

## CONCURRENT USE OF CYCLOPHOSPHAMIDE AND PREDNISOLONE IN CHILDHOOD NEPHROTIC SYNDROME IN SOUTH-EAST NIGERIA; A REPORT OF 5 CASES

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### ABSTRACT

**Introduction:** Nephrotic syndrome is a chronic renal disease that can lead to end stage renal disease. There are different histological types with global variations in frequency. Literatures reviewed showed that the African variant is less likely to be minimal change variant. No clear treatment protocol for it has been most beneficial.

**Objective:** This paper aims to evaluate the outcome of a treatment protocol using cyclophosphamide and prednisolone concurrently.

**Methods:** A low dose and short duration concurrent use of cyclophosphamide and prednisolone was used for treating children with nephrotic syndrome who had not developed derangements of their renal function. The case files of those that were treated and followed up over a 10 year period or until they were above 18years of age were analysed for their clinical parameters.

**Results:** Five cases were treated and all have been in clinical remission for more than 4 years as at the time of the review, though 2 of them relapsed twice initially. They were all aged above 6 years and had microscopic hematuria. The 3 cases whose ESRs were done had high levels. Two cases that presented 1 yr after the onset of their symptoms resolved without relapse while 2 out of the remaining 3 in whom this interval was less than 6 months relapsed.

**Conclusion:** This treatment protocol appears beneficial to childhood nephrotics in this environment and should be used.

**Key Words :** Cyclophosphamide, Prednisolone, Childhood, Nephrotic Syndrome, Nigeria.

### INTRODUCTION

Nephrotic syndrome is a clinical condition of oedema and proteinuria ( $>1\text{gm}/\text{M}^2/24\text{hrs}$  or  $40\text{mg}/\text{M}^2/\text{hr}$ ) in which the renal histology (light microscopy) demonstrates fatty degeneration of the tubules associated with normal appearing glomeruli. The oedema in this chronic renal disease follows the hypoproteinaemia (serum albumin level of  $<2.5\text{g}/\text{dl}$ ) that results from the massive proteinuria.<sup>1</sup> The different renal histological findings include the minimal change nephrotic syndrome (MCNS) which constitutes about 84.5% of cases; focal segmental glomerulosclerosis, (FSGS) 9.5%; membranoproliferative glomerulonephritis (MPGN), 2.5% and membranous glomerulonephritis (MGN), the remaining percentage.<sup>2</sup> African children with nephrotic syndrome rarely show the minimal change lesion.<sup>3</sup>

In a study of nephrotic syndrome in children aged 3 to 16 years in Ilorin, Nigeria, out of the 8 biopsies that were done, focal mesangial proliferative glomerulonephritis was seen in 63% while minimal change, membranoproliferative and mesangial proliferative glomerulonephritis were equally distributed amongst the remaining.<sup>4</sup>

The diagnosis which is both clinical and laboratory is based on the presence of oedema, hypoproteinemia and massive proteinuria. Uncomplicated cases have normal serum urea, electrolytes and creatine levels, though some may have hematuria. Though the hypoproteinemia in this condition is not the only cause of the oedema that makes most of them to present, however the loss of oncotic pressure subsequent on the hypoproteinemia initiates all the bodily responses culminating in the oedema. Without intervention, persistent proteinuria of the magnitude in nephrotic syndrome is expected to ultimately lead to oedema.

Though a chronic disease, spontaneous remission, especially with the minimal change histological type,

is speculated to often occur,<sup>5</sup> whilst a few will progress to end-stage renal disease.<sup>6</sup>

Drug treatment has offered the best chance of reversing the renal process and resolving the biochemical derangements and clinical features. Steroids were initially found to be very useful,<sup>7</sup> and although more than 80% of patients with MCNS responded to the steroids steroid responders, unfortunately, 50-60% of these steroid responders developed frequent relapses or became steroid dependent.<sup>8</sup> The prolonged use of steroids in the frequent relapsers and steroid dependents also made them to suffer from the adverse effects of steroid therapy.<sup>9</sup> The other histological types on the other hand were poorly responsive to steroids.<sup>10</sup> These setbacks led to the discovery of the cytotoxics, and the alkylating agents cyclophosphamide and chloroambucil<sup>11</sup> were found beneficial when steroids failed.<sup>12</sup> Due to the initial favourable response of the commoner MCNS to steroids, the mainstay of treatment or the first line drug for the treatment of nephrotic syndrome became the steroids. The need to improve treatment outcome resulted in the use of the effective drugs singly<sup>9,11,13,14</sup> or as a combination; sequentially<sup>15,16</sup> and concurrently.<sup>17</sup> There appears to be a consensus that the combination therapy gave better results than single drug therapy. Combination treatment have been found useful in other chronic ailments e.g. tuberculosis, HIV/AIDS and hypertension and nephrotic syndrome, a chronic ailment may not be much different.

Many factors however affect the outcome of drug treatment in nephrotic syndrome and include; the histological type,<sup>18</sup> first presentation or relapse,<sup>19</sup> age of the child at the onset,<sup>13,17</sup> duration of treatment,<sup>15,20,21</sup> type of drug,<sup>21</sup> type of response to steroid therapy,<sup>22</sup> dose of the drug,<sup>20</sup> the renal function status<sup>14,15</sup> and the patient's race.<sup>3,4</sup>

Long remission periods have been associated with the use of cyclophosphamide either sequential to or in combination with steroids.<sup>15</sup> A comparative analysis studying the effect of a low dose (2.5mg/kg/day) and a high dose (5mg/kg/day) cyclophosphamide over a period showed that low dose used long enough was capable of giving good results while at the same time avoiding the toxic or side effects of a high dose.<sup>16</sup> A study, using a dose of 3mg/kg/day for 8 weeks, showed beneficial results and concluded that a lower dose may work and that for children, shorter durations may even be effective.<sup>15</sup>

McCrorry et al<sup>16</sup> had commented that there is no agreement regarding the most desirable program of therapy for children with nephrotic syndrome. They recommended the evolution of a new and safer but

effective therapy to control or prevent relapses. Tune et al shared the same view when they suggested that the present conservative approach to the management of steroid resistant focal segmental glomerulosclerosis should be changed since this condition is more likely to progress to end-stage renal disease.<sup>23</sup>

There is therefore the need to work out treatment modality or modalities that will be most beneficial to these patients especially for those in this environment that are not likely to be the MCNS type.

This study therefore tried to look at the outcome of children presenting with nephritic syndrome who were treated with a low dose short course of cyclophosphamide and prednisolone.

## METHODOLOGY

All the children that presented with oedema, hypoproteinemia and massive proteinuria but without deranged serum urea, electrolyte and creatine values seen over a ten year period (Nov 1994 Oct 2004) in a children's specialist hospital at Onitsha, Southeast Nigeria were enrolled after explanation.

Information to be obtained included their ages, sexes, blood pressures, complete blood count and erythrocyte sedimentation rates, serum urea, electrolytes and creatine, serum proteins, 24hr urinary protein, urine stripe test for protein and rbc's using Combur<sup>10</sup>. Abdominal ultrasound was done when abnormal masses were palpated par abdomen.

Patients were followed up and their blood pressures, serum proteins and urinalysis were monitored.

A concurrent use of low dose and short duration protocol using cyclophosphamide and prednisolone was used in treating the children. It consisted of:

Cyclophosphamide in a dose of 2 2.5 mg/kg/day to the approximate total dose obtainable from the available tablet strength of 100mg/tablet. This was given once daily for a total of 8 weeks. The dosage was adjusted as the patient's weight changed with loss of oedema.

Prednisolone was given in a dose of 1.5 mg/kg/day to achieve an approximate total daily dose divisible by 5 since the tablets are in 5mgs strength. It was given in two divided doses and for a total of 12 weeks, with dose adjustment according to changes in the patient's body weight. After 10 weeks, the dose was tapered off at the rate of 0.5 mg/wk.

Adjunctive therapy of furosemide in a dose of 2 4 mg/kg/day in two divided doses was given to those with discomforting oedema or anasarca.

Other clinical problems e.g. infections that were present were treated appropriately.

Relapses during follow up were documented and given the same course of treatment.

The clinical feature, oedema, which the patients related to was used as the determinant of their clinical state i.e. remitted or relapsed.

They were followed up to the time of the report or, up to the age 18 years if they attain that age before the time of the report.

## RESULTS

Nine case files were identified as cases of nephrotic syndrome seen over the 10 year period. Two

however had deranged renal functions and were not treated here but were referred while another two objected to the treatment. The 5 remaining case files were then evaluated.

Table 1 shows the epidemiological features of the patients, any other problems detected, additional treatment given and duration of remission.

Table 2 shows the laboratory results before institution of treatment.

No renal biopsies were done on them.

Patient Identity	Age at Pres. (yrs)	Sex	Duration of Symptoms at Pres.	Other Problems Present	Adjunctive Therapy with Furosemide	Relapses	Duration of Remission (mths)		
							1 <sup>st</sup>	2 <sup>nd</sup>	Till Present or Seen Last
O.I.	14	F	5mths	Bilateral nephromegaly, horse-shoe shaped kidneys and duplex ureters	Yes	2	19	11	48
N.N.	9	M	4mths	Peritonitis	No	Abscent			108
D.M.	9	M	16mths	Scabies	Yes	Abscent			108
I.C.	8	M	24mths	Urinary tract infection	Yes	Abscent			60
N.T.	10	M	3wks		Yes	2	18	11	48

The 1st three attained 18 years and stopped coming for consultation.

yrs - years, mths - months, wks - week, pres. - presentation

Table 2: Laboratory Results.

Pt i.d	Blood pressure mmHg		Full Blood Count					ESR Mm/1 <sup>st</sup> hr	Serum U/E/C				Serum proteins g/l			Urine results		
	SBP	DBP	Hb g/l	Wbc total	Neut %	Lymph %	Others %		Urea Mg/dl	K mEq/L	Na mEq/L	Cr mg/dl	Alb	Glo	Total	Protein		Blood
																Dip stick	g/M/24 hrs	
OI	120	80	11	8600	40	59	1	-	12	3.6	137	0.42	1.6	2.6	4.2	+++	2.3	present
NN	120	95	10	7750	59	49	-	85	29	3.7	134	1.1	2	3	5	+++	4	present
DM	90	60	10.5	9150	61	37	2	-	34	4	139	1.3	2.3	3.6	5.9	+++	3	present
IC	110	80	9.7	10550	56	43	1	135	37	4.9	122	1.4	1.9	0.8	2.7	+++	7.7	present
NT	120	80	11	11500	83	17	-	101	33	4.1	139	1.3	1.5	2.0	3.5	+++	2.3	present

Pt id = patient identity, Alb = Albumin, Glo = Globulin

## DISCUSSION

Unfortunately, time, distance and costs constraints made the necessary blood and urinary biochemical monitoring difficult.

Secondly, 5 cases are inadequate for statistical conclusions but nephrotic syndrome is not a very commonly seen condition in any particular private

practice and since a pattern seemed to have been observed with these 5 cases, it was thought worthwhile to communicate a preliminary report on the evolving pattern.

Finally, no clear different protocol was used for the relapsed cases. It is pertinent to also mention that none relapsed within less than 6 months period.

In this review, there were 4 males and one female which is in keeping with involvement of more males than females in nephrotic syndrome.

Though two cases relapsed, all of them ultimately went into clinical remission, with the least having been in remission for 48 months now. On the other hand, when only steroids were used, the percentage of steroid responders reduced with time.<sup>8</sup> Though all the cases had hematuria, which could also be found in MCNS,<sup>25</sup> the presence of a high ESR in those monitored would suggest that these nephrotics were secondary in origin. That would have meant poor response to treatment as found by some workers.<sup>23</sup> In this review however, two of the initial 3 responders had high ESRs.

Considering the impact of age, they were all above 6 years of age and this may have improved their chances of going into remission since it is known that if the age is less than 6 years, they tended to relapse into adulthood.<sup>26</sup>

Additionally, some other workers have shown that the shorter the time of onset to treatment, the better the response to treatment.<sup>27</sup> This review has findings at variance with this view because the two cases that lasted for more than 12 months before the onset of treatment resolved with the first course while 2 out of the 3 cases that were less than 6 months relapsed 2 times over.

This review also showed that the second relapse took a shorter time than the first to manifest which is the finding in other studies.<sup>28</sup> The subsequent relapse amongst the relapsed cases tends to reinforce the view that a history of relapse increases the frequency of subsequent relapses.<sup>28</sup>

This low dose short duration concurrent use of cyclophosphamide and prednisolone in the treatment of nephrotics seems to offer good results that may be comparative to others. Generally, whilst low dose cyclophosphamide and short duration prednisolone were associated with relapses, this concurrent use of both drugs in this manner seemed to have had a synergistic action of both drugs on the disease process. Other studies seem to support this view.<sup>15</sup>

From the foregoing therefore, it is probable that the concurrent use of cyclophosphamide and prednisolone in the treatment of nephrotics in this environment maybe a type of the non-conservative management of secondary nephrotics that was advocated for by Tune et al.<sup>23</sup>

These findings could result in the childhood nephrotics in our environment enjoying fewer hospital consultations consequent upon fewer relapses, better health without the otherwise laborious medication schedules and the consequent positive impact of these on their socio-economic well being if this protocol is utilized.

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## ERRATUM

In our previous publication titled Neurological Complications of Chronic Myeloid Leukaemia: Any Cure? Vol 11(3): 246-249.

The authors' names appeared as J D Emmanuel and M A Dorusinmi.

The correct names are D E Joseph and M A Durosinmi.

The errors are regretted.