported to be satisfied by the knowledge of being a carrier of thrombophilia (88% and 94%), however several participants reported to be more worried (27% and 43%). Qualitative studies showed that participants experienced testing for thrombophilia not as serious as a genetic test for heritable cancer or a non-genetic test for diabetes, although other participants reported that positive testing for FVL could have led to stigmatisation and problems related to insurance. However, given the large heterogeneity between the studies, no valid conclusion can be drawn. This heterogeneity

refers to large differences in selection of individuals, instruments and points in time, which will be discussed in detail below.

The results are difficult to extrapolate to daily clinical practice for two reasons. Firstly, in 58% of the participants thrombophilia tests were performed for research purposes. It is likely that the way testing is performed and how tested individuals are informed about indication and results differs considerably between settings. Secondly, the majority of the participants did not have a personal history of VTE (71%). It is probable that results of thrombophilia testing have different impact on symptomatic carriers compared to healthy individuals. This was observed in the study by Legnani et al.: a (non-significant decrease) of perceived health score was found in relatives and controls tested positively for thrombophilia compared to baseline, but not in symptomatic carriers.²⁴

The method of counselling or information provision on the test results affects the way these results are perceived by the patient.²⁸ Remarkably, none of the studies takes this into consideration. Three of the included studies did not mention the way counselling had transpired at all^{19,22,23}, two studies informed the participants only in writing^{20,24} and one study reported that “[participants] have been informed the same way and seen in the same place as would be individuals for purposes of clinical practice”, without providing details.²¹

The applied instruments were in depth interviews, validated questionnaires and non-validated questionnaires. The major advantage of application of standardised evaluation approaches, such as validated questionnaires, is the possibility of pooling of the results to perform meta-analyses and the possibility of comparison of different genetic tests. Genetic tests for varying conditions may have a different impact, which might depend on e.g. the severity of the underlying disease or the possible therapeutic options. At present, there are no papers that compare different validated questionnaires in the context of the psychological impact of genetic testing, but there are a few validated questionnaires that have been used several times in genetic evaluation studies.^{29,30}

The points in time of assessment differed substantially amongst all studies (between 20 days and 10 years or more after disclosure of the test results). Except one study, all studies had a retrospective design. Hence, no baseline measurements could be performed in the latter studies, because participants were already informed on their test results. The interpretation of these results is insofar confined, that it is impossible to discriminate between the impact of being ill and the impact of receiving an altered test result. A design in which a baseline measurement is included allows this discrimination. Other conditions in which the impact of genetic testing was assessed applied a prospective design (such as

Huntington's disease, Familial Hemochromatosis, Hereditary Breast and Ovarian Cancer and Familial Adenomatous Polyposis).³¹⁻³⁴

Besides the application of a baseline measurement, a serial assessment of impact of genetic testing provides more insight in the impact of testing, especially since psychological outcomes might change over time. Shortly after receiving the (positive) genetic test result participants may feel anxious and shocked, leading to changes on psychological scales.^{35,36} This initial reaction may change after a while as participants think about their result and incorporate this into their lives. After several years people appear to have adapted their lives and thus may not even remember being shocked or anxious after disclosure of the test result.³⁷ This phenomenon is also known as response shift.²² Repeated measurements and a long term follow-up after the genetic test result might improve the insight into this phenomenon.

A potential drawback of our systematic review (and systematic reviews in general) might be the possible occurrence of publication bias: those studies with significant, positive, results are easier to find than those with non-significant or 'negative' results.³⁸ Nevertheless, as it is concluded that testing for thrombophilia appears to have no major adverse effects, and, taken into consideration that this result might well be an overestimation, it seems unlikely that publication bias affected our results gravely.

Conclusions and recommendations for future research

Overall, we conclude that the external validity of the studies is too much confined to extrapolate the results on psychological impact of testing for thrombophilia to current practice. The published data lack uniformity in various areas, such as types of participants and counselling methods, points in time of measurement(s) and applied instruments. For this reason, the external validity is seriously limited.

Given the large number of individuals tested yearly for thrombophilia, together with uncertain benefits of testing, there is a need for more research into the psychological impact of genetic testing for thrombophilia.

For future research, we would like to make some recommendations. Ideally, a randomised clinical trial between testing and no testing could be performed to assess psychological impact of testing for thrombophilia on top of receiving the diagnosis of VTE. Moreover, this study design limits the potential effects of bias and confounding. However, such a study is difficult to perform and recently, we had to stop our study due to slow recruitment.³⁹

In any type of research, either interventional or observational, we would recommend the application of validated questionnaires as they facilitate comparability within patients with a specific condition and between diseases. Furthermore, completion of these questionnaires both before and after disclosure of the test results, at short term and long term, allows clarification of the course of potential harmful psychological effects.

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