Title Biology of haemostasis disorders: Testing for the G1691A mutation of the factor V gene (Leiden FV) and the G20210A mutation of the factor II gene

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Aim

The National Salaried Workers' Health Insurance Fund (CNAMTS) asked HAS to assess the value of the different laboratory tests for haemostasis abnormalities with a view to updating the section in the Nomenclature of Procedures in Laboratory Medicine (NABM) containing the procedures in laboratory medicine for measuring abnormalities of haemostasis (subsection 5-02). One of those procedures is testing for the G1691A mutation of the factor V gene (Leiden FV) and the G20210A mutation of the factor II gene.

All methods of testing for point mutations can be used to test for the G1691A polymorphism of exon 10 of the FV gene and for G20210A of the untranslated region 3' of the FII gene. The reference technique is still bidirectional sequencing of a specific genetic region of the gene of interest. These methods can be used to identify mutations and to determine their type (homozygous or heterozygous). These examinations can be performed only by laboratories authorised to carry out genetic tests.

The G1691A mutation of the factor V gene (FV) and the G20210A mutation of the prothrombin (or FII) gene are genetic variants, each due to a point mutation of the corresponding genes. These are biological risk factors for VTE. Their predictive value is however poorly defined, since there is no consensus among the various guidelines on this subject.

Conclusions and results

According to the literature identified and analysed, tests for mutations of factors V and II are not indicated in unselected patients. Consensus indications are identified in all the guidelines analysed:

- first episode of VTE:
  - ➢ unprovoked, and occurring before 50/60 years of age;
  - ➢ women of child-bearing age whether or not the episode is provoked;
- recurrence of VTE:
  - ➢ any recurrence of proximal DVT and/or PE, the first episode of which occurred before 50/60 years of age;
  - ➢ any unprovoked recurrence of distal DVT;
- personal history of VTE or pregnant women with a family history of VTE.

Testing for mutations of FV and FII can also be suggested, after case-by-case discussion, in the following indications:

- pregnant women with a family history of hereditary thrombophilia;
- pregnant women with a history of multiple pontaneous abortions or unexplained intrauterine fetal death, preeclampsia, HELLP syndrome, premature detachment of the placenta or retarded fetal growth;
- family history of VTE in a first-degree relative with homozygosity or double heterozygosity of mutations of FV and FII, in women of child-bearing age before the prescription of oestrogen-progestogen contraception.

Testing for mutations of FV and FII is not indicated in asymptomatic women with no family history of VTE or with a family history of obstetric complications. The result of detecting mutations of factor V and factor II can be used as a guide to patient management with, depending on the case, initiation of a treatment, a change in treatment or preventive measures.

Recommendations

On the basis of the literature identified and analysed, G1691A mutations of the gene for factor V (Leiden FV) and the G20210A mutation of the gene for factor II (prothrombin gene) are among the biological risk factors for VTE. Their

predictive value is however poorly defined. Testing for mutations of factor V or factor II is not indicated in unselected patients. The consensus indications identified in all the guidelines analysed are:

- occurrence of unprovoked VTE before age 50/60 years or of provoked or unprovoked VTE in pregnant women;
- recurrence of proximal DVT and/or PE, or of unprovoked distal DVT, the first episode of which occurred before age 50/60 years;
- pregnant women with a family history of VTE.

Testing for mutations of FV and FII can also be suggested, after case-by-case discussion, in the following indications:

- pregnant women with a family history of hereditary thrombophilia;
- pregnant women with a history of multiple spontaneous abortions or unexplained intrauterine fetal death, preeclampsia, HELLP syndrome, premature detachment of the placenta or retarded fetal growth;
- family history of VTE in a first-degree relative with homozygosity or double heterozygosity of mutations of FV and FII, in women of child-bearing age before the prescription of oestrogen-progestogen contraception.

The result of detecting mutations of factor V and factor II can be used to adjust the patient's management. These procedures are of interest in testing for biological risk factors for the occurrence and recurrence of VTE. Analysis of a person's genetic characteristics for medical purposes, conditions for prescribing these procedures, carrying them out in practice, conditions for communication of the result and conditions for storage of the documents must be regulated and must comply with the legislation in force (Articles L. 1131-1 ff and R. 1131-1 ff of the Public Health Code).

Methods

This assessment is based on a critical analysis of the literature carried out by the Haute Autorité de Santé, and reviewed by experts in haemostasis. It takes into account the arguments of a group of experts assembled by CNAMTS on which CNAMTS based its request. The assessment of this procedure is based on a critical analysis of the literature consisting of eight documents, comprising five guidelines, two technological assessment reports (including one published by HAS in 2006) and one experts report on genetic tests in general), plus the review by three experts in haemostasis.

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