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Serum Neudesin Levels in Patients with Congenital Hypothyroidism

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What is already known on this topic?

Neudesin is a newly discovered protein; mainly secreted from adipose tissue and brain, which plays a role as a neurotrophic factor in the brain and as a negative regulator of energy expenditure. Neurodevelopmental delay and cognitive dysfunction are common features in cases with congenital hypothyroidism (CH) without treatment.

What this study adds?

This is the first study investigating the relationship of neudesin with CH. The infant group with CH had similar baseline neudesin levels to infants without CH. However, after one month of thyroxine replacement the levels of neudesin were significantly higher than at baseline in babies with CH.

Abstract

Objective: Neudesin is a newly discovered protein mainly secreted from adipose tissue and the brain. It plays a role as a neurotrophic factor in the brain and a negative regulator of energy expenditure. Neurodevelopmental delay and cognitive dysfunction are common features in cases with congenital hypothyroidism (CH) without treatment. Given the role of neudesin in brain development and its contribution to the survival of mature neurons, the relationship between neudesin and thyroid hormone was evaluated in babies diagnosed with CH.

Methods: Babies aged between 2-4 weeks and diagnosed with CH and healthy controls of similar age were included. All patients were evaluated for thyroid hormones and plasma neudesin levels. The basal neudesin levels between the patient and control groups and the patients' neudesin levels before and after l-thyroxine treatment were compared.

Results: Fifty-two babies [32 with CH, 14 (44%) female, aged 19 ± 7 days and 20 healthy controls, 7 (35%) female, aged 22 ± 8 days] were included. There was no significant difference in baseline neudesin between the CH and control groups (6.77 ± 6.41 vs. 7.93 ± 7.04 ng/mL, respectively; p = 0.552). However, neudesin levels increased significantly following one month of therapy in the CH group [median: 3.93 (minimum: 0.31, maximum: 30.06) vs. median: 6.15 (minimum: 2.17, maximum: 70.05) ng/mL, p = 0.019].

Conclusion: Although there was no difference in baseline neudesin levels between the patient and control groups, neudesin levels increased after short-term treatment. Larger prospective studies are needed to understand the pathophysiological role of neudesin in untreated and treated early CH.

Keywords: Congenital hypothyroidism, neudesin, levothyroxine sodium

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Introduction

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency at birth and occurs as a result of inadequate development or function of the thyroid gland (primary CH) or inadequate pituitary stimulation of the normal thyroid gland (central CH) (1). CH has an incidence of 1:2000 to 1:4000 worldwide (2,3,4). CH is one of the common preventable causes of intellectual impairment if left untreated, but the introduction of screening programs has assisted in the early detection and treatment of CH (5). The thyroid gland produces and secretes thyroid hormones, thyroxine (T4) and triiodothyronine (T3), which are necessary for growth, neurodevelopment, and normal energy metabolism. Thyroid hormones control the development of the central nervous system specifically by affecting myelination, synapsis development, and neuronal differentiation in the prenatal and neonatal periods but remain critical for brain development until around three years of age when this process is largely completed (6,7,8).

Neudesin [neuron-derived neurotrophic factor (NENF)] is a secreted neuronal protein of 21 kDa and 171 amino acids (9). The fundamental structure of neudesin exhibits a heme/steroid binding domain that resembles that of cytochrome b5, and it is categorized as a membrane-associated progesterone receptor (MAPR) (10). NENF is highly expressed in neurons at embryonic stages, particularly in the brain and spinal cord (9). Neudesin expression has been observed during embryonic brain cortical formation in the pre-plate region, in which post-mitotic neurons exist, but not in the regions of precursors that proliferate and migrate (11). Neudesin improves the survival of mature neurons and the proliferation and differentiation of neural precursors into a neuronal lineage (11). Moreover, it has also been shown that neudesin is a negative regulator of energy expenditure (12).

As neudesin and thyroid hormones have similar targets (brain development, energy expenditure), the primary focus of the present study was to examine the association between hypothyroidism and serum neudesin levels in mature newborns referred to the hospital with thyroid dysfunction or clinical suspicion and diagnosed with CH.

Methods

Patients

Newborns who were found to have elevated thyroid stimulating hormone (TSH) in the screening program for CH and who presented to our pediatric endocrinology outpatient clinic were included in the study. Venous blood samples of neonates were obtained at the first visit to confirm the CH diagnosis. In addition, blood samples were centrifuged at 2500 rpm for 10 minutes (Nüve NF 1200 was used as a cooled centrifuge), and obtained serum samples were stored at -80 °C for the study of neudesin levels. Neonates whose serum thyroid function tests (TFTs) were consistent with CH (TSH > 20 IU/mL with low fT4 levels) were included in the patient group. In comparison, neonates with normal serum TFTs (TSH < 6 IU/mL and fT4 levels in the normal range) were included in the control group (1). Children with anatomical anomalies, small for gestational age, and premature children were excluded.

All patients' length standard deviation score (SDS), weight SDS, body mass index (BMI) SDS, head circumference SDS, gestational age, chronological age, gender, and mother's thyroid illness history were recorded in patient records. We also assessed the levels of anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobulin (anti-TG), thyroglobulin, and urinary iodine in the patient group.

Following the initial examination, L-T4 treatment at 10-15 mcg/kg/day was started for CH patients immediately. Initial L-T4 dosage was adjusted on the fifteenth day of treatment based on clinical and biochemical status to preserve blood fT4 and TSH levels within the normal range. The etiology of CH was also investigated by thyroid ultrasonography. After the first month of the visit following L-T4 administration, fT4, and TSH levels were analyzed. In addition, second serum samples were collected from babies attending clinic and stored to assess the effect of L-T4 therapy on serum neudesin levels in CH patients.

Informed consent was obtained from the families of the participants, and the study protocol was approved by the Ethics Committee of Bezmialem Vakıf University (decision no: 17/7, date: 21.09.2022) and supported by the scientific research project department of Bezmialem Vakıf University (project number: 2021220).

Hormone Assays

Serum levels of TSH, fT3, fT4, anti-TG, TG, and anti-TPO were determined at the Bezmialem University Hospital, İstanbul, Türkiye, by chemiluminescent enzyme immunometric assays using commercial kits (procured from Siemens Medical Atellica Solutions Diagnostics, USA). The reference intervals for our study were 13.02 to 25.86 pmol/L (1.02-2.01 ng/dL) for fT4, 4.3 to 8 pmol/L for fT3, and 0.420 to 7.55 uIU/mL for TSH (13). Spot urinary iodine was detected by inductively coupled plasma mass spectrometry (ICP-MS) (ICP-MS; Agilent 770). Serum neudesin levels were measured with "Human Neudesin, NENF Elisa Kit (BT-LAB E4258hu)" (Shanghai Korain Biotech (Head office, Shanghai, China) 1008, 228 Ningguo Rd 200090, Yangpu Dist, Shanghai, China).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 23 (IBM Inc., Armonk, NY, USA). Variables were expressed as mean ± standard deviation, whereas especially neudesin which was non-normally distributed was also presented as median (minimum, maximum). The baseline data of the control and patient groups were evaluated with the Mann-Whitney U test. In contrast, the pre- and post-treatment data in the patient group were analyzed using the Wilcoxon, non-parametric test. Spearman's bivariate correlation analysis method was used to evaluate the relationship between BMI SDS and neudesin.

Results

In total 52 babies were recruited to the study. Of these 32 (61.5%) were diagnosed with CH based on initial serum TFT results while 20 (38.5%) had normal TFTs on formal venous testing. However, at the end of the first month of treatment, 6 of 32 patients with CH did not visit the clinic. Therefore, their control blood could not be obtained. Baseline anthropometric measurements, laboratory results, and comparison of the patient and control groups are shown in Table 1. Patients with CH who were treated with L-T4 and the control group were compared, and the two groups did not differ significantly concerning anthropometric measurements (height SDS, weight SDS, head circumference SDS). The statistical comparison of fT4, fT3, TSH, TG, urinary iodine levels, and neudesin levels of the CH and control groups at admission are summarized in Table 1. All patients in the control group had venous TSH levels below 6 mU/L while the patient group had elevated TSH (2.47 ± 0.74 mU/L vs. 280.99 ± 297.37 mU/L, respectively; $p < 0.001$). Similarly, The fT4 levels in patient and control groups were significantly different (6.31 ± 2.64 pmol/L vs. 14.99 ± 2.03 pmol/L, respectively; $p < 0.001$). Thyroid ultrasonography was performed in CH patients. Two patients had goiter, three had agenesis, and one had hemi-agenesis. The thyroid ultrasound of the remaining patients (26/32) was normal. In addition, iodine deficiency was found in 4 patients, iodine excess in 5 patients, and anti-thyroid peroxidase positivity in 2 patients. Baseline neudesin levels did not differ between the CH and control groups (6.77 ± 6.41 vs. 7.93 ± 7.04 ng/mL, respectively; $p = 0.552$).

At the end of one month of L-T4 treatment, neudesin levels were remeasured in babies diagnosed with CH (Table 2). Their neudesin levels increased significantly following one month of treatment [median: 3.93 (minimum: 0.31, maximum: 30.06) vs. median: 6.15 (minimum: 2.17, maximum: 70.05) ng/mL; $p = 0.019$] after 30 days of L-T4 treatment in the CH group, as expected, there was also an increase in fT4 and a decrease in TSH. The effect of L-T4 treatment on thyroid hormones and serum neudesin levels is shown in Table 2.

No correlation was found between serum neudesin levels and BMI SDS in bivariate correlation analysis ($r = 0.245$, $p = 0.172$).

Table 1. Baseline data of 52 newborns (patients group vs. control group)

Variables	Patients (n = 32)	Control group (n = 20)	p value
Gender M/F	18/14	13/7	0.371
Age (day)	19 ± 7 (7-30)	22 ± 8 (14-30)	0.136
Length SDS	-0.34 ± 0.72	-0.51 ± 0.75	0.26
Weight SDS	-0.041 ± 0.77	-0.35 ± 1.1	0.24
Body mass index (kg/m^2)	14.18 ± 1.56	14.42 ± 1.90	0.418
Head circumference SDS	0.043 ± 0.80	-0.27 ± 0.77	0.16
Mother's thyroid disorder history	7/32 (21%)	1/20 (0.5%)	**< 0.001**
fT3 (pmol/L)	3.14 ± 2.01	6.06 ± 0.86	**< 0.001**
fT4 (pmol/L)	6.31 ± 2.64	14.99 ± 2.03	**< 0.001**
TSH (mU/L)	280.99 ± 297.37	2.47 ± 0.74	**< 0.001**
Thyroglobulin (ng/mL)	1482.68 ± 1351.97	67.74 ± 39.90	**0.002**
Urinary iodine (mcg/L)	400.83 ± 334.23	173.11 ± 96.73	**< 0.001**
Neudesin level* (ng/mL)	6.77 ± 6.41	7.93 ± 7.04	0.552
Thyroid USG	Agenesis: 3 Hemi-agenesis: 1 Goiter: 2 Normal: 26		

*Baseline neudesin levels.

M: male, F: female, fT3: free triiodothyronine, fT4: free thyroxine, TSH: thyroid stimulating hormone, Tg: thyroglobulin, USG: ultrasonography, SDS: standard deviation score

Table 2. Effect of levothyroxine sodium treatment on anthropometric measures, thyroid hormone, and neudesin levels

	Patients before treatment	Patients after treatment	p
Length SDS	-0.03 ± 0.72	-0.15 ± 0.66	0.41
Weight SDS	-0.42 ± 0.77	-0.01 ± 0.51	0.76
BMI	14.23 ± 1.49	15.76 ± 1.32	**< 0.001**
BMI SDS	-0.13 ± 0.91	0.41 ± 0.62	**< 0.001**
Head circumference SDS	-0.43 ± 0.80	-0.18 ± 0.75	0.15
fT4 (pmol/L)	6.31 ± 2.64	20.92 ± 3.97	**< 0.001**
TSH (mU/L)	280.99 ± 297.37 170.23 (32.93, 1100)	4.89 ± 16.07 1.52 (0.08, 24.12)	**< 0.001**
Neudesin level* (ng/mL)	6.46 ± 6.63 3.93 (0.31, 30.06)	12.85 ± 18.74 6.15 (2.17, 70.05)	**0.019**

*The second blood sample obtained only in 26 of 32 children.
Non-normally distributed parameters were also presented as median (minimum, maximum).
fT4: free thyroxine, TSH: thyroid stimulating hormone, BMI: body mass index, SDS: standard deviation score

Discussion

Neudesin is a MAPR protein family member. It has been previously demonstrated that neudesin appears to be involved in energy metabolism, neural development and function, and tumorigenesis (12). Neudesin is primarily expressed in neurons. Moreover, neudesin exhibits significant neurotrophic activity in primary cultured neurons but not mitogenic activity in primary cultured astrocytes, indicating that it is a neurotrophic factor (9,12). Neudesin is also expressed in neural precursor cells before the appearance of neurons in mice, indicating its potential role in neural development (11). Neuronal differentiation may be promoted by neudesin, mediated through activation of the protein kinase A and PI3K pathways in cultured neural precursor cells. Neural cell proliferation may also be promoted by neudesin in the developmental process (11). It is well established that thyroid hormones are necessary for growth and for neurodevelopment (8). Moreover, although no molecular studies have demonstrated a relationship between thyroid hormones and neudesin, a few studies have demonstrated the relationship between thyroid hormones and other neurotrophic factors. Yajima et al. (14) reported that a lack of thyroid hormones induced a developmental delay in primary hippocampal neurons, likely caused by decreased brain-derived neurotrophic factor *(BDNF)* gene expression. Furthermore, *in vivo* experiments have shown that thyroid hormone administration increased BDNF expression in the brain tissue of young adult rats (15). In another study, Lasley and Gilbert (16) showed that BDNF expression decreased in adult rats with hypothyroidism, but this change was not detected in the neonatal period in the same study. As both thyroid hormones and neudesin affect neurodevelopment, we hypothesized that thyroid hormones might have a relationship with neudesin. Our results demonstrated no difference in levels of neudesin in babies with CH before replacement L-T4 was started and non-CH peers but there was a significant short-term increase in neudesin levels after L-T4 was started in patients with CH. However, this study was not designed or able to explain the pathophysiological mechanisms of this relationship.

Activating the parasympathetic system leads to energy expenditure in white adipose tissue and increased heat in brown adipose tissue. A study in neudesin knock-out mice has shown that the parasympathetic nervous system is over-activated in these animals. Based on this, it has been suggested that neudesin has a negative regulatory role in energy balance (17). Neudesin's role in different metabolic disorders, such as obesity, polycystic ovary syndrome, and type 2 diabetes mellitus have been investigated (18,19,20,21). Çelikkol et al. (21) reported a negative correlation between neudesin levels and BMI Z-score. Kratochvilova et al. (18) have also reported that neudesin levels change with chronic weight reduction or during prolonged fasting. Moreover, Polkowska et al. (20) reported that neudesin levels were higher in diabetic patients compared to the control group, again supporting a role in energy homeostasis for neudesin. In light of these data, neudesin levels are expected to decrease with increasing BMI. However, in our study, although there was a small increase in BMI SDS levels, neudesin levels also increased, and no correlation was detected between BMI SDS and neudesin. This conflicting finding is difficult to explain but may be due to differences in study populations. Previously, it has been shown that TRH/TSH is regulated by thyroid hormone feedback, and there is also central modulation by nutritional signals, such as leptin, and peptides regulating appetite (22). The rapid recovery from slow metabolism with the normalization of thyroid hormones can result in increased energy consumption. One mechanism of adaptation to this rapid change in metabolism may be an increase in neudesin levels. Experimental studies are

needed to evaluate the pathophysiological relationship and mechanisms between neudesin and thyroid hormones in terms of energy homeostasis.

Although there are a few studies into neudesin levels in metabolic disorders, to the best of our knowledge, there is no clinical study investigating neudesin levels in patients with CH or other neurodevelopmental diseases. Therefore, the levels of neudesin in children with or without neurological involvement in hypothyroidism are not yet known. The participants in our study were those with no neurological complaints, regular neurological examinations, and early hypothyroidism diagnoses as a result of the screening program. Our patient group was detected and treated relatively early. Investigating the relationship between neurological development and/or pathology and neudesin levels will require much more investigation.

Study Limitations

The most important limitation of our study was that, due to, second blood samples could not be taken from the group in which hypothyroidism was not detected because of ethical reasons. Therefore, we could not observe the change in the neudesin levels in the healthy control group or compare it with the CH group. The second limitation was the low number of patients.

Conclusion

In conclusion, although there was no difference in baseline neudesin levels between the CH patient and control groups, an increase in neudesin levels was observed in babies with CH after one month of replacement L-T4 treatment at 10-15 mcg/kg/day. However, more extensive clinical and/or experimental studies are needed to investigate the pathophysiological implications this finding in CH or the recovery process.

Ethics

Ethics Committee Approval: The study was approved by the Bezmialem Vakıf University of Ethics Committee (decision no: 17/7, date: 21.09.2022).

Informed Consent: Informed consent was obtained from the families of the participants.

Footnotes

Authorship Contributions

Concept: İlker Tolga Özgen, Design: İlker Tolga Özgen, Data Collection or Processing: Semra Bahar, İlker Tolga Özgen, Yaşar Cesur, Emel Hatun Aytaç Kaplan, Zümrüt Kocabey Sütçü, Analysis or Interpretation: İlker Tolga Özgen, Yaşar Cesur, Caner Yıldız, Ömer Faruk Özer, Literature Search: Semra Bahar, İlker Tolga Özgen, Writing: Semra Bahar, İlker Tolga Özgen.

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