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Clinical case

Genetic resistance to vitamin K antagonists: About a patient with a mutation in the enzymatic complex of vitamin K epoxide reductase (VKORC1)

Résistance génétique aux antivitamines K : A propos d'un patient presentant une mutation du complexe enzymatique de la vitamine K epoxide reductase

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Abstract

Genetic factors have been associated with a significant amount of inter-individual variability in response to vitamin K antagonists treatment (VKAs). Polymorphisms of the vitamin K epoxide reductase gene (VKORC1) are associated with hypersensitivity or, more rarely, resistance to VKAs. We report the case of a 65-year-old African who had resistance to acenocoumarol, fluindione and warfarin. Indeed, despite the use of high doses of acenocoumarol (12 mg/day), followed by fluindione (60 mg/day) and warfarin (20 mg/day) for the treatment of non-valvular atrial fibrillation, INR was still below the target therapeutic area. This resistance to VKAs was confirmed by the detection of a Cys58Ala mutation in the vitamin K epoxide reductase gene.

Keywords: Resistance to vitamin K antagonists, Vitamin K epoxide reductase, VKORC1, Cys58Ala.

Résumé

Des facteurs genetiques ont été incriminés pour une large part à la variabilité interindividuelle de la réponse aux antivitamines K (AVK). Des polymorphismes du géne de la vitamine K epoxide reductase (VKORC1) sont associés à une hypersensibilité mais plus rarement à une résistance aux AVK. Nous rapportons le cas d'un patient de 65 ans qui presentait une resistance à l'acenocoumarol, à la fluindione et à la warfarine. Malgré l'utilisation de trés fortes doses (12mg/j d'acenocoumarol), puis 60 mg/j de fluindione puis 20 mg/j de warfarine pour le traitement d'une fibrillation auriculaire non valvulaire ; l'INR restait en dessous de la zone therapeutique. Cette résistance aux AVK a été confirmée par la découverte d'une mutation Cys58 Ala du géne de la vitamine K epoxide reductase.

Mots-clés: Resistance aux antivitamines K, Vitamine K epoxide reductase, VKORC1, Cys58Ala.

Introduction

Vitamin K antagonists (VKAs) are widely prescribed for the prevention and management of arterial and venous thromboembolic disease. [1,2]. Despite

the available alternatives (thrombin and factor Xa inhibitors), several problems related to their high cost and the experience of doctors still favour extensive and continuous use of VKAs [3]. However, several conditions largely limited the use of VKAs, including the narrow therapeutic window, the restrictive surveillance. Their therapeutic window is rather narrow, and their dose must be adjusted according to the International Normalized Ratio (INR). A high target INR carries a high risk of bleeding, while embolism events occur if the target INR is too low. Many clinical and environmental factors, including age, sex, race, body size, comorbidities and concomitant medications, as well as genetic mutations, influence VKAs dose requirements [4]. Cytochrome P450 2C9 and subunit 1 (VKORC1) of the vitamin K epoxide complex are widely considered to be associated with individual variations in the VKAs doses [5].

Clinical case

We report the case of a 65-year-old African male with hypertension and non-valvular atrial fibrillation. His CHA2DS2-VASC score was 2 and his left atrial volume was 52 ml/m2. We started the anticoagulant treatment with acenocoumarol 4 mg, then gradually increased to 8 mg with an INR not exceeding 1.3. After INR testing in another laboratory, which showed an INR of 1,1, we decided to increase acenocoumarol to a daily dose of 12 mg with close monitoring of INR. Control returned to 1,5. We decided to switch to fluindione 20 mg, increasing gradually to 60 mg without reaching the target INR. Even after changing for the second time with warfarin 20 mg, the INR had never exceeded 1,6. The interview confirmed that the patient was indeed taking his anticoagulants and that there was no food or drug interaction. The various INR tests were carried out in three large laboratories. Based on this cross-resistance to VKAs, a VKORC1 mutation search was performed, which revealed a Cys58Ala mutation in VKORC1. The patient was then given rivaroxaban 20 mg daily.

Discussion

VKAs are widely used for the prevention and management of arterial and venous thromboembolic disease. They have a narrow therapeutic index and a high variability between individuals in the therapeutic response. The mysteries behind the complexity of warfarin dose have prompted investigators around the world to look for clues to unravel. They found that there are multiple influencing factors that influence individual responses to warfarin treatment, including age, body size, vitamin K intake, comorbidities. This further complicates the grouping of anticoagulation management approaches [6,7].

In 2004, two teams identified the gene coding for the C1 subunit of vitamin epoxide K reductase (VKORC1), now identified as a VKA target [5]. Inhibition of this enzyme by VKAs blocks the regeneration of vitamin K in its reduced state, resulting in the synthesis of non-functional clotting factors. Many genes are involved in the response to coumarin derivatives; however, two genes represent a significant proportion of inter-individual variability in response to treatment, one related to the pharmacokinetics of coumarin derivatives (cytochrome P450 2C9 [CYP2C9]) and the other to the pharmacology of VKAs (subunit 1 of vitamin K complex epoxide reductase, VKORC1). Mutations in CYP2C9 and VKORC1 genes may account for 40% to 60% of inter-individual variations in VKAs dose requirements [4,6].

Some patients have been identified as VKA-resistant: they require an exceptionally high dose to reach the target INR or, despite high doses, the INR is still below the target therapeutic range [5,8,9]. True warfarin resistance is rare (<0.1%) [5]. Patients who require more than 15 mg/day are considered warfarin resistant. VKAs resistance occurs in patients who cannot achieve INR in the therapeutic range despite high doses of VKAs (> 3 times the usual dose) [5,9]. Doses of up to 45 mg/day warfarin, 80 mg/day fluindione (four tablets) or 12 mg/day acenocoumarol (three tablets) have been reported [10-12]. Various mutations in the VKORC1 gene have been reported

and associated with warfarin resistance. In the coding region, these mutations cause a change of amino acid in the protein sequence. VKAs anticoagulant activity is based on inhibition of an enzyme in the vitamin K cycle, subunit 1 of the vitamin K reductase epoxide complex (VKORC1). The VKORC1 gene has been identified and variants of VKORC1 have been associated with warfarin resistance [5].

The discovery of VKORC1 has made it possible to identify genetic factors modulating the response to VKAs and causing inter-individual variability. Thus, genetic variations in the pharmacological target of VKAs, i.e. VKORC1, can lead, depending on their nature and location on the gene, either to relatively infrequent cases of resistance, requiring high doses, or, more frequently, hypersensitivity that can lead to overdoses and potentially severe bleeding events, leading to dose reduction [6].

Rare mutations in the gene's coding region have been associated with warfarin resistance. These mutations cause a change of amino acids in the protein sequence: Val29Leu, Val45Ala, Arg58Gly, Val66Met and Leu128Arg. Expression of the different mutant proteins showed that the basal activity of VKORC1 was reduced and, more importantly, the mutated enzyme was less sensitive to warfarin inhibition, which could be the cause of resistance to anticoagulant therapy [4-6].

So far, 26 mutations of the VKORC1 gene have been identified in VKA-resistant patients. Asp36Tyr and Val66Met mutations have been reported as the most common variants. The Asp36Tyr allele was identified in 15% of the Ethiopian total and 4% of the total Ashkenazi Jewish population [8]. In turn, the Val66Met mutation appears in literature reports to be fixed in some populations. The VKORC1 Val66Met variant was found in two of the 11 Afro-Brazilians, three of the four Afro-Caribbean relatives, and in a black patient in South Africa, all of whom were resistant to VKA [8,13,14]. The other mutations associated with VKAs resistance appear to be isolated cases, suggesting that these are all de novo events [8]. Mutations of Tyr32Ala and Asp51Ala, Cys58Ala and Trp66Arg, and Leu135Arg are reported to cause high VKORC1 resistance [9].

Polymorphisms affecting other genes encoding proteins involved in VKAs treatment response were also investigated. These include:

- Epoxide hydrolase (EPHX1 gene): this protein is considered part of the vitamin K reductase complex. Some polymorphisms have been identified and their presence implies the need to increase the doses of warfarin to reach the target INR [10].
- CYP4F2: genetic variations of the CYP4F2 gene have been associated with warfarin therapy response. However, the mechanisms by which CYP4F2 is involved in treatment response variability or vitamin K metabolism are currently unknown [5].

In case of resistance to more than 30 mg/day of warfarin, it is recommended to perform a genetic study and issue a certificate to the patient indicating that he is "resistant" to VKA [15].

Conclusion

In patients with persistent subtherapeutic rates of INR, non-adherence, drug interactions, poor treatment adherence, laboratory errors should be excluded for the first time. This case highlights that even if hereditary warfarin resistance is rare, mutations associated with warfarin resistance should be considered and a genetic study conducted. In patients with suspected warfarin resistance, very high doses that maintain INR within the target therapeutic range should be administered, and INR should be closely and regularly monitored. Alternatively, direct oral anticoagulants may be used.

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