Renal Histopathological Changes In Patients Older Than 10 Years With Hemoglobin Ss Disease

W Williams, D Shah, E Williams

Citation

Abstract
Renal involvement in patients with hemoglobin SS disease is common. In children, tubular dysfunctions are the main abnormalities. Glomerular involvement occurs in young adults causing proteinuria in thirty percent of patients and chronic renal failure in four percent. A composite picture of mesangial hypercellularity, focal and segmental glomerulosclerosis, and occasionally mesangiocapillary like changes are seen in the glomeruli. A few patients may show immune complex glomerulonephritis, often superimposed on the changes described above. The glomerular changes seem to be hemodynamically mediated. Small short term studies show that angiotensin converting enzyme inhibitors may be beneficial in patients with proteinuria. Hemodialysis, peritoneal dialysis and renal transplantation should be offered to patients with end stage renal disease.

INTRODUCTION
The first account of renal involvement in sickle cell anemia (SSA) was in 1910 when it was noted that SSA could cause increased urine volume of low specific gravity. This has since been confirmed as a concentrating defect caused by disruption of the vasa recta which became irreversible by the age of 15 years. Since then both distal and proximal tubular defects have been described leading to an incomplete type of distal renal tubular acidosis, hyporeninemic hypoaldosteronism syndrome leading to hyperkalemia, increased re-absorption of microglobulins and phosphorus and increased secretion of creatinine and uric acid by the proximal tubules. Papillary necrosis is also a frequent finding. Interstitial fibrosis with variable degrees of mononuclear cell infiltration and intimal thickening of the blood vessels are also seen. The most recent finding has been renal medullary cell carcinoma in patients with the sickle cell trait.

DISCUSSION
The glomerular changes that have been described will be the main focus of this review.

The onset of proteinuria is often the earliest manifestation of sickle cell nephropathy.

Long term studies have shown proteinuria to develop in approximately thirty percent of patients and renal failure was found in four percent of patients. Forty percent of patients who develop hemoglobin SS (HbSS) nephropathy will have the nephrotic syndrome and is a predictor of progression to chronic renal failure (CRF). In a study from the University Hospital of the West Indies (UHWI) fifty three percent of thirty six patients with HbSS nephropathy had the nephrotic syndrome.

The mean age of onset of proteinuria varies from a low of twenty three years to a high of thirty five years. In the review of patients with HbSS disease from the UHWI who had proteinuria and a renal biopsy the mean age of onset of proteinuria was twenty four years.

However, in a study which looked at patients who had developed renal impairment found the median age to be twenty three years. DNA gene typing found a high incidence of the Central African Republic gene (B's gene) in patients with renal impairment when compared to those patients with Hb SS who did not develop renal impairment. It was postulated that the presence of this gene cluster might predispose the patients to renal impairment and at an early age.

There is generally no gender difference in patients with HbSS disease who develop proteinuria or go on to chronic renal failure and who require renal replacement therapy. In an initial study from the UHWI six of thirteen patients were...
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Irrespective of the initiating insult in the kidneys of patients with Hb SS the renal disease will progress by a mechanism or mechanisms common to most types of progressive renal diseases. In animal models a reduction in renal mass exposes the remaining nephrons to adaptive changes that sustain renal function initially but is detrimental in the long term.

Glomerular changes that have been described in patients with Hemoglobin SS (Hb SS) disease are now felt to be a composite picture and no single glomerular lesion is seen. The composite picture is one of glomerular hypertrophy, glomerular hypercellularity, an increase in the mesangial matrix, and focal and segmental glomerulosclerosis. There may also be areas of splitting of the glomerular basement membrane and when seen in association with mesangial hypercellularity gives rise to a picture similar to mesangiocapillary glomerulonephritis. However no immune complex deposits can be demonstrated in these biopsies and so the lesion is described as a mesangiocapillary -like lesion without the lobular appearance seen in the typical mesangiocapillary glomerulonephritis. Immunofluorescence and electron microscopic studies are usually negative for immune complex deposits. These lesions give rise to proteinuria, CRF and eventually end stage renal disease (ESRD) requiring renal replacement therapy.

Isolated cases of mesangio proliferative glomerulonephritis, immune complex mediated mesangiocapillary glomerulonephritis type 1, and diffuse proliferative and exudative glomerulonephritis have been described. It is uncertain whether these isolated cases are part of the sickle cell nephropathy or an unusual appearance of an immune complex nephropathy modified by the presence of the sickle cell disease.

In a review of thirteen patients with Hb SS disease from UHWI, Jamaica who had proteinuria in excess of 2.5 g/day, six cases had diffuse proliferative glomerulonephritis (DPGN) on renal histology and had clinical and serological findings in keeping with post streptococcal glomerulonephritis (PSGN). Six patients had mesangiocapillary GN; thought by the authors to be the healing phase of PSGN and 1 had DPGN with crescents. This led the authors to conclude that the glomerular lesions seen in Jamaican HbSS patients were primarily due to PSGN. A further review of an additional thirty eight patients from the same institution showed that eleven of these patients had DPGN superimposed on the changes of

The early functional changes are increases in the renal cortical blood flow (RBF) and glomerular filtration rate (GFR). Enlargement in the glomerular size is seen and it is postulated that increased glomerular perfusion leads to the glomerular enlargement that is seen. The increases in RBF and GFR result from increased sludging of red blood cells in the renal microcirculation due to low oxygen tension. This leads to ischemia and micro infarctions, which result in an increased production of renal vasodilatory prostaglandins leading to vasodilatation and hyperfiltration in the glomeruli. In the transgenic mouse model there is an induction of nitric oxide synthase 11 (NOS 11) in the glomeruli that causes vasodilatation and hyperfiltration. It is not clear as yet what role this plays in humans.

The increases in RBF, GFR and glomerular size start beyond the age of 2 years.

It is reasonable to suggest that the glomerular changes seen in Hb SS disease are hemodynamically mediated. This is based on the findings of early hyperfiltration leading to glomerular enlargement and later changes that include proteinuria and segmental and glomerular sclerosis.

However in one study it was found that although the renal plasma flow was increased in Hb SS patients the GFR was similar in the HbSS patients and normal healthy controls. It was also found that the fractional clearances of all dextran sizes (26-64 A) were significantly increased in Hb SS controls and HbSS CRF versus healthy controls. The mean restrictive pore radius was increased in Hb SS controls and Hb SS CRF versus healthy controls, suggesting that there is a distinct pattern of glomerular dysfunction with generalized increased permeability to dextran resulting from increased pore radius.

Based on these findings, the mechanism of injury in sickle cell nephropathy was not similar to that found in other hemodynamically mediated glomerulopathies.

Irrespective of the initiating insult in the kidneys of patients males and this was also seen in another study from the same institution where twenty five patients out of fifty one were males. In a study that looked at patients with renal failure seventeen of thirty one patients were males. In one study however seven of nine patients with renal failure were males. Initially there was a marked male dominance in the US Renal data base system but this has changed in recent years and there is now no gender difference.

As the renal disease progresses there is a reduction in renal mass due to interstitial fibrosis and cortical atrophy. This exposes the remaining nephrons to adaptive changes that sustain renal function initially but is detrimental in the long term.

The increases in RBF, GFR and glomerular size start beyond the age of 2 years.
sickle cell nephropathy. However it was unclear what was the cause of these changes. Apart from the superimposition of DPGN in the kidneys there were no other changes which might be considered due to a primary or secondary glomerulonephritis.

Another study from the same institution looked at post mortem kidney findings in patients with Hb SS disease over the age of 40 years. Twenty one post mortem cases were reviewed, all patients showed glomerulosclerosis, there was also mesangial hypercellularity and lobulation and the capillary basement membranes were thickened and focally split. No other type of glomerular disease was documented.

**Figure 1**

Table 1: Demographics Of Patients With Hemoglobin Ss Disease

<table>
<thead>
<tr>
<th>Mean Age (years)</th>
<th>24.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range (years)</td>
<td>N (%)</td>
</tr>
<tr>
<td>11 – 20</td>
<td>18 (47)</td>
</tr>
<tr>
<td>21 – 30</td>
<td>11 (29)</td>
</tr>
<tr>
<td>31 – 40</td>
<td>8 (21)</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Gender M/F (%)</td>
<td>19/19 (50/50)</td>
</tr>
<tr>
<td>24-hour urinary protein excretion (g/24 hours)</td>
<td>N (%)</td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>16 (52)</td>
</tr>
<tr>
<td>&gt; 0.2 &lt;3.5</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min 1.73 m²)</td>
<td>N (%)</td>
</tr>
<tr>
<td>N = 20</td>
<td>9 (45)</td>
</tr>
<tr>
<td>N = 11 (55)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2**

Table 2: Light Microscopy Changes On Renal Biopsies N = 38

<table>
<thead>
<tr>
<th>Glomerulosclerosis</th>
<th>30 (79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double Contour of the basement membrane</td>
<td>18 (47)</td>
</tr>
<tr>
<td>Mesangial lesions</td>
<td>35 (92)</td>
</tr>
<tr>
<td>(hypercellularity, increase in matrix, fibrosis)</td>
<td></td>
</tr>
<tr>
<td>Diffuse proliferative &amp; exudative glomerulonephritis</td>
<td>11 (29)</td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td>28 (74)</td>
</tr>
<tr>
<td>Tubulointerstitial fibrosis</td>
<td>28 (74)</td>
</tr>
<tr>
<td>Vascular intimal lesions</td>
<td>18 (47)</td>
</tr>
</tbody>
</table>

**Figure 3**

Table 3: Clinical & Laboratory Features Of 11 Biopsies With Diffuse Proliferative & Exudative Glomerulonephritis

<table>
<thead>
<tr>
<th>Present/pos (number required) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of acute nephritis</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Skin sepsis</td>
</tr>
<tr>
<td>Leg ulcers</td>
</tr>
<tr>
<td>Increase in ASOT</td>
</tr>
<tr>
<td>(&gt; 200 Todd Units)</td>
</tr>
<tr>
<td>Depressed complement level</td>
</tr>
</tbody>
</table>

**MANAGEMENT**

The early stage of sickle cell nephropathy (SCN) is manifested by microalbuminuria which then progresses to overt proteinuria, the nephrotic syndrome, CRF and eventually ESRD. The aim of therapy should therefore be to stop the progression of microalbuminuria to overt proteinuria and also to try and reverse it. Isolated reports showed no consistent benefits with nonsteroidal anti-inflammatory drugs (NSAIDS), steroids, or cytotoxic drugs like cyclophosphamide. The use of short term- 2 weeks angiotensin converting enzyme inhibitor (ACEI) and longer 6 months for proteinuria and microalbuminuria have shown a reduction in the proteinuria. There are no long term studies using ACEI or angiotensin receptor blockers (ARB). However because of the known harmful effects of proteinuria on kidney function and the beneficial effects of ACEI and ARB in other patients with proteinuria and renal impairment it would seem reasonable to cautiously use these drugs in patients with SCN in the absence of contraindications until longer term studies become available.
Blood pressure should be lowered to less than 130/80 mmHg according to the seventh report of the joint national committee on prevention and treatment of high blood pressure (JNC 7) guidelines for patients with kidney diseases.

Patients with SCN who develop ESRD should be offered hemodialysis or peritoneal dialysis, and transplantation. Results of the US Renal Data Systems showed that the two year survival of patients with SCN on hemodialysis and who were not placed on the transplant waiting list was worse than similar patients without SCN on hemodialysis. However if the SCN patients on hemodialysis were placed on the transplant list they had similar survival to the patients without SCN. Patients with SCN who had kidney transplantation had a slightly better survival than if they were not transplanted. However the patient and graft survival was worse than patients without SCN who had a kidney transplant.

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References

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