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Genetic Warfarin-Resistance Resulting in Surgery to Change a Prosthetic Valve

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ABSTRACT

Warfarin is a readily available anticoagulant used worldwide in a variety of clinical scenarios. Patients who need more than 15 mg/day are considered to be warfarin resistant. Numerous genes have been implicated in warfarin pharmacogenetics, with genes encoding CYP2C9 and VKORC1 shown to be the most important determinants of drug dosage requirements. A 27-year-old woman was admitted as she had a sub-therapeutic international normalized ratio (INR) after prosthetic mitral valve replacement. Even after a warfarin dose of 50 mg/day, her INR was not in the therapeutic range, so the heart team decided to replace her metallic valve with a bioprosthetic valve, thus alleviating the need for anticoagulation.

LEARNING POINTS

- Genetic warfarin resistance is rare and mainly associated with two genes encoding CYP2C9 and VKORC1.
- In addition to dietary counselling and drug compliance, options in warfarin-resistant patients include increasing the warfarin dose, which carries a risk of bleeding complications, or switching to novel oral anticoagulants, which increases the risk of prosthetic valve thrombosis.
- We replaced a metallic valve with a bioprosthetic valve, which is the first time this has been documented in a patient with warfarin resistance.

KEYWORDS

Warfarin resistance, genetic polymorphism, international normalized ratio, VKORC1, cytochrome P450

INTRODUCTION

Warfarin was discovered by Karl Link and his students in 1940 [1]. The name stems from the acronym WARF, for Wisconsin Alumni Research Foundation, with the ending 'arin' indicating a link to coumarin. It is used as an oral anticoagulant for the treatment of deep vein thrombosis, pulmonary embolism, stroke prevention in atrial fibrillation, and mechanical prosthetic valves [2]. Resistance to warfarin is uncommon and can be acquired through drug interactions, non-compliance and malabsorption, or can be hereditary. We present the case of a young woman with a mechanical prosthetic valve and genetic warfarin resistance.

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CASE DESCRIPTION

A 27-year-old woman was admitted to the outpatient clinic at our institute for sub-therapeutic INR after 3 months of sequential increments of her warfarin dose from 5 mg/day to 25 mg/day. She had rheumatic mitral valve disease and had received a prosthetic mitral valve 4 months previously.

Her history was taken and she denied warfarin non-compliance. She visited an international normalized ratio (INR) clinic every fortnight and her patient data did not show use of any medicines that interact with warfarin. She did not take any over-the-counter medicines at home. She had a normal eating habit and was not a vegetarian. Her examination was unremarkable with an audible prosthetic click. The ECG showed a normal sinus rhythm and there was a normal gradient of 6 mmHg across the prosthetic valve. Fluoroscopy confirmed normal movement of the bi-leaflet valve.

Her laboratory parameters were within normal ranges. However, her INR was 1.2 even on 25 mg/day warfarin. She was started on enoxaparin 40 mg twice daily as she weighed 43 kg. Her warfarin dose was increased by 2.5 mg every 3 days, but even after a dose of 50 mg/day, her INR persisted at 1.3.

Tests for known polymorphisms affecting warfarin metabolism showed she was positive for both vitamin K epoxide reductase (VKORC1) and cytochrome P450 2C9 (CYP2C9) mutations. A heart team meeting was conducted to discuss further interventions. With the consent of the patient, it was decided by the surgery lead to replace the prosthetic mitral valve with a bioprosthetic valve, thus alleviating the need for anticoagulation. The procedure was successful and the patient was sent home on dabigatran 150 mg twice daily and aspirin 75 mg daily for 3 months. She attended weekly follow-up for the first month and fortnightly follow-up for the subsequent 2 months. She remained stable throughout.

DISCUSSION

Warfarin resistance is a rare condition with patients showing different responses to the drug. In incomplete resistance, a satisfactory INR can be achieved with high warfarin doses above 15 mg/day, while in complete resistance the drug does not affect INR at all [3].

Both types of resistance are related to warfarin processing. In some patients, warfarin reacts abnormally with the clotting cascade leading to an imbalanced reaction to the drug. Other patients rapidly break down warfarin, so the drug is metabolized at an increased rate. The severity of the abnormal processes determines whether warfarin resistance is complete or incomplete.

Genetic polymorphism plays a significant role in the body's response to warfarin. Mutations in the genes VKORC1 and CYP2C9 are implicated in warfarin resistance [4]. Warfarin acts by inhibiting the formation of vitamin K-dependent clotting factors as well as regulatory protein C, protein S and protein Z. Vitamin K metabolism is controlled by a rate-limiting enzyme, VKOR. Warfarin inhibits epoxide reductase, particularly the VKORC1 subunit. This decreases the availability of vitamin K in the tissues and produces the anticoagulant effect of warfarin. CYP2C9 is another important P450 enzyme in the liver responsible for metabolizing warfarin. This enzyme exhibits genetic polymorphism with more than 50 single nucleotide polymorphisms (SNPs) associated with reduced enzyme activity causing a significant reduction in warfarin metabolism and increased daily dose requirements [4].

Our patient showed the CYP2C9 wild-type and VKORC1 GG genotype. According to a report by Efrati et al., the CYP2C9 wild-type reduces warfarin metabolism, resulting in warfarin sensitivity and a lower requirement for the drug [5]. Another study in Iran showed the same results [6]. However, research in Japan demonstrated increased metabolism with the CYP2CP*3 homozygous wild-type requiring a high dose of warfarin [7]. Another study showed increased warfarin dose requirements in African American patients [8]. A different report stated that the mean dose of warfarin was higher among Caucasian patients with the VKORC1 CC genotype [9], while another study demonstrated a positive correlation between a higher warfarin dose and the VKORC1 GG genotype [10]. This shows that warfarin metabolism may present differently in different racial groups with different mutations. Our patient showed increased drug metabolism leading to rapid clearance and a sub-therapeutic INR.

Compliance is very important in acquired warfarin resistance. Dietary counselling should be provided regarding the controlled intake of foods rich in vitamin K. In hereditary warfarin resistance, increasing the dose of warfarin is an option, but this raises the risk of bleeding. Other non-haemorrhagic complications include skin necrosis, which is rare and dose-dependent [11]. Some patients are changed to phenprocoumon which has a slower onset and longer duration of action. However, it is not widely available and can cause severe hypersensitivity reactions [12]. Other alternative therapies are novel oral anticoagulants (NOACs) or low-molecular-weight heparin (LMWH). In one study, dabigatran was used as an alternative to warfarin in patients with a prosthetic heart valve, but it increased thromboembolic and bleeding complications [13].

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CONCLUSION

A literature search failed to identify any reports of a metallic prosthetic valve being replaced with a bioprosthetic valve in a warfarin-resistant patient, so to our knowledge, this is the first ever documented case in the world. This strategy can be employed successfully in patients who require high doses of warfarin.

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