TSH AND FT4 VALUES ANALYSIS BY AGE AND GENDER IN PATIENTS WITH HYPOTONIC SYNDROME USING CRT ALGORITHM: A RETROSPECTIVE STUDY

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Abstract: *Deficiency of thyroid hormones associates muscle weakness. Muscle weakness represents an important clinical sign that can occur in cases of subclinical hypothyroidism manifested only by hypotonic syndrome. In our retrospective study performed for 146 cases admitted in the Pediatric Clinical Hospital from Sibiu we have analyzed the levels dynamics of TSH and FT4 to determine whether there are statistically significant particularities by age and gender in pediatric patients suspected with developmental disorders (hypotonic syndrome). We used T-test, Mann-Whitney, ANOVA and CRT decision algorithm and we pointed that the differences in averages of FT4 and TSH between ages 0-1,1-2,2-6 and 6 years are not statistically significant and cohort studies are still necessary. FT4 values are influenced rather by gender and TSH by age. The suspicion of subclinical hypothyroidism should be considered especially in children with hypotonic syndrome even when the values are in the range 3.5-4.5 uIU/mL if TSH.*

INTRODUCTION

Thyroid hormones T4 (thyroxine) and T3 (triiodothyronine) are reversible fixed to their circulating plasma proteins, being transported to peripheral tissues to interact with nuclear receptors. They form a complex that is translocated in the nucleus regulating the transcription of target genes. Their action intensifies carbohydrates and lipids catabolism and stimulates protein synthesis, the end result being an increase in the basal metabolic rate.(1) Thyroid hormone secretion is under the control tropes factors secreted by the hypothalamus such as TRH (thyrotropin releasing hormone, and anterior pituitary TSH (thyroid stimulating hormone).This feed-back is necessary for the homeostasis maintenance regarding hypothalamic-pituitary-thyroid system.(1,2-4) Current studies focus on thyroid hormones action on differentiation, growth, metabolism and muscle regeneration.(5-10) Thyroid hormones deficiency associates muscle weakness. Muscle weakness represents an important clinical sign that can occur in subclinical hypothyroidism cases addressing to the neurology departments being initially diagnosed as hypotonic syndrome. Our study objective was to analyze the levels of TSH and FT4 to determine whether there are particularities of the dynamics by age and gender in pediatric patients with suspected developmental disorders (hypotonic syndrome) and if there is a statistical significance for these findings. Of great interest in current studies is to observe the limits (minimum and maximum) for FT4 and TSH correlated with age and gender, which may be indicative values in cases of suspected subclinical hypothyroidism especially if the patients are associating neurological developmental disorders.(11-13)

MATERIALS AND METHODS

The retrospective study that we have conducted in the Clinical Hospital from Sibiu aimed to assess biomarkers FT4 and TSH dosed by immunoassay methods in pediatric patients diagnosed with developmental disorders (hypotonia) in the context of suspected hypothyroidism whether it is overt and/or subclinical. We have identified in the database 146 cases diagnosed with the neurological development disorder and with the clinical suspicion of hypothyroidism at the time of admission. Data was analyzed in Microsoft Excel 2013 and SPSS version 20.(14) For each parameter, FT4, TSH Kolmogorov-Smirnov test was carried out to analyse the distribution curve of values. Pearson correlations analysis was performed to analyze the link between age and FT4 and TSH values. We have applied T-test and Mann-Whitney test to study the difference of FT4 and TSH mean values by gender (male/female) and also ANOVA test for the analysis of the mean difference in FT4 and TSH values using age intervals. We have considered the level of statistical significance a p value <0.05.(14,15) The influence of age and gender on the FT4 and TSH values (quantitative variables) was emphasized using decision trees, generated by the Classification and Regression Tree method (CRT) with a minimum of 15 cases for the "parent" nodes and 5 cases for "sons" nodes and the 0.05 level of significance both for the group and for splitting nodes respectively.(16)

RESULTS AND DISCUSSIONS

The search in our electronic database generated 146 patients who had both FT4 and TSH measurements. Curve distribution data for 146 cases was Gaussian with the mean value for FT4 (M = 15.82 pmol/L), standard deviation SD=4.87 pmol/L, the minimum value of 1 pmol/L, the maximum value of 34.30 pmol/L and percentiles values P25=13.06 pmol/L, P50=15.38 pmol/L, P75=17.81 pmol/L. In the TSH case, the mean value for all the cases was M=4.59 uIU/mL, the standard deviation SD=8.59 uIU/mL, the minimum value of 0.05 uIU/mL, the maximum value of 60 uIU/mL, and percentiles values P25=1.59 uIU/mL, P50=2.89 uIU/mL, P75=4.35

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uIU/mL.

Analyzing the correlations between FT4 and TSH we have found that the results are consistent with data on the physiology of thyroid hormones namely FT4 values correlate negatively with TSH (r=-0.263, p= 0.001).(12,13) Regarding age, FT4 and TSH correlations with data taken in common for both genders male and female, we have noticed that thyroid hormone levels do not correlate with age (r=-0.042, p=0.617 for FT4 and r=0.080, p=0.335 for TSH).(12,13)

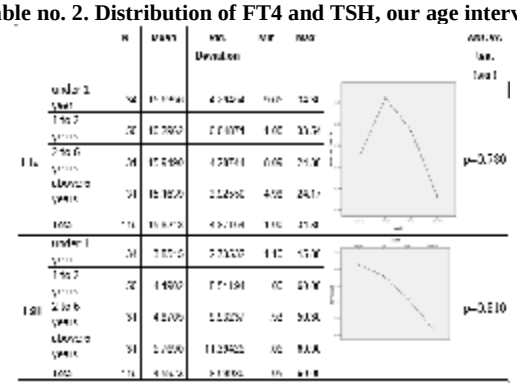
Given the results we have considered useful to test the correlations between age, FT4 and TSH, accordingly to the recommendations of other authors.(12) In this case, the results have changed and there were interesting differences between genders. Thus in male patients FT4 values correlated positively with TSH values (r=0.231, p = 0.051). Also for masculine gender we have found that both TSH and FT4 values tended to correlate negatively with age (FT4: r = -0.220, p = 0.063; TSH: r = -0.180, p = 0.13), the level of significance being quite close to the statistical significance. These results are resembling to those described in cohort studies where the statistical significance was evident.(12) In female patients FT4 values correlated negatively with TSH values (r = -0.378, p = 0.001), but they didn't correlate with age (r = -0.094, p = 0.427). TSH values also didn't correlate with age (r = 0.053,p = 0.656), which comes in contrast with Hadlow et al reports in 2013 (12). One possible explanation is that the studies presented in the literature were conducted on much larger groups of patients. The mean values graphs trends observed for both FT4 and TSH (table no. 1) could turn into statistical significance for large number of patients (cohorts).

Table no. 1. Correlations between age, FT4 and TSH, for the entire group and by gender

		The total number of patients			males			women		
		age	FT4	TSH	age	FT4	TSH	age	FT4	TSH
age	r	1	.042	.080	1	.220	.180	1	.094	.053
	Sig.		.617	.335		.063	.131		.427	.656
	N	146	146	146	72	72	72	74	74	74
FT4	r	.042	1	-.263**	.220	1	.231	.094	1	-.378**
	Sig.	.617		.001	.063		.051	.427		.001
	N	146	146	146	72	72	72	74	74	74
TSH	r	.080	-.263**	1	-.180	.231	1	.053	-.378**	1
	Sig.	.335	.001		.131	.051		.656	.001	
	N	146	146	146	72	72	72	74	74	74

Then we have studied the age variable distribution for our cases obtaining the mean value M=3.73 years of age (SD = 4.33) and the percentiles P25=1 year, P50=2 years, P75=6 years of age. In this context, for the variable age, we have considered the following four age ranges: under 1 year, 1 to 2 years, 2 to 6 years and older than 6 years of age. By analyzing the distribution of FT4 and TSH values correlated with the age intervals just presented we have obtained the followings:

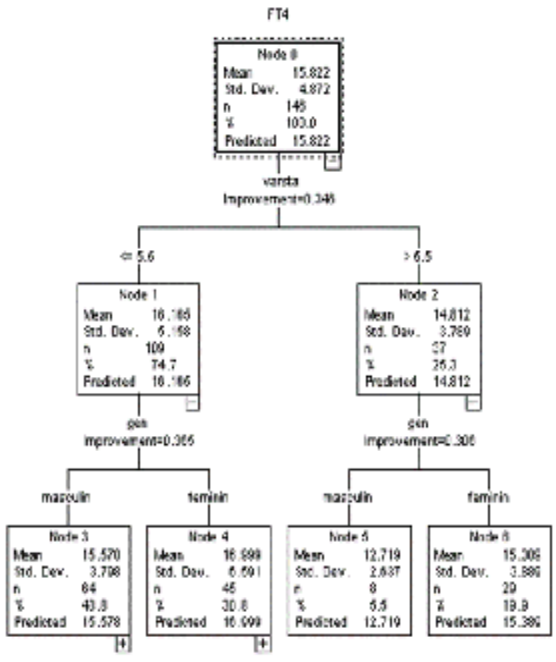
Table no. 2. Distribution of FT4 and TSH, our age intervals



For the entire group of patients the mean values for FT4 and TSH were 15.82 pmol/L and 4.59 uIU/mL respectively. These values fell within the range given by our hospital laboratory for immunoassay method (FT4: 10-23 pmol/L, TSH:0.8-8.2 uIU/mL). The trend of the mean values for the age intervals were consistent with some of the data presented in the literature. For the patients with hypothyroidism are suggested other limitations that should alarm the clinician especially if TSH ranges between 3.0-4.5 mU/L).(11,12) Differences between age groups weren't statistically significant neither for FT4 nor for TSH after applying ANOVA test (table no. 2). It could be noticed a decrease in the TSH mean value with age similar to the model presented by other authors. In a cohort study on 152.261 subjects, Hadlow et al in 2013 reported statistically significant differences but the TSH mean value analysis was performed for larger age groups (1-19 years, 20-39 years, 40-59 years, 60 -79 years > 80 years). The authors reported a statistically significant decrease in the median TSH values correlated with age in patients with hypothyroidism. Dividing patients according to gender and performing statistical analysis between groups, we have found homogeneous lots male/female with close mean values for FT4 (male: M=15.26 pmol/L, SD=3.78 pmol/L; female: M=16.36 pmol/L, SD=5.71 pmol/L) but not for TSH (male: M= 3.13 uIU/ml, SD=2.19 uIU/ml; female: M=6.01 uIU/ml, SD=11.74 uIU/ml). Applying the T-test for FT4 mean values and Man-Whitney test for TSH mean values we haven't found any statistically significant differences neither for FT4 (p = 0.169) nor for TSH (p = 0.795).

Further, to analyze the influence of age and gender on FT4 and TSH values we have used decision trees generated by CRT method. Choosing FT4 as target variable and the independent variables(age and gender), we have obtained a decision tree with 4 levels, consisting of 19 nodes, 10 terminal nodes, including both age and gender variables in the analysis. We present a narrower version of the tree (for reasons of space, only the first 3 levels are illustrated):

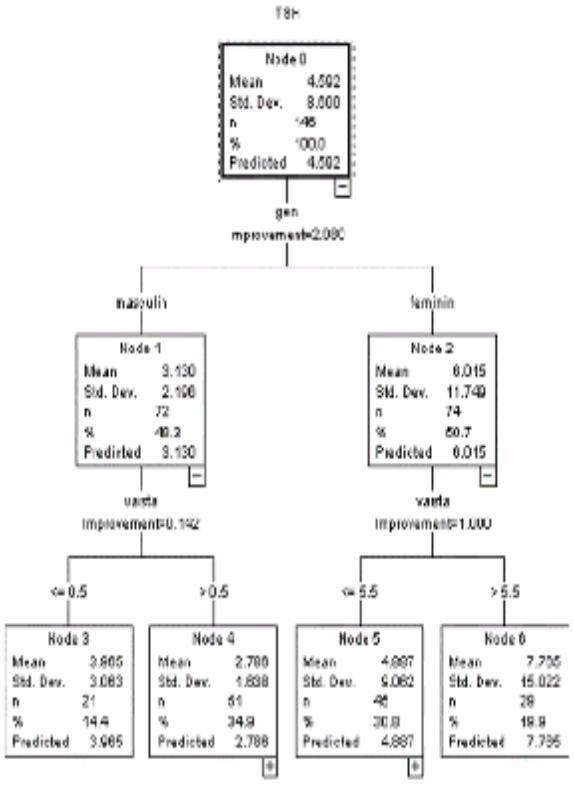
Figure no. 1. Decisional tree for FT4 variable



One might notice that the first node was split based on age as predictor variable, forming the first level of the tree as follows: 1) if the age was under 5.5 years then we had the mean value for FT4, M=16.16 pmol/L (SD=5.15 pmol/L, n=109, 74.7 %), 2) if the age was over 5.5 years then we had a lower mean value for FT4 M = 14.81 pmol/L(SD = 3.78 pmol/L, n= 37, 25.3%). For both age categories (under 5.5 years and over 5.5 years) the following predictor variable to be considered was the variable gender and so we had the second tree form: 1) if the age was under 5.5 years, then the mean value for FT4 was lesser in males patients (M= 5.57 pmol/L, SD = 3.79 pmol/L) than in female patients (M=16.99 pmol/L, SD = 6.59 pmol/L) with over one unit; 2) if the age was older than 5.5 years the mean value for FT4 was lesser in patients males (M=12.71pmol/L, SD=2.63 pmol/L) than in female patients (M = 15.38 pmol/L, SD = 3.88 pmol/L) with over two units. For the group of patients aged over 5.5 years the nodes formed after division by gender were terminal nodes, while for the group of patients aged under 5.5 years the decision tree continued with two levels, both masculine and the feminine. For both of these levels the age was the predictor variable with age intervals 0.5 years, 1.5 years, 2.5 years as benchmarks. Choosing TSH as target variable and age and gender as independent variables we have obtained a decision tree with 4 levels, consisting of 17 nodes, and 9 terminal nodes, both age and gender variables being included in the analysis.

We present a narrower version of the tree (for reasons of space, only the first 3 levels are illustrated):

Figure no. 2. The decisional tree for TSH variable



In this context, the first node was divided based on gender as predictor variable, forming the first level of the tree as follows: 1) whether the patients were males then the TSH mean level was M=3.13 uIU/ml (SD=2.19 uIU/ml, n=72, 49.3%) while 2) whether the patients were females, we recorded a higher mean TSH value, M=6.01 uIU/ml (SD=11.74uIU/ml,n=74,50.7%). For both genders (males and females) the following predictor variable considered was the variable age. We developed the second tree form: 1) if the gender was male then the mean TSH level was higher in patients aged under 0.5 years (M=3.96 uIU/ml, SD=3.06 uIU/ml) than in patients older than 0.5 years (M=2.78 uIU/ml, SD=1.63) with over one unit; 2) if the gender was female, the mean TSH level was lower in patients aged under 5.5 years (M=4.88 uIU/ml, SD=9.06 uIU/ml) than patients older than 5.5 years (M=7.76 uIU/ml, SD=15.02 uIU/ml) by almost three units. For the male gender and the age group under 0.5 years, the node is a terminal node, while for the female gender and the age group older than 5.5 years the node is a terminal node. Both in masculine gender with the age group older than 0.5 years and female gender with age group under 5.5 years, the decision tree continued with two levels, and on both levels the predictor variable was the variable age with reference values 0.5 years, 1.5 years, 2.5 years and 6.5 years.

From the statistical analysis based on the decision tree it could be noticed that both age and gender influenced FT4 and TSH levels. In the case of FT4, the first level of the decision tree was the gender so the gender affected more than age the FT4 values while in the TSH case the age was the first level, this variable being therefore more important than gender.

CONCLUSIONS

Our study revealed several interesting aspects regarding the dynamics of thyroid hormones in patients with suspicion of hypotonic syndrome.

Our application of statistical methods, especially the CRT algorithm decision in interpreting the data, showed that the differences between FT4 and TSH mean values by age intervals 0-1,1-2,2-6 and older than 6 years (as they resulted in statistical analysis)are not statistically significant so cohort studies are needed. We noticed a statistical significance in FT4 and TSH correlations even with the particularity of gender differences in this respect. FT4 values are influenced rather by gender while TSH by age.

We consider it is necessary to maintain the suspicion of subclinical hypothyroidism especially in children with hypotonic syndrome even the TSH values are in the range 3.5-4.5 uIU/mL according to the literature.

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