Possible contribution of cytomegalovirus infection to the high risk of (recurrent) venous thrombosis after renal transplantation

Willem M. Lijfering,[1] Aiko P. J. de Vries[2], Nic J. G. M. Veeger[3], Willem J. van Son[2], Stephan J. L. Bakker[2], Jan van der Meer[1]

[1]Division of Haemostasis, Thrombosis and Rheology; [2]Divison of Nephrology; [3]Department of Epidemiology, University Medical Centre Groningen (UMCG), the Netherlands

Summary

Renal transplant recipients are at an increased risk of venous thrombosis, which has been regarded as a postoperative complication, although it may persist afterwards. As numerous case reports have shown that active cytomegalovirus (CMV) infection can be found at time of onset of venous thrombosis, and is frequently found in renal transplant recipients, we hypothesized that one might be the result of the other. To calculate the risk of (recurrent) venous thrombosis in renal transplant recipients, and to see whether CMV infection influenced this risk, we retrospectively analysed 606 living consecutive renal transplant recipients. CMV status at time of transplantation and at time of enrolment was determined. Absolute risks of first venous thrombosis and recurrence were compared with CMV status, and were corrected for surgery related venous thrombosis, age, and anticoagulant treatment. Annual incidence of venous thrombosis was 0.88% (95% CI, 0.65–1.15) in all recipients and 0.59% (95% CI, 0.41–0.83) corrected for surgery related venous thrombosis. CMV positive and seroconverted recipients tended to have an increased risk of venous thrombosis compared to CMV negative recipients; corrected relative risks were 2.0 (95% CI, 0.9–5.2) and 1.7 (95% CI, 0.6–4.7), respectively. The cumulative 10-year recurrence rate of venous thrombosis in CMV seronegative, seroconverted, and seropositive recipients was 10%, 51% and 59%, respectively. We conclude that CMV infection tended to be associated with an increased risk of (recurrent) venous thrombosis. Prospective studies are warranted to establish this observation, which suggests that CMV infection influences the high risk of (recurrent) venous thrombosis in renal transplant recipients.

Keywords

Renal transplant recipients, cytomegalovirus, venous thrombosis, recurrent venous thrombosis

Thromb Haemost 2008; 99: 127–130

Introduction

Renal transplant recipients are at an increased risk of developing venous thrombosis, with its highest incidence within the first three months after transplantation (1). Whether they remain at an increased risk after three months is largely unknown. Recently, however, two reports showed a recurrence rate of up to 60% within six years after stopping initial anticoagulant treatment (2, 3). The high risk of venous thrombosis in renal transplant recipients has been attributed to surgery, long-term immunosuppressive drugs and antiphospholipid antibodies (4, 5). Active cytomegalovirus (CMV) infection might be interesting as another contributing factor, because it is a very common complication in renal transplant recipients, and CMV has a lifelong latency after initial infection (6). Due to immunosuppressive drugs CMV can easily reactivate (7). CMV infects endothelial cells, causing vascular cell damage (8, 9), induces lupus anticoagulant (10), and enhances factor VIII synthesis or secretion (11, 12). Furthermore, vascular damage has been associated with high levels of soluble vascular cell adhesion molecule-1 (sVCAM-1) (13, 14). Since elevated levels of factor VIII, and sVCAM-1, and lupus anticoagulant are all associated with an increased risk of venous thrombosis (14–16), and, obviously, all recipients require prolonged immunosuppressive therapy, active CMV infection might increase this risk indirectly. This assumption is supported by numerous case reports of venous thrombosis during CMV infection, which recently have been reviewed (17, 18). However, it is not clear whether subjects with primary CMV infection or CMV reactivation indeed have a higher risk of venous thrombosis compared to CMV negative subjects. Only a few seroepi-

Correspondence to:
Dr. Willem Lijfering
Division of Haemostasis, Thrombosis and Rheology
University Medical Centre Groningen
Hanzeplein 1, 9713 GZ Groningen
The Netherlands
Tel.: +31 50 3612791, Fax: +31 50 3611790
E-mail: w.lijfering@int.umcg.nl

Received May 10, 2007
Accepted after major revision November 11, 2007

Prepublished online December 5, 2007
doi:10.1160/TH07-05-0340

demiological studies have reported about this possible association, but were inconclusive, possibly as these studies did not include CMV infection in their primary objectives (2, 3). Recipients with chronic rejection might be an interesting subgroup as it has been associated with CMV infection in allograft recipients (25).

We performed a study to assess the absolute risk of first venous thrombosis and recurrence, respectively in renal transplant recipients. We estimated this risk in recipients who either had CMV infection prior to transplantation or developed CMV infection after transplantation, compared to CMV seronegative renal transplant recipients to ascertain the contribution of CMV infection.

Materials and methods

Subjects

Between October 2001 and November 2005 all renal transplant recipients who were operated in our centre since 1968 and who survived with a functioning allograft were asked to participate in the study at their visit to the outpatient clinic (date of enrolment). Patients who had received a combined transplantation (i.e. kidney and pancreas or kidney and liver) were invited to participate as well. Between 1968 and 1989, after transplantation, patients received a combination of prednisolone and azathioprine as immunosuppressive therapy, between 1989 and 1997 a combination of ciclosporine and low dose prednisolone, and after 1997 a combination of ciclosporine, mycophenolate mofetil and low dose prednisolone. No CMV prophylaxis was given throughout the study period. Induction therapy was not given until January 2000. After this date recipients were standardly given IL-2 receptor blocker (daclizumab) on the date of transplantation, and 14 days after transplantation. A total of 606 out of 847 (72%) renal transplant recipients gave written informed consent.

Relevant donor, recipient and transplant characteristics were extracted from the Groningen Renal Transplant Database. This database holds information of all renal transplantations that have been performed at our centre since 1968. Extracted from the database were primary renal disease, type and date of transplantation, and CMV status at time of transplantation. Information about previous episodes of venous thrombosis and anticoagulant treatment was collected by reviewing medical records. The study was approved by the institutional review board of our hospital.

Laboratory studies and definitions

Blood was drawn at enrolment to determine serum creatinine levels, platelet counts, IgG antibodies against CMV and sVCAM-1 levels. Serum creatinine levels were determined using the Jaffé method. Twenty-four hour creatinine was determined from a 24-h urine sample. CMV IgG antibodies were determined by enzyme immunoassay as previously described (17). Patients were classified as CMV seropositive when they had a CMV IgG titer above 1 IU/ml at time of transplantation. CMV seroconversion was defined when patients were seronegative at time of transplantation, but had a CMV IgG titer above 1 IU/ml at date of enrolment. All other patients were classified as seronegative for CMV. CMV IgG levels > 250 IU/ml at time of enrolment were classified as active CMV infection as previously described (11). Soluble VCAM-1 levels were measured in EDTA plasma by ELISA (Bender MedSystems, Vienna, Austria).

Venous thrombosis was considered established if deep vein thrombosis was confirmed by compression ultrasound or venography, and pulmonary embolism by ventilation and perfusion lung scanning, spiral CT scanning or pulmonary angiography.

Statistical analysis

We analyzed the absolute risk of first venous thrombosis after transplantation in all renal transplant recipients. CMV seropositive and CMV seroconverted renal transplant recipients were compared with seronegative CMV renal transplant recipients. Age, sex and rejection of the graft were also taken into account to assess whether these variables had an additional effect on the risk of venous thrombosis. Annual incidence of venous thrombosis was calculated by dividing the number of events by the number of observation years. Observation time was defined as the period from transplantation until the first venous thrombotic episode or until the end of the observation period. Relative risks were corrected for renal transplant surgery related venous thrombosis by subtracting the first three months after transplantation from the observation time in all recipients, and by excluding recipients from analysis who had venous thrombosis within the first three months after transplantation. Correction for anticoagulant treatment was done by subtracting the treatment time (227 years) from the observation time. As a consequence, patients who were on life-long anticoagulant treatment at time of transplantation for any reason were excluded from analysis, and patients in whom life-long anticoagulant treatment became indicated after transplantation only the remaining period at risk was evaluated. These patients had either recurrent venous thrombosis prior to transplantation (n=4), or prosthethic heart valves (n=11), atrial fibrillation (n=12), chronic heart failure (n=5), peripheral arterial occlusive disease (n=4) or vasculitis (n=4) before or after transplantation. Correction for age was done by using Mantel-Haenszel methods, stratifying recipients in aged younger than 50 years, and aged 50 years or older.

Freedom of first venous thrombosis and recurrence was analyzed by the Kaplan-Meier method. The cumulative recurrence rate was calculated over the period from the end of anticoagulant treatment after the first episode of venous thrombosis until either the date of first recurrence or the end of the observation period.

Continuous variables are expressed as median values and ranges; categorical data as counts and percentages. Differences between groups were evaluated by the Student t test or Mann-Whitney U test, depending on the normality of data for continuous data and by Fisher exact test for categorical data. A two-tailed p-value of less than 0.05 indicated statistical significance. The 95% confidence intervals (95% CI) around the incidence rates were calculated under the Poisson distribution assumption. Statistical analyses were performed using SPSS software, version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics of 606 renal transplant recipients who were enrolled are summarized in Table 1. Forty-five percent were women. Median age at enrolment was 55 years (range, 23–83

Table 1: Clinical characteristics.

	CMV negative	CMV positive	CMV seroconversion	Total
No. of patients	169	285	152	606
Women, no. (%)	68 (40)	139 (49)	67 (44)	274 (45)
Median age at enrolment, year (range)	51 (23–78)	56 (24–83)	55 (24–83)	55 (23–83)
Age at transplantation, year (range)	40 (18–66)	47 (17–77)	41 (15–73)	44 (15–77)
Cause of end stage renal disease, no. (%)				
Primary glomerular disease	44 (26)	71 (25)	55 (36)	170 (28)
Glomerular disease of vascular/autoimmune origin	9 (5)	23 (8)	7 (5)	39 (6)
Tubular interstitial disease	31 (18)	36 (13)	27 (18)	94 (16)
Polycystic renal disease	28 (17)	61 (21)	18 (12)	107 (18)
Dysplasia and hypoplasia	12 (7)	6 (2)	3 (2)	21 (3)
Renovascular disease	9 (5)	17 (6)	7 (5)	33 (5)
Diabetes mellitus	6 (4)	12 (4)	4 (3)	23 (4)
Other or unknown cause	30 (18)	58 (20)	31 (20)	119 (20)
First venous thrombosis, no. (%)	13 (8)	23 (8)	16 (11)	52 (9)
Median age at onset, year (range)	52 (21–65)	51 (31–69)	43 (28–65)	51 (21-69)
Renal transplant surgery induced venous thrombosis, no. (%)	8 (5)	6 (2)	5 (3)	19 (3)
Deep vein thrombosis ipsilateral from kidney transplantate, no. (%)	7 (4)	9 (3)	5 (3)	21 (3)
*Deep vein thrombosis contralateral from kidney transplantate, no. (%)**	4 (2)	7 (2)	2 (1)	13 (2)
Pulmonary embolism, no. (%)	2 (1)	7 (2)	9 (6)	18 (3)
History of transplant rejection, no. (%)	11 (7)	35 (12)	18 (12)	64 (11)
sVCAM-1 (ng/ml), mean (± SD)	896 (343)	1088 (451)	1091 (416)	1035 (432)
CMV IgG > 250 IU/ml	NA	50 (18)	25 (16)	75 (12)
Serum creatinine (μM), mean (± SD)	146 (52)	165 (85)	163 (100)	159 (82)
24-h creatinine clearance, mean (± SD)	58 (20)	53 (25)	52 (22)	53 (23)
Actual platelet number, 10e9/L, median (range)	233 (70–481)	220 (41–591)	214 (44–486)	223 (41–591)
Thrombocytopenia, < 100 X 10e9/L, no. (%)	3 (2)	3 (1)	2 (1)	8 (1)

* *wo renal transplant recipients had axillary vein thrombosis;* SD, denotes standard deviation; NA, not applicable.

years), and 44 years at transplantation (range, 15–77 years). All recipients routinely received perioperative thromboprophylaxis.

Venous thrombosis had occurred in 52 recipients (9%) after transplantation. Median age at onset was 51 years (range, 21–69 years). Of these patients, 37% had venous thrombosis within the first three months, 40% had deep vein thrombosis on the ipsilateral side of the kidney transplant, 25% had deep vein thrombosis on the contralateral side of the transplant, and 35% had pulmonary embolism. Venous thrombotic event-free survival showed that the highest risk of venous thrombosis was in the first six months, but patients remained at risk over the next 10 years (Fig. 1). Recipients received oral anticoagulants because of their first venous thrombosis for a median time of six months (range, 3–156 months). Seven of them still received oral anticoagulants for this reason at date of enrolment and were excluded from analysis of recurrent venous thrombosis.

Annual incidence of venous thrombosis was 0.88% (95% CI, 0.65–1.15) in all recipients (Table 2). It was 0.59% (95% CI, 0.41–0.83) when excluding the first three months after renal transplant surgery from observation time. Recipients who were 50 years or older tended to have a higher risk of venous thrombosis than younger recipients; corrected relative risk 1.7 (95% CI, 0.9–3.5). Annual incidence of venous thrombosis in females was 0.75% (95% CI, 0.46–1.14) compared to 1.00% (95% CI, 0.68–1.41) in males; corrected relative risk 0.9 (95% CI, 0.4–1.6). In CMV seronegative recipients annual incidence of venous thrombosis was 0.81% (95% CI, 0.11–0.82), in CMV seropositive recipients 0.98% (95% CI, 0.62–1.46), and in CMV seroconverted recipients 0.81% (95% CI, 0.46–1.31); corrected relative risks compared to CMV seronegative recipients were 2.0 (95% CI, 0.9–5.2) and 1.7 (95% CI, 0.6–4.7), respectively.

In recipients who were CMV seropositive, mean sVCAM-1 levels were 1088 ng/ml and in CMV seroconverted recipients 1035 ng/ml, which were both higher compared to CMV seronegative recipients (mean sVCAM level 896 ng/ml; $P< 0.001$). In addition, recipients with elevated CMV IgG antibodies had also increased sVCAM-1 levels (mean level 1174 ng/ml vs 1015 ng/ml; $P< 0.001$). In recipients who experienced graft rejection,

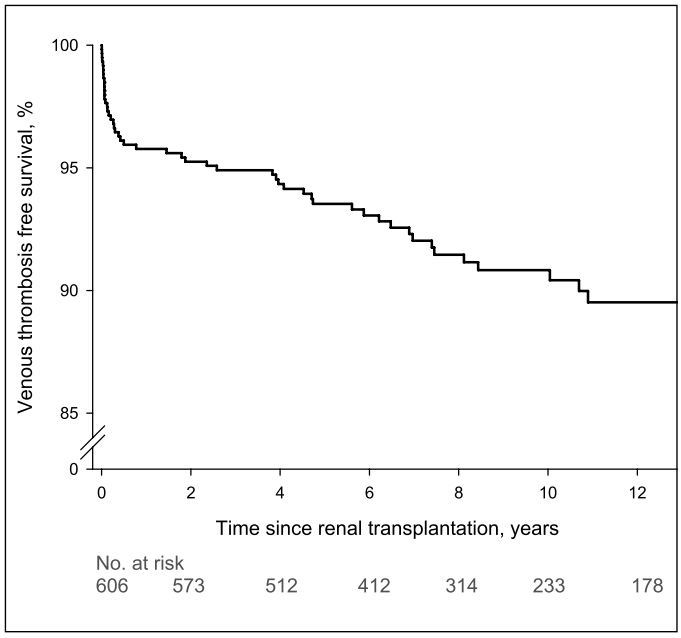

Figure 1: First venous thrombosis event-free survival in renal transplant recipients.

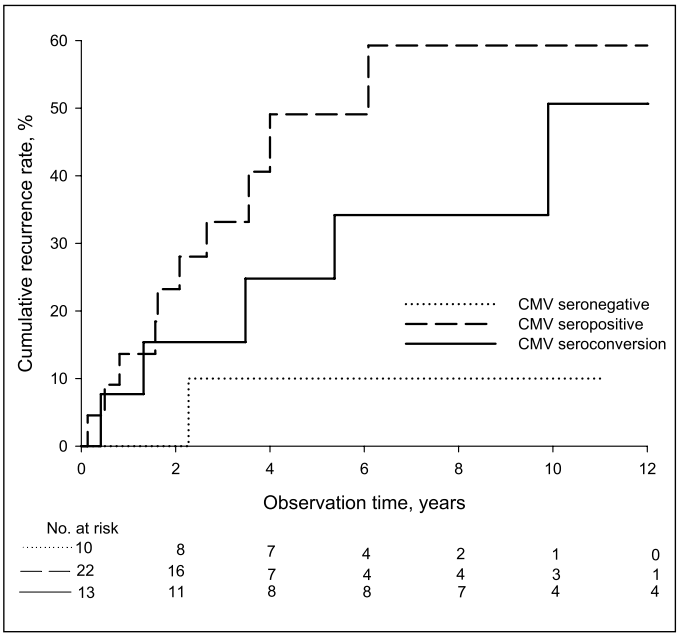

Figure 2: Cumulative recurrent rate of venous thrombosis in renal transplant recipients.

soluble VCAM-1 levels were higher than in patients who had no history of graft rejection (mean level 1921 ng/mL vs 1148 ng/mL; *P*=0.024). Fifty-three of the 64 recipients (83%) with a history of graft rejection were CMV seropositive at time of enrolment, compared to 384 (71%) recipients who had no history of graft rejection (*P*=0.044). Crude relative risk of venous thrombosis in recipients with graft rejection versus no graft rejection was 1.6 (95% CI, 0.7–3.4).

Within five years after withdrawal of oral anticoagulant treatment, 36% of recipients had recurrent venous thrombosis, and within ten years 45% of recipients. Subgroup analysis showed that 10% of CMV seronegative recipients had a recurrence within ten years, while in CMV seroconverted and seropositive recipients this risk was 51% and 59%, respectively (Fig. 2).

Discussion

In this cohort of renal transplant recipients, our most notable findings were a high incidence of first venous thrombosis and a high risk of recurrence. Overall, the absolute risk of first venous thrombosis was 8.8 times higher than reported in the general population (i.e. 0.1%) (18). Although renal transplant surgery had a considerable effect on the absolute risk of venous thrombosis, it remained six times higher compared to the general population after correction for the first three postoperative months. Patients remain at an increased risk of venous thrombosis for six weeks after other major surgical procedures, like hip and knee arthroplasty (27). Therefore, it is unlikely that the persisting high risk more than three months after renal transplantation is attributable to surgery. Despite our finding that aging is a possible confounder, recipients younger than 50 years were still at an increased risk of venous thrombosis. The prevalence of 9% of venous thrombosis in our study cohort is in agreement with two previous studies (2, 3), whereas another retrospective cohort study found an annual incidence of 0.29% of venous thrombosis (23). In the latter study, however, diagnosis of venous thrombosis relied on Medicare claims, and the follow-up of recipients in that study was limited to 1.5 to 3 years after transplantation, which may have caused an underestimation of the annual incidence of venous thrombosis. To our knowledge, no other studies have reported an annual incidence of venous thrombosis in renal transplant recipients. Recipients who died before the date of enrolment, were not included in the study. Thus, even though annual incidences of venous thrombosis were high in our study, it is possible that these risks are underestimated, especially when considering that pulmonary embolism is an important cause of mortality in renal transplant recipients (24).

Although CMV seroconverted recipients and CMV seropositive recipients in our study had a 1.7– and 2.0-fold increased risk of first venous thrombosis compared to CMV negative patients, respectively, the differences were not statistically significant. It is possible that this is a consequence of relatively small numbers of patients in this analysis of subgroups. Another explanation might be that the risk of CMV induced venous thrombosis in our population was diluted, assuming that CMV is mainly thrombogenic at time of primary infection or reactivation (19, 20). Unfortunately, this information was not available in our patients. As venous thrombosis within three months after transplantation was considered as postoperative, CMV induced venous thrombosis in this period was possibly missed. However, 5% of CMV seronegative versus 3% of CMV seroconverted, and 2% of CMV seropositive renal transplant recipients had venous thrombosis within the first three months postsurgery, making it less likely that this has influenced our results. The hypothesis that CMV increases the risk of venous thrombosis does, however, seem likely when considering the high rate of recurrent venous thrombosis in

Table 2: Risk of first venous thrombosis associated with age, sex and CMV status.

	Observation time (years)	Pt no. with event	Annual incidence, % (95% CI)	Corrected annual incidence, %* (95% CI)	Crude relative risk (95% CI)	Corrected relative risk* (95% CI)
Age (years)						
All	5941	52	0.88 (0.65–1.15)	0.59 (0.41–0.83)	-	
15–50	3251	25	0.77 (0.50–1.14)	0.45 (0.25–0.76)	Reference	Reference
≥ 50	2690	27	1.00 (0.66–1.46)	0.78 (0.47–1.22)	1.3 (0.8–2.2)	1.7 (0.9–3.5)
Sex						
Male	3115	31	1.00 (0.68–1.41)	0.63 (0.37–0.99)	Reference	Reference
Female	2826	21	0.75 (0.46–1.14)	0.55 (0.31–0.92)	0.8 (0.4–1.3)	0.9 (0.4–1.6)
CMV status						
Seronegative	1597	13	0.81 (0.43–1.39)	0.33 (0.11–0.77)	Reference	Reference
Pre-transplant seropositive	2359	23	0.98 (0.62–1.46)	0.78 (0.45–1.25)	1.2 (0.6–2.4)	2.0 (0.9–5.2)
Post-transplant seroconversion†	1985	16	0.81 (0.46–1.31)	0.59 (0.29–1.05)	1.0 (0.5–2.1)	1.7 (0.6–4.7)

*Annual incidence and relative risk corrected for anticoagulation use, renal transplant surgery induced venous thrombosis †Of 152 CMV seroconverted recipients, 146 received a CMV seropositive kidney.

our patients, i.e. 51% and 59% in CMV seroconverted and seropositive recipients, compared to 10% in CMV seronegative recipients. These findings, however, have to be handled with caution, as numbers were small. Elevated CMV IgG antibodies were associated with higher sVCAM-1 levels compared to recipients with low CMV IgG antibodies, while graft rejection was associated with elevated sVCAM-1 levels and tended to be more common in patients who had CMV infection and venous thrombosis. These findings support the hypothesis that CMV infection is associated with vascular damage, and that vascular damage during CMV infection is enhanced if patients experienced graft rejection, as postulated in another study (25). This might result in an increased risk of venous thrombosis. Since we only had information on CMV IgG levels at time of enrolment and not on CMV IgM levels or antigenemia, we may have incorrectly included recipients as having a non-active CMV infection while they had an active CMV infection. As other seroepidemiological studies which primarily addressed the effect of cytomegalovirus on the risk of venous thrombosis are lacking, it is difficult to compare our results with those from other studies. However, one other study reported a prevalence of 34% of active CMV infection in renal transplant recipients who had first venous thrombosis (2). This result was not further discussed by the authors, but seems in line with our findings. Another study failed to show CMV-viraemia in renal transplant recipients with recurrent venous thrombosis compared to recipients without recurrence (3). This might be explained as the diagnosis of active CMV infection in that study was made with a PCR method (21), from which it is known that it only detects viraemia levels for a short time, while a patient or doctor delay for diagnosing venous thrombosis is not uncommon in clinical practice. Unfortunately, they did not measure CMV antibodies, which remain increased until months after initial infection or reactivation and are lifelong detectable. Hence, that study might have missed active CMV infection at time of diagnosing recurrent venous thrombosis. In the absence of a controlled prospective study and because our results of the role of CMV infection in the development of venous thrombosis are not statistically significant, we cannot claim a cause-and-effect relationship of cytomegalovirus and the risk of venous thrombosis.

The risk of 36% to develop recurrent venous thrombosis within five years and 45% within ten years is in agreement with other studies that found a risk of 46–60% of recurrent venous thrombosis in renal transplant recipients over a similar time-period (2, 3). In the general population, the risk of recurrent venous thrombosis is 18% within ten years (27), and in antithrombin -, protein C -, or protein S – deficient patients the risk of recurrence is 23% within five years (28). This shows that the risk of recurrent venous thrombosis in renal transplant recipients is excessive, and at least demands the consideration whether renal transplant recipients should have prolonged anticoagulant treatment after their first venous thrombotic episode. On the other hand, our results may have been overstated, as none of our patients were screened for thrombophilia. We cannot rule out whether these patients had inherited thrombophilia. However, deficiencies of antithrombin, protein C or protein S are rare, even in patients who had venous thrombosis (29). Other inheritable thrombophilic risk factors are less likely to have contributed to the high risk of recurrence, as it appears that they do not influence this risk (30). Although other studies showed that recurrences of venous thrombosis in renal transplant recipients were often spontaneous (2, 3), a comment on this is difficult as medical charts often did not provide sufficient information to classify recurrences as spontaneous or secondary to external risk factors. It seems likely that most recurrences were spontaneous, because our recipients usually received thromboprophylaxis at exposure to risk factors such as surgery, pregnancy/puerperium, trauma or

immobilization, whereas the use of oral contraceptives and hormonal replacement therapy were strongly discouraged after a first episode of venous thrombosis.

In conclusion, renal transplant recipients are at a high risk of first venous thrombosis and recurrence. CMV infection tended to be associated with an increased risk of (recurrent) venous thrombosis. Controlled prospective studies are warranted to establish this observation, which suggests that CMV infection contributes to the high risk of (recurrent) venous thrombosis in renal transplant recipients.

References

1. Humar A, Johnson EM, Gillingham KJ, et al. Venous thromboembolic complications after kidney and kidney-pancreas transplantation: a multivariate analysis. Transplantation 1998; 65: 229–234.

2. Poli D, Zanazzi M, Antonucci E, et al. Renal transplant recipients are at high risk for both symptomatic and asymptomatic deep vein thrombosis. J Thromb Haemost 2006; 4: 988–992.

3. Poli D, Zanazzi M, Antonucci E, et al. High rate of recurrence in renal transplant recipients after a first episode of venous thromboembolism. Transplantation 2005; 80: 789–793.

4. Patrassi GM, Sartori MT, Rigotti P, et al. Reduced fibrinolytic potential one year after kidney transplantation. Relationship to long-term steroid treatment. Transplantation 1995; 59: 1416–1420.

5. Ducloux D, Pellet E, Fournier V, et al. Prevalence and clinical significance of antiphospholipid antibodies in renal transplant recipients. Transplantation 1999; 67: 90–93.

6. Kazory A, Ducloux D, Coaquette A, et al. Cytomegalovirus-associated venous thromboembolism in renal transplant recipients: a report of 7 cases. Transplantation 2004; 77: 597–599.

7. Rowshani AT, Bemelman FJ, van Leeuwen EM, et al. Clinical and immunologic aspects of cytomegalovirus infection in solid organ transplant recipients. Transplantation 2005; 79: 381–386.

8. Span AH, van Dam-Mieras MC, Mullers W, et al. The effect of virus infection on the adherence of leukocytes or platelets to endothelial cells. Eur J Clin Invest 1991; 21: 331–338.

9. Grefte A, van der Giessen M, van Son W, et al. Circulating cytomegalovirus (CMV)-infected endothelial cells in patients with an active CMV infection. J Infect Dis 1993; 167: 270–277.

10. Uthman IW, Gharavi AE. Viral infections and antiphospholipid antibodies. Semin Arthritis Rheum 2002; 31: 256–263.

11. Schambeck CM, Hinney K, Gleixner J, et al. Venous thromboembolism and associated high plasma factor VIII levels: linked to cytomegalovirus infection? Thromb Haemost. 2000; 83: 510–511.

12. The TH, Kas-Deelen AM, de Maar EF, et al. Cellular and humoral parameters for vascular damage in blood during cytomegalovirus infections. Transplant Proc 2001; 33: 1813.

13. Lebranchu Y, al Najjar A, Kapahi P, et al. The association of increased soluble VCAM-1 levels with CMV disease in human kidney allograft recipients. Transplant Proc 1995; 27: 960.

14. Gonzalez-Ordonez AJ, Fernandez-Carreira JM, Fernandez-Alvarez CR, et al. The concentrations of soluble vascular cell adhesion molecule-1 and lipids are independently associated with venous thromboembolism. Haematologica 2003; 88: 1035–1043.

15. Bank I, Libourel EJ, Middeldorp S, et al. Elevated levels of FVIII:C within families are associated with an increased risk for venous and arterial thrombosis. J Thromb Haemost 2005; 3: 79–84.

16. Galli M, Luciani D, Bertolini G, et al. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood 2003; 101: 1827–1832.

17. Abgueguen P, Delbos V, Chennebault JM, et al. Vascular thrombosis and acute cytomegalovirus infection in immunocompetent patients: report of 2 cases and literature review. Clin Infect Dis 2003; 36: E134–139.

18. Squizzato A, Gerdes VE, Buller HR. Effects of human cytomegalovirus infection on the coagulation system. Thromb Haemost 2005; 93: 403–410.

19. Grattan MT, Moreno-Cabral CE, Starnes VA, et al. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. J Am Med Assoc 1989; 261: 3561–3566.

20. Van der Giessen M, van den Berg AP, van der Bij W, et al. Quantitative measurement of cytomegalovirus-specific IgG and IgM antibodies in relation to cytomegalovirus antigenaemia and disease activity in kidney recipients with an active cytomegalovirus infection. Clin Exp Immunol 1990; 80: 56–61.

21. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998; 158: 585–593.

22. White RH, Romano PS, Zhou H, et al. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. Arch Intern Med 1998; 158: 1525–1531.

23. Abbott KC, Cruess DF, Agodoa LY, et al. Early renal insufficiency and late venous thromboembolism after renal transplantation in the United States. Am J Kidney Dis. 2004; 43: 120–130.

24. Kreis HA, Ponticelli C. Causes of late renal allograft loss: chronic allograft dysfunction, death, and other factors. Transplantation 2001; 71: SS5–9.

25. Kas-Deelen AM, Harmsen MC, De Maar EF, et al. Acute rejection before cytomegalovirus infection enhances von Willebrand factor and soluble VCAM-1 in blood. Kidney Int 2000; 58: 2533–2542.

26. Gouarin S, Vabret A, Gault E, et al. Quantitative analysis of HCMV DNA load in whole blood of renal transplant patients using real-time PCR assay. J Clin Virol 2004; 29: 194–201.

27. Heit JA, Mohr DN, Silverstein MD, et al. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med 2000; 160: 761–768.

28. van den Belt AG, Sanson BJ, Simioni P, et al. Recurrence of venous thromboembolism in patients with familial thrombophilia. Arch Intern Med 1997; 157: 2227–2232.

29. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet 1999; 353: 1167–1173.

30. Christiansen SC, Cannegieter SC, Koster T, et al. Thrombophilia, clinical factors, and recurrent venous thrombotic events. J Am Med Assoc 2005; 293: 2352–61.