Clin Kidney J (2012) 5: 203–206
doi: 10.1093/ckj/sfs036
Advance Access publication 25 April 2012

Original Article

CKJ

Chickenpox infection after renal transplantation

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Abstract

Background. Chicken pox, although a common infection among children, is rare in immunocompromised patients, particularly renal transplant recipients, and carries a very high incidence of morbidity and mortality There is little data on chickenpox in adult renal transplant recipients, although reports have suggested that it may follow a virulent course requiring frequent hospitalization, and in severe cases can cause death.

Aims. To evaluate the incidence, severity and complications of a varicella/chickenpox infection in renal transplant recipients over 10 years follow-up.

Results. An incidence of 1.48% of our patients were diagnosed with varicella infection during this 10-year period from June 2000 to June 2010 in our live-related renal transplant program, with a median patient age of 39 years (range 21–54 years). Graft dysfunction was observed among five patients following the infection, two of whom became dialysis-dependent. The other three had mild graft dysfunction from which they subsequently recovered, suggesting that infection was responsible for graft dysfunction. None of them developed rejection following exposure or with modification of immunosuppression. All of our patients required admission with 47.8% presenting with various presentations, with orchitis, pancreatitis, encephalitis and gastritis each affecting 8.6% of the patients. All patients were managed with intravenous acyclovir for 2 weeks followed by oral acyclovir for 3 months. The infection was associated with an increased mortality of 13.4% due to superadded infections and central nervous system involvement in one patient with fatal bilateral pneumonia.

Conclusions. This infection, which is a benign disease with a largely stable course among the general population, can have severe outcomes for immunocompromised patients, accounting for almost 90% with significant morbidity and mortality in the 8.6% of infected patients, thus highlighting the importance of pre-transplant vaccination in this subgroup of the population.

Keywords: acyclovir; chickenpox; renal transplant; superadded infections

Introduction

Chickenpox/primary varicella-zoster infection is a common contagious disease of childhood with low risk for mortality. It occurs rarely in immunocompromised patients, especially in renal transplant recipients, but when it occurs it carries a very high incidence of morbidity and mortality [1], developing either as a reactivation of the virus in the form of zoster or as a primary varicella or chickenpox infection. There seems to be little data on chickenpox in adult renal transplant recipients, although reports have suggested that it may follow a particularly virulent course frequently requiring hospitalization and may even have fatal consequences [2, 3].

Transplant recipients exposed to varicella are generally treated with varicella-zoster immune globulin (VZIG) to prevent infection [4, 5]; interferon, acyclovir and vidarabine have been used as antiviral agents to treat varicella infection. Such treatment is not only expensive but also associated with rejections, especially with interferon. The passively acquired immunity is short lived with further doses being required after subsequent exposure.

Universal childhood vaccination against varicella is a controversial issue, however, there is support for immunization of high-risk populations [6, 7]. Vaccination in the high-risk groups, especially prior to the onset of end-stage renal disease (ESRD), may decrease the number of patients with varicella infection, thereby reducing the graft and patient loss in addition to reducing the costs associated with the usual approaches. Immunization in the post-transplant period not only provides suboptimal antibody levels but also raises serious concern regarding the safety of live virus vaccine and allograft rejections.

Aims

The aim of the study was to evaluate the incidence, severity and complications of a vaccine-preventable disease—varicella/chickenpox infection, in a group of renal transplant recipients over a 10-year follow-up period and to develop a successful protocol for prevention and management of varicella in this cohort of the immunosuppressed population.

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Materials and methods

We conducted a retrospective analysis of all renal allograft recipients who underwent live-related renal transplant at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, from June 2000 to June 2010. Records of 1546 patients transplanted in this 10-year period were reviewed to identify documented contacts with varicella, hospitalization for varicella or varicella-related interventions. The patients' outpatient records were evaluated and details regarding history of pretransplant vaccination, history of pretransplant varicella infections, type of immunosuppression, date of infection from transplant, treatment offered for the infection, history of rejections, management of rejections, and morbidity and mortality with varicella infection were examined and documented for infectious or non-infectious problems.

Results

A total of 23 patients were diagnosed as having varicella infection during the 10-year period from June 2000 to June 2010 with an incidence of 1.48% in our live-related renal transplant program. The median age of patients was 39 years (range 21–54 years) and 17 were male. Associated comorbidities in these patients were malnutrition in two, hepatitis B positive status in one and chronic allograft nephropathy in one. None of the patients with varicella infection had any history of pretransplant vaccination or exposure/infection. Their pretransplant varicella-zoster virus (VZV) Ig status was negative for IgG and IgM. History of pretransplant vaccination or exposure was available in 845 patients only. Clinical diagnosis of varicella infection was made with the help of a dermatologist, while microbiological diagnosis was made with the aid of direct fluorescence antibody for VZV from vesicular lesions or polymerase chain reaction from cerebrospinal fluid or visceral tissue samples.

Cyclosporine + mycophenolate + prednisolone protocol was followed in 73.9% of patients with infection, while tacrolimus + mycophenolate + prednisolone was used in 13.04% patients. A total of 86.9% of the patients were on mycophenolate mofetil therapy (Table 1).

The months November to February constituted the major outbreaks in two thirds (66.6%) of our patients. Localized lesions (65.2%) vesicular eruptions was a clinical presentation in 65.2% of these patients, while hemorrhagic eruptions was observed in 13.4%. During the peak of immunosuppression protocol, i.e. <6 months post-transplant, 60.08% suffered from varicella infection. Late infections beyond 5 years were observed in two patients, i.e. 8.6% (Table 2).

Graft function was stable among all these patients before the exposure except one. Graft dysfunction was observed among five patients following the infection and two became dialysis dependant. The other three had mild graft dysfunction which recovered subsequently suggesting infection to be responsible for graft dysfunction. None of them developed rejection following exposure or with modification of immunosuppression. All of the patients who developed graft dysfunction developed secondary infections. Secondary infections were observed among seven of these patients, bacterial in six and fungal in one. Chest infection was the cause for secondary infection among those with septicemia (three patients). Besides a high rate of graft dysfunction secondary to added infections, this vaccine-preventable infection was associated with an increased mortality of 13.4% individuals due to superadded infections and central nervous system involvement in one patient with fatal bilateral pneumonia. One pregnant post-transplant patient developed the varicella infection during the eighth month of her pregnancy, however, she had a stable course and uneventful pregnancy. Other complications related to varicella infection were orchitis in two, pancreatitis in two, while five patients presented with vesicular eruptions with severe gastritis.

All our patients required admission with 47.8% presenting with various presentations: orchitis, pancreatitis, encephalitis and gastritis were each observed in 8.6% patients (Table 3).

A total of 30.4% of the patients had presented with infections in the form of pneumonitis and encephalitis requiring admission and management. All patients were managed with intravenous (IV) acyclovir for 2 weeks followed by oral acyclovir for 3 months. One patient was given a course of 2 weeks of acyclovir and on stopping the therapy, he developed fulminant disseminated varicella infection which had to be treated with IV gancyclovir and his immunosuppression was curtailed to cyclosporine, azathioprine and prednisolone and oral gancyclovir was continued for 3 months. In our kidney transplant unit (KTU), in seven patients, there was an outbreak of varicella infection on exposure to nursing staff who had primary varicella infection. The other four patients during the stay in KTU did not show any signs of infections and on questioning gave a history of chickenpox in childhood. The remaining patients, i.e. 10, were given acyclovir therapy for a period of 3 months and none of them to date have developed varicella infection. Three of our patients who died were also started on IV acyclovir but they came down with late secondary infections. None of our patients showed any renal dysfunction following oral/IV acyclovir. Regarding the immunosuppression, in all these patients, we tried to modify immunosuppression and we switched two of our patients over to azathioprine. Fortunately, none of our patients had any rejections following modification. Thus, this otherwise benign disease with largely stable course has severe overturns in the immunocompromised patients accounting for nearly 90% with significant morbidity and mortality in nearly 8.6% of the patients infected, thus reflecting and highlighting the significance of pretransplant vaccination in this subgroup of population.

Discussion

The incidence of varicella/chickenpox infection in adult renal transplant recipients is low, occurring in just under 1% in a number of case series, which is very much consistent with our study population. This may be due in part to the fact that 94% of adults have evidence of VZV infection [8]. The prognosis, however, appears to be grave, in keeping with that described for other immunocompromised patients [9]. Visceral, ocular or neurological involvement occurs in half of the patients with cutaneous dissemination [10] which was consistent with our study population where systemic manifestation was observed in 47.8% of study population.

The majority of our transplant patients acquired the infection in the phase of intensive immunosuppressive therapy and a fulminant course was observed in 8.6% of them. Of all our patients, 86.9% were on mycophenolate mofetil at the time of harboring the infection, raising the concern regarding potential risk for opportunistic infection with

Table 1. Demographic profile

Variable	Number	Percentage
Male	17	73.9
Female	6	26.1
Median age (years)	30	
CSA + MMF + Pred	17	73.9
TAC + MMF + Pred	3	13.04
Diffuse disease	8	34.7
Localized disease	15	65.2
Hemorrhagic disease	3	13.4
Death	2	8.6

Table 2. Timing of infection

Timing of infection	Number
During immediate post-transplant (<15 days)	7
<6 months of transplant	7
6 months to 1 year	3
1–3 years	4
3–5 years	0
>5 years	2
Complications	
Graft dysfunction	5
Need of dialysis	2
Mild	3

Table 3. Complications associated with varicella infections in transplant population[a]

	Number
Complications	
Orchitis	2
Pancreatitis	2
Gastritis	5
Encephalitis	2
Infections	7
Sepsis	3
Comorbidities	
Malnutrition	3
HBV	2
HCV	1
Pregnancy	1
PTDM	1

[a]HBV, Hepatitis B; HCV, Hepatitis C; PTDM, Post-transplant Diabetes Mellitus.

usage of this agent, as observed by other authors [11]. A history of exposure to varicella within a month of onset of illness (the health worker treating these patients had a varicella infection) was observed in seven of our patients who developed the infection in KTU stay with no past history of vaccination or exposure, suggesting primary varicella infection in this highly sensitized group in immediate post-transplant phase. In one series of five patients [12] with post-transplant varicella infection, 40% acquired infection in the intensive phase of immunosuppression suggesting its association with intensive immunosuppression. As per recommendation for primary varicella infection, the treatment with acyclovir is for 15 days, however, our subset of patients are immunocompromised; in one patient after withdrawal of acyclovir, he developed severe hemorrhagic eruptions with pancreatitis, for which we had to give him IV gancyclovir followed by oral therapy for 3 months with modification of immunosuppression. So we gave them all acyclovir for 3 months and none of our patients relapsed.

Prophylaxis and treatment of varicella infection post-transplant are required in a VZV-naive transplant patient who is exposed to someone infected with varicella and should receive varicella immune globulin within 96 h of exposure (if available).

If VZIG is not available or the patient presents >96 h following exposure, acyclovir may be considered for post-exposure prophylaxis. Post-transplant prophylaxis against reactivation of VZV and herpes simplex virus is recommended to prevent severe recurrences and consists of gancyclovir in patients needing cytomegalovirus (CMV) prophylaxis [13]. Those patients who do not require CMV prophylaxis can receive valacyclovir or acyclovir for approximately 1 to 3 months post-transplant. Recent studies in the immunocompetent host suggest that vaccination with high-dose varicella vaccine (Zostavax) may prevent zoster in patients with a prior history of varicella infection [14]. Vaccination with live virus vaccines should be avoided in the early post-transplant period both to maximize response and minimize adverse events.

In our KTU patients where there was an outbreak of varicella infection on exposure to nursing staff, the remaining patients, i.e. 10, were given acyclovir therapy for a period of 3 months and none of them to date have developed varicella infection. It was observed that acyclovir has been shown to prevent the dissemination of zoster in immunocompromised patients and to reduce the incidence of visceral dissemination of chickenpox in children with renal transplants [15]. The importance of starting treatment early and using the recommended dose of l0 mg/kg three times a day has been stressed. Three of our patients who died were started on IV acyclovir but late. Renal function should be monitored carefully and the dose reduced in the presence of renal impairment. None of our patients showed any renal dysfunction following oral/IV acyclovir. All our patients were managed with IV followed by oral acyclovir for a period of 3 months. One patient was given a course of 2 weeks of acyclovir, and on stopping the therapy, he developed fulminant disseminated varicella infection which had to be treated with IV gancyclovir for 2 weeks, followed by oral gancyclovir for 3 months suggesting a prolonged course in the immunocompromised population. Should resistant strains of varicella develop, foscarnet has been effective. Foscarnet is associated with a decline in renal function. Regarding the immunosuppression in all of these patients, we tried to modify immunosuppression and two of our patients were switched over to azathioprine; fortunately, none of our patients had rejection following modification. In our study, all those patients who developed graft dysfunction, this was associated with superadded infections which settled with control of infection in three of our patients, while the other two succumbed to illness and secondary infection. A study was conducted to assess fatal infections secondary to varicella in a renal transplant population, where in each case steroids were maintained, but azathioprine was stopped after a diagnosis of chickenpox had been made. In addition, four patients were treated with acyclovir.

Acyclovir has been shown to prevent the dissemination of zoster in immunocompromised patients [16] and to reduce the incidence of visceral dissemination of chickenpox in children with renal transplants [12]. The importance of starting treatment early and using the recommended dose of l0 mg/kg three times a day has been stressed. Three patients treated with acyclovir died, although none had evidence of active VZV infection at postmortem examination.

All the patients who died had developed disseminated intravascular coagulation and had cerebral hemorrhage at postmortem examination. In two patients, disseminated bacterial and fungal infections contributed to death. The only patient who survived was started immediately on the recommended dose of acyclovir (l0 mg/kg three times a day) and had been receiving the lowest dose of azathioprine during the incubation period. Despite stopping the azathioprine, no patients had evidence of allograft rejection. Our study group also revealed a higher degree of secondary infection and mortality despite the fact that all patients were given IV acyclovir with modification of immunosuppression. The remaining patients possibly survived due to their better immune status and early administration of antiviral therapy. Renal transplant recipients who do not have a previous history of chickenpox should be advised to report any contact with VZV immediately. Although none of our patients presented during the incubation period, zoster-immune globulin and zoster-immune plasma have been shown to prevent or modify the course of chickenpox in immunocompromised patients, if given at this stage [17].

Despite all these measures, chickenpox remains a potentially fatal infection in adult renal transplant recipients. The recent development of a varicella vaccine [18] may prove useful in preventing infection.

The attack rate in non-immune individuals of household contacts with varicella infections is 80–90%. Therefore, in individuals who have not previously had varicella infections at the time of transplant evaluation, vaccination with a live attenuated strain could be considered whenever possible to avoid primary VZV infection after transplantation, an often severe disease with a high mortality rate.

Recently, this strategy has been used in children prior to renal transplantation. Attack rates in vaccinated individuals may be up to 31%, but the disease that develops is a much milder form compared with those susceptible individuals not previously vaccinated. Attention should be directed towards the identification and immunization of at-risk patients prior to transplantation.

Conclusions

Primary varicella infection/chickenpox remains a potentially fatal infection in adult renal transplant recipients. It may present with complications ranging from allograft rejections, hepatitis, pancreatitis, pneumonia and death. Acyclovir has been shown to prevent the dissemination of zoster in immunocompromised patients and to reduce the incidence of visceral dissemination of chickenpox in children with renal transplants. Thus, its early usage during the disease is not only useful for outcome but also helps in prevention of secondary bacterial and fungal infections contributed to death.

Varicella vaccination in the high-risk groups, especially during the pre-ESRD stage, can possibly decrease the number of patients with varicella infection, thereby preventing or reducing the graft and patient loss besides the cost associated with the usual approaches. The safety of live-virus vaccines like MMR and varicella and the concern of allograft rejections triggered by immunization support a pretransplant vaccination in all pre-ESRD patients thereby decreasing the cost and improving patient and graft survival post-transplant.

Conflict of interest statement. None declared.

(See related article by E. Thervet. Vaccination in solid-organ transplantation candidates: time for a benefit/risk assessment. *Clin Kidney J* 2012; 5: 193–194)

References

1. Naraqi S, Jackson GG, Jonasson O *et al.* Prospective study of prevalence, incidence and source of herpes virus infections in patients with renal allografts. *J Infect Dis* 1977; 136: 531–540
2. Rubin RH, Tolkoff-Rubin NE. Viral infection in the renal transplant patient. *Proc Eur Dial Transplant Assoc* 1983; 19: 513–526
3. Luby JP, Ramirez-Ronda C, Rinner S *et al.* A longitudinal study of varicella-zoster virus infections in renal transplant recipients. *J Infect Dis* 1977; 135: 659–663
4. Rothwell WS, Gloor JM, Morgenstern BZ *et al.* Disseminated varicella infection in pediatric renal transplant recipients treated with mycophenolate mofetil. *Transplantation* 1999; 68: 158–161
5. Parnham AP, Flexman JP, Saker BM *et al.* Primary varicella in adult renal transplant recipients: a report of three cases plus a review of the literature. *Clin Transplant* 1995; 9: 115–118
6. Friedman Ross L, Lantos JD. Immunization against chickenpox. *BMJ* 1995; 310: 2–3
7. Gershon A. Varicella: to vaccinate or not to vaccinate. *Arch Dis Child* 1998; 79: 470–471
8. Broyer M, Tele MJ, Guest G *et al.* Varicella and zoster infection in children after kidney transplantation: long term result in vaccination. *Pediatrics* 1997; 99: 35–39
9. Hurley JK, Greenslade T, Lewy PR *et al.* Varicella-zoster infections in pediatric renal transplant recipients. *Arch Surg* 1980; 115: 751–752
10. Stauss SE. Varicella-zoster virus infection. Biology, natural history, treatment and prevention. *Ann Intern Med* 1998; 108: 221
11. Rothwell WS, Gloor JM, Morgenstern BZ *et al.* Disseminated varicella infection in pediatric renal transplantation with mycophenolate mofetil. *Pediatr Nephrol* 1997; 11: 665–671
12. Bourbigot B, Quillien MC, Airiau J *et al.* Renal failure in the course of reactivation of varicella-zoster virus infection in a renal transplant recipient. *J Infect* 1986; 13: 159–162
13. Green M, Avery R, Preiksaitis J. Guidelines for the prevention and management of infectious complications of solid organ transplantation. *Am J Transplant* 2004; 4 (Suppl 10): 10–17, 57–109, 160–163
14. Kotton CN, Fishman JA. Viral infection in the renal transplant recipient. *J Am Soc Nephrol* 2005; 16: 1758–1774
15. Feldhoff CM, Balfour HH, Simmons RL *et al.* Varicella in children with renal transplants. *J Pediatr* 1981; 98: 25–31
16. Peterson LR, Ferguson RM. Fatal central nervous system infection with varicella-zoster virus in renal transplant recipients. *Transplantation* 1984; 37: 366–368
17. Bradley JR, Wreghitt TG, Evans DB. Chicken pox in adult renal transplant recipients. *Nephrol Dial Transplant* 1987; 1: 242–245
18. Leguen E, Deminiere C, Larue JR *et al.* Fatal varicella or Reye's syndrome: an unusual cause of death in a renal graft recipient. *Nephrol Dial Transplant* 1992; 7: 158–160

Received for publication: 30.8.11; Accepted in revised form: 4.3.12