Early presentation of membranoproliferative glomerulonephritis in Arab children

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ABSTRACT

Objective: Idiopathic membranoproliferative glomerulonephritis (MPGN) is a relatively uncommon cause of progressive renal disease characterized by immune complex deposition resulting in mesangial proliferation and endocapillary inflammation with capillary wall thickening. It has a variable clinical expression and usually thought of as a disease of older children and young adults. In this study we report the spectrum of MPGN in Arab children.

Methods: Eight Arab patients with MPGN type I and type II were described and studied retrospectively. This study was carried out at King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia during a 6 year period, 1996-2002.

Results: Their mean age at presentation was 2.4 ±1.2 years. All patients presented with a steroid resistant nephrotic syndrome. None had macroscopic hematuria. However 5 (62.5%) were hypertensive at presentation. Complements were low in 3 patients (37.5%). The mean follow-up between presentation and last visit was 1.1 ± 0.7 years; range 0.1-2. Three patients were siblings and their parents were 2nd-degree cousins. Another patient had a brother who had a renal failure following steroid resistant nephrotic syndrome (SRNS), but the histological cause of his SRNS was not known. Four patients were on dialysis within 2 years of follow-up, one patient progressed to chronic renal failure with creatinine of 240 umol/l, one patient died and 2 patients were lost follow-up.

Conclusion: Membranoproliferative glomerulonephritis seems to present at earlier age in Arab children and tends to have a severe course with rapid progression to end stage renal disease.

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Membranoproliferative glomerulonephritis (MPGN) is a distinctive form of chronic glomerulonephritis and steroid resistant nephrotic syndrome (SRNS).[1] It usually presents in older children and young adults,[1-3] although it has been described in an infant aged 15 months[4] and we have previously described a case presented at 8 months of age.[5] The morphologic appearance is classified as type I, with interposition of mesangial cells between glomerular basement membrane (GBM) and the endothelium giving rise to an appearance of a double contour in the glomerular capillary wall and type II, with electron dense deposits in the GBM. Type III is a disputed entity with features of both types I and II.[6,7] The number of cases of MPGN is said to be falling in Italy, France, Spain and Japan[6,8,9] but not in Turkey, Nigeria or Thailand, suggesting environmental influences.[6,10,11] We have observed a shift toward an increasing prevalence of focal segmental glomerulosclerosis and MPGN over recent years in the western area of the Kingdom of Saudi Arabia, (KSA).[12]

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In this study, we report the clinical data of 8 Arab children diagnosed as cases of MPGN before 5 years of age.

Methods. Eight patients (4 females and 4 males) presented to our Department during A 6-year-period, 1996-2002, with SRNS and diagnosed after renal biopsies as cases of idiopathic MPGN type I, except one who was diagnosed as MPGN type II (**Table 1**). The diagnosis was established after excluding systemic, hepatic, infectious disorders and malignant neoplasm. They were identified, and their notes were reviewed for clinical presentation, age at first presentation, age at the diagnosis, and results of serum creatinine, complements, hepatitis B surface antigen, antinuclear antibodies, screening for acquired immune-deficiency syndrome and the outcome of renal function. The mean follow-up between presentation and last visit or death was 1.1 ± 0.7 years; range 0.1-2 The diagnosis and the type of MPGN was confirmed by light microscopy (LM), immunoflourecent (IF) and electron microscopy (EM) studies of the renal biopsy tissues. Values expressed as mean ± standard deviation.

Results. The mean age at first presentation was 2.4 ± 1.2 years; range 0.8-4.5 (**Table 1**). All patients presented with a steroid resistant nephrotic syndrome. None of them had macroscopic hematuria. However 5 of them (62.5%) were hypertensive at presentation. Complements were low in 3 patients, normal in 4 patients and the data were unavailable in one patient. Three patients (6A, 6B, 6C) were siblings and their parents were 2nd-degree cousins. They had another sibling aged one year, who did not show signs of the disease until now. Patient 4 had a brother who had renal failure following SRNS and transplanted at the age of 7 years, but the histological cause of his SRNS was not known. Her parents were 2nd-degree cousins, and she had another 2 healthy siblings. Two children, one and 2, presented with renal failure and required peritoneal dialysis (PD) within a month of diagnosis, as they did not respond to intravenous methyl prednisolone (MP) and cyclophosphamide in patient one or oral azathioprine and intravenous MP in patient 2. Patient one's renal biopsy showed MPGN type I with 50% crescents and was diagnosed as rapidly progressive glomerulonephritis. Patient 3, presented with SRNS in infancy, which progressed, to chronic renal failure (CRF) and his creatinine was 240 umol/l, 2 years later. He was reported previously as a case of new association of congenital glaucoma and infantile nephrotic syndrome (NS) due to MPGN that has not been reported before.[5] The patient also had persistent thrombocytopenia and subclinical hypothyroidism. The parents were 2nd-degree cousins, and the affected infant had a sibling who was born with congenital glaucoma. Patients 4 and 5 were lost to follow-up after 6 months. Both of them were treated with oral prednisolone without improvement in their nephrotics. Patient 5 had also received a 12 week course of cyclophosphamide without success to get her into remission. Patient 6 presented with CRF and died a few weeks after presentation from hypovolemia. Her siblings presented with SRNS and normal renal function, but their kidney function worsened very quickly, and both of them required PD after less than a year from diagnosis. **Table 1** shows the clinical details of different patients and laboratory results at presentation.

Discussion. In this paper we report 8 Arab patients with early severe presentation of MPGN. All patients presented before 5 years of age. This is different from previous reports from other countries as the presentation age was around 10-11 years.[1,3,13] Although there are scattered reports of early presentation before 5 years of age,[4,14] it is usually thought of as a disease of older children and young adults.[6] Gulati et al[15] had found that Indian adolescents (aged 12-18 years) presenting with SRNS had a significantly higher frequency of MPGN, compared with younger children aged (one-12 years). While we have reported previously that there was no difference between the presenting age of MPGN nephrotic patients and minimal change nephrotic patients (MCNS).[12] The familial occurrence of MPGN, which was observed in 2 families of our cohort, supports the concept that genetically determined factors may be involved in the pathogenesis of the disease. Membranoproliferative glomerulonephritis was most likely the cause of NS in the dead sibling of patient N4 as histopathological findings in siblings with familial NS show close to a 100% concordance rate.[16] A familial case had been reported previously, particularly with MPGN type I and III.[14,17] Other evidence suggest a genetic basis for MPGN: the extended haplotypes HLA-B8, DR3, SCO1, GLO2 were found to constitute 13% of the disease-associated haplotypes and 1% of control hyplotypes;[4] significantly high percentage of those with MPGN I and III have inherited defects of the complement system[18] and rarity of the disease in Blacks.[7] Lopes et al[19] has reported that there is an association between race, and the incidence of end stage renal disease (ESRD) in patients with glomerulonephritis with a higher incidence of ESRD among normotensive patients in Caucasians (whites) than in negroes or mulattoes, while among hypertensive patients there was a trend for a higher risk of ESRD in negroes. The observation that number of cases of MPGN is falling in developed countries[6,8,9] but not in developing countries, suggests environmental influences.[6,10,11] This could reflect exposure to a common environmental factor or alternatively and more likely, a genetic predisposition that manifests with or without environmental trigger.[14,20,21] All the 6 children who were followed up in our cohort developed CRF with the requirement of dialysis in 4 of them over a short time.

Table 1 - Clinical and laboratory data at presentation.

Patients	Nationality	Sex	Age (years)	Follow-up (years)	Hypertension	Complement	Creatinine (umol/l)	Type of MPGN	Outcome
1	Saudi	Female	2.4	1	positive	Low C3	300	Type I	Peritoneal dialysis
2	Saudi	Male	2.5	1	positive	Low C3	150	Type I	Peritoneal dialysis
3	Saudi	Male	0.9	2	positive	Normal	30	Type I	CRF
4	Saudi	Female	0.8	0.6	positive	NA	50	Type I	Lost to follow-up
5	Yemeni	Female	3	0.7	positive	Low C3	-	Type II	Lost to follow-up
6 (A)	Yemeni	Female	4.5	0.1	negative	Normal	204	Type I	Died
6 (B)	Yemeni	Male	2.4	2	negative	Normal	60	Type I	Peritoneal dialysis
6 (C)	Yemeni	Male	2.5	1	negative	Normal	65	Type I	Peritoneal dialysis

MPGN - membranoproliferative glomerulonephritis, C3 - complement 3, NA - not available, CRF - chronic renal failure

This is a worse than previously reported 50% renal survival at 10 years from MPGN diagnosis.[6,22] Others reported better prognosis particularly with MPGN type III, and it was attributed to early identification by school urinary screening which enabled early management and so improvement of prognosis.[13,23] Marks and Rees, and Ikeda et al[24,25] have reported 2 separate cases of spontaneous clinical improvement in dense deposit disease. The NS at presentation appears to be the most important clinical indicator of subsequent renal failure and a poor prognosis.[6,26] All patients in our study were nephrotics at presentation. Patient 5 was reported previously as unusual association of infantile NS with advanced MPGN type I, and bilateral congenital glaucoma. Other unusual associations of facial telangiectasia in a butterfly distribution, a similar skin lesion on extensors areas, spare hair and type I MPGN has been reported in a boy and his father which seemed to be inherited in an autosomal dominant fashion.[27] In another family, the coexistence of partial lipodystrophy (PLD), compliment 3 (C3) nephritic factor (C3 NeF) and MPGN type I were found in 2 generations.[28] Complements were low in 3 patients (37.5%). This is lower than other reports of 60%.[29] We did not measure C3 NeF, which was found to be positive in patients who had significantly low levels of C3 and C50. There is no significant difference in renal survival probability in patients with or without C3 NeF activity. Neither C3 variants nor continuous low C3 or low CH50 levels had any prognostic value for the clinical outcome in MPGN patients.[14,29]

In conclusion, MPGN seem to present at an earlier age in the Arab population and tends to have a severe course with rapid progression to end stage renal failure.

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