

## PROLONGED DURATION OF NEPHROTIC SYNDROME AND TREATMENT FAILURE AMONG CHILDREN WITH NEPHROTIC SYNDROME IS ASSOCIATED WITH INCREASED HYPERTENSION.

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### ABSTRACT;

**Background;** Nephrotic syndrome (NS) is one of the most common renal diseases found in the paediatric population and is associated with significant complications, including infection and thrombosis. A high proportion of children enter sustained remission before adulthood, and therapy must therefore mitigate the childhood complications, while minimising the long-term risk to health. **Objective;** To determine the frequency of hypertension in children with nephrotic syndrome presenting at a tertiary care hospital. **Material and Methods;** All the patients (n = 146) who meet inclusion of this study were registered from OPD of Department of Pediatrics, Nishtar Hospital, Multan, Pakistan. Informed consent was taken from the parents of these children describing them objectives of this study, ensuring them confidentiality of the information provided and fact that there was no risk involved to the patient while taking part in this study. Children with steroid sensitive nephrotic syndrome were taken in this study. Systolic and diastolic blood pressure was measured by researcher. **Results;** Of these 146 study cases, 92 (63%) were male patients while 54 (37 %) were female patients. Mean age of our study cases was  $7.61 \pm 2.55$  years. Our study results have indicated that majority of our study cases i.e. 91 (62.3 %) were aged more than 7 years. Of these 146 study cases, 76 (52.1 %) belonged to rural areas and 70 (47.9 %) belonged to urban areas. Positive family history was noted in 11 (7.5%) and 129 (88.4%) mothers of these patients were illiterate. Compliance with the treatment was noted only in 31 (21.2%) of our study cases. Mean disease duration was  $18.51 \pm 10.26$  months and 86 (58.9%) had duration of illness more than 12 months. Mean duration of treatment was  $6.58 \pm 2.28$  months and 113 (77.4%) were taking their treatment for equal/less than 1 year. Mean systolic blood pressure was  $135.85 \pm 5.12$  mmHg while diastolic blood pressure was  $90.87 \pm 3.25$  mmHg. Hypertension was noted in 54 (37%) of our study cases. **Conclusion;** Frequency of hypertension was high among children having nephrotic syndrome in our study. Hypertension was significantly associated with family history, treatment compliance and prolonged disease duration. All clinicians treating such patients should monitor such children for hypertension for timely diagnosis and early management which will improve clinical outcomes and decrease disease morbidity. This will help to improve quality of life of our patients and also save them from future hardships.

**Keywords;** Hypertension, Nephrotic Syndrome, Frequency.

## INTRODUCTION;

Nephrotic syndrome refers to the tetrad of edema, 'nephrotic-range' proteinuria, hypoalbuminemia, and hyperlipidemia. Nephrotic-range proteinuria in the pediatric age group is defined as protein excretion of more than 40 mg/m<sup>2</sup>/hour. In children, 24 hour-urine collections are unreliable. Thus, a single, first morning urine sample is now preferably used to quantify protein excretion by the estimation of the urine protein/creatinine ratio. From the new management guidelines released by the Kidney Disease: Improving Global Outcomes (KDIGO) group, urine protein/creatinine ratio of  $\geq 2000$  mg/g correlates with 'nephrotic-range' proteinuria or dip-stick proteinuria of 3+<sup>1,2</sup>. Nephrotic syndrome remains the most common manifestation of glomerular disease in childhood<sup>3</sup>. The disease progresses to frequent relapses, often accompanied by steroid dependence in about 20% to 60% of patients.<sup>4</sup> It is currently recognized that at least 50% of relapses are triggered by a viral upper respiratory tract infection.<sup>5</sup>

Nephrotic syndrome (NS) is the most common glomerular disease of childhood<sup>6</sup>. Most caucasian series report NS as a disease of pre-school aged children with peak age incidence of 2-3 years, affecting more males than females. Seventy to 90% of such cases are due to minimal change lesions in which hypertension, haematuria and poor response to steroid therapy are uncommon. In nephrotic syndrome protein leaks from the blood to the urine through the glomeruli resulting in hypoproteinaemia and generalised oedema. While most children with nephrotic syndrome respond to corticosteroids, 80% experience a relapsing course. Corticosteroids have reduced the mortality rate to around 3%. However corticosteroids have well recognised potentially serious adverse effects such as obesity, poor growth, hypertension, diabetes mellitus, osteoporosis and behavioural disturbances<sup>7</sup>. Hypertension has been reported to be 41.4% among children with nephrotic syndrome<sup>8</sup>. A study from Bangladesh reported 15.8 % hypertension by disease plus taking prednisolone in children with nephrotic syndrome.<sup>9</sup> Another retrospective analysis from Islamabad documented nephrotic syndrome associated with 64% hypertension in children<sup>10</sup>.

This study is designed to ascertain the frequency of hypertension among children with nephrotic syndrome owing to the corticosteroid therapy which has well documented side effect including hypertension.

## MATERIAL AND METHODS;

Children (n = 146) aged 2-12 years of either sex having nephrotic syndrome for more than 6 months were included in our descriptive cross-sectional study. Patients with congenital nephrotic syndrome, secondary nephrotic syndrome e.g. TB, Hepatitis, malaria and drugs/toxins, known cases with the history of Asthma and known congenital heart defects were excluded from our study.

A specialized proforma has been developed to record the findings of this study. All the patients (n = 146) who meet inclusion of this study were registered from OPD of Department of Pediatrics, Nishtar Hospital, Multan, Pakistan. Informed consent was taken from the parents of these children describing them objectives of this study, ensuring them confidentiality of the information provided and fact that there was no risk involved to the patient while taking part in this study. Children with steroid sensitive nephrotic syndrome were taken in this study. Systolic and diastolic blood pressure was measured by researcher. **Nephrotic syndrome;** was defined by the presence of all of the followings; nephrotic-range proteinuria (urinary protein loss in excess of 0.05 – 0.1 g/kg body weight/day) or (+++) proteinuria on dipstick for 3 consecutive days, generalized edema and hypoalbuminemia (Serum Albumin level less than 2.5 g/dl).

**Hypertension;** was diagnosed if a child's BP is greater than the 95th percentile but less than or equal to the 99th percentile plus 5 mm Hg<sup>11</sup>;

- **Equal or Less than 6 Years age;** For boys 120/80 and girls 119/79 mm Hg on two different occasions 24 hours apart.
- **More than 6 years of age;** For boys 130/87 and girls 129/86 mm Hg on two different occasions 24 hours apart.

All the data was entered and analyzed using SPSS-18. Descriptive statistics was applied to calculate mean and standard deviation for the age of the children, duration on corticosteroid therapy, blood pressure and duration of

illness. Frequencies and percentages were tabulated for the categorical variables like age groups, treatment compliance, family history, maternal education, residential status, gender and hypertension (Yes/No).

### RESULTS;

Our study comprised of a total of 146 patients meeting inclusion criteria of our study. Of these 146 study cases, 92 (63%) were male patients while 54 (37 %) were female patients. Mean age of our study cases was  $7.61 \pm 2.55$  years (with minimum age of our study cases was 2 years while maximum age was 12 years). Mean age of the male patients was noted to be  $7.37 \pm 2.95$  years while that female patients was  $8.02 \pm 1.61$  years ( $p=0.139$ ). Our study results have indicated that majority of our study cases i.e. 91 (62.3 %) were aged more than 7 years. Of these 146 study cases, 76 (52.1 %) belonged to rural areas and 70 (47.9 %) belonged to urban areas. Positive family history was noted in 11 (7.5%) and 129 (88.4%) mothers of these patients were illiterate. Compliance with the treatment was noted only in 31 (21.2%) of our study cases. Mean disease duration was  $18.51 \pm 10.26$  months and 86 (58.9%) had duration of illness more than 12 months. Mean duration of treatment was  $6.58 \pm 2.28$  months and 113 (77.4%) were taking their treatment for equal/less than 1 year. Mean systolic blood pressure was  $135.85 \pm 5.12$  mmHg while diastolic blood pressure was  $90.87 \pm 3.25$  mmHg. Hypertension was noted in 54 (37%) of our study cases.

**Table No. 1**  
**Stratification of Hypertension with regards to family history.**

(n = 146)

Family History	Hypertension		P – value
	Yes (n=54)	No (n=92)	
Yes (n=11)	00	11	<b>0.007</b>
No (n=135)	54	81	
<b>Total</b>	<b>146</b>		

**Table No. 2**

**Stratification of Hypertension with regards to treatment compliance.**

Treatment compliance	Hypertension		P – value
	Yes (n=54)	No (n=92)	
Yes (n=31)	00	31	<b>0.000</b>
No (n=115)	54	61	
<b>Total</b>	<b>146</b>		

**Table No. 3**

**Stratification of Hypertension with regards to disease duration.**

(n = 146)

Disease duration	Hypertension		P – value
	Yes (n=54)	No (n=92)	
Up to 1 Year (n=60)	10	50	<b>0.000</b>
More than 1 Year (n=86)	44	42	
<b>Total</b>	<b>146</b>		

**DISCUSSION;**

Nephrotic syndrome refers to the tetrad of edema, ‘nephrotic- range’ proteinuria, hypoalbuminemia, and hyperlipidemia<sup>12,13</sup>. Nephrotic- range proteinuria in the pediatric age group is defined as protein excretion of more than 40 mg/m<sup>2</sup>/hour. In children, 24 hour-urine collections are unreliable. Thus, a single, first morning urine sample is now preferably used to quantify protein excretion by the estimation of the urine protein/creatinine ratio<sup>14</sup>. From the new management guidelines released by the Kidney Disease: Improving

Global Outcomes (KDIGO) group, urine protein/creatinine ratio of  $\geq 2000$  mg/g correlates with 'nephrotic-range' proteinuria or dip-stick proteinuria of 3+. <sup>15,16</sup>

Our study comprised of a total of 146 patients meeting inclusion criteria of our study. Of these 146 study cases, 92 (63%) were male patients while 54 (37 %) were female patients. Different studies done in children with steroid sensitive nephrotic syndrome have documented male gender predominance as has been reported in our study. Abeyagunawardena et al <sup>17</sup> also reported similar results showing male gender predominance. Arun et al <sup>18</sup> reported 67.5 % male gender predominance in children treated with Zn while 63.4 % in those treated with placebo. These findings are similar to that of our study results. Sherali et al <sup>19</sup> also reported male gender predominance with 72 % in Zn group while 76 % in placebo group which is same as that of our study results.

Mean age of our study cases was  $7.61 \pm 2.55$  years (with minimum age of our study cases was 2 years while maximum age was 12 years). Mean age of the male patients was noted to be  $7.37 \pm 2.95$  years while that female patients was  $8.02 \pm 1.61$  years ( $p=0.139$ ). Our study results have indicated that majority of our study cases i.e. 91 (62.3 %) were aged more than 7 years. Arun et al <sup>18</sup> also reported  $95.2 \pm 41.8$  months mean age in children treated with Zinc while  $88.4 \pm 38.3$  months in children treated with placebo. These results are similar to that of our study results. Sherali <sup>19</sup> reported  $7.65 \pm 3.20$  years mean age of these patients. These results are similar to that of our study results.

Of these 146 study cases, 76 (52.1 %) belonged to rural areas and 70 (47.9 %) belonged to urban areas. Positive family history was noted in 11 (7.5%) and 129 (88.4%) mothers of these patients were illiterate. Compliance with the treatment was noted only in 31 (21.2%) of our study cases. Mean disease duration was  $18.51 \pm 10.26$  months and 86 (58.9%) had duration of illness more than 12 months. Mean duration of treatment was  $6.58 \pm 2.28$  months and 113 (77.4%) were taking their treatment for equal/less than 1 year.

Mean systolic blood pressure was  $135.85 \pm 5.12$  mmHg while diastolic blood pressure was  $90.87 \pm 3.25$  mmHg. Hypertension was noted in 54 (37%) of our study cases. A study conducted by Ibadin et al <sup>8</sup> has reported hypertension to be 41.4% among children with nephrotic syndrome <sup>8</sup>. These findings of Ibadin et al <sup>8</sup> are close to our study results. A study from Bangladesh by Roy et al <sup>8</sup> reported 15.8 % hypertension <sup>9</sup> which is quite lower than that of our study results. Another retrospective analysis from Islamabad documented nephrotic syndrome associated with 64% hypertension in children <sup>10</sup> which is quite higher than that of our findings.

## CONCLUSION;

Frequency of hypertension was high among children having nephrotic syndrome in our study. Hypertension was significantly associated with family history, treatment compliance and prolonged disease duration. All clinicians treating such patients should monitor such children for hypertension for timely diagnosis and early management which will improve clinical outcomes and decrease disease morbidity. This will help to improve quality of life of our patients and also save them from future hardships.

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