Association of Hashimoto's Thyroiditis with Antistreptolysin O titer

Voutetakis A.[1], Kanaka-Gantenbein C.[1], Gryparis A.[2], Dacou-Voutetakis C.[1]

[1] Division of Endocrinology, Metabolism and Diabetes, 1st Department of Pediatrics, "Aghia Sophia" Children's Hospital and [2] Unit of Endocrinology, Diabetes Mellitus and Metabolism, 2nd Department of Obstetrics and Gynecology, Aretaieion Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Background knowledge

Hashimoto's Thyroiditis (**HT**) is a relatively common autoimmune disorder that involves both cellular and humoral immunity, the latter characterized by the presence of antithyroid antibodies (ATA). Nevertheless, despite the large number of relevant studies, the underlying pathogenetic mechanisms still remain unclear; evidence and indications pointing to both **genetic and environmental components**.

Genetic studies have uncovered molecular associations that include immunoregulatory and thyroid specific genes Possible environmental triggers and effectors of the autoimmune process have included the hygienic conditions, selenium and vitamin D deficiency, drugs, stressors, smoking, alcohol, toxins and infections such as HHV-6, Yersinia and the Hepatitis C virus.

Streptococcal infections are known triggers of autoimmune processes such as rheumatic fever, glomerulonephritis and CNS autoimmune disorders. Moreover, in a 1978 animal study by Tonooka N et al (Am. J. Pathol 92:681-690, 1978), **severe lymphoid thyroiditis** with detectable antithyroglobulin antibodies and associated hypothyroidism occurred in all male and female rats **immunized against Group A streptococci** for seven successive generations.

Objectives

The objective of this **pilot study** was to examine whether an association between HT, developing during childhood and adolescence, and Streptococcal infections exists.

Patients and Methods

The study group included a total of **106 children** (73 females and 33 males), aged 9.9±2.9 years, initially examined for various reasons in a pediatric endocrinology setting (idiopathic short statue, early puberty, premature adrenarche, elevated TSH levels in routine screening or a family history of HT). Thyroid-related issues comprised 39.4% of total.

Antithyroid antibodies (**ATA**, i.e., antiTPO and antiTg) and **Antistreptolysin O** (ASO) titer, a toxic enzyme used as a marker of Streptococcal infection, were determined. For ASO, a titer >200 IU was characterized as positive.

Statistical analysis: Results are presented as mean±SD for quantitative variables, and as absolute and relative (%) frequency for qualitative variables. We used the X^2 test to investigate the relationship between categorical variables. Differences in the levels of a quantitative parameter between two groups were investigated with either t-test or Mann-Whitney test, as appropriate. Additionally, we used multiple logistic regression to investigate the association between ATA positivity, while adjusting for potential confounders (e.g. age, season). Two-tailed p-values<0.05 were considered statistically significant. All statistical analyses were performed in IBM SPSS (v. 25)

Table 1 Descriptive Statistics

	Female	Male	Total
Number	73	33	106
Age	9.8±2.8	10.2±3.1	9.9±2.9
Cold season	40	19	59
Warm season	33	14	47
Positive ASO (%)	52	54.3	52.6
Positive ASO (%) in ATA (-) group	32.3	42.8	36.3

Results

Antistreptolysin O (ASO): In the total group, 52.6% of children were found positive for ASO, which is considered higher than expected compared to the general population (30-37% for the age group). Nevertheless, among children with negative ATA antibodies the percent of ASO-positive children was 36.3%.

Antithyroid antibodies (ATA, antiTPO and antiTg): In the total group, 48.1% of children were positive for the presence of antithyroid antibodies (i.e., antiTPO and/or antiTg). Among children referred for thyroid-related issues, 85% were ATA-positive whereas among children referred for all other reasons only 12% were ATA-positive.

Association between ASO and ATA: In the group of children with a positive ASO titer, positive antithyroid antibodies were observed in a significantly higher percent of children (in 63.6 %) compared to those with a negative ASO titer (in 31.40%, p = 0.001). With respect to gender, the difference in positive antithyroid antibodies was significant only in females (p=0.002 in girls and 0.282 in boys). ASO titers were significantly increased in the positive with respect to the negative antithyroid antibodies group (p<0.001). ASO positivity was not related to age nor affected by season of specimen's collection (cold months: October through March versus warm months: April through September).

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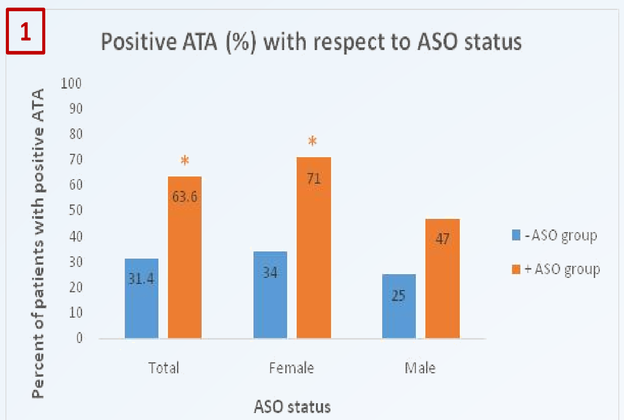

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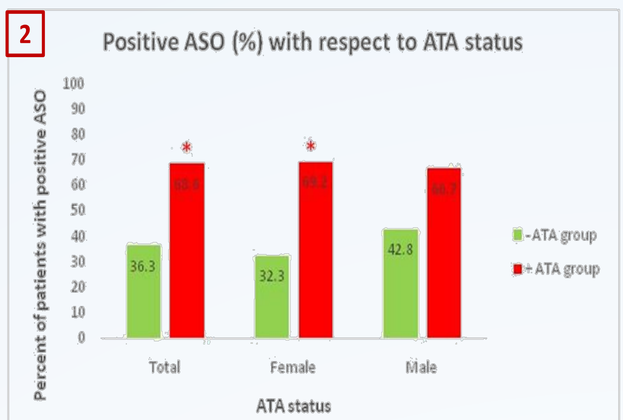

Figure 1: Percent of patients with positive ATA titers: In the group of children and adolescents with a **positive ASO titer**, positive antithyroid antibodies were observed in a significantly higher percent of children (in 63.6 %) compared to those with a **negative ASO titer** (in 31.4%, p = 0.001). With respect to gender, the difference in positive antithyroid antibodies was significant only in females (p=0.002 in girls and 0.282 in boys). **Figure 2:** Percent of patients with positive ASO titers: In the group of children with a **positive ATA titer**, positive ASO titers were observed in a significantly higher percent of children (in 68.6 %) compared to those with a **negative ATA titer** (in 36.3%, p = 0.001). With respect to gender, the difference in positive ASO titers was significant only in females.

Table 2 Antistreptolysin O (ASO) titer

Antithyroid Abs (ATA)	Mean	Median	SD	Min	Max	80th percentile
Negative (-)	223.0	109.0	269.2	5.0	1200.0	426.0
Positive (+)	354.5	324.0	232.0	6.0	1085.0	475.0

* Mann-Whitney p-value <0.001

Table 2: Comparison of ASO titers measured in the **negative** and **positive** antithyroid antibodies (ATA) subgroups. ASO titers were significantly increased in children and adolescents with positive ATAs with respect to the negative antithyroid antibodies group (p<0.001).

Conclusions

We attempted to examine whether the range of autoimmune disorders associated with streptococcal infections includes Hashimoto's Thyroditis. **A significant association of ASO positivity with the presence of antithyroid antibodies (ATA) was revealed in females.**

Our observational data obtained from a relatively small number of children and adolescents cannot reveal whether this association is causal or the result of a common underlying immunoregulatory disorder and therefore, further studies are needed.

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Thyroid

Antonis Voutetakis

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