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ANALYSIS OF CLINICAL PARAMETERS OF PATIENTS WITH GRAVES' DISEASE

Radka Tomova
Faculty of Pharmacy, Medical University of Pleven, Pleven, Bulgaria, Faculty of Natural Sciences, Shumen University "Konstantin Preslavski", Shumen, Bulgaria, rtomova@mail.bg
Pavlina Koseva
Department of Pharmaceutical Science and Pharmaceutical Management, Faculty of Pharmacy, Medical University of Varna, Varna, Bulgaria
Zdravko Kamenov
Clinic of Endocrinology, Faculty of Medicine, Medical University of Sofia, Sofia, Bulgaria
Mariana Nikolova
Department of Mental Health, Social work and Integrative Medicine, Middlesex University – London, United Kingdom
Radka Hadjiolova
Department of of Pathophysiology, Faculty of Medicine, Medical University of Sofia, Sofia, Bulgaria

Abstract: Thyroid disorders are a socially significant problem due to their prevalence, as well as their ability to severely deteriorate the patients' quality of life. The thyroid gland regulates metabolic intensity. Its normal functioning ensures the body's energetic balance. Grave's disease most commonly occurs when the thyroid gland is in hyper function. When the thyroid is in hyper function, it is over-stimulated, and the metabolism is accelerated – the pulse is raised, BMI and cholesterol levels drop, and insulin resistance is observed. Symptoms include increased irritability, hypertension, insomnia, muscle weakness, hand tremor. It is accompanied by goitre and in most cases by endocrine ophthalmopathy. Thyroid eye disease is present in about one out of three people with Graves' disease. Untreated hyperthyroidism can also lead to osteoporosis.
Graves' disease is thyrotoxicosis – T-cell autoimmune aggression on the thyroid gland. The immune system produces antibodies that are thyroid-stimulating immunoglobulins. They connect with the thyroid cells, imitating the TSH (thyroid-stimulating hormone) activity.
Thus, they stimulate the thyroid to produce too much thyroid hormones, which result its increase in size. Thyroid hormones T3 and T4 control the energy usage of the body, hence they affect nearly every organ in the body – even the way heart beats. The increase in T3 and T4 suppresses the secretion of TSH by the negative feedback mechanism. Thus, Graves' disease is associated with high levels of FT3 and FT4, and low levels of TSH.
In this study are presented the results from 13 clinical markers of 40 patients with Graves' disease in various stages of the disease, and an important criterion for the onset of immunological remission.
Data for the fasting serum glucose are presented, as patients with Graves' disease often have insulin resistance. Haemoglobin and creatinine were also measured.
Other clinical markers related to the side effects of the thyrostatic treatment were also measured. The most dangerous one of these is agranulocytosis, which can progress to leukopenia – condition in which the number of white blood cells is reduced below the lower limit. The mean level of the ALAT enzyme was presented as a marker for liver damage over the course of treatment.
The statistical analysis of the data gives us the opportunity to identify specific differences between the factors (group markers) in diseased and healthy individuals; as well as to identify different groups of patients that require an individual treatment approach.
Keywords: Graves' disease, hierarchical and non-hierarchical cluster analysis, clinical markers

1. INTRODUCTION

The thyroid gland regulates metabolic intensity. Its normal functioning ensures the body's energetic balance. Grave's disease most commonly occurs when the thyroid gland is in hyperfunction [1]. When the thyroid is in hyperfunction, it is over-stimulated, and the metabolism is accelerated – the pulse is raised, BMI and cholesterol levels drop, and insulin resistance is observed. Symptoms include increased irritability, hypertension, insomnia, muscle weakness, hand tremor [2]. It is accompanied by goitre and in most cases by endocrine ophthalmopathy [3]. Thyroid eye disease is present in about one out of three people with Graves' disease [4]. People with

hyperthyroidism may experience behavioural and personality changes [5]. Untreated hyperthyroidism can also lead to osteoporosis.

The disease affects about 1 in 200 people [6]. It occurs 7.5 times more frequently in women than in men [7]. It is considered that the possible causes of the disease are genetic predisposition, infection, psychotrauma and nerve tension [3, 8]. It appears at different ages, but most often − between 40 and 60 years [9, 10].

Graves' disease is thyrotoxicosis −T-cell autoimmune aggression of the thyroid gland. The immune system produces antibodies that are thyroid stimulating immunoglobulins. They bind to the cells of the thyroid as they mimic the action of the hormone TSH (thyroid-stimulating hormone). By that they stimulate the thyroid to produce too much thyroid hormone and cause its enlargement [3]. Thyroid hormones T3 and T4 control how the body uses energy, so they affect nearly every organ in the body − even the way heart beats. The increasing of T3 and T4 suppresses the secretion of TSH (thyroid stimulating hormone) in the feedback mechanism. Therefore, diagnosis of Graves' disease is associated with high levels of FT3 and FT4 (free form of thyroid hormones), and low TSH. Specific for the autoimmune diseases of the thyroid gland are three types of antibodies, which have different prevalences. These are the antibodies TRAb, TPOAb and TAT.

In 90% of the patients is discovered the presence of two species TRAb − antibodies to the receptor of TSH: TSI− (thyroid stimulating immunoglobulin) and TBII-antibodies (thyrotropin binding-inhibitory immunoglobulin). TSI-antibodies bind to the N-terminal region of the extracellular domain and mimic the effect of TSH. They stimulate the production of cAMP, the intake of iodine and the producing of thyroglobulin. TSI causes the thyroid make too much thyroid hormones. TBII - block the binding of TSH to its receptor and lower the level of thyroid hormones.

Treatment for hyperthyroidism includes the intake of thyreostatics − drugs that suppress or block the production of the thyroid hormones [11, 12, 13]. These substances block certain enzymes necessary for the synthesis of the hormones. In the course of treatment are required periodic analyzes of the clinical parameters of the patient to monitor the effect of the treatment via control studies. The presence and concentration of TSI- and TBII-antibodies, and their variability are a specific indicator of the progression of the disease and the course of treatment. Once treatment with antithyroid medicine begins, thyroid hormone levels may not move into the normal range for several weeks or months. The total average treatment time is about 12 to 18 months [14] but treatment can continue for many years in people who do not want radioiodine or surgery to treat their Graves' disease.

The reduction of the titre in the antibodies in the course of treatment is an important criterion for the onset of immunologic remission.

During the course of treatment, clinical parameters associated with the side effects from the thyreostatics treatment are also monitored. The most dangerous complication is the so-called agranulocytosis which can lead to leucopenia − a condition in which the white blood cells decrease below the lower limit. This indicates a weakened immune system [15, 16]. This is why a periodic monitoring of the lymphocytes is required. Severe complications such as liver damage and changes in blood picture are rare but dangerous. This is the reason why the liver enzymes are being monitored during the course of treatment.

Below are given the data on fasting blood glucose, as patients with Graves' disease often have impaired glucose tolerance. That's why the glycaemic parameters are being monitored in the course of treatment. Insulin resistance in these patients can be improved after successful treatment of their endocrine disease [17].

Another monitored indicator is the Total Cholesterol, which changes during the various stages of the disease [19].

Although Graves' disease is a disease which generally occurs with hyperthyroidism in a relatively small proportion of the sick TPOAb (thioperperoxidase antibodies) block the synthesis of thyroid hormones and cause hypothryroidism. These antibodies are directed against the enzyme tireoperoksidaza which is involved in the synthesis of the hormones thyroxine (T4) and triiodothyronine (T3) as it catalyzes the pairing of molecules iodine from the bloodstream to the protein thyroglobulin in the gland. This condition is also known as hypothyroid Graves' disease [18] . Autoimmune hypothyroidism can present with Graves' disease ophthalmopathy. Dependent on the relative concentrations of different antibodies, hypothyroidism or hyperthyroidism may occur.

People with hypothyroidism commonly have an elevated total cholesterol [20, 21, 22]. Increasing the thyroid hormone levels will help to decrease the total cholesterol, along with the LDL.

2. AIM

The aim of this work is to find in patients with Graves' disease the specific relationships between the TSH hormone, TRAb and TPOAb antibodies, blood limits and enzymes as well as to find different patterns of similarity between the patients included in the group of observation. The information extracted will help in the optimization

of patient testing or in the finding discriminating medical indicators for the formation of different groups (patterns) of patients with a similar medical status. It will also help in the assessment of the various treatment procedures on the patients' condition.

3. MATERIALS AND METHODS

Data set: In this study are included 40 patients (32 women and 8 men) with Graves' disease and a control group of 11 healthy individuals (7 women and 4 men) from the region of Varna.
The patients are in different stages of the disease.

Parameters used

The tests were performed in a certified Medical Diagnostic Laboratory "Status" in the city of Varna with accepted reference ranges for the relevant parameters mentioned below.

1. Age
2. Gender
3.TSH is a hormone made in the pituitary gland that tells the thyroid how much thyroid hormone to make. Reference values over 20 years is 0.27 ÷ 4.2 mIU/L.
4. FT4 with reference values over 20 years is 10.00 ÷ 25.00 pmol/L.
5. TRAb with reference range less than 1.5 IU/mL.
6. TPOAb with reference range less than 34.05 IU/mL.
7. Glucose (Glu)− blood glucose levels have a baseline of 3.05 ÷ 6.38 mmol/L.
8. Triglycerides (Trig) with reference values 0.7 ÷ 2.3 mmol/L
9. Leucocites (LEU) are the cells of the immune system. They have a protective function. Their reference values are between 4×10^9/L and 1.1×10^{10}/L. They make up about 1% of the total blood volume in a healthy adult.
4. Haemoglobin (Hb) with reference values for women 120 ÷ 160 g/L
5. Creatinine (Crea) is the creatine anhydride contained in the muscles. It is produced in the kidneys and is excreted in the urine. Its urine concentration is an indicator of renal function. It is decreased in impaired renal function. It is increased − in muscle degeneration − in paralysis or muscular dystrophy. The reference values for women are 44 ÷ 134 μmol/L.
6. Total Cholesterol (TChol) with reference values 2.3 ÷ 5.8 mmol/L.
7. Alanine transaminotransferase (ALAT) is an enzyme that is a clinical indicator of liver status. It is found in serum and various body tissues. The reference values are 0 ÷ 41 IU/L

Cluster Analysis

Hierarchical clustering of indicators for all 13 indicators was done for patients with Graves' disease and healthy subjects.

TRAB and TROAb formed groups of similarity for the patients. These indicators are in one cluster with TSH and thus form a "factor of intrinsic indicators of the disease".

Non-hierarchical cluster analysis and finding discriminatory indicators for patients with Graves' disease

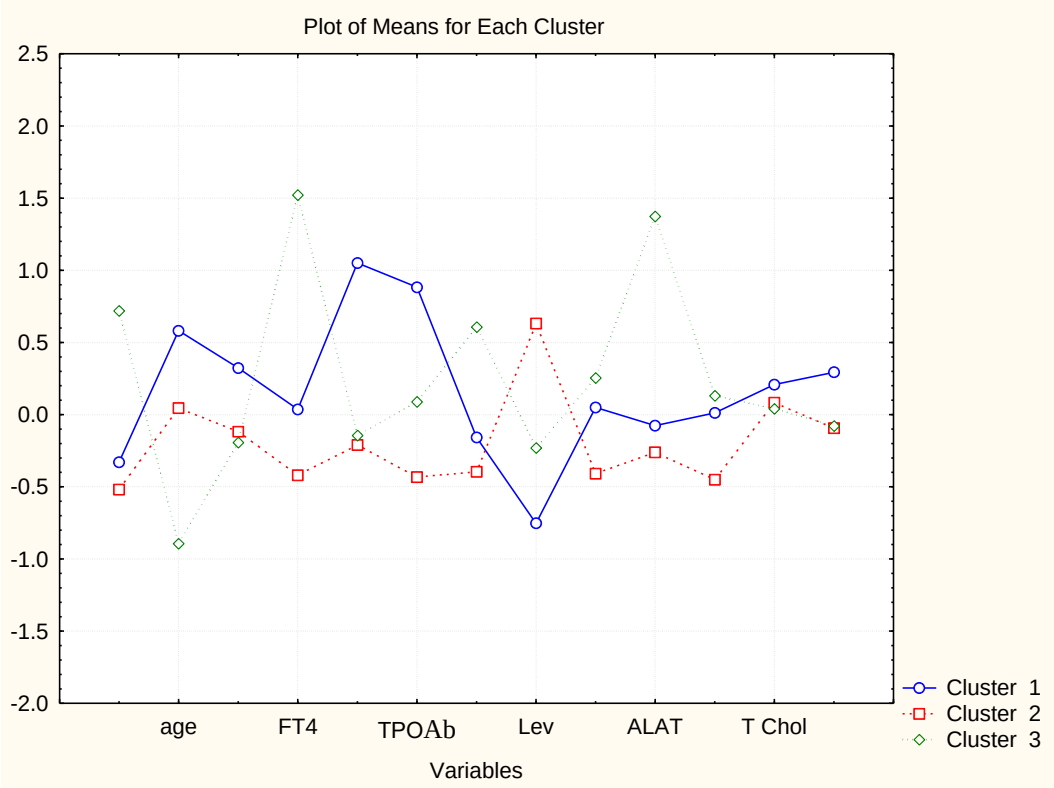

Fig.1 Mean values for each metric with correlation to each identified cluster

It was interesting to see if there were different groups of similarities among the list of 40 patients with Graves' disease and what were the discriminatory indicators for the individual groups (clusters). For this purpose a hierarchical cluster analysis was carried out with the hypothesis of the existence of 3 groups of patients (depending on the hierarchical clustering found in three clusters of indicators in the clusters.)

Figure. 1 shows a graph showing the mean values of each one of the 13 metrics for every identified cluster.

The first cluster consists of 14 patients, the second is from 18, and the third cluster from 8. In the three clusters, the average level of some indicators marks extreme values. For example, the largest cluster with 18 patients, the lowest is the FT4 average and in the cluster with 14 patients with the highest levels are TRAB and TPOAb.

4. CONCLUSION

The statistical evaluation of the data makes it possible to detect specific differences in the factors (groups of indicators) for sick and healthy patients on the one hand and on the other to differentiate groups of patients requiring an individual approach to handle the disease.

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