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Original Article

Age-related Variation in TSH Levels in Patients with Down's Syndrome -A Ten Year Longitudinal Study

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ABSTRACT

Background: A well-established finding is that thyroid disease is seen more commonly in individuals suffering from Down's Syndrome than in people without the condition. Patients are at risk from childhood to adulthood. Thyroid Stimulating Hormone (TSH) levels are essential for diagnosing and managing hypothyroidism. Thyroid dysfunction increases with age in individuals diagnosed with Down's Syndrome, according to a study undertaken by Karlsson B *et al*. in 1998. Our study aims at investigating the TSH level variations over a 10-year period, in individuals affected by Down's Syndrome, belonging to different age groups. **Materials and Methods:** Present study was conducted to include 40 individuals between the ages of 9 years to 27 years who were assessed at the 'Down Syndrome Care Association, Nashik, India'. Between 2009 and 2019, annual testing of thyroid function status was conducted and TSH levels in collected samples were analyzed. Five Different age groups, (9 - 15 years, 16 - 22 years, 23 - 29 years and 30 - 36 years) were identified, and data was segregated. Statistical analysis was performed over collected data and results were drawn. **Results:** The TSH levels in 9-15 years ranged between 5.21 mU/L - 7.13 mU/L, in 16-22 years, it was 5.66 mU/L - 6.56 mU/L, in 23-29 years, it was 4.33 mU/L - 7.37 mU/L and in 30-36 years it was 3.62 mU/L - 9.43 mU/L. **Conclusion:** Variations are observed in the fluctuating TSH values in individuals with Down's Syndrome belonging to different age groups. Periodic analysis of thyroid function is recommended highly as age increases since variations in TSH levels are seen to have a direct relation to it.

Keywords: Down's Syndrome, Thyroid-stimulating hormone, Thyroid disorder, Age-related variation.

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INTRODUCTION

Produced by the anterior pituitary, Thyroid-stimulating hormone (TSH), primarily a glycoprotein hormone that acts as the stimulus to the thyroid gland for the production of various thyroid hormones. TSH is known to have cause growth and enlargement of the thyroid gland due to the flourishing effect it has on thyroid follicular cells.[1]

A decrease in the activity of the thyroid gland results in Hypothyroidism, which typically manifests as decreased tolerance to cold, gastrointestinal incompetence, bradycardia, lethargy, and increase in weight. On the contrary, an increased activity caused by hyperthyroid is characterized by diarrhea, loss in weight, decreased tolerance to heat, fine tremor, and myasthenia.[2]

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Various associations between Down's syndrome and Hypothyroidism have been reported since the late 1860s.[3,4] Down's Syndrome (Trisomy 21) is caused by an abnormal number of chromosomes and is linked to a range of congenital deformities, including heart problems and gastrointestinal anomalies. Congenital primary hypothyroidism, acquired autoimmune thyroid dysfunction amongst other thyroid dysfunctions are commonly seen in Down's Syndrome.[5-9]

Previously conducted studies have shown that the frequency of Congenital Hypothyroidism in individuals with Down's Syndrome are as high as 28 times more than in comparison to the general population.[7,9] It is widely known that individuals diagnosed with Down's Syndrome have a multiplied occurrence of autoimmune problems affecting each endocrine and non-endocrine organ. In older kids and adults diagnosed with Down's Syndrome, a 13% to 63% range of lifetime occurrence of autoimmune thyroid disorder has been noted.[10,11]

A Lancet 2003 study within the United States of America revealed that Down's Syndrome is a common genetic disease affecting

as many as 10 000 newborns (nearly 1 in 700 live births) every year.[12-14] The National Down Syndrome Society within their 2021 fact sheet reported that only 1% of all occurrences of Down syndrome have a hereditary component, despite the fact that all three kinds of the disorder are genetic disorders. A genetic component, which accounts for around 1% of all occurrences of Down syndrome, is present in one-third of translocation-related Down syndrome cases.[15]

Various studies have demonstrated significant fluctuations in TSH levels in numerous age groups. One such study conducted at the Mattel Children's Hospital, University of California reported a 32% prevalence of hypothyroidism amongst children diagnosed with Down's Syndrome in comparison to those who were not.[3,16] In previous studies, TSH concentrations have shown large fluctuations, and a trend toward progressively deteriorating thyroid function has been demonstrated over time.[17-19]

Our study aims at investigating the TSH level variations in individuals of different age groups over a period of 10 years.

MATERIALS AND METHODS

Selection and description of participants: A 10-year longitudinal cohort study was conducted from the year 2009 to 2019. A sample size of 40 participants was established that included individuals between the ages of 9 years to 27 years.

The study was conducted at the 'Down Syndrome Care Association, Nashik, India'. The inclusion criteria was that all participants were proven cases of Down's Syndrome. The exclusion criteria was anybody who did not consent to be a part of the study.

Technical Information: From the time of enrollment, the thyroid function status was tested by analyzing TSH levels in blood samples. Data was collected over a period of 10 years.

4 Different age groups, primarily 9 years to 15 years, 16 years to 22 years, 23 years to 29 years and 30 years to 36 years, were identified, and data was segregated accordingly.

Ethics: Consent was taken from the parents/guardians of participants in the study under 18 years of age.

Statistics: The data was statistically analyzed and *p*-value was calculated to be < 0.05 which is statistically significant. The TSH variations in each age group were compared and results were drawn.

RESULTS

Variations in TSH level in each age group was observed. The population under study was divided into 4 age groups namely 9 years to 15 years, 16 years to 22 years, 23 years to 29 years and 30 years to 36 years.

The TSH levels in the first age group of 9-15 years ranged between 5.21 mU/L - and 7.13 mU/L (Table 1). For the second age group of 16-22 years, it was 5.66 mU/L-6.56 mU/L (Table 2). For the third age group of 23-29 years, it was 4.33 mU/L - 7.37 mU/L (Table 3) and for the fourth age group of 30-36 years, the range was observed between 3.62 mU/L-9.43 mU/L (Table 4). Variations in TSH levels increased as age increased, showing maximum fluctuation in the 30-36 years' age group.

Variations of Mean values of TSH were plotted on individual graphs (Graph 1 to 4) and a singular graph comparing variations in all 4 age groups was drawn (Graph 5).

DISCUSSION

For a majority of individuals with suspected thyroid disorders, TSH levels are considered the first-line amongst the various screening tests.[20] Thyroid hormones are regulated by TSH levels in the blood, making TSH a rather sensitive indicator of any form of thyroid function. It is important to study the feedback processes that governs hormone production in individuals in

Table 1: Mean TSH values 09-15 years.

9-15 years							
Age (in years)	**9yr**	**10yr**	**11yr**	**12yr**	**13yr**	**14yr**	**15yr**
Mean TSH value	5.21	6.98	7.09	7.13	6.33	6.18	6.33
Std. Deviation	0.32	2.44	2.33	2.29	2.97	2.70	2.26
Coeff. of Var.	6.13	34.97	32.90	32.06	46.97	43.75	35.77

Table 2: Mean TSH values 16-22 years.

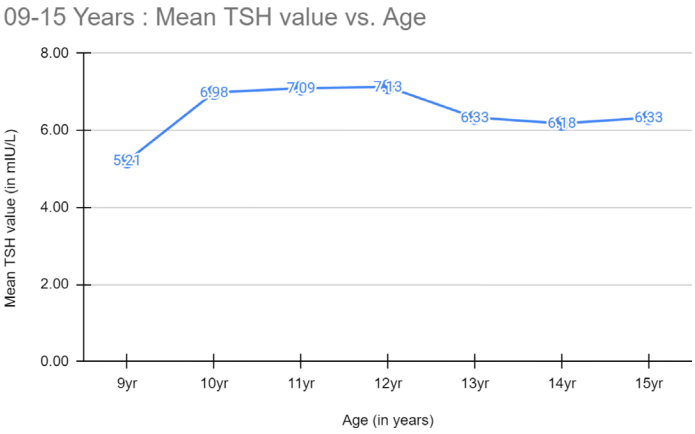
16-22 years							
Age (in years)	**16yr**	**17yr**	**18yr**	**19yr**	**20yr**	**21yr**	**22yr**
Mean TSH value	6.12	6.56	6.06	6.11	5.41	5.82	5.66
Std. Deviation	2.51	2.41	2.61	3.09	2.77	3.05	2.02
Coeff. of Var.	40.95	36.76	43.11	50.65	51.11	52.43	35.61

Table 3: Mean TSH values 23-29 years.

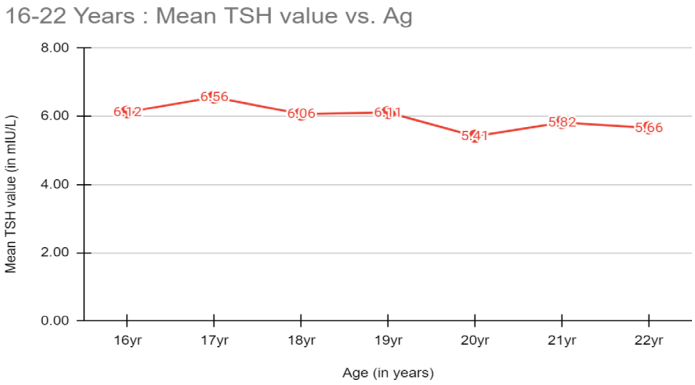
23-29 years							
Age (in years)	23yr	24yr	25yr	26yr	27yr	28yr	29yr
Mean TSH value	7.37	4.44	4.33	5.41	5.89	5.33	6.07
Std. Deviation	9.20	2.27	1.17	2.32	2.37	1.05	0.32
Coeff. of Var.	124.73	51.18	27.12	42.97	40.29	19.77	5.19

Table 4: Mean TSH values 30-36 years.

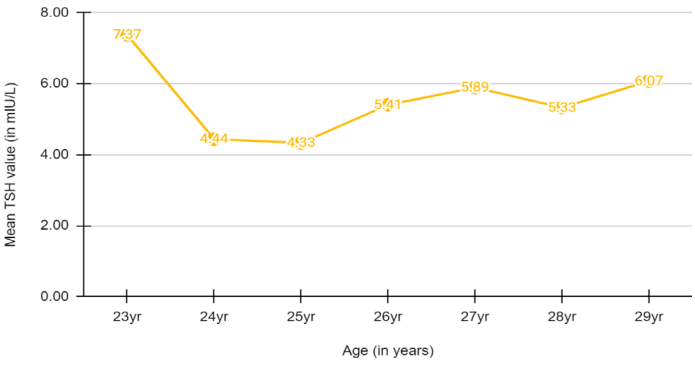
30-36 years							
Age (in years)	30yr	31yr	32yr	33yr	34yr	35yr	36yr
Mean TSH value	6.06	5.46	3.62	5.54	7.02	7.32	9.43
Std. Deviation	1.49	3.79	1.47	2.16	4.29	7.05	8.63
Coeff. of Var.	24.58	69.33	40.53	38.90	61.15	96.38	91.48



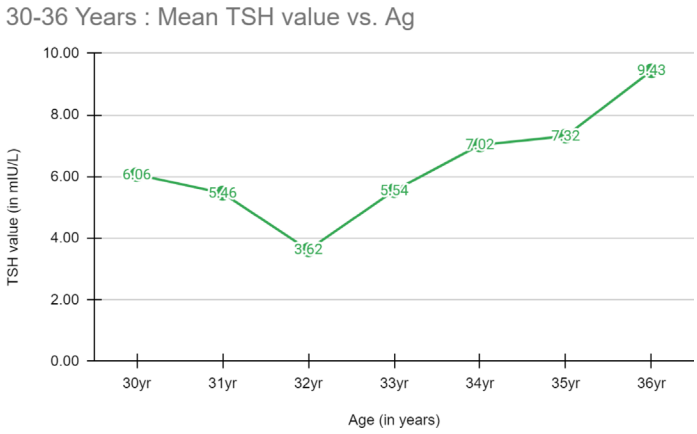
Graph 1: Mean TSH value v/s Age (09-15 years).



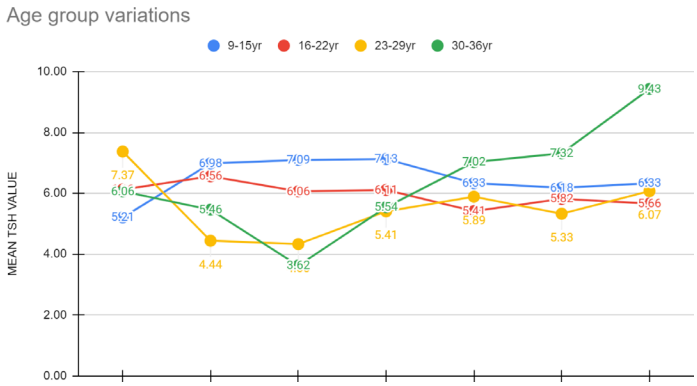
Graph 2: Mean TSH value v/s Age (16-22 years).



Graph 3: Mean TSH value v/s Age (23-29 years).



Graph 4: Mean TSH value v/s Age (30-36 years).



Graph 5: Age group variations.

order to comprehend the changes in the thyroid axis that are prevalent during aging.[21]

TSH levels are typically high in infants and steadily decline with age.[3,6,22-24] According to a study conducted at Duke University Medical Center, individuals affected by Down's Syndrome were 28 times more likely to suffer from Thyroid dysfunction in comparison to those without the condition.[3,9] Another study suggested that the lifetime prevalence ranged from 13 to 63 percent.[3,9,25] Amongst the various genetic disorders, Down's Syndrome is most prevalent at a 1:800 ratio and also a major cause of cognitive problems in the population.[8,26] Hypothyroidism is known to be one of the most frequent endocrine conditions amongst children.[3,22,27,28] Hypothyroidism affects about 9 to 11 percent of Indians and is seen to have a significantly greater range than females than in males. There is also a notable mention of the overlap in clinical signs noted between Down's Syndrome and hypothyroidism.[29] The spectrum of thyroid dysfunction in individuals suffering from Down's Syndrome ranges from Congenital hypothyroidism to Acquired hypothyroidism (autoimmune–non-autoimmune) to hyperthyroidism and also Subclinical hypothyroidism.[26]

In multiple cross-sectional studies over time, it has been observed that there has been an increase in the prevalence of both congenital hypothyroidism and acquired thyroid dysfunction in individuals with Down's syndrome.[6,7,30] Because it's difficult to tell the difference between Down's Syndrome and thyroid dysfunction, investigations have produced mixed results in terms of the findings in such patients.[3,4] A few cases have also reported the occurrence of Dyshormonogenesis (the coexistence of severe persistent primary congenital hypothyroidism and Down's syndrome with a normally placed gland of normal or enlarged size), however these findings could be merely coincidental.[10,31]

In Down's Syndrome patients exhibit thyroid dysfunction and many other conditions such as developmental delay, and cardiac and gastrointestinal problems.[3,22,30] Amongst other overlapping conditions, decreased linear growth, impaired intellectual development in younger children, dry skin and fine hair, dentition abnormalities, increased lethargy, excess weight, and oro dental abnormalities have been observed.[17,32] When taking into account all kinds of thyroid disorder, both treated and untreated, it is estimated that up to 50% of people with Down's Syndrome will have a thyroid disease diagnosis by the time they reach maturity.[33]

In a study undertaken by Karlsson B, *et al*. in 1998, it was established that thyroid dysfunction. evident in older Down's syndrome patients, but this has not been investigated in depth.[31] Variations seen in TSH levels in our studies indicated that maximum fluctuation in TSH level occurs in the age range of 30-36 years. Very minimal fluctuations were observed in the 16-22 years' age range. Demonstrating in coherence with previous studies that as people grow older, the variances become more pronounced.[3] The link between Thyroid Dysfunction and Down's Syndrome has been recognized by a majority of hypothyroidism screening studies in children affected with Down's Syndrome. Periodic monitoring has become a necessity in the monitoring process of Down's Syndrome,[34,35] as it is the use of adequate hormone replacement treatment that could result in the management of such conditions.[36-38] While a majority of studies urge frequent thyroid function testing, a few studies believe it is not necessary.[39] Some studies also advocate that retesting decisions be made based on the first test results. This would be more cost-effective and would cause the least amount of difficulty and suffering to the majority of the population.[40]

CONCLUSION

Thyroid disease has a greater prevalence in individuals suffering from Down's syndrome as compared to the general population. A major cause of concern is the irreversible mental and physical disabilities that can be caused by hypothyroidism when left untreated. Early identification and intervention are preferred, especially in kids who are predisposed to cognitive deficits.

The swings in TSH levels are larger in older age groups, according to our research. Maximum variations are observed in the oldest age group under study. TSH reference values for adults in previous studies have exhibited a similar scenario. As a result, every individual with Down's Syndrome should have a thyroid profile performed to diagnose thyroid dysfunction early followed by proper hormone replacement therapy as part of treatment. Thyroid test results should always be analyzed by a physician who understands that higher TSH levels in Down's syndrome can be transient.

Limitations of our study included the lack of data on the gender of participants in the study. The predilection for TSH variations based on gender could thus not be highlighted. Another limitation included the fact that only TSH levels were noted over the entire period of the study. A full thyroid profile including T3, T4 and TSH levels could be a better indicator for variations associated with thyroid disease in people with Down syndrome. Another limitation of our study is that there were no medical records available to evaluate the proportion of patients who were already under the care of an endocrinologist.

A higher degree of caution, prompt screening, immediate intervention with appropriate therapy, regular therapeutic monitoring, and counseling may all aid in limiting adverse outcomes and achieving the greatest benefit associated with TSH variations in Down's Syndrome. A thyroid profile could hence be done once every 6 months to evaluate the variations and provide valuable data towards timely assessment of the condition.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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