

Treatment of minimal change nephropathy in adults: continuing uncertainty

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■ INTRODUCTION

Minimal change nephropathy (MCN) is characterised by the development of nephrotic syndrome in the absence of histological changes on light microscopy or immune complex deposition on immunofluorescence. Ultrastructural examination typically reveals diffuse epithelial foot process effacement. In children under 10 MCN accounts for up to 90% of those presenting with the nephrotic syndrome¹. Paediatric nephrologists, therefore, reserve renal biopsy for patients with atypical clinical features or those who fail to respond to first line treatment. MCN becomes progressively less common as a cause of nephrotic syndrome through adolescence. In adults, 10-30% of those with nephrotic syndrome are subsequently shown to have MCN^{2;3}. In our own centre, which serves a population of around one million individuals, 173 patients have had a renal biopsy after developing nephrotic syndrome in the last six years. In this population of adult patients MCN was the third commonest diagnosis (13%) after focal and segmental glomerulosclerosis (FSGS) (15%) and membranous nephropathy (34%).

■ PATHOGENESIS

The precise pathogenetic mechanism underlying the development of MCN is unknown. The hypothesis that MCN is a disorder of T cell function is more than 35 years old but remains unproven⁴. The proposal that T cell activation and subsequent cytokine production may mediate epithelial foot process injury is an attractive one⁵. It is possible that one or more elements of the cytokine cascade constitute the putative permeability factor which alters glomerular permeability leading to proteinuria. That this is solely a T cell mediated process has been made less likely by the observation that rituximab, an anti-CD 20 monoclonal antibody, appears to have a beneficial effect in some individuals with resistant MCN⁶. In a minority of cases the disease may occur as an adverse drug reaction, most commonly reported after ingestion of non-steroidal anti-inflammatory agents⁷, or in the setting of malignancy⁸, especially haematological malignancy⁹.

■ NATURAL HISTORY

MCN in adults, as in children, presents with signs of the nephrotic syndrome. Typically the onset of proteinuria and, therefore the development of oedema, occurs more rapidly than in other nephropathies and it may follow a seemingly minor upper respiratory tract or gastro-intestinal infection. Hypertension, non-visible

haematuria and transient acute kidney injury (AKI) are much more common in adults than children with MCN. A case series of 110 adults with idiopathic MCN in our own hospital seen over the last 20 years suggests that at first presentation 45% are hypertensive, 39% have non-visible haematuria and 14% AKI. These figures are similar to those from the largest published case series to date in a North American population¹⁰.

Adults with MCN tend to respond favourably to corticosteroid treatment, 80-90% entering remission. Age appears to influence time to remission but not likelihood of remission, with older adults responding to treatment more slowly¹¹. Up to a third of patients may enter a spontaneous remission without any treatment^{12;13}. However, because of the morbidity associated with the nephrotic syndrome in terms of both infection with encapsulated organisms and venous thrombotic episodes, treatment rather than watchful waiting is the rule.

Patients with MCN have a very low risk of developing end stage renal disease (ESRD). Those who do develop ESRD are often shown on repeat biopsy to have FSGS. In such a situation it may be debated whether FSGS was missed on the original biopsy because of sampling error, or whether MCN and FSGS form two ends of the spectrum of a single disease with progression from one to the other. The lack of progressive renal injury among patients with MCN poses a problem for proponents of the theory that proteinuria is directly injurious to renal tubular cells. This observation may be explained by the fact that the proteinuria among those who suffer MCN tends to follow a relapsing and remitting course. Up to 75% of adults presenting with MCN can be expected to relapse¹⁰. Among our patients, followed up for a mean of eight years, 50% had at least one relapse. Previous work in our unit has shown that the chance of suffering a relapse after 36 months of relapse-free survival is less than 5%, with most relapses occurring in the first six months after entering remission¹⁴. Response to steroid treatment is on the whole good in adults, though up to 25% may become steroid dependant or steroid resistant.

■ TREATMENT

Adult nephrologists lack a firm evidence base to guide their decisions on treatment of patients with

MCN. Much of our practice is based on applying the evidence gained from studies in children, as paediatric nephrologists have been far more proactive in recruiting their patients to randomised controlled trials (RCTs). MCN is less common in adults than in children. The incidence in our centre of three to four cases per million of population per year over the last decade means that studies of sufficient size to be useful would have to be at least national, and probably international. Setting up and running such studies is an expensive and time consuming endeavour and justifying them is made more difficult by the fact that the prognosis of MCN tends to be regarded as benign.

The first line treatment of nephrotic syndrome secondary to idiopathic adult onset MCN is with corticosteroids. This, however, is based on a single trial in adults 40 years ago comparing the use of prednisolone and placebo¹². There are no RCTs comparing steroids and other agents in the treatment of a first episode of MCN. Two small RCTs conducted in the early 1980s compared intravenous and oral steroid regimes. One suggested that oral prednisolone was superior in the treatment of MCN¹⁵, the other that a combination of intravenous and oral steroid was no better than oral steroid alone¹⁶. Evidence in the paediatric literature favours the use of longer courses of prednisolone, with the risk of relapse being lowest with courses of up to six months¹⁷. Our own practice is to use daily prednisolone at a dose of 1mg/kg/day (maximum 60mg) and to continue for at least six weeks, or for two to four weeks after the patient enters a complete remission. Thereafter the dose is reduced to 40mg for two weeks and further reduced by 10mg every two weeks to 10mg per day. The final taper is to 5mg for two weeks after which the prednisolone is stopped. The course may be modified, with a more rapid taper, if the patient develops side effects. Relapse of the disease is treated with a repeat of the above regime, though some nephrologists advocate a shorter course to reduce total steroid exposure.

Some patients require treatment other than prednisolone alone. Patients who respond initially to steroids and then relapse during the tapering regime are termed steroid dependant. Those who fail to respond to a prolonged course, usually at least four months of high dose oral prednisolone, are thought of as having steroid resistant disease. Patients who suffer frequent relapses (for example, three or more

episodes of nephrotic syndrome in 12-18 months) are less likely to achieve a sustained remission with steroids alone and also begin to accrue steroid side effects. These groups of patients generally require treatment with a second line agent. Agents used in these situations include cyclophosphamide and ciclosporin. Retrospective observational work suggests that both agents may be effective in maintaining remission, but that subsequent relapse tends to occur earlier in those patients treated with ciclosporin¹³. The sole RCT in this area recruited both children and adults¹⁸. Patients (n = 73) with frequently relapsing or steroid-dependant disease were randomised to receive either cyclophosphamide or ciclosporin. Of the 11 adults enrolled (six of whom were randomised to the ciclosporin treatment arm) all entered remission, three in each group subsequently suffered relapse. Relapse occurred earlier in the ciclosporin-treated group. Analysis of the whole cohort revealed cyclophosphamide to be superior to ciclosporin in maintaining remission (68% versus 20% remained relapse free at two years). On these grounds, our practice in patients with frequently relapsing, steroid-resistant or steroid-dependant disease is, where possible, to induce remission with high dose oral steroids and then introduce cyclophosphamide 2mg/kg/day for 8-12 weeks (an 8 week course has a much lower chance of causing gonadal injury but may be less effective). Our third line of treatment is to give ciclosporin at a daily divided dose of 4-6mg/kg for up to 12 months.

Where these approaches fail, a variety of other agents have been employed. The evidence available, however, is on a case report level. Tacrolimus appears to be no more effective than ciclosporin¹⁹. Both azathioprine²⁰ and mycophenolate²¹ have been used as fourth line agents with success reported in some patients. In children, the anti-helminthic drug levamisole has been used as a steroid sparing agent²². Finally, there is an increasing number of case reports suggesting that rituximab, a chimeric monoclonal antibody inhibiting CD 20 mediated B cell proliferation and differentiation, may have a role in both adults and children⁶.

SUMMARY

MCN remains a therapeutic, if not a diagnostic challenge, for the nephrologist. It is disappointing

that, almost 40 years after the first small RCTs in this area, we are still operating on a very insecure evidence base. The advent of newer biological agents such as rituximab serves only to emphasise the fact that we still do not know how best to use our first line treatment. In this, as in many areas of general nephrology, more RCTs are required. Owing to the relative rarity of MCN, co-operation between national societies is vital if we are to perform such studies.

Conflict of interest statement. None declared.

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