

Evaluation of Autonomic Nervous System Dysfunction in Hypothyroid Children

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ABSTRACT:

Background: This study explores autonomic nervous system (ANS) dysfunction in children with hypothyroidism, a condition known to disrupt metabolic and neurological regulation. While ANS abnormalities are well-documented in adults with hypothyroidism, pediatric data remain limited. Thyroid hormone deficiency may impair sympathetic and parasympathetic activity, detectable through heart rate variability (HRV) and cardiovascular reflex tests. Early identification of ANS dysfunction is crucial for timely intervention, as it can affect quality of life and development. **Aim of the study:** This study aims to assess autonomic function in children diagnosed with hypothyroidism systematically. **Methods:** This hospital-based, cross-sectional observational study was conducted over 15h months in the Physiology Departments of Prime Medical College and Hospital in Bangladesh. It included 100 children aged 5–16 years diagnosed with primary hypothyroidism, either newly or on levothyroxine ≤ 6 months. Using validated non-invasive methods, participants underwent thyroid and autonomic function testing (AFT). AFT included heart rate variability, deep breathing, Valsalva maneuver, orthostatic, handgrip, and cold pressor tests. Data were collected via structured questionnaires and laboratory evaluations. Statistical analysis was done using SPSS v26.0, with significance set at $p < 0.05$ to assess correlations between TSH and autonomic parameters. **Results:** Among 100 children with primary hypothyroidism (mean age 10.8 ± 2.9 years; 59% female), most were from low or middle socioeconomic backgrounds. Thyroid profiles showed elevated TSH (14.7 ± 5.3 mIU/L) with reduced fT3 and fT4, and 34% had positive anti-TPO antibodies. Autonomic testing revealed reduced HRV (32.1 ± 10.4 ms), Valsalva, and E: I ratio, indicating parasympathetic dysfunction. Sympathetic responses were also altered. Overall, 28% had parasympathetic, 22% sympathetic, and 33% combined dysfunction; only 17% showed normal function. Significant negative correlations were observed between TSH levels and autonomic parameters, suggesting that increasing hypothyroidism severity is associated with greater autonomic dysfunction in affected children. **Conclusion:** Autonomic dysfunction is common in children with hypothyroidism, especially with elevated TSH levels, affecting both sympathetic and parasympathetic systems. Early screening for autonomic abnormalities may aid in detecting subclinical involvement and optimizing management, highlighting the need for a comprehensive approach in pediatric hypothyroid care.

Keywords: Hypothyroidism, Autonomic Nervous System, Thyroid Hormones and Autonomic Function Tests

INTRODUCTION:

Thyroid hormones are pivotal in regulating growth, development, and metabolism, particularly during childhood. These hormones thyroxine (T4) and triiodothyronine (T3) are crucial for normal neurological development and physiological homeostasis, including

the proper functioning of the autonomic nervous system (ANS) [1]. Hypothyroidism, characterized by deficient thyroid hormone production, can thus have widespread systemic effects, with increasing evidence highlighting its influence on autonomic regulation. The autonomic nervous system, comprising the sympathetic and

parasympathetic divisions, governs involuntary physiological functions such as heart rate, blood pressure, thermoregulation, and gastrointestinal motility. Autonomic dysfunction, or dysautonomia, can manifest as a wide range of clinical symptoms, including fatigue, orthostatic intolerance, gastrointestinal disturbances, and cardiovascular irregularities [2]. While adult hypothyroid patients have been extensively studied in this regard, there is a growing need to investigate ANS involvement in pediatric hypothyroidism, given the developmental vulnerability of children and the lifelong implications of untreated autonomic abnormalities. In adults, hypothyroidism has been associated with impaired sympathetic and parasympathetic responses, often evident through altered heart rate variability (HRV), reduced baroreflex sensitivity, and abnormal blood pressure regulation [3]. These abnormalities are primarily due to the effects of thyroid hormone deficiency on cardiovascular and neurological tissues, including reduced beta-adrenergic receptor density and impaired neurotransmitter activity [4]. In children, however, research remains limited, although emerging studies suggest similar patterns of dysfunction. Early detection of ANS impairment in hypothyroid children is crucial, as autonomic abnormalities may precede overt clinical manifestations and can influence quality of life, academic performance, and psychosocial development. Several methods are employed to assess autonomic function, including HRV analysis, blood pressure response to postural changes (tilt-table testing), and sympathetic skin response (SSR). HRV, in particular, is a non-invasive and widely accepted tool to evaluate autonomic balance, reflecting sympathetic and parasympathetic influences on cardiac rhythm [5]. Reduced HRV has been documented in children with various endocrine disorders, including diabetes and obesity, and is increasingly recognized in pediatric hypothyroidism as well [6]. Congenital or acquired hypothyroidism in children can stem from a variety of etiologies, such as thyroid dysgenesis, dysmorphogenesis, autoimmune thyroiditis, or iodine deficiency [7]. Regardless of the cause, delayed diagnosis or suboptimal management may predispose children to autonomic imbalances, which can contribute to comorbidities like attention deficits, emotional lability, and reduced physical endurance. Furthermore, children may not always articulate their symptoms clearly, leading to under-recognition of autonomic symptoms by caregivers and clinicians. Studies in pediatric populations have highlighted subtle autonomic changes in hypothyroid children, including blunted heart rate response to exercise and altered diurnal variation in HRV parameters [8]. These findings warrant further investigation, particularly in resource-limited settings where thyroid screening is not universally implemented,

and subclinical hypothyroidism may remain undiagnosed. Given these considerations, evaluating autonomic nervous system dysfunction in hypothyroid children represents an important step toward comprehensive pediatric endocrine care. This study aims to assess autonomic function in children diagnosed with hypothyroidism systematically.

MATERIALS AND METHODS:

This was a hospital-based, cross-sectional observational study conducted in the Physiology Departments of Prime Medical College and Hospital in Bangladesh over a period of 15th months (from 2.124 to 2.4.25). The study included 100 children aged 5–16 years who were diagnosed with primary hypothyroidism. The diagnosis was based on clinical features suggestive of hypothyroidism and confirmed by elevated serum thyroid-stimulating hormone (TSH) levels with low free T3 (fT3) and free T4 (fT4) concentrations. A total of 100 participants were selected based on convenience sampling, ensuring adequate power to detect meaningful differences in autonomic parameters across severity levels of hypothyroidism, considering resource and time constraints.

Inclusion Criteria:

- Children aged 5–16 years with a confirmed diagnosis of primary hypothyroidism.
- Either newly diagnosed or on levothyroxine therapy for ≤ 6 months.

Exclusion Criteria:

- Children with known congenital heart disease, diabetes mellitus, neurological disorders, or chronic systemic illnesses.
- Use of medications affecting autonomic function (e.g., beta-blockers, anticholinergics).
- Secondary or central hypothyroidism.

Data Collection:

Data collection involved three major components:

- Demographic and Clinical Profile:
- A structured questionnaire recorded age, sex, anthropometric measurements (weight, height, BMI), socioeconomic status (using modified Kuppuswamy's scale), and residence (urban/rural).
- Thyroid Function Tests and Autoimmunity:
- Blood samples were collected after overnight fasting to measure:
 - Serum TSH, free T3, and free T4 (by chemiluminescence immunoassay).
 - Anti-thyroid peroxidase (anti-TPO) antibodies for autoimmune thyroiditis screening.

autonomic function parameters. A p-value of <0.05 was considered statistically significant.

RESULTS:

The demographic data presented in Table 1 show that the study included 100 hypothyroid children with a mean age of 10.8 ± 2.9 years. Females constituted a higher proportion (59%) than males (41%). The mean weight, height, and BMI were 28.6 ± 6.4 kg, 130.2 ± 11.5 cm, and 16.8 ± 2.4 kg/m², respectively. Most participants belonged to low (48%) or middle (44%) socioeconomic status, with a nearly even distribution between urban (58%) and rural (42%) residences. Table 2 details thyroid function, with an elevated mean TSH level of 14.7 ± 5.3 mIU/L and reduced free T4 (0.63 ± 0.18 ng/dL) and free T3 (1.9 ± 0.6 pg/mL), consistent with hypothyroidism. Anti-TPO antibodies were positive in 34% of cases, suggesting autoimmune etiology in a significant subset. Autonomic function test results in Table 3 indicate abnormal autonomic regulation in many patients, with a reduced mean HRV (SDNN) of 32.1 ± 10.4 ms, suggesting impaired parasympathetic activity. The Valsalva ratio (1.16 ± 0.17) and deep breathing E: I ratio (1.11 ± 0.10) were also below normal limits, reinforcing the presence of parasympathetic dysfunction. Sympathetic tests revealed abnormal Δ SBP on standing (-12.2 ± 4.6 mmHg), elevated DBP after handgrip (12.4 ± 4.2 mmHg), and a cold pressor response of 13.6 ± 5.3 mmHg. Table 4 categorizes these findings, showing that 28% had parasympathetic dysfunction, 22% had sympathetic dysfunction, and 33% exhibited combined autonomic dysfunction, while only 17% had normal autonomic function. Correlation analysis in Table 5 revealed significant negative associations between TSH levels and autonomic parameters. Notably, HRV (SDNN) correlated with TSH at $r = -0.46$ ($p < 0.01$), indicating greater autonomic dysfunction with higher TSH levels. Similar negative correlations were seen for the Valsalva ratio ($r = -0.38$, $p = 0.002$), E: I ratio ($r = -0.35$, $p = 0.005$), Δ BP after standing ($r = -0.32$, $p = 0.009$), and Δ DBP after handgrip ($r = -0.29$, $p = 0.014$), supporting the link between hypothyroidism severity and impaired autonomic regulation.

Autonomic Function Testing (AFT):

- Performed under standardized laboratory conditions (quiet, temperature-controlled room, no caffeine or heavy meals 2 hours before testing) using validated non-invasive procedures. The following tests were conducted:

Parasympathetic Function Tests:

- **Heart Rate Variability (HRV)** – measured using SDNN (Standard Deviation of NN intervals) from a 5-minute resting ECG recording.
- **Deep Breathing Test (E: I Ratio)** – the ratio of maximum expiratory to minimum inspiratory heart rate during six cycles of deep breathing.
- **Valsalva Maneuver** – the Valsalva ratio calculated from ECG changes during and after forced expiration against resistance.

Sympathetic Function Tests:

- **Orthostatic Test (Δ SBP on Standing):** Change in systolic blood pressure 3 minutes after standing from a supine position.
- **Isometric Handgrip Test (Δ DBP):** Increase diastolic BP after maintaining 30% maximum voluntary contraction for 3 minutes.
- **Cold Pressor Test:** The blood pressure rises after immersing the hand in cold water ($4-6^{\circ}\text{C}$) for 1 minute.

All measurements were done using a digital automated ECG and BP monitoring system under the supervision of trained personnel.

Classification of Autonomic Dysfunction:

Autonomic dysfunction was categorized as follows:

- **Parasympathetic Dysfunction:** Abnormalities in ≥ 2 parasympathetic tests.
- **Sympathetic Dysfunction:** Abnormalities in ≥ 2 sympathetic tests.
- **Combined Dysfunction:** Abnormalities in ≥ 1 test from both categories.
- **Normal Autonomic Function:** All test results within reference ranges for age.

Statistical Analysis:

All data were entered into Microsoft Excel and analyzed using SPSS version 26.0 (IBM Corp., USA). Descriptive statistics were used to summarize demographic, clinical, and laboratory data. Quantitative variables were expressed as means $\pm$ standard deviations (SD), and categorical variables as frequencies and percentages. Pearson's correlation coefficient (r) was used to assess the relationship between serum TSH levels and

Table 1: Demographic and Anthropometric Characteristics of Hypothyroid Children (n = 100)

Parameter	Frequency (n)	Percentage (%)
	Mean ± SD	
Age (years)	10.8 ± 2.9	
Sex		
Male	41	41.00
Female	59	59.00
Weight (kg)	28.6 ± 6.4	
Height (cm)	130.2 ± 11.5	
BMI (kg/m²)	16.8 ± 2.4	
Socioeconomic Status		
Low	48	48.00
Middle	44	44.00
High	8	8.00
Residence		
Urban	58	58.00
Rural	42	42.00

Table 2: Thyroid Hormone Profile and Anti-TPO Antibody Status in Hypothyroid Children

Parameter	Frequency (n)	Percentage (%)
	Mean $\pm$ SD	
TSH (mIU/L)	14.7 $\pm$ 5.3	
Free T4 (ng/dL)	0.63 $\pm$ 0.18	
Free T3 (pg/mL)	1.9 $\pm$ 0.6	
Anti-TPO Antibodies		
Positive	34	34.00
Negative	66	66.00

Table 3: Autonomic Function Test Results in Hypothyroid Children (Mean $\pm$ SD)

Test	Mean $\pm$ SD
Resting Heart Rate (bpm)	88.4 $\pm$ 12.1
Resting Systolic BP (mmHg)	106.7 $\pm$ 11.3
Resting Diastolic BP (mmHg)	68.9 $\pm$ 8.1
HRV (SDNN)	32.1 $\pm$ 10.4 ms
Valsalva Ratio	1.16 $\pm$ 0.17
Deep Breathing E:I Ratio	1.11 $\pm$ 0.10
BP Response to Standing (Δ SBP)	-12.2 $\pm$ 4.6 mmHg
Handgrip Test (Δ DBP)	12.4 $\pm$ 4.2 mmHg
Cold Pressor Test (Δ BP)	13.6 $\pm$ 5.3 mmHg

Table 4: Distribution of Autonomic Nervous System Dysfunction among Hypothyroid Children

Type of Dysfunction	Frequency (n)	Percentage (%)
Parasympathetic Dysfunction	28	28.00
Sympathetic Dysfunction	22	22.00
Combined Dysfunction	33	33.00
Normal Autonomic Function	17	17.00

Table 5: Correlation between Thyroid Hormone Levels and Autonomic Function Parameters

Autonomic Parameter	Correlation Coefficient (r)	p-value
HRV (SDNN)	-0.46	<0.01
Valsalva Ratio	-0.38	0.002

E:I Ratio (Deep Breathing)	-0.35	0.005
Δ BP after Standing	-0.32	0.009
Δ DBP after Handgrip	-0.29	0.014

DISCUSSION:

This study highlights a significant burden of autonomic nervous system (ANS) dysfunction among children with hypothyroidism. The findings indicate that the ANS's parasympathetic and sympathetic components are adversely affected, with a substantial proportion of participants demonstrating abnormal results in standardized autonomic function tests. These results are consistent with previous literature suggesting that hypothyroidism can lead to multisystemic involvement, including alterations in cardiovascular autonomic regulation. The demographic profile of the study population, with a female preponderance (59%) and a mean age of 10.8 years, aligns with earlier studies indicating a higher incidence of hypothyroidism in females, possibly due to increased susceptibility to autoimmune thyroid diseases in this group [9,10]. The socioeconomic distribution, primarily from low to middle-income backgrounds, may reflect healthcare access disparities and late diagnosis, which could exacerbate complications such as autonomic dysfunction. Thyroid function analysis confirmed overt hypothyroidism, characterized by elevated TSH and reduced free T3 and T4 levels. Anti-thyroid peroxidase (anti-TPO) antibody positivity in 34% of children suggests autoimmune thyroiditis (Hashimoto's thyroiditis) as a common etiology, which is in agreement with global pediatric endocrinology data [11]. The autoimmune basis of hypothyroidism may have implications for systemic immune-mediated alterations affecting neural tissue, including autonomic pathways. The reduced mean heart rate variability (HRV) – as indicated by a low SDNN (standard deviation of NN intervals) – is a hallmark of parasympathetic impairment. HRV is a sensitive marker for cardiac autonomic regulation, and its reduction has been consistently reported in adult and pediatric hypothyroid populations [12]. Similarly, the Valsalva and deep breathing E: I ratios were lower than usual, further supporting parasympathetic dysfunction. These findings suggest that hypothyroidism leads to diminished vagal tone, possibly via altered baroreflex sensitivity and reduced central autonomic drive [13]. Regarding sympathetic function, the abnormal drop in systolic blood pressure on standing and the altered responses in the handgrip and cold pressor tests suggest sympathetic dysregulation. Although the cold pressor and isometric handgrip responses were elevated, such paradoxical findings have been observed in prior

research. They may reflect compensatory mechanisms or altered vascular reactivity secondary to hypothyroidism-induced endothelial dysfunction [14]. The abnormal Δ SBP on standing (-12.2 mmHg) indicates a defective sympathetic response in maintaining vascular tone upon postural change, potentially leading to orthostatic intolerance in some patients [14]. The classification of autonomic dysfunction revealed that nearly one-third (33%) had combined sympathetic and parasympathetic dysfunction, while only 17% exhibited normal autonomic function. This significant prevalence underscores the importance of early detection and monitoring of ANS function in hypothyroid children. Comparable studies have reported variable rates of autonomic involvement. However, the current findings resonate with those of Khandelwal et al. and Bogdan C et al., who documented similar patterns of autonomic impairment in hypothyroid populations [15,16]. Perhaps the most critical finding is the negative correlation between serum TSH levels and several autonomic parameters. The inverse relationship between TSH and HRV ($r = -0.46$), Valsalva ratio ($r = -0.38$), and E: I ratio ($r = -0.35$) strongly suggests that the severity of thyroid hormone deficiency correlates with the extent of autonomic dysfunction. These associations are biologically plausible, as thyroid hormones are known to modulate neurotransmitter levels, sympathetic tone, and catecholamine sensitivity [17]. Moreover, animal studies have shown that hypothyroidism reduces norepinephrine turnover and sympathetic nerve activity, reinforcing this hypothesis [18]. The mechanistic basis for autonomic dysfunction in hypothyroidism may involve multiple factors. Thyroid hormones exert both genomic and non-genomic effects on the cardiovascular and central nervous systems. They influence the expression of beta-adrenergic receptors, modify baroreceptor sensitivity, and regulate neuronal conduction velocities. Hypothyroidism may impair these processes, leading to blunted autonomic responsiveness [19]. Moreover, inflammatory processes associated with autoimmune thyroiditis might further impair autonomic pathways through cytokine-mediated neurotoxicity or autoimmune neuropathy [20]. These findings have important clinical implications. Autonomic dysfunction in children may predispose them to symptoms such as fatigue, dizziness, palpitations, and exercise intolerance, which are often overlooked or attributed

to general hypothyroid symptoms. Early detection of such dysfunctions through non-invasive autonomic testing may aid in risk stratification and monitoring response to thyroxine therapy. Previous research indicates that many of these autonomic changes are partially reversible with adequate hormone replacement, although the recovery timeline may vary [21].

CONCLUSION:

In conclusion, this study provides robust evidence that autonomic nervous system dysfunction is prevalent among children with hypothyroidism, particularly in those with higher TSH levels. Both sympathetic and parasympathetic branches of the ANS are affected, with potential clinical consequences. Routine screening for autonomic function may be warranted in pediatric hypothyroid patients to identify subclinical dysregulation early and to guide comprehensive management strategies.

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