IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 7 Ver. 17 (July. 2018), PP 47-51
www.iosrjournals.org

Pattern of Sodium Retention among Children with Oedematous Nephrotic Syndrome in a Tertiary Care Hospital of West Bengal.

Dr. Santa Saha (Roy), Dr. Dibyendu Raychaudhuri, Dr. Goutam Ghosh, Dr. Debasis Das, Dr. Dona Banerjee, Professor Dr. Kalpana Datta,
Associate Professor, Department of Biochemistry, Medical College, Kolkata.
Assistant Professor, Pediatric Medicine, Medical College, Kolkata.
Medical Officer, Pediatric Medicine, Swasthya Bhaban, Department of Health & Family Welfare, West Bengal.
Associate Professor, Community Medicine, Medical College, Kolkata.
RMO cum Clinical Tutor, Pediatric Medicine, Medical College, Kolkata.
Professor, Pediatric Medicine, Medical College, Kolkata.
Corresponding author: Dr.Dibyendu Raychaudhuri,

Abstract
Background*: Nephrotic syndrome is a common renal disease in childhood where abnormal sodium and water retention occur. This leads to expansion of interstitial fluid volume and oedema. It has been hypothesized that sodium retention by the kidney is a primary phenomenon occurring in response to intrarenal rather than systemic mechanism, i.e., renin-angiotensin-aldosterone system. There are recent evidences of increased Na^+K^+ATPase and enhanced epithelial sodium channel (ENaC) activity leading to primary sodium retention in the collecting duct. Clinical evaluation of volume status in presence of substantial oedema is not always accurate. Urinary markers are very useful as surrogate marker of volume and sodium retention status.* ***Objective:*** *To find out the proportion of primary and secondary sodium retention among oedematous nephrotic syndrome cases, prevalence of hypovolemic and non-hypovolemic cases and to examine relationship between serum albumin level and duration of oedema with different sodium retention status.* ***Methodology:*** *It was a cross-sectional study on children of steroid sensitive and relapsed nephrotic syndrome cases presenting at Pediatric department of Medical College, Kolkata form April 2015 to June 2016. Total 73 patients of 1 to 12 years age and within 14 days of onset of edema were studied who were not already on steroid or diuretic or ACE inhibitor. Study parameters were blood for Na^+, K^+, urea, creatinine, albumin and urine for Na^+, K^+ and creatinine. Data analysis was done in Excel Workbook, Chi-square test was used with $p \leq 0.05$ significance level.* ***Result:*** *Among 73 edematous children 19% have secondary Na^+ retention with intravascular volume depletion, 55% have primary Na^+ retention with non-hypovolemic status and remaining 26% have no Na^+ retention with non-hypovolemic status and mostly associated with natriuresis.* ***Conclusion:*** *Intrarenal mechanism of Na^+ retention play major role in edema formation. Edematous patient with primary Na^+ retention are non-hypovolemic. Serum albumin observed to be significantly low in cases of secondary Na^+ retention. Duration of oedema is comparatively less with primary type of Na^+ retention than the secondary type. Hypovolemia occurs in minority of patients mostly of which have significantly low serum albumin and late presenter with massive edema. Use of diuretic would be safe in the edema forming phase of nephrotic syndrome only if secondary Na^+ retention with hypovolemia can be excluded or intravascular volume corrected.*

Key Words: *Sodium retention, Oedematous nephrotic syndrome, West Bengal.*

Date of Submission: 20-07-2018 Date of acceptance: 04-08-2018

I. Introduction

Nephrotic syndrome (NS) is a common renal disease in childhood characterized by massive proteinuria, hypoalbuminemia, edema and hypercholesterolemia. In oedematous nephrotic syndrome, there is retention of sodium occurs.[1] The age-old concept of sodium retention caused by hypovolemia and activation of the renin-angiotensin-aldosterone system (secondary sodium retention) has been challenged in the recent years.[2, 3] Increasing evidences are found that sodium retention in nephrotic syndrome is primarily due to intrarenal defect. At the onset of natriuresis, blood volume and plasma albumin were still low and do not change significantly. Plasma renin activity and plasma aldosterone are initially high in few cases and both reduced during natriuresis. At the end of the natriuresis when patients have lost their significant oedema, plasma renin activity (PRA) and plasma aldosterone level may be still high, particularly if plasma albumin and intravascular volume remained low and yet the children of NS are no longer retaining sodium. These observations indicates

that the natriuresis during remission is because of the correction of an intrarenal mechanism which induces the sodium retention early during edema forming state.

There are recent evidences of increased Na^+K^+ATPase and enhanced epithelial sodium channel (ENaC) activity leading to sodium retention (primary Na^+ retention) in the cortical collecting duct of nephrotic syndrome children.[2, 4] Secondary sodium retention takes place if proteinuria is severe enough to produce hypovolemia, seen only in a minority of patient specially where diagnosis is late.

There is an evidence that collecting duct Na^+K^+ ATPase activity correlates inversely with urine sodium excretion (expressed as fractional excretion of sodium, $FeNa^+$) in rats with nephrotic syndrome and additionally other mechanisms like proteolytic cleavage of epithelial sodium channel (ENaC) by proteases.[7] However, the measurement of $FeNa^+$ alone cannot distinguish primary and secondary sodium retention. Therefore, urinary sodium and potassium values were related with plasma aldosterone to differentiate primary from secondary sodium retention. Indices like transtubular potassium gradient (TTKG), $UK^+/(UNa^+ + K^+)$ has variable correlation with serum aldosterone, with the highest correlation (r = 0.758) achieved with $UK^+/(UK^+ + UNa^+)$ index . $UK^+/(UK^+ + UNa^+)$ratio has been used as a marker for aldosterone activity with the presumption that Na^+/K^+ exchange occurs in the cortical collecting duct and is induced by aldosterone in hypovolemic patients with nephrotic syndrome.[5] This index has an edge over TTKG that is dependent on osmolality urine.[6]

With this background, the current study was conducted to evaluate the intravascular volume status in children with SSNS(steroid sensitive nephrotic syndrome) and to determine the sodium retention status & it's contribution to intravascular volume changes among patients of Nephrotic syndrome with significant edema. The relationship & proportions of primary and secondary sodium retention with albumin level & with the number of episodes of NS, were also looked for.

II. Methodology

It was a descriptive cross-sectional study conducted among nephrotic syndrome patients(>1 year upto 12 years) in both inpatient and outpatient department of paediatrics in collaboration with department of Biochemistry during April 2015 to June 2016.

Objective of the study was to find out proportion of primary sodium retention, secondary sodium retention and no sodium retention by measuring urinary $FENa^+$ and K^+/Na^+ exchange ratio in Nephrotic Syndrome patients presenting with severe edema. Percentages of Hypovolemic or Nonhypovolumic condition (including Normo & Hypervolumic) by measuring urinary $FENA^+$, urinary K^+/Na^+ exchange ratio and urea/creatinine ratio in nephrotic patients was also calculated. Association between albumin level, duration of edema with different type of sodium retention status was examined.

Inclusion criteria includes steroid sensitive nephrotic syndrome patients, 1st episode or relapse, aged >1 to 12 years, both sexes, presented within 14 days of onset of oedema, attending at paediatric inpatient & outpatient department. Exclusion criteria were Children on immunosupressants, diuretics and ACE Inhibitors on presentation or in last 2 weeks of appearance of edema, secondary nephrotic syndrome like SLE or hepatitis B, children with renal failure or shock, severe infections like peritonitis, pneumonia, tuberculosis, hypertension, gross hematuria and thromboembolism.

73 cases eligible patients were found applying inclusion and exclusion criteria who have given consent. Study Tools includes Electrolyte analyser(Roche), clinical analyzer (Abbott, Saint-Laurent, Quebec, Canada), calculator.

After selecting cases, history taken, clinical assessment done, relevant Laboratory Investigations, Case record forms examined. For establishing diagnosis urine protein, albumin, albumin/ creatinine ratio, serum albumin, serum cholesterol were measured. For determining study parameters urine sodium, potassium, creatinine, serum sodium, serum potassium, serum creatinine, serum urea, serum albumin were measured.

Major determinants measured were i) Fractional excretion of sodium (Fe_{Na}) = $(S_{Cr} \times U_{Na}) / (S_{Na} \times U_{Cr}) \times 100$, ii) Urine Potassium index = $(U_K{}^+/U_K{}^+ + U_{Na}{}^+) \times 100$, iii) Serum albumin level, iv) Serum urea/creatinine ratio.

Working definition for making inference were: In patients with NS- $FeNa^+ < 0.5\%$ and $UK^+/(UK^+ + UNa^+) < 60\%$ would favor primary sodium retention & nonhypovolumic. Whereas $FeNa^+ < 0.5\%$ and $UK^+/(UK^+ + UNa^+) > 60\%$ is defined as secondary sodium retention & functional hypovolumia. $FeNa^+$ of >0.5% and $UK^+/(UK^+ + UNa^+) < 60\%$ indicating no significant sodium retention and no secondary hyperaldosteronism and mostly hyper/ euvolumic(i,e nonhypovolumic). Urea/creatinine ratio>40 observed in most cases of decreased intravascular volume. Albumin<1.5 mg/dl is severe hypoalbuminemia.

Data was compiled and analysed in Microsoft Excel Work book; tabulation made, relevant statistical averages, proportion calculated; chi-square test was used for statistical significance test with $p \leq 0.05$ as significance level.

III. Result

This cross-sectional, observational study has been conducted on 73 edematous children of nephrotic syndrome including 1st episode and relapses which were steroid responsive. Children were recruited as per inclusion criteria as stated above, from in-patient and out-patient set up of pediatric department of Medical College & Hospital, Kolkata. Relevant history was taken & brief clinical evaluation noted according to patient proforma and then blood & urine were collected for blood sodium, potassium, creatinine, urea, albumin and urine for sodium, potassium and creatinine mainly.

Among cases 54(74%) were male and 19(26%) were female. 29(39.73%) children were aged 1 to less than 5 years, 38(52.05%) were 5 to less than 10 years and 6(8.22%) were above 10years. (Table 1)

Nephrotic syndrome patients are also divided on the basis of duration of edema at presentation as early(≤7 days) - 50(68.49%) and late(>7 days) - 23(31.51%).

Among 73 edemetous nephrotic syndrome cases under study, 54(74%) had sodium retention and 19(26%) were without sodium retention initially. Among the cases with sodium retention, 40(74%) had primary and 14(26%) had secodary sodium retention. (Diagram – 1)

Among 54 male children, 39(72.22%) and among 19 female cases, 15(78.95%) were found to have sodium retention. This difference of prevalence of sodium retention among two sexes was found non-significant statistically ($p>0.05$). (Table 2)

Among cases 14(19.2%) found hypovolemic and 59(80.8%) were non-hypovolemic.

Mean Albumin level in nephrotic syndrome cases with primary sodium retention was 1.94±.22 mg/dl, median 1.9 mg/dl and range 1.4 – 2.3 mg/dl. In Secondary sodium retention cases mean was 1.36±0.20 mg/dl, median 1.3 mg/dl and range was 1.1 – 1.9 mg/dl. So severe hypoalbuminemia (<1.5 mg/dl) is found associated with cases of secondary sodium retention. It was observed that difference of mean& median value of albumin among primary and secondary sodium retention cases were found statistically significant ($p\leq0.05$).

Among 50 nephrotic syndrome cases who had oedema of 7 days or less duration at presentation, 38(76.00%) had primary sodium retention 6(12.00%) had secondary retention. Among 23 cases with oedema of more than 7 days duration at presention, 2(8.70%) had primary and 8(34.78%) had secondary sodium retention. (Table - 3 , Diagram - 2) For each case of primary and secondary sodium retention, significant relationship were found with duration of oedema ($p\leq0.05$).

IV. Discussion

The sodium retention in nephrotic syndrome can be due to primary or secondary sodium retention. Nephrotic syndrome patients may present with hypovolumia or non-hypovolumia. Sodium retention in edema forming states was demonstrated in some previous studies not primarily related to plasma aldosterone concentration, suggesting an intrarenal mechanism of sodium retention.

Vande Walle[7] described three presentations of children in Nephrotic syndrome and relapse - (a) massive proteinuria, sodium retention and slightly elevated aldosterone; (b) symptoms of hypovolemia, edema, sodium retention and elevated rennin and aldosterone; and (c) edema, no hypovolemia, no active sodium retention and normal plasma hormones.

In the prospective study by Kapur G et al[8] defined $FeNa^+$<1% as hypovolumic and $FeNa^+$ >1% as hypervolumic in 1st phase and however in phase2, $FeNa^+$<0.2% along with was diagnosed as hypovolumia(VC).

In the present study it is found that among 73 edematous children 14(19%) children have secondary sodium retention with intravascular volume depletion, 40(55%) have primary sodium retention with nonhypovolumic status and rest 19(26%) children have no sodium retention with nonhypovolumia & associated natriuresis. It is observed that significantly low level of albumin was associated with secondary sodium retention.

In 19% of total cases with secondary sodium retention & functional hypovolumia, had also associated features like less urine output, urea/creatinine ratio>40 & edema usually more than seven days. Whereas, primary sodium retention cases(55%) with no evidence of hypovolumia had presented relatively early in the course(<7 days of edema). This also suggests that primary intrarenal mechanism of sodium retention i,e Over-fill hypothesis is most important in edema formation.

Study by A A Iyengar[9] with similar cut-off values showed that during relapse 18% of steroid responsive children had secondary sodium retention and 50% had presented with primary sodium retention while 32% of total cases had no sodium retention. In a similar work by Donckerwolcke *et al*[5, 10] demonstrated that renal sodium handling and rennin/aldosterone levels are within normal limit during remission, with an average $FeNa^+$ of 0.7% and $UK^+/UK^+ + UNa^+$ of 31%. While At onset of incipient proteinuria during a relapse, sodium retention was observed early with an average $FeNa^+$ of 0.2% and $UK^+/UK^+ + UNa^+$ of 60%. In this study nephrotic syndrome cases presented with hypovolumia was 19% while 81% cases were non-hypovolumic .

Mehmet A B et al[11] in their study revealed that mean albumin level is significantly low in the secondary sodium retention cases with functional hypovolumia as compared to cases with primary & no sodium retention (mean albumin level 1.3 mg/ dl versus 1.9 mg/dl). Severe hypoalbuminemia in these cases leads to interstitial edema & associated intravascular volume depletion with resultant secondary sodium retention, thus suggesting role of Under-fill hypothesis in this group (19% of total cases).

In the present study, no significant difference was found in the distribution of different statuses of sodium retention among 1st episode or subsequent relapses. So primary sodium retention seen to be major determinant along with others factors like ANP insensitivity, vasopressin excess, leaky capillary etc for formation of initial edema. Association was observed between secondary sodium retention and late presenting cases along with longer duration of edema. There is statistically significant relationship (p value-<0.05) observed between both primary and secondary sodium retention cases and duration of edema. No significant difference was found between gender, age and sodium retention status. So, from observations of the present study, it can be assumed that primary sodium retention in accordance with over-fill hypothesis is mainly responsible and major determining factor for formation of edema in most cases of the nephrotic syndrome

To conclude, some therapeutic implication could be suggested which needs further study : As intravenous albumin infusion with diuretic (after ensuring intravascular volume normalization) is useful in significant edema with hypovolumia & secondary sodium retention. Whereas increasing dose of loop diuretic[10] with or without Amiloride (EnaC inhibitor) is necessary to manage severe edema with primary sodium retention with associated normovolumia or rare hypervolumia.[12]

V. Conclusion

Intrarenal mechanism of Na+ retention play major role in edema formation. Edematous patient with primary Na+ retention are non-hypovolemic. Serum albumin observed to be significantly low in cases of secondary Na+ retention. Duration of oedema is comparatively less with primary type of Na+ retention than the secondary type. Hypovolemia occurs in minority of patients mostly of which have significantly low serum albumin and late presenter with massive edema. Patients with hypovolumia should not be treated with diuretics, before correction of intravascular volume with either crystalloids or colloids(albumin). Use of diuretic would be safe in the edema forming phase of nephrotic syndrome only if secondary Na+ retention with hypovolemia can be excluded or invascular volume corrected.

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Table and diagram:

Table 1: Distribution of cases of edematous Nephrotic syndrome according to age.

Age group (in years)	Frequency No.(%)
1 to <5	29(39.73)
5 to <10	38(52.05)
≥10	6(8.22)
Total	73(100.00)

Table 2 : Relationship between gender and sodium retention status.

Gender	Sodium retention		
	Yes	No	Total
Male	39(72.22)	15(27.78)	54(100.00)
Female	15(78.95)	4(21.05)	19(100.00)
Total	54(73.97)	19(26.03)	73(100.00)

Table 3: Relationship between duration of edema at presentation and primary sodium retention.

Duration of edema at presentation	Primary sodium retention			Secondary sodium retention		
	Yes	No	Total	Yes	No	Total
≤7days	38(76.00)	12(24.00)	50(100.00)	6(12.00)	44(88.00)	50(100.00)
>7 days	2(8.70)	21(91.30)	23(100.00)	8(34.78)	15(65.22)	23(100.00)
Total	40(54.79)	33(45.21)	73(100.00)	14(19.18)	59(80.82)	73(100.00)

X^2=28.80, df=1, p≤05 X^2=5.27, df=1, p≤05