ECAT Newsletter

Case Report

Interference of antiphospholipid antibodies with point-of-care INR testing.

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Case description

In June 2022, a 48-year-old man presented to the Emergency department of the University Medical Center Utrecht with sudden onset of aphasia and right-sided hemi-paresis. His medical history noted the antiphospholipid syndrome (APS), which had been diagnosed in 2016 on the basis of a spontaneous deep venous thrombosis (DVT) in the left leg, livedo reticularis and migraine, in combination with persistent triple positivity for the serological markers of APS (lupus anticoagulant and high levels of anti-β2-Glycoprotein-IgG antibodies and anticardiolipin-IgG antibodies). There were no additional signs of autoimmune disease. He received indefinite anticoagulant therapy with acenocoumarol (a vitamin K antagonist) at a target internationally normalised ratio (INR) of 2-3, which unexpectedly resulted in the resolution of his migraine. His INR was regularly checked by means of point-of-care (POC) testing with the CoaguChek XS device (Roche), and was usually within the target range. However, in the weeks preceding his admission to our hospital, his INR had been 6.8, leading to an acenocoumarol dosage adjustment. The day before presentation at our hospital, the INR as tested with the POC device was 3.8.

At the Emergency department, a neurological work-up was performed and motoric aphasia and hemi-paresis were confirmed. There were no signs of endocarditis, thrombosis or infection and no further abnormalities were noted on physical exam. Laboratory results indicated a slight decrease in kidney function (estimated glomerular filtration rate 69 mL/min/1.73 m2, reference >90 mL/min/1.73 m2) and a mildly elevated C-reactive protein level (18 mg/L, reference 0-10 mg/L). INR testing in venous blood with a PT-based assay according to Owren's method indicated an INR of 1.3. Ultrasound of the carotid arteries showed only minimal atherosclerotic changes, and no signs of endocarditis or structural heart disease were detected on transthoracic ultrasound. CT-scan showed infarction of the middle cerebral artery and emergency thrombolysis was performed, resulting in partial improvement of the aphasia and paresis. After four days of hospitalisation, the patient was transferred for further neuro-revalidation. Treatment with acenocoumarol was intensified, again with a target INR 2-3, but now monitored with venous blood sampling only.

Conclusion

In this case report, we describe a triple positive thrombotic APS patient with an overestimated INR based on POC testing, followed by undertreatment with a vitamin K antagonist, which led to a new and severe thrombotic event. Antiphospholipid antibodies, especially those with lupus anticoagulant activity, are known to interfere with diagnostic coagulation assays. While prolongation of clotting time due to antiphospholipid antibodies is typically observed in sensitive activated partial thromboplastin time (APTT) assays, interference may also be observed with thromboplastin-based coagulation assays. (1-8) Several studies have addressed interference of antiphospholipid antibodies with thromboplastin-based INR testing and reported that INR differs between the different assays in a number of patients with antiphospholipid antibodies. (1-5) In a recent study of 33 lupus anticoagulant positive patients with thrombotic APS, we observed >20% difference between the INRs measured with the CoaguCheck XS POC device and INRs measured in venous blood samples in a large number of patients, with higher POC INR outcomes in all cases. This difference was observed specifically in patients with a POC-INR >3 and positively correlated with levels of anti-□2-glycoprotein I IgG antibodies (6). Our patient had high levels of these antibodies.

There are differences in sensitivity to interference by antiphospholipid antibodies between thromboplastin-based reagents. Reagents with recombinant thromboplastins were reported to be more sensitive to interference by antiphospholipid antibodies than reagents with other sources of thromboplastin. (7) Data from our study and others indicate that Owren prothrombin time (PT) reagents are less sensitive to interference by antiphospholipid antibodies than Quick PT reagents. (6-8) This is likely attributable to the relatively high dilution of patient plasma in the PT according to Owren, as compared with the PT according to Quick. (7,8) In addition, Owren reagents are supplemented with adsorbed plasma as a source of factor V and fibrinogen, to minimise the contribution of variations in non-vitamin K-dependent proteins on test outcome. (9) We have previously shown that anti-β2-glycoprotein I antibodies with lupus anticoagulant activity interfere with the activation of coagulation factor V by factor Xa. (10) We can speculate that the high levels of factor V relative to the vitamin K-dependent factors help minimise the inhibitory effects of anti-β2-glycoprotein I on activation of factor V.

In conclusion, POC testing of INR with the CoaguChek XS device might lead to an overestimation of the INR in patients with thrombotic APS who test positive for lupus anticoagulant and have high levels of anti-β2-glycoprotein I IgG antibodies. In these patients, we recommend monitoring the INR in venous blood, preferably with Owren PT-reagents. We are currently investigating whether an individualised INR POC vs Owren-ratio can be constructed to re-enable the safe use of POC-testing in selected patients.

References

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