

Relato de caso/Case report

## Long-term follow-up of kidney allografts in patients with sickle cell hemoglobinopathy

### Transplante renal na anemia falciforme

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Although sickle cell anemia and sickle cell disease produce a variety of functional renal abnormalities they uncommonly cause end stage renal failure. Renal transplantation has been a successful alternative for the treatment of the rare terminal chronic renal failure with outcomes comparable with non-sickle recipients. This approach, however, has not been often described on patients with renal failure associated with SC hemoglobinopathy. Here we report the outcomes of two patients with chronic renal failure due to SC hemoglobinopathies who underwent renal transplantation. At the time of the transplantation they were both severely anemic and had frequent vasoocclusive pain crises. Both patients evolved with good allograft function, near normal hematological parameters, and very rare pain crisis, thirteen and eight years after transplant. These cases illustrate that terminal renal failure due to SC hemoglobinopathy can be successfully managed by renal transplantation and satisfactory long-term results are achievable not only in terms of renal allograft function but also of their hematological condition. Rev. bras. hematol. hemoter. 2003;25(2):111-114.

**Key words:** SC hemoglobinopathy; chronic renal failure; renal transplantation.

### Introduction

Sickle cell anemia (SCA) is the homozygous form that results from a single amino acid substitution at the sixth residue of the globin

beta chain. This substitution is due to a single nucleotide mutation (GAG → GTG) in the sixth codon of the beta-globin gene ( $\beta^s$  gene).<sup>1</sup> This mutation places a nonpolar residue on the outside of the hemoglobin molecule and greatly

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reduces the solubility of the deoxygenated form of HbS. As a consequence, red blood cells become prone for sickling in the microcirculation when oxygen tension is low.<sup>2</sup> The  $\beta^s$  gene is inherited in an autosomal codominant fashion. That is, heterozygous inheritance does not cause the disease but it is detectable; homozygous inheritance or compound heterozygous inheritance with another mutant  $\beta$ -globin gene is required for disease. The "sickle cell syndromes" include all conditions in which  $\beta^s$  is inherited. In contrast, "sickle cell disease" includes those genotypes associated with chronic hemolytic anemia and vasoocclusive pain: homozygous sickle cell anemia (HbSS), hemoglobin SC disease (HbSC), and sickle- $\beta^+$  thalassemia (HbS $\beta^+$ ).<sup>3</sup>

The sickle cell syndromes are present among about 8% of the African-American population.<sup>4</sup> Although several local studies have been made in Brazil, the prevalence of those syndromes awaits the results of the neonatal screening being established all over the country. Heterozygosity for SC anemia has a frequency of approximately 0.03% in Southeastern Brazilian black population.<sup>5,6</sup>

Chronic renal failure occurs in 4.2% and 2.4% of patients with sickle cell disease and sickle C disease, respectively. The mean age of onset is 23.1 years for sickle cell disease and 49.9 years for sickle C disease.<sup>7</sup>

Sickle cell nephropathy is now a well-characterized entity with specific manifestations, risk factors, and prognoses. Clinical renal abnormalities are common in sickle cell anemia and include hyposthenuria, incomplete renal tubular acidosis, hyperkalemia, hematuria and papillary necrosis. Hyposthenuria is the first clinical symptom of the defective medullary tonicity and can produce a higher than usual obligatory urine output, thereby increasing the risk of dehydration. Proteinuria is a frequent finding in sickle cell disease sometimes with nephrotic syndrome.<sup>8</sup> Focal segmental sclerosis,<sup>9</sup> membranous and membranoproliferative glomerulonephritis<sup>10</sup> have also been reported in patients with sickle cell anemia. Although the glomerular filtration rate decreases with age in sickle cell anemia, end stage renal failure has

been infrequently documented.<sup>11</sup> Successful long-term management of this complication by renal transplantation has been reported in 62 to 82% of the transplanted patients with sickle cell anemia.<sup>12</sup> The major post-transplant complications are strokes, renal artery thrombosis and recurrence of the painful crises, especially as hemoglobin levels rise.<sup>12-14</sup> A few successful renal transplants have been previously reported in patients with SC hemoglobin.<sup>15-16</sup>

In this report, we present two patients with chronic renal failure due to SC hemoglobinopathy who underwent successful renal transplantation. The patients were among the 12 cases of SC hemoglobinopathy seen at the Sickle Cell Center at the Hospital de Clínicas de Porto Alegre, between 1982 and 1999.

#### Case reports

**Patient 1.** A 20-year-old black woman was first seen as an outpatient in March 1983 for severe anemia, vasoocclusive pain crises and moderate chronic renal failure. She was found to have SC hemoglobinopathy. Shortly after that, she evolved with hypertension with proteinuria and a rising creatinine level. A renal biopsy was performed in April 1983 which revealed a histological condition of crescent glomerulonephritis. The patient's condition worsened considerably and in December 1985, she started hemodialysis. At this point she was severely hypertensive and anemic and had frequent painful bone crises. In March 1986 she received a one-haplotype match kidney allograft donated by her brother. The graft had excellent initial function with prednisone and azathioprine immunosuppression. A steroid-sensitive acute rejection episode was detected and successfully treated with "bolus" IV steroid in the fourth week post-transplantation. Currently, 13 years after transplantation, she has normal renal function (0.9 mg/dL of serum creatinine), 0.5g per 24 hours proteinuria, and 12.6 g/dL of hemoglobin, without hemolytic manifestations or painful crises.

**Patient 2.** A 16-year-old black female was found to have severe anemia, thrombocytopenia,

hypertension, proteinuria and abnormal renal function tests in April 1985. Hemoglobin electrophoresis showed that she was a SC heterozygous. An abdominal ultrasound displayed contracted kidneys compatible with chronic renal failure and partially effected hemodialysis was initiated in June 1985. Up to the moment of renal transplantation, the patient was hospitalized several times for the treatment of acute venoocclusive pain crises, pneumonia and severe anemia for which she received multiple blood transfusions.

A cadaver donor kidney transplant was performed in May 1989 and an acute rejection episode was diagnosed on day 4 post-transplantation. She received IV methylprednisolone 7mg/kg/day given for three days, and subsequently, after a kidney scintigraphy and biopsy displaying persistence of cellular rejection, OKT3® was given for ten consecutive days with normalization of the serum creatinine. Baseline immunosuppression consisted of a combination of low dose cyclosporine A, prednisone, and azathioprine. Regular blood tests showed a normal serum creatinine (0.9 mg/dL) and hemoglobin values of about 10mg/dL. Except for a single recorded venoocclusive episode one year after transplant (1990), she remained asymptomatic from her sickle syndrome derived condition for 7 years on triple immunosuppressive therapy. She died in August 1997 of a sudden refractory episode of septicemia.

## Discussion

Irreversible hypostenuria during childhood, as well as hypertension, proteinuria and nephrotic syndrome with severe anemia during young adulthood, are probably major risk factors for the development of end-stage renal failure in patients with sickle cell anemia. This complication usually manifests itself around the fourth decade of life, but occurrence at a younger age is not uncommon, as the cases presented in this report. Concomitant clinical complications include hematuria, renal papillary necrosis and hypostenuria.<sup>11,18</sup>

Whereas the association of glomerulopathy

with sickle cell anemia is well-documented,<sup>7-11,17</sup> less has been reported about the involvement of such complications in hemoglobin SC disease.<sup>19</sup>

Freedman et al,<sup>20</sup> observed mesangiolytic glomerulopathy in a patient with SC hemoglobinopathy, but the possibility of a low-grade chronic hemolytic uremic syndrome along with the hemoglobinopathic-related hemolysis could not be excluded. In two Brazilian studies, no major renal complications were reported in patients with SC hemoglobinopathy.<sup>5,6</sup>

In the present study, the presence of membranoproliferative glomerulo-nephritis, in at least one patient is unequivocal, and other disease-associated glomerulopathies can not be excluded. This provides support for the suggested involvement of glomeruly in SC hemoglobinopathy.

Painful crises on patients with the hemoglobin SC disease have been reported to respond to a decrease of the hematocrit to 30% by repeated phlebotomy.<sup>14</sup> In the present study, a dramatic decrease was observed in painful crises and venoocclusive complications post-transplant, despite mean hematocrit values in excess of 30%. It should be kept in mind, however, that sickle erythrocytes continue to circulate through the kidney, implying that the cycle of renal damage may eventually restart.

It is likely, that these complications of sickle cell disease will be more effectively prevented by new therapeutic strategies designed to modify cell adhesion (red blood cell/endothelial cell and cell-cell interactions), increase fetal hemoglobin concentration, as well as bone marrow transplantation and gene therapy. Renal abnormalities, together with the new therapeutic approaches, should be closely monitored and apparently an early kidney transplant might be a reasonable option.

The two cases reported here not only benefited from renal transplantation but also evolved with a remission of sickle cell syndrome derived symptoms. We might speculate that immunosuppression could have an anti-inflammatory effect<sup>21</sup> but the reason for this still needs to be defined.

**Resumo**

*Embora a anemia falciforme e as síndromes falciformes frequentemente causem várias alterações funcionais renais, não é comum a insuficiência renal terminal. Nestes casos, o transplante renal é uma alternativa que se acompanha de resultados comparáveis aos obtidos em receptores sem hemoglobinopatia SC. Esta estratégia terapêutica tem sido, no entanto, pouco relatada para portadores de hemoglobinopatia SC. Este relato descreve a evolução de dois pacientes portadores de hemoglobinopatia SC que foram submetidos ao transplante renal. No momento do transplante ambos apresentavam severa anemia e crises dolorosas frequentes. Os pacientes evoluíram com boa função do enxerto, parâmetros hematológicos quase normais e praticamente assintomáticos do ponto de vista da hemoglobinopatia, treze e oito anos após o transplante. Estes casos ilustram que a insuficiência renal terminal causada pela hemoglobinopatia SC pode ser tratada com sucesso pelo transplante renal, não só do ponto de vista renal, propriamente dito, mas também em termos de sua doença hematológica. Rev. bras. hematol. hemoter. 2003;25(2):111-114.*

**Palavras-chave:** Hemoglobinopatia SC; insuficiência renal crônica; transplante renal.

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