ADULT-ONSET NEPHROTIC SYNDROME WITH MINIMAL CHANGES: RESPONSE TO CORTICOSTEROIDS AND CYCLOPHOSPHAMIDE

*F Nolasco, J Stewart Cameron, J Hicks, C S Ogg, D G Williams

*Hospital Curry Cabral, Lisbon, Portugal, Guy’s Hospital, London, United Kingdom

Summary

Eighty-nine patients with onset of nephrotic syndrome over the age of 15 years and minimal changes on renal biopsy have been studied. Seventy-five patients were given a course of prednisone in an initial dosage of 60mg/24hr, tapering over the following 8–16 weeks. Only 45 were in remission after eight week’s treatment, 55 after 16 weeks; eventually, a total of 58 lost their proteinuria completely. Of these, 24 per cent never relapsed, 56 per cent relapsed on a single occasion or infrequently, and only 21 per cent were frequent relapsers. Cyclophosphamide, used in 36 patients, had a similar time to response. Stability of remission was better than in similar children, 66 per cent being in remission at five years, after which no further relapses were seen.

Introduction

About one-quarter to one-third of patients with an onset of a nephrotic syndrome over the age of 15 years have, on renal biopsy, a pattern usually described as ‘minimal change disease’; that is, no obvious abnormality of the glomeruli on light microscopy. Although there are many good descriptions of the short- and long-term outcome in children with this appearance [1], the literature on similar adults is scanty [2]. Until recently, the practice of renal biopsy in all adult onset nephrotics has been unchallenged, whilst in children it has been generally accepted that biopsy is only performed after the demonstration of resistance to corticosteroid treatment at four to eight weeks. If such a policy is to be applied to adults [3,4], then data are needed for adults on just how rapidly they will respond to corticosteroid treatment. In addition, there are no detailed long-term descriptions in the literature of the results of cyclophosphamide treatment of adult-onset nephrotics with minimal change lesions on renal biopsy; this study set out to fill these gaps in our knowledge of the short- and long-term behaviour of adult-onset nephrotics with minimal changes on biopsy.
Patients, materials and methods

The nephrotic syndrome was defined as oedema, proteinuria in excess of 3g/24hr, and a serum albumin of less than 30g/L. Remission was defined as return of proteinuria to normal limits (p<0.3g/24hr), relapse as return of a nephrotic syndrome, defined as above. The pattern of relapses was described as: frequent relapse if two or more relapses occurred within the first six months of stopping corticosteroid treatment, or four or more relapses within the first year of disease. Steroid dependence was defined as two consecutive relapses appearing when the steroid dosage was reduced, or immediately upon stopping. Infrequent relapse was defined as the return of a nephrotic syndrome not satisfying the definitions just given.

During the period 1964–1982, 91 patients satisfying the criteria given above were biopsied at Guy’s Hospital, London. Two patients did not have adequate follow-up and were excluded from analysis. Protein excretion was measured by the biuret method, serum albumin by AutoAnalyser®, as was plasma creatinine and urine creatinine.

The mean age of the patients at presentation was 42 ± 19 years (SD) (range 15–82 years) with a slight preponderance of males (50:39). Mean serum albumin was 19.7g/L (range 2–28g/L), and mean proteinuria was 10.2g/L, range 1.2 (in acute renal failure) to 42g/24hr.

Initial treatment

Eight patients were not treated specifically; six of these eight eventually went into remission. Of the remaining 81, 75 were treated with prednisone alone, four (in 1966–1967) with prednisone and azathioprine, and two with cyclophosphamide alone. Sixty-four of the 75 patients who were treated with prednisone alone were given a mean of 13 ± 5 weeks of treatment, range eight to 20 weeks, but 11 patients received long courses of prednisone, under the care of local physicians, of 25–32 weeks.

Secondary treatment

In general, eight weeks of cyclophosphamide 3mg/kg/24hr was given. Three patients received longer courses of 16, 40 and 70 weeks each.

Results

The rate of entry into remission is shown in Figure 1; by 16 weeks, none of the eight untreated patients had gone into remission (p<0.005 compared with prednisone-treated). Twenty patients still had proteinuria after 16 weeks’ treatment, but three went into remission subsequently; of the remainder, 10 had persistent proteinuria and seven a persistent nephrotic syndrome.
Figure 1. Time course to loss of proteinuria in adult onset nephrotic patients with minimal changes calculated by actuarial methods. Patients were treated with prednisone alone (75 patients), or cyclophosphamide (36 patients). Eleven patients were given both drugs and 25 cyclophosphamide alone. When tested by the logrank method there was no statistical difference between the curves. Corresponding data for children treated with prednisone alone are shown for comparison [1]

Relapses following corticosteroid treatment

Duration of remission in the 55 patients who achieved remission after corticosteroid treatment is shown in Figure 2: only 34 per cent remained in remission after two years. Eventually all but nine relapsed. The majority of relapses were within the first year of follow-up, and were more frequent in younger patients, relapse being infrequent in those over 50 years of age. Only six patients were steroid-dependent, as defined above.

Treatment with cyclophosphamide

The rate of remission with cyclophosphamide was similar to that achieved with corticosteroids in the 36 patients treated (Figure 1); 69 per cent lost proteinuria within 16 weeks of starting treatment. Those with rapid induction of remission with corticosteroids, also showed rapid loss of proteinuria with cyclophosphamide, but the age at presentation had no effect upon the results. Two-thirds of the patients treated with cyclophosphamide were still in remission after four years (Figure 2); of the 16 patients followed beyond this point, only one relapsed.

590
Figure 2. Long-term stability of remission in adult onset minimal change nephrotics following treatment with prednisone (broken line, 58 patients) and cyclophosphamide (continuous line, 28 patients). Remission is more prolonged after treatment with cyclophosphamide, and is superior to results obtained in similar children, even though relapse after prednisone is more frequent

**Status in last follow-up**

The median follow-up period was $91 \pm 63$ (SD) months, range two years to 24 years potential follow-up; 30 patients had been followed for more than 10 years. Fifteen patients had died (17%); all the patients who died were aged more than 42 years at onset, and the majority were aged over 60 years. Eleven of the 15 deaths occurred within three years of presentation, but only one was in chronic uraemia. Another four deaths related to complications of the nephrotic syndrome: one from pulmonary oedema following an albumin infusion whilst anuric, one from a pulmonary embolus, another during a prolonged acute renal failure during which it was discovered that she had extensive cerebral atrophy, and another from myocardial infarction. The other deaths were from incidental causes all malignant, and vascular disease in older patients.

Of the surviving patients, 59 (80%) were in complete remission, 10 had persisting proteinuria and only five (7%) had a persisting nephrotic syndrome. Surprisingly even when allowance was made for age, 14 per cent of survivors had some evidence of renal function impairment, and 21 per cent hypertension. All the patients with renal functional impairment were over 45 years of age, and four had suffered episodes of acute renal failure.
Complications

Thrombosis was noted in 12 patients, venous in 11 and a femoral arterial thrombosis in one. Major infection was seen in 10 patients, cellulitis in three, pneumonia in three, other sepsis in three and pneumococcal peritonitis in one aged 21 years. Acute renal failure was a major problem, occurring in 10 patients, requiring dialysis in eight. Two myocardial infarctions were observed, in two males aged 49 and 69. One patient on corticosteroids developed duodenal ulceration, and another vertebral collapse; psychosis appeared in a third. Two patients had severe steroid-induced myopathy, and two developed pulmonary oedema during volume replacement, one fatal. Three patients later developed malignancy, one of whom had received cyclophosphamide and one azathioprine.

Discussion

Minimal change disease is the most frequent cause of the nephrotic syndrome overall, the majority of cases occurring before the age of 10 and the peak incidence being at two to three years of age. Over the age of 15 years, a fairly consistent proportion of about 20 per cent of nephrotic patients will be found to have minimal change lesions up to the age of 80 years or more [5]. Although there is a wealth of data on the immediate and long-term outcome of patients who present during childhood or adolescence [6], there is little information on those who present during adult life [2].

It is clear that the spontaneous evolution of the minimal change nephrotic syndrome in adults is, as in children, towards remission [2]. However, these data, and our own, indicate that this spontaneous remission in general takes one to three years. During this period the patient is at risk from the many complications of the nephrotic syndrome, often in its most severe form, since the patients have relatively large protein losses through a well-preserved glomerular filtering surface. Controlled trials have shown that minimal change adult nephrotics will enter remission much more rapidly than those not treated [2,7], but the rate of remission is slower than in comparable children: only 60 per cent of our adults were in remission at eight week's treatment compared with 93 per cent of children. Again, of those 30 patients not in remission by eight weeks, only 43 per cent subsequently lost their proteinuria, compared with 60 per cent of comparable children. This may relate to relatively lower doses of prednisone given to adults than children, on a body weight or surface area basis, but response to identical body weight doses of cyclophosphamide was also slower (Figure 1).

Relapse after steroid treatment was as frequent in our adult population as in the reported children (Figure 1), but the total number of relapses per patient was fewer. In particular, steroid dependence and a frequent relapsing course were less often seen. This phenomenon was age-dependent in the adult group, in that relapse became progressively less common with age.

Treatment with cyclophosphamide resulted in an almost identical response to that observed with corticosteroids (Figure 1), even though patients with complete or relative corticosteroid resistance were included. Eight weeks of 3mg/kg/24hr
of cyclophosphamide produced a stable remission in the majority of adults, two-thirds remaining in remission five years from treatment (Figure 2). This is considerably better than comparable children, but not better if only those with infrequent relapses are considered [8]. Thus, the general impression of a more mild disease with increasing age of onset is sustained.

However, for the older patients was poor, mainly from complications of the nephrotic syndrome and/or its treatment; only one patient (who was not biopsied again) went into renal failure and had been corticosteroid-resistant from the outset. Only five of the 15 deaths in the older patients could be directly related to the nephrotic syndrome, or its treatment, but thrombosis and sepsis were, in this group, as overall in the nephrotic syndrome, the major problem [9].

Thus adults respond more slowly and less completely to treatment with corticosteroids than comparable children with minimal change nephrotic syndrome, but adults show greater long-term stability of remission after cyclophosphamide, which is concordant with their less frequent relapses. If adults are to be treated blind without biopsy, as some have advocated [3,4], then at least 16 weeks’ treatment with its attendant toxicity will be necessary to establish ‘steroid resistance’.

References

3 Hatley MA, Lancet 1982; ii: 1264
4 Kassirer J. Kidney Int 1983; 24: 561