Ten-year follow-up of children after acute renal failure from a developing country

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Abstract

Objective. The acute-stage mortality and morbidity of acute renal failure (ARF) is well documented, but there are few long-term follow-up studies in children with ARF, particularly from developing countries. The aim of this study was to look at the spectrum of ARF on presentation at a tertiary centre in Kolkata, India, with subsequent 10 years of follow-up.

Subjects and methods. All cases of ARF between the ages of 1 month and 10 years presenting between April and September 1996 were included. We did exclude children with any known renal abnormality. The study group was subsequently monitored for renal survival and mortality until 10 years post-ARF episode.

Results. A total of 37 (n = 37) cases were enrolled. Glomerulonephritis and snakebite were the two most common aetiologies (n = 17 and n = 9). The acute mortality was 35% (n = 13), and it was significantly associated with peak creatinine and presence of multiple organ failure (P < 0.05). The outcome at 6 months could be assessed for 92% (n = 22) of acute survivors and at 10 years for 67% (n = 16). The children that were traced showed in 32% (n = 7) at 6 months and 38% (n = 6) at 10 years, respectively, at least one of the four (abnormal creatinine, hypertension, haematuria and proteinuria) abnormal renal parameters. Snakebite, acute-stage peak creatinine and duration of oliguria were significantly associated with adverse long-term outcome (P < 0.05).

Conclusion. We found that nearly 25% (n = 6) of the survivors of an acute episode of renal failure had renal morbidity after 10 years, a percentage significant enough for these children to need long-term follow-up.

Keywords: acute renal failure; long-term follow-up; paediatric

Introduction

Despite major advances in renal replacement therapies, acute renal failure (ARF) continues to have significant mortality and morbidity in both adult and paediatric patients [1,2]. Recent studies have reported hospital-based mortalities between 30 and 46% in both developed and developing countries [3–5]. There are not many long-term studies in paediatric populations [6–9]. Most of these studies are highly selective in their study population, and all are from developed countries. Their results might thus not be possible to extrapolate to children from developing countries as there are differences in epidemiological and etiological factors and also limitations in availability, accessibility and affordability of modern therapeutic techniques. We here present a long-term follow-up study that to the best of our knowledge is the first of its kind from a developing country like India. The aim of this study was to prospectively document the spectrum of ARF in children on presentation and thereafter follow-up of the survivors up to 10 years.

Subjects and methods

The study was conducted at Institute of Post-Graduate Medical Education and Research, Kolkata—a tertiary care University Hospital that acts as the primary renal referral centre for the state of West Bengal as well as the eastern part of India. It was a prospective observational study with plans for studying the spectrum of ARF during acute admission and thereafter follow-up of the survivors post-ARF at 6 months, 5 years and 10 years. Unfortunately, the primary investigators involved with data collection were unable to conduct the 5-year follow-up due to extraneous circumstances and lack of external funding. However, we were determined to proceed with the 10-year follow-up due to the lack of long-term prognosis in the literature.
Patients

All children of ARF admitted to the paediatric ward between the age of 1 month and 12 years from April to September 1996 were included. ARF was defined as an acute rise of serum creatinine to more than twice the upper limit of normal range for age and sex. Children with previously documented renal problems like nephrotic syndrome or congenital renal malformations were excluded.

Written consent was taken from the guardians of the children at the start of the study, and informed consent was repeated at 10 years as most of the original subject had by now grown into adolescents or adults.

Methods

In the acute-stage baseline data on age, sex, investigations undertaken to find the cause and severity of renal failure, daily creatinine and electrolyte levels, mode of management (conservative/dialysis) and complications were recorded. At subsequent follow-up, information was collected on blood pressure (BP), urinalysis and serum creatinine.

BP was measured manually using a mercury sphygmomanometer and classified as per fourth US Task Force on hypertension recommendations [10]. Sitting-relaxed BP on two separate visits was used for the study. Early morning urine was tested by dipstick (Albustix®). Proteinuria was defined as 2+ or more on two or more occasions. Dipstick positive proteinuria at 10 years was confirmed with 24 h protein measurement, measured by immunoturbidometry (ROCHE®). Haematuria was defined as a minimum of ≥5 red blood cells/high power field in a centrifuged sample.

Creatinine was measured by Jaffe method-CREA (Roche911) analyzer®. Estimated GFR (eGFR) was calculated at 10-year follow-up based on either Modification of Diet in Renal Disease (MDRD) formula for those ≥18 years or Schwartz formula if they were <18 years old.

Peritoneal dialysis was usually the first dialysis modality of choice unless there were any contraindications when haemodialysis was attempted.

Statistical analysis

Descriptive statistics were expressed as median and range or mean ± standard deviation. Student’s t-test was used for quantitative variables and the chi-square test to detect significance between different proportions. A P-value of <0.05 was considered significant. Skewed data were transformed to normal distribution before applying significance tests. Statistical analysis was done with StatsDirect package Version 1.9.8 (Copyright (c) 2007 StatsDirect Ltd., UK).

Results

Demography

A total of 37 children were admitted with ARF during the study period. Twenty-three (62%) were male and 14 (38%) were female. Median age was 7 years (range 1 month to 10 years). Two children were younger than 1 year.

Acute stage

A wide range of aetiological factors were identified (Figure 1) with glomerulonephritis (GN) being the most common (n = 17). Among the GN, post-streptococcal glomerulonephritis (PSGN) was identified in a majority (n = 11) and the rest (n = 6) were designated as ‘other GN’ since they had features of GN but were not proved to be PSGN. Snakebite was the second most common cause identified (n = 9).

Five (14%) children had non-oliguric ARF, of which three were caused by septicaemia and two by poisoning (dapsone and copper sulphate). The children in this group were younger (median 2 years, range 1 month to 3 years) compared to the oliguric group (median 7 years, range 0.8 month to 10 years, P < 0.05). Four of the children with non-oliguric ARF died in the acute stage, and the only survivor had hypertension at the 10-year follow-up.

Peak creatinine during the acute stage ranged from 97 to 990 μmol/l, median 230 μmol/l, and was significantly associated with mortality (Table 1). In the acute phase, renal replacement therapy was required in 27% (n = 10) of

![Fig. 1. Aetiology and acute mortality of the acute renal failure. Key = ATN, acute tubular necrosis; GN, Glomerulonephritis; HUS, haemolytic uraemic syndrome; PSGN, post-streptococcal glomerulonephritis.](image-url)
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Table 2. Evolution of renal disease in patients with abnormal findings at follow-up of 6 months and/or 10 years

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>At 6-month follow-up</th>
<th>At 10-year follow-up</th>
</tr>
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<tbody>
<tr>
<td>Snakebite</td>
<td>HTN (Hypertension)</td>
<td>HTN + proteinuria</td>
</tr>
<tr>
<td>Snakebite</td>
<td>Proteinuria</td>
<td>Proteinuria + eGFR</td>
</tr>
<tr>
<td>Snakebite</td>
<td>No abnormalities detected</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Other GN</td>
<td>Haematuria</td>
<td>No abnormalities detected</td>
</tr>
<tr>
<td>Other GN</td>
<td>Proteinuria</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>Other GN</td>
<td>↑ Creatinine and HTN</td>
<td>Died at 8 years of follow-up</td>
</tr>
<tr>
<td>Other GN</td>
<td>↑ Creatinine and proteinuria</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>Copper sulphate</td>
<td>Proteinuria</td>
<td>No abnormalities detected</td>
</tr>
<tr>
<td>HUS</td>
<td>No abnormalities detected</td>
<td>HTN + ↑eGFR</td>
</tr>
<tr>
<td>PSGN</td>
<td>No abnormalities detected</td>
<td>HTN + ↑eGFR</td>
</tr>
</tbody>
</table>

the children. Peritoneal dialysis was done in eight patients and an additional two patients required both peritoneal and haemodialysis.

The most common complications were hypertension (54%) and haematological problem (35%), with disseminated intravascular coagulation (DIC) being the most common haematological problem as it was present in all children with snakebite as well as in two children with septicaemia. Other complications included infection (19%), encephalopathy (5%), convulsion (13%) and pulmonary oedema (8%). Multiple organ failure (MOF) defined as involvement of one or more organs in addition to kidney was seen among 59% of the children. All of the children who died (n = 13) had MOF. In contrast, MOF was present in only 8 out of the 24 survivors.

Mortality was quite high in the acute stage at 35% (13/37). Septicaemia and snakebite carried the worst outcome. All of the three patients with septicaemia and two-third of children with snakebites died. No death was reported in the acute stage among the children with GN and acute tubular necrosis (ATN) (Figure 1).

Predictors of acute mortality. A significant association was found between short-term mortality and peak creatinine and MOF (Table 1). Most of the patients (76%) who died in the acute phase arrived to the hospital more than 24 h after onset of symptoms, but this finding did not achieve statistical significance. Neither age, sex nor the need for dialysis showed any significant association with acute-stage mortality.

Six-month follow-up. At 6 months, 2 children were lost to follow-up and 22 of the 24 survivors could thus be reviewed. Both of the children who were lost to follow-up at 6 months had features of GN but not PSGN. Seven of the 22 reviewed (32%) had abnormalities in at least one of the recorded parameters (Table 2 and Figure 2). Three hypertensive children required anti-hypertensive medications (although one child on immunosuppressive therapy soon went into end-stage renal disease requiring dialysis). Among the other four with abnormality, investigation (including renal biopsy) and further management could not be conducted on one with raised creatinine (Table 2) due to the failure to return to hospital, whereas the rest were managed without any active interventions.

Ten-year follow-up. At 10 years, a further six were lost to follow-up (Figure 2). Two of these had abnormal findings at 6 months; both were classified as other GN. The

Fig. 2. Long-term follow-up and outcome. Key = ATN, acute tubular necrosis; CuSO4, copper sulphate; GN, glomerulonephritis; HUS, haemolytic uraemic syndrome; PSGN, post-streptococcal glomerulonephritis.
remaining four had normal findings at 6 months (Figure 2). The outcome of 16 of the initial 24 survivors could be analysed at 10 years. There was no significant difference in age, sex, peak creatinine, time lag to presentation, duration of oliguria, hypertension or the need for dialysis between those lost to follow-up and the children possible to trace.

Among the 16 whose outcome was known at 10 years, 6 showed one or more abnormalities including one who had died at 8 years with end-stage renal disease (Table 2). He was the one who had been classified as other GN and had hypertension and a raised creatinine level at 6 months with subsequent development of ESRD needing dialysis. Of the remaining 15, 5 (33%) were abnormal (Figure 2 and Table 2). All of the five children with abnormal findings were clinically asymptomatic with a normal creatinine. Estimated GFR showed that three of the five had values greater than 125 ml/1.73 m²/min (183, 164 and 151 ml/1.73 m²/min) and the rest had eGFR within normal range (121 and 98 ml/1.73 m²/min). Only one of the children with eGFR >125 ml/1.73 m²/min showed dipstick proteinuria. eGFR was within normal range among those with normal renal parameters, with the minimum being 97 ml/1.73 m²/min and the maximum 132 ml/1.73 m²/min.

Predictors of long-term morbidity. Peak serum creatinine at presentation correlated significantly with long-term morbidity as survivors with signs of renal abnormality had a serum creatinine of 168–990 µmol/l (median 632 µmol/l) while those with no detected abnormalities had 159–654 µmol/l, P < 0.048 (median 198 µmol/l).

The median duration of oliguria was also significantly longer (12–29 days) (median 18 days) among survivors with signs of renal abnormality at 10 years than in those who had made complete recovery (1–20 days) (median 7 days, P < 0.05).

None of the three children with elevated BP at 10 years had any predisposing condition like obesity, diabetes or family history of high BP. Interestingly, two of them had normal BP at 6 months. The three children with dipstick proteinuria had a 24-h urinary protein excretion of 522, 520 and 640 mg per day. Notably, two of them did not have proteinuria at 6 months follow-up.

Discussion

GN (46%) and snake poisoning (24%) were the two most common causes of ARF in this review from eastern India. The fate of two-thirds of the survivors could be traced at 10 years, and among them over a third did show one or more signs of renal abnormalities. We believe this prospective descriptive study to be the first to be published looking at outcome of a group of paediatric ARF of varied aetiology beyond 5 years.

Our spectrum of diagnosis is not only different from previously published reports from centres in the developed world but also surprisingly different from other Indian reports [2–4]. Aetiologies of ARF are influenced by the study population, place of the study as well as by the time of the year when the study was conducted [11]. Renal ischaemia was reported as the commonest aetiology from Texas whereas haemolytic uraemic syndrome (HUS) was the commonest cause in a study from Leeds, UK [3,12]. Previous reports from India including Agarwal et al. in 2004 and Arora et al. in 1994 found acute gastroenteritis (AGE) to be a leading cause of paediatric ARF contributing to 85% and 29% of cases, respectively [4,13]. Apart from AGE, HUS has been the other leading aetiology identified in Indian reports [13,14]. In contrast, we found only two (5%) children each with these two diagnoses. Our findings were more similar to the experience published in Thailand where HUS contributed to 2% of cases and hypovolaemia to 12% [5]. As we provide the only renal service for the whole state, this might explain the low number of milder ARF secondary to AGE that is usually managed in local paediatric centres.

Our overall acute-stage mortality of 35% compared well with the recent literatures from both developed and developing countries [3,4]. The high mortality rate in sepsicaemia was not very different from the 83% mortality previously reported [4]. A striking feature of our series is the high incidence of snakebite-induced renal failure (24%) and its associated high mortality (67%). Snakebite has similarly contributed to a substantial number of cases in some other series of ARF from tropical countries [15,16]. Singh et al. from South India reported a mortality of 40% among snakebites with ARF [17]. The median delay to presentation in their study was 30 h, ranging from 17 to 84 h. In our present study, the median was 96 h with a range 24–120 h. The children with snakebites in our study thus arrived significantly later to hospital and had late initiation of anti-venom therapy, which might explain the high mortality. As previously shown in a number of other studies, we also found a significant association between acute-stage mortality with peak serum creatinine and presence of MOF respectively [3,5,16,18].

One of the primary aims of this study was long-term follow-up, and we could trace 67% of our acute survivors up to 10 years. One of them had died of ESRD 8 years after his ARF, and of the surviving children 33% showed some renal abnormality (Table 2).

There is a dearth of publications on long-term follow-up of ARF in children. A study from Guy’s Hospital in London evaluated the tubular and glomerular function among 10 children 7–12 years post-ARF and showed elevated filtration fraction among six out of eight for which they had complete data [8]. Long-term outcome studies focusing on children post-cardiac surgery and HUS have also been published [6,9]. More recently, a study from Texas was reported in 2006 on 3–5 years of follow-up after ARF. Similar to our study, they did not focus on any special subgroup of ARF [7]. Though different in study population and geography, their 29% acute mortality correlated well with our study. We had fewer children lost to follow-up, 33%, than the 55% they reported, and both the long-term morbidity and mortality at 10 years were low in our study compared to the Texas report (33% 10-year morbidity compared to 59%, and 6% mortality compared to 20%).

Snakebite had the worst long-term prognosis, as all three of its survivors had some abnormality. The children with ARF due to ATN or PSGN showed on the other hand a very
good long-term outcome. A recent study from Sri Lanka did find a significant association between history of snakebite and late onset chronic kidney disease of unknown aetiology [19]. The presence of residual renal abnormality at the end of 10 years among all the three survivors of snakebite in this study further justifies the need for long-term follow-up for this particular group.

It is interesting to note that in our study there were children with pathological findings at 6 months that had normalized at 10 years, but also that some children with abnormalities at 10 years were normal at the 6-month follow-up (Table 2). Children with renal failure may suffer from substantial loss of nephrons as a result of the acute insult, especially in those who have suffered severe insult. These children may be at risk of late development of renal insufficiency, even long after the acute episode, due to hyperfiltration of the remaining nephrons [8,20].

Our study does have some limitations, and the results should be interpreted in light of it. Quantifying urinary protein among all the survivors could arguably have improved the sensitivity, but screening is more economically feasible by urinary dipstick. Hence we decided to quantify protein only among those with dipstick proteinuria >2+. A formal GFR would have been most appropriate, particularly since estimating formulas are less accurate at higher GFR, but this was not financially possible. We did not have baseline creatinine on our population prior to their onset of GFR, but this was not financially possible. We did not have baseline proteinuria among all the survivors could argue that the sensitivity, but screening is more economically feasible by urinary dipstick. Hence we decided to quantify protein only among those with dipstick proteinuria >2+. A formal GFR would have been most appropriate, particularly since estimating formulas are less accurate at higher GFR, but this was not financially possible. We did not have baseline creatinine on our population prior to their onset of ARF, and hence underlying chronic renal failure remains a possibility. But the fact that creatinine normalized in all but two of the survivors who could be followed up at 6 months makes this unlikely.

Despite these shortcomings, this is probably the first analysis that prospectively evaluates a decade-long outcome in children post-ARF.

Conclusion

ARF continues to have a high mortality and morbidity in children. At 10 years of follow-up, more than a third of the acute-stage survivors who could be traced were found to have at least one sign of an underlying renal problems, thus emphasizing the need for long-term follow-up of children who have experienced ARF.

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Conflict of interest statement. None declared.

References


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