Original Article

Activation of endothelium, coagulation and fibrinolysis is enhanced and associates with renal anti-neutrophil cytoplasmic antibody-associated vasculitis†

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†This paper is intended to consideration for inclusion in the special issue dedicated to ANCA-associated vasculitis.

ABSTRACT

Background. While the incidence of thromboembolism in anti-neutrophil cytoplasmic antibodies-associated vasculitis (AAV) is high, the coagulation and fibrinolysis profile in AAV patients remains poorly characterized. We aimed at studying this profile in association with vasculitis activity and renal function.

Methods. This prospective study included 21 AAV patients with renal disease and 40 controls with other chronic kidney disease. Platelet count, antithrombin, FVIII:C, von Willebrand factor (VWF) activities (VWF:RCo) and antigen (VWF:Ag), fibrinogen, prothrombin fragments (F1 + 2), fibrin degradation product d-dimer and the presence of antiphospholipid antibodies were measured during the active and remission states of the AAV and at the baseline in controls. Occurrence of thromboembolic events was recorded.

Results. F1 + 2 was 2.6-fold and d-dimer was 5-fold higher during the active AAV than its remission (median 563 versus 212 pM and 3.0 versus 0.6 mg/L, P = 0.001 for both). FVIII:C (median 228%), VWF:RCo (198%) and VWF:Ag (222%) were the highest among the patients with active AAV and remained elevated also under remission. In active AAV, both F1 + 2 and d-dimer clearly associated with impaired renal function (r = −0.67, P = 0.001 and r = −0.66, P = 0.001). In AAV patients, two thromboembolic events occurred during the follow-up.

Conclusions. In active renal AAV, thrombin formation and especially fibrin turnover prevail compared both with remission and other kidney diseases. Overall, AAV is characterized by an enhanced coagulation, especially FVIII activity, which continues partly in remission.

Keywords: ANCA, coagulation, fibrinolysis, kidney, vasculitis

INTRODUCTION

The most common forms of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are granulomatosis with polyangiitis (Wegener’s) (GPA) and microscopic polyangiitis (MPA). In both entities, renal involvement is prevalent in the initial stages of disease: 67–92% of the MPA [1, 2] and 20–77% of the GPA patients [1–5].

The high risk of venous thromboembolic events (VTEs) was originally reported in paediatric AAV patients [6]. Later, several cohorts of AAV patients with increased incidence of venous thromboses were published [7–9]. In the Dutch cohort, VTE was more common in patients with MPA and renal-limited vasculitis than among patients with GPA (24 versus 7%) [9].

Neither established risk factors for thrombosis, nor deficiencies of protein C, protein S or antithrombin (AT) deficiencies were noted in a German cohort where all patients had kidney involvement [8]. Although the prevalence of antiphospholipid antibodies (aPLab) in patients with GPA is slightly higher compared with the general population, aPLab and VTE did not associate [10, 11]. Additionally, in patients with
GPA and VTE, the prevalence of mutations such as factor V Leiden, prothrombin (G20210A) and methylenetetrahydrofolate reductase did not differ from the general population [11].

Coagulation markers, especially the impact of renal impairment on coagulation factors, in the context of AAV are poorly documented. The aim of this study was to characterize the profile of coagulation factors in renal AAV in the acute phase of the disease and later on when the patients achieved remission. Furthermore, we aimed at evaluating whether the markers of coagulation and fibrinolysis could reflect the AAV disease activity. The AAV patients were compared with two groups of patients having various kidney diseases with varying kidney dysfunction, which enabled us to examine also the association of kidney function with coagulation activity.

**MATERIALS AND METHODS**

**Study design**

This prospective observational study was carried out at the Helsinki University Hospital Divisions of Nephrology and Haematology, Unit of Coagulation Disorders, Department of Medicine, Clinical Chemistry and HUSLAB Laboratory Services, and Department of Pathology during 2008–11. The study was approved by a local Ethics Committee and conducted according to the Helsinki Declaration. All patients were informed about the aim of the study and gave their written, informed consent.

**Patients**

The study group consisted of 21 consecutive patients with active, renal AAV diagnosed at the Division of Nephrology. Of these, seven patients had GPA, including one with the overlapping syndrome of GPA and anti-glomerular basement membrane disease. Fourteen patients were classified to have MPA, including three patients with renal-limited AAV. Diagnosis was based on renal biopsy in all but one patient with clinically evident MPA. In his case, renal biopsy was impossible due to acute coronary syndrome attributable to AAV. All AAV patients were newly diagnosed and were classified according to the consensus algorithm by Watts [12]. Patients on immunosuppressive medication for longer than 1 week were excluded.

Vasculitis disease activity and organ involvement were measured with Birmingham Vasculitis Activity Score (BVAS) [13].

The rationale for two control groups was to create a scenario where AAV patients could be compared with (i) patients having minimal renal damage and clinically and ethically justified renal biopsy material available (control group 1) and (ii) patients with anticipated similar renal impairment as the AAV patients (control group 2). Control group 1 consisted of 20 patients with mild, biopsy-proven kidney disease with estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m² and mild renal histology. Control group 2 comprised 20 patients with moderate to severe chronic kidney disease (CKD) (eGFR < 60 mL/min/1.73 m² and renal histology with sclerotic findings). Patients with diabetes mellitus, history of previous thromboembolic events, nephrotic syndrome or anticoagulant medication other than aspirin were excluded from the control groups.

The demographic data of all study patients are given in Table 1 and the histologic data in Table 2.

**Laboratory analysis**

To assess the activation of coagulation and fibrinolysis, blood samples were collected from each patient. From the AAV patients, blood samples were obtained during the active phase of the disease and repeated when the patient was in stable remission (median 6.1 months, range 3.2–18.3). In AAV patients, blood samples were collected as early as possible after the patient had entered the study.

Citrate-anticoagulated (109 mM sodium citrate) samples were centrifuged at 2500 g for 10 min, and separated plasma samples were frozen at −70°C.

Laboratory analysis consisted of plasma prothrombin time (PT, Nycotest PT®, Axis-Shield PoC As, Oslo, Norway), activated partial thromboplastin time (APTT, Actin FSL®), thrombin time (TT, BC Thrombin Reagent®), AT activities (a chromogenic assay, Berichrom®Antithrombin III), fibrinogen (a modification of the Clauss method, Multifibren® U), factor VIII activity (FVIII:C, one-stage clotting assay, Pathromtin SL).

### Table 1. Characteristics of the study patients

<table>
<thead>
<tr>
<th></th>
<th>Vasculitis (N = 21)</th>
<th>Control group 1 (N = 20)</th>
<th>Control group 2 (N = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>16/5</td>
<td>11/9</td>
<td>14/6</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 (18–84)</td>
<td>44 (21–66)</td>
<td>57.5 (25–77)</td>
<td>0.03a</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>9</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>On ACEi or ARB</td>
<td>7</td>
<td>7</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>Statin</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>ASA</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>CAD</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Smokers</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>21 (7–45)</td>
<td>91 (66–107)</td>
<td>44 (31–50)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>du-U-Prot (mg/day)</td>
<td>850 (60–1340)</td>
<td>800 (312–1485)</td>
<td>600 (260–1390)</td>
<td>–</td>
</tr>
</tbody>
</table>

Data are presented as median (range) for age and median (25th and 75th percentiles) for eGFR and du-U-Prot.

F, female; M, male; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin renin blocker; ASA, acetylsalicylic acid; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate (CKD-EPI formula); du-Prot, daily urine protein excretion.

*aComparison between active vasculitis and control group 1; dashes indicate P ≥ 0.05.

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and Coagulation Factor VIII Deficient Plasma), von Willebrand factor antigen (VWF:Ag with VWFag Latex Reagent) and ristocetin cofactor activity (VWF:RCo with BC von Willebrand Reagent); all analysed with the WCS XP analyser (Siemens Healthcare diagnostics, Marburg, Germany); and prothrombin fragments (F1 + 2, enzyme immunoassay Enzygnost® F1 + 2, monoclonal) and all reagents from Siemens Healthcare Diagnostics. D-dimer was measured with an immunoturbidimetric assay (Tina-quant D-Dimer®, Roche Diagnostics, Mannheim, Germany). The reference values for PT were 70–130%, APTT 23–33 s, TT 17–25 s, AT 84–108%, fibrinogen 1.7–4.0 g/L, FVIII:C 52–148%, VWF:Ag 50–169%, VWF:RCo 44–183%, F1 + 2 69–229 pmol/L and d-dimer ≤0.5 mg/L, respectively.

The lupus anticoagulant (LA) was detected using two screening tests based on APTT (IL Test APTT-SP, Instrumentation Laboratory, Italy) and Russell Viper Venom activated clotting time (DVVtest 10, American Diagnostica, Inc.). Anticardiolipin (aCL) and anti-beta2 glycoprotein I-specific phospholipid antibodies of IgG class (aβ2GP) were detected with immunological assays (Varelsa Cardiolipin IgG Antibodies and Beta-2-Glycoprotein I IgG Antibodies, Phadia GmbH, Freiburg, Germany) (respectively) with reference values of <15 U/mL.

To assess the accumulation or load of acquired coagulation abnormalities in different groups, the abnormality of each nine variable (thrombocytosis, short thrombin time, low AT, high fibrinogen, FVIII:C, VWF:Ag, VWF:RCo, F1 + 2 and d-dimer above reference) was included (one point for every variable), providing a total score of 0–9.

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used for eGFR [14].

### Statistical analyses

Platelet count and markers of coagulation and fibrinolysis were the primary response variables in this study. The variable distributions were checked using Kolmogorov–Smirnov test and graphical plots. Means and standard deviations are provided for normally distributed data. Non-normally distributed demographic variables are expressed as medians with ranges and non-normally distributed response variables are expressed as medians with IQR (25th–75th percentiles). The logarithmic transformation was used for variables skewed to the right, when appropriate, to normalize the distributions. The paired samples $t$-test or non-parametric Wilcoxon signed-ranks test was used to evaluate changes between acute and remission phase. Comparisons between study groups were based on analysis of variance (ANOVA) or the non-parametric Kruskal–Wallis test. After Kruskal–Wallis test, the adjusted Mann–Whitney $U$-test was used for paired comparisons. The Spearman’s rank (rho) or Pearson’s correlation ($r$) coefficients were used to study the associations between the response variables. All the correlations were confirmed with the scatter plots. Two-tailed P-values <0.05 were considered statistically significant. Analysis was performed using IBM SPSS Statistics for Windows (version 22.0, IBM Corp., Armonk, NY).

### RESULTS

#### Kidney function and dialysis treatment

Kidney function of the majority (56%) of AAV patients improved upon remission, was unchanged in 22% of patients and decreased in 22% of patients. However, the change in GFR from active phase to remission was non-significant (medians 21 and 35 mL/min/1.73 m², $P = 0.15$). Three out of the four patients who were on dialysis at time of diagnosis continued on dialysis also at the time of remission and one died (2 months after diagnosis, regarded as an acute ischaemic heart disease event, no autopsy). Later, soon after diagnosis, dialysis was needed in three other patients, one of them with reversible kidney function at the remission.

#### Anaemia, platelets and inflammation

Anaemia was frequent in 62% of AAV patients (median 105 g/L, IQR 91–134) in the acute phase of disease, while in remission median haemoglobin (Hb) increased to 122 (119–141). In control group 1, only one patient had anaemia (in the whole group median 141 mg/L, IQR 131–152), whereas median Hb in control group 2 was 124 (IQR 110–140) and 50% of patients were anaemic. Platelet counts, even though not particularly high in active AAV, decreased during remission to the level of the control groups (Figure 1). In active AAV, all four dialysis patients had platelet counts below the mean of the whole AAV group.

Median C-reactive protein (CRP) of AAV patients at diagnosis was 113 mg/L (IQR 19–134), whereas upon remission it was normalized in all (median 2, IQR 2–5). In contrast, in the control groups, CRP was low (group 1: median 2, IQR 2–2.5 and group 2: median 2, IQR 2–5, respectively). The highest fibrinogen levels were also detected during active AAV (Table 3). Nevertheless, remission values still exceeded normal values in 78% of AAV patients. Noteworthy, in the majority of patients in control groups 1 and 2, fibrinogen was also above normal (65 and 70%, respectively).
Figure 1: Platelet counts (A), AT activity (B), prothrombin fragments (C) and d-dimer (D) in vasculitis patients during the active phase of disease and in remission. d-dimer is plotted on a logarithmic scale.

Table 3. Platelet count and coagulation variables during the acute phase and at remission in AAV and control patients

<table>
<thead>
<tr>
<th></th>
<th>AAV patients</th>
<th>Control group 1</th>
<th>Control group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Remission</td>
<td>N = 20</td>
</tr>
<tr>
<td>Platelets (E9/L)</td>
<td>290 ± 116</td>
<td>224 ± 59</td>
<td>246 ± 60</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>123 ± 19</td>
<td>145 ± 19</td>
<td>125 ± 23</td>
</tr>
<tr>
<td>Thrombin time (s)</td>
<td>17 (16–17)</td>
<td>17 (16–19)</td>
<td>17 (17–19)</td>
</tr>
<tr>
<td>AT activity (%)</td>
<td>99 ± 15</td>
<td>116 ± 14</td>
<td>111 ± 14</td>
</tr>
<tr>
<td>Factor VIII (%)</td>
<td>228 (187–266)</td>
<td>191 (177–256)</td>
<td>140 (113–158)</td>
</tr>
<tr>
<td>VWF:RCo (%)</td>
<td>198 (164–292)</td>
<td>196 (170–304)</td>
<td>95 (79–119)</td>
</tr>
<tr>
<td>VWF:Ag (%)</td>
<td>222 (168–266)</td>
<td>193 (165–236)</td>
<td>104 (88–129)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>6.9 ± 2.6</td>
<td>5.2 ± 1.5</td>
<td>4.5 ± 1.3</td>
</tr>
<tr>
<td>F1 + 2 (pM/L)</td>
<td>563 (385–730)</td>
<td>212 (184–318)</td>
<td>164 (126–196)</td>
</tr>
<tr>
<td>d-dimer (mg/L)</td>
<td>3.0 (1.1–6.6)</td>
<td>0.6 (0.2–0.8)</td>
<td>0.2 (0.1–0.4)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or median (25th–75th percentiles). Dashes indicate P ≥ 0.05.

AAV, ANCA-associated vasculitis; APTT, activated partial thromboplastin time; F1 + 2 prothrombin fragments; VWF:RCo, von Willebrand factor ristocetin cofactor activity; VWF:Ag, VWF antigen.

1Comparison with active vasculitis.

2Comparison with vasculitis in remission.
Laboratory markers of coagulation and fibrinolysis

Coagulation data during the acute phase and at remission in AAV patients were compared with the control groups (Table 3). The most distinct finding was the high level of F1+2 during acute AAV, as 18 of the 21 patients exceeded normal values (Supplementary Data, Table S1). All four dialysis patients had F1+2 above the median (563 pM/L); the same applied to two patients requiring dialysis within 1 month after dialysis, as well as those two developing thromboembolic events later on (Figure 1). All five patients with the lowest F1+2 levels (25% quartile, levels < 385 pM/L) exhibited a disease course without complications or otherwise low disease activity.

Moreover, D-dimer was 5-fold higher during active AAV compared with remission phase. Only four AAV patients, all with a lower disease burden (BV AS 10–12), had normal D-dimer (Figure 1). Even though D-dimer decreased considerably when remission was achieved, 50% of patients continued to have a D-dimer above normal reference.

The vast majority (81%) of the patients with active AAV had high levels of FVIII compared with reference levels. Indeed, during active AAV, 62% of patients had FVIII over 200%, a level commonly considered as a risk for thrombosis. FVIII remained substantially elevated in remission. Again, VWF:RCo and VWF:Ag exhibited high levels during both active and remission phases of AAV.

AT activity was within normal limits in 76% of patients with active AAV. Whereas in remission, a notable shift upwards was observed, as 67% of the patients expressing supranormal AT activity (Figure 1). Interestingly, TT was shorter than normal in 43% of the patients during active AAV, and moreover, it remained unchanged during remission.

Suprisingly, our AAV patients presented virtually no aPLAbs.

Associations between renal function, proteinuria, vasculitis disease activity and coagulation and fibrinolysis

Intriguingly, during active AAV, F1+2 levels and D-dimer negatively correlated with eGFR (after logarithmic transformations \( r = -0.67, \ P = 0.001 \) and \( r = -0.66, \ P = 0.001 \), respectively) (Figure 2). In contrast, these associations were absent in the control groups. Again, F1+2 levels and D-dimer associated with daily protein excretion (dU-prot) in active AAV \( (r = 0.68, \ P = 0.001 \) and \( r = 0.47, \ P = 0.04 \)). D-dimer, unlike F1+2, correlated also with BVAS \( (r = 0.52, \ P = 0.02 \).

Load of coagulation abnormalities

At least one abnormality was noted in all but one (95%) active AAV patient. In remission, the situation remained unchanged, as no patient presented without any coagulation abnormalities. However, the cumulative load of coagulopathies alleviated from active AAV to remission (Figure 3). Also, in the control groups, abnormalities were common: 85% of the patients in group 1 and 90% in group 2 had at least one acquired coagulation abnormality. Nevertheless, the total load of abnormalities was limited in the control groups compared
with both active AAV. The coagulation load in the remission phases of AAV was comparable with group 2.

Thromboembolic events

Two VTE cases occurred among AAV patients (9.5%) during the induction treatment period: one deep venous thrombosis at 3 months after the MPA diagnosis and one pulmonary embolism at 4 months after the GPA diagnosis. Neither patient was immobilized or dialysis dependent. Thus, the incidence of VTE in our AAV patients was 9 per 100 patient years (two events during 18.5 person years of observation). In the control groups, VTE did not occur. Moreover, one arterial thrombosis in coronary arteries occurred resulting in the death of one patient during the active AAV phase. Further clinical data of the AAV patients are provided as Supplementary data.

DISCUSSION

We observed that active, renal AAV associates with accumulation of prothrombotic features. Especially, thrombin formation and fibrin turnover were emphasized during active AAV compared with remission and other kidney diseases. In addition, the lower the eGFR in patients with active AAV, the higher were the F1 + 2 and d-dimer, suggesting that thrombin formation and fibrin turnover were associated with renal impairment of AAV patients. Up-regulation of FVIII and VWF manifested both during active and remission phases of AAV.

Renal impairment per se influences on coagulation. Patients in early stages of CKD are reported to exhibit several coagulation abnormalities, such as increased levels of tissue factor, VWF, activated protein C, FVII, FXII, fibrinogen, plasminogen activator inhibitor-1 and d-dimer, but reduced tissue-type plasminogen activator [15, 16]. Also in our study, 85–90% of the CKD patients without AAV had at least one acquired manifestation of coagulopathy. Fibrinogen levels were elevated in patients with mild renal insufficiency already without clear difference among patients with more severe CKD or AAV at remission. In these groups, fibrinogen failed to associate with CRP, suggesting that instead of being a surrogate marker of inflammation fibrinogen is an independent procoagulant indicator of the early stages of CKD.

Also, the effect of medication on thrombogenesis and risk of VTE in vasculitis must be considered. On a population-based level, the risk of VTE is increased among glucocorticoid (GC) users, as recently the reported risk of VTE was as high as 3.06 (95% CI 2.77–3.38) for the novel users (<90 days) of systemic GC [17]. On the other hand, GC use in the setting of increased inflammatory activity could improve the milieu by decreasing the levels of fibrinogen, VWF activity, and increasing the levels of natural anticoagulants AT, protein C and protein S [18].

To our knowledge, this is the first study examining markers of coagulation and fibrinolysis in AAV patients with renal disease, including also patients with end-stage renal disease and the need of dialysis. Hergesell and co-authors initially reported that d-dimer and thrombin–AT complexes differentiated in active AAV versus remission state of AAV and additionally correlated with the clinical disease activity [19]. In their cohort, AAV patients with low creatinine clearance (<25 mL/min) were excluded. In our study, d-dimer was markedly elevated during the active phase of AAV. In addition, d-dimer correlated with BVAS, suggesting that activation of coagulation and fibrinolysis is exceedingly linked to multi-organ manifested AAV. Furthermore, during active AAV, in contrast to remission or in the control groups, both d-dimer and F1 + 2 negatively correlated with eGFR, implying that enhanced thrombin formation and fibrin degradation could exert a pathogenetic role in the kidney disease in AAV. Active AAV increased thrombin formation, demonstrated as elevated F1 + 2. Furthermore, F1 + 2 seemed to distinguish AAV patients with more complicated course of disease from those with the milder disease.

Neutrophil-derived microparticles (NPMs) can contribute to thrombosis by delivering tissue factor to a blood clot and modifying neutrophil–platelet crosstalk [20, 21]. Daniel et al. [22] reported increased levels of NPMs in various nephrological subgroups; interestingly, the patients with acute vasculitis showed the highest degree of NMPs expression. Microparticle-mediated thrombin generation is shown in children with active vasculitis suffering from thromboembolic complications [23]. In vitro, ANCs are capable of inducing NMPs from primed neutrophils; furthermore, these NMPs promote the generation of thrombin [24]. These results could contribute to the mechanisms of our findings.

Recently, Hilhorst et al. [25] reported that AAV patients in stable remission express increased levels of both tissue factor pathway inhibitor and FVIII. In our study, too, FVIII, as well as VWF activity, remained elevated throughout the phases of AAV. This is in agreement with the original observation of Hergesell and co-authors [19] who showed elevated VWF activity in AAV, regardless of disease activity. High level of VWF and FVIII could reflect not only the ongoing endothelial involvement in AAV, but also the renal dysfunction since elevated levels were observed in the control group 2 as well.

Interestingly, AT being mainly normal during active AAV increased over normal limits in remission. Elevated AT could compensate the otherwise increased procoagulant state towards remission.

In this study, the VTE incidence of AAV patient was 9 per 100 person years. This is consistent with previous studies showing an incidence of 4.3–7.0 VTE per 100 person years [7–9, 26]. These numbers signify around 50-fold increment in the risk of VTE in AAV patients compared with the common Western population [27, 28].

Previously [10, 11], but not in our study, aPLAbs have been found in higher numbers in patients with AAV. However, we only included IgG class aCL and β2GPI antibody detection in addition to LA in our panel, while others commonly found IgM and IgA classes in vasculitis.

One limitation of this study is the limited number of individuals in the different patient groups and the single centre data. Additionally, as all patients had kidney disease the results may not be generalized to AAV patients without renal manifestations. Second, the AAV group was heterogeneous with the number of factors and complications interfering with the
delicate system of hemostasis. Also, the amount of smokers was highest (albeit statistically non-significant, P = 0.40) among the AAV patients, imposing them on a more thrombotic state. However, the prospective setting of our study allows us to assess many contributors of coagulation, whereas the low number of patients in different subgroups precludes complex statistics and adjustment of related factors.

In conclusion, active AAV with renal manifestation presents a state of enhanced coagulation and fibrinolysis, which somewhat but not completely alleviates when remission is achieved. However, the coagulation profile of vasculitis does not reflect the disease alone. Impact of other conditions, such as renal impairment and treatment, must be taken into account and has to be addressed in future studies. AAV with kidney disease may be a special subgroup among AAV patients due to accumulation of different prothrombotic features. More research is required to target the role of coagulation management and treatment for the patients at risk to reduce the organ damage and co-morbidities.

ACKNOWLEDGEMENTS

We thank MD Sari Aaltonen for her help in recruiting the study patients; thank Mrs Tarja Porskka, Marja Lemponen and Ellen Saarela for help in the laboratory analysis; thank Tuija Poussa, MSc, for her assistance in statistical analysis and producing the figures. A.S. was financially supported by the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital, Medical Society of Finland (Finska Läkaresällskapet) and Kidney Foundation in Finland.

CONFLICT OF INTEREST STATEMENT

None declared.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

REFERENCES


Received for publication: 29.6.2014; Accepted in revised form: 19.11.2014