Thyroid function Tests among Children with Interstitial Lung Disease: A Single Center Pilot Study

by

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ABSTRACT

Introduction: Interstitial lung disease (ILD) and thyroid illnesses are common pediatric diseases. However, to date their link is not well-studied.

Aim: To study thyroid hormone levels in children with interstitial lung disease (chILD) and to assess the relationship between thyroid hormone abnormalities and disease severity.

Method: This is a case-control pilot study that was conducted on 25 patients with chILD and 25 healthy controls recruited from Pulmonology clinic, Children's Hospital Ain Shams University during the period from October 2023 to April 2024. History taking and clinical examination, FEV1%, and FVC %, oxygen saturation, chest computed tomography and FT3, FT4 and TSH were done for the patients and control.

Method of Selection: consecutive sample method.

Results: Mean ±SD of weight SDS (-0.68±3.26) and height SDS (-1.6±2.2) were statistically significantly lower in chILD patients compared to controls (1.3±0.69 & 1.17 ±0.81 respectively) ($p < 0.0001$). Symptoms suggestive of thyroid hyperfunction were higher in patients than in controls as weather intolerance (48% vs. 0%) ($p < 0.0001$) and weight loss (32% vs. 0%) ($p = 0.002$). Free T3 levels were normal yet statistically significantly higher in patients (3.379 ± 0.6900 pg/L) compared to controls (2.099 ± 0.4552 pmol/L) ($p < 0.0001$). TSH levels were normal yet not statistically significantly lower in patients (1.880±0.8447) than in controls (2.058 ± 0.4821). Mean ±SD of FEV1 % was 41.00 ± 15.51, FVC % was 46.27 ± 14.92, and MEFF % was 26.30 ± 17.44. Oxygen saturation was 93.00 ± 3.041% at rest and 88.48 ± 3.938% during exercise. No correlation was found between thyroid hormone levels and spirometry values, clinical severity, or oxygen saturation.

Conclusion: Children with chILD may exhibit symptoms of thyroid gland dysfunction in the form of (heat intolerance, cold intolerance, weight loss and weight gain) and have normal thyroid hormone levels. Further research is needed to explore the relation between thyroid hormones and chILD.

Keywords: Interstitial Lung Disease (ILD), Thyroid Dysfunction, Pulmonary Function Tests

Introduction

Background: Children's interstitial lung disease (chILD) is a heterogeneous group of rare and diffuse lung conditions that significantly impact pediatric health. ILD affects the interstitium, airways, alveolar spaces, vascular beds, lymphatic channels, and pleural spaces, and are characterized by considerable morbidity and mortality (Ferraro et al., 2020; Ionescu et al., 2022). The increasing incidence of chILD in recent years likely resulted from better diagnostic tools and the greater awareness of rare pediatric diseases among healthcare providers (Nayir et al., 2023). Thyroid hormones (TH), essential endocrine regulators of metabolic and developmental processes, have been implicated in a wide range of physiological and pathological processes, including those affecting the pulmonary system. Assessing TH in lung diseases has been of riding interest over the last few years (Gloriane et al.,2022).

Despite accumulating evidence in adult populations, the impacts of thyroid function on pediatric lung diseases, particularly chILD, have not been well investigated. The existing literature focuses mainly on adult conditions and shows that there is a scarcity of information on how these dynamics play out in children. Few studies have pointed out possible areas of interest but have not explored the specific applications in children (Oldham et al., 2015). This study aims at filling this gap by exploring the correlation between thyroid hormone levels and the severity of ILD in pediatric populations. By doing so, it could offer basic foundational knowledge that may result in new therapeutic strategies tailored to the specific needs of children with chILD (Breitzig et al., 2018).

Aim of the Study: To study thyroid hormone levels in children with interstitial lung disease (chILD) and to assess the relationship between thyroid hormone abnormalities and disease severity.

Methods:

Ethical considerations:

1.The study was conducted after approval of the protocol by The Research Committee local and The Studies Committee well as the Research Ethics Committee under number: FMASU MS 515/2023

2.An informed written consent was obtained from all study population and it will contain the following: The aim and methods of the study in simple way.

3.The patients have the right to refuse participation or withdraw without affecting medical care at any time without any penalty.

4.Confidentiality of all data and results of all study population was preserved.

5.declaire: there is no conflict of interest or funding for the study and publication.

Sample Size calculation:

Considering that chILD is a rare disease, all available patient fulfilling inclusion criteria during study duration were included in the study.

No formal sample size calculation was performed.

Inclusion criteria: Children diagnosed with interstitial lung diseases.

Age group: 2- 18 years

Exclusion criteria included patients younger than 2 years, those with other lung diseases, suspected syndromes, proven thyroid disorders, or those taking drugs that affect thyroid function. The study also included 25 age and sex matched healthy children serving as controls.

Study Setting and Design

The study was conducted at the Pulmonology clinic, Children's Hospital Ain Shams University. It employed a cross-sectional design over a period of six months from October 2023 to April 2024.

Type of the Study: case - control pilot Study

Study Population

The study population included 25 children aged 2-18 years diagnosed with interstitial lung diseases, with at least three of the following criteria: respiratory symptoms, clinical signs of respiratory insufficiency, hypoxemia or low pulsed oxygen saturation, and diffuse parenchymal lung disease on chest radiography or thoracic CT scan (Nathan et al., 2023).

Study Tools and Data Collection:

All studied patients were subjected to:

1.Full history was collected from patients and their caregivers, including socio-demographic data (age, gender, socioeconomic status, consanguinity of parents), history of symptoms related to interstitial lung diseases (dyspnea, shortness of breath, exercise intolerance, chronic cough), history suggestive of thyroid disorders (weight changes, temperature intolerance, exophthalmos), family history of thyroid disorders or interstitial lung diseases, and history of drug intake.

2.Clinical examination included vital data measurements (respiratory rate, heart rate, and blood pressure), anthropometric measurements (height and its standard deviation score (SDS), weight and its SDS, systemic examination with stress on respiratory examination and thyroid dysfunction (goiter and exophthalmos) and other systemic examination (neurological, cardiac, abdominal), and signs of hypo or hyperthyroidism (goiter, exophthalmos). The chILD severity score was recorded for each subject on presentation as follows:

Grade 0: Asymptomatic

Grade 1: Symptomatic: normal oxygen saturation under all conditions

Grade 2: Symptomatic: normal resting room air saturation, but hypoxemia <90% with exercise or sleep Grade 3: Symptomatic, hypoxemia <90% at rest

Grade 4: Symptomatic, hypoxemia at rest and pulmonary hypertension (Schapiro AH et al., 2022).

3. Spirometry pulmonary function tests (forced expiratory volume in the first second (FEV1%), forced vital capacity (FVC%), maximum expiratory flow (MEFF%)) was done for cooperative children with age above 7 years and obtained values were expressed as percentage of expected for age and sex. Laboratory investigations by collecting a 5 ml blood sample from each patient to measure free T4, free T3, and TSH levels using the available ELISA kits.

4. Computed tomography of the chest for all patients.

Statistical Methods

- The data were collected and statistically analyzed using the latest version of the Statistical Package for the Social Sciences (SPSS).
- Qualitative data was described using number and percent, Quantitative data was described using data and mean, standard deviation for parametric data after testing normality using Shapiro Wallik test. Significance of the obtained results was judged at the (0.05) level.
- For qualitative data, chi-Square test was used for comparison of 2 or more groups,
- For parametric quantitative data, student t-test was used to compare 2 independent groups. The Pearson's correlation was used to determine the strength and direction of a linear relationship between

two normally distributed continuous variables.

Results :

Table (1): Demographic and anthropometric of the studied groups

Parameters		Cases group (N=25)		Control group (N=25)		P
		N	%	N	%	
Age(years)	Mean	9.683		10.50		0.4503
	SD	4.122		3.434		
Sex	Male	12	48	14	56	0.57
	Female	13	52	11	44	
Tanner staging	Stage 1	19	76	17	68	0.5287
	Stage 2	0	0	0	0	
	Stage 3	6	24	8	32	
Weight SDs	Mean	-0.6864		1.307		0.0044
	SD	3.263		0.6976		
Height SDs	Mean	-1.618		1.169		<0.0001
	SD	2.215		0.8114		

This table shows that weight and height were significant lower in cases than control patients.

Table (2): clinical and laboratory finding of thyroid dysfunction of the 2 groups

Parameters		Cases group (N=25)		Control group (N=25)		P
		N	%	N	%	
Symptoms of hyperthyroidism						
Weight loss	Negative	17	68	25	100	0.0020
	Positive	8	32	0	0	
Exophthalmos	Negative	25	100	25	100	-
	Positive	0	0	0	0	
Heat intolerance	Negative	21	84	25	100	0.0371
	Positive	4	16	0	0	
Symptoms of hypothyroidism						
Weight gain	Negative	22	88	25	100	0.0740
	Positive	3	12	0	0	
Cold intolerance	Negative	17	68	25	100	0.0020
	Positive	8	32	0	0	
Thyroid profile						
FT3 (pg./mL)	Mean	3.379		2.099		<0.0001
	SD	0.69		0.4552		
	Min-Max	2.22-4.8		1.24-3.15		
FT4 (ng/dL)	Mean	1.421		1.556		0.2495
	SD	0.4555		0.3561		
	Min-Max	1-3.4		1-2.6		
TSH (mIU/L)	Mean	1.880		2.058		0.3647
	SD	0.8447		0.4821		
	Min-Max	0.03-3.88		1.48-2.99		

This table shows that:

- As regards hyperthyroidism symptoms, the prevalence of heat intolerance and weight loss was significantly higher among chILD cases compared to controls
- the prevalence of weight gain did not show significant difference between the two groups, cold intolerance showed significantly higher prevalence among chILD cases compared to controls.

Table (3): Symptoms and Signs of Interstitial Lung Disease among Cases

Symptoms of ILD		chILD cases (N=25)	
		N	**%**
Dyspnea	Positive	24	96
	Negative	1	4
Exercise intolerance	Positive	23	92
	Negative	2	8
Chronic cough	Positive	16	64
	Negative	9	36
RD staging	1	4	16
	2	15	60
	3	5	20
	4	1	4
ILD staging	0	1	4
	1	12	48
	2	3	12
	3	3	12
	4	6	24

ILD: Interstitial lung disease.

This table shows that:

- The most common symptom among chILD cases was dyspnea (96%), followed by exercise intolerance (92%), then chronic cough (64%).
- The most common RD stage was stage 2 (60%), followed by stage 3 (20%).
- The most common ILD stage was stage 1 (48%), followed by stage 4 (24%), then stage 2 (12%) and stage 3 (12%).

Table (4): Vital Signs and Spirometry Findings among Cases

Vital signs and spirometry findings		**chILD cases (N=25)**
SPO_2 at rest (%)	Mean	93.00
	SD	3.041
	Min-Max	88-99
SPO_2 at exercise (%)	Mean ± SD	88.48
	SD	3.938
	Min-Max	88-93
FEV1 (%)	Mean	41.00
	SD	15.51
	Min-Max	16-83.2
FVC (%)	Mean	46.27
	SD	14.92
	Min-Max	16-90.2
MMEF (%)	Mean	26.30
	SD	17.44
	Min-Max	8-82

FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, MMEF: Maximum mid-expiratory flow, SPO_2: Oxygen saturation.

This table shows that**:**

- The mean SPO_2 at rest was 93.00 ± 3.041%, and during exercise was 88.48 ± 3.938%.
- The mean FEV1 was 41.00 ± 15.51%, FVC was 46.27 ± 14.92%, and MMEF was 26.30 ± 17.44% (of expected according to age, weight and sex)

Table (6): Correlation of Thyroid Function Tests with Other Parameters

Parameters	T3 (pg./mL)		T4 (ng/dL)		TSH (mIU/L)	
	r	p	r	p	r	p
RD staging	-0.22	0.29	-0.037	0.86	0.213	0.307
ILD staging	-0.14	0.504	-0.289	0.161	-0.066	0.754
Radiological changes	-0.05	0.811	-0.051	0.809	-0.226	0.279
SPO_2 at rest (%)	-0.013	0.952	0.267	0.196	-0.077	0.714
SPO_2 at exercise (%)	-0.104	0.619	0.245	0.237	-0.351	0.086
FEV1 (%)	-0.236	0.397	-0.022	0.938	-0.286	0.302
FVC (%)	0.11	0.696	-0.04	0.887	-0.043	0.889
MMEF (%)	-0.126	0.654	-0.151	0.592	-0.476	0.073

FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, ILD: Interstitial lung disease, MMEF: Maximum mid-expiratory flow, RD: Respiratory distress, SPO_2: Oxygen saturation. FT3: free triiodothyronine, FT4: free thyroxine, TSH: Thyroid stimulating hormone, r: correlation coefficient, p: p-value >0.05: Non-significant; p-value <0.05: Significant; p-value< 0.01: Highly significant

This table shows that:

- There was no statistically significant correlation between each of FT3, FT4, TSH and other parameters including: clinical characteristics, vital signs and spirometry findings

Discussion

the impacts of thyroid function on pediatric lung diseases, particularly chILD, have not been well investigated.

Our aim of this study was to assess TH abnormalities in children with interstitial lung disease (chILD) and their relationship to the severity of the disease.

Our result showed that the anthropometric measurements (weight and height) were significantly lower in children with chILD compared to controls, aligning with the chronic nature of chILD that often affects growth and development. Symptoms such as weather intolerance and weight loss were significantly more prevalent among children with chILD. Free T3 levels were significantly higher in children with chILD compared to controls, indicating a potential disruption in thyroid function associated with the disease. Although TSH levels were lower in the chILD group, this difference was not statistically significant. These finding suggest a possible link between thyroid dysfunction and clinical symptoms in this disease. Pulmonary function tests indicated significantly reduced FEV1, FVC, and MMEF values in children with chILD, reflecting the impact of the disease on lung function. No significant correlations were found between thyroid hormone levels and spirometry values, clinical severity, or oxygen saturation percentages.

The findings of this study align with previous research that indicates a link between thyroid dysfunction and pulmonary diseases. Previous research has shown the impact of thyroid hormones on metabolic rate, energy expenditure, and mitochondrial function, all of which are linked to lung function (Nathan et al ,2023). The imbalance of thyroid hormones can lead to metabolic disorders affecting systemic metabolism and lung function, which emphasizes the interconnectedness of the endocrine and respiratory system. Furthermore, Nathan et al. (2023) discussed the approach to children with interstitial lung disease and emphasized that patients should undergo extensive diagnostic workup, including endocrine assessments. Their finding suggests that understanding the patient's endocrine status can help develop better management strategies and enhance clinical results (Nathan et al., 2023). Garg et al. (2023) recruited 30 newly diagnosed hypothyroid adult patients and 30 healthy controls in India to assess pulmonary function in newly diagnosed hypothyroid patients. 17% of the hypothyroid patients were normal, whereas 33% had mild restrictive lung impairment and the rest 50% had moderate to severe restrictive impairment on spirometry where the ventilatory functions were diminished and improved after levothyroxine therapy for 6 months but could not reach the normal healthy values. This aligns with the current study's recommendations for regular thyroid function screening in children with ILD.

Ali ER (2016) explored the functional lung impairment in patients with thyroid disorders and revealed significant respiratory complications associated with both hypothyroidism and hyperthyroidism. Ali's study showed that hypothyroidism was linked to decreased respiratory drive and various respiratory complications, while hyperthyroidism could increase respiratory drive and also caused dyspnea on exertion. These findings highlighted the important need for managing thyroid function in patients with lung diseases to prevent further respiratory impairment. The focus of this study, was the relationship between thyroid hormone abnormalities and disease severity in children with ILD, aligning with Ali's findings, which emphasizes the importance of early detection and the comprehensive management of thyroid hormonal imbalances, especially in patients with ILD. In addition, Oldham et al. (2015) found a high prevalence of hypothyroidism in patients with idiopathic pulmonary fibrosis (IPF) and suggested that hypothyroidism might serve as a mortality indicator. This aligned with the altered TH levels observed in this study, which may

reflect an altered metabolic state associated with chILD. However, the absence of significant correlations between thyroid hormone levels and clinical parameters suggests that the relationship between thyroid function and lung disease severity is complex and depends on multiple factors.

The clinical implications of these findings are significant. The results of the study indicate the necessity of periodic thyroid function assessment in children with pulmonary diseases as the abnormalities in thyroid function tests could be early signs of the progression of the disease and detecting them could guide its treatment. Given the complex interplay between TH and lung health, a multidisciplinary approach involving endocrinologists and pulmonologists may be necessary to optimize patient outcomes. Therefore, the results of the current study and its findings are consistent with previous research that emphasized the importance of thyroid hormones in lung development and pathology. The observed increase in T3 levels in children with ILD supports the general trend of TH disruption in regulating pulmonary function and disease progression. These findings highlight the need for integrated clinical strategies that address both endocrine and respiratory health to improve outcomes for pediatric patients with lung diseases.

Strengths and Limitations

The study utilized a well-defined cohort of children with chILD, thus allowing for focused assessment of thyroid function in this particular population. Robust data collection methods, including comprehensive clinical assessments and standardized thyroid function tests were used to ensure the accuracy of the data.

The number of cases used was relatively small, which may reduce the generalizability of the results so the second question of the study could not be answered. Further research with a higher patient population is required to confirm this study's findings. Additionally, the cross-sectional design of the study prevents the establishment of casual relationships between thyroid function and chILD severity. Future research has to involve the performance of longitudinal analysis to establish the causal link between dysfunction and diseases progression. Moreover, some limitations of the study include the lack of information on the patients' nutritional status, medication use, or other co-existing conditions that may affect thyroid function and lung disease severity, which could have impacted the results.

Conclusion

The findings of this study suggest that there is a complex relationship between thyroid function and interstitial lung disease in children. The observed increase in free T3 levels in children with chILD suggests that there may be a potential link that warrants further investigations. Routine thyroid function tests should be done in this population to assist in early detection and management of thyroid abnormalities. Understanding these connections might lead to new therapeutic options, which could improve clinical outcomes for children with chILD.

Recommendation

Based on the findings of this study, the study underlines the importance of considering thyroid health in managing pediatric interstitial lung diseases. So, the following recommendations can be proposed. Firstly, implementing routine thyroid function tests for children diagnosed with chILD is recommended to assist in early detection of thyroid abnormalities. Secondly, more studies should be done to analyze the causal relationships between the two conditions in children through the use of longitudinal research. Thirdly, it is recommended to investigate the molecular mechanisms linking thyroid hormones and lung pathology to identify potential therapeutic targets. Lastly, developing comprehensive care protocols that includes both the pulmonary and endocrine aspects of chILD can enhance patient outcomes and quality of life.

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