Genetically determined hypersensitivity to vitamin K antagonists caused by a c.109G>A (p.Ala37Thr) mutation in the factor IX propeptide: the first case identified in Poland

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OBJECTIVES

Factor IX (FIX) is a vitamin K dependent plasma glycoprotein that plays an important role in blood coagulation pathway consisting in cleaving and activating of clotting factor X. Hypersensitivity of FIX to vitamin K antagonists (VKA) is a rare congenital bleeding disorder that manifests only during VKA therapy. The bleeding tendency is related to severe reduction of FIX clotting activity, the level of which is much lower than that of other vitamin K-dependent coagulation factors. Two genetic alterations at locus 37 (previous -10) in exon 2 of the F9 are associated with hypersensitivity to VKA: c.109G>A (p.Ala37Thr) and c.110C>T (p.Ala37Val). The aim: Up to now bleeding diathesis associated with c.109G>A (p.Ala37Thr) mutation in F9 have been reported in very few cases only.

METHODS

A 74-year-old male patient was admitted to our Centre with recently presented bleeding disorder. Few months earlier he received acenocoumarol due to mechanical heart valve implantation. Plasma coagulation studies comprised screening tests and assessment of coagulation factors activity with one-stage assay using BCSXP Coagulation Analyzer and Siemens reagents. Mutation analysis of F9 was performed by direct Sanger sequencing of all coding regions and exon / intron splicing sites on ABI 3130XL Genetic Analyzer (Applied Biosystems, USA).

RESULTS

Laboratory tests revealed anemia (hemoglobin 6.9 g/dl, ref. 2.0-16.8) and prolongation of PT with INR 1.95. APTT was significantly prolonged (61.2s, ref. 25-33s), fibrinogen and thrombin time - within reference range. Our attention attracted the disproportionally prolongation of APTT, because normally, during VKA therapy the APTT remains within a normal range or is only slightly prolonged, but in our patient it was nearly twofold prolonged. Measurement of FIX:C demonstrated activity level less than 2 IU/dl (ref.50-150 IU/dl), while levels of other vitamin K-dependent factors II, VII and X were 51.5 IU/dl (ref.70-140 IU/dl), 26.5 IU/dl (ref.70-140 IU/dl) and 26 IU/dl (ref.70-140 IU/dl), respectively. Factor V, VIII, XI and XII activity was normal. Severe reduction of FIX activity prompted the suspicion of hypersensitivity to VKA treatment caused by presence of a specific mutation in the F9 gene. Molecular analysis of exon 2 in F9 gene revealed c.109G>A variant. VKA was discontinued and normalization of coagulation test results and bleeding was reported.

CONCLUSIONS

To our best knowledge, this is the first case of genetically determined FIX hypersensitivity to VKA identified in Poland. Although the genetic mechanism of congenital hypersensitivity to VKA was discovered about 20 years ago, such cases are still worth presenting to increase the awareness of physicians and laboratory diagnosticians.