Original Article

Subclinical Hypothyroidism in Children with Idiopathic Childhood Nephrotic Syndrome at a Tertiary Institution in South-West Nigeria

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Abstract

Background: Hypothyroidism in children with nephrotic syndrome (NS) is often attributed to prolonged loss of thyroxine binding globulin and thyroid hormones alongside protein in the urine. It has been historically associated with steroid-resistant NS alone. However, recent evidence supports the fact that subclinical hypothyroidism (SCH) does occur even in children with steroid responsive NS. Complications such as weight gain, hypercholesterolemia, delayed growth, delayed puberty, and depression could result from hypothyroidism and be erroneously attributed to NS, or the effect of steroid used in treatment. Incidentally salt intake, the major form of dietary iodine is often restricted in children with NS, possibly exacerbating any underlying hypothyroid state. **Aim:** The study aimed to determine the burden of SCH among our cohort of NS patients. **Patients and Methods:** A comparative cross-sectional study was designed to assess SCH [defined by high TSH (>6.0 mU/L and normal free T4 (0.8–2.0 ng/dl)] in hundred children with NS aged between one and fifteen years compared with hundred age and gender matched comparison group without NS. Blood and urine samples were collected to analyze thyroid function, serum albumin, serum protein and urinary protein. **Results:** The prevalence of SCH was significantly higher in subjects with NS than their age, sex matched comparison group (12% vs. 2%, P = 0.006). The highest proportion (24.1%) of the children with NS who had SCH was found in the age range of 11–15 years and majority were females (19.4% vs. 7.8%, respectively, P = 0.086). The proportion of children with SCH were higher in those with steroid-resistant NS than those responsive to steroids (26.3% vs. 8.6% P = 0.033). The average values of serum albumin and protein were also significantly lower in children with SCH than those without (2.91 mg/dl ± 0.8 vs. 3.78 mg/dl ± 0.9 and 3.99 mg/dl ± 1.3 vs. 5.02 mg/dl ± 1.3, respectively, P < 0.005). Also, the average value of urinary protein was significantly higher in those with SCH than those without [94.29 mg/dl (42.3–101.0) vs. 69.19 mg/dL (31.2–108.2), respectively, P = 0.023]. Participants with steroid-resistant NS have almost three-folds odd of developing SCH compared to steroid sensitive subjects (AOR 2.901; 95% CI 1.831–4.012; P = 0.038). **Conclusion:** Screening of children for SCH with NS especially steroid-resistant NS and frequent relapsing steroid sensitive NS for hypothyroidism before complications arise is pertinent to their holistic management. This becomes even more imperative in our environment as iodine deficiency hypothyroidism is still prevalent in some parts of the country.

Keywords: *Childhood, hypothyroidism, idiopathic, nephrotic syndrome, subclinical*

Introduction

Hypothyroidism is one of the least studied complications of nephrotic syndrome (NS)

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in children. Hypothyroidism has been largely attributed to prolonged loss of thyroid hormones and thyroxine binding globulin together with protein in the urine.[1-4] It was historically described in congenital forms of NS which are often steroid resistant, necessitating the use of thyroid hormone supplementation as a routine practice in this group of patients.[3,4] Subclinical hypothyroidism (SCH) has also been demonstrated in children with steroid-resistant nephrotic syndrome (SRNS) when in and out of remission.[5,6] There has been various arguments about routine evaluation of thyroid profile in patients with NS, but no concession has been made till date.[6] Patients often remain euthyroid because free thyroxine (T4) and triiodothyronine (T3) levels are usually normal. This suggests a possible compensation by the thyroid gland for loss of hormones in the urine.[4] SCH is defined by a normal total or free T4 level (0.8–2.0 ng/dl) and a mildly elevated TSH (>6.0 mU/L).[5] Several studies have been conducted on thyroid hormone changes in children with NS,[6-11] however, in much smaller sample sizes. SCH has been hitherto described only in children with steroid-resistant NS.[3-6] Oyemade *et al*.[9] over three decades ago reported elevated TSH levels in Nigerian children with NS. Since then, there has been paucity of studies in the tropics. In this study, we documented the prevalence of SCH in our cohort of 100 NS patients, compared the proportion of children with SCH in both the steroid-sensitive and resistant groups and identified independent predictors of SCH.

Materials and Methods

This was a comparative cross-sectional study which was carried out in the Pediatric nephrology clinic between August and December 2020. The study comprised of 100 patients with NS aged between one and fifteen years attending the clinic and 100 apparently healthy age, sex matched children that served as a comparison group. Participants with previously diagnosed thyroid disorders were excluded. Informed written consent was obtained from the parents or legal guardians of the patients and assent taken from children seven years and above.

Data was collected in English language using a self-designed proforma, administered by the researchers. Data including duration of diagnosis, duration of use of steroids, cumulative dose of steroid and response to steroid was extracted from the case notes. Blood and urine samples were collected and transported immediately to the research laboratory to ensure accuracy of results. Serum free T_3, free T_4 and TSH levels were assessed using equilibrium dialysis technique and SCH was defined by TSH values >6.0 mU/L and free T4 values between 0.8–2.0 ng/dl.[12] Total serum protein was analyzed using the Biuret method, serum albumin was analyzed using the colorimetric method (Bromocresol Green).[12] Urinary protein was analyzed using colorimetric method (Pyrogallol Red).[12]

Data was analyzed using Microsoft Excel and Statistical Package for Social Sciences (SPSS) version 24.0 (IBM, Inc, Chicago, Illinois). Demography of participants was presented as frequency and percentages. Tables and figures were used to present the variables as appropriate.

Bar chart was used to present prevalence of SCH (which is the dependent variable/outcome) among patients with NS and the comparison group. Fisher's exact test was used to compare prevalence of SCH between the two groups. Association between categorical independent variables (sex and age group) and outcome variable (SCH) was assessed using Pearson's chi square or Fisher's exact test for expected frequencies less than five.

For numeric independent variables (e.g. serum protein, albumin, cumulative steroid dose), Kolmogorov–Smirnov test was used to assess data normality. Independent Student's *t* test was used to compare means according to the presence or absence of SCH when normally distributed. Mann Whitney U test was used for comparison of the median values of two groups when data were skewed.

Multiple logistic regression was used to determine independent predictors of SCH among NS participants among a list of covariates (clinical and biochemical parameters). Probability (*P*) value was considered significant at less than 0.05 and at a confidence interval of 95%.

Ethical approval

Approval was granted by the Health and Research Ethics committee. The personal details of the patients were used in a nonidentifiable and confidential manner. Written informed consent was obtained from the

Table 1: Age and gender distribution of participants

Variables	Case (*n*=100) *n* (%)	Control (*n*=100) *n* (%)	Total
Age group (years)			
1-5	31 (31.0)	31 (31.0)	62 (31.0)
6-10	40 (40.0)	40 (40.0)	80 (40.0)
11-15	29 (29.0)	29 (29.0)	58 (29.0)
Mean±SD	8.41±3.2	8.32±3.2	8.37±3.2
Gender			
Male	64 (64.0)	64 (64.0)	128 (64.0)
Female	36 (36.0)	36 (36.0)	72 (36.0)

Table 2: Association between sub-clinical hypothyroidism and selected parameters

Variables	Present (*n*=12) *n* (%)	Absent (*n*=88) *n* (%)	Total	χ^2	*P*
Age group (Years)					
1-5	2 (6.5)	29 (93.5)	31 (100.0)	5.717	0.057*
6-10	3 (7.5)	37 (92.5)	40 (100.0)		
11-15	7 (24.1)	22 (75.9)	29 (100.0)		
Mean±SD	11.94±3.4	8.13±3.2			
Gender					
Male	5 (7.8)	59 (92.2)	64 (100.0)	3.019	0.086
Female	7 (19.4)	29 (80.6)	36 (100.0)		
Duration since diagnosis (months)					
≤60	9 (11.0)	73 (89.0)	82 (100.0)	0.453	0.501
>60	3 (16.7)	15 (83.3)	18 (100.0)		
Response to steroid					
Steroid resistance	5 (26.3)	14 (73.7)	19 (100.0)	4.552	0.033*
Steroid sensitive	7 (8.6)	74 (91.4)	81 (100.0)		
Cumulative steroid dose (mg)					
≤3,000	2 (8.7)	21 (91.3)	23 (100.0)	0.330	0.566
>3,000	10 (13.2)	66 (86.8)	76 (100.0)		
Albumin	2.91±0.8	3.78±0.9		−3.341**	0.002*
Serum protein	3.99±1.3	5.02±1.3		−5.032**	0.012*
Urine protein	94.29 (42.3-101.0)	69.19 (31.2-108.2)		−3.901#	0.023*

**Indepndent *t*-test; #Mann-Whitney *U* test

Table 3: Logistic regression model showing independent predictors of sub-clinical hypothyroidism

Variable	AOR	95% CI	*P*
Age group (Years)			
1-5	1	0.393-2.930	0.273
6-10	1.210	0.283-3.032	0.391
11-15	1.495		
Gender			
Male	1	0.364-2.492	0.193
Female	1.205		
Response to steroid			
Steroid sensitive	1	1.831-4.012	0.038*
Steroid resistance	2.901		
Albumin	0.754	0.283-2.742	0.201
Plasma protein	0.684	0.392-1.932	0.147
Urine protein	0.592	0.183-2.005	0.338

AOR; Adjusted odds ratio, CI; Confidence interval

caregivers and in addition assent from children 7 years and above.

Results

Two hundred (200) children were recruited into the study which comprised of 100 subjects with NS aged between 1 and 15 years and 100 age and gender matched controls. The age group 6 to 10 years predominated (40%) and more males were recruited than females 64% vs. 36%, respectively [Table 1].

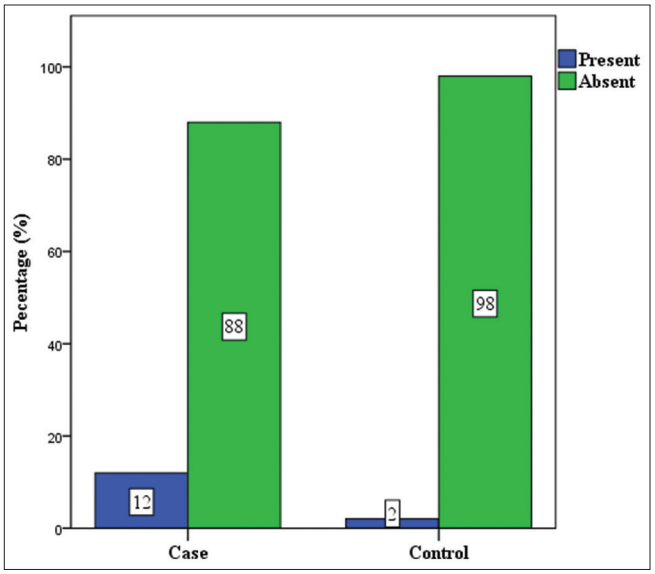

Figure 1: Prevalence of subclinical hypothyroidism in cases and control

The prevalence of SCH was significantly higher among cases (12%) than in the age, sex matched comparison group (2%), *P* = 0.006 [Figure 1].

A higher proportion of children with NS in the age bracket of 11 to 15 years had SCH. There was no significant association between gender and hypothyroidism state (*P* = 0.086). There was also no significant association between duration since diagnosis and hypothyroidism (*P* = 0.501) [Table 2].

The proportion of children with SCH was higher in those with steroid-resistant NS than those with steroid sensitive NS (26.3% vs. 8.6% $P = 0.033$). The average values of serum albumin and protein were also significantly lower in children with SCH than those without (2.91 mg/dl ± 0.8 vs. 3.78 mg/dl ± 0.9 and 3.99 mg/dl ± 1.3 vs. 5.02 mg/dl ± 1.3, respectively, $P < 0.005$). Also, the average value of urinary protein was significantly higher in those with SCH than those without [94.29 mg/dl (42.3–101.0) vs. 69.19 mg/dl (31.2–108.2), respectively, $P = 0.023$].

Table 3 shows the result of a multiple logistic regression model that was set up to identify independent predictors of SCH. Participants with steroid-resistant NS have almost three-folds odd of developing SCH compared to steroid sensitive subjects (AOR 2.901; 95% CI 1.831–4.012; $P = 0.038$).

Discussion

Our finding of a higher proportion of children with NS having SCH compared to apparently healthy children is not entirely surprising. It was comparable with the study done by Kapoor *et al*.[7] Another study revealed that although most children with NS were clinically euthyroid, they had an increased risk of SCH during relapse with elevated TSH levels while serum T3 and T4 were within normal.[8]

Our finding of a higher proportion of children with SCH in the older age group of 11 to 15 years was different from what was reported by Choudhury *et al*.[6] who noted that children with NS had an increased risk of SCH especially in the younger age group. A possible explanation for this is that older children may have a more advanced disease than younger ones longer duration of diagnosis of NS in the older age group. Studies have shown that functional defects in reabsorption of hormone from the proximal tubule are more severe in advanced disease.[13] SCH was commoner in females in the current study albeit not significant. A study by Lazar *et al*.[14] concluded that girls are at a greater risk for persistently abnormal TSH levels and also identified female gender as a predictive factor for elevated TSH levels.

SCH was associated with significantly reduced levels of serum albumin and protein and increased levels of urine protein. Mohamed *et al*.[15] reported that patients with NS in relapse had significantly lower levels of total serum albumin and protein in comparison with cases in remission and control group. Iglesias *et al*.[16] further stated that proteinuria leads to loss of thyroid hormones with a consequent rise in TSH levels. Based on our results, the most important predictor of SCH is steroid resistance which results in a three-fold odds of developing SCH in comparison with steroid sensitive patients. It has been reported in previous studies that there is a difference in protein selectivity and renal handling of free and protein bound thyroid hormone and TSH in steroid sensitive and steroid-resistant NS.[10] Patients with steroid-resistant NS tend to have less protein selectivity thus making them more prone to losing the thyroid binding proteins and, hence developing hypothyroidism. Corticosteroids act on the hypothalamus to reduce thyrotropin releasing hormone messenger ribonucleic acid levels and also on the anterior pituitary gland to decrease TSH secretion which explains why SCH is more common than overt hypothyroidism in NS.[17,18] It could also be a possible explanation for higher prevalence of SCH in steroid-resistant NS. Steroid treatment has been shown to repair the glomerular filtration barrier resulting in decreased proteinuria.[4] However, isolated studies on the link between hypothyroidism and steroid sensitive NS are uncommon and more evidence may be required to elucidate the mechanism. Despite paucity of data on SCH in steroid sensitive NS and the almost exclusive nature of SCH to steroid-resistant NS, our finding of SCH among steroid sensitive NS subjects was similarly documented by Kankananarachchi *et al*.[19]

Conclusion

The prevalence of SCH is increased especially in steroid-resistant NS therefore physicians should have a high index of suspicion. Screening may help in early detection and avert the progression to overt hypothyroidism. Normalization of thyroid hormones with replacement therapy may preserve thyroid function.

Limitation

A follow up of the patients to ascertain those who develop full clinical hypothyroidism is warranted as the cross-sectional design of this study cannot address that.

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Conflicts of interest

There are no conflicts of interest.

References

1. Jung SH, Lee JE, Chung WY. Changes in the thyroid hormone profiles in children with nephrotic syndrome. Korean J Pediatr

2019;62:85-9.
2. Hassan FO, Nooruldeen SF, Ali SH. Screening for hypothyroidism in children with nephrotic syndrome. Biochem Cell Arch 2019;19:2781-7.
3. El-Aal A, Hegab AM, Masoud EE. Thyroid function in children with nephrotic syndrome: A prospective hospital-based study. Sohag Med J 2020;24:153-7.
4. Das AK, Barua T, Dey D, Roy M, Choudhury Z, Karim MR. Thyroid function in children with idiopathic nephrotic syndrome. Chattagram Maa-O-Shishu Hosp Med Coll 2020;19:51-4.
5. Kaplowitz PB. Subclinical hypothyroidism in children: Normal variation or sign of a failing thyroid gland? Int J Pediatr Endocrinol 2010;2010:1-8.
6. Choudhury J. A study on thyroid function test in children with nephrotic syndrome. Int J Contemp Pediatr 2016;3:752-4.
7. Kapoor K, Saha A, Dubey NK, Goyal P, Suresh CP, Batra V, *et al*. Subclinical non-autoimmune hypothyroidism in children with steroid resistant nephrotic syndrome. Clin Exp Nephrol 2014;18:113-7.
8. Ito S, Kano K, Ando T, Ichimura T. Thyroid function in children with nephrotic syndrome. Pediatr Nephrol 1994;8:412-5.
9. Oyemade OA, Lukanmbi FA, Osotimehin BO, Dada AO. Biochemical hypothyroidism in Nigerian children with nephrotic syndrome. Ann Trop Paediatr 1983;3:93-6.
10. Dagan A, Cleper R, Krause I, Blumenthal D, Davidovits M. Hypothyroidism in children with steroid-resistant nephrotic syndrome. Nephrol Dial Transplant 2012;27:2171-5.
11. Nandi M, Basu B, Tarai A, Sar T. Thyroid profile in idiopathic childhood steroid-sensitive nephrotic syndrome. Med J DY Patil Vidyapeeth 2021;14:637-41.
12. Burtis CA, Ashwood ER, Bruns DE. Clinical chemistry and molecular diagnostics. Tietz Textbook of Clinical Chemistry. Philadelphia, 5th ed. 2012. p. 1905-44.
13. Eddy AA, Symons JM. Nephrotic syndrome in childhood. Lancet 2003;362:629-39.
14. Lazar L, Frumkin RB, Battat E, Lebenthal Y, Phillip M, Meyerovitch J. Natural history of thyroid function tests over 5 years in a large pediatric cohort. J Clin Endocrinol Metab 2009;94:1678-82.
15. Mohamed S, Zanon M, Elaskary A, Abdel-aal M, Abdelrahman Y, *et al*. Evaluation of thyroid function, oxidative stress and anti-oxidant in Egyptian children with nephrotic syndrome. Kidney Res J 2016;6:9-14.
16. Iglesias P, Diez JJ. Thyroid dysfunction and kidney disease. Eur J Endocrinol 2009;160:503-15.
17. Haugen BR. Drugs that suppress TSH or cause central hypothyroidism. Best Pract Res Clin Endocrinol Metab 2009;23:793-800.
18. Alkemade A, Unmehopa UA, Wiersinga WM, Swaab DF, Fliers E. Glucocorticoids decrease thyrotropin-releasing hormone messenger ribonucleic acid expression in the paraventricular nucleus of the human hypothalamus. J Clin Endocrinol Metab 2005;90:323-7.
19. Kankananarachchi I, Jayantha UK, Madhuranga ALA. Thyroid status in children with steroid sensitive nephrotic syndrome. Sri Lanka J Diabetes Endocrinol Metab 2020;10:7-10.