15. Acquired autoimmune myasthenia gravis - Heterogenous entity

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Abstract. Acquired autoimmune myasthenia gravis (MG) is an organ specific autoimmune disorder of the neuromuscular junction. In the majority of the patients (~85%) antibodies are directed to muscle postsynaptic nicotinic acetylcholine receptor (AChR), but in others the target is non-AChR protein at neuromuscular junction, such as Muscle-specific receptor tyrosine kinase (MuSK), or low density lipoprotein receptor related protein 4 (LRP4). This autoantibodies can be detected by specific assays and implicate different therapeutic strategies and prognosis of the disease. The basic pathophysiological finding in MG is muscle endplate dysfunction with fluctuating fatigue and weakness of skeletal muscles. The clinical presentation of MG is heterogenous, from pure ocular form on the one side, to severe bulbar or respiratory weakness on the other side. The onset of the disease may be in childhood period (under 2 years of age), juvenile period (2-16 years of age), young adult period (between 16 and 50 years of age) and late adult period (after the age of 50 years). Also, the disease is heterogenous in the aspect of thymus pathology. In 60-70% of patients there is thymus hyperplasia, in 10-15% thymic tumor (thymoma), while in the remaining 20% persistent or atrophic thymic tissue.

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Good knowledge about heterogeneity of MG is of outstanding importance, not only because of the better understanding of the disease pathogenesis and differences in interpretation of the conducted diagnostic procedures (for example, prostigmine test in patients with MuSK MG can induce worsening of the symptoms), but also because of the different therapeutic approach to the patients with different forms of MG (for example, in MuSK positive patients, patients with ocular form of MG and in late onset patients with generalized form of the disease thymectomy is not recommended). In that way, knowledge about all subentities of the disease contributes to the improved diagnosing and the disease outcome, which is noted in the last ten years and this trend still continues.

Myasthenia gravis comprises numerous, heterogenous disorders of the neuromuscular junction, which are in the majority of cases clearly defined and caused by autoimmune processes or genetic mutations. Among these disorders, the most frequent is acquired autoimmune myasthenia gravis (MG) which is caused by the disruption of the postsynaptic muscle membrane by different autoantibodies.

The first clinical description of this disease was published by Thomas Willis in 1672 in the journal “De anima brutorum” (1), and its autoimmune origin was assumed by Simpson (in 1960.) on the basis of clinical similarities between MG and systemic lupus erythematoses (2). The major clarifying of the MG pathogenesis is the results of the experiments performed by Patric and Lindstrom, who registered signs of myasthenic weakness in the experimental rabbits imunized by nicotinic acetylcholine receptor (AChR) of Torpedo californica, and detected the presence of anti-acetylcholine receptor antibodies in their sera (anti-AChR Ab) (3). In the later period, lot of studies proved the pathogenetic role of anti-AChR Ab in the structural and functional disruption of the neuromuscular junction (4, 5) and this form of MG is the most frequent clinical presentation.

MG is relatively rare disorder with the incidence of 3 to 30 per million and the prevalence of 15 to 200 per million inhabitants (6-8). Disease onset is in most of the patients between 20 and 30 years, predominantly in females in this age group and between 60 and 80 years with the similar incidence in both genders. Alltogether, among patients with MG there is clear female preponderance (6-9).

Nevertheless, it is well known that MG presents heterogenous entity in many different aspects. It is neccessary to get informed about all disease variants because of the different diagnostic algorythm, treatment and prognosis.

**Heterogenity of MG in the clinical presentation**

MG is clinically characterized by the fluctuating weakness of the striated muscles, which worsens after prolonged or repetitive muscle activation,
while it improves after the rest or treatment with anticholinesterase drug. In over 50% of patients with MG, initial symptom is the weakness of the extraocular muscles (9, 10), and in 5-25% of patients ocular symptoms remain the only clinical presentation. This form of MG is so called ocular form and in the clinical terms it represents the distinct entity (9, 10). In most of the patients (70-80%) symptoms of MG generalize during the course of the disease, with the development of the weakness and fatiguability of other skeletal muscles, which usually happens during the first two years after the disease onset (9-11). It is believed nowadays that this percentage is much lower, because early and adequate immunosuppressive therapy decreases the risk of symptom generalization up to 75% (12). Frequent finding in MG patients is bulbar muscle weakness, present in more severe forms of the disease, although in 15-26% of patients this clinical presentation can be initial symptom of MG (9-11). Weakness can affect any other skeletal muscle in the body, for example different extremity muscles, more frequently proximal than distal, respiratory muscles, neck, and rarely auditory muscles or voluntary sphincters of the bladder and bowel. Weakness of oropharyngeal and respiratory muscles is present in the most severe forms of the disease (myasthenic crysis) and it often requires assisted ventilation (10).

Finally, in relation to the clinical presentation, it is important to mention also focal form of MG, which is characterized by the affection of only one muscle (for example rectus lateralis, obliquus inferior or other muscles) or localized muscle group (for example fingers extensors, with the „dropped fingers” phenomenon, or external urethral sphincter with the urine incontinence (13). Knowledge about this form of the disease is of great importance in the neurological practice because prolonged isolated weakness of only one muscle or the muscle group rarely associates the doctor with the diagnosis of MG, and more frequently to the presence of some other disease, for example the mononeuropathy associated with diabetes.

Regarding different clinical presentations of the disease, which direct the further diagnosis and treatment, Osserman and Genkins classification from 1971. has been previously used (14). However, during every day neurological practice, this classification of MG showed significant imperfections in the classification of all MG patients, which is why Myasthenia gravis Foundation of America (MGFA) suggested new clinical classification of the disease (15). This classification enables more precise clinical definition of each patient and is presented in Table 1.
Table 1. Myasthenia Gravis Foundation of America (MGFA) classification of the MG severity.

<table>
<thead>
<tr>
<th>Form of MG</th>
<th>Clinical manifestations of the disease</th>
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<tbody>
<tr>
<td>I</td>
<td>Exclusively ocular symptoms</td>
</tr>
<tr>
<td>IIA</td>
<td>Mild weakness of the predominantly trunk and/or extremity muscles</td>
</tr>
<tr>
<td>IIB</td>
<td>Mild weakness of the predominantly bulbar and/or respiratory muscles</td>
</tr>
<tr>
<td>IIIA</td>
<td>Moderate weakness of the predominantly trunk and/or extremity muscles</td>
</tr>
<tr>
<td>IIIB</td>
<td>Moderate weakness of the predominantly bulbar and/or respiratory muscles</td>
</tr>
<tr>
<td>IVA</td>
<td>Severe weakness of the predominantly trunk and/or extremity muscles</td>
</tr>
<tr>
<td>IVB</td>
<td>Severe weakness of the predominantly bulbar and/or respiratory muscles</td>
</tr>
<tr>
<td>V</td>
<td>Need for intubation</td>
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According to this classification, all patients with MG can be classified into 5 different groups:

1) class I – presence of isolated affection of extraocular muscles;
2) class II – presence of mild generalized weakness, with or without affection of extraocular muscles;
3) class III – presence of moderate generalized weakness, with or without affection of extraocular muscles;
4) class IV – presence of severe generalized weakness, with or without affection of extraocular muscles;
5) class V – the most severe form of MG, with the presence of severe generalized weakness, with the affection of the vital muscle groups, oropharyngeal and respiratory muscles, and the need of nasogastric tube feeding and intubation with or without assisted ventilation.

Classes II, III and IV have 2 subclasses: subclass (a) presents predominant affection of trunk and extremity muscles, with the possibility of mild oropharyngeal muscle weakness, while subclass (b) presents predominant affection of oropharyngeal and/or respiratory muscles with the possibility of mild affection of trunk and extremity muscles.

Knowledge of this classification is necessary because of the different treatment procedures in the patients with different forms of MG, and also
because it helps in analyzing the effects of the applied therapy during the follow up period. For example, in patients with purely ocular form of MG thymectomy should not be performed, but the treatment consists of anticholinesterase therapy alone or in combination with immunosuppressive drugs, in young patients with IIIb or IVa forms of the disease thymectomy is always recommended in combination with the dual immunosuppressive therapy with corticosteroids and azathioprin or cyclosporin A, while in patients with IVb or V forms of the disease treatment with plasma exchange or intravenous immunoglobulines is often necessary, usually as the preparation for the thymectomy or acceleration of the effects of the applied immunosuppressive therapy.

**Heterogeneity of MG regarding age at the disease onset**

In relation to the time at the symptom onset, MG can be classified as juvenile MG, early onset and late onset MG.

**Juvenile MG**

The age dividing juvenile and early onset MG is according to some authors 16, a according to the others 18 years, and it is classified as prepuberty, peripuberty and postpuberty MG. Juvenile form of the disease comprises in white population 10-15%, while in the Asian population it comprises around 50 % of all cases of MG (16). Postpuberty MG is very similar to the early onset MG, while prepuberty MG differs in many aspects. In this group of patients gender frequency is similar, ocular form of the disease is more frequent, there is higher rate of spontaneous remissions and extremely rare presence of thymoma (in 3.8% of patients) (17, 18). Percentage of seronegative patients is much higher in the youngest patient population and it is between 36-50% (19), and the significance of thymectomy is less clear in this group of patients. According to some authors, good efficacy of thymectomy was present in only 27-30%, while other authors registered good efficacy of thymectomy in much higher proportion of patients (16, 19). Besides that, there are also dilemmas about possible negative effects of thymectomy in the youngest patients, so this issue still remains controversial (16, 20).

**Early onset MG**

Early onset MG begins between 16 or 18 and 50 years of life and it comprises around 65% of all cases. There is female preponderance
(male/female ratio is 1:4) and the onset of the disease is usually in the second or the third decade of life. In this group of patients, there is significant correlation with several HLA haplotypes: in white patients with HLA A1, B8, DQB1, DR3, DR52a (21), and in Japanese with HLA DRB1, DQB1, DR9 (22). The most frequent thymus pathology is hyperplasia, which is present in 65-80% of patients. Since there is high frequency of remission after thymectomy, this treatment is recommended in all patients with generalized clinical presentation and positive anti-AChR antibodies. In this group of patients, besides anti-AChR antibodies, the presence of other autoantibodies is also detected, as well as other associated autoimmune disorders, most often autoimmune diseases of the thyroid gland (9, 23, 24). On the other hand, the presence of antibodies against other antigens of the neuromuscular junction is rare (24).

**Late onset MG**

The borders between early onset and late onset MG is according to some authors 40 (24), and according to the others 50 years (6, 9, 23, 25, 26). These patients are characterized by the similar gender frequency or even male preponderance (25), with the disease onset peak between 70 and 80 years. In comparison to early onset MG ocular form of the disease is much more frequent, although clinical presentation is usually more severe. Anti-AChR antibodies are present less frequently and in lower concentration, while antibodies against other antigens of the neuromuscular junction are much more frequent. Antibodies against titin and ryanodine receptor are present in around 50% of patients. In this group of patients there is weak correlation with the HLA A3, B7, DR2, DR4 and thymus is most often normal or atrophic (24, 26).

**Heterogenity of MG regarding thymus pathology**

The role of thymus in the pathogenesis of MG was assumed by the observation that the thymus is pathological in 80% of patients and that after thymectomy most of the patients experience significant clinical improvement. The most frequent thymus finding is lymphopholicular hyperplasia (LFH), which is present in 50-70% of patients. Thymoma is present in 10-15% of patients, while normal or atrophic thymus tissue is present in the remaining 20% of patients (9, 27).

It is important to mention that thymus pathology directs the therapeutic approach, for example in the case of thymoma, it is necessary to perform thymectomy, regardless the age, disease form, presence of antibodies or
therapeutic response. On the other hand, in the absence of thymoma, thymus pathology is not important in making the treatment protocol. In that case, thymectomy is performed concerning the presence of anti-AChR antibodies, disease form and the patients age.

**Thymus lymphophollicular hyperplasia**

LFH is the most frequent thymus finding in the patients with MG, and it is especially frequent in the early onset disease patients. It is often associated with the elevated titer of anti-AChR antibodies (in around 2/3 of cases), much less frequent in seronegative MG (SNMG) (in around 1/3 of cases), while it is extremely rare in patients with MuSK MG (27, 28). Thymus hyperplasia is characterized by the hyperplastic medulla with lot of germinal centers, surrounded by the T lymphocytes. These thymuses contain large number of AChR-specific T lymphocytes and increased number of B cells, which produce anti-AChR antibodies. In the thymus medulla are present B cell lymphoide foliculles with developed germinal centers, while cortex remains unchanged or it shows signs of partial atrophy. This pathohystological profile is typically present in AChR positive and SNMG patients. Opposite from this, in MuSK positive patients, there are T and B lymphocytes in lymphoid infiltrates, epithelial border is usually intact, and morphology of thymus perivascular spaces is usually dependant on the patients age (28). Since myoid cells express MusK (29), it could be expected that MuSK positive patients have similar perivascular infiltrates as AChR positive patients, but such finding is extremely rare in MuSK MG patients (30). In the group of SNMG patients, thymus pathology is similar as in AChR positive patients, although they have milder changes.

**Thymoma**

Thymomas represent the heterogenous group of the thymus gland tumours. According to the pathohystological finding they can be cortical, medullar and mixed, benign or malignant. In the patients with MG most frequent are cortical thymomas and well differentiated thymus carcinomas. Unlike hyperplastic thymus, the presence of AChR is not registered, but proteins which share the similar antigen determinant with cytoplasmic part of AChR have been detected (31). The possible explanation for the association of MG and thymoma could be that thymomas develop by LFH progression, or antitumorous or paraneoplastic autoimmune reaction gets induced by the tumor antigenes (32). Thymoma is present in 10-15% of patients with MG, more often in older patients, with similar gender
distribution (9, 24). Patients with thymoma associated MG usually have severe forms of the disease, although they have similar disease outcome as patients with non-thymomatous MG (24). Patients with thymoma usually have high titer of anti-AChR antibodies, and besides that also frequent presence of antibodies directed against other antigens on the neuromuscular junction. Antibodies against titin are present in 90% of patients, while antibodies against riandoin-receptor (RyR) are encountered in half of the patients (24). Presence of thymoma is exceedingly rare in patients with MuSK MG and is presented only in the form of individual case reports (33).

**Thymus atrophy**

Thymus atrophy is present in 17-36% of patients with MG, more often in patients older than 50 years. The main characteristics of thymus atrophy are involutive changes of thymus, which gets replaced by fatty tissue. However, it is not unusual that parts of thymic parenchima remain in the fatty tissue, while sometimes even lymphoid phollicules, B cell infiltration and increased number of interdigitate cells can be found, which clearly implies involvement of atrophic thymus in the pathogenesis of MG.

**Normal thymus (thymus persistens)**

Normal thymic tissue is present in 10-25% of patients with MG. Since involutive changes are milder than in healthy persons, such thymus is called thymus persistens. Nevertheless, even in this so called normal thymic tissue there are enlarged perivascular spaces, B cell infiltration of medulla and increased number of interdigitate and myoid cells, which suggests that these changes would evolve into LFH in the later course of the disease.

**Heterogenity of MG regarding the presence of different autoantibodies**

MG represents the prototype of humoral-mediated autoimmune disease. However, since anti-AChR antibodies, which have proven pathogenetic role (3-5), are present in around 80% of patients, there was long standing dilemma weather AChR negative form of the disease is also of autoimmune origin. The autoimmune origin of the disease was supported by the facts that babies of mothers with AChR negative MG had transitory neonatal MG, that AChR negative patients have improvement after plasma exchange and immunosuppressive therapy, and that disease was passively induced in experimental animals by the immunoglobulines from sera of these patients.
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(34,35). Great discovery in revealing the etiology of AChR negative MG was in 2001, when Hoch et al. detected antibodies against muscle specific tyrosine kinase (MuSK) in around 40% of patients with AChR negative generalized MG, and defined new entity – MuSK MG. Ten years later Zhang et al. detected antibodies against low-density lipoprotein receptor-related protein 4 (LRP4) in small number of double seronegative (AChR and MuSK negative) patients (37). LRP4 is nowadays studied as the new target of immune response in MG. Anyway, in around half of the AChR negative patients target antigen is still unidentified and the etiopathogenesis of this group of patients is not completely understood.

AChR positive MG

MG with antibodies against nicotinic AChR of the postsynaptic muscle membrane is the most frequent and best defined form of the disease. It comprises 80% of patients with generalized and 50-70% of patients with ocular form of MG (24). The pathogenetic role of anti-AChR antibodies is definitelly proven (3-5), and its presence is one of the diagnostic criteria for MG, although the correlation between disease severity and antibody titer was not established (24, 38). Anti-AChR antibodies are predominantly of IgG1 and IgG3 subclass, and the major mechanism of the neuromuscular transmission impairment is complement mediated lysis of the postsynaptic muscle membrane, destruction of its secondary folds and reduction of AChR number in the end plate region. This immune response is T-cell dependant, with the key role of CD4 T lymphocytes which stimulate B cells to produce pathogenetic autoantibodies.

This form of MG has onset at any age and can be associated with different thymus pathology, most often with thymus hyperplasia or thymoma. In cases with early onset disease, the most frequent is thymic hyperplasia, with the finding of T, B and plasma cells in the thymus, as well as myoid cells which express nicotinic AChR (nAChR). It is proven that thymocytes isolated from these thymuses spontaneously produce anti-AChR Ab in the cell culture, which implies that in hyperplastic thymus, probably induced by Ebstain-Barr or other virus, begins immune response against nAChR (39). That is the reason why in early onset AChR MG thymectomy is considered to be one of the major therapeutic procedures, which is at the moment confirmed empirically with the positive effects of thymectomy on the disease course (9, 10, 24). In the group of AChR MG, early onset disease is present in around 65% of patients. In this group of patients, there is absolute female preponderance and frequent presence of other autoimmune diseases.
On the other hand, in late onset AChR MG patients, there is similar gender distribution, and thymus is most often atrophic or rarely associated with thymoma (24, 26). Serum anti-AChR Ab titer is usually lower, and antibodies against other neuromuscular junction antigens, like titin or RyR are present in around one half of patients.

**MuSK positive MG**

MuSK is transmembrane end plate polypeptide involved in the signalling pathway responsible for the maintenance of the normal functional integrity of the neuromuscular junction. Together with proteins LRP4 (37) and “tumorous imaginal discs” (Tid1) (40) MuSK plays the role in the development and maintenance of the neuromuscular junction, and especially in clustering of AChR on the postsynaptic membrane and acetylcholinesterase (AChE) fixating for the basal lamina of the synaptic cleft by interaction with its binding protein, “collagen tail of the AChE” (ColQ) (41). Current opinion is that MuSK is stimulated “from the inside” of the muscle cell by Dok7, and from the “outside“ by LRP4 protein, with or without agrin (42). It is shown that serum anti-MuSK Ab bind to the external part of MuSK, decrease agrin induced AChR clustering in the culture of myotubules (36) and block binding of ColQ to MuSK (43). In that way, although there is no loss of AChR on the postsynaptic membrane, they decrease the concentration of MuSK, disrupting the AChR clusters and retracting the terminal nerve ending (44, 45). Their pathogenetic role in the induction of MG is clearly confirmed by the experiments in which immunization of the animals with recombinant ectodomain of MuSK resulted in the myasthenic weakness (46). Anti-MuSK antibodies are predominantly of IgG4 class, which do not activate complement, although in a small proportion they can be also of IgG1 class (44). In the last 10 years, it has been shown that anti-MuSK Ab are present in sera of 30-70% of AChR negative patients with generalized form of MG (45).

MuSK MG is also specific in the terms of genetic predisposition, influence of the enviromental factors, clinical presentation and response to the therapy (24, 47-49). In patients with this form of MG, HLA DR14 and DQ5 alleles are frequently present, unlike patients with AChR MG (47). MuSK MG is the most frequent in the countries around 40°N latitude and its prevalence gets lower towards north, which suggests the influence of some enviromental factors in the disease development (48). On the other hand, AChR MG is geographically ubiquitous disease. In the group of patients with MuSK MG, there is marked female preponderance (up to 7.5:1), and the onset of the disease is in most of the patients before 40 years
of age (24, 49, 50). Regarding clinical presentation of the disease, MuSK MG is characterized by the generally more severe forms of the disease and more frequent myasthenic crisis, while the mildest form of the disease with affection of exclusively extraocular muscles is extremely rare and is reported only in the form of case reports (50,51). The most frequent clinical presentation of MuSK MG is characterized by severe oculobulbar weakness with dysphonia, dysphagia and chewing impairment. The second clinical pattern is characterized by the focal weakness, predominantly of the neck, shoulder and respiratory muscles. In this group of patients, ocular symptoms are mild and mostly present in the later course of the disease (50). The third clinical presentation of MuSK MG is very similar to AChR positive MG, so that these two forms can not be distinguished clinically. MuSK MG is characterized by the atrophy of the affected muscle groups, most frequently of the tongue and facial muscles, with intramyocellular lipid deposition in the tongue, which is also confirmed by the magnetic resonance spectroscopy (52). Ultrastructural muscle changes in MuSK MG are myopathic, with the evidence of mitochondrial abnormalities, unlike changes in AChR MG, which are consistent with mild neurogenic atrophy (53).

Regarding therapy, this form of MG is characterized by the specific response to anticholinesterase drugs, which is often absent or even reverse (50,54). Only 30% of patients with MuSK MG have improvement with anticholinesterase therapy and usually low doses of these drugs are recommended. Repetitive nerve stimulation test is, in MuSK MG patients, less sensitive than in AChR MG, because during this examination significant decrement is registered in weak muscles in less than 50% of patients. In these cases, more sensitive examination is single fiber electromyography (SFEMG), but only if clinically affected muscles are tested, predominantly facial, shoulder and neck muscles. Thymus pathology is in MuSK positive patients very rare, thymus is similar as in healthy subjects, without lymphoid folliculles and germinal centers (55). This finding speaks clearly in favour of the assumption that thymus has no role in the induction of the disease.

**LRP4 MG**

Further clarification of the MG pathogenesis was made in 2011., when anti-LRP4 antibodies were identified in the sera of double seronegative patients (anti-AChR and anti-MuSK antibody negative) (56-58). These antibodies were registered in 9 out of 300 seronegative patients and in several patients with anti-MuSK antibodies, while in the group of AChR positive MG were not detected in any patients (56). It is shown that these antibodies inhibit binding of LRP4 with agrin and are predominantly of IgG1
subclass, meaning that they can activate complement (57). There are experimental proofs that sera of patients with anti-LRP4 antibodies inhibit agrin induced AChR aggregation in the culture of myotubuls, suggesting the pathogenetic role of anti-LRP4 antibodies in the neuromuscular junction failure (58). It is believed that anti-LRP4 antibodies have pathogenetic effect through agrin-LRP4-MuSK signal pathway, which defines LRP4 protein as the third autoantigen in the patients with MG (58).

**Seronegative (AChR i MuSK negative) MG**

Even after discovery of new antibodies against different antigenes of the neuromuscular junction, in the small proportion of MG patients any of the known antibodies could nor be identified. Since there is clinical similarity between seronegative and AChR positive early onset MG, it is assumed that these patients could have anti-AChR antibodies, which can not be detected by standard radioimmunoassay. Furthermore, it is experimentally proven that more than 60% of seronegative MG patients have anti-AChR antibodies of predominantly IgG1 class, similar as in classical AChR MG. In the first part of the experiment, human embrional kidney cells (HEK 293) which expreme the whole AChR molecule (with \( \alpha, \beta, \delta \) and \( \epsilon \) subunits) were incubated with the sera of seronegative MG patients, but after adding immunofluorescent alexa-flor-anti-humane IgG there was no binding of antibodies with AChR. On the other hand, in classical AChR positive patients this binding was very strong. In the second part of the experiment, the same HEK293 cells transfected with AChR and rapsyn, which induces conglomeration of AChR, and afterwards was repeted the same procedure from the first experiment and at that time, clear binding was proven not only in all AChR positive, but also in more than 60% of seronegative sera (59). In that way was definitelly confirmed that seronegative MG patients also have anti-AChR antibodies, which can not be detected by standard radioimmunoassay due to the low affinity to the receptor. These antibodies are predominantly of IgG1 class and they activate complement (59). In favour of this speaks the reduction of the AChR number and the complement deposits found in the biopsy muscle tissue of the patients belonging to this group of MG (60).

In the group of seronegative MG, thymus tissue abnormalities are similar as in AChR MG: thymus hyperplasia is often found, with lymphocyte infiltration and germinal centers, T and B cells (59). Because of all above mentioned similarities, patients without both anti-AChR and anti-MuSK antibodies are treated identically as AChR positive patients. In this group, besides anticholinesterase and immunosuppressive therapy,
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Thymectomy is always recommended, because it has favourable effect to the disease outcome.

Good knowledge about heterogenity of MG is of outstanding importance, not only because of the better understanding of the disease pathogenesis and and differences in interpretation of the conducted diagnostic procedures (for example, prostigmine test in patients with MuSK MG can induce worsening of the symptoms), but also because of the different therapeutic approach to the patients with different forms of MG (for example, in MuSK positive patients, patients with ocular form of MG and in late onset patients with generalized form of the disease thymectomy is not recommended). In that way, knowledge about all subentities of the disease contributes to the improved diagnosing and the disease outcome, which is noted in the last ten years and this trend still continues.

References


