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Original Research Article

Neurological manifestations in Basedow Graves disease

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Abstract

A personal five years clinical prospective study, conducted on patients with Basedow Graves disease, hospitalized in the Clinical Neurology and Endocrinology Departments of Emergency Hospital Galati, targeted the neurological manifestations associated to this type of thyroid pathology, referring to the frequency, clinical aspect and therapeutic response to neurological determinations from Basedow disease.

Keywords: Basedow disease, Neurological and endocrinological manifestations, Paraclinic investigations, Therapeutic response

ABREVIATIONS: CPK- creatinphosphokinase; **CSF**- cerebrospinal fluid; **CT**- computed tomography; **EEG**- electroencephalogram; **EMG**- electromyography; **FAN**- antinuclear factor; **FO**- oculus fundus; **Hb**- haemoglobin; **Ht**- haematocrit; **MRI**- magnetic resonance imagery; **PUM**- motor unit potential; **RBW**- Bordet Wasserman reaction; **T3**- triiodothyronine; **FT3**- free triiodothyronine; **T4**- thyroxine; **FT4**- free thyroxine; **TCD**- transcranial Doppler; **TGO**- aspartat aminotranspherase; **TGP**- alanine aminotranspherase; **TRH**- thyroid releasing hormone; **TSH**- thyroid stimulating hormone; **TSI**- thyroid stimulating immunoglobuline; **VCM**- motor nerve conduction velocity; **VCS**- sensitive nerve conduction velocity

INTRODUCTION

Given the high frequency of patients with Basedow Graves disease which associate neurological signs and symptoms, we conducted a clinical study supported by laboratory examinations which had as purpose to determine the neurological manifestations of this type of thyroid pathology, referring to frequency, clinical and therapeutic response of neurological determinations and revealing the diagnostic difficulties of the damage done to the nervous system by Basedow Graves disease.

MATERIAL AND METHOD

The type of study: the research followed the recommended methodology for conducting the clinical and epidemiological studies.

Choosing the subjects

The study focused on a group of 34 patients with Basedow Graves disease, who were examined in the Neurological and Endocrinological Departments in Galati Emergency Hospital, followed for a period of five years. Patients were examined clinically and paraclinically every 3 months.

Clinical examination was associated with paraclinical tests. Paraclinical data was recorded in the observations sheets.

Data gathering

For the clinical diagnosis of hyperthyroidism the New-

castle index was used, and in the clinical assessment of the hypothyroidism the Billewicz index was used.

For the paraclinical endocrinological diagnosis there were used: hormone dosage T3, FT3, T4, FT4, TSH, thyroid ultrasound exam and thyroid scintigraphy with technetium- 99mTcO4, in doses of 2mCi, fine needle thyroid biopsy, sella turcica radiography, CT brain scan or mediastinum scan, brain MRI, biochemical usual tests of blood and urine: cholesterol, Hb, Ht, number of white cells, liver tests, CPK, TGO, TGP, total proteins, bilirubin, alkaline phosphatase, immunoassay, immunoelectrophoresis, FAN, lupus cells, C-reactive protein, complement serum, circulating immune complexes, RBW, antithyroglobulin antibody, bone scan, electrocardiogram evaluation.

For the study of neurological damage there were used: electroneuromyography data, VCM, VCS, ocular fundus exam FO, EEG, nervous and muscular biopsy with microscopic evaluation, anatomopathological exam of some parts gathered after brain excision, lung x-ray, mediastinum x-ray, bone x-ray, Doppler ECD exam-extracranial and transcranial, CSF study.

Processing and statistical analysis of the data

Processing and statistical data analyses were performed using specialized software SPSS version 11. We calculated central tendency indicators (mean and standard deviation), structural indicators and frequency indicators (prevalence).

Basedow Graves Parry disease represents one of the main forms of hyperthyroidism.

The prevalence is about 15-20‰ with a gender ratio of F/M = 2/1 – 10/1. It usually appears between the ages of 30-40 years old and is sometimes associated with other autoimmune disease. It is a specific organ autoimmune disease with strong family predisposition.

Thyroid stimulation is given by thyroid stimulating immunoglobulin (TSI) that acts on the receptor for TSH. TSH membrane receptor antibodies that are on the thyroid follicular cell surface are part of the subclass IgG1 and by binding with TSH receptor they activate adenylylcyclase thereby stimulating the thyroid function.

Clinically we have characteristic the symptomatic triad: thyrotoxicosis syndrome – goiter – ophthalmopathy at which there can be added acropachy and pretibial myxedema, thus making 5 typical signs of the disease.

Thyrotoxicosis syndrome is the most common in all thyrotoxicosis types.

Goiter is usually diffuse, homogeneous, elastic, and vascular with systolic-diastolic blast during auscultation and sometimes trill on palpation. Sometimes it may be nodular. About 10-15% of the patients have thyroid nodules. The autoimmune process may occur and evolve in a patient with nodular goiter history (Basedow nodular goiter) or can coexist with a toxic adenoma – Marine Lenhart syndrome (Zbranca et al., 1999).

Endocrine orbitopathy is an autoimmune process which affects the ocular extrabulbar tissues, the main role being played by the fibroblast.

Infiltration of orbital tissues is activated by immunocompetent cells through a cascade of vascular and cellular adhesion molecules: VCAM – 1 – VLA – 4, ICAM – I – LFA – I which determine co-stimulatory signals facilitating the presence of HLA DR, TSH – R 72kDa protein, CD44 hyaluronic acid receptor etc. Enabling adhesion molecules and other immune-modulation molecules is stimulated by numerous cytokines: INF gamma interferon, tumor necrosis factor – TNF alpha, interleukins IL, tumor growth factor – TGF beta, insulin growth factor IGF – 1, prostaglandin E2, free radicals. All these lead, in the end, to the fibroblast producing glycosaminoglycans GAGs, which attract water and cause edema of retrobulbar and interstitial tissues of the extraocular muscles – acute phase. Loss of CD8T – suppressant may contribute to the inflammatory process and production of specific antibodies for the extra ocular tissue. Subsequently, fiber changes occur. Diplopia occurs due to extrinsic muscle fibrosis of the eyeball which do not properly elongate when their antagonists contract, most frequently the right inferior one being affected (Weatherall et al., 2000).

The ophthalmopathy is infiltrative defining the set of pathological modifications regarding the orbital tissues and the exophthalmos designates eyeball protrusion. Even though ophthalmopathy is clinically obvious, only in 50% of the patients with the help of ultrasound examination, computed tomography of the orbital area and by measuring the intraocular pressure we have found that occult abnormalities exist in approximately all patients with Basedow disease. On the other hand there have also been reported cases of “endocrine” ophthalmopathy without obvious alteration of the thyroid function in which the TRH stimulation tests and determination of thyroid stimulating immunoglobulin revealed disorders regarding the thyroid function of the majority.

Related ocular modifications were also observed in Hashimoto’s chronic lymphocytic thyroiditis and in hypothyroidism, elements which raise the question of an organ autoimmune condition.

Werner (1969) divided the ocular manifestations in 6 degrees (Table 1) and in 1977 he establishes the NOSPECS index (Table 2).

Pretibial myxedema (infiltrative dermopathy) is not a common manifestation and it occurs in 4% of the basedowian patients as a skin infiltration which begins through a plate or node, to ultimately evolve into a dermo-epidermal, localized infiltration, more frequently in the calves, bilateral or unilateral. It may have other localizations. The injury has clearly defined edges with bright pink infiltrated and hard skin without leaving any well. Regarding the affection of the hands it is very

Table 1. Classification regarding the degrees of damage done by ocular manifestations (Werner, 1969)

Stage	Manifestations
0	- without any signs and symptoms
1	- no subjective complaints - objective: - upper eyelid retraction - stare - ocular palpebral asynergy with lid-lag phenomena
2	– soft tissue damage – conjuctival congestion, chemosis eyelid edema
3	- exophthalmos (proptosis) – it is measured with the exophthalmometer Hertel or by tomodensitometry: • normal: - white race: 20 mm - yellow race: 18 mm - black race: 22 mm • mild exophthalmos: +3 - +4 mm • medium exophthalmos: +5 - +7 mm • severe exophthalmos: +8 mm and more
4	- impairment of the external ocular muscles with diplopia, and limitation of the eyeball movements
5	- corneal damage: ulcers, necrosis, perforation
6	- vision loss by optic nerve damage

Table 2. N O S P E C S INDEX (*Werner S.C., 1977)*

	Signs and symptoms
N	Without clinical signs or symptoms
O	Only signs, no symptoms
S	Soft tissue involvement
P	Proptosis: a. 3-4 mm b. 5-7 mm c. 8 mm and over
E	Extra ocular muscles: a. the limitation of ocular movement in extreme position b. the obvious limitation of ocular movement c. immobile eyeball - eyeballs
C	Corneal damage: a. stippling b. ulceration c. necrosis, perforation
S	Vision loss: a. papillary pallor or visual field deficiency regarding the eyesight 1.0-0.3 b. the same but the eyesight from 0.3-0.1 c. blindness

rare but it is possible in the phalanges and the metacarpals.

It may precede hyperthyroidism, it is often in co-development or most commonly occurs after a radical treatment of the disease showing in 2/3 of the cases the aspect of hypothyroidism.

Acropachia means an enlargement of the extremities due to the periosteal hypertrophy especially in the phalanges and distal ends of the bones of the hands and legs. Nails have glass-clock aspect.

DISCUSSIONS

We followed 34 cases of Basedow disease.

Gender distribution: all the 34 cases present were females.

In other studies gender ratio is F/M = 2/1 – 10/1.

Age distribution (Figure 1.):

- Between 20-29 years old – 6 cases, 17.64%;
- Between 30-39 years old – 8 cases, 23.52%;
- Between 40-49 years old – 6 cases, 17.64%;
- Between 50-59 years old – 8 cases, 23.52%;
- Between 60-69 years old – 4 cases, 11.76%;
- 70 years old and over – 2 cases, 5.88%;

The data obtained is consistent with the data quoted in other studies according to which there are affected mostly people between 30-40 years old.

Distribution regarding the urban/rural environment (Figure 2):

- 26 cases, 76.48% - urban environment;
- 8 cases, 23.52% - rural environment;

Out of the total of 34 patients, 10 were smokers.

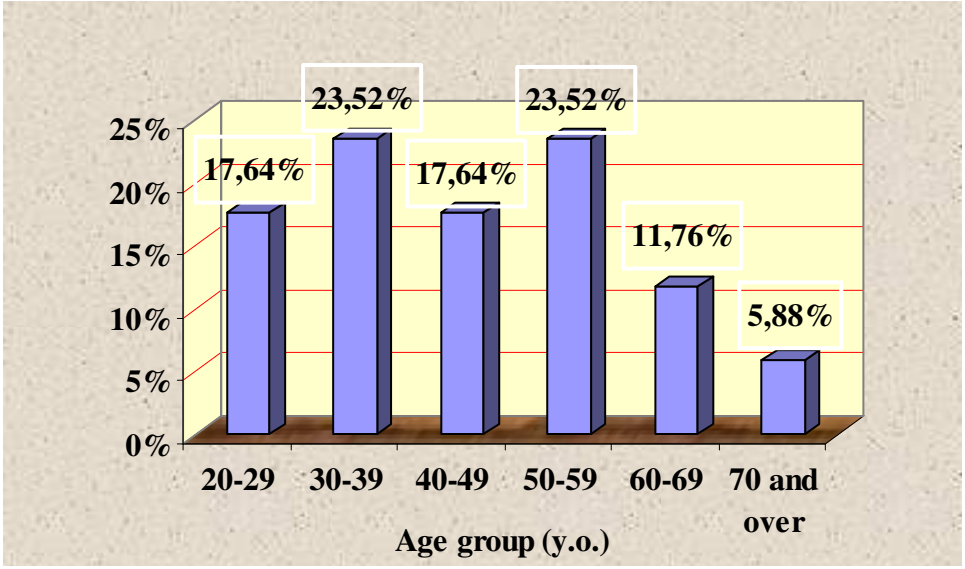

Figure 1. Distribution regarding the ages of the patients with Basedow disease from the study group.

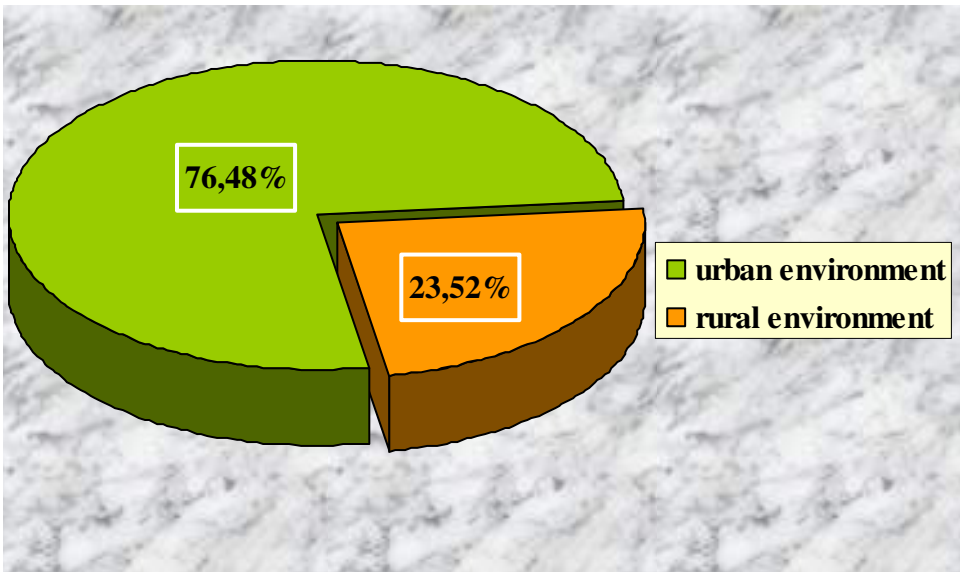

Figure 2. Distribution on urban/rural environment regarding the patients with Basedow disease from the study group.

Basedow disease associated with other extra thyroid disorders included:

- Dyslipidemia – 6 cases;
- Hypocalcemic tetany – 10 cases;
- Paroxysmal disorders of the heart rhythm – 2 cases;
- Ischemic heart disease -2 cases;
- Vitiligo – 2 cases;
- Bilateral glaucoma – 2 cases;
- Surgical climax for uterine fibroids with secondary neurodegenerative disorders – 2 cases;
- Ovarian cysts – 6 cases;
- Diabetes mellitus – 2 cases;

The association of Basedow disease with other thyroid disorders:

We mention that one case of adenocarcinoma was associated with Basedow disease.

In other studies this association is quoted in 3% of the cases with Basedow disease.

The endocrinological clinical diagnosis was established based on clinical signs and symptoms – the symptomatic triad for ophthalmopathy – goiter – thyrotoxicosis through

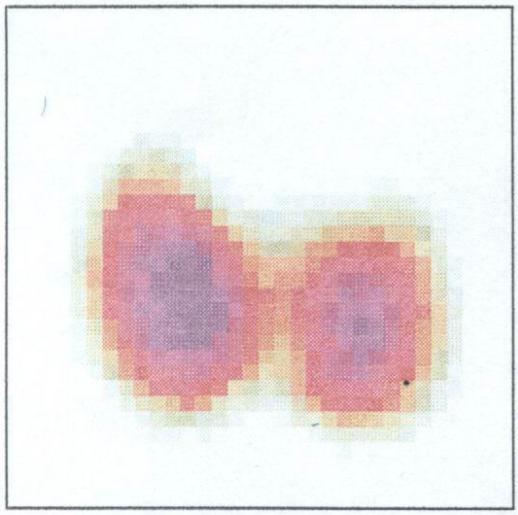

Figure 3. Thyroid scintigraphy – patient D.A., 44 years old.

the Newcastle index and NOSPEC index.
Eight patients presented a large weight loss, the symptoms including dyspnea, palpitations.
Thyroidectomy was imposed in 6 cases, 2 patients presenting post thyroidectomy myxedema.
Neuropsychiatric manifestations encountered in patients with Basedow disease included:

1. Manifestations of psychic order – 22 cases – 64.70%, which presented:
- Emotional liability – 8 cases – 23.52%;
- Insomnia – 4 cases – 11.76%;
- Depressive reactions – 8 cases – 23.52%;
- Anxiety – 2 cases – 5.88%;
- Autolytic ideation – 2 cases – 5.88%;
- Fatigue – 2 cases – 5.88%;
- Confusional state – 2 cases – 5.88%;
- Schizophrenia – 1 case – 2.94%;
- Panic attack – 2 cases – 5.88%;
- Lack of initiative – 1 case – 2.94%;
- Adynamia – 2 cases – 5.88%;
- Asthenia – 4 cases – 11.76%;
- Spontaneous hyperprosexia with voluntary hyperproxesia – 8 cases – 23.52%;
- Fixation hypomnesis – 6 cases – 17.64%;

We noticed in the studied patients a large proportion of psychiatric symptoms: depression episodes, panic attacks, autolytic ideation.
Regarding the stated ideas we exemplify with the following case:
- Patient D.A. 44 years old

Admission grounds: large weight loss, upper limb tremor, sleep disorders,
psychomotor agitation episodes, visual and auditory hallucinations.
Pathological personal history: schizophrenia, paroxysmal heart rhythm disorders.

Medical history: patient diagnosed with schizophrenia, treated for these disorders by the psychiatric ward for 2 years, is admitted for the causes previously mentioned.

Clinical exam: bilateral exophthalmos, rhythmic tremor with increased frequency in the upper limbs, sweating, clammy skin.
Laboratory:
- Hormone dosages: T3 – 1.2ng/dl, TSH – low 0.2microm/ml;
- Exophthalmometry: OD – 24mm, OS – 23mm;
- Thyroid ultrasound: left thyroid lobe of 40/38/20mm, right thyroid lobe of 39/33/23mm, glandular structure intense inhomogeneous, with hyper echoic nodular areas of 5 and 7mm;
- Thyroid scintigraphy (Figure 3)

Projection areas of the thyroid lobes are moderately increased. Homogeneous capture, much increased in the right lobe, increased in the left lobe.

The patient was confirmed with Basedow disease, after the treatment with antithyroid synthesis drugs, the psychiatric acuses were completely remitted, which allowed their interpretation as being caused by the thyroid affection.

The frequency of psychiatric manifestations in patients with Basedow disease was particulary high, 64.71% (Figure 4):

In other studies (Uldry et.al.,1991) it is estimated that real psychosis occurs in about 2% of the patients with hyperthyroidism, other authors noting that very frequently they have encountered neurotic symptoms (Zbranca et.al.,1999).

2. Muscle manifestations – we encountered:

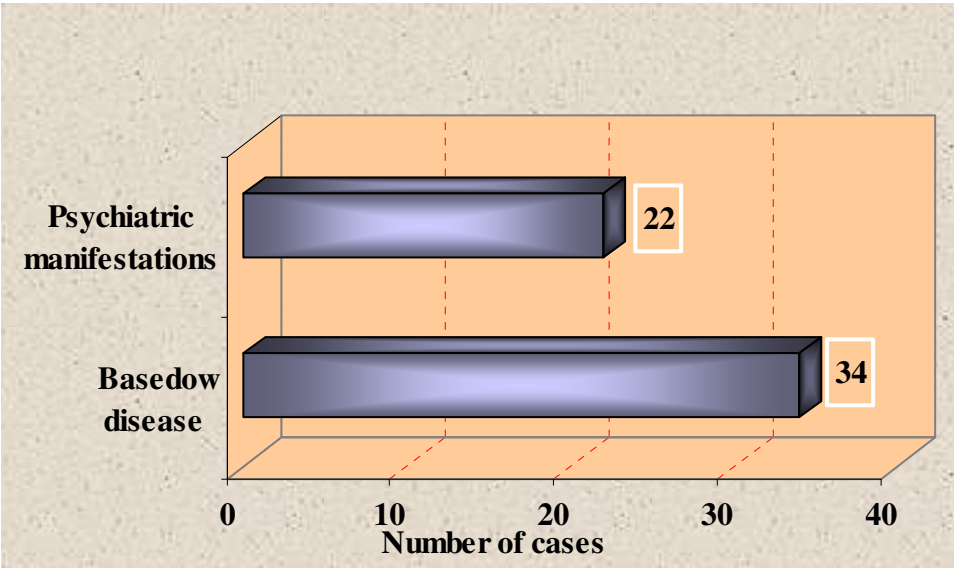

Figure 4. Frequency of patients with psychic manifestations from the total studied cases with Basedow disease.

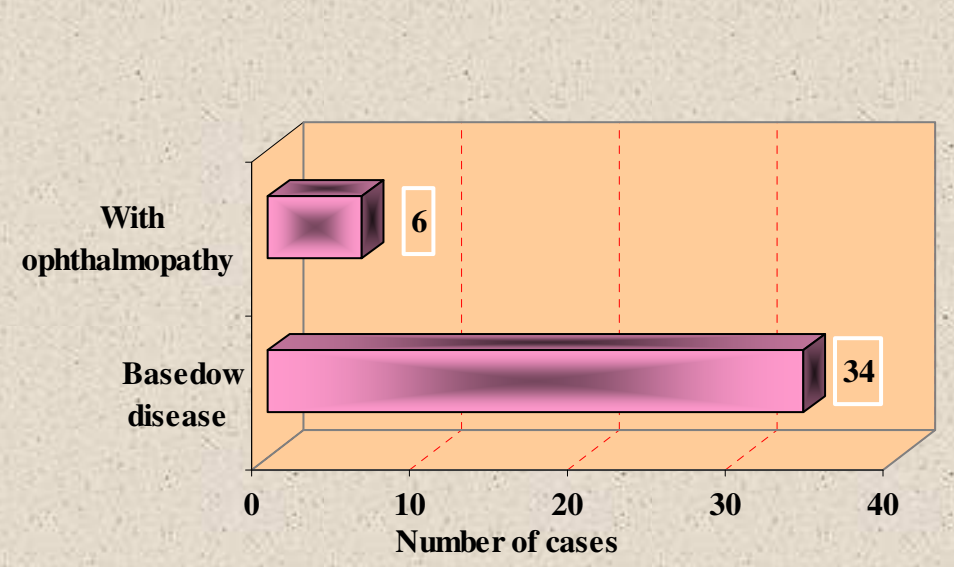

Figure 5. Frequency of cases with basedow ophthalmopathy in patients from the study group.

• Unilateral ophthalmopathy – 2 cases – 5.88% and bilateral – 4 cases – 11.76% of the cases with Basedow disease (Figure 5), assigned regarding the Werner classification in grade 4. (Table 3).

These data are below the values mentioned in other studies where it is estimated that ophthalmopathy occurs in 20-25% of the patients with Basedow disease (Goh et a., 2004).

Tataru et al. (2003) mentions that ocular affection is unilateral in 12% of the patients and bilateral in 88% of them.

In the previously mentioned cases, 4 patients presented bilateral exophthalmos, ocular palpebral asynergia, chemosis, eyelid edema, and tomodensitometric – orbital CT measures – showing exophthalmos of +4 - +7 mm which classified the ophthalmopathy in grade 4 of Werner classification.

Basedow ophthalmopathy occurred in all the cases in first months after the thyroid disorder onset, progress being slow, regressive under the treatment with anti-thyroid synthesis drug.

In other studies it is estimated that ophthalmopathy is simultaneous to thyrotoxicosis in 40% of the cases, it precedes it 20% of the cases and follows hyperthyroi-

Table 3. Basedow ophthalmopathy

No.	Identification data of the patient	Affection		Grade by Werner classification						
		Unilateral	Bilateral	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
1.	S.I.,fem,38 years old	+	-	-	Upper eyelid retraction	Chemosis	Exophthalmos OD + 7mm	-	-	-
2.	E.E.,fem,31 years old	+	-	-	Stare	Eyelid edema	Exophthalmos OD + 4mm	Left lateral horizontal diplopia	-	-
3.	I.D.,fem,42 years old	-	+	-	Upper eyelid retraction	Eyelid edema Chemosis	OD:+ 5mm OS:+ 4mm	Bidirectional horizontal diplopia	-	-
4.	T.F.,fem,31 years old	-	+	-	Lid-lag, upper eyelid retraction	Eyelid edema Chemosis	OD:+ 6mm OS:+ 5mm	Bidirectional horizontal diplopia	-	-
5.	C.C.,fem,44 years old	-	+	-	Lid-lag, upper eyelid retraction	Eyelid edema Chemosis	OD:+ 7mm OS:+ 7mm	Bidirectional horizontal diplopia	-	-
6.	R.F.,fem, 26 years old	-	+	-	Lid-lag, upper eyelid retraction	Eyelid edema Chemosis	OD:+ 5mm OS:+ 7mm	Bidirectional horizontal diplopia	-	-

dism in 20% of the cases (Vlase et al., 2002).

From the study group we noted the case of one patient who had average unilateral exophthalmos of +7mm associated with training headache, the patient was directed to the neurology ward under the suspicion of intracranial expansive process (sphenoid wing meningioma). The neurological exam and brain and orbit CT evaluation excluded the possibility of tumors, but the data obtained in conjunction with those provided by the general clinical exam oriented the diagnosis towards Basedow disease with hyperthyroidism, diagnosis confirmed by the endocrinological exam, immunoassay and hormone dosages. The patient went under treatment with antithyroid synthesis drugs and corticosteroids with improvement of the clinical symptoms but with minimal regression of the exophthalmos. Another patient who was presented with unilateral exophthalmos, headache, neuro-vegetative disorders and repeated episodes of loss of consciousness was originally addressed to the neurologist, brain CT excluding intracranial expansive processes, the final diagnosis being of Basedow disease – a form with unilateral exophthalmos.

Two of the cases listed in the table presented diplopia as an inaugural sign of the thyroid affection, diplopia causing the patients to initially present themselves for neurological examination. Diplopia preceded in both cases, with 3 months, the emergence of other signs of thyroid suffering. Ocular form of Myasthenia gravis was ruled out, the patients being guided towards endocrinology, where the diagnosis of Basedow disease was confirmed.

We have not encountered in the followed patients complete paralysis of the ocular motility, although this is quoted in other studies as occurring in 4-8% of the patients with Basedow disease (Uldry et. al., 1991).

- Muscle cramps – 8 cases – 23.52%;
- Myalgia – 6 cases – 17.64%;

Duyff et. al. (2000) states that hyperthyroidism is not accompanied by myalgia, fact that was not confirmed in our study.

- Chronic thyrotoxic myopathy – 3 cases – 8.82%;

Chronic thyrotoxic myopathy was seen in 3 cases, exclusively in women.

We have not encountered cases of acute thyrotoxic myopathy in patients from the study group, neither any situations of acute myopathy with the aspect of a pseudoparalysis in the territory of the cranial nerves, mentioned even by Serratrice et al. (1997).

Asbury et al. (2000) estimated that most patients with hyperthyroidism have clinical signs of myopathy, fact which was not confirmed in our study, although the patients were followed for a long time. Other studies state that myopathy is one of the 3 major neurological symptoms of hyperthyroidism, along with the embolic stroke caused by rhythm disorders determined by

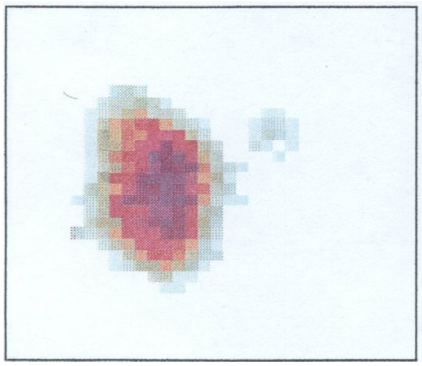

Figure 6. Thyroid scintigraphy – patient A.I., 36 years old: the projection area of the right thyroid lobe is moderately enlarged, irregularly defined, with increased capture, inhomogeneous. Some remnant thyroid tissue captured on the projection area of the left thyroid lobe.

thyrotoxicosis and hypokalemia paralysis.

Serratrice et. al. (1997) specifies the existence of muscle weakness in 80% of the patients with hyperthyroidism.

Muscle damage consisted of progressive muscle strength deficit, difficulty in walking, climbing stairs and resume standing, associated with muscle pains and the emergence of distal amyotrophies, to the hands. Muscle symptoms appeared, on average, after 18 months of the onset of the thyroid pathology.

CPK dosages were within normal limits.

EMG showed resting PUM appearance of reduced duration and amplitude, with the presence, during medium contraction of the interference route, reaching potential. VCM and VCS were within normal limits.

Muscle biopsy, with optical microscope evaluation was of myogenic type, nonspecific for the thyrotoxicosis etiology.

We exemplify in this regard the following aspects:

- Patient A.I., 36 years old

Admission grounds: decrease of muscle strength in the limbs, difficulty in
walking on long distances and climbing stairs, weight loss, tremor, sweating, sleep disorders and palpitations.

Personal history: Basedow disease with subtotal thyroidectomy.

Medical history: patient with subtotal thyroidectomy fro Basedow disease under thyroid hormone replacement therapy is hospitalized for the symptoms mentioned above that occurred a few months before.

Clinical exam: rhythmic mild tremor in the upper limbs, sweating, extrasystoles, mild muscle deficit in the belts, with difficulty in resuming orthostatism position from sitting position, equal present ROT without any sensory disturbances.

Laboratory:

- hormone dosages: T3 – 188.5 ng/dl, T4 – 13.2µg/ml, TSH – low 0.2 microm/ml;
- CPK – 51 mUI/ml;
- Thyroid ultrasound: remnant thyroid tissue in the left lobe of 13/14mm with inhomogeneous echostructure, right thyroid lobe inhomogeneous, nodular, hypoechoic of 29/23/21mm;
- Thyroid scintigraphy (Figure 6):

- VCM and VCS in the external popliteal sciatic nerve – within normal limits;
- Muscle biopsy: nonspecific aspect of muscular suffering – Figure 7:

Deltoid muscle biopsy, H.E. staining, OBx10, O.C. x20:

The case was interpreted as a Basedow disease relapse with secondary chronic myopathy. The treatment with antithyroid synthesis drugs led to the improvement of the symptoms of muscle damage after about 6 months.

- Patient A.M., 36 years old

Admission grounds: muscle strength deficit in the belts, tremor, palpitations, weight loss.

Personal history: Basedow disease with subtotal thyroidectomy, followed by thyroid hormone replacement therapy.

Medical history: patient with subtotal thyroidectomy for Basedow disease is admitted for science of muscular distress that debuted with a few months earlier, associated with relapse signs of the thyroid pathology.

Clinical exam: upper limb tremor, sweating, moderate muscle strength deficit in the belts, equal present ROT without any sensory disturbances.

Laboratory:

- Hormone dosages: T3 – 196.4 ng/dl, T4 – 13.2 µg/ml, TSH – low 0.2 microm/ml;

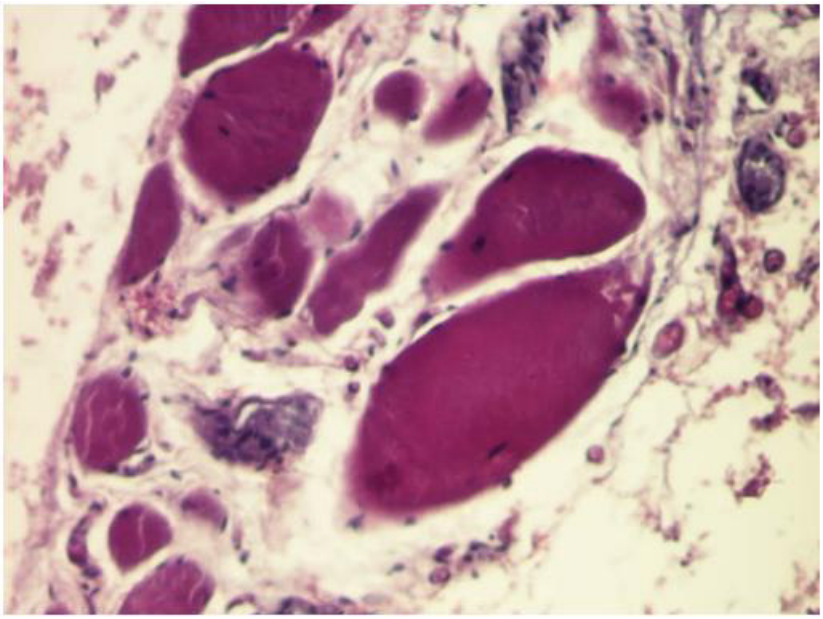

Figure 7. Muscle biopsy – Patient A.I., 36 years old: association of mildly atrophied fibers and fibers increased in volume, with homogenization of the cytoplasm or undergoing necrosis. A capillary with a mild mononuclear inflammatory infiltrate. The muscle fibers are dissociated due to the presence of an adipose tissue.

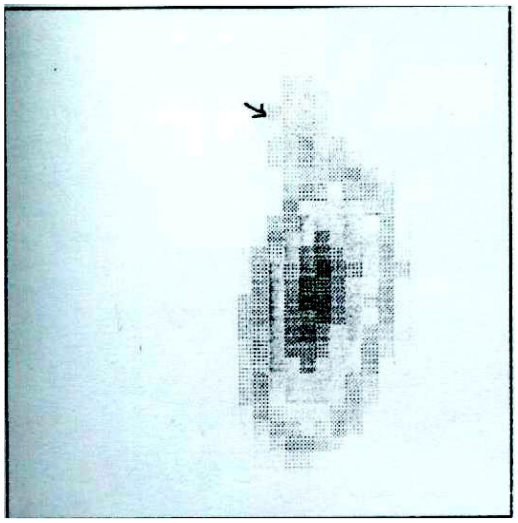

Figure 8. Thyroid scintigraphy – patient A.M., 35 years old: absent capture on the projection area of the right thyroid lobe. Projection area of the left thyroid lobe is enlarged with homogeneous capture, intensely increased. Accessory lobe attached to the internal edge of the left upper pole.

- Thyroid ultrasound: small residue of thyroid tissue in the right lobe, hypoechoic, left lobe 23/14/18 mm, homogeneous, hypoechoic.
- VCM and VCS in the external popliteal sciatic nerve – within normal limits;
- Thyroid scintigraphy (Figure 8):
- Muscle biopsy of myogenic type – Figure 9:

Deltoid muscle biopsy, H.E. staining, OB x20, O.C. x10:

The case exemplifies a situation of Basedow disease relapse associated with secondary chronic myoptahy.

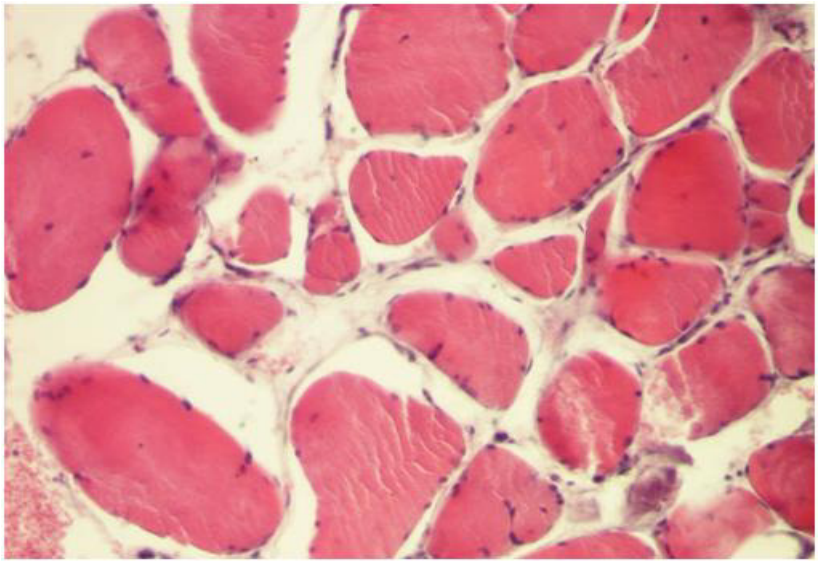

Figure 9. Muscle biopsy – patient A.M., 35 years old: striated muscle with a mild conjunctiv – adipose proliferation in the endomysium and with relatively rare atrophic fibers arranged randomly.

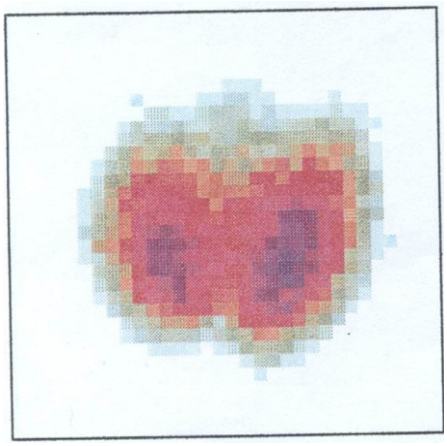

Figure 10. Thyroid scintigraphy – patient V.I., 38 years old: enlarged projection areas of the thyroid lobes, homogeneous capture especially increased in the left lobe. Accessory lobe attached to the upper edge of the isthmus.

The symptoms improved after 6 months of treatment with antithyroid synthesis drugs.

- Patient V.I., 38 years old

Admission grounds: diplopia, weight loss, tremor in the upper limbs, muscle strength deficit in the belts.
Personal history: without importance.
Medical history: the patient has horizontal diplopia, tremor in the upper limbs and weight loss for almost a year and recently she notifies lack of strength when climbing stairs and walking longer distances.
Clinical exam: mild bilateral exophthalmos, bidirectional horizontal diplopia, upper limb tremor, muscle strength deficit in the belts, equal ROT without sensory disturbances.
Laboratory:
- Hormone dosages: T3 – 175.4 ng/dl, T4 – 14.4µg/ml, TSH – low 0.2 microm/ml;
- CPK – 51 mUI/ml;
- Thyroid ultrasound: left thyroid lobe of 25/21 mm, isthmus of 7.7 mm, right thyroid lobe of 29/25 mm, pseudo nodular aspect, microcystic.
- Thyroid scintigraphy (Figure 10):
- Muscle biopsy of myogenic type: nonspecific;

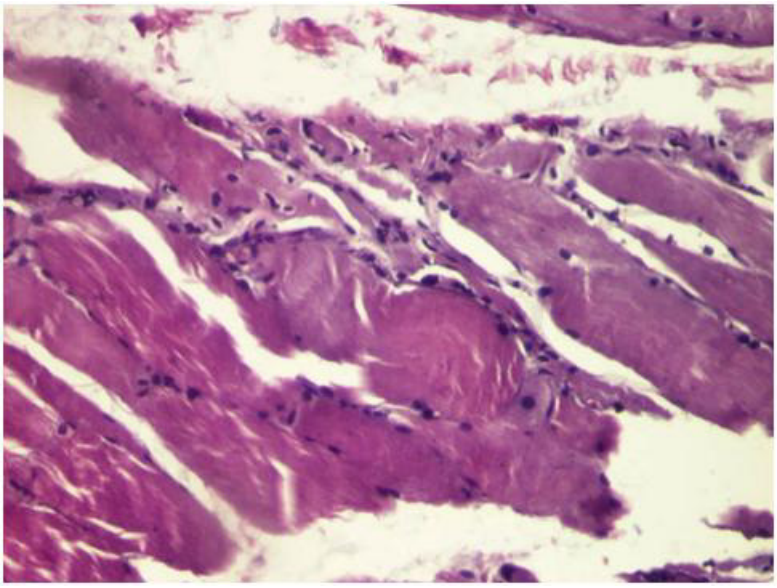

Figure 11. Muscle biopsy – patient V.I., 38 years old: striated muscle with groups of atrophied muscle fibers.

Table 4. Neuropathies in Basedow disease

No.	Patient identification data	Hormone dosages	Conducting speeds in the external popliteal sciatic nerve – knee-ankle segment		Neuropathy type
			VCM	VCS	
1.	D.A., fem, 65 years old	T_3 - 182 ng/dl T_4 - 8,5 □g/ml TSH - 0,2 microm/ml	43,2 m/s	37,25 m/s	Sensory
2.	T.M., fem, 46 years old	T_3 – 175 ng/dl T_4 – 13,5 □g/ml TSH - 0,2 microm/ml	42,35 m/s	36,45 m/s	Sensory
3.	D.V., fem, 50 years old	T_3 – 190,2 ng/dl T_4 – 12,75 □g/ml TSH - 0,2 microm/ml	36,25 m/s	34,25 m/s	Sensory motor
4.	E.I., fem, 31 years old	T_3 - 215 ng/dl T_4 - 109.2 □g/ml TSH < 0,1 microm/ml	37,34 m/s	37,35 m/s	Sensory motor

Muscle biopsy – calve, H.E. staining, OB x10, O.C. x10 – Figure 11.

In this patient, the clinical improvement of mypoathy suffering produced after a proper treatment with antithyroid synthesis drugs after about 6 months from the initiation of the therapy.

After this study, we conclude that chronic myopathy debuted in the study group after more than a year since the diagnosis of hyperthyroidism, muscle biopsy was nonspecific and muscle enzymes were within normal limits (Serratrice et. al. – 1997 – states the same aspects).

Clinical improvement occurred under treatment after at least 6 months, fact which was also confirmed by other studies.

3. Peripheral nerve manifestations:

- Sensory neuropathies – 2 cases – 5.58%;
- Sensory and motor neuropathies – 2 cases – 5.58%;

The suffering of the peripheral nerves included 2 cases of sensory neuropathy and 2 cases of sensory motor neuropathy (Table 4).

The sensory neuropathy manifested subjectively through distal paralysis in the lower limbs, objectively being recorded the decrease of superficial sensitivity in the distal 1/3 of the calves, but also through the decrease of the vibratory sensitivity in the lower limbs. VCS had low values in both the cases for the external popliteal sciatic nerve – knee-ankle segment but with normal

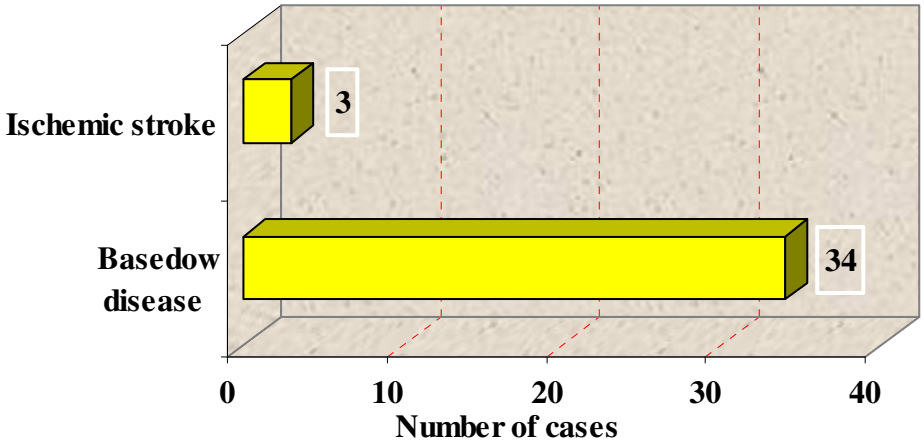

Figure 12. The frequency of ischemic stroke in patients with Basedow disease from the study group.

VCM values.

The sensory motor neuropathies associated to the symptoms described above a discreet lack of muscle strength in the lower limbs, predominantly distal. VCS had low values for the external popliteal sciatic nerve – knee-ankle segment. VCM in the same segment also had low values.

After the initiation of the treatment with antithyroid synthesis drugs, there was a slow clinical improvement of the electromyographic parameters within 6 months.

The frequency of the neuropathies registered in our study group was lower than the one quoted in other studies.

Thus, although it does state that peripheral nerve damage in hyperthyroidism is rare, Duyff et. al. (2000) mentions the occurrence of an axonal neuropathy in 19% of the patients with hyperthyroidism and the EMG changes showing an aspect of neurogenic suffering quoted in 24% of the cases with hyperthyroidism.

There are clinical trials that state that motor neuropathies occurring due to axonopathies in the subclinic stage occur in ½ of the patients with hyperthyroidism.

We have not encountered in the study group cases of Basedow paraplegia – acute neuropathy described by Feibel and Campa and confirmed by Duyff et. al. (2000).

Improvement of the symptoms after at least 6 months after the treatment initiation is also confirmed by other studies (Pandit et al., 1998).

4. Cranial nerves manifestations:

- Bilateral recurrent peripheral facial palsy with post paralytic hemifacial spasm – 4 cases – 11.76%;

5. The ischemic stroke in context of primary hypertension was found in 2 cases of Basedow disease – 5.88% and in 1 case of myxedema that appeared due to post thyroidectomy for Basedow disease with dyslipidemia and secondary stroke (although the patient was under thyroid hormone replacement therapy) – Figure 12.

The stroke has occurred, on average, after 3 years of the diagnosis of Basedow disease, the patients having ages between 50 – 70 years old. We found that the occurrence of an ischemic stroke was more frequent in patients with hypothyroidism and secondary dyslipidemia in the study group than in those with hyperthyroidism and with heart rhythm disorders.

Some studies state that the ischemic embolic stroke secondary to the heart rhythm disorders caused by thyrotoxicosis is one of the major neurological manifestations of hyperthyroidism.

6. Headaches:

- Training diffuse headache – 10 cases – 29.41%;
- Classic migraine – 2 cases – 5.88%.

7. Other neurological manifestations:

- - upper limb tremor – 10 cases – 29.41%;

Fine bilateral rhythmic tremor in the extremities was found in 10 out of the 34 cases, being obviously improved by treatment with antithyroid synthesis drugs.

Uldry et al. (1991) mentions that the tremor occurs in 90-95% of the patients with hyperthyroidism, sometimes being unilateral.

- - training vertigo – 10 cases- 29.41%;
- - fainting – 6 cases – 17.64% and syncopes – 2 cases – 5.88%.

The patients presented themselves initially in the neurology service due to fainting and confusional states, the clinical and paraclinical neurological and endocrinological evaluation establishing the diagnosis of Basedow disease. After the treatment initiation with antithyroid synthesis drugs the clinical symptoms have clearly improved.

- - epileptic seizures with polymorphic crisis – 2 cases – 5.88%.

In our patients we noted a decrease in the frequency of the seizures after the treatment with antithyroid synthesis drugs fact also mentioned by Uldry et al. (1991) which finds that in 1-9% of the cases of hyperthyroidism there are generalized convulsive seizures which respond better to anticonvulsive treatment when the patient are put under therapy and also under antithyroid synthesis drugs.

- Patient T.F. 25 years old.

Medical history: The patient is in the neurology ward for epilepsy with polymorphic crisis (temporal, tonic-chronic convulsions) for 2 years, with brain CT of normal aspect and moderate control of the crisis under anticonvulsive medication properly administrated. Symptoms are associated with tremor of the extremities, insomnia, weight loss, headache, mnesic disturbances, followed by bilateral progressive exophthalmos. There is a clinical suspicion of Basedow disease diagnosis which is confirmed in an endocrinology clinic where treatment with antithyroid synthesis drugs is initiated. What is noteworthy in this case is the obvious decrease regarding the frequency of epileptic seizures after thyroid pathology treatment initiation even though we could not establish a proper causal relationship between the 2 conditions (in neither of the 2 cases with epileptic seizures and Basedow disease from the study group).

Uldry (1991) mentions that epilepsy with generalized seizures occurs in 1-9% of the patients with hyperthyroidism, the frequency of the seizures decreasing under treatment with antithyroid synthesis drugs, fact confirmed by the data obtained in our study as well.

- Unorganized sensitivity disorders – 2 cases – 5.88%;
- Hyperreflexia of osteotendinous reflexes – 10 cases – 29.41%;

The elderly diagnosed with Basedow disease mainly presented physical asthenia, confusion, sleepiness, tremor, fatigue, adynamia, extrasystoles, training headache, vertigo, balance disorders, osteotendinous hyperreflexia, in some of the cases if the symptoms persisted, even performing brain CT which did not detect brain atrophy or cerebellar atrophy – 3 cases.

We have not encountered in the study group cases of myasthenia gravis even though this association is frequently quoted in other studies, in 0.1-0.35% of the cases with hyperthyroidism (Uldry et al.,1991).

As well we have not encountered any periodic hypokalemia palsy, the association being quoted by Asbury (2002), Rousset (2003), Uldry (1991) in minimum 2% of the cases with thyrotoxicosis.

Other studies quote the association between hyperthyroidism and choreoatetosis, also the association between hyperthyroidism and a SLA type syndrome, facts which we have not encountered in our study.

- The laboratory endocrinological diagnosis was supported by:

- Hormone dosages, antiperoxidase antibodies and antithyroglobulin dosages;
- Thyroid ultrasound;
- Thyroid scintigraphy;
- Exophthalmometry through orbit CT;

These investigations have been previously detailed.

- The laboratory neurological diagnosis included:

- FO exam;
- Electromyographic examination;
- Brain CT;
- Histopathological exam of muscle fragments.

Also these laboratory measurements were exposed in the cases described above.

CONCLUSIONS

1. In the study group we frequently met psychiatric accuses ranging from
emotional liability, anxiety, sleep disorders, psychogenic headache, adynamia to severe psychiatric suffering with severe depression, autolytic ideation and different types of schizophrenia.

The psychiatric symptoms are obviously improved by antithyroid synthesis drugs.

2. Basedow ophthalmopathy manifested in 6 cases out of the 34 from our study group regarding Basedow disease. It is noteworthy the situation of unilateral exophthalmos as an inaugural symptom that imposes different diagnosis with intracranial expansive processes.

3. The presence of diplopia as inaugural sign imposes the differential diagnosis with the other neurological diseases such as myasthenia gravis, brain stem etc.

We note that diplopia preceded by a few months the occurrence of other signs of thyroid pathology.

4. A characteristic clinical picture is identified in the elderly patients with Basedow disease, the dominant symptoms consisting of: sleepiness,
confusion, adynamia, headache and vertigo which require neuroimaging evaluation and which improve under treatment with antithyroid synthesis drugs.

5. It is unable to establish a causal relationship between epilepsy and Basedow disease even though patients who presented an association between the 2 conditions experienced an improvement of the symptoms and seizures after treatment initiation based on antithyroid synthesis drugs.

6. Association between Basedow disease and ischemic stroke is rare in our clinical trial on patients with hyperthyroidism with dyslipidemia secondary to thyroid hypofunction.

7. Myopathies, occurring exclusively in women were found only under a chronic form. The clinical diagnosis was electromyographically and morphopathologically, through muscle biopsy, confirmed showing myogenic suffering but without particulary aspects regarding the etiological context. Muscle enzymes were within normal limits. We have not encountered any acute thyrotoxic myopathies in the patients of our study group. Clinical

improvement requires a proper treatment with antithyroid synthesis drugs over a period of months.
8. Sensory and sensory motor neuropathies with clinical aspects and no EMG particularities have a favorable response to treatment with antithyroid synthesis drugs.
9. Although we commonly encountered associative disorders, we have not recorded any cases of myasthenia gravis in patients with hyperthyroidism from the study group nor any periodic hypokalemia palsies or choreoatetosis syndromes.

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