

Extraocular Muscle Involvement in Patients with Thyroid-Associated Orbitopathy

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SUMMARY

Aim: To determine the frequency of extraocular rectus muscle involvement in patients with thyroid-associated orbitopathy (TAO).

Materials and methods: A total of 154 orbits of 77 adult patients (53 women and 24 men) with TAO aged from 18 to 81 years (median 49 years) were investigated. Only patients with clear signs of TAO and confirmed thyroid disease who had been referred to the Department of Ophthalmology of the Olomouc University Hospital from May 2007 to December 2012 were included. All patients underwent general ophthalmic examination and ultrasonographic and MRI examinations of the orbit. The largest short and long cross-sectional diameter for every rectus muscle was measured on MRI scans. Spearman correlation analysis was used to determine the correlations between the diameters of rectus muscles and exophthalmos values obtained.

Results: A positive moderate correlation ($r = 0.514$) was shown between the sum of short parameters of all rectus muscles and exophthalmos values. When compared with the normative values and taking gender into account, enlargement of the medial rectus muscle (RM) was found in 55.2 %, of the lateral rectus muscle (RL) in 33.8 %, the inferior rectus muscle (RI) in 57.1 %, and of the superior muscle group (RS) in 59.1 %. In the cases of single-muscle enlargement, the most frequently affected muscle was the RS (48.8 %), followed by the RI (31.7 %) and RM (19.5 %). No case of single-muscle enlargement of the RL was observed. In the cases of two-muscle enlargement, the RS was involved in 64.3 %, the RI and RM in 60.7 %, and the RL in 14.3 %. In the cases of three-muscle enlargement, the most frequently affected muscle was the RM (93.1 %), followed by the RI (86.2 %), RS (69%), and RL (51.7 %).

Conclusion: Our study found that, in cases with single-muscle enlargement in patients with TAO, the vertical rectus muscles were most likely involved. On the other hand, in cases with multiple-muscle enlargement, the muscle most likely involved was the medial rectus muscle. In addition, the superior muscle group was noted to be affected more frequently than reported in the world literature.

Key words: thyroid-associated orbitopathy, extraocular muscles, magnetic resonance imaging

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INTRODUCTION

Endocrine orbitopathy (EO) is a chronic eye disorder which we encounter most frequently in patients with Graves-Basedow disease. In the majority of cases the disorder is manifested by typical ocular symptoms in patients with already diagnosed thyreopathy. Quick determination of the diagnosis and timely application of therapy is then the key to ensuring that the course of the disorder takes place under an image of a mild form of EO, without permanent consequences. Even despite adequately applied therapy, the disorder may progress to medium severe or severe form. In 10-25 % of cases, EO may also be the first symptom of a disorder of the thyroid gland. If there is a lack of data in the anamnesis concern-

ing a past or ongoing disorder of the thyroid gland, diagnostic problems may ensue, in particular if the finding is asymmetrical. In these cases, determination of the correct diagnosis is the result of a relatively extensive examination, which requires close co-operation between the endocrinologist and the ophthalmologist. One of the characteristic symptoms of EO which helps verify the diagnosis, as well as to monitor the efficacy of therapy and evaluate which phase of the disorder the patient is in, is affliction of the extraocular muscles. The advantages and disadvantages of the most widely used methods of imaging the orbit in patients with EO are frequently discussed in the literature [8, 18]. Ultrasonic diagnostics is a quick, non-invasive, widely used method. It enables not only assessment of the width of the extraocular muscles,

but also provides information about the degree of oedema in the muscles. Its disadvantage, however, is its low reproducibility and dependence on the experience of the examiner [9, 17]. At present CT is a highly accessible and relatively quick method. However, for the patient it represents exposure to radiation and does not provide any information about the activity of the disorder. The advantage of MRI is better distinction of the orbital soft-tissue structures than on CT. MRI also provides information about the activity of the disorder and does not expose the patient to radiation. Nevertheless, the examination is longer and financially more costly than CT. The aim of our study was to determine frequency of affliction of the individual extraocular rectus muscles in patients with EO. With regard to the fact that

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in regular ophthalmological practice, very often only the horizontal extraocular muscles are examined ultrasonographically [5], it was our another aim to determine the percentage of patients with EO in whom only the vertical extraocular muscles are afflicted, and who are thus at risk of a false negative result of the ultrasound examination upon the use of this procedure.

METHODOLOGY

Design of study

In total we assessed 154 orbits of 77 adult patients (53 men and 24 women) with EO, between the ages of 18 and 81 years (median age 49 years). Patients with clear clinical symptoms of EO and demonstrated thyreopathy, who were sent for examination and taken into care at the Department of Ophthalmology of the Medical Faculty of Palacký University and Olomouc University Hospital in the period from May 2007 to December 2012, were included in the study. A complete ophthalmological examination was conducted on all patients (determination of visual acuity, measurement of intraocular pressure, examination of anterior and posterior segment of eye and periorbital region). We measured exophthalmos using a Hertel exophthalmometer. We examined motility monocularly and binocularly. In all patients we conducted an ultrasound examination of the horizontal extraocular muscles and MRI of the orbit. We took a detailed anamnesis

with emphasis on the patients' subjective symptoms. On the basis of the results of the examination, we stipulated the Clinical Activity Score (CAS).

The study protocol was approved by the Ethics Committee of the University Hospital and Medical Faculty of Palacký University Olomouc. The study was conducted in accordance with Good Clinical Practice and the Helsinki Declaration.

MRI examination and measurement of extraocular rectus muscles

All MRI examinations were conducted immediately after the ophthalmological examination (at the latest within 10 days). The examinations were conducted natively on a Magnetom Avanto 1.5 T (Siemens, Erlangen, Germany) instrument, using a "CP head-array Tim" coil in the following sequences: T1-weighted inversion recovery sequence in a transverse plane (width of layers 0.9 mm), T2-weighted turbo spin echo sequence coronally (width of layers 3 mm), T2-weighted 3D sequence coronally (width of layers 0.7 mm) and T2-weighted spin echo sequence with 16 echoes in a coronal plane (width of layers 3 mm). All the sequences recorded the entire area of both orbits. We measured the dimensions of the extraocular muscles on the review station PACS (IMPAX version 6.4, Agfa Health Care, Mortsel, Belgium) with the assistance of multiplanar reconstructions produced

from a T1-weighted inversion recovery sequence. We measured the short (s) and long (l) dimensions of the transverse cross-section of the individual extraocular rectus muscles in the place of their greatest width on a reconstruction on a plane perpendicular to the course of the long axis of the orbit (Fig. 1 and 2). With regard to the fact that it was difficult to distinguish the superior rectus muscle and the elevator of the upper eyelid (musculus levator palpebrae superioris) from one another, we measured both muscles in all cases together as the "superior muscle group". This procedure is considered also in the published studies [2, 16]. All the measurements were performed by a single radiologist (one of the authors, RK) within a period of 3 weeks following the completion of the enrollment of the patients.

Statistical analysis

SPSS software version 15 (SPSS Inc., Chicago, USA) was used for the statistical analysis. The individual dimensions of the extraocular muscles were described with the help of the average value, standard deviation (SD) and median. The values obtained for each patient were compared with the standards for the width of the extraocular muscles in healthy individuals [16]. The muscles were evaluated as extended if their short dimension was greater than the stated physiological values (Table 1). For each muscle the

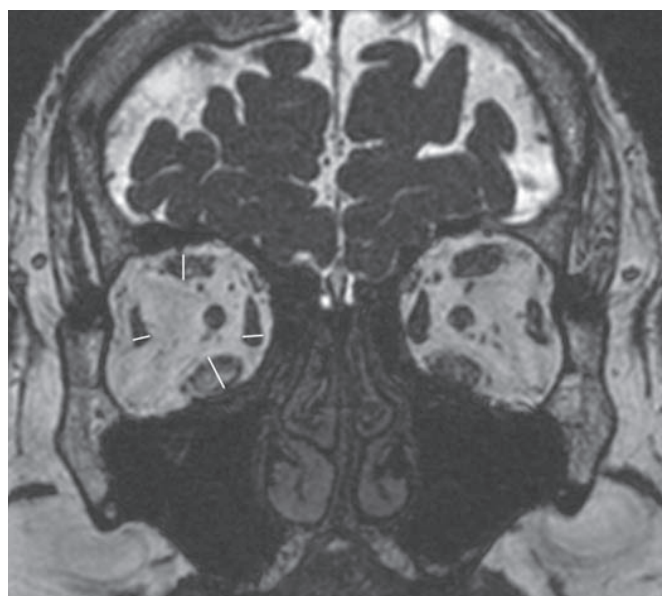


Fig. 1 Illustration of measurement of short diameters of extraocular muscles (for the sake of clarity displayed on a single MRI scan). Each scan was measured in practice in the point of its greatest width in a reconstruction on a plane perpendicular to the course of the long axis of the orbit.

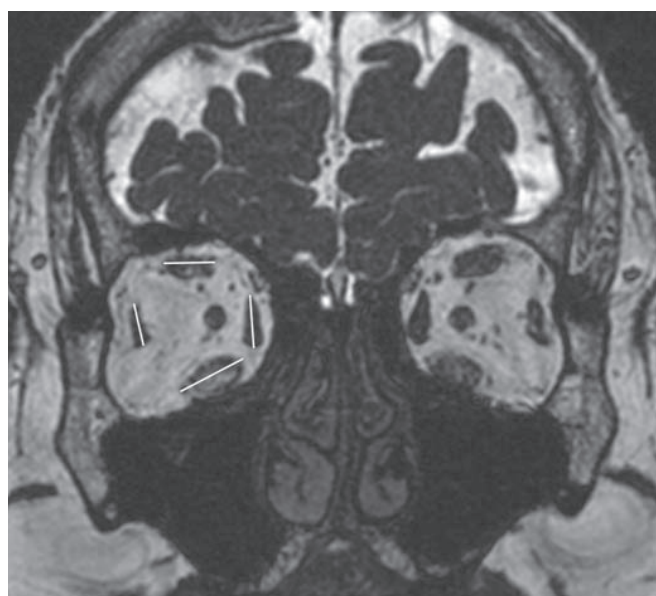


Fig. 2 Illustration of measurement of long diameters of extraocular muscles (for the sake of clarity displayed on a single MRI scan). Each scan was measured in practice in the point of its greatest width in a reconstruction on a plane perpendicular to the course of the long axis of the orbit.

Table 1 Upper limits of standard of width of extraocular muscles (short dimension) in healthy individuals in mm according to Özgen et al. [16]. Calculated as average +2SD.

	all	men	women
Internal rectus muscle	4.9	5.0	4.8
External rectus muscle	4.8	5.0	4.5
Inferior rectus muscle	6.0	6.2	5.8
Superior muscle group	5.6	5.9	5.4

index R (the ratio of short and long dimension) was also calculated. The relationship between the dimensions of the extraocular muscles and the degree of protrusion was assessed with the help of a Spearman correlation analysis. The normality of the data was verified using a Shapiro-Wilk test. The tests were conducted on a level of significance of 0.05.

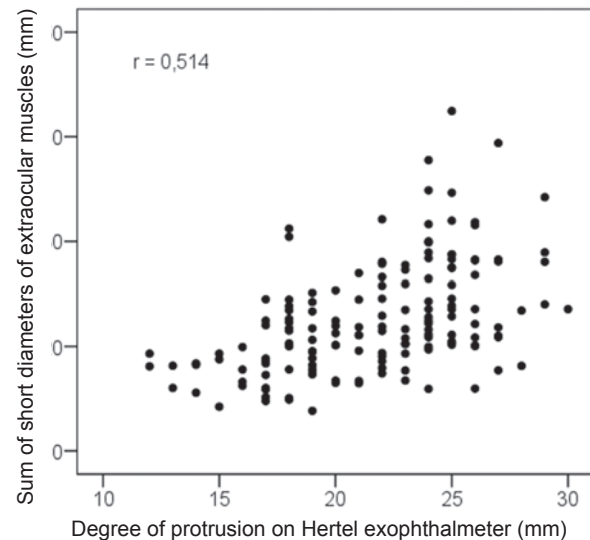
RESULTS

In the entire group, the average width of the short dimension (s) of the internal rectus muscle (musculus rectus medialis – RM) was 5.49 ± 1.72 mm, the external rectus muscle (musculus rectus lateralis – RL) 4.30 ± 1.19 mm, the inferior rectus muscle (musculus rectus inferior – RI) 6.49 ± 1.91 mm and the superior muscle group (musculus rectus superior + musculus levator palpebrae superioris – RS) 6.32 ± 2.24 mm. The details are stated in Table 2. The average width of the longer dimension (l) of RM was 10.75 ± 1.76 mm, RL 10.19 ± 1.25 mm, RI 10.94 ± 2.23 mm and RS 9.06 ± 2.40 mm. The details are presented in Table 3. The values of the average ratio of the short and long dimension ($R = s/l$) for each muscle including the standards for physiological orbits according to Aydin et al. [2] are presented in Table 4.

The values of exophthalmos within the whole group ranged from 12 to 30 mm (average 21.64 ± 3.97 mm). We demonstrated a medium-strong positive correlation ($r = 0.514$) between the degree of exophthalmos and the sum of short diameters of all four extraocular muscles (graph 1). Upon determining the correlation of the degree of exophthalmos with the short diameters of the individual extraocular muscles, the strongest correlation was determined for the short diameter of RS ($r = 0.478$), then RM ($r = 0.398$), RL ($r = 0.329$) and the weakest between RI ($r = 0.281$).

If we assessed the affliction of the extraocular muscles using the index R, the most commonly afflicted extraocular muscle was the RI (86.4 %), followed by RS (85.1 %), RM (63.0 %) and least often RL (53.9 %).

Upon a comparison with the normative values of only the short dimension of the extraocular muscles (16), without taking the gender into account, the RM was extended in 53.2 % of cases, RL in 31.2 %, RI in 57.1 % and RS in 57.1 %. If we took into account the different standards for men and women, RM was extended in 55.2 % of cases,



Graph 1 Spearman correlation analysis demonstrated a medium-strong positive correlation between the coefficient of the short diameters of all extraocular rectus muscles and the degree of exophthalmos ($r = 0.559$).

Table 2 Average values of the short dimension of width of extraocular muscles in mm in the entire group.

	average \pm SD	median	min - max
Internal rectus muscle	5.49 ± 1.72	4.97	3.08 – 11.20
External rectus muscle	4.30 ± 1.19	4.01	2.22 – 8.70
Inferior rectus muscle	6.49 ± 1.91	6.31	3.36 – 11.80
Superior muscle group	6.32 ± 2.24	5.85	2.71 – 17.80

Table 3 Average values of the long dimension of width of extraocular muscles in mm in the entire group.

	average \pm SD	median	min - max
Internal rectus muscle	10.75 ± 1.76	10.40	7.10 – 16.70
External rectus muscle	10.19 ± 1.25	10.10	7.10 – 14.20
Inferior rectus muscle	10.94 ± 2.23	10.45	7.40 – 19.10
Superior muscle group	9.06 ± 2.40	9.12	4.12 – 18.60

Table 4 Average values of R (the ratio of long and short dimension) for individual extraocular muscles in mm, normative values are stated according to Aydin et al. [2].

	Average \pm SD in our group	Average \pm SD for physiological orbits
Internal rectus muscle	0.506 ± 0.134	0.38 ± 0.03
External rectus muscle	0.432 ± 1.22	0.35 ± 0.025
Inferior rectus muscle	0.591 ± 0.104	0.44 ± 0.03
Superior muscle group	0.752 ± 0.441	0.41 ± 0.045

Table 5 Number of orbits with various numbers of extended extraocular muscles (expressed as percentage).

	No muscle	One muscle	Two muscles	Three muscles	Four muscles
Right orbit (n = 77)	11 (14.3 %)	23 (29.9 %)	13 (16.9 %)	12 (15.6 %)	18 (23.4 %)
Left orbit (n = 77)	12 (15.6 %)	18 (23.4 %)	15 (19.5 %)	17 (22.1 %)	15 (19.5 %)
Both orbits (n = 154)	23 (14.9 %)	41 (26.6 %)	28 (18.2 %)	29 (18.8 %)	33 (21.4 %)

RL in 33.8 %, RI in 57.1 % and RS in 59.1 %. We continued to work with these acknowledged norms. Upon a more detailed analysis we determined that in 14.9 % of cases (23 orbits) no muscle was afflicted, in 26.6 % (41 orbits) only one muscle was afflicted, in 18.2 % (28 orbits) two muscles were afflicted, in 18.8 % (29 orbits) three muscles and in 21.4 % (33 orbits) all four muscles, the details are presented in table 5.

If only one muscle is extended, this most frequently concerned the RS (48.8 %), followed by RI (31.7 %) and RM (19.5 %), whilst the RL was not afflicted in isolation in any single case. Upon affliction of two extraocular muscles, the RS was extended in 64.3 % of cases, RI and RM 60.7 % and RL in 14.3 %. Upon affliction of three extraocular muscles the RM was most commonly afflicted (93.1 %), followed by RI (86.2 %), RS (69 %) and RL (51.7 %).

We recorded isolated affliction of the vertical extraocular muscles (RI and RS) in at least one eye without concurrent affliction of the horizontal extraocular muscles (RM and RL) in 17 patients (22.1 %). In 4 patients RI was afflicted in isolation, in 5 patients RS and in 6 patients RI and RS simultaneously.

DISCUSSION

The course of EO and the actual affliction of the extraocular muscles is characterised by a number of phases. In the acute phase of the disorder, inflammation infiltration and swelling of the soft orbital tissues takes place, including the extraocular muscles. As a result of the inflammation oedema in the muscle, there is a restriction of its function, as well as a malfunction of its relaxation capability. Clinically we mostly find only discrete malfunctions of motility in ma-

ximum angles of view. Patients mostly subjectively state only intermittent, fluctuating diplopia – after awakening, during fatigue or in maximum lateral view. In this phase of the disease, it is possible to reverse the condition with sufficiently aggressive therapy. In the next phase of EO, fibrosis progressively occurs in the muscles. In the terminal stage of EO, the muscles may be altered into stiff, fibrous strips with a loss of both active and passive capacity for movement. Diplopia is manifested in the primary position. Progressive scarring of muscles leads to deviation of the eye. After some time it is often necessary in such cases to resolve the condition by a restrictive strabismus surgery [10]. According to the literature, the most frequently afflicted muscles are RI and RM [13, 14]. The first clinical symptom of affliction of these extraocular muscles is malfunction of elevation (initially only in abduction), in the terminal stage as far as hypotropia of the bulb (upon affliction of RI), or rotation of the eye to convergence (affliction of RM). The RS and RL are less commonly afflicted. A case of isolated affliction of the external rectus muscle [4] has also been described, as well as a number of cases of affliction of the superior oblique muscle [20]. In our clinical practice we also recorded patients with an extended superior oblique muscle.

In healthy individuals the extraocular muscles in a transverse cross-section are characterised by their ellipsoid shape. It is therefore possible to measure both their shorter and their longer diameter. In patients with EO, they become “rounded” as a consequence of lymphocyte infiltration and the accumulation of mucopolysaccharides – thus their shorter diameter is increased. Upon an evaluation of the width of the extraocular muscles, their shorter diameter is therefore usually assessed. The standards

for the width of the extraocular muscles in healthy individuals available in the literature differ slightly according to the used imaging methods and the author [3, 11, 15, 16]. Lee et al. [11] are of the opinion that the differences in the diameter of extraocular muscles in various studies may be caused by ethnic, socio-economic and nutritional differences. A number of the used normative values for the different imaging methods are presented in Table 6. A range of studies have also indicated the potential influence of gender and age on the resulting normative values [2, 11, 15]. For this reason, Aydin et al. [2] introduced the R index (ratio of short and long diameter of muscle in transverse cross-section) for the evaluation of affliction of the extraocular muscles in the case of EO. In their study they demonstrated that this index is not dependent upon either age or sex. They also demonstrated that a greater extension of the extraocular muscles in the direction of their shorter diameter occurs in the case of EO, thus an increase of the value of the R index. In several published studies it has been confirmed that wider extraocular muscles correlate to higher values of exophthalmos [5, 7]. We recorded the same results in our study. Surprisingly, from the individual extraocular rectus muscles, in our study the width of the RS correlated most strongly with the degree of exophthalmos. This result would confirm the results of the study by Hudson et al. [6], who determined that in patients with only slightly extended extraocular muscles only the volume of the superior rectus muscle correlated with the degree of exophthalmos. They assumed that it was the extension of the superior rectus muscle that could cause a deterioration of the venous drainage from the orbit, congestion and enlargement of the volume of the orbital fat, thus causing exophthalmos.

Table 6 Physiological values for width of extraocular rectus muscles in mm.

Author	Imaging method	RM	RL	RI	RS
Byrne et al. (3)	US	2.3 – 4.7	2.2 – 3.8	1.6 – 3.6	3.9 – 6.8
Özgen et al (15)	CT	3.3 – 5.5	1.7 – 4.8	3.2 – 6.5	3.2 – 6.1
Özgen et al (16)	MRI	3.2 – 4.9	2.6 – 4.8	3.1 – 5.6	3.7 – 6.0

US – ultrasound, MRI – magnetic resonance imaging, RM – internal rectus muscle, RL – external rectus muscle, RI – inferior rectus muscle, RS – superior muscle complex

For the purposes of our study we used the normative values for the width of the extraocular muscles for MRI according to Özgen et al. [16], and we also took into account the gender of the patients. In our group the RL was least often afflicted, which is in accordance with the international literature. Surprisingly, however, we recorded that the most frequently extended muscle was the RS, closely followed by the RI and RM. Also, upon use of the R index as the normative values for affliction of the extraocular muscles [2], RI and RS were afflicted with virtually the same frequency, followed by RM and least often again RL. In percentage terms, upon the use of this index, affliction of all the extraocular muscles was more frequent. Aydin et al. [2] in their study also recorded an increased R index in 7.5 % of 80 orbits of patients with EO, despite the fact that the short diameter of the muscle was within the limits of the standard. In our study we did not work further with this index.

It is possible that the frequent affliction of the RS in our group could have been caused by an error in the measurements, because it is precisely this superior group that is the worst defined. On the other hand, Szucs-Farkas et al. [19] in their study determined with the help of MRI that in a group of patients with EO, the widest muscles were the RI and RS, and only afterwards the RM followed. It is therefore possible that the development and use of more precise imaging methods has also enabled better distinguishing of the superior muscle group and more precise verification of its affliction. According to observations from clinical practice, in our opinion affliction of the superior muscle group may be overlooked also for the reason that even relatively pronounced extension of the RS need not lead to a restriction of motility (depression) of the bulb. On the contrary, even a relatively slight extension of the RI may lead to a restriction of elevation. Our clinical observation is in accordance with the studies by Lennerstrand et al. [12] and by Adams et al. [1], who determined that the function of the muscle or subjectively perceived diplopia does not correspond with the sonography finding on the extraocular muscles or with the volumes of muscles measured using MRI.

Our more detailed analysis then confirmed the observations of Murakami et al. [13], who evaluated the frequency of extension of extraocular muscles on CT on a large group of patients with thyreopathy. In this study, they pointed inter alia to the interesting fact that in patients with only one extended muscle this most frequently concerned the RI or RS, whereas the RM was extended only as an isolated case in a small percentage of cases. In patients with a number of extended muscles, however, it was surprisingly the RM that was most frequently extended, followed by the RI. We recorded exactly the same results in our study. To the best of our knowledge, this interesting phenomenon has never been clarified in any way. As a rule EO is diagnosed within the context of a hyperactive thyroid gland. Less often we may also encounter manifestations of EO in patients who have demonstrably never had and at the given moment do not have a demonstrably altered thyroid function in the classic sense. It is therefore indisputable that above all immunogenicity plays a fundamental role in the origin of EO. The markedly negative effect of cigarette smoke, as well as the positive effect of modulation of the function of the lymphocytes CD 19 and 20 by means of a specific monoclonal antibody also attest to this. Despite these facts, our own experience guides us ever increasingly towards the use of morphometric parameters in assessing the course and burden of EO. In regular practice for all patients with EO we conduct an ultrasound examination of the orbit and evaluate the finding on the extraocular muscles. In contrast with the immunological parameters, this procedure enables an assessment of the degree of organic changes in the area of the retina in real time, especially on the extraocular muscles, and according to this it is possible to apply sufficiently intensive, effective therapy. However, ultrasound examination of the vertical extraocular muscles is difficult in certain cases. Access to the RI may be facilitated by the anatomical ratios (markedly prominent superciliary ridge); ultrasound evaluation of the superior muscle complex requires considerable experience on the part of the examiner. For this reason, in regular daily

practice only the horizontal extraocular muscles are examined [5]. According to the results of our study, affliction of the extraocular muscles would have been overlooked in 17 patients (22.1 %) upon the use of this procedure. We need to be aware of this fact. We must consider the possibility of isolated affliction of the vertical extraocular muscles especially in the case of a clinical finding of restriction of elevation and intermittent diplopia stated by the patient.

The weakness of our study is indisputably the fact that with regard to the financial demands of the examination, we were unable to set up a control group and create our own standards for physiological orbits. On the other hand, we adhered precisely to the recommended protocol for the procedure of measurement of the diameters of the extraocular muscles.

CONCLUSION

Imaging methods of the orbit are of great benefit in determining the correct diagnosis of EO and for follow-up observation of patients. In the majority of cases, ultrasound examination of the finding on the horizontal extraocular muscles in connection with an ophthalmological examination is a sufficient, fast and relatively cheap method for determining the correct diagnosis. On the basis of our study, however, we confirmed the fact that in the case of isolated affliction of only one extraocular muscle, this will most probably be a vertical muscle. It is necessary to remember this fact. Conversely, with affliction of a number of extraocular muscles, the greatest probability is affliction of the internal rectus muscle. In our group we also indicated a more frequent affliction of the superior muscle group than is stated in the international literature. CT and MRI thus indisputably have their place especially in the verification of the diagnosis in patients with opaque clinical symptoms of EO or intermittent diplopia, since only timely diagnosis and quickly applied therapy can prevent serious consequences of this disease.

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