Original Article

The Relation between Thyrotoxicosis and Risk of Cognitive Disorders in Older Adults at a Tertiary Care Centre in Pakistan

Risk of Incident Cognitive Disorders in Older Adults

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ABSTRACT

Objective: To ascertain whether there's a heightened risk of cognitive disorders linked to both endogenous and exogenous causes of thyrotoxicosis.

Study Design: Case control, Cohort study

Place and Duration of Study: This study was conducted at the Department of Medicine at Nishtar hospital, Multan, from March 2021 to February 2022.

Methods: Two hundred and ten patients were enrolled and divided into case group (105) and control group (105). The clock drawing test and Mini Mental State Examination was used for evaluation of cognitive function, both administered by a single observer. Subjects included in the study had received a minimum of primary education or higher and were above the age of 65 years.

Results: Regarding thyrotoxicosis, 53.3% patients were exogenous, 15.7% was endogenous and 31.0% patients was unknown thyrotoxicosis. Exogenous 68.5% was most common in cases as compare to the controls 48.1%. In this study MMSE (25-30) score was 65.7% in cases and 85.7% in controls. Status of cognitive impairment evaluated by clock drawing test 32.4% in cases and 20.0% in controls.

Conclusion: The prevalence of cognitive impairment was notably elevated in individuals with thyrotoxicosis, whether endogenous or exogenous, compared to control subjects. Additionally, the presence of cognitive impairment exhibited a correlation with the level of thyroid-stimulating hormone (TSH), with cognitive function declining as TSH levels increased.

Key Words: Cognitive disorders, Thyrotoxicosis, older adults, Exogenous, Endogenous

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INTRODUCTION

Thyrotoxicosis refers to a condition characterized by excess thyroid hormone levels in the bloodstream, typically resulting from an overactive thyroid gland[1]. There are several types of thyrotoxicosis, including Graves' disease, toxic multinodular goiter, toxic adenoma, and thyroiditis. Graves' disease is an autoimmune disorder where the immune system mistakenly attacks the thyroid gland, leading to excessive hormone production. Toxic multinodular goiter involves the development of multiple overactive nodules within the thyroid gland[2].

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Toxic adenoma refers to the presence of a single overactive nodule within the thyroid tissue. Thyroiditis is inflammation of the thyroid gland, which can lead to a temporary increase in hormone levels[3].

A recent study conducted by Johns Hopkins Medicine has revealed a correlation between thyrotoxicosis, characterized by elevated thyroid hormone levels, and a heightened risk of cognitive disorders in older adults, encompassing both exogenous (resulting from medication intake) and endogenous (stemming from thyroid disorders like hyperthyroidism and Graves' disease) forms of the condition[4].

Thyrotoxicosis, characterized by an excess of thyroid hormones in the bloodstream, can significantly impact cognitive function in older adults[5]. The overstimulation of thyroid hormones, particularly triiodothyronine (T3) and thyroxine (T4), can lead to symptoms such as anxiety, irritability, and difficulties with concentration and memory[6]. In older adults, these cognitive impairments may present as confusion, forgetfulness, and a decline in overall cognitive function[7]. Additionally, untreated or inadequately managed thyrotoxicosis in older adults can exacerbate pre-existing cognitive disorders such as dementia or

Alzheimer's disease, further complicating cognitive function[8].

Overall, the findings of this study underscore the importance of recognizing and addressing thyroid dysfunction as a potential risk factor for cognitive disorders in older adults, highlighting opportunities for improved clinical care, patient education, and public health initiatives.

METHODS

This case control, cohort study was conducted at department of medicine at Nishtar hospital, Multan, from March 2021 to February 2022. A total of 210 patients with age above 65 years having thyrotoxicosis were selected and aligned in case and control group. Serum levels of thyroid stimulating hormone (TSH) were assessed.

The intra-assay coefficient of variation (CV) for TSH ranged from 3.8% to 6.0% across concentrations with mean 0.025 to 30.00 mIU/L. Hypothyroidism was characterized by elevated serum TSH levels (>5.5 mIU/liter) while serum-free T4 and T3 concentrations remained within the reference range. The clock drawing test and Mini Mental State Examination was used for evaluation of cognitive function, both administered by a single observer. Various cognitive characteristics can be assessed with MMSE like attention, memory, orientation, motor skills and language using upper limit of score 30, score 24 and less that indicate cognitive impairment.

Administering the MMSE typically takes about 8 minutes in hospitalized elderly patients, though the duration can range from 4 to 21 minutes. Additionally, the Clock Drawing Test (CDT) used for executive impairment, visuospatial, constructional praxis utilizing the Shulman scoring system where a score of ≥3 indicates cognitive deficit, and normal score was 1 or 2.

Subjects included in the study had received a minimum of primary education or higher and were above the age of 65; however, individuals on thyroxine therapy., those previously treated for hyperthyroidism, and individuals with major illnesses such as uncontrolled diabetes and associated complications, hypertension, cerebrovascular accidents (CVA), chronic kidney disease (CKD), sepsis, or those unable to give consent were excluded.

The control group consisted of normal healthy volunteers matched in age, sex, and education to the cases, and both groups were further matched for blood pressures (systolic, diastolic), HbA1c, PPBS, and FBS values. Exclusion criteria for the control group were identical to those for the cases, ensuring comparability. Control subjects were selected from the same socioeconomic background to minimize potential biases, and they underwent thorough physical and mental examinations, assessed using the same parameters as the patient group.

Cases and controls underwent examination with both the MMSE and CDT test. Subsequently, the data were analyzed utilizing suitable statistical methods, including the Chi-square test and Two Sample Proportion Tests, to determine the P value. Significance was attributed to tests with P values below 0.05.

RESULTS

Overall, 210 patients were included in our study. The whole patients were equally divided into two groups as Cases 105 (50.0%) and Controls 105 (50.0%). Both the groups were almost equal with respect to demographic variables, (p>0.050). (Table 1).

Table No.1: Demographic variables between the study groups

Variable	Cases 105 (50.0%)	Controls 105 (50.0%)	p-value
Age	66.44±10.92	65.61±11.47	0.597
Gender			
Male	63 (60.0)	72 (68.6)	0.195
Female	42 (40.0)	33 (31.4)	
Area of living			
Urban	30 (28.6)	37 (35.2)	0.300
Rural	75 (71.4)	68 (64.8)	
Marital status			
Married	103 (98.1)	104 (99.0)	0.561
Un-married	2 (1.9)	1 (1.0)	
Education status			
Educated	59 (56.2)	63 (60.0)	0.576
Un-educated	46 (43.8)	42 (40.0)	
Mean ± S.D, N (%)			

Table No.2: Outcome variables between the study groups

Outcome	Cases 105 (50.0%)	Controls 105 (50.0%)	p-value
Cognitive impairment			
Yes	35 (33.3)	19 (18.1)	0.012
No	70 (66.7)	86 (81.9)	
TSH levels	7.28±1.34	6.32±0.73	<0.001
MMSE scores			
25-30	69 (65.7)	90 (85.7)	0.002
19-24	24 (22.9)	8 (7.6)	
≤18	12 (11.4)	7 (6.7)	
Status of cognitive impairment evaluated by clock drawing test			
Yes	34 (32.4)	21 (20.0)	0.041
No	71 (67.6)	84 (80.0)	
Mean ± S.D, N (%)			

Cognitive impairment was presented in 35 (33.3%) cases and 19 (18.1%) in controls, (p=0.012). The mean TSH levels in cases and controls was 7.28±1.34 mIU/lite and 6.32±0.73 mIU/liter, respectively, (p<0.001). MMSE (25-30) score was 69 (65.7%) in cases and 90 (85.7%) in controls, (p=0.002). Status of cognitive impairment evaluated by clock drawing test 34 (32.4%) in cases and 21 (20.0%) in controls, (p=0.041). (Table 2).

According to thyrotoxicosis, 112 (53.3%) patients was exogenous, 33 (15.7%) was endogenous and 65 (31.0%) patients was unknown thyrotoxicosis. (Figure I). Exogenous 37 (68.5%) was most common in cases as compare to the controls75 (48.1%), (p=0.019). (Table 3)

Table No.3: Association of thyrotoxicosis with cognitive impairment

Thyrotoxicosis	Cognitive Impairment		p-value
	Yes 54 (25.7%)	No 156 (74.3%)	
Exogenous	37 (68.5)	75 (48.1)	0.019
Endogenous	8 (14.8)	25 (16.0)	
Unknown	9 (16.7)	56 (35.9)	
N (%)			

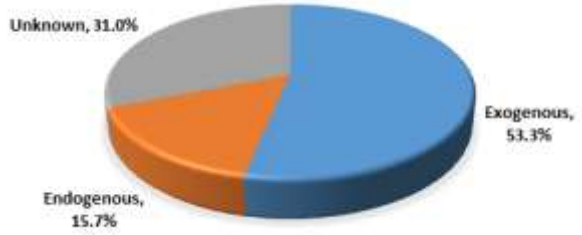

Figure No.1: Thyrotoxicosis distribution in all patients

DISCUSSION

Thyroid hormones exert significant influence on the central nervous system, with well-established consequences of overt hypothyroidism, yet there remains a dearth of evidence concerning the cognitive impacts of hypothyroidism and thyrotoxicosis, particularly with its prevalence among older patients who may already be experiencing cognitive decline[9]. Several comprehensive studies have thoroughly investigated the correlation between cognitive impairment and thyrotoxicosis, consistently revealing a robust association between the two conditions. These studies have explained the profound impact of thyrotoxicosis on cognitive function, highlighting the significant cognitive deficits experienced by individuals affected by this thyroid disorder[10,11].

In this study according to thyrotoxicosis, 53.3% patients were exogenous, 15.7% was endogenous and 31.0% patients was unknown thyrotoxicosis. Exogenous 68.5% was most common in cases as compare to the controls 48.1%. Another study examining the US population found that individuals aged 65 and older with low TSH levels due to either endogenous or exogenous thyrotoxicosis were at a heightened risk of developing incident cognitive disorders. It was noted that iatrogenic thyrotoxicosis, often resulting from thyroid hormone therapy, contributed significantly to this association.

Ye Y et al[12] conducted a study wherein they reported a significant association between hypothyroidism and cognitive impairment. In their research, they observed that individuals with subclinical hypothyroidism exhibited cognitive deficits compared to those without the condition. This finding suggests that even in its subclinical form, hypothyroidism may have noticeable effects on cognitive function. Furthermore, Cook et al[13] conducted a separate investigation focusing on elderly patients with hypothyroidism, and they similarly found that this group performed more poorly on cognitive assessments when compared to individuals with normal thyroid function.

In their study, Jorde et al[14] conducted an extensive battery of cognitive function tests found no association with thyroid status. However, through secondary analyses, they did report a negative correlation between TSH levels and cognitive impairment. Samuels et al[15] conducted a randomized controlled trial (RCT) involving 19 female participants with thyrotoxicosis, revealing a notable decrease in working memory by the conclusion of the hypothyroidism phase in contrast to measurements taken at the conclusion of the euthyroid phase.

In this study MMSE (25-30) score was 65.7% in cases and 85.7% in controls. Status of cognitive impairment evaluated by clock drawing test 32.4% in cases and 20.0% in controls. Additionally, Bono et al[16] research suggested that while subclinical hypothyroidism in 36 women had minimal impact on cognitive status, it potentially contributed to an age-related decline in attentive function.

Limitations: Longitudinal nature of study may experience loss to follow-up over time, which can introduce bias and affect the validity of the findings, especially if those lost to follow-up differ systematically from those retained in the study.

The study's findings may not be generalizable to populations outside of the study's geographic region, healthcare system, or time period.

CONCLUSION

The prevalence of cognitive impairment was notably elevated in individuals with thyrotoxicosis, whether endogenous or exogenous, compared to control subjects. Additionally, the presence of cognitive impairment exhibited a correlation with the level of thyroid-stimulating hormone (TSH), with cognitive function declining as TSH levels increased.

Author's Contribution:

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Drafting:	Feras Almarshad, Ghulam Mustafa
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