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CLINICAL SPECTRA OF PRIMARY NEPHROTIC GLOMERULOPATHIES: A COMPARATIVE ANALYSIS BASED ON 102 BIOPSIED CHILDREN

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Introduction

Minimal change lesion (MCL) is the commonest histologic expression of primary (idiopathic) nephrosis of infancy and childhood.[1-3] In the absence of expertise in and facilities for kidney biopsy, it is safe to presume that a child between 1 and 16 years of age with nephrotic syndrome has MCL until proven otherwise. The International Study of Kidney Disease in Children (ISKDC), in its 1970 Collaborative Report,[4] calls attention to three (3) other significant morphologic changes associated with primary nephrotic syndrome. These are: (1) focal glomerular sclerosis (FGS), (2) mesangial proliferative glomerulonephritis (MesPGN) and, (3) membranoproliferative glomerulonephritis (MPGN). These lesions have been investigated extensively over the past decade and there are sufficient data to suggest that they differ from MCL in terms of overall prognosis.[2,4,6-11]

In the Philippines, we started a prospective series on primary nephrotic syndrome in January 1979. Since that time, 104 first kidney biopsies have been performed on 104 children, representing almost half of the total number of primary nephrotics (218) diagnosed until December 1982.

For this paper, we limit the discussion to only 102 patients. We delve into their clinical characteristics, therapeutic responses and latest disease status, summarize the clinical picture that suggests one pathology over another, and pinpoint salient details which may guide clinicians in their choice of therapeutic agents.

Materials and Methods

The collective biopsy experience of three (3) hospitals for the years 1979 to 1982 was reviewed. Due to the meager number of patients with membranous

nephropathy (only 2 out of 104 patients), they were excluded from analysis. None of the remaining 102 children had evidence of a previous episode of poststreptococcal nephritis, a preexisting systemic disease, or prior exposure to physicochemical agents known to cause nephrotic syndrome. All had a minimum follow-up period of 6 months.

On the basis of predominant histologic changes, 4 groups were identified – MCL, FGS, MesPGN and MPGN. These lesions were then compared with each other as to clinical presentation, response to conventional drug therapy and eventual outcome. Important areas of dissociation were subjected to statistical analyses using the chi-square method and the students' t-test.

Definitions

1. Steroid-responder – one who remits within four (4) weeks of steroid therapy at high daily doses (2 mg per kg/day);
2. Steroid-resistant – one who fails to remit within four (4) weeks of steroid therapy at high daily doses;
3. Frequent-relapser[2] – a steroid-responder who relapses at least twice within any consecutive six-month period; a drug-free interval exists between attacks;
4. Minimal change lesions (MCL)[3] – the glomeruli look normal under light microscopy;
5. Focal glomerular sclerosis (FGS)[4,5] – glomerular obsolescence, hyalinosis and/or sclerosis limited to a few glomeruli or segment of a glomerulus;
6. Mesangial proliferative glomerulonephritis (MesPGN)[8,12] – there is an increase in mesangial cytoplasm and/or cellularity; no thickening of the capillary walls;
7. Membranoproliferative glomerulonephritis (MPGN)[10] – there is both an increase in mesangial cytoplasm and/or cellularity and thickening of the capillary walls.

Results

Table 1 depicts the case materials for this study. Primary nephrotic syndrome was due to MCL in 38% of cases, FGS in 12%, MesPGN in 24%, and MPGN in 26%.

Clinical Presentations (Table II)

In all four types, there was an obvious predominance of boys over girls. The average age at onset of MPGN was significantly higher than that of MCL, FGS or MesPGN ($p, < .05$). MCL patients had significantly lower average diastolic blood pressures at admission when compared with patients having the other pathologic types ($p, < .005$). Initial average 24-hour proteinuria was significantly higher in FGS and in MPGN in contrast to either MCL or MesPGN ($p, < .005$). The former

Table 1. Pathologic Causes of Primary Childhood Nephrosis

Pathology	*No. of Patients*	*%*
MCL	39	38%
FGS	12	12%
MesPGN	24	24%
MPGN	27	26%
Total	102	100%

two lesions also registered higher initial average serum creatinine levels but the difference was not significant (p, $< .20$). The incidence of gross or microscopic hematuria was higher in FGS (66.6%) and in MPGN (55.5%) than that in MesPGN (33.3%) and in MCL (12.5%). This finding was highly significant (p, $< .005$). And so was the incidence of hypocomplementemia in MPGN (70.4% vs. 25%, 21.7% and 13.5% in FGS, MesPGN and MCL, respectively), p, $< .005$.

Ten (10) of 39 MCL patients (25%) presented with nephritic signs, i.e., diastolic BP $\geqslant$ 90 mm Hg, significant microhematuria, or serum creatinine $\geqslant$ 1.8 mg%, during the first weeks of the illness. These disappeared within four weeks of steroid therapy. Hypocomplementemia ($CH_{100} < 1:40$ or $C_3 < 50$ mg%) was detected in 5 out of 37 patients with MCL who were tested.

Therapeutic Responses (Table III)

All patents uniformly received corticosteroids initially at 2 mg/kg/day for four weeks. MCL and MesPGN accounted for most of the initial steroid-responders (92.3% and 83.3%, respectively). Steroid-responsiveness in both lesions was very significant (p, $< .005$) unlike that in FGS and in MPGN wherein steroid-resistance was the rule.

Cyclophosphamide or chlorambucil was added to the steroid regimen as indicated, at maximum total doses of 225 mg/kg and 9 mg/kg, respectively (duration of treatment, 3 to 6 months). Twenty-five (25) out of 36 MCL patients who were steroid-responsive but frequently-relapsing received either drug; all remitted for periods longer than those obtainable from solitary steroid regimes. One (1) initially steroid-resistant MCL case was lost to follow-up and was unable to undergo cytotoxic treatment but two (2) others who had such treatment remitted.

Two (2) FGS patients were initially steroid-responsive. One developed steroid-resistance in a later relapse; she was also resistant to further therapy with cyclophosphamide. The other patient (histology, focal glomerular obsolescence) always responded to steroids alone during repeat attacks. Seven (7) initially steroid-resistant FGS patients were given cytotoxic agents; all remained proteinuric post-therapy. Dipyridamole was tried in two (2) patients and a remission of 1 and 3 months while on therapy was induced.

Table 2. Clinical Presentations of Various Pathologic Lesions

Pathology	*Ave. Age at Onset (Yr)*	*Sex Ratio*	*Initial Ave. Diastolic BP (MM Hg)*	*Initial Ave. 24-Hr Protein-uria (GM)*	*Initial Ave. Serum Creat-inine (MG%)*	*Hematuria*		*Low Serum Complement Level*
						Gross	*Microscopic*	
MCL (n, 39)	6.5 (1-15)	28M : 11F	70.5 (60-120)	4.32 (1.12-10.2)	1.12 (0.6-3.0)	0	5/39	5/37
FGS (n, 12)	6.4 (2-13)	9M : 3F	77.5 (60-100)	8.07 (2.09-19.03)	1.76 (0.8-8.3)	1/12	7/12	3/12
MesPGN (n, 24)	6.9 (2-13)	17M : 7F	79.4 (50-110)	4.28 (1.06-9.99)	1.22 (0.7-2.1)	1/24	7/24	5/23
MPGN (n, 27)	8.7 (3-15)	19M : 8F	80.7 (50-100)	7.03 (1.76-27.2)	1.51 (0.7-5.6)	7/27	8/27	19/27

Table 3. Therapeutic Responses of Various Pathologic Lesions

Pathology	*Initial Steroid-Sensitivity*		*Subsequent Therapeutic Response*			
			Steroid-Responsive		*Steroid-Resistant*	
	Responsive	*Resistant*	*Cytotoxic Responsive*	*Cytotoxic Resistant*	*Cytotoxic Responsive*	*Cytotoxic Resistant*
MCL (n, 39)	36/39 (92.3%)	3/39 (7.7%)	25/25 (100.0%)	0	2/3 (66.6%)	0
FGS (n, 12)	2/12 (16.6%)	10/12 (83.4%)	1/2 (50.0%)	1/2 (50.0%)	0	7/7 (100.0%)
MesPGN (n, 24)	20/24 (83.3%)	4/24 (16.6%)	4/5 (80.0%)	1/5 (20.0%)	0	2/2 (100.0%)
MPGN (n, 27)	10/27 (37.0%)	17/27 (63.0%)	6/7 (86.0%)	1/7 (14.0%)	4/14 (29.0%)	10/14 (71.0%)

Cyclophosphamide was given to five (5) initially steroid-responsive MesPGN cases. Four (80%) remitted following therapy while one who became steroid-resistant in a later relapse failed to respond also to that agent. Two (2) of four initially steroid-resistant MesPGN patients received cyclophosphamide. Both were treatment failures: one subsequently died of end-stage renal disease (ESRD) 2 years from diagnosis and the other was lost to follow-up.

Of 10 MPGN patients who were initially steroid-responsive, seven (7) had cyclophosphamide therapy. They included one patient who later became steroid-resistant. She did not respond to cyclophosphamide but remitted with dypyridamole. The other six (6) patients responded to cyclophosphamide (remission rate, 86%). On the contrary, out of 14 MPGN patients given cyclophosphamide because of steroid-resistance, only four successfully responded. Ten (10) patients or 71% failed to respond: four were given other drugs (e.g. indomethacin) to no avail, two had no further treatment (still normofunctional), two were in chronic renal failure (CRF), one was dead and one was lost to follow-up.

Eventual Outcome (Table IV)

Ninety-one (91) patients were religiously followed up for an average period of 24 months (range, 6-72 mos.). Their disease duration was 39 months on the average (range, 6-120 months). Among all four lesions, MCL had the highest remission rate (97%) with or without therapy. Next was MesPGN (remission rate, 85%). Both rates were found to be significantly higher than those observed in FGS and in MPGN ($p, < .005$). Only one patient with MCL had proteinuria as of this reporting; he just

Table 4. Eventual Outcome of Various Pathologic Lesions After an Average Follow-up Period of 24 Months (N, 91)

Pathology	*Average Duration of Illness (Mos)*	*Average Length of Follow-up (Mos)*	*In Remission*	*Persistent Proteinuria*	*In CRF*	*Renal Death (ESRD) or Actual Death*
MCL (n, 35)	33.0 (6-120)	21.7 (6-60)	34 (97%)	1	0	0
FGS (n, 11)	45.0 (6-120)	18.6 (6-48)	4 (36%)	4	0	3
MesPGN (n, 20)	42.6 (6-83)	24.9 (6-60)	17 85%)	2	0	1
MPGN (n, 25)	43.6 (14-100)	28.4 (6.72)	16 (64%)	6	2	1

relapsed. The incidence of persistent proteinuria, CRF or death was high in the non-MCL groups. FGS and MPGN registered the highest morbidity and mortality figures.

In this series, the overall mortality rate (ESRD, CRF or actual death) was 7.7% (7/91) whereas the overall remission rate with or without treatment was 78% (71/91). The rest (14.3%) had persistent disease.

Discussion

Primary nephrotic syndrome due to MCL has the mildest clinical signs and the best long-term outlook. Initial steroid-responders are expected to respond to subsequent courses of steroids in future attacks. Those who frequently relapse enjoy longer remission periods following use of cytotoxic agents.[13-15] Even a few who are initially steroid resistant respond to cytotoxic therapy.[16-17] Notwithstanding the initial and transient nephritic features of some patients (25% in this study), therapeutic behavior with either steroids or cytotoxic agents is the same. The hypocomplementemia that is observed in 13.5% of patients presumably reflects loss of complement via the urine concomitant with heavy proteinuria rather than consumption of this protein in an immune-mediated process.

The nephrotic syndrome seen in FGS affects the same age bracket and initially presents with normal kidney function as MCL does. A distinctive finding in FGS in this and other studies,[18] however, is very heavy proteinuria (up to 19.03 grams in one patient) on top of a fairly high incidence of hematuria (66.6% here). Nephrotic syndrome due to FGS is usually refractory to therapy.[8,19] The ability of dipyridamole to induce remission in two steroid- and cytotoxic-resistant cases in

this series is a welcome observation and certainly warrants further evaluation. Futrakul[20] has had similar successes using that drug in FGS. It is perhaps more beneficial and less costly, in the light of the above findings, to proceed to dipyridamole therapy after resistance to steroids has been proven among FGS patients. The benefits are translated in terms of saving some children from certain death within 6-7 years from diagnosis[5] and circumventing many of the undesirable side effects related to cytotoxic treatment.[21] The long-term prognosis of the singular case of focal glomerular obsolescence is uncertain. He remits easily with steroids and his kidney function is normal. Other investigators[5,8] have reported similar histories.

MesPGN appears to approximate MCL in terms of age at onset of disease, degree of proteinuria, normal kidney function and infrequent occurrence of hypocomplementemia.[19] Unlike in MCL, however, hypertension and hematuria are notable.[7,8,12] Corticosteroids are capable of inducing remission in 83.3% of cases. Those who are steroid-responsive but frequently-relapsing are likewise benefited by cytotoxic agents in 80% of children so treated. These figures are comparable to those of other studies.[12] Also comparable is the failure of cytotoxic agents to induce remission among patients who are initially steroid-resistant.[22] Long-term prognosis in this disease seems to be better than that of either FGS or MPGN but no better than that of MCL.[19] In fact, one death recorded here is due to MesPGN.

Among the four histologic types, MPGN can easily be sorted out on the basis of the following clinical traits: (1) older age at onset; (2) higher incidence of hypertension, hematuria and very heavy proteinuria, and; (3) prevalence of hypocomplementemia. More than half of patients are initially steroid-resistant; furthermore, those who are steroid-resistant are also resistant to cytotoxic agents. It appears that only those cases who initially and continually respond to steroids are likely to have variable remission periods post-therapy with cytotoxic drugs. Even then, the remission rate in this disorder is third only to MCL and MesPGN. Nine patients have either persistent proteinuria or end-stage kidney disease. One of them is dead after 51 months of therapy-resistant nephrotic syndrome.

Our cumulative experience these past four (4) years can be viewed from a non-operative standpoint. Much as we advise kidney biopsy for all its informative benefits, many circumstances hinder its consummation in many settings in the country. In these limited situations, constant steroid-responsiveness during nephrotic attacks may be used as a relatively good prognostic gauge,[2,23] irrespective of the age at onset or clinical presentation. This study uniformly shows a favorable remission rate among steroid-responders in any of the four pathologic lesions. Patients who are initially steroid-resistant are more likely to have glomerular changes that augur a poor prognosis.[3] For the simple reason that cytotoxic drugs may also be unable to control the proteinuria, non-cytolytic preparations like dipyridamole may be tried. The alternative use of the latter may prevent infliction of iatrogenic disorders resulting from misuse of cytotoxic agents.

Summary

102 primary nephrotic children who had kidney biopsy between January 1979 and December 1982 were studied. The histopathology was MCL in 38%, FGS in 12%, MesPGN in 24% and MPGN in 26%. MCL patients had the most benign clinical presentation. They were steroid- and/or cytotoxic-responsive, and had excellent remission rates with or without treatment. The other three pathologie were characterized by varying degrees of hematuria, hypertension and azotemia. Hypocomplementemia was most frequently observed in MPGN. MesPGN appeared to approximate the steroid- and cytotoxic-responsiveness of MCL but its prognosis seemed not as good. FGS and MPGN were associated with very heavy proteinuria and a high incidence of hematuria and steroid/cytotoxic resistance. Death and therapy-resistant proteinuria in this series were mainly attributed to these two latter lesions.

This study corroborates the findings of other investigators that initial and continual responsiveness to steroids in nephrotic syndrome is a good prognostic index. Steroid-resistant patients should have the benefit of kidney biopsy for definite diagnosis. If this is not possible, cytolytic therapy should not be tried as it can be both ineffective and hazardous.

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Benjamin Canlas, Discussant

This is a very special paper and would like to congratulate Dr. Alfiler for having been able to collect this number of cases in the relatively short time he has been with us. Our experience with renal biopsies has been relatively recent. Dr. Alfiler and Dr. F. Alano have made renal biopsies important procedures in their management of renal disease and for this reason we have been virtually forced to familiarize ourselves with the study of renal morphology in renal disease. I, therefore, do not consider myself to be an expert in this field.

Renal biopsy as a means of guiding the clinician in the management of renal disease has been going on for the last few decades in other parts of the world. There has also been considerable advancement in the techniques utilized for evaluating morphology. This has resulted in enormous increase in our knowledge in the nature and pathogenesis of renal disease. By correlating morphology with clinical manifestations various forms of renal disease have evolved, early diagnosis is possible, institution of the correct management is arrived at, efficacy of therapy can be correctly evaluated, prognostication is more reliable, and the natural history of the disease may be provided.

There are generally acceptable classifications of glomerulopathies that various authorities in this field postulate. While nomenclature and classification may vary somewhat according to authorities concerned, most pathologists and clinicians would understand each other even when these variations are utilized. The entities enumerated in the paper of Dr. Alfiler are generally accepted and, therefore, can be made comparable with other studies abroad.

There are, however, certain shortcomings in the study of biopsies in our country. Generally, we depend on the ordinary hematoxylineosin stain in our studies often supplemented with such special stains as PAS, trichrome and sometimes silver stains. In more sophisticated countries, all four stains enumerated above are a must and in addition they utilize immunoflourescent techniques and electron microscopy. Dr. J. Zamuco, who is another pathologist delving in renal biopsies, sometimes performs immuno-flourescent methods. Since our methods of study are limited to light microscopy accuracy in diagnosis may be open to question. However, when we compare the results of Dr. Alfiler with those noted abroad, there is general correlation of the figures. We are quite confident, therefore, that inspite of the shortcomings that we have, the pathologic diagnoses made are generally accurate.

Studies such as these can give us a better insight of renal diseases in our country which can help not only in the management but probably in the prevention of these diseases. Again, let me congratulate Dr. Alfiler for his efforts in this basic investigation.