Vilnius University Press

Contents lists available at Vilnius University Press

Acta Medica Lituanica
2023. Online ahead of print

ISSN 1392-0138 eISSN 2029-4174
DOI: https://doi.org/10.15388/Amed.2023.30.2.4

Overt Hypothyroidism and Severe Growth Retardation in a Preschool Girl with Poorly Controlled Nephrotic Syndrome: Case Report and Literature Review

Joana Mikulevič*
Faculty of Medicine, Vilnius University, Lithuania

Karolina Tumelienė
Faculty of Medicine, Vilnius University, Lithuania

Robertas Kemežys
Centre of Pediatrics, Faculty of Medicine, Vilnius University, Lithuania

Augustina Jankauskienė
Centre of Pediatrics, Faculty of Medicine, Vilnius University, Lithuania

Abstract. ***Background.*** Nephrotic children may develop thyroid hormone dysfunction due to urinary excretion of thyroid hormones. In contrast to the subclinical hypothyroidism that affects around 30% of children with nephrotic syndrome (NS), the patient in this case had overt hypothyroidism and severe growth retardation.

Clinical case. A 5 years and 8 months old girl with steroid-dependent NS was referred from another center due to persistent edema and decreased diuresis, being treated with mycophenolate mofetil (MMF) 250 mg once a day and L-thyroxine 50 mcg daily since 4 months of NS onset because of hypothyroidism. Her albumin was 12.64 g/l, cholesterol 25.64 mmol/l and proteinuria 5 g/l. Severe growth retardation was observed: patient's height was 93.5 cm (–13 cm <3 percentile), weighted 17.2 kg (15–25 percentile). Her disease vintage was over 3 years. Girl's growth velocity has slowed down from 3.5 months. The patient received a high cumulative dose of prednisolone (approx. 7800 mg in 1 year and 8 months). Thyroid-stimulating hormone was higher (18.04 mU/L) with reduced FT4 11.43 pmol/l and IGF-1 < 15 µg/L. Kidney biopsy revealed minimal change disease, and genetic testing was negative. Intensive NS treatment with methylprednisolone pulse therapy, enlarged doses of MMF and albumin infusion were started and L-thyroxine dose was increased to 75 mcg. TPOAb was in normal range (12.65 IU/ml). After 3 weeks she was discharged with no edema and after stopping methylprednisolone treatment thyroid function normalized and L-thyroxin was discontinued. Two weeks later standard growth hormone stimulation test with clonidine showed partially insufficient growth hormone secretion. During NS remission with normalization of thyroid function (TSH 6.680 mU/l, FT4 13.85 pmol/l) and normalization of IGF-1 level (132 mcg/l) partial catch-up growth was observed (height velocity increased from 3.5 cm/year to 7.3 cm/year, based on 4-month calculation period).

* Corresponding author: Joana Mikulevič, Faculty of Medicine, Vilnius University, Lithuania. E-mail: joana.mikulevic@santa.lt

Received: 16/12/2022. **Revised:** 25/05/2023. **Accepted:** 09/06/2023

Conclusions. Clinicians should be aware of a risk of developing hypothyroidism and consider thyroid function testing during the treatment of children with NS, as well as actively treat hypothyroidism and evaluate growth.

Keywords: Hypothyroidism, nephrotic syndrome, children, growth retardation

Kliniškai reikšminga hipotirozė ir ryškus augimo sulėtėjimas ikimokyklinio amžiaus mergaitei blogai kontroliuojamo nefrozinio sindromo metu: atvejo aprašymas ir literatūros apžvalga

Santrauka. ***Apžvalga.*** Vaikams, sergantiems nefroziniu sindromu (NS), gali sutrikti skydliaukės funkcija dėl skydliaukės hormonų netekimo su šlapimu. Skirtingai nuo subklinikinės hipotirozės, kuri nustatoma apie 30 % vaikų, sergančių NS, šiuo atveju pacientei nustatyta kliniškai reikšminga hipotirozė ir ryškus augimo sulėtėjimas.

Klinikinis atvejis. 5 metų ir 8 mėnesių pacientė, kuriai prieš trejus metus diagnozuotas nuo steroidų priklausomas NS, buvo atsiųsta iš kito centro dėl išliekančių edemų ir sumažėjusios diurezės. Pacientė buvo gydoma mikofenolato mofetiliu (MMF) 250 mg 1 k/d. ir L-tiroksinu 50 mcg 1 k/d., nes praėjus 4 mėnesiams nuo NS pradžios jai buvo diagnozuotas hipotiroidizmas. Atvykus albuminas buvo 12,64 g/l, cholesterolis 25,64 mmol/l ir proteinurija 5 g/l. Hospitalizacijos metu taip pat buvo ryškus augimo atsilikimas: pacientės ūgis buvo 93,5 cm (-13 cm < 3 procentilio), svoris 17,2 kg (15–25 procentilio). Mergaitės ūgio atsilikimas pastebėtas nuo 3,5 mėnesio amžiaus. Ji yra gavusi didelę suminę prednizolono dozę (apie 7800 mg per vienus metus ir 8 mėnesius). Hospitalizuojant skydliaukę stimuliuojantis hormonas (TTH/TSH) buvo padidėjęs (18,04 mU/L), o sumažėję FT4 (11,43 pmol/l) ir IGF-1 < 15 µg/L. Atlikus inkstų biopsiją nustatyta minimalių pokyčių liga, o genetiniu ištyrimu pokyčių nerasta. Pacientė dėl NS pradėta intensyviai gydyti metilprednizolono pulsine terapija, padidinta MMF dozė, taip pat skirtos albumino infuzijos ir padidinta L-tiroksino dozė iki 75 mcg. Po 3 savaičių išnykus edemoms mergaitė išleista į namus, o remiantis dinamika nutrauktas gydymas metilprednizolonu, normalizavusis skydliaukės funkcijai nutrauktas ir L-tiroksino vartojimas. Praėjus 2 savaitėms atliktas standartinis augimo hormono stimuliacijos mėginys su klonidinu parodė iš dalies nepakankamą augimo hormono sekreciją. Pasiekus NS remisiją, kurios metu normalizavosi skydliaukės funkcija (TSH 6,680 mU/l, FT4 13,85 pmol/l) ir IGF-1 koncentracija (132 mcg/l), buvo matomas dalinis augimo greičio prisivijimas (augimo greitis padidėjo nuo 3,5 cm/m iki 7,3 cm/m, remiantis 4 mėnesių skaičiavimais).

Išvados. Gydytojams būtina žinoti hipotirozės išsivystymo riziką ir apsvarstyti skydliaukės funkcijos tyrimų skyrimo vaikams, sergantiems NS, būtinumą bei aktyviai gydyti hipotirozę ir stebėti vaikų augimo greitį.

Raktažodžiai: hipotirozė, nefrozinis sindromas, vaikai, augimo sulėtėjimas

Introduction

The incidence of nephrotic syndrome (NS) in children ranges from 1.15 to 16.9 per 100,000 depending on country [1]. NS is frequently associated with other pathologies, such as systemic diseases. Nephrotic children may also rarely develop thyroid hormone dysfunction due to urinary excretion of thyroid-binding globulin, transthyretin, and thyroid hormones [2]. Thyroid hormones are essential for normal growth [3], however, thyroid function tests are not generally performed in children with NS. Child's growth may be impaired in NS even with normal kidney function as long steroid treatment can affect growth is. In contrast to the subclinical hypothyroidism that affects around 30% of children with NS, our patient had overt hypothyroidism [2, 4]. This is our first such patient in our clinic over 30 years of practice, though we usually diagnose around 5 new NS cases per year and have on regular follow up to 40 NS children /year.

Clinical case

A 5 years 8 months old girl addressed pediatric nephrologist from another center and country due to persistent edema and decreased diuresis for over a month and was hospitalized because of generalized edema.

At the age of 2.5 years she was diagnosed with steroid-dependent NS and was treated with prednisolone but due to persistent proteinuria after 1 year and 8 months of treatment Prednisolone was changed to mycophenolate mofetil (MMF) 250 mg x 1 daily. Level of persistent proteinuria is unknown due to the lack of past medical history. After 4 months of NS onset the patient was diagnosed with hypothyroidism and got L-thyroxine 50 mcg daily. Unfortunately, thyroid hormone, albumin, creatinine and proteinuria levels at this time are not available.

Mother informed, that at the age of 3.5 months the girl's growth velocity has slowed down significantly. There is no information about thyroid hormone levels (TH) that time. The reason for poor growth during infancy prior to clinical diagnosis of NS is unclear. Wrist X-ray to assess patient's bone age was performed at the age of 4 years and 8 months and evaluated as being of 3 years and 6 months. Auxological data presented by mother was available only from the birth to the age of one year and from the age of 5 years and 8 months, when the patient arrived to our clinic. Patients' growth chart is shown in Figure 1.

On admission patient's height was 93.5 cm (–13 cm <3 percentile), weight 17.2 kg (15–25 percentile), abdominal circumference 63 cm, blood pressure 99/65 mmHg (90 percentile), generalized edema: periorbital edema, edema in hands and legs, sacrum area, ascites with umbilical hernia, pleural effusion. Initial laboratory results were specific to NS (Table 1) with severely expressed hypoalbuminemia, hypercholesterolemia. Patient's kidney biopsy revealed minimal change disease.

Table 1. Laboratory data on admission and in NS remission

Diagnostic test	**On admission**		**In remission**	
White blood cell count (10^9)	9,93	↔	10.86	↔
Serum haemoglobin (g/l)	113	↔	98	↓
Platelet count (10^9)	725	↑	447	↔
Electrolytes: Na (mmol/l)	132	↓	135	↔
Serum creatinine (mkmol/l)	18	↔	17	↔
eGFR (mL/min/1.73 m^2)	185.6	↔	210.8	↔
Urea (mmol/l)	8.19	↔	3.77	↔
Albumin (g/l)	12.64	↓	46.77	↔
Cholesterol (mmol/l)	25.48	↑	4.76	↔
HDL-cholesterol (mmol/l)	0.35	↓	1.12	↓
LDL-cholesterol (mmol/l)	19.65	↑	3.17	↔
Thyroid-stimulating hormone (TSH) (mU/l)	18.040	↑	6.680	↑
Free Thyroxine (FT4) (pmol/l)	11.43	↓	13.85	↔
IGF-1 (µg/L)	<15.0	↓	132	↔
Urine tests				
Proteinuria (g/l)	5	↑	0.25	↑
Haematuria	3+ (50/mcl)	↑	1+ (10/mcl)	↑
Urine microscopy	Hyaline casts		-	

↔ – in normal range; ↑ – increased; ↓ – decreased.

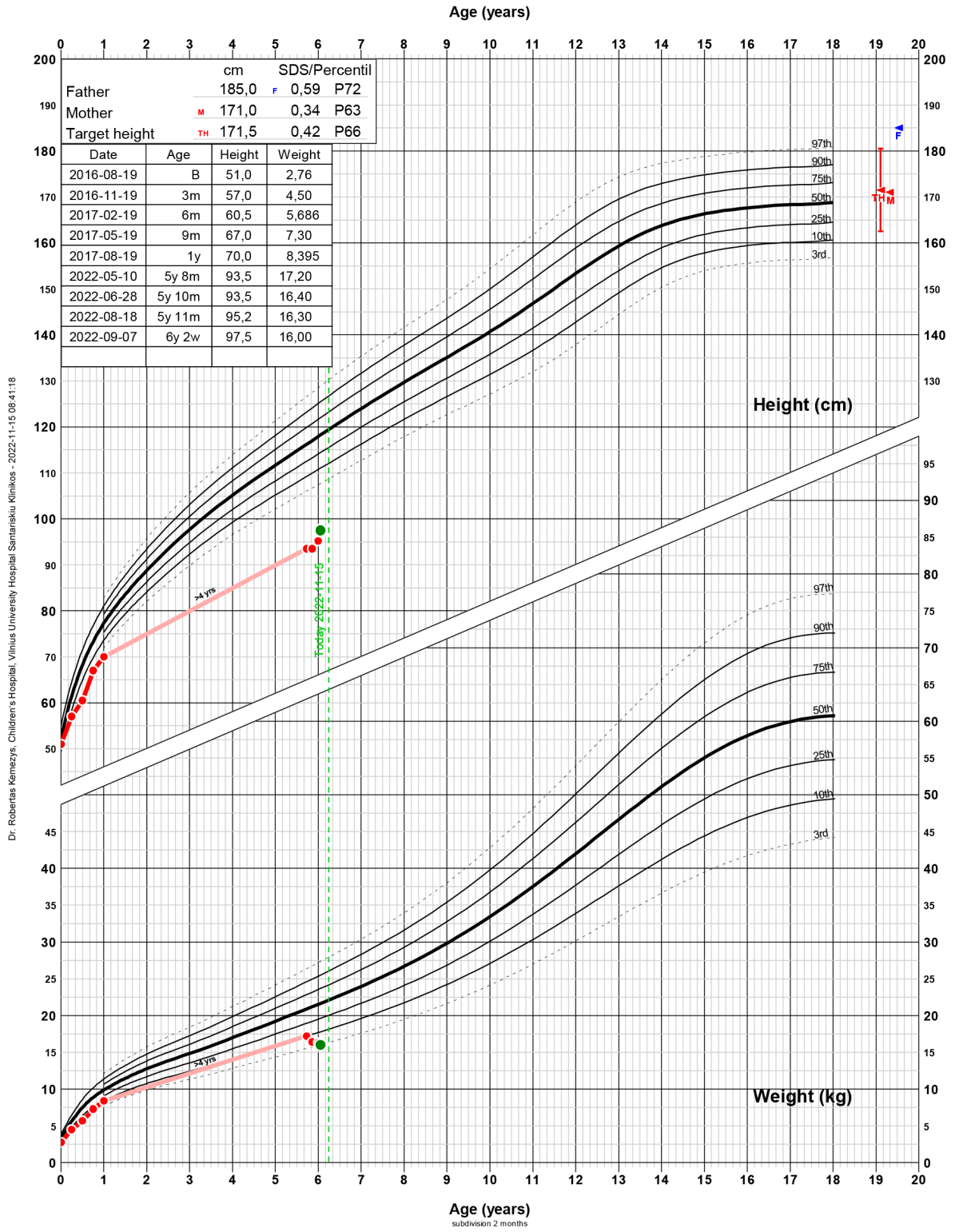

Fig 1. Patient's growth chart

Treatment with albumin infusion, methylprednisolone pulse therapy, diuretics and increased dosage of MMF (0.77 g/m²) was started. It took 14 days to achieve partial remission, edema decreased very slowly. Urine dipstick test on three consecutive days showed proteinuria 2+ after the treatment, compared to 4+ before the treatment. To control overt hypothyroidism due to urinary excretion of thyroid transporting proteins and thyroid hormones, L-thyroxine dose was increased to

75 mcg. To rule out other etiologies of hypothyroidism, such as autoimmune thyroiditis, TPOAb was performed and it was normal (12.65 IU/ml). Before being admitted to our clinic, the patient received a high cumulative dose of prednisolone (approx. 7800 mg in 1 year and 8 months) which could have impacted patient's growth. Hypothesizing that patient's short stature was caused by thyroid dysfunction because of NS and high cumulative dose of steroids, it was decided to perform growth hormone stimulation test after achieving partial/full NS remission to evaluate growth hormone (GH) secretion and to rule out severe GH deficiency. After 3 weeks of hospitalization the girl was discharged with no edema, unsignificant proteinuria with MMF 250 mg x 2 daily and daily methylprednisolone (24 mg/day for 4 weeks followed by gradual reducing over 1 month) which resulted in NS remission (proteinuria 1+ in urine dipstick test on three consecutive days) (Table 1).

One month after discontinuation of treatment with methylprednisolone thyroid function normalized and treatment with L-thyroxine was stopped. Two weeks later standard growth hormone stimulation test with clonidine was performed resulting in partially insufficient growth hormone secretion (Table 2). During NS remission with normalization of thyroid function (TSH 6.680 mU/l, FT4 13.85 pmol/l) and normalization of IGF-1 level (from unmeasurable (<15 mcg/l) to 132 mcg/l) partial catch-up growth was observed (height velocity increased from 3.5 cm/year to 7.3 cm/year, based on 4-month calculation period) (Fig 2). Assuming that basal growth hormone level was not low, reflecting possible spontaneous peak prior to the stimulation procedure, interpretation of growth hormone response is somewhat arbitrary, therefore it was decided to continue careful growth rate monitoring and then decide for a need of another growth hormone stimulation test. Genetic testing was also done with no findings.

Table 2. Growth hormone levels during clonidine (5 mcg/kg orally) stimulation test

Time (minutes)	0	30	60	90
GH (ng/ml)	2.45	2.37	5.66	3.27

Normal stimulated value >10 ng/ml

The patient is regularly followed by a pediatric nephrologist and her remission continues with MMF 750 mg (1.23 g/m^2), Enalapril 2.5 mg and Vit. D 2000 IU daily.

Discussion

Hypothyroidism is the most common disorder of thyroid function in children, caused primarily by autoimmune thyroiditis [5] characterized by the presence of TPOAb. Other less common causes of hypothyroidism include iodine deficiency [6] or excessive iodine intake that interferes with the production of thyroid hormones [7], obesity [8], late-onset congenital hypothyroidism, infiltrative thyroid disease or as a result of certain syndromes, e.g., DiGeorge or Prader–Willi syndrome [7], and, in very rare cases, loss of thyroid hormones in the urine. In our opinion, in this case, primary hypothyroidism was unlikely during infancy prior to clinical diagnosis of NS, because after achievement of partial remission of NS, thyroid levels became normal and TPOAb level was normal as well.

It is impossible to precisely determine the incidence of hypothyroidism in children with NS [9]. 34.7–46.9% nephrotic children may develop subclinical hypothyroidism [2, 4]. It has historically been linked to steroid-resistant NS; however, new evidence suggests that subclinical hypothyroidism can occur even in steroid-sensitive NS (SSNS) [10]. We consider this presented case as a special one, because our patient developed not subclinical hypothyroidism as described before, but overt hypothyroidism, requiring rather high L-thyroxine dose to normalize TSH. This overt hypothyroidism disappeared after a few months, when full NS remission was achieved.

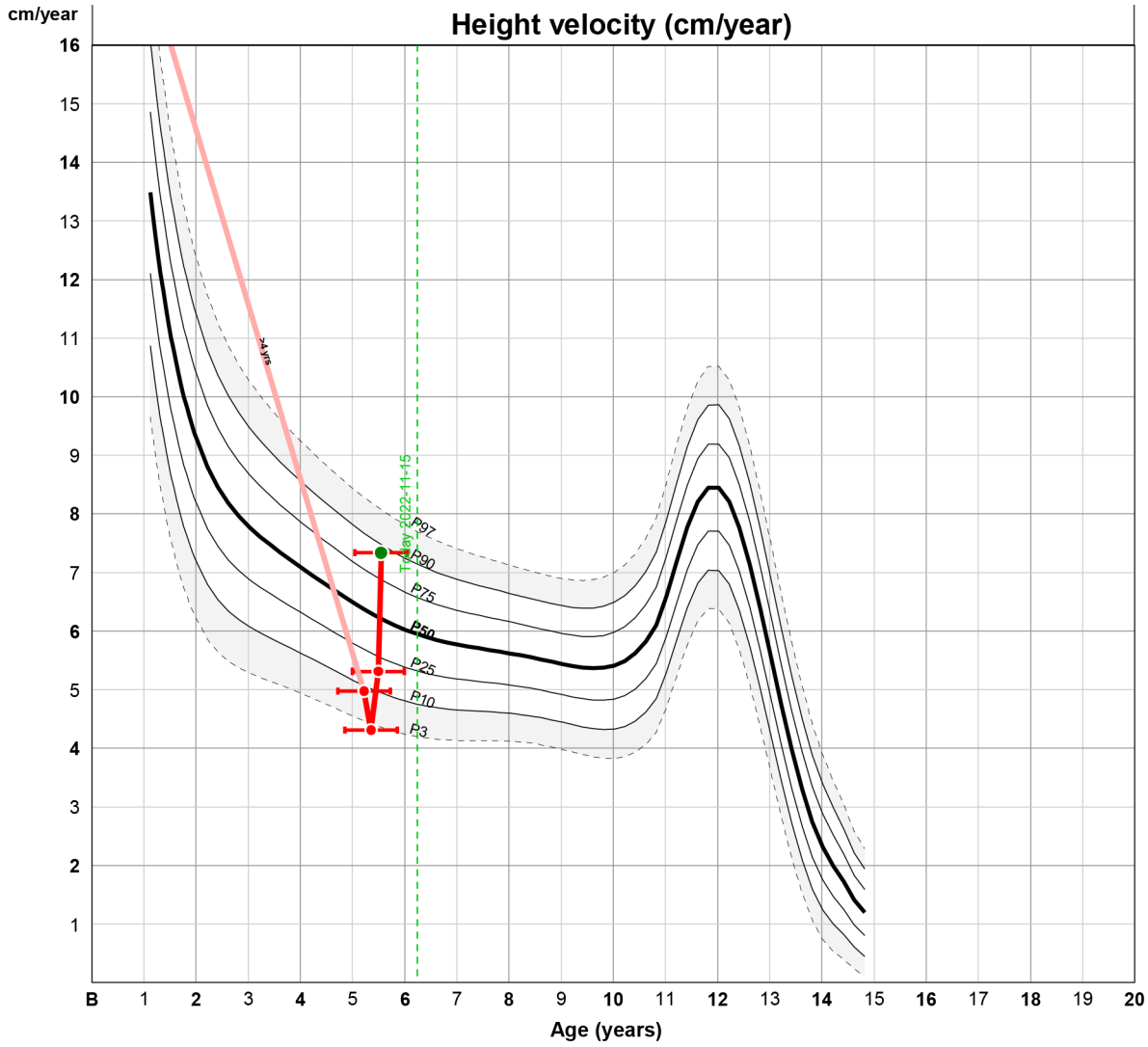

Fig 2. Patient's growth velocity dynamics

The loss of TH into urine has been proposed as a cause of hypothyroidism in NS [11], because more than 99% of TH in circulation is bound to plasma proteins, primarily thyroid binding globulin (TBG), transthyretin (TTR), and albumin [12] (Fig. 3). Furthermore, renal tubule injury can coexist and impair free TH reabsorption [13]. However, proteinuria alone cannot explain why hypothyroidism only manifested in a subset of SSNS patients and why it did not develop already at disease onset [9]. After NS exacerbation, it was shown that thyroxine levels decreased, and TSH levels increased; these levels returned to normal during remission [14].

Nephrotic children with low thyroid reserves may develop subclinical hypothyroidism, which, if not treated with thyroxine (T4), will likely progress to overt hypothyroidism [15]. The findings of Saffari et al. study underline the importance of conducting thyroid function tests in NS children with prolonged and severe urinary protein loss [4]. Almost one-third of children with idiopathic steroid resistant NS have overt or subclinical hypothyroidism [16]. Early diagnosis and treatment of thyroid hormone deficiency in children is critical for preserving normal linear growth and bone development [3].

Subclinical hypothyroidism is defined by elevated levels of TSH alone, usually not higher than 10 mU/l. Patients with subclinical hypothyroidism have an increased risk of cardiovascular morbidity and mortality due to high serum cholesterol levels and other cardiac risk factors. TH assessment is

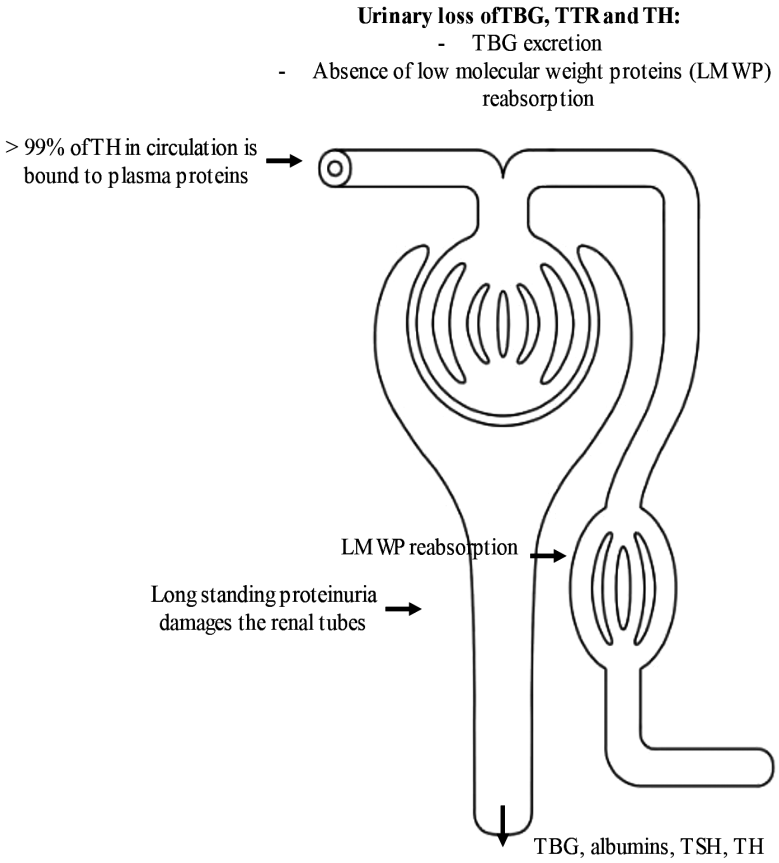

Fig. 3. Suggested schematic explanation of thyroid dysfunction due to urinary loss of thyroid-binding proteins in NS

strongly recommended for NS patients with elevated serum cholesterol [2]. Weight gain, hypercholesterolemia, delayed growth, delayed puberty, and depression can all occur because of hypothyroidism and may be mistakenly attributed to NS or the effect of steroid treatment. In addition, salt intake, the main source of dietary iodine, is frequently restricted in children with NS, potentially exacerbate any underlying hypothyroidism [5]. TH therapy has been shown to improve growth velocity in children with subclinical hypothyroidism and short stature, particularly in prepubertal groups [17]. Furthermore, treatment for hypothyroidism showed to improve renal function [18].

In our described case severe growth retardation occurred not only due to hypothyroidism, but also due to high cumulative dose of prednisolone. In children with NS, growth retardation is proportional to the cumulative dose of steroids. The dosage and duration of glucocorticoid treatment in NS is one of the most important factors influencing growth [19]. In our case GH peak of 5.66 ng/ml during the clonidine stimulation test we defined as partially insufficient, based on historical interpretation of severity of GH deficiency (GH deficiency is defined as severe when peak GH level on provocative testing is either <3 or <5 μg/L while it is defined as partial when peak GH level is between 5 and 10 μg/L [20]). Recently many centers have started to use lower peak GH cutoff values for GH deficiency diagnosis after the introduction of the new recombinant hGH standard 98/574 (1 mg = 3 IU), which replaced the old hGH standard 80/505 with lower activity (1 mg = 2.6 IU). Therefore, most of the GH stimulation test cutoffs currently used in Europe range from 6 to 8 ng/ml [21]. However, due to insufficient data of past medical history, it is difficult to determine the reason of impaired growth before the onset of NS. All available height and weight measurements were analyzed by commercially available software GrowthXP (version 2.6), which indeed showed poor linear growth already during the first year of life. This indicates that the patient requires further follow up by pediatric endocrinologist and nephrologist.

Conclusions

Clinicians should be aware of a risk for developing hypothyroidism and consider thyroid function testing during the treatment of children with NS especially for those on long term prednisolone treatment with severe impairment of linear growth. A relation between remission phase of NS and normalization of thyroid function and normalization of growth rate confirms the transient hypothyroidism origin and requirement for frequent thyroid function testing in such patients. Prospective observational studies are required to determine the precise etiology and pathogenesis of this potentially treatable and transient thyroid dysfunction.

References

1. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *Lancet*. 2018;392(10141):61–74.
2. Saffari F, Ahadi S, Dalirani R, Esfandiar N, Yazdi Z, Arad B. Thyroid Dysfunction in Children with Idiopathic Nephrotic Syndrome Attending a Paediatric Hospital in Qazvin, Iran. *Sultan Qaboos Univ Med J*. 2020;20(4):e332–e338. doi: 10.18295/squmj.2020.20.04.009
3. Leung AM, Brent GA. The Influence of Thyroid Hormone on Growth Hormone Secretion and Action. In: Cohen L, ed. *Growth Hormone Deficiency*. Springer, Cham; 2016:29–46. https://doi.org/10.1007/978-3-319-28038-7_4
4. Hajizadeh N, Marashi SM, Nabavizadeh B, Elhami E, Mohammadi T, Nobandegani NM, et al. Examine of thyroid function in pediatric nephrotic syndrome: Tehran-Iran. *Int J Pediatr*. 2015;3:59–65. https://doi.org/10.22038/IJP.2015.4051
5. Hunter I, Greene SA, MacDonald TM, Morris AD. Prevalence and aetiology of hypothyroidism in the young. *Archives of Disease in Childhood*. 2000;83(3):207–210. doi: 10.1136/adc.83.3.207
6. Brooks MJ, Post EM. Acquired hypothyroidism due to iodine deficiency in an American child. *J Pediatr Endocrinol Metab*. 2014;27(11-12):1233–1235. doi: 10.1515/jpem-2014-0226
7. Vigone MC, Capalbo D, Weber G, Salerno M. Mild Hypothyroidism in Childhood: Who, When, and How Should Be Treated? *J Endocr Soc*. 2018;2(9):1024–1039. doi: 10.1210/js.2017-00471
8. Niranjan U, Wright NP. Should we treat subclinical hypothyroidism in obese children? *BMJ*. 2016;352:i941. doi:10.1136/bmj.i941
9. Dagan A, Cleper R, Krause I, Blumenthal D, Davidovits M. Hypothyroidism in children with steroid-resistant nephrotic syndrome. *Nephrol Dial Transplant*. 2012;27(6):2171–2175. doi:10.1093/ndt/gfr665
10. Solarin A, Dada A, Akinyosoye G, Oladimeji A, Akinola I, Njokanma F. POS-463 Subclinical hypothyroidism in children with nephrotic syndrome attending Lagos State University Teaching Hospital, Ikeja. *Kidney International Reports*. 2022;7(2):S206. https://doi.org/10.1016/j.ekir.2022.01.493
11. Chandurkar V, Shik J, Randell E. Exacerbation of underlying hypothyroidism caused by proteinuria and induction of urinary thyroxine loss: Case report and subsequent investigation. *Endocr Pract*. 2008;14(1):97–103. doi:10.4158/EP.14.1.97
12. Burch HB. Drug effects on the thyroid. *N Engl J Med*. 2019;381(8):749–761. doi:10.1056/NEJMra1901214
13. Jung SH, Lee JE, Chung WY. Changes in the thyroid hormone profiles in children with nephrotic syndrome. *Korean J Pediatr*. 2019;62(3):85–89. doi:10.3345/kjp.2018.06891
14. Ito S, Kano K, Ando T, Ichimura T. Thyroid function in children with nephrotic syndrome. *Pediatr Nephrol*. 1994;8(4):412–415. doi:10.1007/BF00856516
15. Di Mario F, Pofi R, Gigante A, Rivoli L, Rosato E, Isidori AM, et al. Hypothyroidism and nephrotic syndrome: Why, when and how to treat. *Curr Vasc Pharmacol*. 2017;15(5):398–403. https://doi.or g/10.2174/1570161115999170207114706
16. Marimuthu V, Krishnamurthy S, Rajappa M. Non-Autoimmune Subclinical and Overt Hypothyroidism in Idiopathic Steroid-resistant Nephrotic Syndrome in Children. *Indian Pediatr*. 2017;54(11):925–929. doi: 10.1007/s13312-017-1183-2
17. Rapa A, Monzani A, Moia S, Vivenza D, Bellone S, Petri A, et al. Subclinical hypothyroidism in children and adolescents: A wide range of clinical, biochemical, and genetic factors involved. *J Clin Endocrinol Metab*. 2009;94(7):2414–2420. https:// doi.org/10.1210/jc.2009-0375

18. den Hollander JG, Wulkan RW, Mantel MJ, Berghout A. Correlation between severity of thyroid dysfunction and renal function. *Clin Endocrinol (Oxf)*. 2005;62(4):423–427. https://doi. org/10.1111/j.1365-2265.2005.02236.x
19. Mohan KR, Kanitkar M. Growth in Children with Steroid Sensitive Nephrotic Syndrome. *Med J Armed Forces India*. 2009 Jan;65(1):4–6. doi: 10.1016/S0377-1237(09)80043-9.
20. Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, Rossi WC, Feudtner C, Murad MH. Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. *Horm Res Paediatr*. 2016;86(6):361–397. doi: 10.1159/000452150
21. Binder G, Reinehr T, Ibáñez L, et al. GHD Diagnostics in Europe and the US: An Audit of National Guidelines and Practice. *Horm Res Paediatr*. 2019;92(3):150–156. doi:10.1159/000503783