"THE PREVALENCE OF HYPERTENSION IN CHILDREN OF NEPHROTIC SYNDROME DIAGNOSED AS FREQUENTLY RELAPSING NEPHROTIC SYNDROME AND STEROID DEPENDENT NEPHROTIC SYNDROME IN KLES DR PRABHAKAR KORE HOSPITAL BELAGAVI -A ONE YEAR HOSPITAL BASED PROSPECTIVE STUDY.".

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LIST OF ABBREVIATIONS

1.	SRNS	-	Steroid Resistant Nephrotic Syndrome
2.	SSNS	-	Steroid sensitive nephrotic syndrome
3.	MCNS	-	Minimal change nephrotic syndrome
4.	SDNS	-	Steroid dependent nephrotic syndrome
5.	FRNS	-	Frequently relapsing Nephrotic syndrome
6.	ADH	-	Antidiuretic Hormone
7.	IgG	-	Immunoglobulin G
8.	IgM	-	Immunoglobulin M
9.	FSGS	-	Focal segmental glomerulosclerosis
10.	MPGM	-	Mesangial proliferative glomerulonephritis
11.	ISKDC	-	International Study of Kidney Disease in Children
12.	MMF	-	MycophenolateMofetil
13.	ACTH	-	Adrenocorticotropic Hormone
14.	GFR	-	Glomerular Filtration Rate
15.	ENaC	-	Epithelial Sodium Channel
16.	ANP	-	Atrial Natriuretic Peptide
17.	RAAS	-	Renin Angiotensin Aldosterone System
18.	AIIMS	-	All India Institute Of Medical Sciences
19.	BMI	-	Body Mass Index
20.	LVH	-	Left Ventricular Hypertrophy
21.	BP	-	Blood Pressure
22.	LVMI	-	Left ventricular mass index
23.	2D ECHO	-	Two Dimensional Echocardiography
24.	DNA	-	Deoxyribonucleic Acid

25. ATP - Adenosine Triphosphate
26. GH - Growth hormone
27. WHO - World health Organization
28. hsCRP - High Sensitivity C reactive Protein
29. ANA - Antinuclear Antibody
30. ANCA - Antineutrophil Cytoplasmic Antibody
31. UTI - Urinary Tract Infection
32. SBP - Systolic Blood Pressure
33. DBP - Diastolic Blood Pressure
34. CKD - Chronic Kidney Disease

ABSTRACT

Background and objectives

Nephrotic syndrome is one of the most common glomerular diseases in children. Hypertension in nephrotic syndrome is a major cause for morbidity in children. This study was aimed to find the prevalence of hypertension in children with FRNS and SDNS. These children had higher chances of cardiovascular morbidity, ocular morbidity growth failure.

Methods

This one-year cross sectional study was conducted in department of paediatrics, KLES Dr PrabhakarKore Hospital and Medical Research Centre, Belagavi. All the children in the age group of 1-18 who are diagnosed with SDNS and FRNS were enrolled. Ambulatory Blood Pressure Monitor was used to detect hypertension. All the children with hypertension were further evaluated for target organ damage and growth retardation.

Results

During the study period there were 49 patients were enrolled. Prevalence of hypertension in children diagnosed as SDNS and FRNS in the age group of 1-18 years is 61.22%. Hypertension includes both Masked and Ambulatory hypertension. Prevalence of hypertension among the groups SDNS and FRNS are 55.17% and 70% respectively. Association of left ventricular hypertrophy with hypertension at a risk of organ damage were separately looked for in SDNS and FRNS cases and it was proven that it is significantly associated with each other. The odds ratio was 40 and 15 in SDNS and FRNS cases respectively. 7% of the patients with hypertension have

hypertensive retinopathy. 20% of the patients with hypertension have cataract in the eye. Growth retardation was seen in 37.93% and 20% of SDNS and FRNS cases respectively

Conclusion and interpretation

Prevalence of hypertension in children diagnosed as SDNS and FRNS in the age group of 1-18 years is 61.22%. Children with hypertension at a risk of organ damage is significantly associated with development of left ventricular hypertrophy in both FRNS and SDNS.

Keywords :ABPM; Hypertension in SDNS and FRNS; Cardiovascular Morbidity;

CONTENTS

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INTRODUCTION

Nephrotic syndrome is characterized by the triad of massive proteinuria (3-4+), hypoalbuminemia and edema. It is one of the most common glomerular diseases in children.

Nephrotic syndrome has a severe impact on the quality of life of children and their parents. Most of the children have multiple episodes of relapse for which they require multiple hospital visits and regular follow ups leading to frequent missing of school. They also have a devastating cumulative psychological impact due to the disease as well as the side effects of medications.[1]

It is the most common kidney disease in childhood with incidence of 2-16.9 per 1 lakh population.[2,3,4]

Clinically the child presents with edema which begins in the periorbital region which is more in the morning and reduces as the day passes but can sometimes progress to anasarca. The urine output can be reduced. These symptoms may be preceded by infection.

It can be broadly classified as Steroid Resistant Nephrotic Syndrome (SRNS) and Steroid sensitive nephrotic syndrome (SSNS) based on the treatment response.

It is diagnosed as SRNS when there is a persistence of proteinuria (3+ - 4+), edema or hypoalbuminemia despite therapy with prednisone in adequate doses for at least 4 weeks. If they respond earlier to this it is considered as SSNS. Most patients respond to prednisone by 2 weeks from the start of treatment.

Most common type of nephrotic syndrome in children is Minimal change nephrotic syndrome (MCNS).

The onset of MCNS is usually between the ages of 2-6 years. It is more common in boys (60-70%) and occurrence in siblings are rare. When nephrotic syndrome starts after the age of 12-16 years, the chances of presence of significant underlying lesions are higher. Very few cases have none or single episode of relapse.

Steroid dependent nephrotic syndrome (SDNS) is defined as Steroid sensitive nephrotic syndrome with 2 or more consecutive relapses during tapering or within 14 days of stopping steroids.[2,3]

Frequently relapsing Nephrotic syndrome (FRNS) is defined as steroid sensitive nephrotic syndrome (SSNS) with 2 or more relapses within 6 months, or 4 or more relapses within a 12-month period.[2,3]

Among the patients who are diagnosed to be steroid sensitive, 25-40% of them have infrequent relapses ,40% have frequent relapses and the remaining have shown to have steroid dependence.

Many studies have been done which shows that Steroid sensitive nephrotic syndrome is not associated with hypertension and Steroid resistant nephrotic syndrome is more commonly associated with hypertension.[5,6]

Hypertension has been detected more frequently in both Steroid Dependent Nephrotic Syndrome (SDNS) and Frequently Relapsing nephrotic syndrome (FRNS).[5,7]

Standard Mercury Sphygmomanometer is used for routine blood pressure monitoring. But this method has many limitations. Observer bias is an important limitation. They can occur due to many reasons such as end digit preference and availability of the previously known readings of the patient. Difficulty in listening to the Korotkoff sounds in young children is a known problem. White coat hypertension can lead to the false positive diagnosis of hypertension. Masked and nocturnal hypertension can be missed.[8]

Ambulatory blood pressure monitoring (ABPM) device eliminates all the limitations which are seen in standard mercury sphygmomanometer. ABPM is considered as a gold standard for measuring Blood pressure in children and is routinely recommended.[9] It also helps to detect the possibility of end organ damage more accurately and reduces the burden of Cardiovascular and ophthalmologic complications in children with hypertension.

Growth retardation is also observed in many cases of nephrotic syndrome.

OBJECTIVES

Primary objective:

1. To study the prevalence of hypertension in patients of Nephrotic syndrome diagnosed as Frequently relapsing nephrotic syndrome and Steroid dependent nephrotic syndrome

Secondary objective:

1. To assess for target organ damage (eyes and heart) in the patients diagnosed with frequently relapsing nephrotic syndrome and steroid dependent nephrotic syndrome.
2. To find the association of short stature in the patients diagnosed with frequently relapsing nephrotic syndrome and steroid dependent nephrotic syndrome

REVIEW OF LITERATURE

Evolution of Blood pressure monitors in children

The standard mercury sphygmomanometer was used for blood pressure monitoring in children for about 75 years. Still this instrument is being used for office practice. These devices are preferred as they are transport friendly, inexpensive and easy to maintain. Training the study personnel is also easy, but this method has many limitations. Observer bias is an important limitation. They can occur due to many reasons such as end digit preference and availability of the previously known readings of the patient. Difficulty in listening to the Korotkoff sounds in young children is a known problem. White coat hypertension can lead to the false positive diagnosis of hypertension. Nocturnal and masked hypertension can be missed.[8]

The second device which came into existence in 1960's for blood pressure monitoring is the Random-zero sphygmomanometer. This device has a reservoir storing mercury determined by but unknown to the observer before each blood pressure reading. At the end of the blood pressure reading, the amount of mercury is visible. This amount is deducted from the observed reading to get the actual reading. This results in the blinding of the observer from the actual reading but the digit preference is only minimized. But the problems in Random-zero Sphygmomanometer is that they are about 10 times more expensive than the standard mercury sphygmomanometer. Transportation and maintenance are difficult. More extensive training is required. When compared to the standard mercury sphygmomanometer, it underestimates systolic and diastolic pressures.[8]

In the 1980's the next generation of blood pressure monitors were available. These devices were automated and worked on oscillometric principle. The advantages of this apparatus are that very little training is enough, there is no observer bias leading to end digit preference or the bias caused due to the previous known values. It is comparatively easier to use in small children as it does not involve auscultation. But there are many disadvantages. The device is very expensive, about 100 times the cost of standard mercury sphygmomanometer, they have not been used frequently in epidemiological studies, there can be motion artefacts, they do not correspond to the auscultatory measurements. The first few readings measured in this device shows 3-5 mm hg higher reading than the readings which are obtained later.[8]

The next generation of blood pressure monitors which came into existence in 1990's was Ambulatory blood pressure monitors. There are many advantages of this device. These monitors help in assessing various activities such as blood pressure monitoring during sleep, mental and physical activities. It helps in assessing the within – person variability as it provides multiple blood pressure measurements in short span of time. It helps in monitoring of the treatment. It has a very few practical problems such as high cost, requirement to monitor the child's activity when the child is wearing the cuff and during the blood pressure monitoring in the night sudden inflation of the cuff may cause a startle reaction. [8]

Epidemiology of Nephrotic syndrome

Nephrotic syndrome is the most common kidney disease in childhood with incidence of 2-16.9 per 1 lakh population. Idiopathic nephrotic syndrome is the most common type of nephrotic syndrome in childhood. It is two times more common in boys than girls. MCNS is more common in the age group of 2-6 years. About 85% -

90% of children with first episode of nephrotic syndrome below 6 years of age have MCNS. But only 20-30% of adolescents with first episode of nephrotic syndrome presents with MCNS. Most common cause of nephrotic syndrome in older age group of about 12-16 years is Focal Segmental Glomerulosclerosis. Idiopathic nephrotic syndrome is rare in siblings.[2,3,4]

It can be both primary and secondary. It results in leakage of proteins into urine due to physical damage to the glomerular filtration membrane.

Classification of nephrotic syndrome

It can be broadly classified as Steroid Resistant Nephrotic Syndrome (SRNS) and Steroid sensitive nephrotic syndrome (SSNS) based on the treatment response, of these only 20 % of cases belonged to steroid resistant nephrotic syndrome.[11] Among the steroid sensitive nephrotic syndrome it can classified into Steroid dependent nephrotic syndrome, Frequently relapsing nephrotic syndrome and infrequently relapsing nephrotic syndrome.

Comorbidities associated with nephrotic syndrome

Patients of nephrotic syndrome have higher risk for infections. Sepsis is still an important cause of death and children treated with cytotoxic drugs have higher chances of infection than those patients who are treated only with steroids. Primary peritonitis is caused mainly by Streptococcus pneumoniae. But Hemophilus and other gram-negative bacteria can also be isolated. These children can also present with cellulitis. The higher chances of infection in these children may be due to many immunological factors, which are decreased T cell function, low serum transferrin,

low serum immunoglobulin G, reduced factor B and factor I and dilution of local humoral defenses.[10]

The children with nephrotic syndrome are predisposed to the formation of venous and arterial thromboembolism. Higher risk of venous thromboembolism is present in patients with massive proteinuria and patients with steroid-resistant nephrotic syndrome. This predisposition is due to the increase in production of prothrombotic factors by activation of glomerular hemostatic system and loss of proteins involved in inhibition of hemostasis. Other factors are reduction in the intravascular volume, platelet abnormalities and activation of factors which are involved in coagulation pathway.[10]

Patients with nephrotic syndrome have higher chances of developing cardiovascular disease due to higher chances of thrombus formation, endothelial dysfunction hyperlipidemia and hypertension which may be due to medication usage.

Other problems in nephrotic syndrome includes anemia, acute renal failure and hypotensive crisis.[10]

Diagnosis of nephrotic syndrome

Urine analysis in a child with nephrotic syndrome have 3-4+ proteinuria. High protein/creatinine ratio is present. Urine should be evaluated for microscopic hematuria, if persistent microscopic hematuria is present, the child is suspected to have non minimal change nephrotic syndrome.[2,3]

We should also evaluate for albumin levels, cholesterol, electrolytes and renal function tests. Albumin level is less than 2.5g/dl. Cholesterol is raised to more than 250mg/dl. Pseudohyponatremia may be due to increased cholesterol levels or due to water retention. Creatinine levels are normal in minimal change nephrotic syndrome. In Patients with massive edema, ADH values may be increased. Serum IgG levels are reduced and IgM levels are increased. Complement levels should be looked for to rule out Membranoproliferative glomerulonephritis.[2,3]

Management of nephrotic syndrome

About 93% of the children diagnosed with minimal change disease responded to steroids and 25%-50% of children who were diagnosed with Focal segmental glomerulosclerosis (FSGS) or mesangial proliferative glomerulonephritis (MPGN) also responded to steroids ,this data was according to the International Study of Kidney Disease in Children (ISKDC).[11]

Most of the children with relapses have good prognosis and many of them are steroid responsive through the entire course of their illness and normal kidney function is maintained during this period.[11]

Management of first episode of nephrotic syndrome

"First episode of nephrotic syndrome can be treated with oral prednisone being administered as a single daily dose starting at 60mg/m^2 /d or 2mg/kg/d to a maximum 60mg/d. It is recommended that daily oral prednisone be given for 4–6 weeks followed by alternate-day medication as a single daily dose starting at 40mg/m^2 or 1.5mg/kg (maximum 40mg on alternate days) and continued for 2–5 months with tapering of the dose."[11]

Management of relapse in nephrotic syndrome

"In Corticosteroid therapy for children with infrequent relapses of SSNS it is suggested that the children should be treated with a daily dose of prednisone 60mg/m^2 or 2mg/kg with a maximum limit of 60mg/d until the child has been in complete remission for 3 consecutive days. It is suggested that, after achieving complete remission, children should be given oral prednisone as a single dose on alternate days (40mg/m2 per dose or 1.5mg/kg per dose, with maximum of 40mg on alternate days) for at least 4 weeks. In Corticosteroid therapy for frequently relapsing and steroid-dependent SSNS, it is suggested that relapses in children are to be treated with daily prednisone until the child has been in remission for at least 3 consecutive days, followed by alternate-day prednisone for at least 3 months. It is suggested that prednisone should be given on alternate days in the lowest dose to maintain remission without major adverse effects in children with Frequently relapsing and steroid dependent SSNS. Daily prednisone at the lowest dose is to be given to maintain remission without major adverse effects in children with Steroid dependent SSNS where alternate-day prednisone therapy is not effective."[11]

Use of steroid sparing medications in nephrotic syndrome

Steroid sparing medications may also be required. Cyclophosphamide should be given at 2 mg/kg/day for maximum duration of 12 weeks or till maximum cumulative dosage reaches 168mg/kg. It should be started only after remission is achieved with prednisolone. Repeat doses should not be given. Intravenous cyclophosphamide has less relapses than cyclophosphamide which is taken orally at 6 months but there is no difference at 1 year. If cyclophosphamide is used instead of

prednisolone then there are less relapses at 6 months- 1 year and 1 year - 2 years interval.

Levamisole to be given at a dose of 2.5 mg alternate day for a duration of 12 months as large proportion of children will have a relapse when levamisole is stopped early. The probability of number of relapses decreases if steroids are used in combination with levamisole compared to steroids with placebo.

Cyclosporine should be started at a dose of 4–5mg/kg/d at 12^{th} hourly interval. Tacrolimus should be started at 0.1mg/kg/d (starting dose) given at 12^{th} hourly interval. Calcineurin inhibitors should be used at least for a year as major proportion of children has a relapse once these agents are stopped. If a combination of Prednisolone and Cyclosporine is used the number of relapses has been proven to reduce when compared with usage of prednisolone alone at 6 months and 1year interval.

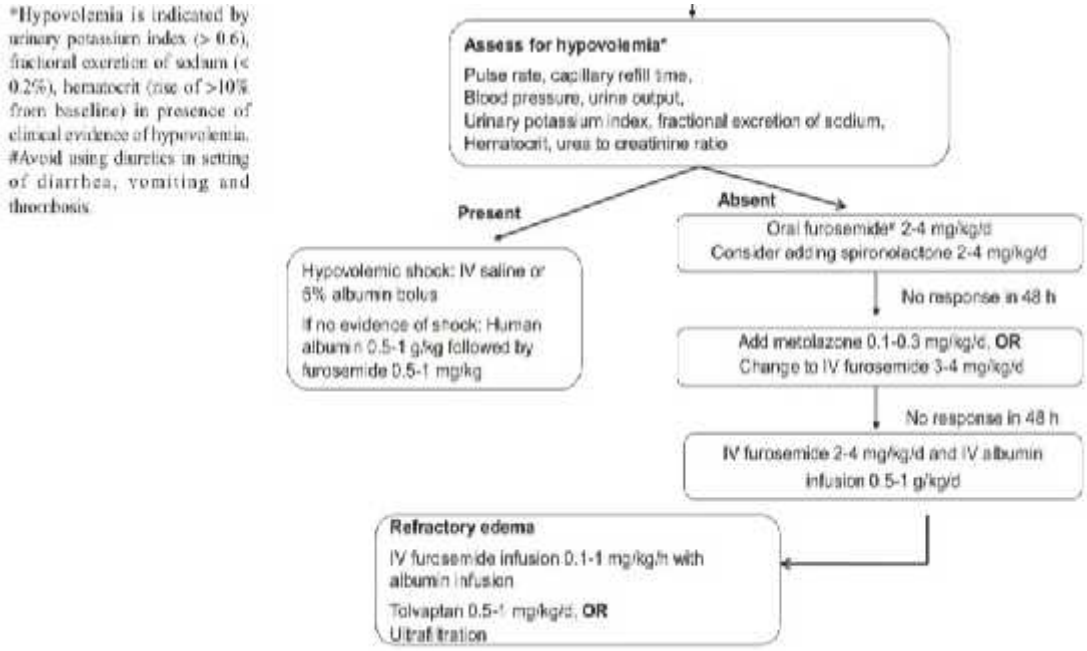
Mycophenolate Mofetil(MMF) should be started at 1200mg/m^2 per day and to be given twice a day for a minimum of 12 months as majority of the children will have an episode of relapse when MMF is stopped.

Rituximab, a monoclonal antibody can be planned to be used if the children continue to have frequent relapses despite the usage of prednisolone in combination of other steroid sparing drugs. Rituximab, if used in combination with prednisolone and calcineurin inhibitors, there is a reduction in number of relapses when compared to a placebo. Other steroid sparing agents such as ACTH(Adrenocorticotropic hormone), Azathioprine and Mizoribine usage in the treatment of SSNS has no advantage when it is compared to a placebo.[12]

Management of edema in nephrotic syndrome

Management of edema in nephrotic syndrome is a vital part. Many patients present to the hospital with hypovolemia. These patients should be first treated for shock followed by treatment for edema. The children are classified based on the severity of edema. Children with mild edema do not require any diuretic administration as the steroids would cause diuresis. Sodium restriction is advised.[13]

The patients with severe edema will be treated as follows[13]



Pathophysiology of hypertension

The causes of hypertension in nephrotic syndrome is multifactorial. It can be both renal and non-renal. In non-renal, it can be either due to environmental, intrinsic and extrinsic factors. Fluid shifts and drug side effects can cause hypertension which can be both episodic and acute. Renal fibrosis, decreased GFR(Glomerular Filtration rate) and progression to chronic renal disease can cause sustained hypertension.[14]

The defect in sodium handling causes the development of edema, sodium retention is caused by activation of renin-angiotensin aldosterone system secondary to hypoalbuminemia. Hypoalbunemia causes low oncotic pressure leading to pleural effusion, ascites and pedal edema. Activation of Epithelial Sodium Channel(ENaC) leads to absorption of sodium in the distal parts of nephron. These ENaC channels can also be activated by aldosterone, vasopressin and proteases. There is blunted response to elevated serum Atrial Natriuretic Peptide(ANP) levels in nephrotic syndrome, due to decreased conversion of pro ANP to active ANP, and abnormal ANP dependent signaling mechanisms. Animal models showed decreased production of kidney nitric oxide synthase which reduced the fractional excretion of sodium. This can lead to hypertension. Many drugs used in nephrotic syndrome can cause hypertension.[14] Calcineurin inhibitors such as cyclosporin and tacrolimus cause systemic vasoconstriction, sympathetic excitation and sodium retention. Thus, it can cause hypertension. The children who are on these agents should be looked for new onset hypertension or worsening of the present hypertension. They also decrease the renal perfusion thus leading to nephrotoxicity. The hypertension is seen within few days of starting of therapy even before the kidney functioning and sodium balance is affected.[14,15]

El-Husseini et al showed that there was development of hypertension in 10% of the children with nephrotic syndrome who received cyclosporin for more then 2 years.[16] Synthetic steroids cause hypertension by elevated plasma renin activity, increased sympathetic nerve activity, altered prostaglandin synthesis. Increased vascular smooth muscle responsiveness to catecholamines and angiotensin 2, impaired vasodilation and decreased nitric oxide synthesis.[11]

Albuminuria is caused by endothelial dysfunction, abnormal kidney function and decreased excretion of sodium which may also lead to hypertension. Increase in albuminuria was predicted by higher systolic pressure which in turn was related to genetically elevated albuminuria.[14]

Etiology of hypertension in nephrotic syndrome

Renal factors	**Extra renal factors**
Albuminuria	Medication side effects
Sodium Retention	Genetic Predisposition
Renin-Angiotensin-Aldosterone system activation	Diet and Life style
Fibrosis	Cardiovascular Risk Factors

Hypertension in patients with nephrotic syndrome is more in patients with frequent relapses, Steroid dependent nephrotic syndrome and steroid resistant nephrotic syndrome.[5,6,7]

Studies prove that Steroid resistant nephrotic syndrome are more prone for hypertension.[5,6]

Management of hypertension in nephrotic syndrome

Higher chances of developing hypertension are even seen for many years after stopping the therapy hence it is very crucial for hypertension to be diagnosed and managed early. Most important part of managing hypertension is restriction of salt in diet and RAAS(Renin Angiotensin Aldosterone System) inhibition in the children

who are having proteinuria. RAAS inhibition can have Reno protective effect in glomerular disease.

Many classes of diuretics are used which result in loss of fluid as well as sodium which reduces the blood pressure and edema. Inhibition of ENaC channels prevents the reabsorption of sodium from the distal parts of the nephrons thus reducing the blood pressure. The use of beta blockers helps in reduction of hypertension without affecting the glomerular filtration rate. Calcium channel Blockers are preferred for monotherapy in hypertension as they have very good side effect profile. They do not cause water and sodium retention and has no nephrotoxic effect.

A study done by Arvind Bagga et al AIIMS(All India Institute Of Medical Sciences) New Delhi, India in the year 2015 which included 99 participants with 72 boys. The average age being 10 years. The Clinic blood pressure was considered to be high if it is more than 95^{th} centile. It was high in 63 patients (63.6 %) and the rest 33% had Hypertension detected by the Ambulatory Blood Pressure Monitor(Ambulatory). They also had 14 patients with severe hypertension.16% had masked hypertension and 30% had White coat Hypertension. Hypertension which was non dipping were found in 72 patients and 55 patients had nocturnal high systolic pressure load. About 43 % with increased left ventricular mass index had ambulatory hypertension ,14% had masked and 28% had white coat hypertension. The risk factors seen in the patients with ambulatory hypertension were younger onset nephrotic syndrome, longer duration of Frequently Relapsing disease and higher Body Mass Index (BMI). The patients with high Body Mass index were associated with high ambulatory blood pressure and high left ventricular mass index. This study concluded that clinic,

ambulatory and white coat hypertension were more prevalent in patients diagnosed with FRNS. A significant number of patients with masked hypertension would be missed if only clinic blood pressure is used to detect hypertension.[7]

A study was done by Nahla et al in Iraq in the year 2008 about prevalence of hypertension in steroid sensitive nephrotic syndrome, steroid resistant nephrotic syndrome, steroid dependent nephrotic syndrome, frequently relapsing nephrotic syndrome and infrequently relapsing nephrotic syndrome. 71 patients participated in the study, among them 9 patients had new onset nephrotic syndrome ,42 had frequent relapses and 20 had infrequent relapses. Among the 71 patients, steroid sensitive nephrotic syndrome were 33, steroid resistant were 10 and steroid dependent were 28 patients. 5.6% patients presented with hypertension in the initial attack of nephrotic syndrome and 32 % presented with hypertension later. In this 32%, 5.6% had infrequent relapses, 22% had frequent relapses and 4.2 % with no relapse had hypertension. 7% of patients with steroid sensitive nephrotic syndrome had hypertension, 12% of steroid resistant nephrotic syndrome had hypertension and 19.7% patients with steroid dependent nephrotic syndrome had hypertension. This study concluded that the hypertension was more common in males than females and in nephrotic syndrome with frequent relapses, steroid dependent nephrotic syndrome and steroid resistant nephrotic syndrome.[5]

A multicentric study done by Ibrahim F. Shatat et al published in the year 2019 has considered data from many studies.[14]

1. A study done by Koster et al in the year 1990 has shown that 95% cases of minimal change nephrotic syndrome were detected with hypertension in the pretreatment phase and 19.5% during remission.[17]

2. Another study done by Kontchou et al in the year 2009 has considered cases of steroid sensitive nephrotic syndrome which shows 65% of the patients in active phase (in the first week of edema) and 34% in remission(after completing a course of steroids for 4 weeks) have been detected to hypertensive(> 90^{th} centile, systolic or diastolic blood pressure).[18]

3. A study done by Keshri et al showed that 23.4% of the patients who were diagnosed to have steroid sensitive nephrotic syndrome had hypertension in remission.[19]

Importance of ABPM to look for secondary organ damage

ABPM is superior to office blood pressure measurement in predicting the higher risk for target organ damage. In children who has been confirmed to have hypertension using ABPM, the chances of detecting Left Ventricular Hypertrophy (LVH) were 7.23 times when compared to 4.13 times in patients detected with hypertension using office BP measurements.[20]

Another study done by Xu et al showed that hypertension were detected in 88.6% of patients that is 101 patients out of 114 patients. Among these 45 patients had masked hypertension and 80 had non dipping hypertension.[21]

This is the hypertension classification approved by the American heart association in the year 2016.[22]

Classification of hypertension

Classification	Office BP*	Mean Ambulatory SBP or DBP†,‡	SBP or DBP Load, %‡,§
Normal BP	<90th %tile	<95th %tile	<25
White coat hypertension	95th %tile	<95th %tile	<25
Prehypertension	90th %tile or >120/80 mm Hg	<95th %tile	25
Masked hypertension	<95th %tile	>95th %tile	25
Ambulatory hypertension//	>95th %tile	>95th %tile	25–50
Severe ambulatory hypertension (at risk for end-organ damage)	>95th %tile	>95th %tile	>50

%tile indicates percentile; BP, blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*Based on National High Blood Pressure Education Program Task Force normative data.[101a]

†Based on normative pediatric ABPM values in Appendix Tables A1 through A4.

‡For either the wake or sleep period of the study, or both.

§For patients with elevated load but normal mean ambulatory BP and office BP that is either normal (<90th percentile) or hypertensive (95th percentile), no specific ambulatory BP classification can be assigned based on current evidence and expert consensus. These "unclassified" patients should be evaluated on a case-by-case basis, taking into account the presence of secondary hypertensiona or multiple cardiovascular risk factors.

//Some clinicians may prefer the term *sustained hypertension* rather than *ambulatory hypertension*.

Hypertension leading to Left ventricular hypertrophy:

In children, elevated ambulatory blood pressure is associated with increased Left ventricular mass index (LVMI) and wall thickness as well as the presence of concentric hypertrophy. This LVMI is calculated using devereux's formula by the following equation LVM = 0.80 [1.04 × (interventricular septal thickness + posterior wall thickness + end-diastolic diameter)^3 - (end-diastolic diameter)^3] + 0.6. LVM obtained will be divided by the body surface area to get LVMI.[23]

These values were obtained using Two Dimensional Echocardiography(2D ECHO) done using standard views in the left lateral decubitus position at the end diastole. Images was acquired at passive end expiration by which global cardiac

movement was reduced in both the views, parasternal long axis and apical planes. By Simpson method end diastolic and end systolic volumes will be calculated. If LVMI is more than 38g/hg$^{2.7}$ then patient is considered to have left ventricular hypertrophy.[23]

A study done by Linyuan Jing et al in USA in the year 2017 showed that elevated ambulatory blood pressure is associated with increased LVMI in children. It suggests that interventions targeted to those who have hypertension may be effective in reversing or preventing cardiac remodeling and future cardiovascular risk. Thus, using ambulatory blood pressure monitor, hypertension can be detected early and treatment for this can be started.[7]

Hypertensive changes in the eye:

There is evidence that the adverse effects caused by corticosteroids to the eye may be severe and can even cause permanent visual dysfunction. There is increased resistance to the of aqueous outflow due to the increased of collection of extracellular matrix in the trabecular outflow. This leads to increase in the intraocular pressure and this can affect visual function.

A study done by E Kawaguchi et al in 2013 showed that early and frequent development of ocular hypertension in children with nephrotic syndrome is seen so routine ophthalmologic examination should be conducted from the early phase after the start of prednisolone treatment. Children with episodes of ocular hypertension may be at a greater risk of its reappearance with relapse of the nephrotic syndrome.[24]

Steroids causing Posterior subcapsular cataract:

Usage of steroids for a prolonged period is a major risk factor for the patients to develop posterior subcapsular cataract. This develops faster in children than adults as the steroids has a more significant effect in children. In some children rarely it has been observed that there is resolution of cataract once the steroids are stopped but however, they do not regain the vision completely. Multiple mechanisms have been proposed for the development of cataract due to the usage of corticosteroids.[25]

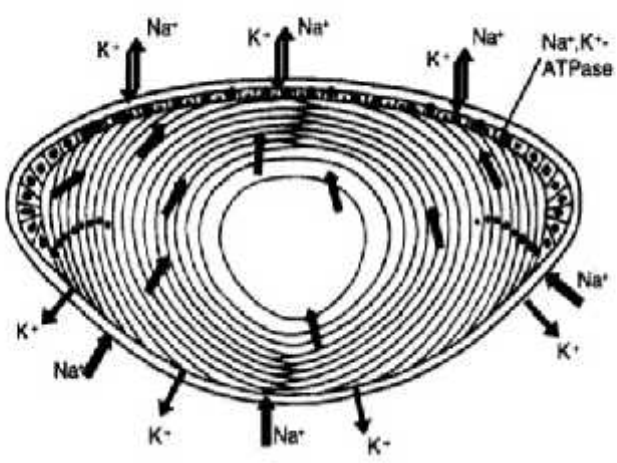
Mechanisms of formation of subcapsular cataract in the eye:

1. **Metabolic disturbances**

Glucocorticoids may directly interact with the enzymes in the lens or may act through the receptor leading to its decreased synthesis in the cell [26] These changes may be seen mostly in younger population. There are some studies which suggest that Deoxyribonucleic Acid (DNA) synthesis is decreased in the epithelial cells of the lens as they are controlled by the glucocorticoids.

2. **Osmotic Failure**

Some studies says that the formation of intracellular clefts, vacuoles and swelling of the cells were seen in patients using steroids. This may be due to the alteration caused by the glucocorticoids to the hydration of the lens. Sodium potassium ATPase (Adenosine Triphosphate) is mainly responsible for the transport of ions between the cells and the extracellular environment. This ionic balance is very important in maintaining the transparency of the lens thus, the changes in this balance can lead to the formation of cataract.[27]



3. Oxidation

Some studies suggest the steroids affect the glutathione and free radical scavenging system which act as protective mechanisms preventing damage to the lens. This may result in formation of cataract.[28]

4. Protein adduct formation

Some studies suggest that the protein adduct formation is seen in the children using corticosteroids. Concentration of proteins present in the lens are high and long lived which is required for adduct formation hence they may lead to cataract formation. The adducts which was formed by prednisolone in the lens were not soluble in contrast to the ones formed by dexamethasone which are soluble.[29]

Association of growth retardation with nephrotic syndrome:

Most common etiology of nephrotic syndrome is minimal change disease, majority of which responds to steroids. After the initial 6 weeks of daily steroids, the dosage has to be changed to alternate day steroids immediately. Growth retardation was seen only in the patients who continue daily steroid therapy for a long duration, while steroid therapy taken alternate day showed no association with growth failure. It has been demonstrated that the usage of steroid sparing agents had a good improvement in height as these agents lower the usage of steroids as well.[30]

Growth hormone therapy

It has been demonstrated that the usage of Recombinant human GH(Growth hormone) Norditropin at a dosage of 0.32 mg /kg at weekly intervals in steroid dependent nephrotic syndrome has shown improvement in the linear growth and mineralization of the bones which was measured by bone mineral densitometry. Bone age has accelerated with this intervention.

A study done by Loke et al showed that 8 children diagnosed with steroid dependent nephrotic syndrome requiring regular high dose steroid therapy, in them has been demonstrated that the usage of steroid sparing agents had a good improvement in height as these agents lower the usage of steroids. There are no adverse effects such as increase in glucose levels, insulin levels in the blood or evidence of increase in the level of glycosylated hemoglobin after the growth hormone therapy. There is no change in the requirement of the prednisolone dosage as compared to the dosage of prednisolone one year before the treatment with growth hormone.[31]

A study done by Y K Tsau et al in Taiwan assessed for the growth in children suffering from nephrotic syndrome. The children were divided into two groups, Group A included children with FRNS, SDNS and SRNS. Group B had children with occasional or no relapse. Majority (88%) of the children had growth impairment in group A, in contrast to only 17% of the children in group B had growth impairment. This study showed that there is stunted growth with prolonged usage of steroids. Steroid usage of more than 6 months per year with a dose higher than 0.2 mg/kg/day (and/or 0.4 mg/kg/48h) was found to be the major determinant on the growth pattern of nephrotic children. So, these children who are diagnosed with SDNS and FRNS are more prone for stunted growth.[32]

METHODOLOGY

STUDY DESIGN: Hospital based prospective study

STUDY PERIOD: The study is planned to be conducted in KLES Dr Prabhakar Kore hospital, Belagavi during the period of January 2019 to January 2020.

SAMPLE SIZE CALCULATION:

- Cochran's formula is used to calculate the sample size, which is given by,
- $n=\frac{Z^2 P(1-P)}{d^2}$
- Where z=1.96 for 95% Confidence interval, p=prevalence of disease in a population, and d= acceptable margin of error (10%)
- From the 140 number of nephrotic patient hospital data, incidence of relapsing nephrotic syndrome in children was found to be 15 % (21/140*100) with 21 FRNS + SDNS. So, considering the 15% as incidence and substituting in the above formula, the sample size required is:
- $n=\frac{1.96^2 * 0.15 * (1-0.15)}{0.10^2} = 48.9$
- Hence 49 samples are required for the analysis. More the sample size better the precision.

SELECTION CRITERIA:

Inclusion criteria:

Patients diagnosed with Frequently relapsing nephrotic syndrome and Steroid dependent nephrotic syndrome.

Exclusion criteria:

Steroid Resistant nephrotic syndrome.

ETHICAL CLEARANCE

It has been obtained from the institutional ethics committee

INFORMED CONSENT:

The parents fulfilling the selection criteria were briefed about the nature of the study and a written informed consent was obtained from the parents/caregivers to participate in the study prior to enrollment.

METHOD OF COLLECTION OF DATA

The patients who come to the Out Patient Department (OPD) and those who are getting admitted to the pediatric wards were considered for the study population.

Among these patients who were fulfilling the inclusion criteria of the study were identified and enrolled into the study. Prior to the conduct of the study, consent was taken from the parents. All the patients who were enrolled in the study were admitted in the pediatric ward. Blood and urine were collected for investigations. The patients were categorized into two groups, steroid dependent nephrotic syndrome and Frequently relapsing nephrotic syndrome after the appropriate history.

Each patient was monitored for blood pressure via ambulatory BP monitor which is approved by Association for the Advancement of Medical instrumentation the British hypertension society and European society of hypertension for children.

In our study, we are utilizing an ABPM monitor which uses oscillometric technique of blood pressure measurement. Appropriate cuff sizes were used for each patient. The cuff was placed on the non-dominant arm. The device was programmed such that it takes 3 readings during the awake state and 2 readings during the sleep state. The patient attenders were told to maintain a record of the administration of the antihypertensive medication.

A minimum limit of 1 reading per hour was fixed, both during the awake and sleep period for full 24 hours. The ABPM monitor was adjusted such that, systolic blood pressure less than 60mm/hg or more than 220mm/hg and diastolic BP less than 35mm/hg and more than 120mm/hg were excluded. The data will be analyzed using new hypertension guidelines for children less than 5 years which was released by American Association of Pediatrics in the year 2017[33] as there is no data on the normative ABPM. The children whose age was ≥5 years, normative values of ABPM readings appropriate for age and sex approved by the American Heart Association approved in the year 2014 were used.[22]

The patients who have been diagnosed with hypertension will be undergoing further evaluation for end organ damage. ECHO will be done by pediatric cardiologist to detect cardiac changes associated with hypertension and ophthalmic examination (fundus) will be done by an ophthalmologist to detect the hypertensive changes in the eyes. We also look for the changes in the eye due to steroid toxicity such as posterior subcapsular cataract. These patients diagnosed with FRNS and SDNS will be looked

for short stature using the standardized World health organization (WHO) growth charts for their height, age and sex. Patients having height less than 3rd centile will be considered to be having short stature.

INVESTIGATIONS

- Ambulatory blood pressure monitoring to detect hypertension
- ECHO and ophthalmologic examination to detect the end organ damage in the heart and the eyes done by a pediatric cardiologist and an ophthalmologist respectively.
- Other investigations such as Complete Blood Count, Serum Electrolytes, Serum Creatinine, Blood Urea, Urine Routine Microscopy, Urine Albumin, Protein Creatine ratio in the urine.
- Investigations such as blood culture, HsCRP (High Sensitivity C reactive Protein), urine culture, diagnostic ascitic tap and others to look for infectious etiology causing relapse.
- Some patients may need other special investigations such as Complement levels, ANA (Antinuclear Antibody) and ANCA.(Antineutrophil Cytoplasmic Antibody)

RESULTS

This is a hospital based cross-sectional prospective study for the period of one year from January 2019 to January 2020.It was done among the children admitted under the Department of Pediatrics, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

All the children who came to OPD and who were admitted to wards satisfying the inclusion criteria were enrolled into the study.

Totally there were 53 children satisfying the inclusion criteria who were enrolled into our study.

4 patients were excluded from the study as the consent for echocardiography was not given by the parents. Hence 49 patients remained in the study.

Table 1. Distribution of the study subjects according to age

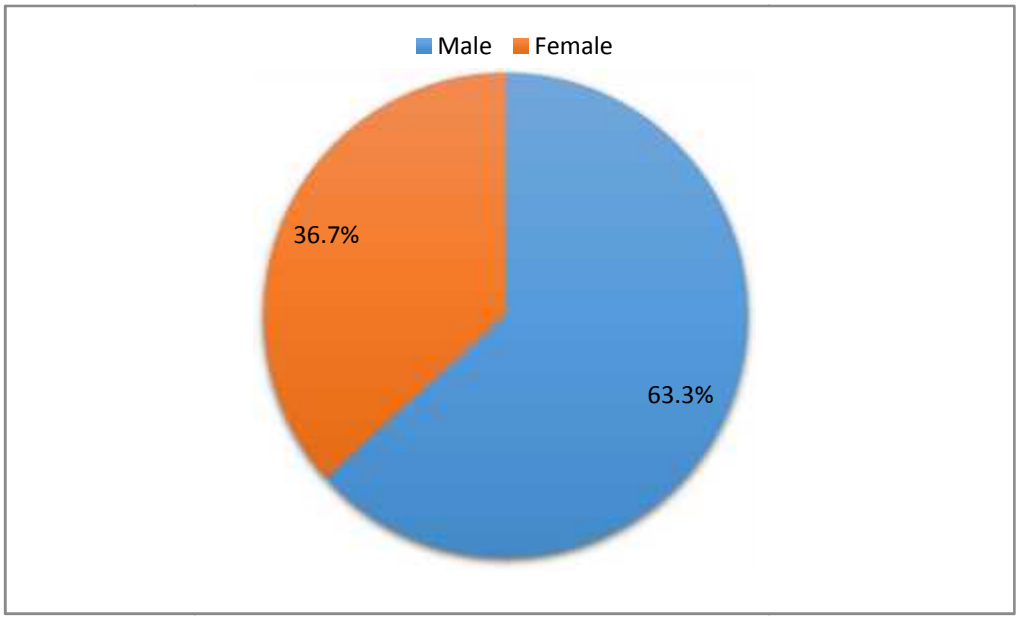
Sl No	Age group	Count (%)
1	≤5	16 (32.65%)
2	6-8	9 (18.37%)
3	9-11	15 (30.61%)
4	12-17	9 (18.37%)

- In our study, 49 subjects with mean age of 8.15±3.85 years were included.
- It has been observed that 16 of 49 subjects in the sample are in the age group of ≤5 years followed by 15 patients in the age group of 9-11 years .9 each are in the age group of 6-8 years as well as 12-17 years.

Table 2. Distribution of the study subjects according to sex

Sex	Distribution (n=49)
	Count (%)
Male	31 (63.27%)
Female	18 (36.73%)

Graph 1Distribution of the study subjects according to the type of nephrotic syndrome

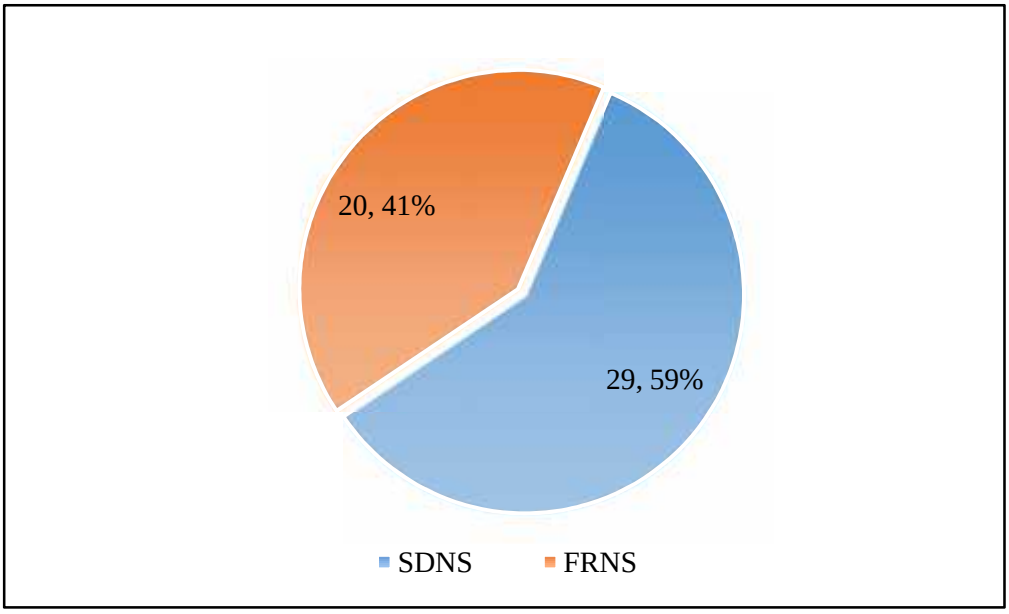


In our study, Male: Female ratio of the study subjects was 1.72: 1

Table 3. Distribution of the study subjects according to the type of nephrotic syndrome

Type	Distribution (n=49)	
	Number	**Percentage**
SDNS	29	59.2
FRNS	20	40.8
Total	**49**	**100.00**

Graph 2: Distribution of subjects according to the type of Nephrotic syndrome

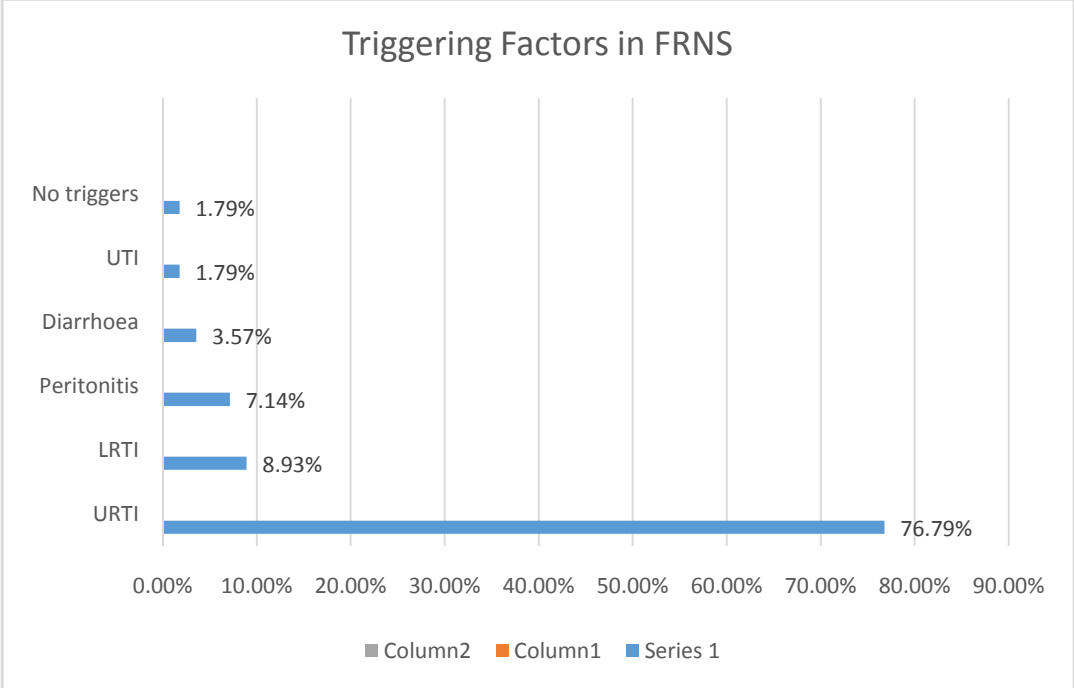


In our study, 59.2% cases belonged to the category of Steroid Dependent nephrotic syndrome and 40.8% cases belonged to the category of Frequently Relapsing nephrotic syndrome.

Table 4. Distribution of Triggering Factors causing Relapse

Sl. No	Triggering factors	Count (%)
1	URTI	43(76.79%)
2	LRTI	5(8.93%)
3	Peritonitis	4(7.14%)
4	Diarrhea	2(3.57%)
5	UTI	1(1.79%)
6	None	1(1.79%)

Graph 3: Distribution triggering factors causing relapse



In our study, 20 children were diagnosed with FRNS, majority of the episodes of relapse were due to Upper Respiratory Tract Infection (76.79%) followed by Lower Respiratory Tract Infections**.** (8.93%)

Table 5: Distribution according to the age of onset of the disease

Onset age in years	Male	Female	Total	P-value
1-5	26 (72.22%)	10 (27.78%)	36 (73.47%)	0.0520
6-10	5 (41.67%)	7 (58.33%)	12 (24.49%)	
>10	0 (0%)	1 (100%)	1 (2.04%)	

In our study, it has been observed that, 36 of 49 subjects were diagnosed between 1-5 years of age, among them 26(72.22%) were males. 12(24.49%) subjects diagnosed in between 6-10 years of which 5(41.67%) were males. Only one female subject was diagnosed after 10 years. It has been concluded that Onset age and gender is not significantly associated.

Table 6: Prevalence of hypertension according to the type of nephrotic syndrome

TYPE	Distribution (n=49)		
	Number	**Hypertension**	**P-value**
SDNS	29	16 (55.17%)	0.2951
FRNS	20	14 (70%)	
Total	**49**	**30(61.22%)**	

- Prevalence of hypertension as measured by the Ambulatory Blood Pressure Monitor in nephrotic syndrome is 61.22%. Age appropriate standardized values for ambulatory hypertension was considered. 22 (73.33%) hypertensive children were found to be non-dippers.
- In our study, prevalence of hypertension among the groups SDNS and FRNS are 55.17% and 70% respectively. Using sample proportion test, it has been concluded that prevalence of hypertension is not significantly different between SDNS and FRNS groups(p-value=0.2951).

Graph 4: Prevalence of hypertension according to the type of nephrotic syndrome

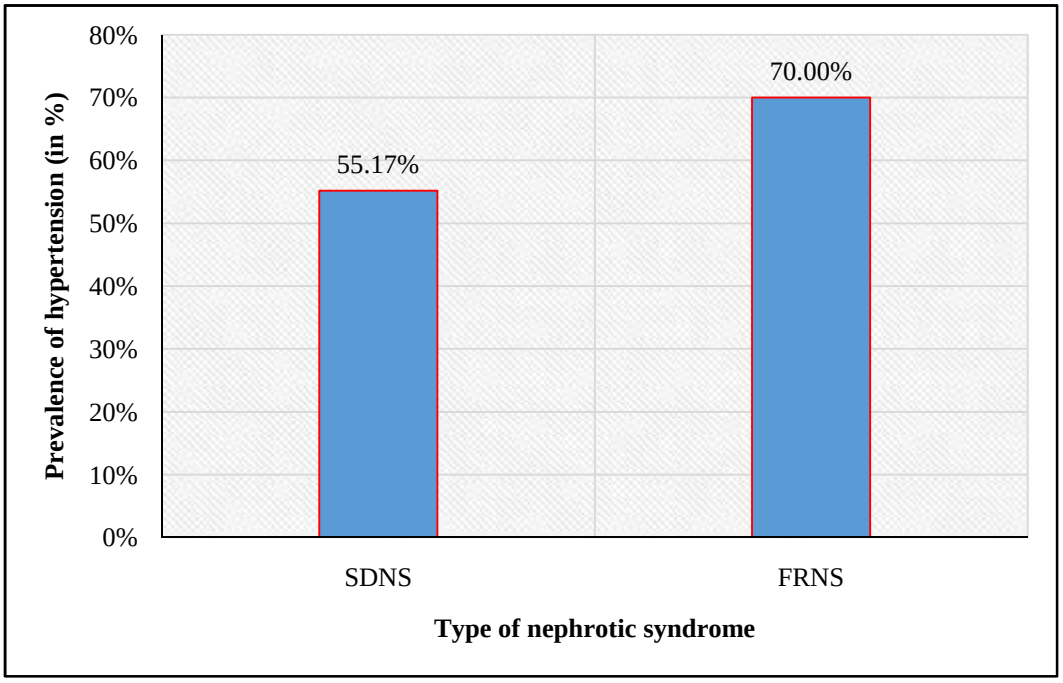
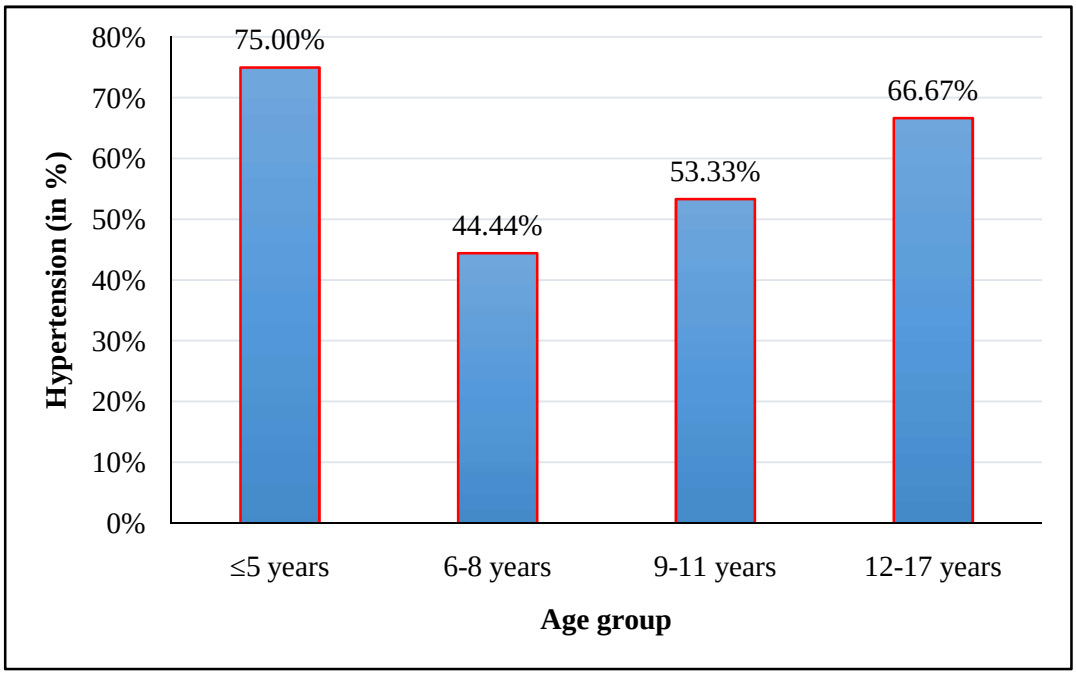


Table No 7: Association of hypertension with other factors:

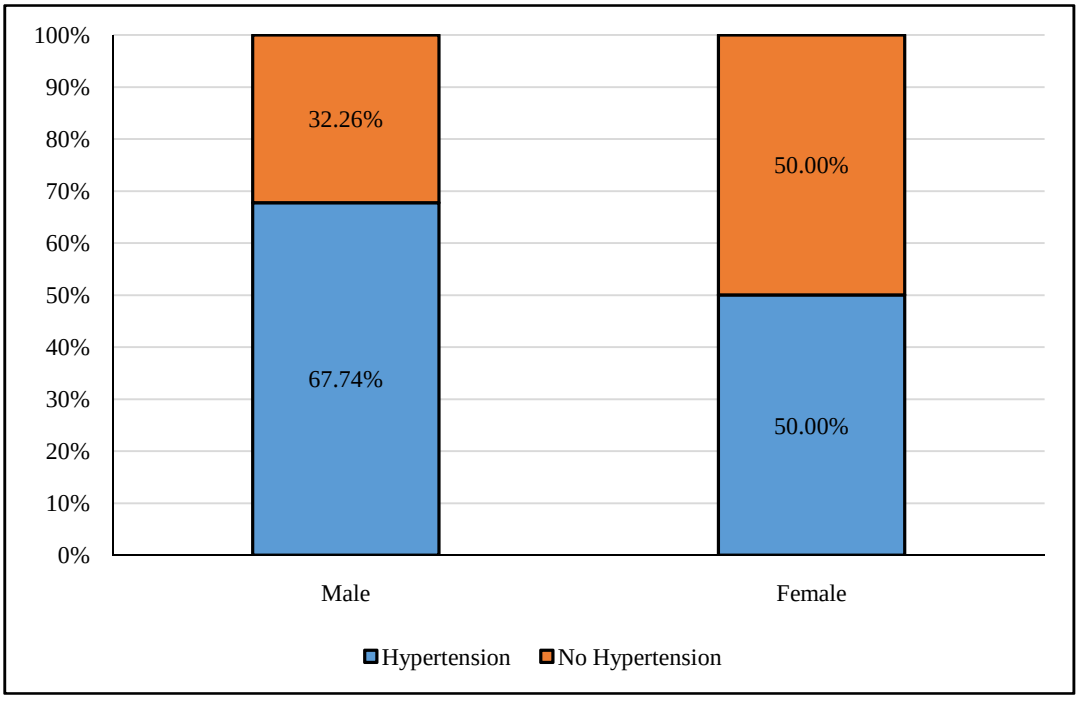
Factor		Total	Hypertension		P-value
			Yes	No	
Age in years		8.15±3.85	7.98 ± 4.13	8.42 ± 3.02	0.6921
Age group	≤5	16 (32.65%)	12 (75%)	4 (25%)	0.5272
	6-8	9 (18.37%)	4 (44.44%)	5 (55.56%)	
	9-11	15 (30.61%)	8 (53.33%)	7 (46.67%)	
	12-17	9 (18.37%)	6 (66.67%)	3 (33.33%)	
Gender	Male	31 (63.27%)	21 (67.74%)	10 (32.26%)	0.2191
	Female	18 (36.73%)	9 (50%)	9 (50%)	
Cyclosporine	Yes	8 (16.33%)	7 (87.5%)	1 (12.5%)	0.1349
	No	41 (83.67%)	23 (56.1%)	18 (43.9%)	
Classification	SDNS	29 (59.18%)	16 (55.17%)	13 (44.83%)	0.2951
	FRNS	20 (40.82%)	14 (70%)	6 (30%)	
Relapse	Relapse	19 (38.78%)	12 (63.16%)	7 (36.84%)	0.8251
	No relapse	30 (61.22%)	18 (60%)	12 (40%)	

Using Cochran Armitage trend test, it has been concluded that there is no significant linear trend in Proportion of HTN over age group. using chi-square test, it has been concluded that Hypertension is not significantly associated with Gender, Cyclosporine, type of syndrome and relapse.

Graph 5: Association of hypertension with Age group

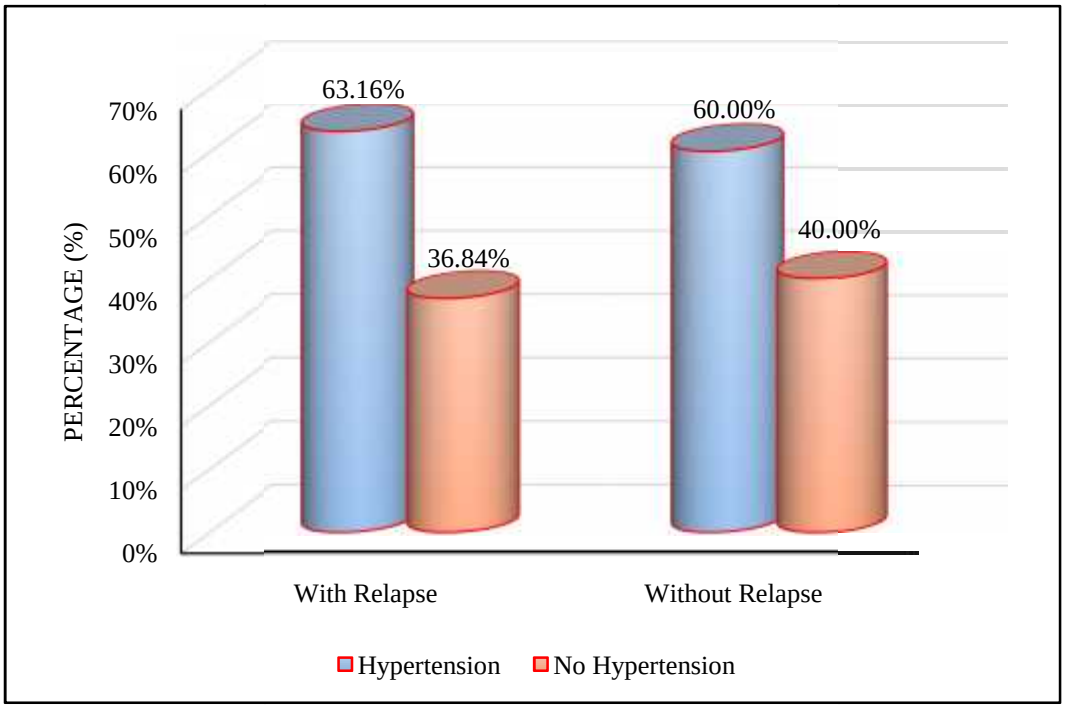


Graph 6: Prevalence of hypertension According to Sex



- 67.74% of males and 50% of females were detected with hypertension

Graph 7: Prevalence of hypertension in subjects with Relapse and Remission



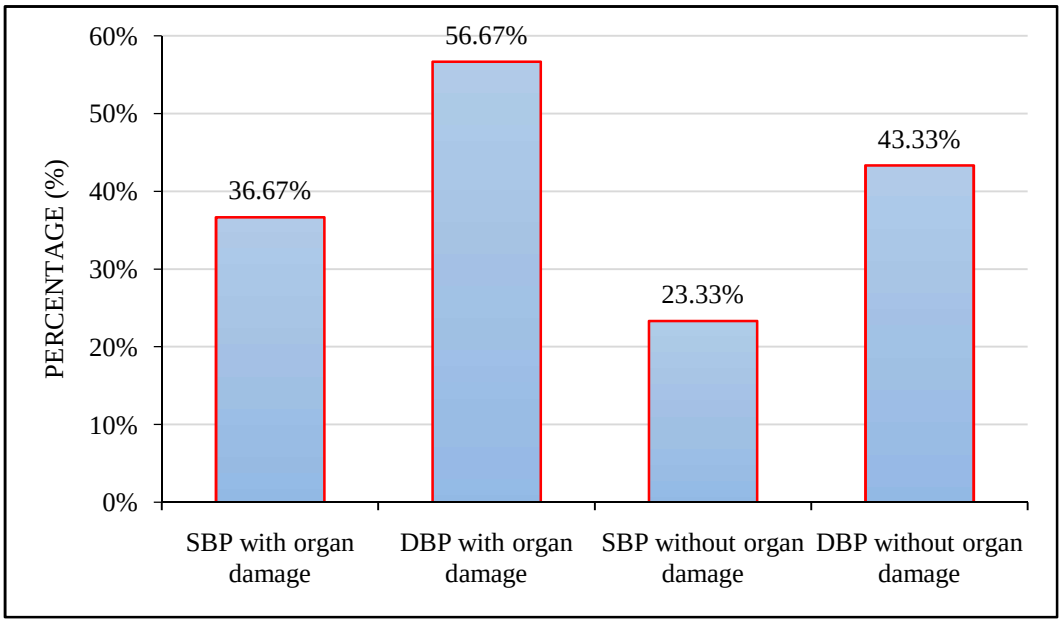
In our study ,19 patients (38.78%) were in relapse and 30 patients (61.22%) were in remission. Among them 12(63.16%) had hypertension in patients with relapse and 18(60%) had hypertension in remission.

Table No 8: Distribution of children by different Hypertension categories

Type of Hypertension	Count (%)
SBP with organ damage	11 (36.67%)
DBP with organ damage	17 (56.67%)
SBP without organ damage	7 (23.33%)
DBP without organ damage	13 (43.33%)

All the patients who have been diagnosed to have hypertension have diastolic hypertension30(100%) and 18(60%) children have systolic hypertension

Graph 8: Distribution of children by different Hypertension categories



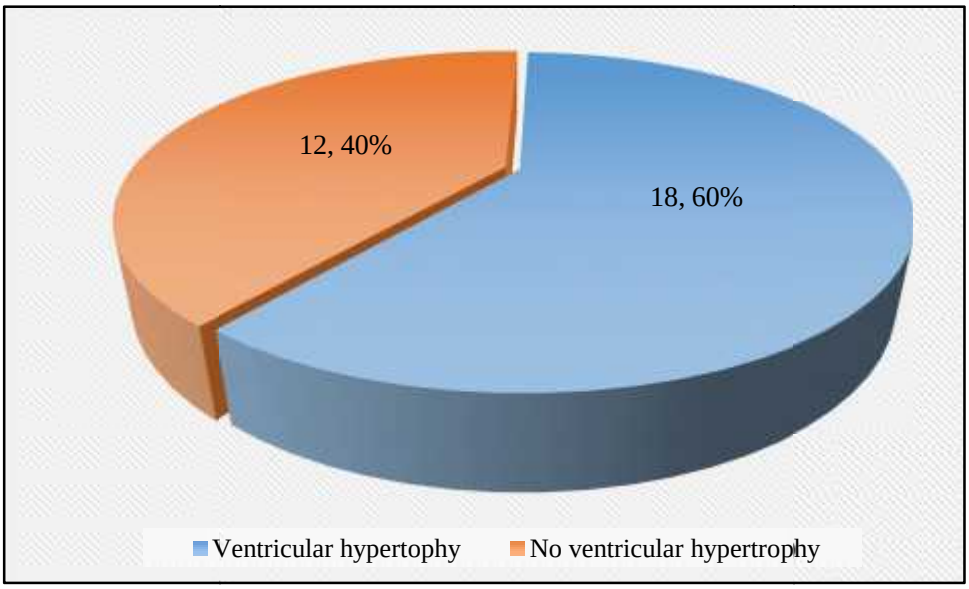
Maximum number of patients 17(56.67%) had diastolic hypertension with a risk of organ damage followed by 13 (43.33%) had diastolic hypertension without the risk of organ damage.

Comorbidities

Table No 9: Distribution of subjects by Ventricular hypertrophy in Hypertensive subjects:

Ventricular hypertrophy	Count (%)
Yes	18 (60.00%)
No	12 (40.00%)

Graph 9: Distribution of subjects by Left Ventricular hypertrophy in Hypertensive subjects



It has been observed that, 18(60%) of 30 hypertensive subjects had Ventricular hypertrophy. Here the hypertensives include both the categories, the children who belong to the category of hypertension without risk for organ damage and hypertension with risk organ damage according to the classification approved by the American Heart Association.

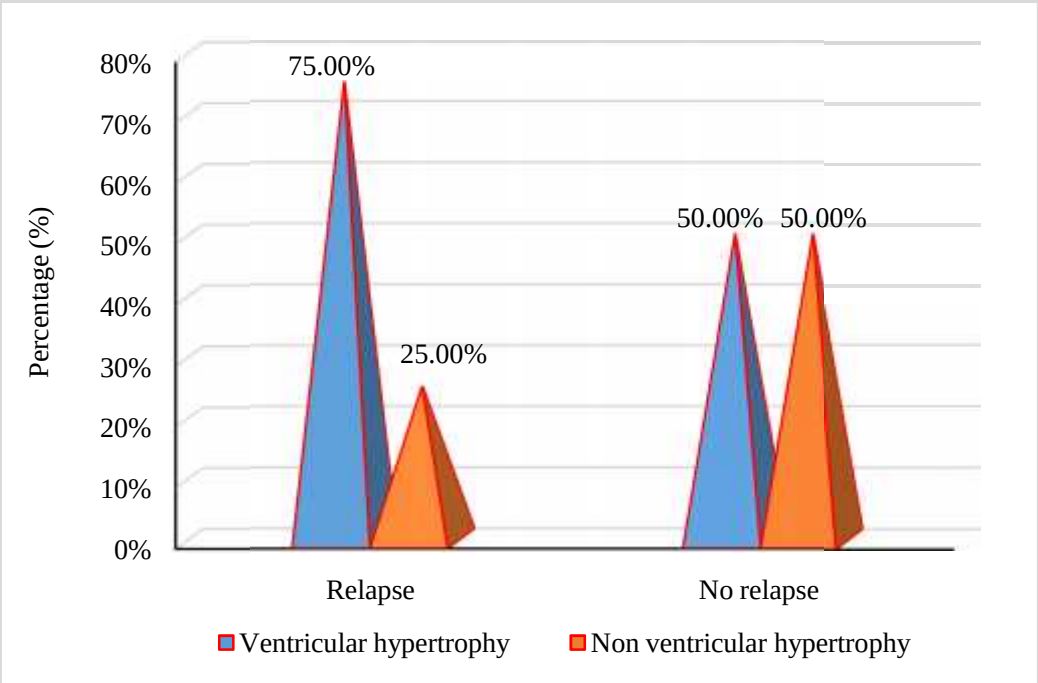
Table No 10: Association of Ventricular hypertrophy with other factors in hypertensive subjects

Factor	Sub-category	Ventricular Hypertrophy		P-value
		Yes	No	
Relapse	Yes	9 (75%)	3 (25%)	0.2459
	No	9 (50%)	9 (50%)	
HTNat a risk for organ damage	Yes	15 (88.24%)	2 (11.76%)	**0.0010**
	No	3 (23.08%)	10 (76.92%)	
Classification	SDNS	11 (68.75%)	5 (31.25%)	0.2956
	FRNS	7 (50%)	7 (50%)	

Using chi-square test with simulation, it has been concluded that**Hypertension with a risk of organ damage is significantly associated with Ventricular hypertrophy**. Using odds ratio, it has been concluded that odds of developingventricular hypertrophy is 25 (95% CI: [3.51,177.48]) times higher for the subjects belonging to the category of hypertension at a risk of organ damage than those subjects belonging to the category of hypertension without the risk of organ damage.

Ventricular hypertrophy is not significantly associated with Relapse as well as type of nephrotic syndrome in hypertensive subjects.

Graph 10: Distribution of Hypertensive subjects having ventricular hypertrophy during relapse



Graph 11: Association of ventricular hypertrophy with hypertension at a risk of organ damage

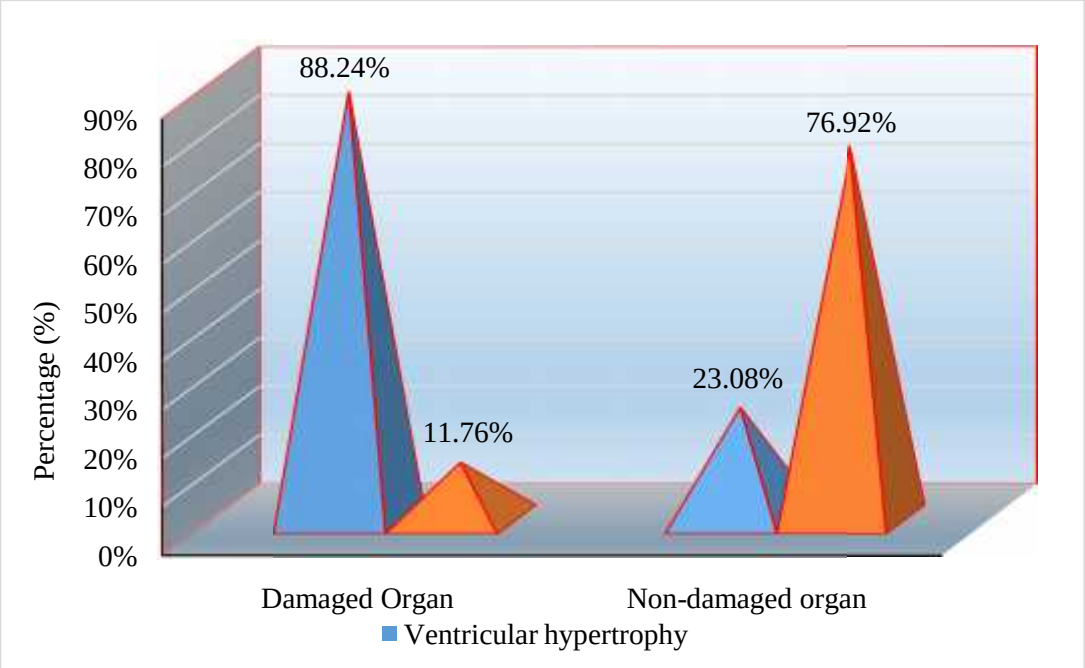


Table No 11: Association of ventricular hypertrophy with hypertension at a risk of organ damage according to the type of nephrotic syndrome

Factors	Sub-category	SDNS			FRNS		
		Ventricular hypertrophy					
		Yes	No	P-value	Yes	No	P-value
HTN With a risk for Organ damage	Yes	10 (90.91%)	1 (9.09%)	**0.0175**[MC]	5 (83.33%)	1 (16.67%)	**0.0475**[MC]
	No	1 (20%)	4 (80%)		2 (25%)	6 (75%)	

It has been concluded that children with hypertension at a risk for organ damage is significantly associated with Ventricular hypertrophy in SDNS as well as FRNS cases. Using Odds ratio, it has been concluded that Odds of developing ventricular hypertrophy in hypertensive subjects with organ damage in SDNS is 40 (95% CI:[1.98,807.1]) times higher than hypertensive subjects without organ damage in SDNS. It has also been concluded that Odds of developing ventricular hypertrophy for hypertensive subjects with organ damage in FRNS is 15 (95% CI: [1.03,218.30]) times higher than hypertensive subjects without organ damage in FRNS.Using Woolf test, it has been concluded that there is no significant 3-way association between Ventricular hypertrophy, Organ damage and type of syndrome (p-value=0.6329).

Table No 12: Association of hypertension with Hypertensive retinopathy and cataract

Hypertensive changes in the eye	Count (%)
Hypertensive retinopathy	2 (6.67%)
Cataract	6 (20%)

Seven percent of the patients with hypertension have hypertensive retinopathy and twenty percent of the patients with hypertension have cataract in the eye.

Graph 12: Prevalence of changes in the eye in Hypertensive subjects

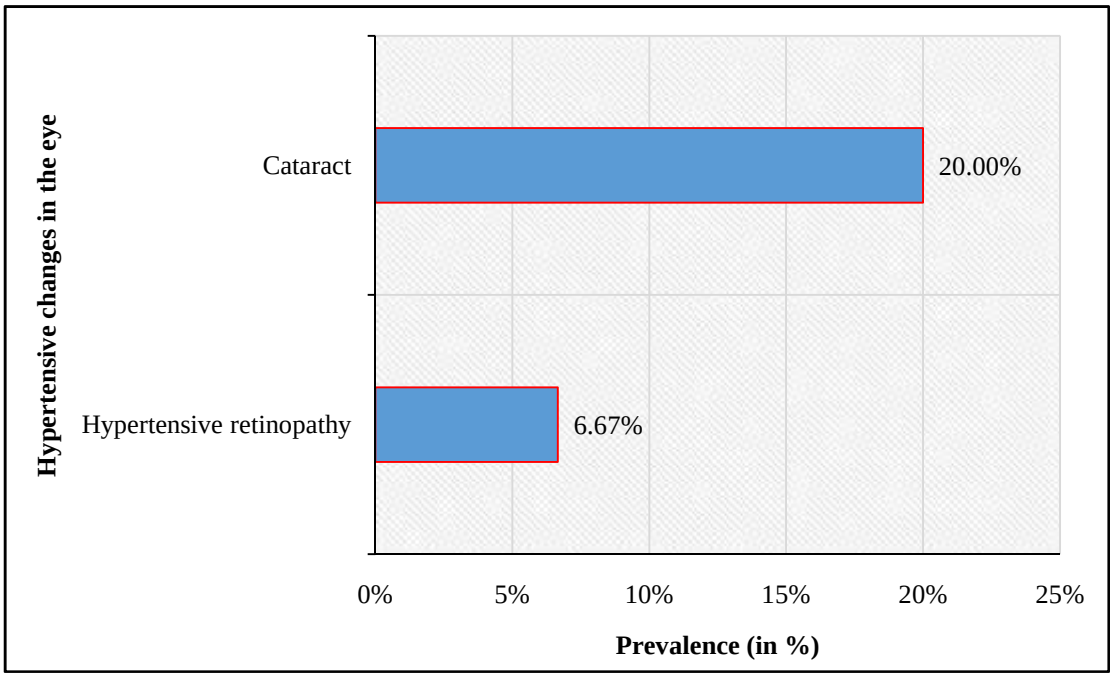
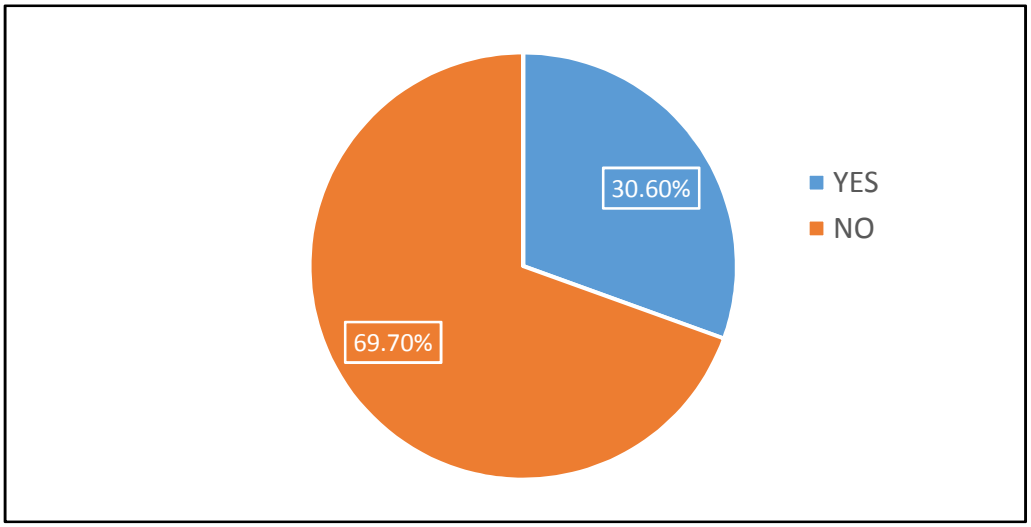


Table No 13. Association of growth retardation with FRNS and SDNS

Type	Present	Absent	P- value
SDNS	11(37.93%)	18(62.07%)	0.1807
FRNS	4(20%)	16(80%)	

Graph 13: Prevalence of growth retardation in Hypertensive subjects



- **In our study, among the 49 study subjects 15(30.6%) patients were having short stature.**
- It has been observed that 11(37.93%) of 29 SDNS cases had Growth retardation whereas 4(20%) of 20 FRNS cases had Growth retardation. Using chi-square test, it has been concluded that Growth Retardation is not significantly associated with the type of nephrotic syndrome.
- Among the patients with steroid dependent nephrotic syndrome, the mean steroid dependent dosage of the patients with growth retardation was 0.21 mg/kg/day and in the patients without growth retardation, the mean steroid dependent was 0.17 mg/kg/day.

Table No 14: Association of left ventricular hypertrophy with Nocturnal hypertension

Night-time HTN	Ventricular hypertrophy		P-value
	Yes	No	
SBP night-time with organ damage	6 (100%)	0 (0%)	NA
SBP night-time without organ damage	4 (100%)	0 (0%)	
DBP night-time with organ damage	15 (83.33%)	3 (16.67%)	0.1374
DBP night-time without organ damage	1 (33.33%)	2 (66.67%)	

It has been observed that all subjects with nocturnal systolic hypertension with or without organ damage had Ventricular hypertrophy. Among 18 subjects with night-time DBP with organ damage, 15 had Ventricular hypertrophy whereas among 3 subjects with nocturnal DBP without organ damage, 1 had Ventricular hypertrophy.

Table 15: Association of non-dippers with ventricular hypertrophy

Non dippers	Ventricular hypertrophy		P-value
	Yes	No	
Yes	15 (68.18%)	7 (31.82%)	0.2134
No	3 (37.5%)	5 (62.5%)	

Using chi-square test with simulation, it has been concluded that dipping is not significantly associated with Ventricular hypertrophy.

Majority of the patients 15 (68.18%) who were non-dippers had ventricular hypertrophy.

DISCUSSION

Nephrotic syndrome is the most common glomerular disorder in children. Hypertension is a major problem in nephrotic syndrome. The children who are diagnosed with steroid dependent and frequently relapsing nephrotic syndrome have more chances of developing hypertension either due to the medications or due to the disease itself.

In our study comprising of 49 patients aged 1 -18 years , had a Male : Female ratio of 1.72:1 which is consistent with the epidemiological findings found in a study done in Iraq by Nahla et al which showed Male : Female ratio to be 1.8:1 and another study done in New Jersey showed Male : Female ratio of 2:1

The prevalence of hypertension which was measured using Ambulatory blood pressure monitor was 61.22 %. It includes both masked as well as ambulatory hypertension. It was less compared to a study done in China by Xu et al which detected hypertension in 88.6% among 114 patients with steroid sensitive nephrotic syndrome.[35] The accuracy to detect hypertension is much higher with Standardized Ambulatory Blood pressure monitor than the regular mercury Sphygmomanometer as they overcome many limitations such as observer bias, false positive diagnosis of white coat hypertension and failure to diagnose masked and nocturnal hypertension.

These monitors help in blood pressure monitoring during sleep, mental and physical activities. It helps in assessing within – person variability as it provides multiple blood pressure measurements in short span of time.[8] Ambulatory blood pressure monitoring are used in the adult population since many decades but recently its usage is gradually increasing in the pediatric population as well. In the adult

population, hypertension detected by ABPM predicts cerebrovascular and cardiovascular events better than the clinic hypertension. The recent studies done in the pediatric population has proven an association between ABPM patterns and organ damage in children with Chronic kidney disease.[36] We want to extrapolate those results in the children diagnosed with steroid dependent nephrotic syndrome and Frequently relapsing nephrotic syndrome in our study. ABPM is now considered as gold standard for noninvasive blood pressure monitoring. [9] So wide extensive usage of Ambulatory blood pressure monitor is required.

In our study 55.1% was the prevalence of hypertension in SDNS and 70% in FRNS. A study done by Sarkar et al detected 33% patients of FRNS with ambulatory hypertension and 63% cases with clinic hypertension. There is no previous data pertaining to the prevalence of ambulatory hypertension in the patients with steroid dependent nephrotic syndrome.[7] But the data regarding the prevalence of clinic hypertension which was found in a previously done study by Nahla et al was 19.7% and 5.6% in SDNS and FRNS respectively.[5]

In our study,19 patients (38.78%) were in relapse and 30 patients (61.22%) were in remission. Among them 12(63.16%) had hypertension during relapse and 18(60%) had hypertension in remission. Prevalence of hypertension in relapse was not significantly higher than those patients in remission. A study done by Koster et al in the year 1990 has shown that 95% cases of minimal change nephrotic syndrome was detected with clinic hypertension in the pretreatment phase and 19.5% during remission.[17] A study done by Kontchou et al in the year 2009 has considered cases of steroid sensitive nephrotic syndrome. 65% of the patients in active phase and 34% in remission have been detected to have hypertension.(more than 90th centile, systolic or

diastolic blood pressure).[18] Another study done by Keshri et al which showed that 23.4% of the patients who were diagnosed to have steroid sensitive nephrotic syndrome had hypertension in remission.[19] Another study done by Flynn et al showed that patients with sub-nephrotic proteinuria(60% had systolic hypertension and 54% had diastolic hypertension)had higher prevalence of hypertension than patients with nephrotic range proteinuria(17% had systolic hypertension and 23% had diastolic hypertension).[40]

Many studies have shown a higher prevalence of hypertension during relapse than remission. However, patients in both categories have been detected with hypertension in all studies. So, blood pressure monitoring is necessary in all patients to initiate the treatment for hypertension at the earliest and prevent ocular and cardiovascular morbidity.

In our study, Cyclosporine was used in 8(16.33%) patients of which 7 patients (87.5%) had hypertension. Prevalence of hypertension was more in our study compared to a study done by Saca et al in Saudi Arabia[37] and an Iraqi study done by Nahla et al[5] which were 20% and 76.9% respectively. The usage of Cyclosporine is a significant risk factor for developing hypertension hence it is very important that the blood pressure monitoring is carried out for all the patients receiving Cyclosporine.

In our study, 20 children were diagnosed with FRNS, majority of the episodes of relapse were triggered by Upper Respiratory Tract Infections (76.79%) followed by Lower Respiratory Tract Infections (8.93%).Other causes observed were UTI, peritonitis and acute gastroenteritis. A study done by Khemchand in the year 2011 showed that infectious causes were the major triggering factors for relapse (62.88%) followed by 25% who had no triggering factors for relapse. Among the infectious

causes, acute respiratory tract infections (54.49%) followed by diarrhea (22.34 %) and then Urinary Tract Infection (UTI) which was 8.17% and then peritonitis (4.9%) were seen. Hence the caretakers of the children with nephrotic syndrome have to be educated about the risk factors which lead to relapse. We should advise them a visit to the hospital if the above triggering factors are observed so that the screening for relapse can be done. Thus, we can detect the relapse early and prevent the complications of nephrotic syndrome. We should also create awareness regarding the use of the pneumococcal and influenza vaccines. By taking these simple measures we can reduce both mortality as well as morbidity in patients with nephrotic syndrome [38]

Masked hypertension is defined as clinic hypertension $<95^{th}$ centile and ambulatory hypertension of $>95^{th}$ centile appropriate for age and sex. Ambulatory hypertension is defined as both clinic hypertension and ambulatory hypertension $>95^{th}$ centile. We have included both, masked as well as ambulatory hypertension in our study as recent studies prove that both these categories of hypertensive children are associated with increased LVMI and left ventricular hypertrophy.[39] In our study, Left Ventricular hypertrophy was detected in 18(60%) hypertensive patients. Hypertension with a risk of organ damage was significantly associated with Ventricular hypertrophy. Our study proved that chances of developing ventricular hypertrophy is 25 times higher for the subjects belonging to the category of hypertension at a risk of organ damage (>50% BP load) than those subjects belonging to the category of hypertension without the risk of organ damage. This association was also seen in the study done by Linyuan Jing et al in USA in the year 2017 which showed that elevated ambulatory blood pressure is associated with increased LVMI in children with obesity. Cardiovascular magnetic resonance was used to detect left ventricular hypertrophy in contrast to our study where echocardiography was used.

Echocardiography has many advantages over cardiovascular magnetic resonance such as easy availability, technological accessibility and is economical for the patients. In our study, LVMI was calculated using devereux's formula to detect left ventricular hypertrophy. This study suggests that interventions targeted to those who have hypertension may be effective in reversing or preventing cardiac remodeling and future cardiovascular risk. Thus, with the usage of ambulatory blood pressure monitor, hypertension can be detected early and treatment can be started.[20]

In our study we also looked for the association of left ventricular hypertrophy with hypertension at a risk of organ damage separately for SDNS and FRNS and it has been proven that it is significantly associated with each other. The chances of developing left ventricular hypertrophy for hypertensive subjects with organ damage in SDNS is 40 times higher than hypertensive subjects without organ damage. The chances of developing left ventricular hypertrophy for hypertensive subjects with organ damage in FRNS is 15 times higher than hypertensive subjects without organ damage.

Nocturnal hypertension has proven to have prognostic implications in adults and children having CKD (Chronic Kidney Disease) and diabetes mellitus. Significant predictor of cardiovascular outcome in hypertensive adults has been nocturnal hypertension. So, it is important to look into the sleep blood pressure abnormalities. In patients with solid organ transplantation, nocturnal hypertension has been observed.[22] In our study, all patients diagnosed with SDNS and FRNS having nocturnal systolic hypertension have been detected to have left ventricular hypertrophy and majority of patients with nocturnal diastolic hypertension also have been found to have left ventricular hypertrophy (76%). There is a multicenter study done by Flynn et al in the

year 2012 which states that the prevalence of diastolic hypertension is high in cases with secondary hypertension.[40] Another study done by Flynn et al in the year 2005 showed that isolated systolic hypertension is found in children with primary hypertension[41]. In our study, all the patients who have been diagnosed to have hypertension have diastolic hypertension 30(100%) and 18(60%) children have systolic hypertension which is consistent with both the above studies.

A dipping status of ≥ 10 % is considered as physiological. So, dipping < 10% belongs to the category of non-dippers. In our study 22 (73.33%) hypertensive children were found to be non-dippers. Majority of the patients, 15 (68.18%) who were non dippers had ventricular hypertrophy. Certain adult studies in patients with hypertension who were non-dippers had higher risk of adverse cardiovascular outcomes.[42]

Seven percent of the patients with hypertension have hypertensive retinopathy. The prevalence of hypertensive retinopathy was less compared to a study done by Joen et al which was 25%. Twenty percent of the patients with hypertension have cataract which was high compared to a study done by Joan et al where prevalence of cataract was 10.3% among the patients diagnosed with frequent relapses and steroid dependency. In nephrotic syndrome, ocular complications occur due to the disease as well as the treatment. Cataract is the most complication seen. Early initiation of treatment leads to higher chances of developing cataract. There is a risk of developing Amblyopia in younger patients due to immature eyes. Red reflex has to be checked in all patients who receive corticosteroid therapy. Early ophthalmic examination is important to detect cataracts early.[43]

In our study, among the 49 study subjects, 15(30.6%) patients were having short stature. It has been observed that 11(37.93%) of 29 SDNS cases had growth retardation whereas 4(20%) of 20 FRNS cases had growth retardation. According to a study done by Tsau et al which considered 2 groups of patients where one group contained patients with SDNS, FRNS and SRNS and the other group contained Steroid sensitive nephrotic syndrome with occasional or no relapse. Majority of the patients who had growth retardation (88%) were from the first group.[32] As our study cohort consists of steroid dependent nephrotic syndrome and frequently relapsing nephrotic syndrome, we have looked for the association of growth retardation. Growth retardation is defined as Height < 3rd centile according to the WHO growth chart appropriate for age and sex.

In our study, higher number of patients with Steroid dependent nephrotic syndrome have been found to have growth retardation. Among the patients with steroid dependent nephrotic syndrome, the mean steroid dependent dosage of the patients with growth retardation was 0.21 mg/kg/day and in the patients without growth retardation, the mean steroid dependent dosage was 0.17 mg/kg/day. This is consistent with the findings demonstrated by the study done by Tsau et al where the patients with the daily steroid dosage of 0.2 mg /kg/day or 0.4 mg/kg/48hrs have been detected with growth retardation.[32] Thus, we can predict the children who are at a risk of developing growth retardation and explain to the parents regarding this complication. Parents can be offered the treatment with the growth hormone. Recombinant human GH Norditropin at a dosage of 0.32 mg /kg at weekly intervals in Steroid dependent nephrotic syndrome has shown improvement in the linear growth and mineralization of the bones. A study done by Loke et al showed that the usage of growth hormone in 8 children with Steroid dependent nephrotic syndrome

had no adverse effects and there was no change in the requirement of prednisolone dosage before and after starting of growth hormone. So, it is safe for usage.[31]

Some limitations are present in our present study. The study population is small and limited to a single center with cross-sectional study design. In spite of a small sample size, this study contains a homogenous cohort of patients who are diagnosed with SDNS and FRNS. There is a requirement for a large multicenter study to substantiate the data in our study.

CONCLUSION

- Based on the observations from this study it may be concluded that, prevalence of hypertension in children diagnosed as SDNS and FRNS in the age group of 1-18 years is 61.22%.

- Children with hypertension at a risk of organ damage is significantly associated with development of left ventricular hypertrophy in both FRNS and SDNS.

RECOMMENDATIONS

- ABPM should become a routine in all cases of steroid dependant and frequently relapsing nephrotic syndrome.
- ECHO should be done compulsorily in all the patients who have masked and ambulatory hypertension, especially for those who are classified as hypertension with a risk of organ damage (>50% BP load) to look for left ventricular hypertrophy.
- Ophthalmological examination should be performed in all the cases of SDNS and FRNS for detection of glaucoma, cataract and hypertensive retinopathy.
- The patients have to be followed up regularly for cardiovascular and ocular morbidity.

SUMMARY

Nephrotic syndrome is the most common glomerular disorder in children. Hypertension is a major problem in nephrotic syndrome. The children who are diagnosed with steroid dependent and frequently relapsing nephrotic syndrome have more chances of developing hypertension either due to the medications or due to the disease itself. Cardiovascular and ocular comorbidities should be detected at the earliest.

The present hospital based cross-sectional prospective study for the period of one year from January 2019 to January 2020 was done among the children admitted under the Department of Pediatrics, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. The important findings of the study are highlighted as below.

- All the children who came to OPD and who were admitted to wards satisfying the inclusion criteria were enrolled into the study.
- Totally 49 children were included in our study.
- Mean age of the subjects who were included for the study was 8.15±3.85 years.
- Maximum number of patients, 16 were of the age group ≤5 years followed by 15 who were of the age group 9-11 years .9 each who were of the age group 6-8 years and 12-17 years.
- Male: Female ratio in our study was 1.72: 1.

- Among the study subjects, 59.2% cases belonged to the category of Steroid Dependent nephrotic syndrome and 40.8% cases belonged to the category of Frequently Relapsing nephrotic syndrome.

- Majority of the episodes of relapses in FRNS were due to Upper Respiratory Tract Infection (76.79%) followed by Lower Respiratory Tract Infections**.** (8.93%).
- Prevalence of hypertension measured by the Ambulatory Blood Pressure Monitor in nephrotic syndrome is 61.22%. It includes both categories of patients who have masked as well as ambulatory hypertension as both the categories were associated with cardiovascular morbidity. Majority, 22 (73.33%) hypertensive children were found to be non-dippers.
- Prevalence of hypertension among the groups SDNS and FRNS are 55.17% and 70% respectively.
- Higher number of male patients (67.74%) were detected to have hypertension than the female patients (50%).
- All the hypertensive patients were detected with diastolic hypertension.

- Maximum number of patients 17(56.67%) had diastolic hypertension with a risk of organ damage followed by 13 (43.33%) patients who had diastolic hypertension without the risk of organ damage.

- Many hypertensive patients (60%) were detected to have left ventricular hypertrophy.

- Association of left ventricular hypertrophy with hypertension at a risk of organ damage was separately looked for in SDNS and FRNS cases and it was proven

that it is significantly associated with each other. The chances of developing ventricular hypertrophy for hypertensive subjects with organ damage (>50% BP load) in SDNS is 40 times higher than hypertensive subjects without organ damage in SDNS and chances of developing ventricular hypertrophy for hypertensive subjects with organ damage in FRNS is 15 times higher than hypertensive subjects without organ damage.

- It has been observed that all subjects with nocturnal systolic hypertension with or without organ damage had Ventricular hypertrophy. Among 18 subjects with night-time DBP with organ damage, 15 had Ventricular hypertrophy whereas among 3 subjects with nocturnal DBP without organ damage, 1 had Ventricular hypertrophy.

- Seven percent of the patients with hypertension have hypertensive retinopathy.

- Twenty percent of the patients with hypertension have cataract in the eye.

- Growth retardation were seen in 15 (33%) patients.

- 11(37.93%) of 29 SDNS cases and 4(20%) of 20 FRNS cases had Growth retardation.

- Among the patients with steroid dependent nephrotic syndrome, the mean steroid dependent dosage of the patients with growth retardation was 0.21 mg/kg/day and in the patients without growth retardation, the mean steroid dependent was 0.17 mg/kg/day. Thus incidence of growth retardation is higher in patients with higher dependent dosage.

Overall, based on the observations from this study it may be concluded that, prevalence of hypertension in children diagnosed as SDNS and FRNS in the age group of 1-18 years is 61.22%. Children with hypertension at a risk of organ damage is significantly associated with development of left ventricular hypertrophy in both FRNS and SDNS.

BIBLIOGRAPHY

1. Sonia A, Sriram K. Assessment of quality of life in children with nephrotic syndrome at a teaching hospital in South India. Saudi J Kidney Dis Transpl.2017;28(3):593-598.

2. Bagga A, Srivastava RN. Nephrotic syndrome. Pediatric Nephrology. 4th ed. New Delhi: Jaypee; 2016.

3. Robert M, Bonita. S, Joseph S, Nina F. Nelson textbook of paediatrics.20th edition 2015.

4. Chanchlani R, Parekh RS. Ethnic differences in childhood nephrotic syndrome. Front Pediatr.2016; 4:39.

5. Nahla I, Essam, Haider. Nephrotic syndrome and hypertension. Iraqi Journal of Community Medicine.2010;23(4):271-276.

6. Gabriela A, María A, María D, Miguel Á. Cardiovascular risk factors in children with primary nephrotic syndrome. Rev Med Inst Mex.Seguro Soc. 2015;53 Supl 3: S284-93.

7. Sarkar S, Sinha A, Lakshmy R, Agarwala A, Saxena A,"et al" . Ambulatory Blood Pressure Monitoring in Frequently Relapsing Nephrotic Syndrome.Indian J Pediatr. 2017 Jan;84(1):31-35.

8. Matthew, Nancy R. Blood Pressure Measurement in Childhood Epidemiological Studies. Circulation. 1995; 92:1049–1057.

9. Abanti C. Pediatric ambulatory blood pressure monitoring: diagnosis: of hypertension. Pediatr Nephrol (2013) 28:995–999.

10. Se Jin Park,Jae Il Shin. Complications of nephrotic syndrome, Korean J Pediatr. 2011 Aug; 54(8): 322–328.

11. KIDGO. Steroid-sensitive nephrotic syndrome in children. Kidney International Supplements. 2012; 2, 163–171.

12. Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid sensitive nephrotic syndrome in children.2020; (4).

13. Jitendra Meena, Arvind Bagga. Current Perspectives in Management of Edema in Nephrotic Syndrome. The Indian Journal of Pediatrics.2020; 87:633–640

14. Ibrahim F, Lauren J, Robert. Hypertension in childhood nephrotic syndrome. Frontiers in paediatrics.2019;287(7).

15. Renata C, Hermann H. Cyclosporin-induced hypertension. European society of hypertension. 2001; 2: No.8.

16. El-Husseini A, El-Basuony F, Mahmoud I, Sheashaa H, Sabry A, Hassan R. “et al”. Long-term effects of cyclosporine in children with idiopathic nephrotic syndrome: a single-centre experience. Nephrol Dial Transplant.2005;20:2433–8.

17. Küster S, Mehls O, Seidel C, Ritz E. Blood pressure in minimal change and other types of nephrotic syndrome. Am J Nephrol.1990; 10(Suppl. 1):76–80.

18. Kontchou LM, Liccioli G, Pela I. Blood pressure in children with minimal change nephrotic syndrome during edema and after steroid therapy: the influence of familial essential hypertension. Kidney Blood Press Res.2009; 32:258–62.

19. Keshri S, Sharma S, Agrawal N, Bansal S, Guilliani BP, Aggrawal KC. Hypertension and its severity in children with steroid sensitive nephrotic syndrome during remission. Clin Exp Nephrol. 2018; 22:1157– 62.

20. Linyuan J, Christopher D, Cassi M, Jonathan D. Suever 1, Arichanah P. "et al" Ambulatory systolic blood pressure and obesity are independently associated with left ventricular hypertrophic remodeling in children. J Cardiovasc Magn Reson.2017; 19: 86.

21. Xu zq, Yi zw, Dang xq, Wu xc, He xj. Relationship of 24-hour ambulatory blood pressure and rennin-angiotensin-aldosterone system in children with primary nephrotic syndrome. Zhongguo Dang Dai Er Ke Za Zhi. 2010 ;12(10):788-92.

22. Joseph T, Stephen R, Laura L, David M, Brian W, Mark Mitsnefes, et al. Update: Ambulatory Blood Pressure Monitoring in Children and Adolescents. 2014; 63(5): 1116–1135.

23. Patnaik SK, Kumar P, Bamal M, Patel S, Yadav MP, Kumar V, "et al". Cardiovascular outcomes of Nephrotic syndrome in childhood (CVONS) study: a protocol for prospective cohort study. BMC Nephrology.2018;19:81.

24. Kawaguchi E, Ishikura K, Hamada R, Nagnoka Y, morikawa Y, Sakai.”et al”. Early and frequent development of ocular hypertension in children with nephrotic syndrome. Pediatric.2014;29(11):2165–2171.

25. Andrew I, Robert C. What causes steroid cataracts? A review of steroid-induced posterior subcapsular cataracts; Clin Exp Optom 2002; 85: 2: 61-75.

26. Korte I, Hockwin , Fischer H, Klemm H, Kraft U. Studies on the influence of corticosteroids on the carbohydrate metabolism of calf and bovine lenses in uitm. Jap JOphthalmol.1976; 20: 204-211.

27. Jacob TJC, Karim AKA, Thompson GM. The effects of steroids on human lens epithelium. Eye.1987; 1: 722-727.

28. Richer S. Antioxidants and the eye. Int Ophthalmol Clin. 2000; 40: 1-16.

29. Spencer RW, Andelman W. Steroid cataracts. Posterior subcapsular cataract formation in rheumatoid arthritis patients on long-term steroid therapy. Arch Ophthalmol.1965;74: 38-41.

30. Mohan KR, Kanitkar M. Growth in Children with Steroid Sensitive Nephrotic Syndrome. Med J Armed Forces India.2009; 65(1): 4–6

31. Loke KY, Yap HK, Zhou X, et al. Efficacy and safety of one year of growth hormone therapy in steroid-dependent nephrotic synGrowth in Children with Steroid Sensitive Nephrotic Syndrome drome. J Pediatr. 1997; 130:793-9.

32. Tsau YK, Chen CH, Lee PI .Growth in children with nephrotic syndrome. Taiwan.1989; 88(9):900-906].

33. Joseph T, David C, Carissa M. Baker S, Douglas B, Aaron E. “et al” Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics.2017;140(3).

34. Constantinescu AR, Shah HB, Foote EF, Weiss LS. Predicting first-year relapses in children with nephrotic syndrome. Pediatrics. 2000; 105: 492-5.

35. Xu Z, Yi Z, Dang X, et al. Sympathetic nervous system level and ambulatory blood pressure in children with primary nephrotic syndrome. Zhong Nan Da Xue Xue Ban. 2010; 35:693–8.

36. Flynn JT, Mitsnefes M, Pierce C, Cole SR, Parekh RS, Furth SL, et al. Blood pressure in children with chronic kidney disease: a report from the chronic kidney disease in children study. Hypertension.2008; 52:631–7.

37. Saca E, Hazza I. Cyclosporine-A Therapy in Steroid Dependent Nephrotic Syndrome. Saudi Arabia J. 2002; 13:520-523.

38. Khemchand. N. Infections are Common Cause of Relapse in Children with Nephrotic Syndrome. Pak Paed J.2011; 35(4): 213-19.

39. Susan H. Practical application of ABPM in the pediatric nephrology clinic. Pediatric Nephrology.2020; 35:2067–2076.

40. Flynn J, Zhang Y, Susan S, Shi V. Clinical and demographic characteristics of children with hypertension. Hypertension.2012; 60:1047–1054

41. Flynn JT, Alderman MH. Characteristics of children with primary hypertension seen at a referral center. Pediatr Nephrol.2005; 20:961–966.

42. Hermida R, Ayala DE, Mojon A, Fernandez JR (2013) Blunted sleep-time relative blood pressure decline increases cardiovascular risk independent of blood pressure level—the “normotensive non-dipper” paradox. Chronobiol Int.2012; 30(1–2):87–98.

43. Joan SK, William W, Ricky WK , Joannie H, Esther N, Dennis S. Ocular complications of pediatric patients with nephrotic syndrome. Clinical and Experimental Ophthalmology.2001; 29, 239–243.

ANNEXURE I – CONSENT FORM

"The prevalence of hypertension in children of Nephrotic syndrome diagnosed as Frequently Relapsing Nephrotic Syndrome and Steroid Dependent Nephrotic Syndrome in KLES DrPrabhakarKore Hospital Belagavi -a one year hospital based prospective study."

Objective and purpose of the study

This research is intended to find the prevalence of hypertension using AMPM in patients diagnosed with FRNS and SDNS and also to detect the target organ damage in the heart and the eyes in the age group of 1- 18 yearsof age.

Procedure

If you agree for your child to be part of the research study, he/she will be asked the relevant history, clinical examination and few routine blood and urine investigations will be done.There are some questionnaireswhich needs to be answered by the parents and intervention is done in the form of measuring blood pressure using ABPM for 24 hours. If the child is detected to have hypertension then ECHO and ophthalmologic examination is done.

Riskand Benefits

There are no risks associated with the study. The child will be benefited from the study as hypertension will be detected using the ABPM which is a gold standard to detect hypertension non-invasively. The extent of the damage to the heart and eyes can be assessed and the treatment for it can be started at the earliest.

Alternatives

Taking part in this study is voluntary. You may choose your child not to take part in this study, or if you decide your child to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that your child will receive. The study doctor may stop his/her participation in this study any time.

Privacy and Confidentiality

All information collected about your child during the course of this study will be kept confidential to the extent permitted by law. Information from this study may be published but my identity will be confidential in any publication.

Financial incentives for participation

Your child will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLEUniversity, Belgaum as part of requirement towards the completion of MD degree, review, and publishing.

If you have any questions about your child's rights as a participants parent/ guardian you may call Dr.RoopaM Bellad, professor Department of Paediatrics,J.N.M.C Ethical Committee for Human Research phone number 0831-247135.,

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant or legally authorized representative: _____

Signature / Thumb print _____

In case of the queries during study or in future you may contact following person.

Principal investigator : _____

Co-investigator : _____

Name of the Witness _____

Signature _____

Investigator Name and Signature _____

Date: Place:

ANNEXURE II: PROFORMA

TITLE: The prevalence of hypertension in children of nephrotic syndrome diagnosed as frequently relapsing nephrotic syndrome and steroid dependent nephrotic syndrome in KLEs Dr Prabhakar Kore hospital Belagavi -a one-year hospital based prospective study.

Principal Investigator:Dr. RITESH. B. R

Guide: DR. MAHANTESH. V. PATIL

Date:

Name:

Age:

Sex:

Date of enrollment:

Father's/guardian's name:

Phone number:

Email id:

Complete Postal Address:

A. Date of onset of the disease:

B. Steroid usage:

1. Starting Date:

2. Dosage:

3. Duration:

C. Classification:

SDNS	YES	NO

Dependentdose:

FRNS

YES	NO

Sl No	Date of relapse:	Triggering Factor For relapse:	Drug usage during relapse:

D. Other specific medications:

E. Hypertension:

1. Onset:

2. Symptoms:

3. Blood Pressure Readings:

1st:

2nd:

3rd:

4. BP CENTILE Chart: **Height:**

	SYSTOLIC	DIASTOLIC
50TH		
90TH		
95TH		
95TH + 12 mm hg		

5. Antihypertensives:

SL. NO	Start Date	Medications	Duration	End date

F. ABPM Readings:

G. ECHO Findings

H. Ophthalmologic Findings:

I. Anthropometry:

Anthropometry	Actual Value	Expected Value	Centile	Analysis
Height				
Weight:				
Head circumference:				

J. Investigations:

1. Blood investigations:				
CBC:	**Hb**			
	WBC			
	Plt			
Serum electrolytes:	**Na**			
	K			
	Cl			
Urea:				
Creatinine:				
Bicarbonate:				

2. Urine Investigations:				
Urine Albumin:				
Urine routine:				
Urine microscopy:				
Urinary Protein Creatine Ratio				

3. Special investigations:

Complement levels:

ANA:

ANCA:

K. Interpretation:

1.

FRNS	SDNS

2. ABPM

Centile	**%SBP load**	**%DBP load**	**Interpretation**
90th			
95th			

Dipping	**Percentage**
Systolic	
Diastolic	

3. Target organ damage:

A. Heart

B. Eyes:

3.Growth Retardation:

ANNEXURE-III-ETHICAL CLEARANCE LETTER

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/07 **Date: 24/11/2018**

To,

(REG NO.BM0118004)
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"THE PREVALENCE OF HYPERTENSION IN CHILDREN OF NEPHROTIC SYNDROME DIAGNOSED AS FREQUENTLY RELAPSING NEPHROTIC SYNDROME AND STEROID DEPENDENT NEPHROTIC SYNDROME IN KLES DR PRABHAKAR KORE HOSPITAL BELAGAVI- ONE YEAR HOSPITAL BASED PROSPECTIVE STUDY",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

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ANNEXURES IV - MASTER CHART

Sl No	Hospital number	Date	Name	Age (years)	age category	Sex	Date of onset disease	Classification	hypertension (mean)	Triggering factors 1	Triggering factors 2	Triggering factors 3	Triggering factors 4	Other specific medication	Cyclosporine	amlodepine	dose	depin	dose	Carvedilol	dose	dipping	Type of HTN	Time Point	Hypertension category	HTN	ECHO(left ventricular hypertrophy)	Hypertensive Retinopathy	Cataract	Height (<3rd centile)	Urine Albumin	Type of HTN	sl no	Dependent dose
1	1731763	43668	SHABANA	13	12-17	Female	8 YEARS	SDNS	s,o;d,o					cyclosporine	Yes	Yes	7.5 MG			Yes	3.125 MG	4.7,7.4			No Hypertension, No Hypertension with medication	Yes	Yes	No	No	Yes	3+	No hypertension	1	12.5 MG
2	2659090	43670	Rajawardhan	8	6-8	Male	10 months	SDNS	s,o;d,o					Vermizol, cyclophosphamide	No			Yes	5mg			8.2,7.2			Amb BP with organ damage, Hypertension with meds, Hypertension without relapse	Yes	Yes	No	No	Yes	2+	SBP day time, SBP Night time with organ damage, DBP day time with organ damage, DBP night time with organ damage	2	10
3	4944731	43672	MAHESH	3	L5	Male	1.5 YEARS OF AGE	FRNS	d,o	LOOSE STOOLS	URTI	URTI	URTI	Vermizol	No							minus 0.9, minus 2.7			Amb BP with organ damage, Hypertension without meds, Hypertension during relapse	Yes	Yes	No	No	No	3+	DBP day time with organ damage, DBP night time with organ damage	3	
4	960346	43673	sadik	10	9-11	Male	6 years	SDNS	s;d,o					Vermizol, cyclosporine, Tacrolimus,MMF	Yes	Yes	5mg					5.8,8			Amb BP with organ damage, Hypertension with meds, Hypertension without relapse	Yes	Yes	No	No	Yes	2+	SBP night time, DBP day time with organ damage, DBP night time with organ damage	4	10
5	4981874	43682	aishwarya	12	12-17	Female	11 years	FRNS	*no	URTI	URTI	URTI	URTI	Vermizol	No							5.3,6.9			Amb BP without Organ damage, Hypertension without meds, Hypertension without relapse	no	Not done	Not done	Not done	No	Absent	DBP night time	5	
6	4909777	43684	yellamma	9	9-11	Female	6	SDNS	no					Vermizol	No							8.1,9.6			No Hypertension, No Hypertension without medication	No	Not done	Not done	Not done	No	Absent	No hypertension	6	2.5
7	5319794	43695	vedanth	4	L5	Male	4years(2 months back)	FRNS	s,d	URTI	URTI	-	-		No							13.4,11.8			Amb BP with organ damage, Hypertension without meds, Hypertension during relapse	Yes	No	No	No	Yes	3+	SBP day time with organ damage, DBP day time with organ damage	7	
8	4443716	43697	omkar	4	L5	Male	2yrs of age	FRNS	s,o;d,o	URTI	ACUTE GE	PERITONITIS	URTI		No							12.1,8.8			Amb BP with organ damage, Hypertension without meds, Hypertension during relapse	Yes	Yes	No	No	No	3+	SBP day time with organ damage, DBP day time with organ damage, DBP night time with organ damage	8	
24	4563621	43770	punit	9	9-11	Male	3 1/2	FRNS	d	URTI	URTI	URTI	URTI	Vermizol	No							6.4,6.9			Amb BP with organ damage, Hypertension without meds, Hypertension without relapse	Yes	No	Yes	Yes	No	2+	DBP night time with organ damage	9	
9	3752992	43704	pritam kadappa	7	6-8	Male	3 1/2	SDNS	d					Vermizol	No							9.6,11.7			Amb BP with organ damage, Hypertension without meds, Hypertension during relapse	Yes	no	No	No	Yes	4+	DBP day time, DBP night time with organ damage	9	7.5 mg
37	4453726	43847	Tayakka	10	9-11	Female	7 1/2	SDNS	s,o;d,o						No	Yes	7.5					4.9,2.2			Amb BP with organ damage, Hypertension with meds, Hypertension without relapse	Yes	Yes	No	No	Yes	2+	SBP day time, SBP Night time with organ damage, DBP day time with organ damage, DBP night time with organ damage	10	15
10	441996	43706	prajwal shirol	5	L5	Male	2 years	SDNS	*no						No							12.4,11.2			Amb BP without Organ damage, Hypertension without meds, Hypertension during relapse	no	Not done	Not done	? Not done	Yes	3+	DBP night time	10	10 mg
11	4259801	43707	Kalmesh	12	12-17	Male	10 years of age	FRNS	s,o;d,o	no triggers	peritonitis	LRTI	peritonitis	Vermizol, cyclophosphamide	No							0.1,0.1			Amb BP with organ damage, Hypertension without meds, Hypertension during relapse	Yes	no	No	Yes	No	3+	SBP day time, SBP night time, DBP day time, DBP night time, SBP day time with organ damage, SBP Night time with organ damage, DBP night time with organ damage	11	
12	683510	43717	Manjunath	17	12-17	Male	2 1/2 years	SDNS	s,o;d,o					Vermizol, cyclophosphamide, cyclosporine, MMF, RITUXIMAB	Yes	Yes	2.5 mg					15.1,24.3			No Hypertension, No Hypertension with medication	Yes	No	No	No	No	1+	No hypertension	12	7.5 mg
13	5385749	43779	MAHANTESH	5	L5	Male	4 YEARS	FRNS	s;d,o* on meds	LRTI	DIARRHOEA	-	-	Vermizol	No	Yes	2.5 MG					3.4,2.4			Amb BP with organ damage, Hypertension with meds, Hypertension without relapse	Yes	Yes	No	No	No	Trace	SBP day time, SBP night time, DBP day time with organ damage, DBP night time with organ damage	13	
15	5412673	43723	Khushi santosh	6	6-8	Female	3 years	FRNS	s,d	URTI	URTI	-	-		No							15.2,19.6			Amb BP without Organ damage, Hypertension without meds, Hypertension without relapse	Yes	No	Yes	No	No	Absent	SBP day time, DBP day time	15	
16	5421464	43725	Siddhi	9	9-11	Female	4 years	FRNS	d	URTI	URTI	-	-		No							7.1,13			Amb BP without Organ damage, Hypertension without meds, Hypertension without relapse	Yes	Yes	No	No	No	1+	DBP day time, DBP night time	16	
17	5418259	43727	nagaraj	6	6-8	Male	4	SDNS	no						No							4.9,10.7			No Hypertension, No Hypertension without medication	No	Not done	Not done	Not done	No	3+	No hypertension	17	5 mg
18	5425246	43729	Aithal	5	L5	Male	1 1/2	FRNS	d,o	URTI	URTI	URTI	URTI		No							4.6,8.9			Amb BP with organ damage, Hypertension without meds, Hypertension during relapse	Yes	Yes	No	Yes	Yes	3+	SBP night time, DBP day time, DBP night time with organ damage	18	
19	974992	43742	Anup	10	9-11	Male	2years 8 mon	SDNS	no					Vermizol	No							12.4,16			No Hypertension, No Hypertension without medication	No	Not done	Not done	Not done	Yes	3+	No hypertension	19	10
20	975181	43745	prajwal sukumar	14	12-17	Male	3 years	SDNS	d,o					cyclophosphamide, cyclosporine, MMF,tacrolimus,rituximab,envas	Yes	Yes	10					3.3,0.1			Amb BP with organ damage, Hypertension with meds, Hypertension during relapse	Yes	Yes	No	No	Yes	3+	DBP day time, DBP night time with organ damage	20	10
21	382993	43749	Jyothi	11	9-11	Female	8 years	SDNS	no					Vermizol	No							10.4,14.5			No Hypertension, No Hypertension without medication	No	Not done	Not done	Not done	No	Absent	No hypertension	21	7.5 mg
22	3957272	43750	Rajesh	14	12-17	Male	4 years	FRNS	no	URTI	URTI	-	-	Vermizol, cyclophosphamide	No							5.8,8.5			No Hypertension, No Hypertension without medication	No	Not done	Not done	Not done	No	Absent	No hypertension	22	
23	3378312	43762	naveen	7	6-8	Male	2	SDNS	no					cyclosporine, MMF	Yes							8,8.4			No Hypertension, No Hypertension without medication	No	Not done	Not done	Not done	No	3+	No hypertension	23	10
25	4146229	43771	Aditya	5	L5	Male	2 1/2	SDNS	s;d,o					cyclosporine	Yes							5.2,8.7			Amb BP with organ damage, Hypertension without meds, Hypertension during relapse	Yes	Yes	No	No	No	3+	SBP Night time with organ damage, DBP day time with organ damage, DBP night time with organ damage	25	12.5 mg
26	5476882	43535	basavaraj	5	L5	Male	4years	FRNS	no	URTI	URTI	-	-		No							4.9,9			No Hypertension, No Hypertension without	No	Not done	Not done	Not done	No	4+	No hypertension	26	

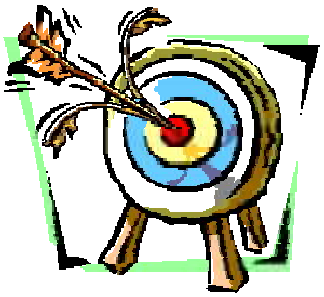
29	2462355	43778	pritam vijayakumar	8	6-8	Male	2 years	SDNS	s,d					Vermizol, cyclophosphamide	No							19.9,24.4			Amb BP without Organ damage, Hypertension without meds, Hypertension without relapse	Yes	No	No	No	No	Absent	SBP day time, DBP day time	29	7.5 mg
30	5167301	43781	Mithun	9	9-11	Male	8 years	SDNS	s,o;d,o						No	Yes	5 mg			Yes	3.125 mg	11.5,15.1			Amb BP without Organ damage, Hypertension with meds, Hypertension without relapse	Yes	Yes	No	No	No	Trace	SBP day time	30	10 mg
31	3654070	43782	Prem	6	6-8	Male	4	SDNS	no*						No							2.9,8.2			Amb BP without Organ damage, Hypertension without meds, Hypertension without relapse	no	Not done	Not done	Not done	No	Absent	SBP day time	31	2.5
32	5500153	43788	dhyaneshwari	2	L5	Female	1 year	FRNS	d	URTI	URTI	URTI	URTI		No							8.9,9.3			Amb BP without Organ damage, Hypertension without meds, Hypertension without relapse	Yes	Yes	No	No	No	Absent	SBP day time, DBP day time	32	
33	5501680	43795	Bhavana	9	9-11	Female	4 years	FRNS	no	URTI	URTI	-	-		No							7.9,10.2			No Hypertension, No Hypertension without medication	No	Not done	Not done	Not done	No	3+	No hypertension	33	
34	4849922	11/27/0019	Preetham ravi	4	L5	Male	1 1/2	SDNS	d					Vermizol	No							9.9,21.5			Amb BP with organ damage, Hypertension without meds, Hypertension without relapse	Yes	Yes	No	No	No	1+	DBP day time with organ damage	34	5
35	5068185	43798	moinuddin	4	L5	Male	1.5 years	FRNS	*no	LRTI	LRTI	-	-		No							11.2,14.9			Amb BP without Organ damage, Hypertension without meds, Hypertension during relapse	no	Not done	Not done	Not done	No	3+	DBP night time	35	
36	5471311	43843	karthik	4	L5	Male	2 1/2	SDNS	s,o;d,o						No							5.5,8.2			Amb BP with organ damage, Hypertension without meds, Hypertension during relapse	Yes	Yes	No	No	Yes	3+	SBP day time with organ damage, DBP day time with organ damage, DBP night time with organ damage	36	5
38	5294935	43848	Sarah	2.5	L5	Female	2	SDNS	S,o;d,o						No							minus 3.6,0.1			Amb BP with organ damage, Hypertension without meds, Hypertension without relapse	Yes	Yes	No	No	No	Trace	SBP day time with organ damage, SBP Night time with organ damage, DBP day time with organ damage, DBP night time with organ damage	38	15
39	3583993	43853	Samarth	11	9-11	Male	4 years	SDNS	no *					Vermizol	No							6.4,12.6			Amb BP without Organ damage, Hypertension without meds, Hypertension without relapse	no	Not done	Not done	Not done	No	Absent	DBP night time	39	7.5mg
40	4618317	43855	Khushi sidrai	6	6-8	Female	3	FRNS	no	URTI	URTI	URTI	LRTI	Vermizol	No							7.9,12			No Hypertension, No Hypertension without medication	No	Not done	Not done	Not done	No	Absent	No hypertension	40	
41	2783323	43858	Hiba	9	9-11	Female	6 years	SDNS	*no					Vermizol, cyclophosphamide, MMF	No							5.8,7.4			Amb BP without Organ damage, Hypertension without meds, Hypertension without relapse	no	Not done	Not done	Not done	No	Absent	DBP night time	41	7.5 mg
42	5600628	43859	Sanjana	11	9-11	Female	4 years	SDNS	no						No							2.7,10.2			No Hypertension, No Hypertension without medication	No	Not done	Not done	Not done	No	Absent	No hypertension	42	10
43	1005470	43898	KAVERI	9	9-11	Female	8 years	FRNS	s,d	URTI	Peritonitis	-	-	Vermizol	No							12.9,16.1			Amb BP with organ damage, Hypertension without meds, Hypertension without relapse	Yes	No	No	No	Yes	2+	DBP day time, DBP night time, SBP day time with organ damage	43	
46	2592394	43481	Ajay	10	9-11	Male	1 1/2 YEARS	FRNS	d	URTI	URTI	-	-	Vermizol	No							8.7,11.3			Amb BP with organ damage, Hypertension without meds, Hypertension without relapse	Yes	No	No	Yes	No	Absent	DBP day time, DBP night time with organ damage	46	
47	1012129	43986	Pranit	4	L5	Male	7 months	FRNS	s,o;d,o	URTI	URTI	-	-	Vermizol, cyclosporine	Yes							11.1,13.5			Amb BP with organ damage, Hypertension without meds, Hypertension during relapse	Yes	Yes	No	No	Yes	3+	SBP night time, SBP day time with organ damage, DBP day time with organ damage, DBP night time with organ damage	47	
48	1013524	43986	Shubha	14	12-17	Female	9 years	SDNS	S,o;d,o					cyclophosphamide, cyclosporine, MMF	Yes	Yes						4.4,4.2			Amb BP with organ damage, Hypertension with meds, Hypertension during relapse	Yes	Yes	No	Yes	Yes	3+	SBP day time with organ damage, SBP Night time with organ damage, DBP day time with organ damage, DBP night time with organ damage	48	12.5 mg
49	1731477	43990	Sakshi	11	9-11	Female	6 years	FRNS	d	URT	URTI	-	-	Vermizol	No							minus 0.9,minus 2.8			Amb BP with organ damage, Hypertension without meds, Hypertension without relapse	Yes	No	No	No	No	Absent	DBP night time with organ damage	49	
50	1015284	43999	bhargavi	5	L5	Female	9 months	SDNS	no					Vermizol	No							6.4,10.1			No Hypertension, No Hypertension without medication	No	Not done	Not done	Not done	No	Absent	No hypertension	50	7.5 mg
51	1014719	43996	Basavaraj	16	12-17	Male	10	SDNS	d					tacrolimus	No							0.9,3.8			Amb BP with organ damage, Hypertension without meds, Hypertension without relapse	Yes	No	No	Yes	No	1+	DBP night time, DBP day time with organ damage	51	20 mg
52	1015817	44004	ziya	7	6-8	Female	1 year 10 m	SDNS	no					Vermizol	No							9.7,15			No Hypertension, No Hypertension without medication	No	Not done	Not done	Not done	No	Absent	No hypertension	52	2.5mg
53	1016206	44006	Abhijith	5	L5	Male	3 years	SDNS	d					Vermizol	No							9.7,12.2			Amb BP without Organ damage, Hypertension without meds, Hypertension without relapse	Yes	No	No	No	Yes	2+	SBP day time, DBP day time	53	7.5 mg

ANNEXURE-V

KEY TO MASTER CHART

HTN	–	Hypertension
s	–	Systolic hypertension
s,o	–	Systolic hypetension with organ damage
d	–	Diastolic hypertension
d,o	–	Diastolic hypertension with organ damage

Introduction



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