Combination of APC resistance and acquired protein S deficiency in a haemodialysis patient with recurrent A-V shunt thrombosis

Ivaylo Mitsiev, Simone Reinhold, Sabine Ziemer, Hans-H. Neumayer and Berthold Hocher

Department of Nephrology and Clinical Biochemistry, Charité, Berlin, Germany

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Introduction

A-V shunt thrombosis is a well known complication in haemodialysis patients although thrombotic events are uncommon in these patients probably due to the antithrombophilic status in uraemia. APC resistance and protein S deficiency recently were exposed as independent risk factors for thromboembolic events [1,2]. Here we report the case of a young female patient suffering from multiple thrombotic events of her A-V shunt due to a combination of APC resistance and acquired protein S deficiency.

APC resistance

Protein C is a vitamin K-dependent serine protease which inactivates factor Va (FVa) and FVIIIa after activation to activated protein C (APC) by thrombin. Normally, FVa is inactivated by an initial cleavage of the peptide bond on the carboxyl side of Arg506 followed by a second cleavage at Arg306. The FV Leiden mutation is characterized by a single cleavage at Arg506 (see Figure 1). This results in a 10-fold slower inactivation of FVa [3]. The resistance to APC was discovered by Dahlback et al. when they were unable to observe the expected prolongation of the partial thromboplastin time after adding exogenous APC to the plasma of a middle-aged man [4]. Bertina et al. identified the molecular defect as a point mutation in FV one year later [5]. The mutation was a G to A substitution at nucleotide 1691 resulting in the replacement of arginine at position 506 by glutamine. The mutant FV can therefore be represented as FV R506Q, but is more often referred to as FV Leiden.

The FV Leiden mutation was observed as an autosomal dominant trait [6] in >90% of cases with APC resistance [7]. Some reports suggested that there must also be another cause for APC resistance apart from the FV Leiden mutation [8]. A recent publication described a new mutation: FV Cambridge [9]. This is a mutation leading to substitution of Arg306 with Thr (Arg306→Thr).

In Caucasians, the prevalence of APC resistance was found to range from 1 to 12%, whereas it is rarely found in other ethnic groups such as Asian populations [10–12]. FV Leiden is found in up to 20% of all cases of deep vein thrombosis (DVT) [13]. It is the most common genetic cause of thrombophilia. It is found in 50% of cases of DVT with a family history and in 60% of pregnancy associated thromboses. The APC resistance increases the risk of thrombosis in users of oral contraceptives 30-fold [14]. The relative risk in a population without any other risk factor is estimated to be increased 7-fold for heterozygous individuals and 80-fold in homozygous subjects. These patients experience their thrombosis at a much younger age (31 vs. 44 years) [15]. The heterozygous inheritance of both FV deficiency and APC resistance is called pseudohomozygocity. These patients show the phenotypic picture of a homozygous APC resistance, but have a FV level about half of normal [16]. Some authors also report cases of cerebral venous thrombosis [17,18]. An association of APC resistance with artery embolism is unlikely [19].

Protein S deficiency

Protein S inhibits coagulation by serving as a cofactor for activated protein C. Protein S is a vitamin K-dependent plasma protein synthesized in the liver, vascular endothelium and megakaryocytes. In normal plasma, ~60% of protein S is complexed to C4b-binding protein, while 40% circulates in its functionally active free form [20]. Both free protein S and complexed protein S can bind to APC, but only the free form has cofactor activity. The importance of the regulatory role of protein S in blood coagulation has been established by the
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Heterozygous APC-resistant haemodialysis patients seem not to have an additional risk for thrombosis, whereas the risk is not known for homozygous patients [1]. A functional protein S deficiency in haemodialysis patients has been thought to occur most probably as a result of a synthesis defect by impaired endothelial cells due to vascular calcifications [2] caused by secondary hyperparathyroidism, which is very common in these patients. Free protein S deficiency could be determined as an additional risk factor for thrombosis in haemodialysis patients [2]. The management of patients requiring renal replacement therapy with inherited thrombogenic disorder is also complicated by the fact that renal transplant failure occurs earlier, with a 3.5-fold higher risk for 1 year graft loss compared with controls [38].

Case

The 36-year-old female non-smoking haemodialysis patient was admitted in our hospital with an occlusion of her cimino A-V shunt. This was the tenth shunt thrombosis within 2 years.

The renal disease was first diagnosed in 1981 as chronic glomerulonephritis. A biopsy was not performed. The patient at this time had no complaints.

One year later (1982), the patient underwent elective sectio caesarea due to oedema and hypertension during the last 3 months of pregnancy. She delivered a healthy son. In 1984, she was started on haemodialysis. Three years later (1987), a kidney transplantation was performed, but the transplant function failed due to severe thrombosis of the graft vein. A transplantectomy was done 12 days later. A second kidney transplantation was performed successfully in 1988. This time the patient received heparin (250 IE/h i.v.) for 3 weeks. This graft initially worked well, but later kidney function was declining function. Biopsy revealed signs of chronic rejection. The patient became hypertensive in 1995 and developed a secondary hyperparathyroidism (parathormon was 921 ng/ml; normal range: <70 ng/ml). A partial parathyroidectomy was performed in April 1996. Since May 1996 the patient had again needed haemodialysis. At dialysis, our patient became hypotensive. In 1996, a dyslipidaemia was detected (cholesterol: 9.41 mmol/l).

A thrombectomy of the old cimino shunt was performed. Ten weeks later, a shunt thrombosis occurred. A further correction of the shunt’s situation was impossible so a new cimino shunt had to be placed. Three months later, a further shunt thrombosis occurred and the thrombectomy initially was successful. Therapy with oral anticoagulants (Marcumar®) started; INR was between 2 and 3. Two thrombotic events of the cimino shunt followed in December 1997.

Since all native vessels were occluded or not suitable,
a plastic graft shunt was made at the end of December 1997. However, further thrombotic events occurred: one in February, two in March, two in July and one in October 1998. Marcumar® therapy was stopped in June 1998, because this treatment obviously did not prevent further shunt thrombosis.

A heterozygous inherited APC resistance with FV Leiden was determined by genotyping and functional analysis of APC resistance. In addition, a protein S deficiency was found by clotting test and by enzyme-linked immunosorbent assay (ELISA) (both from Boeringer Mannheim). In addition, we could not detect an inhibitor of protein S. No thrombotic events in the family were reported. We determined, using the same methods, a pathological APC resistance ratio of 1.5 in the father and a normal ratio in the mother. This was confirmed by sequencing. No pathological plasma levels of protein S were assessed in either of the parents. The last laboratory findings were (oral anticoagulation was paused): Quick 105%; PTT 33.9%; AT III 118%; fibrinogen 334 μmol/l; protein C 91%; protein S 6%; APC resistance 1.5; FV 155%; FVIII 404%; vWF 294%.

The patient underwent successful cadaver kidney transplantation in November 1998. In order to prevent early thrombosis of the graft, we treated our patient with heparin (300 IE/h i.v.) for the first 3 days after transplantation and continued thereafter with low molecular heparin s.c. (100 antiXa/kg/day).

Discussion

Thrombosis of the A-V shunt is the leading cause of hospital admission in haemodialysis patients. APC resistance is the most common genetic cause of thrombophilia. A heterozygous form of APC resistance does not represent an additional risk for thrombosis in haemodialysis patients, whereas the risk is not known for the homozygous patients [1]. On the other hand, free protein S deficiency could be determined as an additional risk factor for thrombosis in these patients [2]. In our case, the patient with a combination of these thrombogenic disorders suffered multiple thrombotic occlusions of the A-V shunt, suggesting that a combination of a heterozygous APC resistance and protein S deficiency represents a very potent thrombophilic condition.

Since neither of the parents had a protein S deficiency, we assume that our patient presents a case of acquired protein S deficiency. This could occur for one of two reasons. First, a new mutation could have occurred; however, this would represent a very rare condition. Secondly, and most probably, it could be the result of a synthesis defect of impaired endothelial cells due to vascular damage [2] caused by the secondary hyperparathyroidism as observed in our patient. Hypercholesterinemia, as also present in our patient, might likewise contribute to vascular damage. The concept of an acquired form of protein S deficiency is supported by the course of the thrombotic events. Recurrent shunt thromboses were only observed during her second period on haemodialysis (1996–1998). A congenital form of protein S deficiency should have led to shunt thrombosis also during her first period on haemodialysis (1984–1988). However, we have to consider that some of the thrombotic events during her second period on haemodialysis occurred in a plastic graft. Plastic grafts have a higher risk of a thrombotic occlusion, thus being an additional risk factor for our patient.

The combination of APC resistance and protein S deficiency in a haemodialysis patient presents a challenge for the treating physician. Several point have to be considered. (i) Life-long anticoagulation therapy with heparin might offer a possible solution since heparin does not interfere with the impaired synthesis of the protein S/protein C system in our patient. (ii) Oral anticoagulation, on the other hand, could not prevent the thrombotic events in our case, probably due to the additional inhibition of the synthesis of both protein C and the residual protein S. They are both vitamin-K-dependent factors, which are synthesized in the liver and in the endothelial cells [2,20]. This might explain that we observed multiple thromboses in our patient even when the oral anticoagulation therapy had the result of INR 2.5. Only a few reports have described a phenotypic correction of APC resistance following orthotopic liver transplantation [39,40].

In summary, we report on a patient with heterozygous APC resistance and secondary protein S deficiency, most probably due to secondary hyperparathyroidism, suffering from recurrent shunt thrombosis. To our knowledge, this is the first report describing this condition. However, we would expect that this pathophysiological situation might be rather frequent, since secondary hyperparathyroidism in haemodialysis patients is often seen, and the heterozygous form of APC resistance is seen in ~5% of the entire population.

References


