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NEW APPROACHES TO THE QUANTIFICATION OF THERAPEUTIC RESPONSE IN NEUROMUSCULAR DISEASES

Thesis in the field of Neurosciences

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Abstract

Background: Neuromuscular diseases include disorders of motor neurons, peripheral nerves, neuromuscular transmission, and skeletal muscles. Most neuromuscular diseases are rare diseases, and that brings up number of difficulties and challenges for patients, for their caregivers and for conducting the clinical trials. In the last two decades, we have witnessed remarkable progress in therapy of several neuromuscular disorders, mainly thanks to the advances in translational research and drug development possibilities. The determination of the treatment effect is crucial to any clinical trial and the subsequent regulatory approval of a new drug. There have been many challenges to overcome in finding a valid, reliable, and responsive outcome capable of measuring fluctuating symptoms of neuromuscular disorders, such as muscle weakness in myasthenia gravis and myotonia in myotonic dystrophy and to detect any improvement or worsening in very slowly progressive muscular dystrophies. Our goal was to identify the most relevant outcomes based on the statistical parameters of validity, reliability, and responsiveness, and also based on their feasibility and employment in clinical trials so far. We aimed to establish several of them as routinely used outcomes at our centre and in our national registries to have data on the natural course of the disease in the future.

Methods and Results: The thesis summarizes the outcome measures currently being used in myasthenia gravis and myotonic dystrophy type 1 and type 2 and discusses the history of their development, its performance based on statistical parameters, and future perspectives. We performed the validation and cross-cultural adaptation of the Myasthenia Gravis Composite Score, Myasthenia Gravis Quality of Life 15 and Myotonia Behaviour Scale. We established a quantitative assessment of myotonia using a commercially available dynamometer and employed this method in assessing the myotonia severity in myotonic dystrophy type 1 and type 2 and in a case-report demonstrating myotonia cessation after methylprednisolone. We also used the outcomes from the national myasthenia gravis registry to determine the predictive factors for a severe course of COVID-19 infection in myasthenia gravis.

Conclusion: The outcomes in myasthenia gravis are well established and all relevant outcomes are now validated for use in the Czech Republic. The outcomes in myotonic dystrophy have not been well established yet. The myotonia assessment developed by our group is valid, reliable, responsive and easy to use in routine clinical practice and one of the disease-specific questionnaires is now validated for Czech.

Keywords: outcome measures, rare diseases, myasthenia gravis, myotonic dystrophy, validity, reliability, responsiveness

Abstrakt

Úvod: Mezi neuromuskulární onemocnění se řadí poruchy motoneuronů, nervů, nervosvalového přenosu a kosterních svalů. Většina neuromuskulárních onemocnění spadá pod vzácná onemocnění, což přináší řadu problémů pacientům, jejich pečovatelům, ale také to významně ztěžuje organizaci klinických studií. V posledních desetiletích jsme byli svědky výrazného pokroku v terapii několika nervosvalových chorob, a to zejména díky pokroku v translačním výzkumu a novým možnostem vývoje léčiv. Pro klinické studie a následné schválení nového léku je naprosto zásadní umět kvantifikovat terapeutickou odpověď. Pro symptomy, které kolísají (svalová slabost u myastenie, nebo myotonie u myotonické dystrofie) je velmi těžké najít parametr, který je validní, spolehlivý, a navíc citlivý ke změně stavu. Současně je obtížné sledovat terapeutickou odpověď u velmi pomalu progredujících onemocnění, jako jsou například svalové dystrofie. Naším cílem bylo identifikovat nejrelevantnější parametry na základě jejich validity, spolehlivosti a citlivosti na změnu a také na základě jejich praktické použitelnosti a dosavadního uplatnění v klinických studiích a tyto implementovat do rutinně používaných škál v našem centru a národních registrech, abychom měli v budoucnu data o přirozeném průběhu onemocnění.

Metodika a výsledky: Práce shrnuje aktuálně používané škály a jiné parametry u myastenie a myotonické dystrofie, jejich historii vzniku a statistické ukazatele. Provedli jsme validaci a jazykovou adaptaci kompozitního skóre myastenie (Myasthenia Gravis Composite), dotazníku kvality života (Myasthenia Gravis Quality of Life 15) a dotazníku na tíži myotonie (Myotonia Behavior Scale). Dále jsme zavedli kvantitativní hodnocení myotonie pomocí komerčně dostupného dynamometru a tuto metodu jsme použili při hodnocení závažnosti myotonie u myotonické dystrofie 1. a 2. typu a v kazuistice prokazující vymizení myotonie po methylprednisolonu. Data z národního registru myastenie jsme využili ke stanovení prediktivních faktorů pro závažný průběh infekce COVID-19 u myastenie.

Závěr: Škály využívané k hodnocení tíže myastenie jsou již velmi dobře ustáleny a všechny relevantní škály jsou nyní k dispozici v českém jazyce. Měření příznaků myotonické dystrofie bohužel dosud není jednotné, ale naší skupinou bylo vyvinuto velmi spolehlivé a jednoduché kvantitativní testování myotonie a dále byl validován jeden ze specifických dotazníků k subjektivnímu hodnocení tíže myotonie.

Klíčová slova: parametry, škály, vzácná onemocnění, myastenie, myotonická dystrofie, validita, spolehlivost

Hereby I declare that this paper is my original authorial work, which I have worked out by my own under supervision of MUDr. Stanislav Voháňka, CSc. All sources, references and literature used or excerpted during elaboration of this work are properly cited and listed in complete reference to the due source.

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Contents

1 Background

1.1 Neuromuscular diseases

The term neuromuscular disease includes disorders of motor neurons, peripheral nerves, neuromuscular transmission, and skeletal muscles. Neuromuscular diseases usually manifest with muscle weakness, muscle pain, cramps, fatiguability, muscular atrophy or hypertrophy, stiffness, fasciculation, or sensory disorders. Various entities may present with the same clinical symptoms. In some neuromuscular disorders, the involvement of other organs, such as cardiomyopathy or skin rashes, may help with the correct diagnosis.

Many neuromuscular diseases are caused by genetic defects, some are acquired, and in some entities the cause is unknown. The acquired neuromuscular diseases (such as autoimmune myasthenia gravis or chronic inflammatory demyelinating polyneuropathy) were until recently the only ones with sufficient therapeutic modalities, yet in last few years there has been a remarkable progress in therapy of several genetic disorders. The advances in translational research and drug development capabilities enabled development of therapy based on modification the gene transcription and translation, such as ataluren (approved in 2014) and eteplirsen (2016) for Duchenne muscular dystrophy and nusinersen (2016), onasemnogene abeparvovec (2019) and risdiplam (2020) for spinal muscular atrophy. However, the approval of these drugs was preceded by decades of intensive collaborative research and developing instruments to measure the therapeutic response.

1.2 Concept of rare diseases

The majority of neuromuscular diseases are among the rare diseases, with the exception of some mononeuropathies and polyneuropathies. Even though there is no widely accepted definition of rare disease, the term in Europe and in the United States is well defined. In Europe, the rare disease is defined as a disease with low prevalence that affects less than 1 in 2 000 people (that equals less than 50 in 100 000 people, a ratio more used in Czech Republic) [European Commission regulation # 141/2000]. In the United States, the Rare Diseases Act of 2002 defines it as a disease affecting fewer than 200,000 people in the United States. The term “rare diseases” should not be confused with “orphan diseases”. Orphan disease provides a larger concept that includes all rare diseases but also diseases, either for which the cost of developing the drug will not be recovered from sales (as defined by Orphan

Drug Act in United States) or some neglected diseases that mainly affect patients living in developing countries (as defined in Europe[1]).

Rare diseases bring up number of difficulties and challenges for patients, for their caregivers but also for investigators developing drugs. Patients' diagnosis might be misdiagnosed or completely unrecognized and they might be harmed by the long duration of the disease without adequate treatment. There are only few guidelines for managing the rare diseases and the clinicians' expertise is usually proportional to the number of the treated patients[2]. This problem is partly solved by establishing few specialized centres to concentrate the patients' care.

There are also several difficult aspects of performing a clinical trial in rare disease. First problem is identification of enough patients which requires multi-centre collaboration. Another problem is poor understanding of natural history that is essential in planning the trial and finding the right outcome measures, thus stressing the need of patient registries. A problem was also the practical aspect of developing drugs and that was the poor motivation for pharmaceutical companies to develop a drug with so few potentially treated patients. Hence, in 1983, the Orphan Drug Act was passed in the United States to encourage development of drugs for orphan diseases[3]. An orphan drug was defined as a drug against a condition affecting fewer than 200 000 people in the United States or a drug that is expected to be no profitable for seven years after Food and Drug Administration approval. Generally, that law makes it easier to gain approval for an orphan drug as the number of participants in Phase III trial might be lower and it further extends the period of exclusivity for marketing the drug. The similar legislation was implemented in European Union in 2000 [European Commission regulation # 141/2000].

In 2017, the first European Reference Networks were launched including the network EURO-NMD for rare neuromuscular diseases[4]. Two neuromuscular centres in Czech Republic (Motol University Hospital and University Hospital Brno) became part of it. The purpose of creating this network was the development and application of care guidelines, facilitating translational and clinical research, harmonising data and samples for research reuse, and sharing of high-quality data.

1.3 Patient registries

Patient registry is a database providing data for defined populations. Registries can be patient-reported, professional-reported or combination of both. Registries are very important in designing the clinical trial and in patient recruitment. The data collected over time are also essential for the healthcare planning, natural course studies, and overall improvement of patient care.

Registries in rare diseases have some specifics[5,6]. Because of the rarity of the disease, usually no single hospital provides enough patients, thus stressing the need of national or global registries[7]. Together with patient's groups they serve as a tool to connect patients or their caregivers. Patients with rare diseases are especially interested in others sharing the same condition. The planning of the clinical trial and patient recruitment is also notably difficult in rare diseases and patient registries are extremely helpful. The knowledge of natural history of rare diseases is often scarce and sometimes the "textbook description" of the disease no longer applies when an effective therapy emerges, and the life expectancy extends. The patient registry provides valid and easily accessible information that responds immediately to change in therapy and patient's background. And finally, the choice of treatment usually varies across different clinicians and centres based on their experience, custom and regulatory directive. And even in a known nosological entity, such as myasthenia gravis, it may later turn out, that there are few subtypes of the disease, each responding differently to different therapy[8]. Without patient registries and guidelines, clinician must rely solely on his individual expertise, while the registry gives such information very soon.

1.4 Outcome measures

The reliable determination of the treatment effect is crucial to any clinical trial and a subsequent regulatory approval of a new drug. The value (score) of an outcome suitable for clinical trial should change when the patient's health status improves. Outcome measures can be divided to patient-reported outcomes (PRO) and non-patient-reported outcomes that include clinical (functional) outcome measures reported by observers and biomarkers, such as biochemical analysis of blood tests [9].

1.4.1 Patient-reported outcome measures

Patient-reported outcomes (PRO) are defined as information coming directly from patients, without interpretation of the patient's responses by anyone else[10]. They are located on the right side of Wilson and Cleary Model (Figure 1)[11].

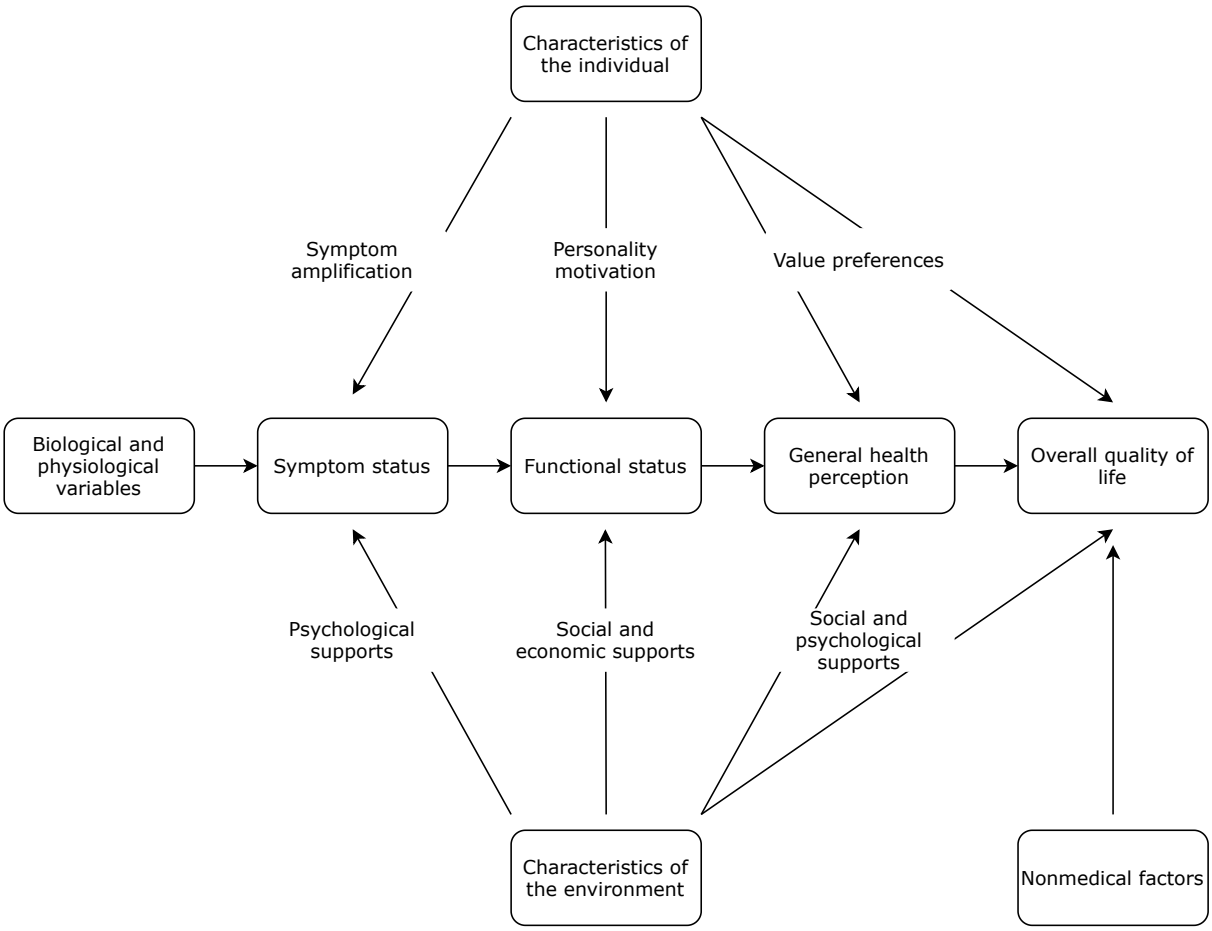


Figure 1: Wilson and Cleary Model (adapted from Wilson and Cleary, 1995[11])

Health related quality of life (HRQOL) questionnaires are perfect examples of PRO. How patients perceive their health depends not only on severity of the disease but also on their personality, coping behaviour and social factors such as financial situation or the ability to perform their job in worsened functional status. HRQOL questionnaires have to be comprehensible to a total target population and they should be written in a simple language that anyone over 12 years understands[12]. An extensive review proved that the reliability of HRQOL is comparable to other clinical measures[13].

However, the improvement or deterioration in PRO does not imply improvement or deterioration in functional status, such as muscle weakness. For example, a quality of life

questionnaire for neuromuscular diseases (INQoL)[14] did improve in myotonic dystrophy type 1 (MD1) patients despite their diseases progression measured by muscle weakness, myotonia severity, pain and other outcomes in 6 years[15]. Authors discussed this findings as a possible response shift phenomenon that means that patients are able to adjust to their situation and change their expectations[16]. A similar phenomenon might occur when introducing new treatment that improves the functional status and subsequently leads to rapid improvement of perceived quality of life; however, after adapting to better functional status, the perceived quality of life might drop despite no change in functional outcome. Therefore, the correlation between PROs and functional outcomes does not have to be strong.

1.4.2 Non-patient-reported outcome measures

Non-patient-reported outcomes are located to the left side of Wilson and Cleary model. In the strict sense, biomarkers are the only objective outcomes, as there is no personal judgement involved and they are obtained by direct measurement. Many outcomes are labelled as objective, even though there is a subjective element, for example the imaging methods, that must be interpreted by an expert. In functional measurement, either the patient being measured or the clinician performing the test can sway the result. In neuromuscular diseases, a functional outcome measure usually assesses gross motor function or ability to perform daily activities. The advantage of a functional outcome measure is quantifying a clinically meaningful concept. However, functional tests are susceptible to motivation of the patient, to inter-rater variability and they might be time-consuming. On the other hand, the biomarkers are usually easily measured and perform high reliability. But the relation of change in biomarker level to patient's functional status and quality of life is seldom well established.

Furthermore, regulatory requirements for approval of any treatment in European Union demand that an observed treatment effect needs to lead to a clear clinical benefit[17]. In other words, only functional improvement is considered to be a relevant primary outcome. In exceptional cases, a biomarker can be used as a primary outcome measure instead of a functional outcome (surrogate endpoint). Nevertheless, prior to using a biomarker as a primary outcome, a clear correlation with functional tests must be confirmed.

1.4.3 Development of new outcome measures

A lot of outcomes are obtained by direct measurement, for example the blood pressure, level of blood glucose or forced vital capacity. These are also called observable variables.

However, outcomes can be also non-observable, such as the severity of disease or quality of life of a patient, and these are difficult to measure. They have to be measured indirectly, usually using multiple items of observable variables, resulting in scales and scores of questionnaires and performance tests. Items are not chosen randomly; there is a specific scientific discipline called "measurement theories" that considers the relation of each item to the unobservable variable and proposes the appropriate tools in development a new scale.

In most cases, it is not desirable to develop a new outcome measure for a disease if many already exist. Developing an outcome may take years and if an existing scale can be translated or adapted to our specific use, it will produce results comparable with existing studies. Further, the outcome measure, which has been used in registries so far and for which the natural history is already known, is ideal for the clinical trial. Therefore, it is always better to use an existing scale. However, sometimes it is not possible. For example, the scales used in Spinal Muscular Atrophy 1 directs at very young children and as the therapy emerged, these children, that before therapy would never have walked, now are able to walk and new scales have to be developed.

Development of new outcome measure requires detailed literature review, review of current scales and engagement of both experts and patients [18,19].

1.4.4 Automated outcome measurement

Automated measurement is generally more reliable and more time-saving[20]. With the expanding importance of imaging methods in neuromuscular diseases [21] a great need emerges for automated measurement of specific muscle volume, fat fraction and other parameters, as the manual assessment is very time consuming and rater-dependent, thus rendering the multi-centre studies in rare diseases very difficult. In most cases, as the automated approach is in its infancy, a semi-automated procedure with partial manual control is the method of choice.

Recently, development of Deep Learning[22] methods have achieved and in many cases surpassed the human-level performance in image classification and image segmentation. Deep learning is a machine learning method where information is obtained directly from the raw data by multilayer nonlinear computational models. For example, an image is an array of pixel values. The first layer detects the presence or absence of edges and their orientation and location in the image. The second layer then detects basic patterns by specific arrangement of these edges. The third layer compiles patterns and motifs into combinations and next layers

detect known objects as a combination of previous parts[22]. The layers are obtained directly form data during the learning process of deep learning model (based on neural networks), therefore they are not designed by human engineers. The accuracy of deep learning model depends on the quantity and quality of data used to its general learning process.

The utilization of deep learning methods in neuromuscular disorders lies mainly in imaging, such as MRI image segmentation[23,24] and muscle ultrasound postprocessing[25], but it has also been employed for detection of gait disorders[26] and classification of neuromuscular disorders[27].

1.5 Statistical terms and background

1.5.1 Reliability

Reliability of medical measures is defined as the extent to which repeated measurements produce the same results for patients who have not changed[28]. It can also be viewed from the point of measurement error; the lower the error, the higher the reliability of the measurement. Depending on the nature of repeated testing, we distinguish test-retest reliability (over time), inter-rater reliability (performed by different raters), intra-rater reliability (performed by the same rater multiple times) and internal consistency (performed with different selection of items from a multiple-item instrument). A whole range of different terms is used for the same concept, such as reproducibility, repeatability, variability, consistency or agreement.

To express the reliability, coefficients ranging from 0 (unreliable) to 1 (perfect reliability) are used. The reliability coefficients are defined as a ratio of "true" variance between patients to total variance, which equals true variance + variance of measurement errors. Therefore, the reliability depends not only on the measurement error, but also on "true" variability between patients in tested population. Thus, if the measurement error is low compared to difference between patients, the test is able to distinguish the patients despite the measurement error and the reliability coefficient approaches 1. And vice versa, the more homogenous the tested population, the lower value of coefficients we get. Therefore, reliability is not a characteristic of measurement method only, it is a characteristic of an instrument used in specific population, as is demonstrated in the following example.

The example is based on the methodological article establishing myotonia measurement with handgrip dynamometer[29]. The Figure 2 shows the homogeneity of mean relaxation time in

healthy controls (varying from 0.1 to 0.3 seconds) and the large heterogeneity of patients with myotonic dystrophy type 1 (MD1) ranging from 0.3 to 9 seconds. As expected, the intraclass correlation coefficient (ICC) of repeated measurement in MD1 was 0.945 and the ICC in healthy controls was only 0.437, despite the obvious larger absolute measurement error in MD1 group.

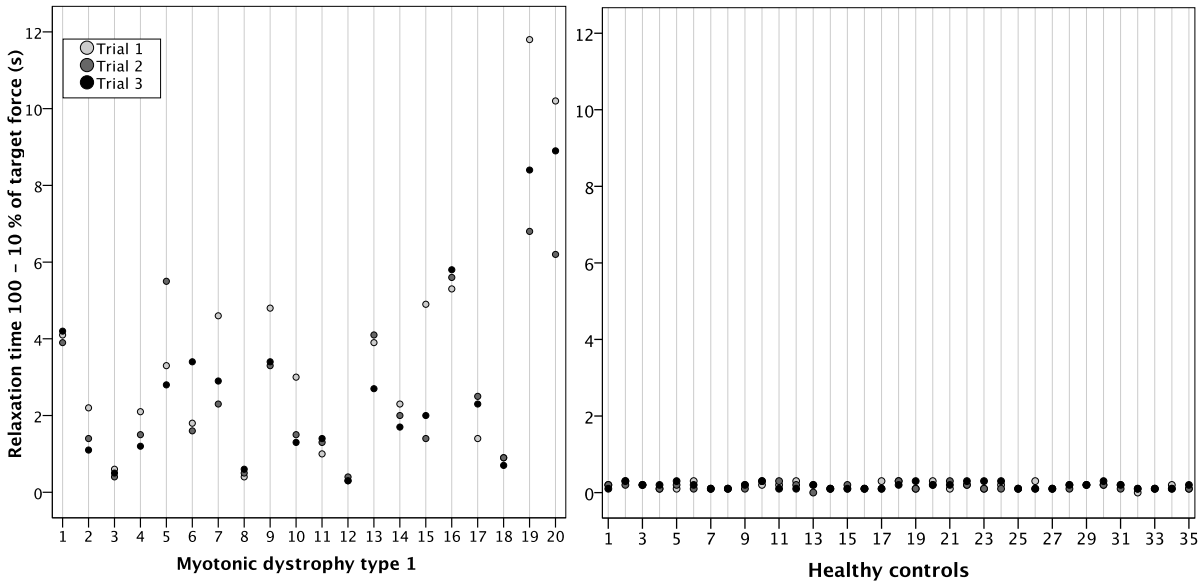


Figure 2: Example of reliability calculation. Relaxation time measured by handgrip dynamometer in patients with myotonic dystrophy type 1 and healthy controls. The assessment consisted of three trials (repeated measurements). Each number on the x-axis represents one participant, each dot represents one of the three trials.

1.5.1.1 Internal consistency

Internal consistency is a special type of reliability. It is defined as the relatedness among the items[28]. It measures the extent to which the items of a multi-item scale measure the same, for example the burden of the disease. The most used parameter for assessing the internal consistency of a scale is Cronbach's alpha. It assumes that items measuring the same thing should have positive correlations between each other. It generally compares the sum of variances of each item to the variance of the total score and ranges from 0 (no internal consistency) to 1 (absolute internal consistency). The lower the variances in each item compared to the variance of the total score, the higher the Cronbach's alpha. If the items are not measuring the same construct, different subjects can score the same total score, yet have completely different answers in each item. In this case, the variance of items would be high, the variance of total score low and the Cronbach's alpha low. If the items do measure roughly the same, subjects with same total scores would generally score the items very similarly, thus

the variance of the items would be low and Cronbach's alpha high. A recommended value for Cronbach's alpha is around 0.8-0.9. Values higher than 0.95 indicate that the items measure exactly the same and thus some of them are redundant.

1.5.2 Validity

Validity is defined as the extent to which an instrument truly measures the real value[28]. Despite the simplicity of this definition, it is difficult to determine what a real value is, as it is the case with patient-reported outcomes, that almost always lack a gold standard. PROs are usually developed through several iterative phases. There is no single statistical parameter for validity of such questionnaires. Validity is evaluated by experts in the field based on correlation with other existing scales, consistency of previously defined hypothesis, differences in groups etc.

In situations in which there is a gold standard (such as histological diagnosis of tumour or scale that is well established), validity is expressed as agreement with this gold standard. The statistical parameters used depend on the variable of measurement. ICC[30] and Bland and Altman plots[31] are used for continuous variable with the same unit. For other continuous variables the correlation coefficients are used. For dichotomous outcome, for example diagnosis of tumour with options "yes" or "no", validity is expressed in sensitivity and specificity. If the gold standard is dichotomous and the new variable is ordinal or continuous, receiver operating characteristic curves can be used.

It is important to notice, that validity is associated with reliability. If the reliability is low (i.e. two measurement performed with the same instrument provide different results), the level of agreement between two different instruments cannot be expected to be higher. In statistical terms, the maximum of expected correlation between gold standard and new instrument is

$$\sqrt{rel(A) \times rel(B)}$$

where rel(A) is reliability of gold standard, and rel(B) is reliability of new instrument [32].

1.5.2.1 Cross-cultural validity

Cross-cultural validation of scales and questionnaires starts with forward translation by two translators having the target language as their mother tongue. One translator should be an expert in the field of the translated scale, the second one should be a language expert. Then, a

combined version of the translation is made by consensus. The agreed version is then translated back into original language, this time by two other translators, both language experts, having the original language as their mother tongue. All discrepancies have to be reviewed and a consensus has to be reached upon a pre-final version. This version is then tested by small sample of patients (target population) for interpreting the items and comprehensibility[33]. Further, it should be checked if the scores of the translated scale in one population correspond to the scores of original scale in a different population with the same severity of disease, because some items of the questionnaire can be irrelevant in other cultures. This is seldom done, as it is quite difficult to gain data of a different population with the same severity of disease. Instead, the strength of correlations with other related scales and the ability to distinguish between specific groups are checked. Further, advanced methods of statistical analysis, such as factor analysis and item response theory techniques might be employed, but all these methods require data from two population, yet this time the same disease severity is not a prerequisite.

1.5.3 Responsiveness

Responsiveness is defined as the ability of an outcome measure to detect a change[28]. Responsiveness is closely related to validity, as validity refers to a single score and the responsiveness refers to a change of scores (difference between two repeated measurements). It is a crucial aspect of all outcomes used in clinical trials. The methods to assess responsiveness are similar to methods assessing validity.

1.5.4 Minimal detectable change

Minimal detectable change is an important statistical term closely related to reliability and measurement error. Observed changes in repeated measurement might represent a true change or might appear only due to measurement error. Therefore, the measurement error of repeated measurements in a stable population should be determined and the minimal detectable change is than defined as a change beyond the measurement error.

In more detail, a minimal detectable change is a change larger then $\pm 1.96 \times SD_{difference}$. In other words, it is a change that falls outside the limits of agreement in the Bland and Altman graph. An example is shown in Figure 3[34] and Figure 4[35]. Figure 3 shows the differences between two measurements (in this case performed by two independent raters within an hour) in relation to the mean of patients' two scores. Similarly, Figure 4 shows the

same parameters in two consecutive completions of MG-QOL15 questionnaire by myasthenia gravis patients in 2-4 days.

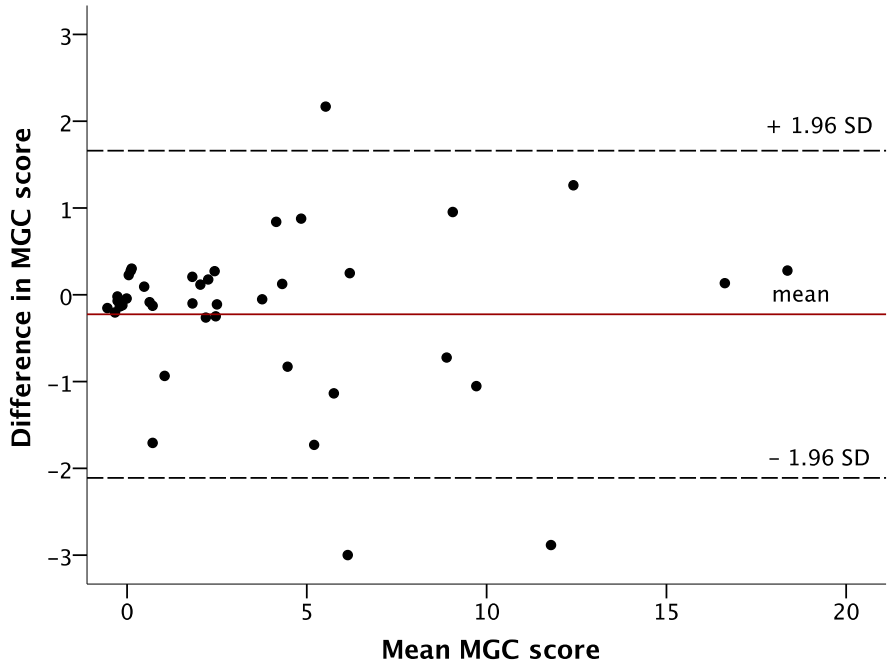


Figure 3: Bland-Altman graph of repeated measurements of MGC score performed by two independent raters.

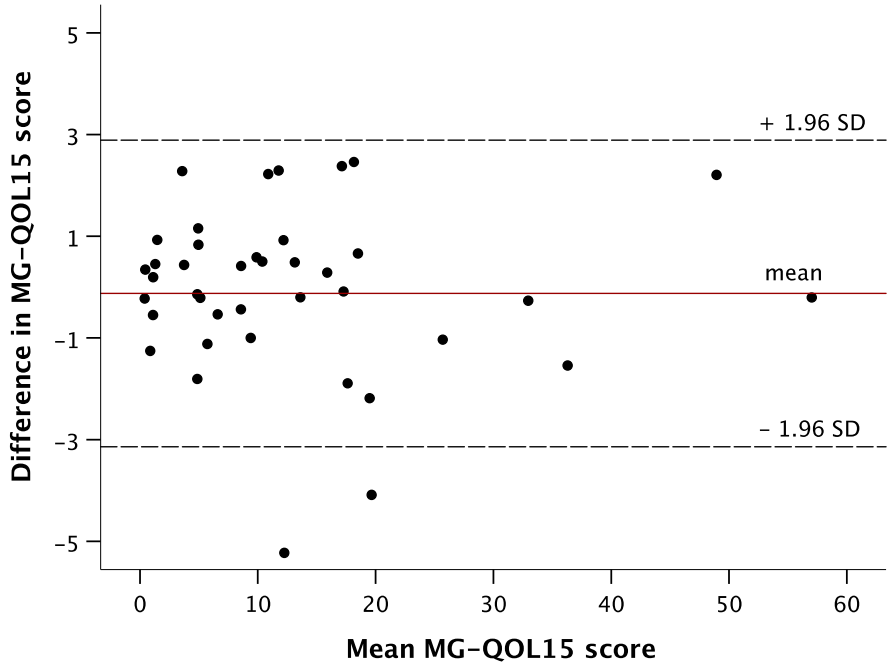


Figure 4: Bland-Altman graph of repeated completions of MG-QOL15 questionnaire

Based on these results, the minimal detectable change should be established as 3 points in MGC scale and 4 points in MG-QOL15 questionnaire.

The measurement error can be reduced by repeated measurement and calculated average scores by $\sqrt{n}$, where n is the number of measurements. Similarly, considering the groups of patients instead of individual patients, as is the case in clinical trials, the minimal detectable change is also reduced by $\sqrt{n}$, in this time the n representing the number of patients. Therefore, in individual clinical practice, a greater change in an outcome is required than that of clinical trials[33].

1.5.5 Minimal clinically important difference

Minimal clinically important difference (MID) is defined as the smallest change in score that is perceived as important by patients, clinicians or others[33]. In large clinical trials, even the small change in scores gets statistically significant (in terms of minimal detectable change, as mentioned above), but those changes don't have to be relevant for patients and clinicians. And on the contrary, the scale is not able to detect the important change perceived by the patient, if the measurement error is too high, so these two terms must not be confused. There are several statistical approaches to determine MID. Generally, in patient-reported outcomes, the perspective of patients must be considered, while in non-patient-reported outcomes usually the experts' opinion is considered to divide the patients into groups with important improvement, important deterioration and without important change. Then the advance statistical methods (ROC analysis, visual anchor-based distribution method, effect size) can be applied.

1.5.6 Floor and ceiling effect

A floor and ceiling effects describes the inability of a scale to detect the change in subjects on lower or upper end of the scale, respectively. It is characterized by very low variance of the score results because the "floor" is too high, or the "ceiling" is too low. Those effects pose problems mostly in longitudinal studies. During the development stage of a scale, those effects can be remedied by simply adding more items at the lower or upper end of the scale. So it usually occurs, if an existing scale is used in a different population, who is less or more severely affected, in which most of the subject score at either end of the scale at the baseline and even if their health improves or worsens, the scale cannot detect it.

2 Myasthenia Gravis

2.1 Summary

Myasthenia gravis is a chronic autoimmune neuromuscular disorder manifesting with fluctuating fatigable weakness caused by antibodies targeting the structures at neuromuscular junction. The neuromuscular junction is a specialized synapse that is particularly vulnerable to circulating factors (auto-antibodies, neurotoxins, nerve agents), as it has no blood-brain barrier.

Physiologically, the nerve action potential opens voltage-gated calcium channels (VGCC) at the presynaptic terminal which leads to influx of calcium and exocytosis of packets of acetylcholine (see Figure 5). About 65 % reaches the acetylcholine receptors (AChR) located at the top of the deep folds of the postsynaptic muscle membrane[36]. AChR is a Na^+, K^+ and Ca^{2+} ion channel and binding of two molecules of acetylcholine leads to opening of the channel and generating the endplate potential. If the depolarisation reaches a critical threshold, the voltage gated sodium channels located at the bottom of the deep folds of muscle membrane propagates the action potential along the muscle fibre leading to contraction. The AChRs close spontaneously, as does the VGCC on the presynaptic membrane. Acetylcholine diffuses or is hydrolysed by acetylcholinesterase. Repolarization is completed with opening of voltage-gated potassium channels (VGKC) at the presynaptic membrane.

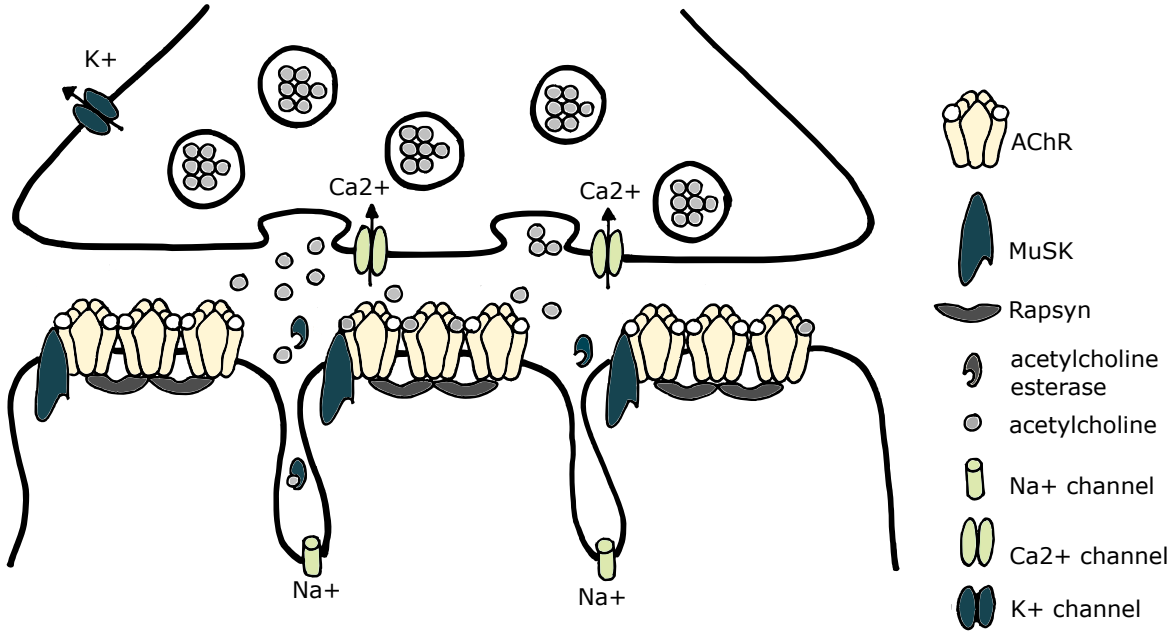


Figure 5: Neuromuscular junction (adapted from Meriggioli and Sanders, 2009[37])

Several types of antibodies against structures of neuromuscular junction have been described[38]. In most cases (85-90%), the autoimmune response is mediated by AChR antibodies. The AChR antibodies are usually IgG_1 or IgG_3, and they cause the complement-mediated destruction of postsynaptic membrane. Few AChR antibodies directly block the function or causes the cross-linking of AChR[36]. Interestingly, AChR antibodies are present also in up to 40% patients with thymoma without myasthenia gravis, however, it serves as a predictive factor of developing myasthenia in the future[39]. In some patients, the AChR antibodies cannot be detected by radioimmunoprecipitation methods because of their low affinity, yet a "cell-based" method was developed with AChRs expressed in a cell line clustered with rapsyn and the authors were able to detect these low-affinity antibodies in 60% of previously seronegative patients[40]. Up to 70% of patients without AChR antibodies have antibodies against the muscle-specific tyrosin kinase (anti-MuSK)[41]. The role of MuSK in adult muscle is not clear but it is well established in development of neuromuscular junction [42]. First, agrin, a large proteoglycan, is released from motoneurons termination and binds on low-density lipoprotein receptor-related protein 4 (LRP4), that serves as a co-receptor of agrin. LRP4 than interacts with MuSK that starts the signalling cascade leading to rapsyn mediated AChR clustering on muscle cell. Anti-MuSK are IgG_4 subclass, which is not a complement activator, and that has consequences in the treatment choice[43]. There are few other structures of the neuromuscular junction targeted by immune response, namely the LRP-4 and agrin, but the occurrence of these antibodies is very rare[44].

The clinical manifestation of myasthenia gravis is very heterogenous and varies from pure ocular forms to generalised severe life-threatening course. At the onset of the disease, the ocular symptoms are the only symptoms present in more than 50% of patients[45], yet only 15%-25% of patients have pure ocular form all along the disease[8,45]. The motor unit sizes are very small in extraocular muscles and multiple neuromuscular junctions are located on one muscle fiber, directly responsible for contraction instead of generating action potential[36]. Therefore, any reduction in endplate potential has a direct effect on the muscle contraction and that might be the cause of ocular symptoms being very frequently the first symptoms of myasthenia. Approximately 85% of the patients have generalized form manifesting as a fluctuating muscle weakness, deteriorating after exercise and during repetitive movements. Involvement of respiratory muscles can be life-threatening. Based on the type of antibody, age of onset and the presence of thymic pathology, few classification of myasthenia subtypes have been proposed with consequences in therapeutic strategy [8,36,43].

2.2 Therapy

A review[46] from 1937 stated, that "*the treatment of myasthenia gravis until very recently has been a source of discouragement to the patient and a cause of nightmare for the physician.*" Until 1930, there was no effective treatment and roughly one third of the patients died from respiratory failure, the average duration of the illness up to time to death being four years and six months[46]. Strychnine and thyroid extract were used most frequently, operations of the thyroid gland and application of roentgen therapy to the region of thyroid and thymus gland were recommended. In 1930, Harriet Edgeworth announced promising results in one case treated with ephedrine sulphate[47]. The real breakthrough came in 1934, when the British physician Mary Walker noticed the similarity of symptoms with curare poisoning and administered the patient with myasthenia subcutaneously injection of physostigmine. The significant, yet temporary, improvement was published in Lancet[48]. The first attempts of treatment potentially affecting immunity came in 1949, when patients were given adrenocorticotropic hormone (ACTH). However, ACTH was given as an attempt to reduce the volume of thymus and increase the synthesis of acetylcholine that was thought to be insufficient[49]. The first report of thymectomy to treat myasthenia is from 1941[50]. At this time, the autoimmune nature of the disease has not been clarified yet. It was not until 1960 that the autoantibodies in the serum of patients with myasthenia were detected[51] and the key hypothesis that myasthenia is an autoimmune disorder was proposed[52]. Subsequently, corticosteroids and immunosuppressants originally used in different indications (organ transplants, lymphomas, leukaemia) were administered.

Since 1966, 6-mercaptopurine and azathioprine (a precursor of 6-mercaptopurine) were tested in different countries[53,54]. Unfortunately, one of the four patients treated with 6-mercaptopurine in USA developed severe bone marrow suppression and subsequently died[53], which had generally delayed the use of immunosuppressants in myasthenia therapy in the USA. Cyclosporin was first used in therapy myasthenia in 1986, just three years after approval use for organ transplants[55].

Interestingly, in international consensus guidance for management of myasthenia gravis published in Neurology in 2016[56], azathioprine remained as first line immunosuppressant agent in myasthenia. Cyclosporine was also recommended, but not as a first line due to its potential severe side effects (nephrotoxicity). Even though mycophenolate mofetil, methotrexate and tacrolimus were widely used at that time, it was not supported by evidence

form clinical trials[57–60]. Severe exacerbations are treated with intravenous immunoglobulins (IVIG) or plasmapheresis. Also in 2016, the first randomized trial proving the efficacy of thymectomy in nonthymomatous myasthenia gravis was published[61]. The update of international consensus guidance in 2020[62] emphasised the early use of rituximab in patients with anti-MuSK antibodies and introduced eculizumab to be considered as a treatment for refractory anti-AChR positive myasthenia[63,64].

The last few years have seen a great upswing of phase 3 clinical trials with directed therapeutic agents, such as terminal complement C5 inhibitors (eculizumab, ravalizumab – trial NCT03920293, zilucoplan – trial NCT04225871), neonatal Fc receptor inhibitors (rozanolixizumab[65], efgartigimod[66], nipocalimab - trial NCT04951622), B cell depleting agents (inebilizumab, anti-CD19 agent, trial NCT04524273), and cytokine-based therapies (satralizumab, anti-IL6, trial NCT04963270). Therapeutic options for the treatment of myasthenia are thus likely to be expanded in the coming years.

2.3 Outcome measures

Assessment of myasthenia severity evolved from individual clinical description to disease-specific, validated, and reliable scales. The clinical description of a patient in the case report of physostigmine efficacy in 1934[48] looked as follows: "*Her jaw then began to droop, she had to hold it up with her hand, and the left eyelid began to droop. Speech became indistinct when she was excited, swallowing was difficult, and fluid sometimes regurgitated through her nose.*" And after injection of physostigmine salicylate the description changed: "*In from half an hour to an hour after the injection the left eyelid 'goes up', arm movements are much stronger, the jaw drops rather less, swallowing is improved, and the patient feels 'less heavy'. The effect wears off gradually in from 2-4 hours.*"

In the 1960s, the widespread use of corticosteroids and immunosuppressants dramatically improved the quality of life and survival rates of myasthenia patients and the need of quantifying the disease severity and measuring the treatment response emerged. However, measuring myasthenia severity provides specific challenges due to the fluctuating nature of the disease. Therefore, symptoms may not be present during the single-point clinical assessment, they may appear after exercise only, and further, the severity of symptoms is affected by the time since the last dose of cholinesterase inhibitors. Many myasthenia specific

outcome measures thus include the patient's perspective and clinical trials often requires 10 to 12 hours interval without cholinesterase inhibitors prior to objective outcome measure testing.

The first myasthenia specific scales were introduced in 1980s. **Myasthenia Muscle Scale** was used in the clinical trial of plasma exchange in 1983[67] but the scale is now frequently used only in France[68]. In the same year, the **Myasthenia Gravis Score**[69] was introduced and after two modifications[70,71] it led to **Quantitative Myasthenia Gravis Score** (QMG) that is currently in use. Another measure, developed for the clinical trial of azathioprine in 1988 in Italy is called **The Besta Neurologic Institute Rating Scale for Myasthenia Gravis**[72], but it has not been used in any clinical trial since then. The current version has 11 items, all based on physical examination and history. In 1999, **Myasthenia Gravis Activities of Daily Living** (MG-ADL) was developed for the purpose of a trial of IVIG[73]. MG-ADL was the first patient-reported outcome and it has become one of the most used primary outcome in clinical trials since 2020[74]. In 2003, the **Manual Muscle Test** (MMT) was developed[75], as an assessment with no need of any equipment. It measures strength in 30 muscle groups usually affected by myasthenia in a single muscle contraction. In 2008, selected items from MMT, QMG and MG-ADL were combined into one scale called **Myasthenia Gravis Composite Score** (MGC)[19]. The items were chosen based on their performance in two large clinical trials of mycophenolate[58,59] by a large group of myasthenia experts. In the same year, the first myasthenia-specific HRQoL, **Myasthenia Gravis Quality of Life 60** (MG-QOL) was developed and tested in the same mycophenolate trial[58]. The original measure, consisting of 60 items, was later reduced to 15 items[76], mainly based on the item's responsiveness in the mycophenolate trial. Another patient-reported outcome, **Myasthenia Gravis Disability Scale** (MG-DIS) based on the International Classification of Functioning, Disability and Health with focus on patient disability was developed in 2014[77]. And two years later, a composite measure **Myasthenia Gravis Impairment Index** (MGII) consisting of 22 patient-reported items and 6 examination items was developed[78]. Neither MG-DIS nor MGII has been used in a clinical trial yet. Further, since 2018, QMG, MG-ADL, MGC, MG-QOL and steroid sparing effect are the only myasthenia-specific outcome measures used in randomized clinical trials[74].

2.3.1 Quantitative Myasthenia Gravis Score (QMG)

As mentioned above, the QMG evolved from the MG Score developed in 1983. It originally had 8 items[69], but it was later modified to 13 items for the purpose of a clinical trial proving the efficacy of cyclosporine[70]. Later, in 1998[71], it was modified again to its current version of

13 items all based on examination. The QMG considers the fluctuation of myasthenia by measuring the fatigability and endurance. It requires spirometer and dynamometer and is quite time-consuming, as it can take up to 20-25 minutes to complete. All items are scored from 0 to 3 and total score ranges from 0 to 39, see Table 1.

Test items weakness	**None**	**Mild**	**Moderate**	**Severe**
Grade	**0**	**1**	**2**	**3**
Double vision (lateral gaze) Sec.	60	11-59	1-10	Spontaneous
Ptosis (upward gaze) Sec.	60	11-59	1-10	Spontaneous
Facial Muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete
Swallowing 4 oz. Water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing, choking or nasal regurgitation	Cannot swallow (test not attempted)
Speech following counting aloud from 1-50 (onset of dysarthria)	None at #50	Dysarthria at #30-49	Dysarthria at #10-29	Dysarthria at #9
Right arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9
Left arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9
Forced vital capacity	≥80%	65-79%	50-64%	<50%
Rt hand grip: male (Kg) : female	≥45 ≥30	15-44 10-29	5-14 5-9	0-4 0-4
Left hand grip: male (Kg) : female	≥35 ≥25	15-34 10-24	5-14 5-9	0-4 0-4
Head, lifted (45%, supine) Sec.	120	30-119	1-29	0
Right leg outstretched (45-50%,supine) Sec.	100	31-99	1-30	0
Left leg outstretched (45-50%,supine) Sec.	100	31-99	1-30	0

Table 1: Quantitative Myasthenia Gravis Score (QMG)

The construct validity was established by correlation between QMG and MMT[75], MMS[79], and by comparing the scores of subgroups of patients across different MGFA classes[80]. Based on the reliability study[71], and the assessment of responsiveness in cyclosporine trial[70] and IVIG trial[81], the minimal detectable change greater than 3 is considered as significant. The MID cut offs are below the change of 3 points as well[82].

2.3.2 Myasthenia Gravis Activities of Daily Living (MG-ADL)

MG-ADL is an 8-items, patient-reported outcome, with each item scored in the range of 0 to 3 and total scored between 0 and 24 (Table 2). It is very easy to use, without the need of special equipment. There is no specific recall time frame in the scale, as the interval is left for the clinician to decide based on the current situation (e.g., stable patient for weeks, severe

deterioration in two days), but in clinical trials the time frame is usually specified as 7 days or since the last visit.

Grade	0	1	2	3
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal speech, but can be understood	Spontaneous
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube
Swallowing	Normal	Complete, weak, some resistance	Complete, without resistance	Incomplete
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant

Table 2: Myasthenia Gravis Activities of Daily Living (MG-ADL)

Reliability was determined by test-retest scoring within a week in 20 subjects. The reliability coefficient was very high (ICC of 0.937)[83] and the scores were within 2 points in 85% and never differed more than 3 points. Construct validity was assessed by correlations with QMG, MGC[19] and MG-QOL15. The correlation was only moderate with QMG with Pearson correlation coefficient of 0.583[84], while there was a strong correlation with MG-QOL15 (0.763-0.775)[83]. The strongest correlation was between MG-ADL and MGC (0.846 – 0.869), as expected due to the fact, that MGC combines items from MG-ADL. The responsiveness was also assessed in 76 patients with variable time between two visits and variable interventions. The improvement was defined as an improvement in MG-QOL15 plus the improvement in physician impression and MID was calculated using the effect size approach and 2-points change was determined to be both clinically important and reliable enough. The MG-ADL is prone to floor effect[78].

2.3.3 Myasthenia Gravis Composite (MGC)

MGC is a hybrid of patient-reported and clinician-reported items[19]. It was developed in 2008 by combining items form three existing scales. First three items are slight modification of first items in QMG, items 3-6 are based on items form MG-ADL and the last three items are based on MMT (see Table 3)[85]. The items were selected by committee of myasthenia experts based on the item performance (responsiveness, concordance, score distributions, and correlations with MG-QOL15) in two large mycophenolate trials[58,59]. Further, the responses were

weighted according to the opinions of the experts. In 2012, MGC was recommended by the MGFA scientific board to be used as an outcome in clinical trials[86].

Ptosis, upward gaze (physician examination)	>45 seconds = 0	11– 45 seconds = 1	1–10 seconds = 2	Immediate = 3
Double vision on lateral gaze, left or right (physician examination)	>45 seconds = 0	11– 45 seconds = 1	1–10 seconds = 2	Immediate = 3
Eye closure (physician examination)	Normal = 0	Mild weakness (can be forced open with effort) = 0	Moderate weakness (can be forced open easily) = 1	Severe weakness (unable to keep eyes closed) = 2
Talking (patient history)	Normal = 0	Intermittent slurring or nasal speech = 2	Constant slurring or nasal but can be understood = 4	Difficult to understand speech = 6
Chewing (patient history	Normal = 0	Fatigue with solid food = 2	Fatigue with soft food = 4	Gastric tube = 6
Swallowing (patient history)	Normal = 0	Rare episode of choking or trouble swallowing = 2	Frequent trouble swallowing, e.g. necessitating changes in diet = 5	Gastric tube = 6
Breathing (thought to be caused by MG)	Normal = 0	Shortness of breath with exertion = 2	Shortness of breath at rest = 4	Ventilator dependence = 9
Neck flexion or extension (weakest) (physician examination)	Normal = 0	Mild weakness = 1	Moderate weakness (i.e., ~50% weak, ±15%) = 3	Severe weakness = 4
Shoulder abduction (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4	Severe weakness = 5
Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4	Severe weakness = 5
Moderate weakness for neck and limb items should be construed as weakness that equals roughly 50% ±15% of expected normal strength. Any weakness milder than that would be mild and any weakness more severe than that would be classified as severe.				

Table 3: Myasthenia Gravis Composite (MGC)

Reliability assessment was performed in 38 patients, with excellent results (the ICC of 0.98). Construct validity was based on correlations with other measures: MMT (r = 0.80), MG-ADL (r = 0.85), and MG-QOL15 (r = 0.68)[19]. Responsiveness was assessed also by comparing the change in MGC to change in other scores. The MID was determined as ≥ 3 points. Just as it is in MG-ADL, there is no specific time frame for patient history items.

The MGC was validated to Czech language in 2016[34] and the authors also performed test-retest analysis of the reliability of the Czech version on 40 subjects. The ICC was 0.989 and 95% of patients had a score within the 2-points difference, see Figure 6.

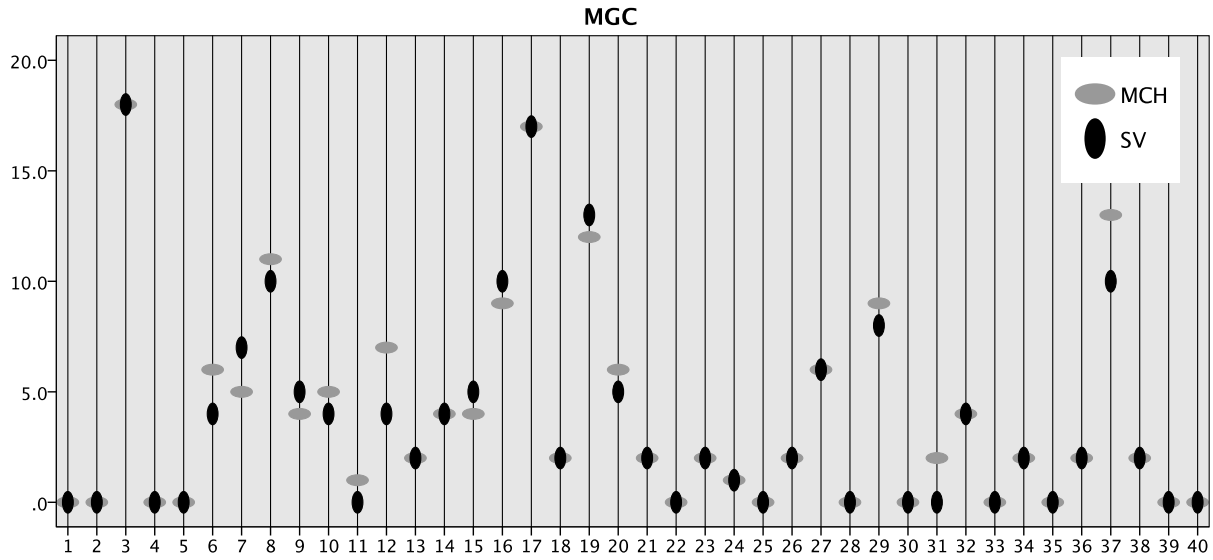


Figure 6: The MGC assessment by two raters (MCH and SV)

2.3.4 Myasthenia Gravis Quality of Life

Task force of the MGFA recommended development of HRQoL measure specific for myasthenia gravis in 2000. The first version, MG-QOL with 60 items was developed in 2008.The items were formulated based on interviews with myasthenia patients, questions from similar multiple sclerosis quality of life measure[87] and experience of the authors. Test-retest reliability was not assessed, construct validity was determined by correlations between Short-Form 36 (SF-36) questionnaire (r = -0.80), MG-ADL (r = 0.72), QMG (r = 0.53) and MMT (r = 0.46)[88]. The MG-QOL was quickly simplified to 15-item MG-QOL15 (Figure 7)[76]. Factor analysis of each of the 60 items was performed, based on the changes in other scales, specifically looking at how often the item was scored as improved when the patient improved. The MG-QOL15 proved to be reliable (ICC of 0.986)[89] and responsive in a randomized controlled trial of IVIG and plasmapheresis[90]. The construct validity was assessed, similarly to other MG scales, with correlation among each other, as well as correlation with SF-36 subscales[76].

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Grade	**0**	**1**	**2**	**3**	**4**
I am frustrated by my condition					
I have trouble using my eyes					
I have trouble eating					
I have limited my social activity because of my condition					
My condition limits my ability to enjoy hobbies and fun activities					
I have trouble meeting the needs of my family					
I have to make plans around my condition					
My occupational skills and job status have been negatively affected					
I have difficulty speaking					
I have trouble driving					
I am depressed about my condition					
I have trouble walking					
I have trouble getting around public places					
I feel overwhelmed by my condition					
I have trouble performing my personal grooming needs					

Figure 7: Myasthenia Gravis Quality of Life 15 (MG-QOL15)

Since 2008, the MG-QOL15 has been translated to many languages (Japanese, French, Persian, etc.)[91–99]. It can be assumed that it was translated into many other languages, even though not published. As the patients fill the questionnaire themselves, the translation must be clear and understandable. The Czech version was validated in 2016[35] and the authors confirmed excellent test-retest reliability.

In 2016, revised form, MG-QOL15r was published[100]. Rasch analysis was performed on more than 1300 completed MG-QOL15 questionnaires and consequently, three items were revised and the 5-options scale (scoring each item as 0-4) was changed to 3-options scale (scoring each item as 0-2). Yet, the revised form has not substituted the previous version in clinical trials so far[74].

2.3.5 Steroid sparing effect

Another frequently used outcome in clinical trial is a steroid sparing effect. Long-term steroid treatment brings many side effects and several open-label studies reported lower dose requirement or even discontinuation of corticosteroids after starting the treatment with immunosuppressant. Reduction of corticosteroid dose thanks to introduction of immunosuppressant may result in better life quality while maintaining the stability of myasthenia course. The steroid sparing effect can be measured as area under curve of the dose over time. The steroid sparing effect was primary outcome in several recently conducted trials of methotrexate[60], thymectomy[61], IVIG (trial NCT02473965) and rituximab (trials NCT02110706, NCT02950155), as well as the previous studies of azathioprine[101] and cyclosporine[102].

2.4 National registry of myasthenia gravis MyReg

As mentioned in the introduction, registries of rare diseases are of an extreme importance to patients, healthcare providers and for planning the clinical trial.

The Czech national myasthenia gravis registry (MyReg) was established in 2015 and since then, records of more than 1300 patients with myasthenia gravis have been enrolled including follow-up visits every year. According to raw data from all Neuromuscular centres in Czech Republic, the estimated total number of patients with myasthenia gravis come up to 2000–2500, thus the prevalence in Czech Republic might be higher than expected[103].

The project data are stored in an electronic database based on the CLADE-IS system. The online registry application is available to users through any internet browser. The records are stored under unique identification codes, which do not allow any retrospective identification of the patient. The patient's identity is thus known only to the attending physician or authorized healthcare professional. The guarantees of the registry cooperate with the Czech patient organization (MYGRA-CZ) and every enrolled subject is allowed to view his own data after logging into his user account, thus helping to ensure the data accuracy.

The structure of the registry was based on the model for international European Database for Myasthenia Gravis[104] and the common data elements recommendations of National Institute of Neurological Disorders and Stroke (version 0.0). The whole database is designed in

English to allow future integration into international database. The basic data summaries are available on myreg.registry.cz in real time (see Figure 8).

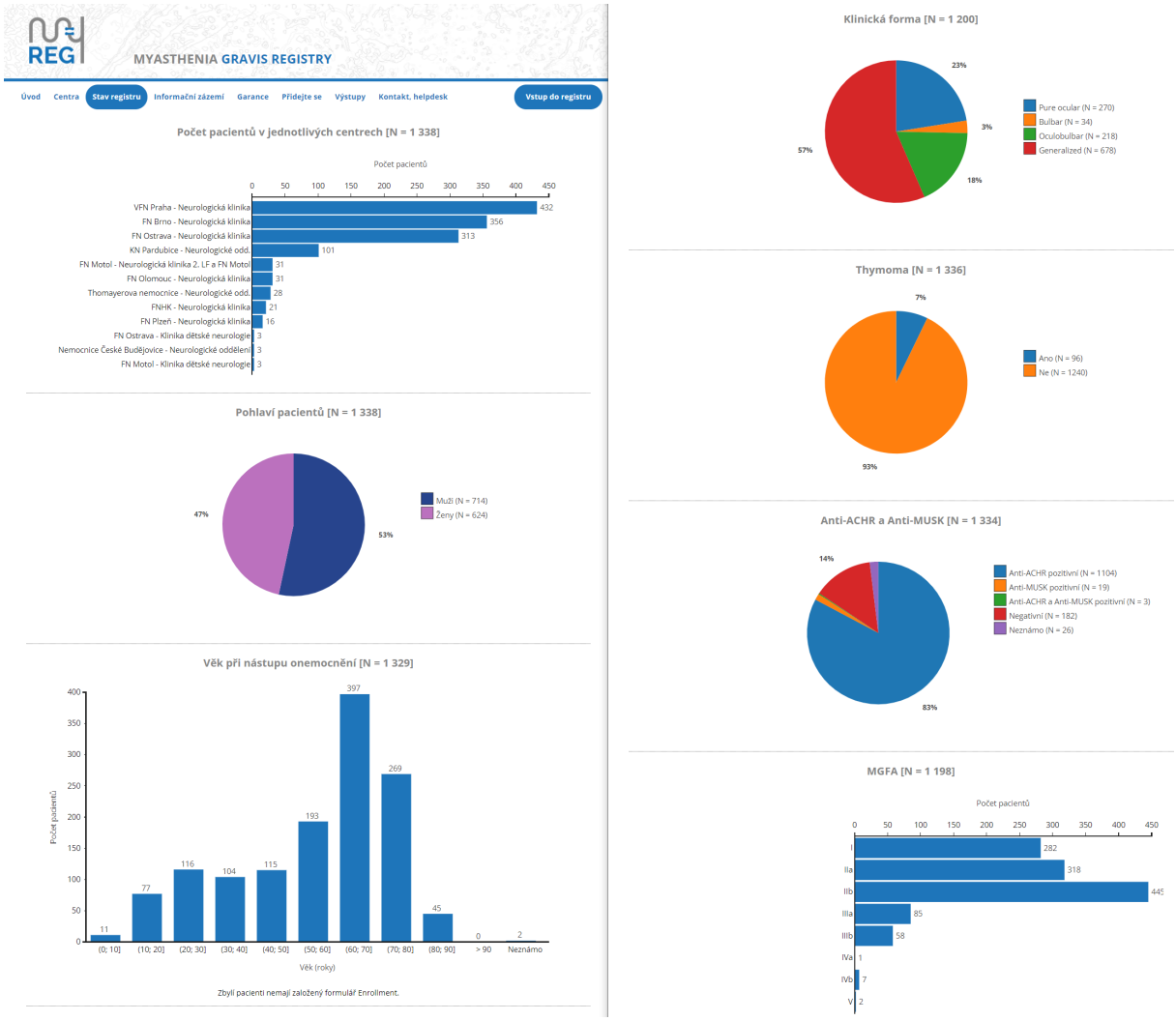


Figure 8: Basic data summaries from MyReg [available on myreg.registry.cz, accessed on 04/08/2021]

Among the outcome measures chosen to be followed in the registry are Forced Vital Capacity (FVC), MGFA classification and MGC as mandatory entries and MG-QOL15, QMG and MG-ADL as optional entries. Recently, the data from registry have been used to assess the predictive factors for severe course of COVID-19 infection in myasthenia gravis[105].

In addition to group analyses and summaries, registry can be used also as a quick overview for the patient's physician. The Figure 9 shows an example of the visualization of information gathered in registry for an individual patient, who participated in the IVIG trial. In the middle of 2016, corticosteroids were discontinued per protocol, however, a severe exacerbation requiring high dose of IVIG and switch to cyclosporine occurred.

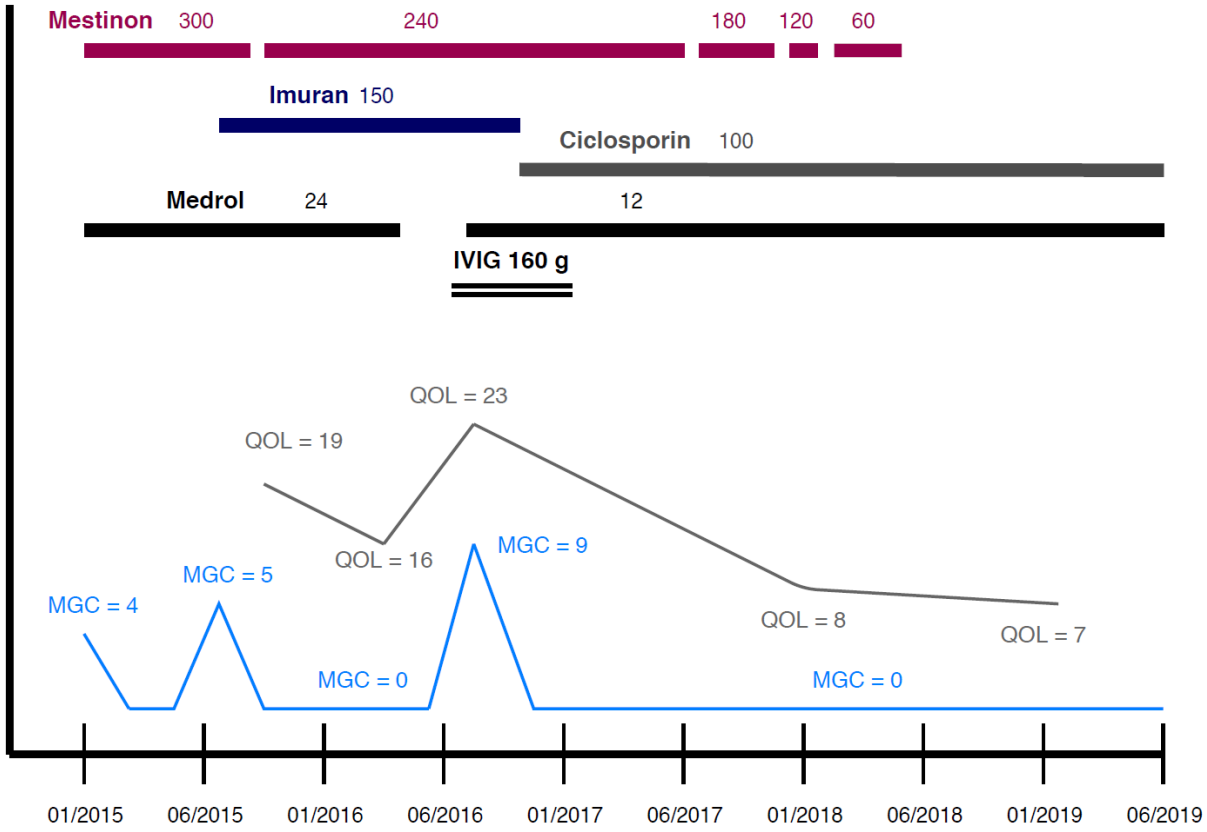


Figure 9: Visualization of the relation between therapy and scores of MG scales from MyReg

3 Myotonic dystrophy

3.1 Summary

Myotonic dystrophy type 1 (MD1) and type 2 (MD2) are hereditary multi-systemic disorders in which muscle weakness and myotonia are the most prominent symptoms. MD1 arises out of expansion of CTG trinucelotide repeats in the DMPK (dystrophia myotonica protein kinase) gene[106,107]. MD2 results from expansion of the CCTG tetranucleotide repeats in the CNBP (cellular nucleic acid-binding protein) gene[108]. Mutant DMPK (CUG) and CNBP (CCUG) RNA transcripts fold into double stranded stem-loop structures with U-U mischmatches and bind to muscleblind-like (MBNL) nuclear regulatory proteins[109], thus causing alternative splicing (splicopathy) that affects hundreds of genes in different tissues[110].

Even though the disease was first described in 1909[111], the existence of more than one genetic cause was not recognized until the unstable expansion of CTG trinucleotides was found in 1992[107]. Few years later, the distinct phenotype of myotonic dystrophy without the CTG expansion and with accentuated proximal muscle weakness was described and labelled as proximal myotonic myopathy[112,113]. Later, the term MD2 instead of proximal myotonic myopathy was established and the CCTG expansion causing MD2 was found in 2001[108].

Myotonia and muscle weakness are common symptoms of both types, yet in MD1, another characteristic features are muscle atrophy, facial weakness, ptosis, frontal baldness, and weakness of distal muscle groups. The allele length of CTG repeat correlates with the disease severity[114,115]. CTG expansions over 1,000 repeats are associated with the severe congenital form, sometimes stated as a distinct entity. MD2 is generally milder and more variable, with proximal weakness, calf muscles hypertrophy and muscle pain being very frequent. Both types are associated with cataract, cardiac conduction defects, cognitive and execution dysfunction, and digestive problems. Therefore, multidisciplinary approach is important for the patient care.

The prevalence estimates wary widely in different populations. The highest known prevalence of MD1 has been reported in Saguenay region in Quebec (1/475), which is attributed to the founder effect and based on genealogy study, the number of founders in these region could have been less than 57[116]. Even though MD1 is considered to be the most frequent muscular dystrophy in adults[117], the prevalence of MD1 in Czech Republic based on the records in Czech national registry of muscle dystrophies (REaDY) is 3.1/100 000, while the prevalence

of MD2 is higher, roughly 4.1/100 000[118]. This is in agreement with several other studies[117,119] suggesting that MD2 might be underdiagnosed, as the symptoms frequently occur in the elderly population.

Common symptoms of most patients, both MD1 and MD2, are myotonia and myopathy. Myotonia is an abnormal delay in muscle relaxation after contraction. It is caused by increased excitability of the muscle fibres, leading to repetitive action potentials in response to stimulation. The most typical symptom of myotonia is difficulty in releasing a forceful handgrip, problems with talking, chewing, and swallowing. Myotonia can vary from mild to severe and might cause a substantial disability. It significantly deteriorates the quality of life[120]. The myotonia is caused by aberrant splicing of chloride channel pre-mRNA, leading to loss of chloride channel protein from the surface membrane[121]. Reduced transmembrane chloride conductance leads to hyperexcitability and myotonia. Another study has described slower inactivation of sodium channels in myotonic dystrophy myocytes that results in sodium ion accumulation and prolonged depolarization[122]. Myopathy is manifested with muscle weakness, muscle atrophy or hypertrophy, muscle cramps and pain. It is also caused by aberrant splicing of several genes, namely the bridging integrator-1 (BIN1)[123], TNNT3, LDB3[124], myomesin 1 gene (MYOM1)[125], non-muscle myosin heavy-chain gene (MYH14)[126].

3.2 Therapy

So far, there is no treatment to slow down the progression of the disease and to alleviate the muscle weakness. However, number of other symptoms are treatable, and their recognition and treatment significantly increase the quality of life and, to a lesser extent, also the life expectancy.

Cardiac conduction abnormalities affect roughly 30-75% MD1 patients[127] and ECG Holter examination is recommended annually to prevent malign arrhythmias and to assign patients for cardiac pacemaker implant. Similarly, the respiratory function and routine polysomnography for signs of sleep apnea should be performed[128], as sleep apnea may cause an increase in morbidity and mortality and can be solved with CPAP (Continuous positive airway pressure). Fatigue and daytime sleepiness can be treated with modafinil[129] and methylphenidate[130] and a trials with pitolisant (NCT04886518) and caffeine and theobromine

(NCT04634682) have started recently. Some patients also require dietary adjustments due to difficulties with swallowing and risk of aspiration.

The first published attempts to treat myotonia are dated to 1930s[131,132]. Since then, many trials have been conducted with different type of drugs, such as procainamide, phenytoin, clomipramine, imipramine, quinine, benzodiazepines, calcium antagonists, taurine, etc. Considering the fact that the molecular basis of MD1 was not discovered until 1992, the tested cohorts were mixture of different types of diseases prior that date. Further, a Cochrane review and its latest amendment in 2009 pointed out the poor quality of majority of trials conducted prior to 2009[133]. Since then, several new trials have been conducted. In 2010, a study of mexiletine demonstrated reduction of myotonia in MD1[134], yet more recent study from 2021 doubted its effect, because even though there was significant reduction of myotonia measured with handgrip myotonia, it was not reflected in participants' perceptions of their myotonia. Further, mexiletine is a lidocaine analogue and can potentially increase QRS duration, shorten the QT interval and may compromise hemodynamic function in patients with heart failure[135]. In 2017, studies of lamotrigine [136] and ranolazine [137] proved their partial anti-myotonic effect on non-dystrophic myotonias. The effect of ranolazine was recently confirmed on small subset of MD1 patients[138], while the results from lamotrigine trial in MD1 have not been published yet (NCT01939561). Interestingly, one case report described complete cessation of myotonia after methylprednisolone[139].

Because of the detailed knowledge of the molecular underlying mechanisms of myotonic dystrophy, existing cell and mouse models, advances in translational research and drug development capabilities, it is not foolish to believe, that even the pathogenetically oriented therapy would seek the market approval in next few years[140]. There are many small molecule drugs, oligonucleotide-based drugs and genetic therapeutic approaches in the preclinical stage of development. Further, there are several drugs currently in phase 2 or 3 of clinical trials, (tideglusib, IONIS-DMPKRx, erythromycin, metformin), and phase 1 (ERX-963).

3.3 Outcome measures

As the myotonic dystrophy is a multisystemic disorder, outcomes assessed in myotonic dystrophy includes variety of disease symptoms. Further, as the severe form of MD1 affects children and might cause cognitive impairment and mental retardation, sometimes, the caregiver’s opinion of potential improvement must be considered instead of the patient. The

Table 4 summarizes the outcome measures used in interventional clinical trials, phase 2 and 3, since 2000 [available on clinicaltrials.gov, accessed on 05 Aug 2021]. The table shows very little overlap of used scales and even the most frequently used tests, such as relaxation time (RT), MMT and quantitative muscle assessment (QMA) employ different methodology, different muscle groups and different number of tested muscles. Similarly, functional tests, such as time to raise from the chair and time to climb up stairs vary across the trials, thus rendering the meta-analyses impossible. It resembles the situation in clinical trials of myasthenia roughly 20 years ago before the myasthenia specific scales had been developed. It can be assumed that it will take some time to establish myotonic dystrophy-specific scales to be routinely used in clinical trials as well.

In 2011, the Outcome Measure in Myotonic Dystrophy (OMMYD) working group was assembled and several international workshops of outcome measures in myotonic dystrophy type 1 have already taken place[141]. On the last report of such meeting, the first outcome mentioned was the Myotonic Dystrophy Health Index (MDHI), which has been recommended also by the NIH's Common Data Elements group. Otherwise, there was not much consensus between the recommendations of OMMYD group and NIH's Common Data Elements group. For example, the OMMYD group strongly arguments against the usage of Manual Muscle Test (MMT) in favour on the use of Quantitative Muscle Assessment (QMA). Further, the report emphasised the muscle endurance, muscle strength of the long finger flexors, and myotonia as significant biomarkers[141].

Year	MD Type	Phase	Drug intervention	Primary endpoint	Secondary endpoint	Results
2004	MD1	2	dehydroepiandrosteron	MMT	ESS FVC RT	[142]
2007	MD1	2	rhIGF-I/rhIGFBP-3	Safety	6mWT DEXA functional tests FVC MMT PPT QMA RT SIP	[143]
2008	MD1	2,3	methylphenidate	DSS ESS	MSLT POMS SF-36	[130]
2011	MD1	2	mexiletine	6mWT	BPI DEXA ESS functional tests FVC GSRS	[144]

					IBSIS INQoL MDHI MMT M-VAS PPT QMA RT SF-36	
2013	MD1	3	lamotrigine	MBS	RT SF-36	NCT01939561
2016	MD1	2	tideglusib	Safety	9HPT 10mWT ASRS CGI DEXA FVC M-VAS PPVT QMA RT Top 3 CC VAS	[145]
2021	MD1	3	tideglusib	CDM1-RS	CC-CDM1-RS CGI Top 3 CC VAS	NCT03692312
2021	MD1 and MD2	3	mexiletine	RT	10mWT DM1-Activ scale EQ-5D functional tests INQoL MBS M-VAS	NCT04700046
2021		2	pitolisant	Maintenance of Wakefulness Test	CGI Cogstate Tests ESS FSS MDHI, PGI SART	NCT04886518

Table 4: The Phase 2 and phase 3 clinical trials registered at clinicaltrials.gov as trials for Myotonic Dystrophy, with the study start date since 2000 [available on clinicaltrials.gov, accessed on 05 Aug 2021]

6mWT = 6-Minute Walking Test
9HPT = Nine-Hole Peg Test
10mWT = 10-Meters Walking Test
ASRS = Autism Spectrum Rating Scales
BPI = Brief Pain Inventory Score
CC-CDM1-RS = Caregiver Completed Congenital DM1 Rating Scale
CDM1-RS = Clinician-Completed Congenital DM1 Rating Scale
CGI = Clinical Global Impressions Scales
DEXA = Dual Energy X-ray Absorptionmetry
DSS = Daytime Sleepiness Scale
ESS = Epworth Sleepiness Scale
EQ-5D = EuroQol- 5 Dimension
FSS = Fatigue severity scale
functional tests = time to get up from chair, time to climb 10 stairs, etc., no unity in these tests.
FVC = Forced Vital Capacity
GSRS = Gastrointestinal Symptom Rating Scale
IBSIS = Irritable Bowel Syndrome Impact Scale
INQoL = Individualized Neuromuscular Quality of Life Questionnaire
MBS = Myotonia Behaviour Scale
MDHI = Myotonic Dystrophy Health Index scores

MMT = Manual Muscle Test
MSLT = Mean Sleep Latency Test
M-VAS = Myotonia Visual Analog Scale
PGI = Patient Global Impression Scales
POMS = Profile of Mood States questionnaire
PPT = Purdue Pegboard test
PPVT = Peabody Picture Vocabulary Test
QMA = Quantitative Muscle Assessment
RT = Relaxation time (myotonia evaluation)
SART = Sustained Attention to Response Task
SF-36 = Short Form 36
SIP = Sickness Impact Profile
Top 3 CC VAS= Top 3 Caregiver Concerns visual analog scale
VAS = Visual Analog Scale

3.3.1 Myotonic Dystrophy Health Index (MDHI)

MDHI is a patient-reported outcome measure that was designed specifically for use in MD1 clinical trials[146]. It consists of 18 subscales: short form, mobility, upper extremity function, the ability to perform activities, fatigue, pain, gastrointestinal issues, vision, communication, sleep, emotional issues, cognitive impairment, social satisfaction, social performance, myotonia, breathing, swallowing, and hearing. Participants provide responses to symptomatic questions using a 6-point Likert scale. The validity was determined by correlations with other tests and scales[147], test-retest reliability of the total score was excellent (ICC = 0.951)[148,149] and all subscales except pain (with ICC = 0.678) had ICC>0.750. It was already translated and validated into Italian[149], Japanese[148] and French[150]. The responsiveness of the scale has not been determined yet.

3.3.2 Myotonia assessment

Measuring of myotonia severity evolved from basic presence of percussion myotonia to computerized methods measuring the relaxation time (RT). Myotonia can be also assessed by functional tests, such as time to open a fist 10 times and time to climb up 10 stairs. Finally, it can be self-evaluated by patients on a grading scale. Probably the most accurate and specific is measuring the RT of muscles. It can be measured either by electromyography, clinically using the stopwatch or using a computerized approach.

In the review from 2006[133], the lack of a validated method for the quantitation of myotonia was considered one of the main shortcomings of previous studies for the treatment of myotonia. The degree of myotonia is extremely variable between patients, between seasons of the year and even within the same patient on the same day. It is affected by factors such as outside temperature, prior exercise or rest, pregnancy, or menses. Because repeated

contraction and relaxation may temporarily improve myotonia (the "warm-up phenomenon"[151]), it may influence results, depending on the duration and frequency of muscle contractions.

3.3.2.1 Relaxation time

In 2007, a computerized approach to the quantitation of myotonia in patients with myotonic dystrophy type 1 (MD1) employing a handgrip dynamometer was published[152] and subsequently employed in several trials[144,145,153,154]. The forearm was stabilized on a pegboard. Each measurement was taken over 6 voluntary contractions, each lasting 3 seconds, with a 10-second rest period between each contraction. Three sets of measurements took place with 10-minute intervals of rest between trials. The dynamometer produced an analogue signal that was sent to computer via an analogue-to-digital transducer and subsequently analysed by customized software that identified the peaks of the force curves. RT was then calculated as time from 90%–5% of maximal force. The inter-trial variation was expressed as coefficient of variation and the mean was 33.2% in MD1. This method is very hard to reproduce, possibly explaining the fact, that many other clinical trials used a different approach. A later study (with lamotrigine) employed the Myotonic Behaviour Scale (MBS)[155], which consists of six statements from which the patient has to choose, ranging from asymptomatic (score 0) to severe myotonia (score 5). This study used a stopwatch to measure the duration of myotonia[136]. Similarly, the authors of an open-label trial with ranolazine in 2017 chose stopwatch and subjective grading of stiffness severity by participants[137].

In 2020, a quantitative myotonia assessment using a commercially-available dynamometer without any other special need of equipment was published[156]. The protocol was quite similar to the previous approach (3 trials with 10-minute interval rest) but to reduce the inter-trial variability, the target forces were established prior to RT measurement. Patients were encouraged to perform a maximal voluntary contraction in real-time mode, and the actual force after 3 s was recorded. The target force was then defined as 75% of the previously recorded maximal force. In the course of all attempts, patients were asked to exceed the target force for 3 s in visual response to an arrow on the display of dynamometer. Relaxation time was then automatically measured (by using a built-in feature of the dynamometer), from target force to 10% of target force. The intraclass correlation coefficients were excellent, 0.945 for MD1 and 0.931 for MD2. The coefficient of variation (for comparison to previous

method) was reduced to 22% in MD1. The validity of the method was determined by correlations with MBS questionnaire (0.627 for MD1 and 0.581 for MD2).

3.3.2.2 Myotonia Behaviour Scale (MBS)

The MBS questionnaire is a very simple scale, consisting of six statements, from which the patient selects the one with whom he most identifies (Table 5). The scale was created for patients with congenital myotonia in 2005[155] by modifying the scale originally intended for pain assessment[157]. The range is from 0 (= no myotonia) to 5 points (= very severe myotonia).

Grade	
0	No stiffness
1	Some stiffness exists, which can be ignored
2	Some stiffness exists, which can be ignored at times, but doesn't impair daily activities
3	Stiffness exists, which demands a higher level of mental awareness when performing some duties and activities
4	Severe stiffness exists, which impairs every duty and activity
5	Incapacitating stiffness exists, which demands constant moving not to be totally locked up, with regard to movement

Table 5: Myotonia Behaviour Scale (MBS)

The Czech version was validated in 2018[158]. The test-retest reliability was excellent (0.965 for MD1 and 0.991 for MD2). The Figure 10 illustrates the relation between MBS and RT. The MD1 patients generally scored lower scores than MD2. It can be explained by the fact, that myotonia in MD1 presents a relatively mild symptom compared to the other symptoms they suffer, thus causing different perception of myotonia severity. Similar bias was described in the perception of muscle pain, as the muscle pain is a frequent complaint in MD2 only, even though the targeted exploration and comparison showed that the frequency, intensity and nature of pain did not differ substantially between those two forms of MD[159]. This finding implies that MBS cannot be compared across different diseases. However, while the RT was above the upper normal limit in all MD1 patients, 6 MD2 patients subjectively reporting myotonia were below this limit. Therefore, the MBS scale can be advantageously used in patients with mild myotonia as a more sensitive marker.

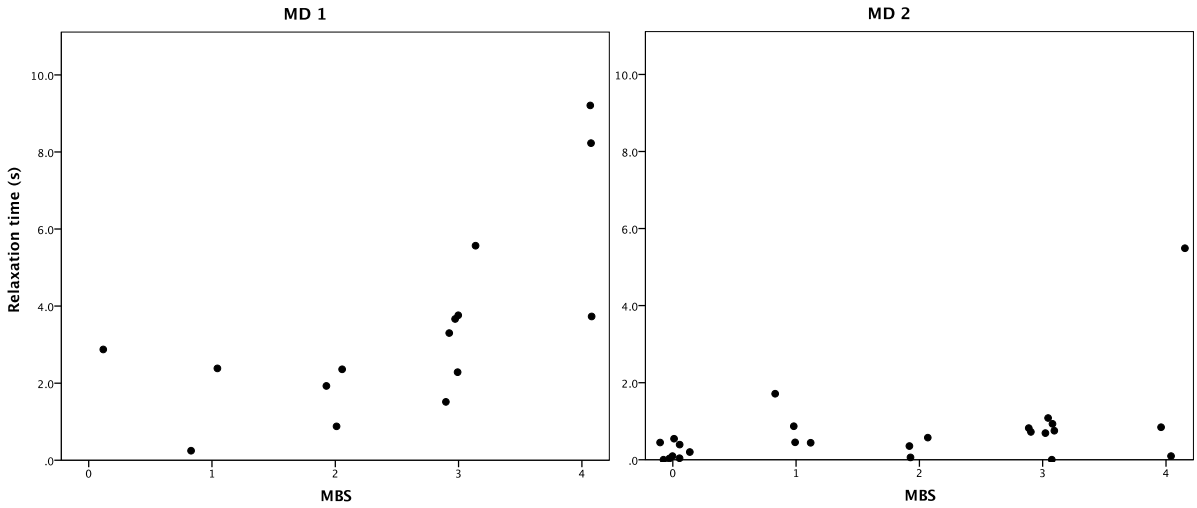


Figure 10: Relation of MBS and handgrip relaxation time

3.3.3 Myopathy assessment

3.3.3.1 Motor function evaluation

Among the outcomes assessing the motor function are tests quantifying the muscle strength (MMT, QMA) and functional tests (6-minute walking test, 10-meter walking test, time to climb 10 stairs, time to raise up from chair, etc.). There is no consensus in selecting muscle and muscle groups in testing muscle strength in clinical trials. MMT of 34 muscle groups scored by a modified Medical Research Council's scale (MRC)[160] was till 2001 the only validate outcome measure for Duchenne muscular dystrophy trials[161]. MMT is performed by a clinician who scores each of the muscle groups on a scale from 0 to 5 in relation to the maximum expected for that muscle. The assessment is thus subjective, and to measure MMT reliably requires extensive experience and training. As mentioned previously, the OMMYD group strongly arguments against the usage of Manual Muscle Test (MMT) in favour on the use of Quantitative Muscle Assessment (QMA)[141]. However, QMA measures the force using a strain gauge and requires special equipment[162,163]. Such condition limits its use to clinical trials only and renders the comparison to MMT used in patient registries to follow the natural history quite difficult.

The 6-minute walking test was originally designed to assess the adults with cardiopulmonary conditions[164]. Since then, it has been extensively used in both adults and children's neuromuscular disorders. It measures the distance a person can walk quickly in 6 minutes[165]. The nature of the test limits its use in clinical practice as there is hardly enough space to let the patient walk for six-minutes. Therefore, the 10-meter walking test, measuring the time

required to walk/run 10 meters, might be an alternative. The disadvantage of all the functional tests, and to a lesser extent event of the force measurement, is the dependence on patient-cooperation and motivation. Further, it is restricted to patients with substantial residual muscle function.

3.3.3.2 Magnetic resonance imaging of muscles

In a slowly progressing neuromuscular disorder, conventional functional tests, such as 10mWT and 6mWT, are not able to detect change in a few-years trial duration. Quantitative assessment of muscle fat fraction has been proposed as an imaging biomarker in neuromuscular diseases by several experts in the field[166–168].

Several studies have described changes in the muscle fat in upper[169] and lower extremities[170–173]. Interestingly, in muscular dystrophies (Duchenne, limb-girdle muscle dystrophies, myotonic dystrophy, etc.) specific patterns of muscle involvement can be recognised and in some cases the diagnosis can be made by imaging only[174]. In myotonic dystrophy, the MRI of lower limbs shows the affliction of the anterior compartment of the thigh, with the rectus femoris muscle spared (see Figure 11, Figure 12). The gastrocnemius medialis and soleus are most severely affected on the calf, followed by the tibialis anterior[172,173]. And on the upper limbs, high-intensity areas were found in the flexor digitorum profundus, flexor pollicis longus, and extensor pollicis, followed by affliction of abductor pollicis longus, short head of biceps brachii, medial head of triceps brachii, and deltoid muscles in more severe stage of the disease[169].

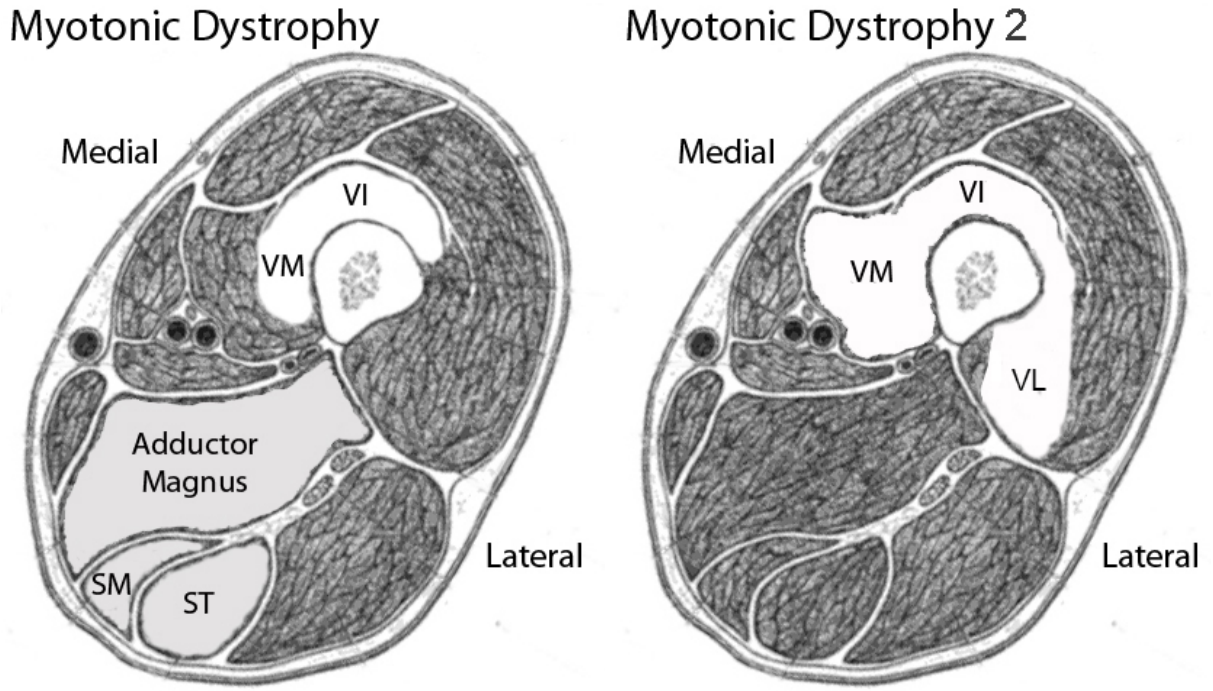


Figure 11: MRI of muscles in MD1 and MD2 [available on neuromuscular.wustl.edu/pathol/diagrams/musclemri.htm, accessed on 07/08/2021]

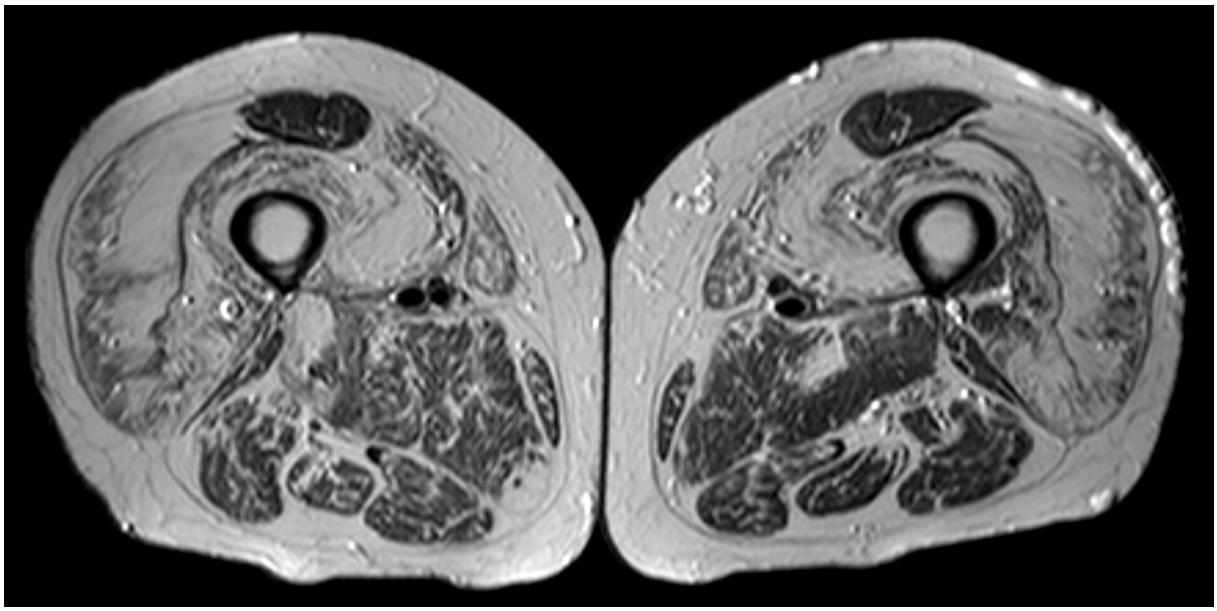
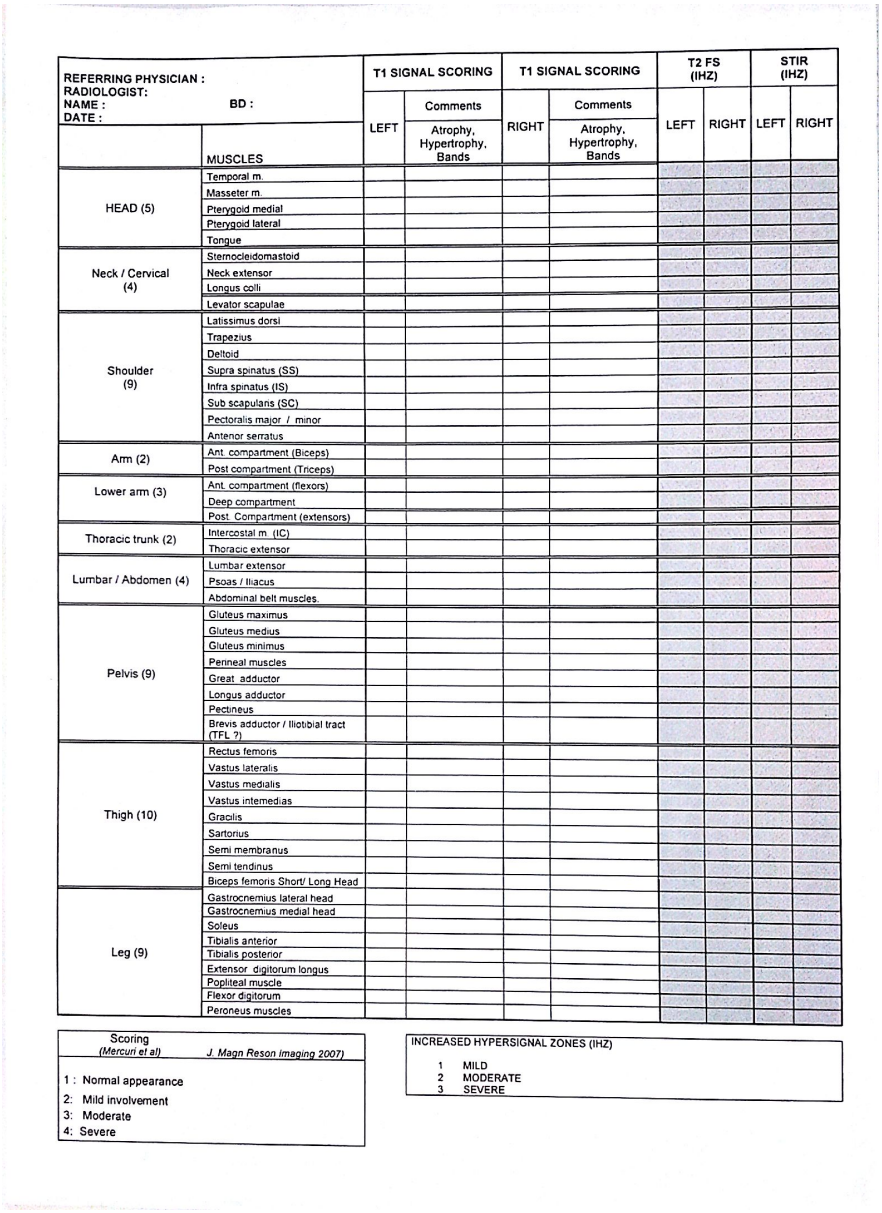


Figure 12: Advanced symmetrical muscle atrophy of thigh muscles in patient with MD2. Almost all muscles are affected, with the rectus femoris spared and relatively preserved adductor muscles (source: archive of University Hospital Brno).

The reason for selective involvement of different muscles in different disorders is unknown. The role of metabolic and developmental properties of each muscle and the proportion of muscle fiber types is being speculated[174]. Conventional MRI can be used for diagnosis,

however quantitative approach is needed for monitoring over time, as is the case in clinical trials.

Manual quantitative approach to score each muscle, typically limited to a scale of 4–6 grades, is very time-consuming and subjective. The Figure 13 shows an example of Muscle scoring protocol that was used in Institute de Myologie in Paris, France.



REFERRING PHYSICIAN :
RADIOLOGIST:
NAME : BD :
DATE :

	MUSCLES	T1 SIGNAL SCORING LEFT	T1 SIGNAL SCORING Comments Atrophy, Hypertrophy, Bands	T1 SIGNAL SCORING RIGHT	T1 SIGNAL SCORING Comments Atrophy, Hypertrophy, Bands	T2 FS (IHZ) LEFT	T2 FS (IHZ) RIGHT	STIR (IHZ) LEFT	STIR (IHZ) RIGHT
HEAD (5)	Temporal m.								
	Masseter m.								
	Pterygoid medial								
	Pterygoid lateral								
	Tongue								
Neck / Cervical (4)	Sternocleidomastoid								
	Neck extensor								
	Longus colli								
	Levator scapulae								
Shoulder (9)	Latissimus dorsi								
	Trapezius								
	Deltoid								
	Supra spinatus (SS)								
	Infra spinatus (IS)								
	Sub scapularis (SC)								
	Pectoralis major / minor								
	Anterior serratus								
Arm (2)	Ant. compartment (Biceps)								
	Post compartment (Triceps)								
Lower arm (3)	Ant. compartment (flexors)								
	Deep compartment								
	Post. Compartment (extensors)								
Thoracic trunk (2)	Intercostal m. (IC)								
	Thoracic extensor								
Lumbar / Abdomen (4)	Lumbar extensor								
	Psoas / Iliacus								
	Abdominal belt muscles.								
Pelvis (9)	Gluteus maximus								
	Gluteus medius								
	Gluteus minimus								
	Perineal muscles								
	Great adductor								
	Longus adductor								
	Pectineus								
	Brevis adductor / Iliotibial tract (TFL ?)								
Thigh (10)	Rectus femoris								
	Vastus lateralis								
	Vastus medialis								
	Vastus intermedias								
	Gracilis								
	Sartorius								
	Semi membranus								
	Semi tendinus								
	Biceps femoris Short/ Long Head								
Leg (9)	Gastrocnemius lateral head								
	Gastrocnemius medial head								
	Soleus								
	Tibialis anterior								
	Tibialis posterior								
	Extensor digitorum longus								
	Popliteal muscle								
	Flexor digitorum								
	Peroneus muscles								

Scoring (Mercuri et al) J. Magn Reson Imaging 2007)

1 : Normal appearance
2: Mild involvement
3: Moderate
4: Severe

INCREASED HYPERSIGNAL ZONES (IHZ)

1 MILD
2 MODERATE
3 SEVERE

Figure 13: Muscle Scoring Protocol, Institute de Myologie, Paris, France (source: Training School - MYO-MRI, 2017)

Using the advanced MRI techniques (Dixon[172], phosphorus magnetic resonance spectroscopy[175]) and automated segmentation of the muscles[24,176] might lead to establishing of a feasible, reliable and most of all, responsive outcome to be used in clinical trials in the future.

3.4 National registry REaDY

The Czech national registry REaDY (Registry of muscular dystrophies) was established in 2011[118]. It has 5 main domains: Duchenne/Becker muscular dystrophy (DMD/BMD), spinal muscular atrophy (SMA), myotonic dystrophy (MD), facioscapulohumeral muscular dystrophy (FSHD) and limb-girdle muscular dystrophy (LGMD). Till now, it gathered records of almost 800 MD1 and MD2 patients. The structure of the registry was compiled according to the structure of international registers kept within the TREAT-NMD project and in 2021 it received a TREAT-NMD Global Data systems Oversight Committee membership certificate. Its data were already presented in large international study[177]. Every enrolled subject is allowed to view his own data after logging into his user account and can even directly fill the quality-of-life questionnaires. Among the outcomes followed in registry are MMT (quantified by MRC scale), ESS, BPI, SF-36, Short-form McGill Pain Questionnaire, Beck Depression Inventory (BDI), International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms Modules (ICIQ-FLUTS), International Consultation on Incontinence Questionnaire Anal Incontinence Symptoms and Quality of Life Module (ICIQ-B) and International Prostate Symptom Score (I-PSS).

The basic data summaries are available on ready.registry.cz in real time (see Figure 14).

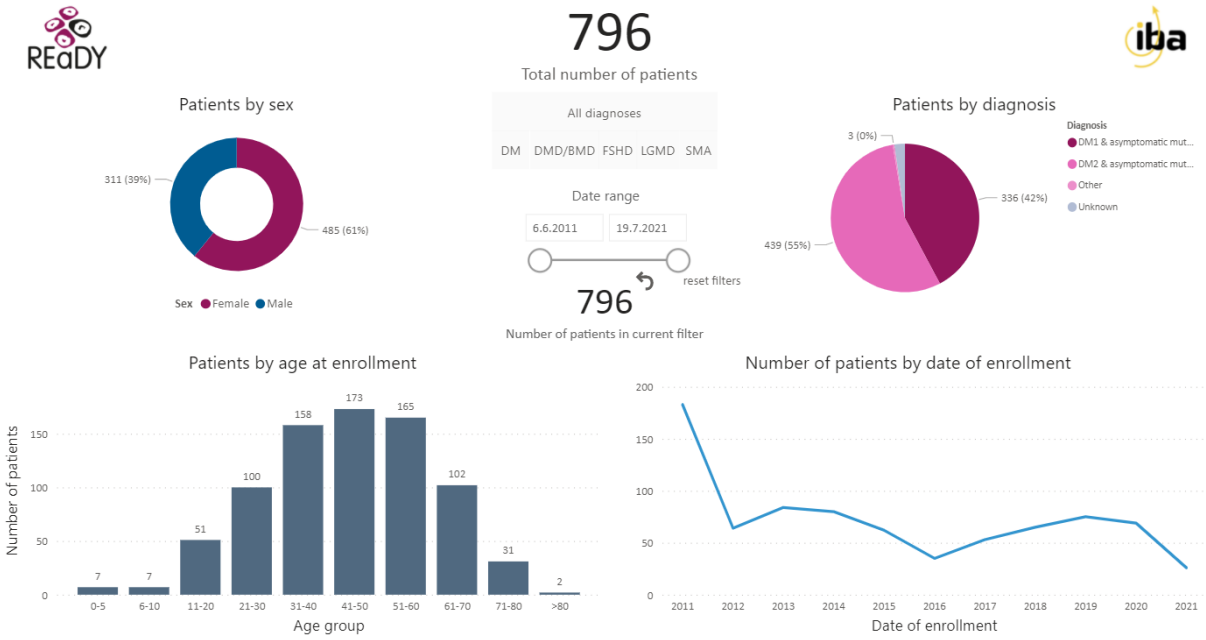


Figure 14: Basic data summaries from REaDY [available on ready.registry.cz, accessed on 06/08/2021].

4 Commented Studies

4.1 Horáková M, Voháňka S, Bednařík J. Myasthenia Gravis Composite – Validation of the Czech Version.

Cesk Slov Neurol N 2016; 79/112(5): 585-590.

The aim of this paper was to translate and validate the Myasthenia Gravis Composite (MGC) score developed in 2008 and test in on a small sample of myasthenia patients from Czech Republic. Standard procedure of forward-backward was employed and the final version was reached by consensus. Special focus was given to the time frame of the items based on the patient's history. The main author of the original MGC score, prof. Ted Burns, was contacted with this query, yet he confirmed that the specific time frame is left for the clinician to decide depending on the current situation (e.g., stable patient for weeks, severe deterioration in two days), using the "common-sense" approach.

The test-retest reliability tested on sample of 40 patients was excellent with ICC of 0.989. We also investigated the variability of each item, and the most variable item was surprisingly the neck flexion or extension, while the breathing item (which we intuitively expected to be the most variable one) was most reliable.

MGC score is now a crucial, and mandatory outcome measure in Czech national registry of myasthenia gravis (MyReg) and all Neuromuscular centres in Czech Republic have implemented this outcome to routine examination.

Myasthenia Gravis Composite – validace české verze

Myasthenia Gravis Composite – Validation of the Czech Version

Souhrn

Cíl: V roce 2008 byla z vybraných položek stávajících škál myastenie (QMG, MG-MMT, MG-ADL) vytvořena nová škála s názvem MG Composite (MGC). Cílem práce bylo validovat českou verzi této škály a ověřit spolehlivost na skupině pacientů Neuromuskulárního centra FN Brno trpících myastenií. *Metodika:* Český překlad byl validován metodou zpětného překladu. Shoda mezi hodnotiteli byla ověřena na vzorku 40 pacientů v rámci akutní hospitalizace nebo rutinní kontroly. Pacienti byli hodnoceni dvěma neurology (SV a MCH) nezávisle na sobě v časovém rozmezí 10–60 min. *Výsledky:* Pro analýzu shody hodnotitelů byl použit koeficient ICC (Intraclass Correlation Coefficient) s výsledkem 0,989 a intervalem spolehlivosti CI = (0,98–0,994). Regresní analýzou jsme v našich datech neprokázali větší odchylku s rostoucím MGC (p = 0,616). Spearmanův korelační koeficient mezi absolutní velikostí rozdílu v hodnocení a průměrnou hodnotou MGC jednotlivých pacientů byl 0,561. *Závěr:* Škála MGC je efektivní nástroj k spolehlivému sledování stavu pacientů, účinku terapie a porovnávání výsledků použitelný v běžné klinické praxi.

Abstract

Objective: In 2008, the new MG Composite score was constructed from selected items of existing scales of myasthenia (QMG, MMT-MG, MG-ADL). The aim of this study was to validate the Czech version of MGC and to check reliability of the new scale in a group of patients from the Neuromuscular Centre of the University Hospital in Brno. *Methods:* The Czech translation of MGC was validated by forward-backward translation. Inter-rater reliability was assessed with 40 patients (during a routine outpatient visit or hospitalization). Patients were assessed independently by two neurologists on the same day within 10–60 min (SV and MCH). *Results:* Intra-class correlation coefficient was 0.989 (CI = 0.98–0.994). Regression analysis of our data did not prove any systemic bias of difference according to MGC score (p = 0.616). Spearman correlation coefficient for the absolute difference in MGC value and the mean MGC of individual patients was 0.561. *Conclusion:* MG Composite is an effective tool for long-term monitoring of patients, evaluation of treatment effect and comparing data suitable for use in routine clinical practice.

Tato publikace vznikla na Masarykově univerzitě v rámci projektu MUNI/A/1072/2015 podpořeného z prostředků účelové podpory na specifický vysokoškolský výzkum, kterou poskytlo MŠMT v roce 2016.

Autoři práce děkují pacientům, kteří podstoupili vyšetření.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.
Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.
The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.

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Klíčová slova

myastenie – škála – Quantitative Myasthenia Gravis

Key words

myasthenia – score – Quantitative Myasthenia Gravis

Úvod

Myastenie je autoimunitní onemocnění charakterizované postsynaptickou poruchou nervosvalového přenosu. Autoprotilátky namířené proti acetylcholinovému receptoru nebo jiným strukturám nervosvalové ploténky blokují jejich funkci. Výsledkem je oslabení kosterních svalů. Pro onemocnění je typické kolísání tíže příznaků. Zpravidla se pacienti cítí nejhůře po námaze a k večeru.

Důležitým požadavkem pro dlouhodobé sledování pacienta, hodnocení efektu léčby a pro většinu klinických studií je možnost kvantifikovat tíži postižení. K posouzení odpovědi na léčbu je nezbytné zachytit i malou změnu ve smyslu zlepšení nebo naopak zhoršení. Pro každodenní praxi by hodnocení mělo být rychlé, nezatěžující personál ani pacienta a především by mělo být porovnatelné mezi jednotlivými vyšetřujícími. Pokud všechny tyto podmínky budeme chtít splnit

Příloha 1. Jazykově validovaná česká verze MGC.

MG COMPOSITE SCALE

Jméno pacienta: ..... Jméno vyšetřujícího: .....

Datum vyšetření: ..... Čas vyšetření: .....

1. Ptóza při pohledu nahoru	> 45 s **= 0**	11–45 s **= 1**	1–10 s **= 2**	okamžitě **= 3**
2. Dvojité vidění při pohledu laterálně (doleva nebo doprava)	> 45 s **= 0**	11–45 s **= 1**	1–10 s **= 3**	okamžitě **= 4**
3. Zavření očí	norma **= 0**	lehké oslabení (lze pasivně otevřít s úsilím) **= 0**	střední oslabení (lze pasivně otevřít snadno) **= 1**	těžké oslabení (neschopen udržet oči zavřené) **= 2**
4. Řeč	norma **= 0**	intermitentní setřelá řeč nebo mluvení přes nos (nazolalie) **= 2**	trvale setřelá řeč nebo mluvení přes nos (nazolalie), ale lze porozumět **= 4**	je obtížné řeči porozumět **= 6**
5. Žvýkání[1]	norma **= 0**	únava tuhou stravou **= 2**	únava měkkou stravou **= 4**	sonda do žaludku **= 6**
6. Polykání[1]	norma **= 0**	vzácné epizody zaskakování potravy či ztíženého polykání **= 2**	časté obtíže při polykání, nutná změna diety **= 5**	sonda do žaludku **= 6**
7. Dýchání (způsobené MG)	norma **= 0**	dušnost po námaze **= 2**	klidová dušnost **= 4**	nutnost umělé plicní ventilace **= 9**
8. Flexe nebo extenze krku (nejslabší)	norma **= 0**	lehké oslabení **= 1**	středně těžké oslabení **= 3**	těžké oslabení **= 4**
9. Abdukce ramene[2]	norma **= 0**	lehké oslabení **= 2**	středně těžké oslabení **= 4**	těžké oslabení **= 5**
10. Flexe kyčle[2]	norma **= 0**	lehké oslabení **= 2**	středně těžké oslabení **= 4**	těžké oslabení **= 5**
Celkem bodů				

[1] Hodnotí se potíže za posledních 24 hod, pokud se jednalo o běžný den. Lze se zeptat i na delší časový úsek, pokud je to vhodné.

[2] Středně těžké oslabení odpovídá zhruba 50 ± 15 % očekávané normální síly. Jakékoliv mírnější oslabení je klasifikováno jako mírné a jakékoliv těžší oslabení jako těžké.

u onemocnění, jehož příznaky navíc kolísají v čase, jedná se téměř o nemožný úkol. Svědčí pro to i poměrně pestrá nabídka mnoha různých škál, které byly pro hodnocení stavu pacienta s myastenií vytvořeny.

První bodová škála (multiple-item ordinal scales) s názvem MG-Score byla pro hodnocení myastenie vytvořena v 80. letech 20. století [1]. Po několika úpravách se z ní postupně stala dnes široce používaná škála QMG (Quantitative Myasthenia Gravis) [2]. Měří se výdrž několika svalových skupin, síla stisku a síla sevření víček, doba do rozvinutí dvojitého vidění nebo ptózy, vitální kapacita plic, hodnotí se řeč a polykání. Zlepšení v hodnocení QMG je dnes primárním cílem mnoha klinických studií. Tato škála ale není standardně využívána v běžné klinické praxi a to hned z několika důvodů. Vyžaduje několikaminutové upažení, zvednutí dolních končetin a hlavy, a je tak fyzicky náročná pro pacienta, ale především časově velmi náročná pro personál. Kompletní vyšetření zabere asi 20 min. Navíc vyžaduje speciální přístroje (spirometr, dynamometr).

V roce 2003 byl vytvořen jednoduchý svalový test s názvem MG-MMT (Manual Muscle Test for Myasthenia Gravis). Hodnotí se síla 30 svalových skupin proti odporu vyšetřujícího. Autory bylo navrženo ji používat jako alternativu QMG pro její jednoduchost a menší časovou náročnost [3]. Tento test ale není schopen zachytit únavu svalů po námaze a další charakteristické potíže (bulbární příznaky).

Ani jedna z těchto škál ale nezohledňuje fakt, že symptomy nemusí být při objektivním vyšetření přítomny a zpravidla jsou zřetelněji vnímány pacientem než vyšetřujícím lékařem. V roce 1999 bylo vytvořeno skóre s názvem MG-ADL (MG Activities of Daily Living) [4]. Dotazník se skládá z osmi otázek, na něž odpovídá pacient. Otázky jsou zaměřeny na zvládání běžných každodenních činností (řeč, žvýkání, polykání, česání atd.). Ukázalo se, že ve srovnání s QMG je citlivější ke změně stavu [5]. Skóre ADL společně se specifickým dotazníkem kvality života (Myasthenia Gravis Quality of Life; MG-QoL) je standardní součástí subjektivního hodnocení ve většině klinických studiích.

Každá z výše uvedených škál má své limitace. Mezi hlavní patří časová náročnost a nutnost speciálního vybavení u QMG a čistě subjektivní hodnocení pomocí ADL. V roce 2008 byla z vybraných položek výše zmíněných škál (QMG, MG-MMT, MG-ADL) vytvořena nová škála s názvem MG Composite (MGC) [6]. Jednotlivé škály se pro některé položky (např. ptóza, diplopie, řeč) překrývají, ačkoliv každá testuje funkci odlišným způsobem. V konstrukci nové škály byl vybrán test s nejlepšími vlastnostmi. Podkladem pro výběr položek byly dvě studie hodnotící účinek terapie mykofenolát mofetilem u pacientů se seropozitivní generalizovanou myastenií [7,8]. Položky byly vybrány na základě četností abnormálního výsledku, korelace s MG-QoL a shody s celkovým posouzením stavu ze strany pacienta i lékaře.

Výsledkem je 10 položek s jasným klinickým významem pro lékaře i pacienta. První tři vycházejí z QMG a soustředí se na vyšetření očí, 4.–7. položka vychází z ADL a je subjektivně referovaná pacientem a poslední tři položky jsou převzaty z MG-MMT a zaměřily se na axiální a kořenové svaly nejčastěji zasažené myastenií. Na základě zkušenosti, že u méně než 1 % subjektů došlo ke zhoršení očních příznaků mezi 46. a 60. s, byly zkráceny intervaly pro vyšetření očních příznaků oproti QMG [9].

Další důležitou změnou je nerovnocenné neboli vážené skórování položek. Například při hodnocení dýchacích obtíží může pacient dosáhnout až 9 bodů, zatímco nejtěžší oslabení očních víček je hodnoceno pouze 2 body. Váhy byly stanoveny na základě expertního posouzení 36 specialisty z 10 zemí [6] a ověřeny Raschovým modelem [10].

Validace originální verze byla provedena v letech 2008–2009 v 11 neuromuskulárních centrech (z toho dvě v Evropě – Glasgow a Milán) [9]. Používání této škály je dále podpořeno faktem, že v roce 2012 Task Force of the Medical Scientific Advisory Board (MSAB) of the Myasthenia Gravis Foundation of America (MGFA) doporučila užívání MGC jako kvantitativní škály pro hodnocení stavu nemocných s generalizovanou myastenií [11].

Cílem práce je validovat českou verzi této škály a ověřit spolehlivost na skupině pacientů Neuromuskulárního centra FN Brno trpících myastenií.

Příloha 2. Pokyny k vyplnění MGC.

Formulář k vyplnění lze nalézt v příloze 1. Škála MGC má celkem 10 položek. Minimální počet bodů je 0, maximální možný počet bodů je 50. Protože položky jsou vybrané z různých škál, část vychází z klinického vyšetření (1–3, 8–10) a část z anamnézy (4–7). V originální škále není nijak stanoveno, za jaké období by měl pacient své symptomy u položek 4–7 hodnotit. Je to ponecháno na „zdravém rozumu" vyšetřujícího. Přesto v rámci zjednodušení považujeme za vhodné ptát se na poslední 24 hod a pouze v případě, že byl předchozí den zcela výjimečný, lze se zeptat i na delší časové období, např. týden. Jednotlivé položky by měly být vyšetřovány v pořadí tak, jak jsou uvedeny.

1. Ptóza při pohledu nahoru

Pacient pohodlně sedící se vyzve ke sledování prstu vyšetřujícího tak, aby se pacient díval vzhůru. Sledujeme, zda do 45 s nedojde k poklesu víčka.

2. Dvojité vidění při pohledu laterálně

Pacient se znovu vyzve ke sledování prstu vyšetřujícího nejprve na jednu stranu po dobu 45 s a poté na druhou stranu také po dobu 45 s. Pacient nám musí sám nahlásit jakmile prst začne být rozmazaný nebo přímo dvojitý. Zaznamenává se horší výsledek. Prst by měl být asi 50–80 cm od oka, v úhlu kolem 45 stupňů.

3. Zavření očí

Pacient se vyzve k usilovnému sevření očí, které se snažíme proti odporu rozevřít.

4. Řeč

Ptáme se na subjektivní pocit řeči. Pokud je objektivně přítomna lehká dysartrie, ale pacient referuje, že se mu mluví normálně, hodnotí se jako 0.

5. Žvýkání

Ptáme se na potíže se žvýkáním. Pacient, který má zavedenou sondu do žaludku automaticky skóruje 6 bodů, bez ohledu na to, zda je schopen přijímat potravu i perorálně.

6. Polykání

Ptáme se na obtíže při polykání, váznutí soust v krku, zaskakování soust. Důležitá je otázka, zda došlo k změně stravovacích návyků nebo složení stravy. Pokud např. pacient sdělí, že mu zaskakovala rýže a proto už ji nejí, skóruje 5 bodů.

7. Dýchání

Ptáme se na dýchací obtíže, zadýchávání při námaze nebo i v klidu. Hodnotí se pouze obtíže, u kterých předpokládáme, že jsou myastenického původu.

8. Flexe nebo extenze krku

Vyšetřuje se síla flexe a extenze krku proti odporu. Středně těžké oslabení odpovídá přibližně 50 % očekávané normální síly (± 15 %). Jakékoliv lehčí oslabení se hodnotí jako lehké a jakékoliv těžší oslabení jako těžké. Zaznamenává se horší výsledek.

9. Abdukce ramene

Pacient vsedě zvedá paže nad horizontálu proti odporu. Pokud je slabost asymetrická, tak se hodnotí slabší strana.

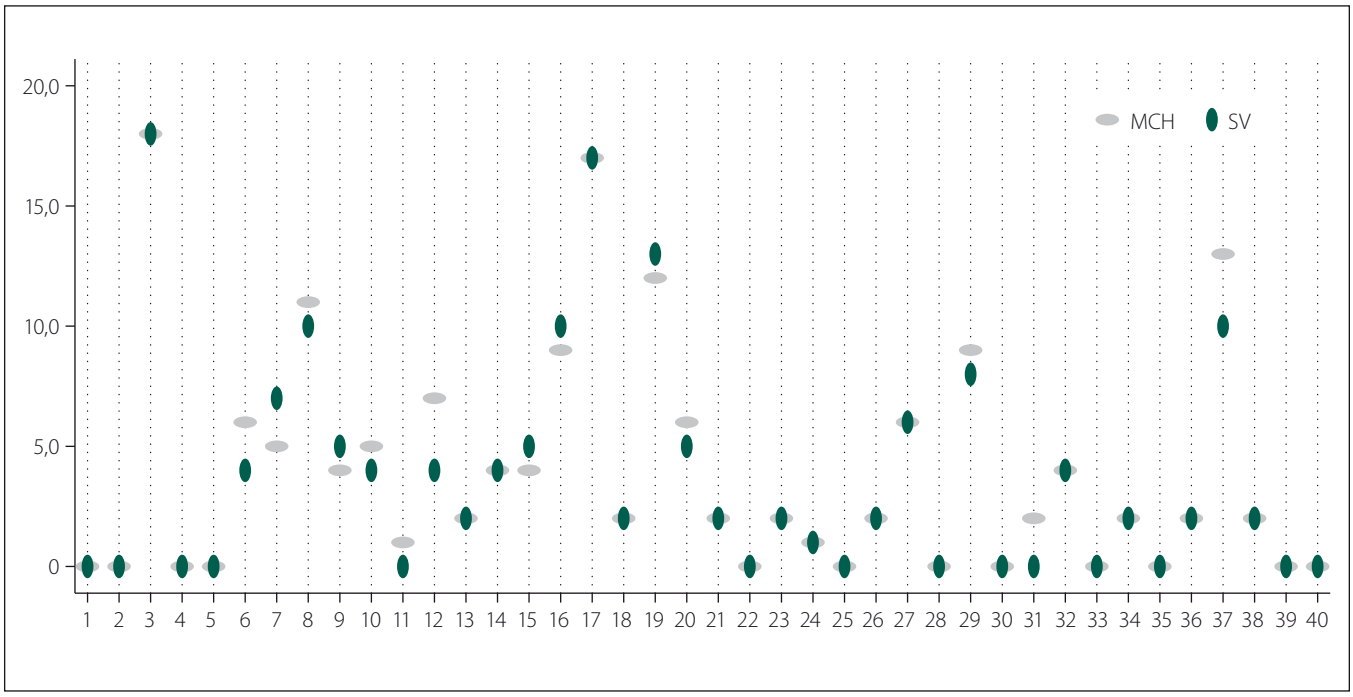
10. Flexe kyčle

Pacient vsedě zvedá nohu pokrčenou v kyčli a v koleni proti odporu (při asymetrii platí stejné pravidlo, jako v bodu 9).

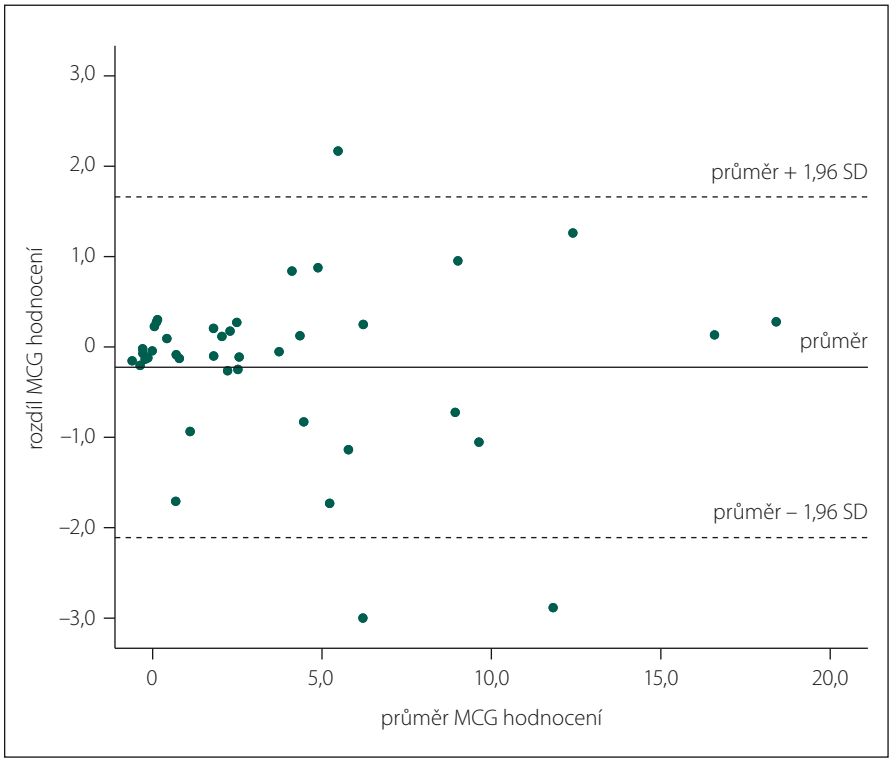
Soubor a metodika

První fází validace byl český překlad a ověření správnosti a jednoznačnosti překladu metodou zpětného překladu do angličtiny [12]. K zhodnocení jednoznačnosti překladu byl originál i zpětný překlad zkontrolován rodilým mluvčím.

Další fází bylo stanovení spolehlivosti hodnocení mezi různými hodnotiteli. Zařazeno bylo celkem 40 pacientů buď v rámci akutní



Graf 1. Hodnocení MGC dvěma hodnotiteli (MCH a SV).



Graf 2. Blandův-Altmanův graf – závislost velikosti rozdílu v hodnocení na tíži myastenie (průměr MGC mezi hodnotiteli).

Plná přímka odpovídá průměru, čárkované přímky odpovídají 95% limitům shody.

hospitalizace na lůžkovém oddělení neurologické kliniky nebo v rámci rutinní kontroly v ambulanci v časovém rozmezí květen 2014–únor 2016.

Ze 40 pacientů bylo 21 žen (52,5 %) a 19 mužů (47,5 %). Věkové rozmezí pacientů bylo 30–84 let a věkový průměr 61 let. Zařazeni byli pacienti s časným i pozdním nástupem myastenie (13–77 let, průměr 53 let). Protilátky proti acetylcholinovým receptorům byly pozitivní u 35 pacientů (87,5 %). Čistě okulární formu mělo pět pacientů (12,5 %), 35 pacientů (87,5 %) mělo formu generalizovanou. Thymom v anamnéze mělo osm pacientů (20 %).

Pacienti byli hodnoceni dvěma neurology (SV a MCH) nezávisle na sobě ve stejný den. Pořadí hodnotitelů bylo náhodné, ale zpravidla byli ambulantní pacienti nejprve hodnoceni SV a hospitalizovaní pacienti nejprve MCH. Interval mezi měřeními byl stanoven uměle na 10–60 min. Byl zvolen tak, aby pacient nebyl unavený z předchozího vyšetření a současně se snížila pravděpodobnost běžného zakolísání příznaků během dne.

Data byla zpracována v softwaru SPSS 23. Pro analýzu shody hodnotitelů (inter-rater reliability) byl použit koeficient ICC (Intraclass Correlation Coefficient), varianta two-way random, absolute, average-measures [13]. K vyloučení systémového zkreslení byl použit Blandův-Altmanův graf, lineární regresní model a Spearmanův koeficient.

Jazykově validovaná česká verze MGC je přílohou 1. Příloha 2 je návod na hodnocení jednotlivých položek a vychází z práce Burnse et al, osobní komunikace s autorem (Ted Burns) a vlastních zkušeností při validaci české verze [6,9,14].

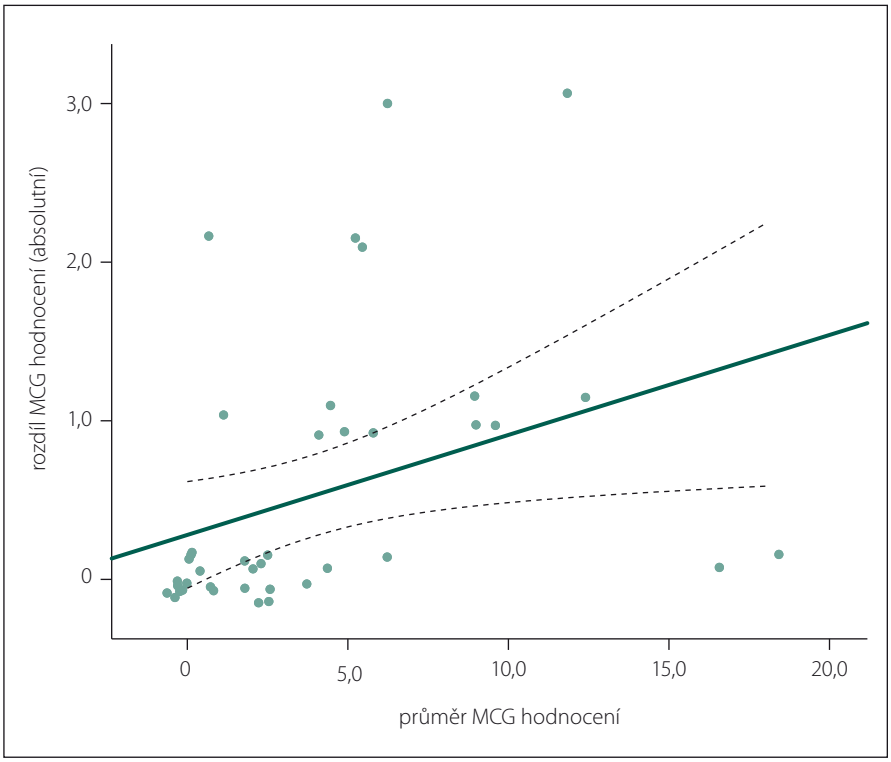
Výsledky

Hodnocení všech 40 pacientů je zobrazeno na grafu 1. Průměrné hodnocení MGC bylo 3,9. Průměrná hodnota diference (absolutního rozdílu) mezi vyšetřujícími byla 0,5 bodu. MGC skóre se u žádného pacienta nelišilo o více než 3 body a 95 % pacientů mělo skóre v rámci odchylky 2 bodů.

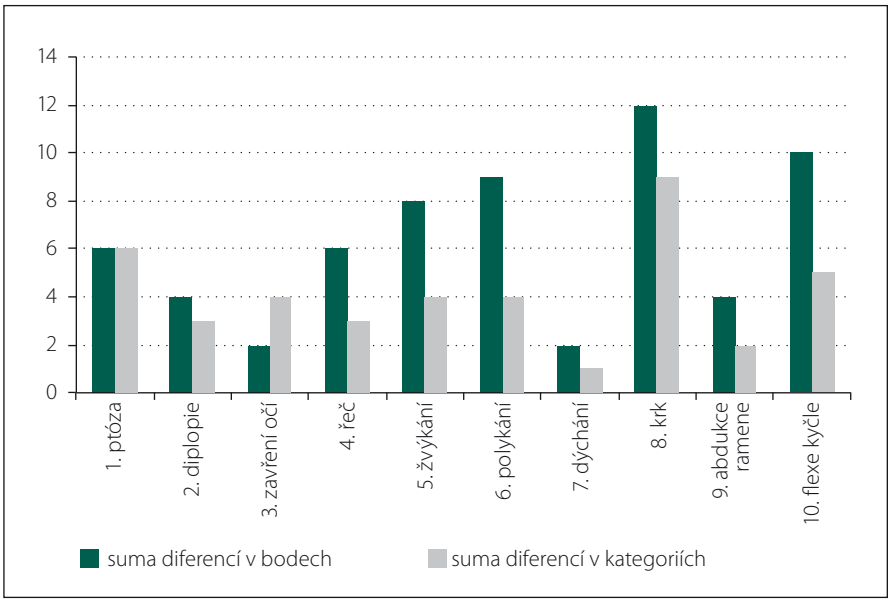
Pro statistickou analýzu shody hodnotitelů byl použit koeficient ICC. Výsledná hodnota, ICC = 0,989 s intervalem spolehlivosti CI = (0,98–0,994), svědčí pro výbornou spolehlivost nové škály.

K vyloučení systémového zkreslení byl vykreslen Blandův-Altmanův graf s 95% limity shody (graf 2). Graf zobrazuje vztah mezi rozdílem v hodnocení a průměrným MGC pro každého pacienta [15]. Regresní analýzou jsme v našich datech neprokázali závislost rozdílu v MGC hodnocení a průměrem MGC hodnocení (koeficient –0,017; p = 0,616). Spearmanův korelační koeficient závislosti absolutní hodnoty rozdílu hodnocení MGC a průměrem hodnocení MGC byl 0,561 (graf 3).

Variabilita jednotlivých položek je zobrazena na grafu 4. Pro každou položku jsou vykresleny dva sloupce. Na osy y je celkový součet odchylek v hodnocení pro všech 40 pacientů. První sloupec odpovídá součtu bodů, zatímco druhý sloupec odpovídá pouze součtu kategorií (0, 1, 2, 3), a není tak zohledněno vážené skórování (kromě položky zavření očí tak nabývá nižších hodnot).



Graf 3. Závislost absolutní velikosti rozdílu mezi hodnotiteli na tíži myastenie (průměr MGC mezi hodnotiteli) s lineární regresní přímkou a 95% intervalem spolehlivosti.



Graf 4. Suma rozdílů mezi hodnotiteli rozdělená podle jednotlivých položek MGC.
První sloupec odpovídá celkovému součtu rozdílů bodů, druhý sloupec odpovídá součtu rozdílů v kategoriích.

Diskuze

Z vlastní zkušenosti můžeme potvrdit, že skóre MGC je jednoduché a časově nenáročné. Nezbytné dvě a čtvrt minuty trvá vyšetření očních příznaků, které je z testu časově nejnáročnější. Celkově vyšetření trvá max. 4–5 min a není na něj potřeba žádné speciální vybavení. Postačí pouze stopky (dnes běžné v každém mobilním telefonu).

Spolehlivost nové škály je výborná. Důležitým výsledkem je i nezávislost velikosti odchylky na tíži myastenie. Rozdíl mezi hodnotiteli je náhodný, bez systémového zkreslení a nezvětšující se s velikostí MGC.

V našem souboru byla nejvariabilnější položka flexe nebo extenze krku. Navzdory našemu očekávání a poněkud volné formulaci u sedmé položky – dýchání (způsobené MG) – byla tato položka nejméně variabilní.

Autoři MGC doporučují za klinicky významnou změnu stavu považovat změnu skóre o 3 body a více [9]. Naše výsledky potvrzují, že u 95 % pacientů bylo skóre v rámci odchylky 2 bodů. Tříbodový rozdíl tak s 95% pravděpodobností musí odpovídat skutečné změně zdravotního stavu.

Jednotné a spolehlivé hodnocení stavu umožňuje porovnání velkých souborů dat a sledování pacienta v čase. Doposud nebylo k dispozici žádné dostatečně jednoduché a rychlé hodnocení, které by bylo použitelné v běžné klinické praxi. Naším cílem je kromě validace této perspektivní a mezinárodně uznávané škály také její rozšíření do

center a pracovišť zabývajících se myastenií. Jde o efektivní nástroj k spolehlivému sledování stavu pacientů, účinku terapie a porovnávání výsledků.

Seznam použitých zkratek

ADL – Activities of Daily Living
QMG – Quantitative Myasthenia Gravis
MGC – Myasthenia Gravis Composite
ICC – Intraclass Correlation Coeficient
CI – Confidence Interval
SV – Stanislav Voháňka
MCH – Magda Chmelíková

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Cesk Slov Neurol N 2017; 80/113(1): 66-69.

In this paper, we also aimed to translate and validate the Myasthenia Gravis Quality of Life 15 questionnaire. Again, standard procedure of forward-backward was employed. We placed great emphasis on clarity of the translation, as we considered it even more important than in MGC score. Patients at our centre receive a MG-QOL15 form on each visit and fill it by themselves while sitting in the waiting room.

Test-retest reliability was tested on sample of 40 patients, with the correlation coefficient of 0.993. We also performed simple linear regression to test the hypothesis, whether the difference is dependent on the absolute total score but there was no systematic bias. Cronbach's alpha of internal consistency was 0.947, perhaps even too high, suggesting that some of the items might be redundant. The most correlating items were "I have limited my social activity because of my condition" and "My condition limits my ability to enjoy hobbies and fun activities" with correlation coefficient of 0.877 and then items "I have to make plans around my condition" and "My occupational skills and job status have been negatively affected" with correlation coefficient of 0.864. The MG-QOL15 was later revised to MG-QOL15r, yet we have not implemented the new version yet.

Validace dotazníku kvality života pro pacienty s myastenií – česká verze MG-QOL15

Validation of Myasthenia Gravis Quality of Life Questionnaire – Czech Version of MG-QOL15

Souhrn

Úvod: V roce 2000 Task Force MGFA (Myasthenia Gravis Foundation of America) doporučila vytvoření MG-specifického QOL dotazníku. V roce 2008 byl vytvořen 15bodový dotazník s názvem Myasthenia Gravis Quality of Life 15 (MG-QOL15). Dotazník prokázal výbornou spolehlivost a velmi dobrou korelaci s ostatními škálami (QMG, MG-ADL, MMT) a rychle se stal součástí hodnocení pacientů v klinických studiích. Cílem naší práce bylo vytvořit oficiální český překlad, provést jeho validaci a především rozšířit MG-QOL15 do běžné klinické praxe. *Metodika:* Český překlad byl schválen profesionálním překladatelem a validován metodou zpětného překladu. Opakovatelnost a reprodukovatelnost byla ověřena na vzorku 40 pacientů. První dotazník pacienti vyplnili v rámci rutinní kontroly, druhý vyplnili s 2–4denním odstupem. *Výsledky:* Pro analýzu opakovatelnosti byl použit Pearsonův koeficient s výsledkem 0,993. U 95 % pacientů bylo skóre v rámci odchylky 2 bodů. Regresní analýzou jsme v našich datech neprokázali větší odchylku s rostoucím celkovým skóre. Hodnota Cronbachova alfa 0,947 prokazuje vysokou vnitřní konzistenci dotazníku. *Závěr:* Dotazník MG-QOL15 je efektivní nástroj k monitorování kvality života u pacientů s myastenií. Oficiální český překlad umožní využití dotazníku v klinické praxi.

Abstract

Background: In 2000, the Myasthenia Gravis Foundation of America task force recommended development of an MG-specific QOL measure. A 15-item Myasthenia Gravis Quality of Life 15 (MG--QOL15) scale was constructed in 2008. The questionnaire proved to be reliable and well correlated with other MG-scales (QMG, MG-ADL, MMT) and it quickly became a part of the evaluation of patients in clinical trials. The aim of our study was to establish an official Czech version, perform validation and enable the MG-QOL15 use in routine clinical practice. *Methods:* Czech translation was approved by a professional translator and then validated through forward-backward translation. Repeatability and reproducibility were tested on a sample of 40 patients. Patients completed the MG-QOL15 during a neuromuscular clinic visit and were asked to complete the second MG- QOL15 2–4 days later. *Results:* The Pearson correlation coefficient between the first and second completion was 0.993. For 95% of patients, the score did not differ by more than 2 points. Regression analysis of our data did not prove systematic bias with higher MG-QOL15 score. Cronbach alpha of 0.947 corresponds to high internal consistency of the questionnaire. *Conclusion:* The MG-QOL15 is an effective tool for monitoring the quality of life in patients with myasthenia. The official Czech translation allows the use of the questionnaire in routine clinical practice.

Tato publikace vznikla na Masarykově univerzitě v rámci projektu MUNI/A/1072/2015 podpořeného z prostředků účelové podpory na specifický vysokoškolský výzkum, kterou poskytlo MŠMT v roce 2016 a v rámci projektu institucionální podpory FN Brno MZ ČR – RVO (FNBr – 6526970).

Autoři práce děkují pacientům, kteří podstoupili vyšetření.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.
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Klíčová slova

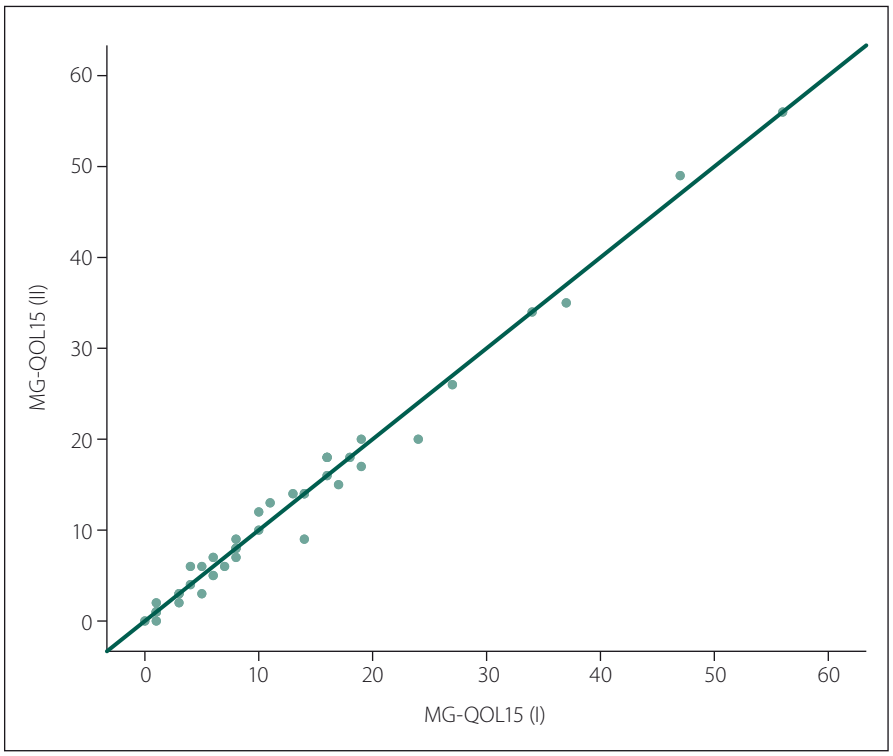
myastenia gravis – škála – kvalita života – validace – dotazník

Key words

myasthenia gravis – outcome measure – quality of life – validation – questionnaire

Úvod

Již od 80. let 20. století se v medicíně klade důraz na škály, které hodnotí vliv onemocnění na kvalitu života pacienta a jeho běžné denní aktivity. Zejména jsou takové škály důležité u chronického, vyčerpávajícího a v čase kolísajícího onemocnění, kterým myastenie bezpochyby je. Tyto škály zachycují odlišné aspekty nemoci, než je síla a výdrž měřená objektivními metodami. Souhrnné označení pro škály hodnotící kvalitu života v souvislosti se zdravím je HRQOL (Health-Related



Graf 1. Korelace mezi celkovým skóre MG-QOL15.
Na ose x je skóre prvního vyplnění v rámci rutinní kontroly a na ose y je skóre s odstupem 2–4 dní.

Quality Of Life scales). Kvalita života je ovlivněna mnoha různými vlivy, např. fyzickou zdatností, psychickou pohodou, společenskou aktivitou nebo profesním postavením, a správný HRQOL dotazník by měl tyto domény zahrnovat. Výběr otázek v dotazníku hodnotící kvalitu života by měl být ušitý na míru onemocnění. Při konstrukci dotazníku se vychází z toho, co už je o nemoci a populaci pacientů známo, otázky by měly být relevantní dané nemoci a neměly by se překrývat [1]. Názor pacienta je rozhodující, protože někteří dobře tolerují i těžké postižení, zatímco jiní hůře snáší i lehčí projevy nemoci. Tato skutečnost nemusí být dána jen premorbidním nastavením pacienta, ale i okolnostmi, jako je pacientova profesní role a nakolik ji onemocnění omezuje [2].

Nejrozšířenějším HRQOL dotazníkem je Short-Form Survey (SF-36) – obecný dotazník využívaný u mnoha různých onemocnění [3]. Ve studiích ale bylo prokázáno, že SF-36 není dobře využitelný u myastenie, protože pouze otázky na fyzickou zdatnost byly signifikantně rozdílné mezi pacienty a zdravými kontrolami. Opakovaně bylo dokázáno, že myastenie nemá vliv na bolest a mentální zdraví, a tyto otázky jsou tak nadbytečné [4,5]. V roce 2000 proto Task Force MGFA (Myasthenia Gravis Foundation of America) doporučila vytvoření MG-specifického QOL dotazníku [2]. V roce 2002 byl v Itálii vytvořen první MG-specifický dotazník – Myasthenia Gravis Questionnaire (MGQ). Klinickými experty i pacienty samotnými bylo navrženo 56 položek, které byly pomocí statistických nástrojů redukovány do konečného čísla 25 [6]. Dotazník dobře obsáhl otázky na fyzickou zdatnost a zvládání běžných denních aktivit (nákupy, čistění zubů atd.), ale nezahrnoval psychické aspekty nemoci. O 6 let později byl vytvořen nový, 60bodový dotazník s názvem Myasthenia Gravis Quality of Life (MG-QOL), který zahrnoval i otázky na sociální a psychickou pohodu [7]. Konstrukce byla obdobná – nejprve bylo experty vytvořeno 100 otázek, a to i na základě rozhovorů s pacienty, a následně byl počet otázek redukován. Výsledný dotazník prokázal výbornou spolehlivost a velmi dobrou korelaci s ostatními škálami (QMG, MG-ADL, MMT) [7]. Přesto téhož roku vznikla nová, 15bodová škála MG-QOL15 odvozená z původního MG-QOL. Důvodem byla příliš velká časová náročnost pro vyplnění i vyhodnocení 60bodového dotazníku. Patnáct otázek bylo vybráno na základě metaanalýzy studie s využitím MG-QOL a následně validováno multicentrickou studií 11 center. Korelace s objektivními škálami byla velmi podobná [8,9].

Od roku 2008 je tak MG-QOL15 hojně rozšířeným HRQOL dotazníkem využívaným téměř ve všech klinických studiích jako jeden ze sekundárních cílů. Každá z 15 otázek může být ohodnocena 0–4 body. Čím vyšší je celkový součet, tím výraznější negativní vliv má myastenie na kvalitu života. Dle dostupné literatury byl přeložen do několika jazyků (japonská, perská, turecká a brazilská verze) [10–13]. Lze předpokládat, že byl přeložen i do mnoha dalších jazyků, ačkoliv toto nebylo publikováno. I v České republice je MG-QOL15 už nyní využíván v několika klinických studiích. Protože pacienti dotazník vyplňují sami, je zřejmé, že musí být v jejich rodném jazyce a překlad musí být jednoznačný a srozumitelný. Ve své podstatě jsou na něj kladeny mnohem vyšší nároky než na překlady objektivních škál, které jsou vyplňovány vyšetřujícím. Překlady využívané v klinických studiích nejsou oficiální a bohužel nejsou ani validované. Cílem naší práce bylo vytvořit oficiální český překlad, provést jeho validaci a především rozšířit MG-QOL15 do běžné klinické praxe.

Soubor a metodika

První fází validace byl český překlad a ověření správnosti a jednoznačnosti překladu metodou zpětného překladu do angličtiny [14]. Český překlad byl schválen profesionálním překladatelem. K zhodnocení jednoznačnosti překladu byl originál i zpětný překlad zkontrolován rodilým mluvčím.

K vyhodnocení opakovatelnosti a reprodukovatelnosti MG-QOL15 v českém jazyce bylo použito opakované testování (test-retest). Pacienti z Neuromuskulárního centra FN Brno vyplnili dotazník při běžné kontrole a byli požádáni, aby vyplnili druhou kopii s 2–4denním odstupem. Časový odstup byl zvolen ve shodě s validací originální verze MG-QOL15 [15] tak, aby pacienti zapomněli na své předchozí odpovědi a současně se eliminovalo riziko změny zdravotního stavu. Ze stejného důvodu nebyli zařazeni pacienti, u kterých byla při rutinní kontrole navýšena nebo snížena chronická medikace. Do vyhodnocení bylo zahrnuto celkem 40 pacientů, kteří vyplnili oba dotazníky v období únor až srpen 2016.

Ze 40 pacientů bylo 16 žen (40 %) a 24 mužů (60 %). Věkové rozmezí pacientů bylo 34–91 let s věkovým průměrem 63 let. Věk v době prvních příznaků myastenie u na-

šeho souboru byl 13–77 let s průměrem 54 let. Protilátky proti acetylcholinovým receptorům byly pozitivní u 38 pacientů (95 %). Čistě okulární formu mělo devět pacientů (22,5 %). Pozitivní anamnéza thymomu byla u čtyř pacientů (10 %).

Data byla zpracována v softwaru SPSS 23. Jako koeficient opakovatelnosti (test-retest coefficient) byl použit Pearsonův korelační koeficient. K posouzení systémového zkreslení byl použit lineární regresní model a Blandův-Altmanův graf [16]. K analýze vnitřní konzistence dotazníku bylo použito Cronbachovo alfa [17].

Výsledky

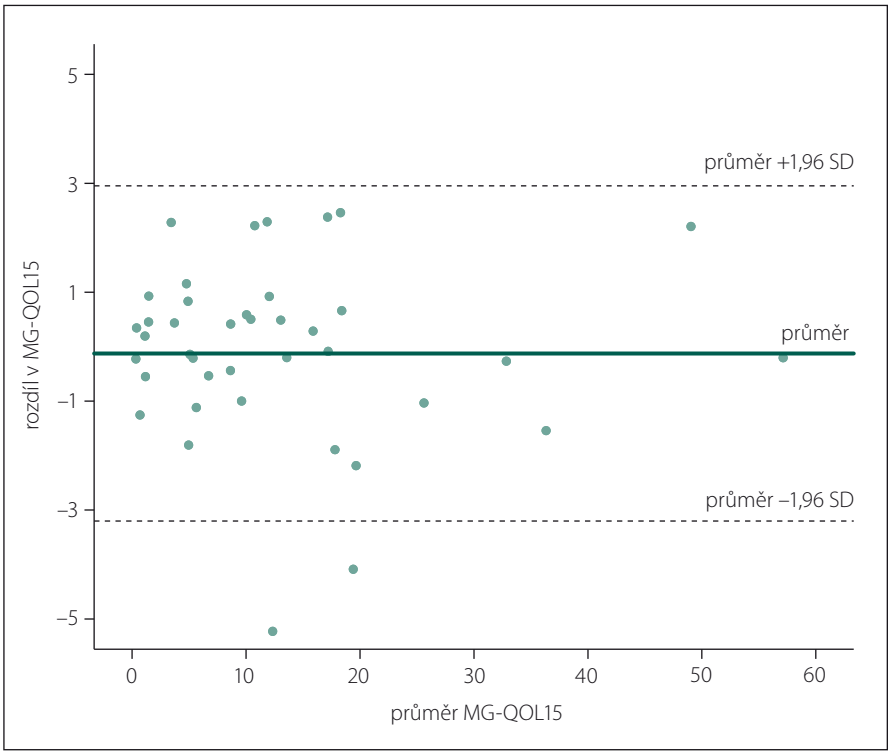
Na grafu 1 je zobrazeno vyhodnocení dotazníků a korelace mezi prvním a druhým vyplněním. Průměrné celkové skóre bylo 12,8 (min. 0, max. 56). Průměrná hodnota absolutního rozdílu v hodnocení činila 1 bod (min. 0, max. 5 bodů). U 95 % pacientů bylo skóre v rámci odchylky 2 bodů. Pouze u dvou pacientů byla odchylka vyšší – při druhém vyplnění o 4 a 5 bodů méně.

Pearsonův korelační koeficient s výsledkem 0,993 ($p \leq 0{,}001$) svědčí pro výbornou opakovatelnost (repeatability) dotazníku.

K vyloučení systémového zkreslení byl vykreslen Blandův-Altmanův graf s 95% limity shody (graf 2). Graf zobrazuje vztah mezi rozdílem v MG-QOL15 skóre a průměrem MG-QOL15 skóre. Z grafu je patrná výrazná odchylka dvou již dříve zmiňovaných subjektů. Regresní analýzou jsme v našich datech neprokázali závislost rozdílu na průměrném skóre MG-QOL15 (intercept –0,12 s $p = 0{,}741$, koeficient 0,001 s $p = 0{,}978$).

Cronbachovo alfa 0,947 dokazuje, že jednotlivé položky vykazují vysokou vnitřní konzistenci.

Maximální rozdíl v hodnocení v rámci jedné položky byly 2 body. Nejčastěji se pacienti lišili svými odpověďmi na otázku 1 („jsem frustrován myastenií“). Rozdílně na ni odpovědělo celkem 12 pacientů. Druhou problematickou položkou byla otázka 4 („omezil jsem své společenské aktivity“), na kterou celkem odpovědělo rozdílně devět pacientů, z toho tři s rozdílem 2 bodů.



Graf 2. Blandův-Altmanův graf – závislost velikosti rozdílu v celkovém skóre na tíži myastenie (průměr MG-QOL15).

Plná přímka odpovídá průměru, čárkované přímky odpovídají 95% limitům shody.

Diskuze

Dotazník MG-QOL15 představuje jednoduchý a efektivní nástroj ke zhodnocení fyzického, sociálního a psychického vlivu myastenie z pacientské perspektivy. Je také vhodný pro dlouhodobé sledování pacientů v rámci studií, ale i v běžné klinické praxi [15]. Výhodou je časová nenáročnost pro personál. Pacienti dotazník vyplňují sami a bez pomoci. Z vlastní zkušenosti můžeme potvrdit, že i pacienti přistupovali k vyplnění dotazníku pozitivně.

Při prvním vyplnění měli pacienti možnost zeptat se na nejasné otázky. Dvakrát byla položena otázka, co přesně znamená být frustrován. Současně i výsledky našeho vyhodnocení potvrzují, že v této otázce nejčastěji docházelo ke změně odpovědi. Po konzultaci s psychology, dle kterých ale neexistuje jiný český ekvivalent a pojem frustrace je v psychologii běžně používán, jsme ji ponechali v původním stavu.

Naše data prokazují výbornou opakovatelnost. S výjimkou dvou subjektů bylo skóre při druhém vyplnění v rámci odchylky 2 bodů, což je na 60bodové škále výborný výsledek. U obou pacientů s výraznější změnou v odpovědích se zřejmě jedná o náhodnou chybu. V žádné položce se nelišili o více než o bod a změny v odpovědích si nebyli vědomi. I s ohledem na tuto náhodnou chybu ale můžeme uzavřít, že rozdíl v celkovém MG-QOL15 skóre o 3 a více bodů je statisticky významný a s 95% pravděpodobností odpovídá změně v pacientově vnímání nemoci. Odchylka v hodnocení je náhodná, bez systémového zkreslení a nezvětšující se s hodnotou celkového skóre. V našich datech jsem také potvrdili vysokou vnitřní konzistenci MG-QOL15. Dokonce hodnota Cronbachova alfa 0,947 je pro potřeby takového dotazníku až příliš vysoká a naznačuje, že některé položky mohou být nadbytečné. Nejvíce korelující byly položky 4 a 5 („omezil jsem své společenské aktivity“ a „myastenie omezuje moji schopnost užívat si koníčků“) s hodnotou korelačního koeficientu 0,877. Dále se jednalo o položky 6 a 7 s hodnotou korelačního koeficientu 0,864 („mám potíže s uspokojením potřeb své rodiny“ a „musím své plány přizpůsobit myastenii“). To je ale spíše otázka pro autory originální verze dotazníku.

V souhrnu, česká verze MG-QOL15 je subjektivní dotazník kvality života pro pacienty s MG, který je velmi dobře využitelný v běžné praxi. Pro dlouhodobou monitoraci je vhodná kombinace s objektivní nebo kompozitní škálou. V úvahu připadá použití QMG, které se ale v praxi příliš neosvědčilo pro časovou i přístrojovou náročnost (spirometr, dynamometr). V našem centru využíváme kompozitní škálu MGC (Myasthenia Gravis Composite) [18], která je složena z položek QMG, MG-ADL a jednoduchého svalo-

Příloha 1. Česká verze MG-QOL15.

Jméno pacienta: Datum vyplnění dotazníku:	Uveďte prosím, do jaké míry je každý výrok pravdivý (v posledních několika týdnech)				
	Vůbec ne = 0	Trochu = 1	Poněkud ano = 2	Docela dost = 3	Velmi mnoho = 4
1. Jsem frustrován myastenií					
2. Mám potíže s očima					
3. Mám potíže jíst kvůli myastenii					
4. Omezil/a jsem své společenské aktivity kvůli myastenii					
5. Myastenie omezuje moji schopnost užívat si koníčků a zábavných činností					
6. Mám potíže s uspokojením potřeb mé rodiny kvůli myastenii					
7. Musím své plány přizpůsobit myastenii					
8. Mé profesní dovednosti a pracovní postavení byly negativně ovlivněny myastenií					
9. Mám potíže s mluvením kvůli myastenii					
10. Mám potíže s řízením kvůli myastenii					
11. Jsem v depresi kvůli myastenii					
12. Mám potíže s chůzí kvůli myastenii					
13. Mám problémy navštěvovat veřejná místa kvůli myastenii					
14. Cítím se zdrcen myastenií					
15. Mám problém s vykonáváním svých osobních denních potřeb					
Celkem bodů					

vého testu, je časově nenáročná a byla validována pro český jazyk [19]. Kombinace MGC a MG-QOL15 umožňuje srovnání pacientů jak v čase, tak i mezi skupinami, a to s ohledem na fyzickou zdatnost, zvládání běžných denních činností i vlivu na kvalitu života nemocného. Česká verze MG-QOL15 je v příloze 1.

Seznam použitých zkratek

ADL – Activities of Daily Living
HRQOL – Health-Related Quality Of Life scales
MG – Myasthenia Gravis
MGC – Myasthenia Gravis Composite
MGFA – Myasthenia Gravis Foundation of America
MGQ – Myasthenia Gravis Questionnaire
MG-QOL – Myasthenia Gravis Quality Of Life
QMG – Quantitative Myasthenia Gravis
SF-36 – 36-item Short-Form Survey

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4.3 Horáková M, Martinka I, Voháňka S, Špalek P, Bednařík J. A comparative study of myasthenic patients in the Czech and Slovak Republics.

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This paper investigated the heterogeneity of the Czech and Slovak myasthenia patients. The data of the Czech patients were gathered from the MyReg registry in 2016, only a year after its founding when it was not established as national registry yet. We observed marked differences between the two populations (age of onset, sex, positivity of AChR antibodies, presence of thymus pathology), yet after matching data by age and sex, both groups showed very similar clinical and laboratory characteristics. In particular, even the MGC score and MGFA classification were not significantly different.

Interestingly, there was a difference in therapy approach that was not reflected in MGC score, thus suggesting that particular drug choice is probably based on local practice or insurance coverage and does not affect the therapeutic response.

In conclusion the study suggests that some of the heterogeneity between different populations with myasthenia might be explained by different age and sex distributions, therefore those parameters should be always taken into the account.

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A comparative study of myasthenic patients in the Czech and Slovak Republics

Srovnávací studie pacientů s myastenií České a Slovenské republiky

Abstract

Aim: Existing epidemiological studies of myasthenia feature differences in incidence, prevalence, age- and gender-specific incidences, mortality rate, and even the prevalence of myasthenia subtypes. The aim of this study was to compare the overall management of patients with myasthenia, the severity of the disease, and a number of clinical and laboratory characteristics and therapy approaches amongst patients in the Czech Republic and the Slovak Republic. *Patients and methods:* Data were retrospectively collected from two registries in the Czech Republic (Brno) and the Slovak Republic (Bratislava). Data were randomly matched by age of onset of myasthenia and gender. The resulting groups consisted of 152 patients each. *Results:* There was almost no significant difference between the matched groups. The clinical form, positivity of antibodies to acetylcholine receptor, Myasthenia Gravis Composite Score, time to diagnosis, and percentage of thymomas and thymectomy were not significantly different. There were significant differences only in the occurrence of limb weakness at the onset of disease and in the choice of treatment modality. *Conclusions:* Our data suggest that at least part of previously observed heterogeneity between populations might be based on different age and gender distribution.

Souhrn

Cíl: Stávající epidemiologické studie vykazují rozdíly v incidenci, prevalenci, incidenci specifické dle věku a pohlaví pacientů, mortalitě, a dokonce i v prevalenci jednotlivých subtypů myastenie. Cílem této studie bylo porovnat celkovou péči o pacienty s myastenií, závažnost onemocnění, celou řadu klinických a laboratorních charakteristik a terapeutický přístup mezi pacienty v České a Slovenské republice. *Soubor a metody:* Data byla hodnocena retrospektivně ze dvou registrů v České republice (Brno) a Slovenské republice (Bratislava). Pacienti byly náhodně spárováni dle pohlaví a věku v době prvních příznaků myastenie. Výsledné skupiny sestávaly ze 152 pacientů. *Výsledky:* Mezi spárovanými skupinami nebyl téměř žádný signifikantní rozdíl. Klinická forma, pozitivita protilátek proti acetylcholinovým receptorům, Myasthenia Gravis Composite skóre, doba do stanovení diagnózy, procentuální zastoupení tymomů a tymektomie se významně nelišily. Významný rozdíl byl ale ve zvolené terapii a také v zastoupení oslabení končetin v úvodu onemocnění. *Závěr:* Naše výsledky svědčí pro fakt, že alespoň část dříve pozorované heterogenity mezi skupinami pacientů s myastenií může být vysvětlena rozdílným zastoupením mužů a žen a různou věkovou distribucí.

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myasthenia gravis – population characteristics – comparison – registries

Klíčová slova

myastenie – charakteristiky populace – srovnání – registry

Introduction

Myasthenia gravis (MG) is a typical autoimmune disorder, since the pathogenic role of auto-reactive antibodies is evident. Detection of muscle-binding antibodies in patients' sera [1] led to the autoimmune theory of MG in the early 1960s [2]. Further studies described antibodies to several compounds derived from muscle membrane [3] that led to symptoms typical of MG if passively transferred to mice, notably acetylcholine receptor (AChR) and muscle specific kinase (MuSK). [4,5]. Thus, the pathogenesis of MG is clear.

Nevertheless, the triggering factors and the natural course of the disease remain to be elucidated. As the monozygotic twin concordance rate in MG is 35.5% [6], it is certain that genetics plays at least a partial role. Nevertheless, the remaining percentage leaves options open for other factors, such as the environment. According to one systematic review, the incidence and prevalence rates vary greatly depending on where the study took place. The incidence rate ranges from 1.7 to 21.3 cases per mil person-years and the prevalence rate ranges from 15 to 179 per mil [7]. The reason for this marked heterogeneity remains unclear. As different populations have variable access to neurological healthcare, the numbers may by slightly biased by under-diagnosis. However, genetic and environmental factors are very likely to play key roles.

Epidemiological studies revealed still more differences. In European countries, the disease affects mainly adults, while child-onset MG (at under 14 years old) accounts for almost 45% of the MG population in China [8]. Even in European countries, age- and gender-specific incidences are significantly different between populations [7]. Although detailed population-based data on serological subtypes of MG are lacking, the prevalence of MG subtypes does not correlate with overall prevalence. According to unpublished data from Prof. Vincent of Oxford University in the United Kingdom, the reported number of MuSK-MG patients indicates a north-south decline in Europe [9]. Published data on therapy approach and severity expressed by specific outcome measures across different populations are scarce, but the mortality rates (defined as MG-related deaths) range from 0.06 to 0.89 per mil person-years [7].

The aim of this study was to compare the overall management of patients with MG, the severity of the disease, and a number of clinical and laboratory characteristics and therapy approaches in the Czech and Slovak Republics. The Czech and Slovak Republics are neighbouring countries in central Europe that once constituted a single federal republic, known as Czechoslovakia, until 1993. Even though each country has a separate healthcare system now, they share similar systems of compulsory general healthcare insurance, largely accessible to the general population.

Tab. 1. Basic characteristics of Czech and Slovak groups (unmatched data).

		Czech group (unmatched n = 189)	Slovak group (unmatched n = 508)	statistical significance
age of onset	mean	58.8	54.2	P = 0.001
	95% CI for mean	(56.4, 61.2)	(52.6, 55.7)	
	median	63	58	
gender	female	77 (40.7%)	265 (52.2%)	P = 0.008
	male	112 (59.3%)	243 (47.8%)	
AChR antibodies	positive	166 (89.7%)	414 (82.3%)	P = 0.021
	negative	19 (10.3%)	89 (17.7%)	
clinical form	ocular	51 (27.0%)	120 (23.6%)	P = 0.206
	generalized	138 (73.0%)	388 (76.4%)	
pathology of thymus	thymoma	21 (11.8%)	45 (10.5%)	P = 0.001
	hyperplasia	8 (4.5%)	10 (2.3%)	
	none	149 (83.7%)	373 (87.2%)	

AChR – acetylcholine receptor; CI – confidence interval; n – number

Patients and methods

Data were retrospectively collected from two registries in the Czech Republic (Brno, a regional capital city) and the Slovak Republic (Bratislava, the national capital city). The Slovak registry is nationwide (from a state with 5.4 mil inhabitants [10]), and data have been collected since 1977 [11]. The registry in Brno is more local, gathering data from the south-eastern part of the Czech Republic (a region with 1.2 mil inhabitants [12]) since 2001. The following characteristics were retrieved from visits during the January–December 2016 period: age of onset, gender, clinical form, Myasthenia Gravis Composite (MGC) score at the last visit, Myasthenia Gravis Foundation of America (MGFA) classification at the maximum severity of the disease, first symptoms referred to neurologist, time to diagnosis, AChR antibody positivity, history of thymoma, thymectomy, thyreopathy, and modality of treatment at the last visit. The drugs were grouped into cholinesterase inhibitors (ChEI), corticosteroids, azathioprin, ciclosporin, and other immunosuppressants (cyclophosphamide, mycophenolate mofetil). The term "early-onset MG" was defined as that occurring at the age under 50 years at first manifestation. All patients who had visited in the period of January–December 2016 were included. The criteria were fulfilled by 189 patients from Brno and 508 from Bratislava.

Patients from each group differed significantly both in age of onset and gender. Therefore, the data were randomly matched by age of onset and gender to enable comparison of all characteristics. The resulting groups consisted of 152 patients each. In consideration of the lack of data normality, the Mann-Whitney U test was employed to compare differences in continuous variables. Fisher's exact test or Pearson chi-squared test ($\chi 2$) was used to compare categorical variables. Statistically significance was set at $P < 0.05$. Bonferroni correction for multiple testing was used as required. Data analysis was performed using IBM-SPSS software (Version 22, SPSS Inc., Chicago, IL, USA) and Statistica (Version 12, StatSoft Inc., Tulsa, OK, USA).

Results

The basic characteristics of the two groups appear in Tab. 1. There was a statistically significant difference between groups in

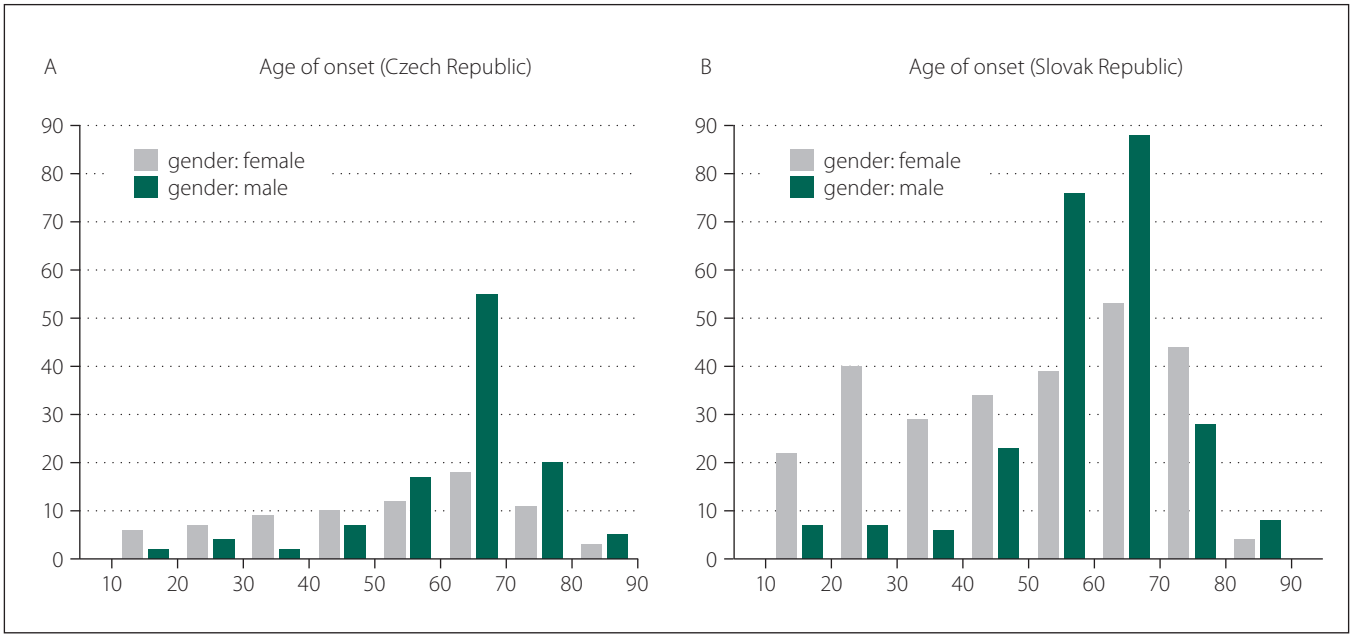

Fig. 1. Distribution of age of onset (in years) in the Czech Republic (A) and the Slovak Republic (B).
Obr. 1. Rozdělení podle věku v době nástupu onemocnění (v letech) v České republice (A) a ve Slovenské republice (B).

both age of onset (P = 0.001) and gender (P = 0.008), as appears in Fig. 1 A, B. As above, data were then matched by age of onset and gender to enable comparison of all characteristics. Both groups consisted of 152 patients, of whom 44.7% were female. The average age of onset was 57 years in both groups.

Clinical characteristics

There was almost no significant difference in clinical characteristics between the two groups (Tab. 2), apart from initial occurrence of limb weakness, the proportion of which was higher in the Slovak group. The most common initial symptoms in both groups were diplopia and ptosis (ocular). Furthermore, the ocular symptoms were the only ones present in more than half the patients at the onset of disease; however, only about a quarter of patients sustained with pure ocular form. Half the patients with initially pure ocular symptoms, therefore, developed generalized MG. Even though the average MGC score was higher in the Slovak group, the proportion of patients without symptoms (MGC zero) was also higher in the Slovak group.

Time to diagnosis

In 88.8% of patients from the Czech group and 84.8% of patients from the Slovak group, the diagnosis was made within one year of initial manifestation. The mean and median

Tab. 2. Clinical characteristics.

		Czech group (matched: n = 152)	Slovak group (matched: n = 152)	statistical significance
clinical form	generalized	113 (74.3%)	115 (75.7%)	P = 0.447
	pure ocular	39 (25.7%)	37 (24.3%)	
MGC score	mean	1.89	2.45	P = 0.678
	95% CI for mean	(1.32, 2.46)	(1.68, 3.23)	
	median	0	0	
	maximum	26	35	
	patients with MGC=0	79 (52.0%)	94 (61.8%)	
MGFA classification	I	39 (25.7%)	37 (24.3%)	P = 0.210
	IIa	16 (10.5%)	21 (13.8%)	
	IIb	63 (41.4%)	75 (49.3%)	
	III	24 (15.8%)	14 (9.2%)	
	IV	5 (3.3%)	1 (0.7%)	
	V	5 (3.3%)	4 (2.6%)	
initial symptoms	ocular	120 (78.9%)	110 (72.4%)	P = 0.114
	only ocular	83 (54.6%)	78 (51.3%)	P = 0.323
	bulbar	51 (33.6%)	51 (33.6%)	P = 0.548
	neck	10 (6.6%)	17 (11.2%)	P = 0.113
	extremities	15 (9.9%)	37 (24.3%)	P = 0.001
thyreopathy	yes	27 (17.8%)	35 (23.0%)	P = 0.319
	no	125 (82.2%)	117 (77.0%)	

CI – confidence interval; MGC – Myasthenia Gravis Composite; MGFA – Myasthenia Gravis Foundation of America; n – number

Tab. 3. Time to diagnosis.

		Czech group	Slovak group	statistical significance
time to diagnosis (months)	mean	6.8	7.5	P = 0.391
	median	2.5	3.0	
	minimum	1.0	0.25	
	maximum	120.0	72.0	

Tab. 4. Thymoma and thymectomy.

		Czech group	Slovak group	statistical significance
thymoma	yes	18 (11.8%)	19 (12.5%)	P = 0.362
	hyperplasia	8 (5.3%)	3 (2.0%)	
	no	126 (82.9%)	130 (85.5%)	
thymectomy	yes	30 (19.7%)	40 (26.3%)	P = 0.110
	no	122 (80.3%)	112 (73.7%)	

Tab. 5. Therapy.

		Czech group	Slovak group	statistical significance
therapy	ChEI	113 (74.30%)	130 (85.50%)	P < 0.001
	corticosteroids	93 (61.20%)	57 (37.50%)	
	azathioprin	77 (50.70%)	118 (77.60%)	
	ciclosporin	31 (20.40%)	10 (6.60%)	
	other	2 (1.3%)	3 (1.90%)	

ChEI – cholinesterase inhibitors

were similar (Tab. 3) and the difference was not statistically significant.

AChR antibodies

Serology of AChR-antibodies is a routine examination supporting the diagnosis of MG in both countries. Seronegative results appeared in 10.5 and 14.5% of patients in the Czech and Slovak groups respectively, and the difference was not statistically significant. Positivity of AChR-antibodies in both groups increased with age. Whereas 37% of patients in the early-onset group were seronegative, the proportion decreased to 7% in the late-onset group.

Thymoma and thymectomy

Imaging of the mediastinum represents also a routine procedure in both countries. Thymoma was diagnosed in approximately 12% of patients in both groups (Tab. 4). Occurrence of thymoma did not differ with age in the Slovak group (11.6% in early-onset and 12.8% in late-onset), while in the Czech group thymoma was diagnosed in 27.9 and 5.5% of early- and late-onset MG, respectively.

Therapy

Therapy approaches differed (Tab. 5). Patients in the Czech group received corticosteroids more often compared to ChEI and immunosuppressants.

Discussion

Our data suggest that at least part of the observed heterogeneity between different populations [7] may be based on different gender and age distributions. As the basic characteristics of both unmatched groups reveal in Tab. 1, some differences (particularly in age of onset, gender, and seropositivity of AChR) are obvious. Nevertheless, after correction for differences in age and gender, both groups showed very similar clinical and laboratory characteristics. In particular, MGC score and MGFA classification were not significantly different.

The fact that the MGC score was used uniformly in both groups lends weight to this study. It describes the actual severity of symptoms and thus reflects the patient care and enables more comprehensive comparisons.

As there were only few differences even in matched groups, they should be mentioned. Patients from the Slovak group presented more often with limb weakness among the first symptoms. The reason for this distinction is unclear. As limb weakness in elderly patients might be caused by other comorbidities (spinal and intervertebral disc diseases, polyneuropathy, ischemia, obesity, etc.), such weakness could have been attributed to other causes in the Czech group and not recorded as an MG symptom. Another possible explanation, later diagnosis in the Slovak group with more pronounced symptoms, is not supported by the almost identical time to diagnosis. While there was no difference in the total number of patients with histories of thymoma, there was a clearly higher percentage of thymoma in early-onset myasthenia in the Czech group. This finding is not in agreement with published studies [13,14]. In general, MRI was used as a mediastinal imaging modality in the Czech group, while contrast CT was used in the Slovak group. As the sensitivity of MRI and contrast CT is similar for detecting thymoma, the difference in early-onset thymoma is not explained and the reason for it remains unclear. Nevertheless, the imaging method used might partly explain the higher percentage of hyperplasia in the Czech group, for which MRI is more accurate [15].

Even though there was a clear difference in the choice of treatment modality (Tab. 5), the MGC score in both groups was similar. Therefore, it seems that particular drug choice is probably based on local practice or insurance coverage and does not affect therapeutic response. As more than half the patients were without symptoms at the last visit and the median time to diagnosis was under three months, patient care in both countries appears to be excellent.

Our study has a number of limitations. First, the registry in the Czech Republic is not nationwide, since it covers only a part of the country that is not strictly defined (approximately 1.2 mil of 10.6 mil out inhabitants [12]). Further, as only patients who had visited in the defined period were included, the entire MG population in the Slovak Republic was not covered. This rendered it impossible to calculate and compare prevalence in the two countries. Also, a partial explanation of the observed differences in age and gender may be found in the fact that some patients in a given area were referred to other Czech neuromuscular centres, and diagnosed and treated in them.

Conclusion

We report a comparative study of two MG groups from central Europe. Both groups differed significantly both in age of onset and gender. Nevertheless, the groups were very similar after correction for these factors. The heterogeneity among MG populations is certainly largely due to genetic and environmental factors, but our study suggests that some of this heterogeneity might be explained by different age and gender distributions. This should be taken to account when comparing MG populations.

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4.4 Jakubíková M, Týblová M, Tesař A, Horáková M, et al. Predictive factors for a severe course of COVID-19 infection in myasthenia gravis patients with an overall impact on myasthenic outcome status and survival.

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The present outbreak of coronavirus (COVID-19) brought many questions about the predictive factors for a severe course of the infection. As myasthenia gravis is an autoimmune neuromuscular disorder, in some cases causing the weakness of respiratory muscles, we aimed to investigate the course of the infection in myasthenia gravis patients.

We informed all patients in the national myasthenia registry (MyReg) about our study by means of text messages and all patients with the history of COVID-19 were then contacted. We identified 93 patients, 35 (38%) of which were diagnosed with severe pneumonia and in 10 (11%) the disease eventually led to death. However, these values do not have to represent the whole myasthenia population in Czech Republic, as we generally did not contact the patients who have not replied to the initial test message. Instead, we investigated the predictive factor for severe course of COVID-19 in these 93 patients.

Pre-infection data were obtained directly from the registry and from the medical documentation for each patient, the post-infection data were obtained directly from the patients by telephone (including the MG-ADL scale).

There were several important findings in this study. 14 patients (15%) had an exacerbation of myasthenia during COVID-19. Further, higher FVC and better preinfectional status of myasthenia (measured with MGFA, QMG, MGC) was associated with a lower risk of severe course of the infection (defined as the requirement of hospitalization). For example, the odds ratio (OR) for every 10% increase of FVC was 0.644 and the OR for every increase of ten points was 3.580 in QMG and 3.247 in MGC.

On the contrary, there was no significant increase in the OR for severe course of infection for azathioprine, cyclosporine, and mycophenolate mofetil. Only 4 patients received biologic therapy rituximab, 3 of which had exacerbation of myasthenia during the infection and eventually died. Therefore, rituximab proved to be the most important predictive factor for death due to COVID-19 (OR = 35.143), yet this finding should be interpreted with great caution, as the rituximab is not a first-choice treatment in myasthenia gravis and thus, patients

treated with rituximab have generally more severe course of myasthenia as well. Similarly, we found that a higher dosage of corticosteroids increased the odds of severe pneumonia (OR = 1.774 for 10 mg increase of prednisone equivalent). However, patients with worse myasthenia symptoms usually take higher dosage of corticosteroids. We were not able to perform multivariate logistic models due to small number of patients, therefore we were not able to determine the real impact of corticosteroid dose.

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ORIGINAL ARTICLE

Predictive factors for a severe course of COVID-19 infection in myasthenia gravis patients with an overall impact on myasthenic outcome status and survival

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Abstract

Background and purpose: Myasthenia gravis (MG) patients could be a vulnerable group in the pandemic era of coronavirus 2019 (COVID-19) mainly due to respiratory muscle weakness, older age and long-term immunosuppressive treatment. We aimed to define factors predicting the severity of COVID-19 in MG patients and risk of MG exacerbation during COVID-19.

Methods: We evaluated clinical features and outcomes after COVID-19 in 93 MG patients.

Results: Thirty-five patients (38%) had severe pneumonia and we recorded 10 deaths (11%) due to COVID-19. Higher forced vital capacity (FVC) values tested before COVID-19 were shown to be protective against severe infection (95% CI 0.934–0.98) as well as good control of MG measured by the quantified myasthenia gravis score (95% CI 1.047–1.232). Long-term chronic corticosteroid treatment worsened the course of COVID-19 in MG patients (95% CI 1.784–111.43) and this impact was positively associated with dosage (p = 0.005). Treatment using azathioprine (95% CI 0.448–2.935), mycophenolate mofetil (95% CI 0.91–12.515) and ciclosporin (95% CI 0.029–2.212) did not influence the course of COVID-19. MG patients treated with rituximab had a high risk of death caused by COVID-19 (95% CI 3.216–383.971). Exacerbation of MG during infection was relatively rare (15%) and was not caused by remdesivir, convalescent plasma or favipiravir (95% CI 0.885–10.87).

Conclusions: As the most important predictors of severe COVID-19 in MG patients we identified unsatisfied condition of MG with lower FVC, previous long-term corticosteroid treatment especially in higher doses, older age, the presence of cancer, and recent rituximab treatment.

KEYWORDS
corticosteroids, COVID-19, immunosuppression, myasthenia gravis, rituximab

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in which the host reaction can include antibody-mediated inflammation and a cytokine storm that is thought to have a major impact on the outcome [1]. Chen et al. [2] found that the risk of severe disease course increases with age and with certain types of comorbidities.

Myasthenia gravis (MG) is an autoimmune neuromuscular disease that carries the risk of respiratory muscle weakness, the treatment for which, for more than half the patients older than 60 years of age, is immunosuppressive therapy. These three main factors could play an important role in COVID-19 infection increasing the likelihood of SARS CoV-2 complications in MG patients [3].

Among various trigger factors for MG exacerbation and crisis, infections are the most common cause [4,5]. Some drugs, which are being tested for COVID-19 treatment such as inosine pranobex [6], hydroxychloroquine and some antibiotics (azithromycin) [7,8], may also adversely affect MG patients, especially those with bulbar symptoms and/or with severe muscle weakness who are at greater risk for another destabilization of myasthenic symptoms due to such risk medication. Treatment considerations in MG with COVID-19 are even more complex. MG is treatable with corticosteroids (CS), long-term immunosuppressive drugs, intravenous immunoglobulins (IVIG) and plasmapheresis, or biologic treatment in refractory forms. CS normally used in MG are very controversial in COVID-19 cases. In the early stages, CS can prolong viremia [9], as they inhibit immune reactions by acting on migration and chemokine production, but in contrast they can be beneficial during acute respiratory distress syndrome. However, there is still scant evidence on the positive effect of CS treatment for this critical condition [10]. Immunosuppressive treatment can affect the risk of infections and some therapies are associated with an increased risk from particular types of pathogens. The use of biologic agents in generalized MG is generally limited to therapy-refractory cases [11] and long-term use of rituximab is also associated with an increased risk of severe infection [12]. Furthermore, there may be a reduction in the production of COVID-19 antibodies and the risk of a more severe disease course in patients who have developed this infection recently after administration of rituximab [13].

In contrast, IVIG therapy has the potential to be beneficial in conjunction with COVID-19 infection and acute myasthenic exacerbation [3,14,15] through its immunomodulatory effect, thereby suppressing cytokine storm syndrome [16]. However, we have to be aware of the risk of thromboembolic complications associated with IVIG treatment, which may accentuate the hypercoagulable state during COVID-19 [17].

In this second phase of severe COVID-19, some immunotherapies might have the potential to attenuate or even prevent critical illness [18]. A very promising cure also seems to be tocilizumab (interleukin 6 [IL-6] inhibitor), which is currently in clinical trials for the treatment of severe cases of COVID-19 [19] and offers the possibility of this therapy being used in myasthenic patients with a more severe course of COVID-19 in addition to IVIG therapy. This is because IL-6, which is also involved in the immunopathogenesis of MG [20] and COVID-19 and levels of IL-6 also correlated with increased mortality due to COVID-19 infection [21].

Our primary goal was to determine the important predictive factors of the severity of COVID-19 in 93 patients with MG including treatment modalities, comorbidities and degree of MG control, and identify which therapies should be modified in those patients with confirmed SARS-CoV-2 infection if possible. Secondly, we wanted to identify the impact of a severe course of COVID-19 and its therapy on MG patients and risk of MG exacerbation.

METHODS

All patients fulfilling diagnostic criteria for MG (based on positive antibodies against acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK), or at least 10% decrement on repetitive stimulation studies) were followed up in two specialized centers for MG in the Czech Republic (in Prague and Brno). We informed all patients in the national myasthenia registry about our study by means of text messages. COVID-19 infection was confirmed by a positive throat/nose smear real-time polymerase chain reaction (RT-PCR) assay on SARS-CoV-2 viral RNA. Pre-infection data were obtained from the medical documentation for each patient, and patients or attending physicians were consulted by telephone about the post-infection course. The informed consent of all subjects was obtained according to the procedures of the Ethics Committee of the General University Hospital in Prague and University Hospital in Brno.

We were interested in risk factors for severe COVID-19 in patients suffering from MG. The severity of COVID-19 was classified on a seven-point scale (1 = asymptomatic COVID-19, 2 = isolated symptoms such as anosmia, headache, etc., 3 = mild infection such as fatigue, cold and cough, 4 = influenza-like infection without admission to hospital, 5 = hospitalized patients with proven COVID-19 pneumonia requiring oxygen therapy, 6 = severe COVID-19 pneumonia with artificial lung ventilation and 7 = death due to COVID-19). We defined severe COVID-19 as a value on the scale ≥5. Exacerbation of MG was measured as a deterioration of one category in the Myasthenia Gravis Foundation of America (MGFA) classification or as a deterioration on the Activity of Daily Living (ADL) scale of at least 2 points. All the statistics were processed using MATLAB R2018b statistic tools (MathWorks).

We applied the Shapiro–Wilk normality test for all parameters. With the exception of weight, height and forced vital capacity (FVC), the test values were below the level of significance (p = 0.05). Therefore, we used the median and interquartile range for the descriptive characteristics (see Table 1). An odds ratio (OR) with a 95% confidence interval (95% CI) was calculated to estimate the difference between defined subgroups for binominal variables. Values for p were calculated using Fisher's exact test. The OR for continuous/ordinal variable was identified by univariate logistic regression

TABLE 1 Descriptive characteristics of the cohort of 93 patients suffering from myasthenia gravis and COVID-19 infection

Parameter	Median	Q1	Q3	Parameter	*n*	%
Age (years)	65.33	48.63	75.46	Women	46	49
Height (cm)	172	164	180	Men	47	51
Weight (kg)	82	70	96.5	Anti-AChR positivity	73	78
MG duration (months)	72	36	163.25	Anti-MuSK positivity	2	2
CS dosage (mg)	5	5	10	Thymoma	9	10
FVC (%)	75	65.95	86.05	Thymectomy	34	37
MGFA scale before COVID-19 infection	IIa	IIa	IIb	Azathioprine	25	27
MGFA scale during COVID-19	IIb	IIa	IIIa	Mycophenolate mofetil	11	12
MGFA scale after COVID-19 infection	IIa	IIa	IIb	Ciclosporin	6	6
ADL scale before COVID-19 infection	2	0	4	Tacrolimus	2	2
ADL scale during COVID-19 infection	3	1	6	Change in medication due to COVID-19 infection	12	13
QMG score before COVID infection	5	2.75	9	Number of patients admitted to hospital	34	37
MGC scale before COVID-19 infection	5	2	9	Non-myasthenic complications during COVID-19 infection	23	25
Duration of symptomatic COVID-19 infection (days)	14	7	21	Remdesivir therapy	11	12
Days with fever (*n*)	2	0	5	Acetylcholine inhibitors	72	77
Severity of COVID-19 infection scale	4	3	5	Rituximab	4	4
				IVIG	7	8
				Exacerbation of MG	14	15

Parameter	*n*	%	Parameter	*n*	%
Cardiac/vascular comorbidity	14	15	Bronchial asthma	11	12
Arterial hypertension	50	54	Cancer	13	14
Smoking	7	8	Diabetes mellitus	18	19

Abbreviations: AChR, acetylcholine receptor; ADL, Activity of Daily Living scale; CS, corticosteroid; FVC, forced vital capacity: IVIG, intravenous immunoglobins; MG, myasthenia gravis; MGC, Myasthenia Gravis Composite scale; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific tyrosine kinase; Q1, quarter 1; Q3, quarter 3; QMG, Quantitative Myasthenia Gravis score.

with the ordinal model of COVID-19 severity scale. We used the Benjamini–Yekutieli procedure to compensate for multiple comparisons problem (critical p value > 0.005). The Wilcoxon rank-sum test was used to study the effect of immunosuppression on the severity of COVID-19. The dependence of the severity of COVID-19 on a dosage of CS was also calculated by univariate logistic regression for binary classification (severe COVID-19 vs. mild COVID-19) without respect to the exact value on the severity scale.

RESULTS

Descriptive characteristics

We identified 93 MG patients with confirmed COVID-19. Some 35 patients (38%) were diagnosed with severe pneumonia and we recorded 10 deaths (11%) due to COVID-19. The majority of patients (72 subjects, 77%) were treated with acetylcholinesterase inhibitors and with CS (75 subjects, 80%). Forty-four patients (47%) had another type of immunosuppressive therapy, namely azathioprine, mycophenolate mofetil, cyclosporine or tacrolimus. Six patients were treated with biologic therapy (four with rituximab, one with the study drug anti-neonatal Fc receptor immunoglobulin and one with glatiramer acetate). Seven patients were also treated with IVIG due to worsening myasthenic symptoms during COVID-19. The results are summarized in Table 1.

Older patients had a higher chance of suffering from severe COVID-19 pneumonia (OR 1.062, 95% CI 1.037–1.088, $p < 0.001$). Conversely, higher FVC (%) was associated with lower odds of severe pneumonia (OR 0.957, 95% CI 0.934– 0.98), $p < 0.001$). For a decrease of 1% in FVC, the odds of severe pneumonia was 4.5% higher (Figure 1).

CS medication increased the odds of contracting severe pneumonia (OR 14.098, 95% CI 1.784–111.43, $p = 0.002$) and higher dosage of

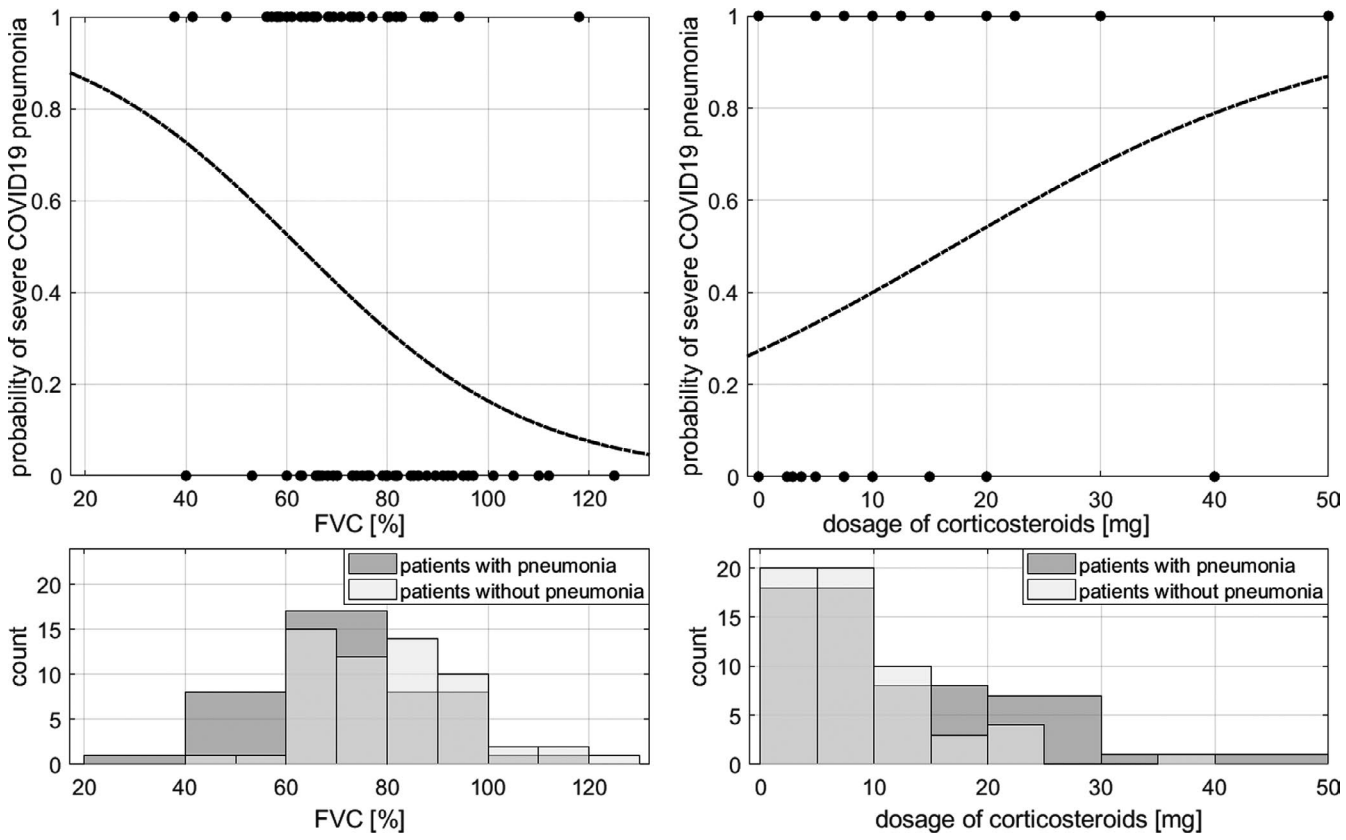

FIGURE 1 Sigmoid function of logit regression of severe COVID-19 pneumonia with a histogram for dependence on forced vital capacity (FVC) (%) (left) and dosage of corticosteroids (mg) (right)

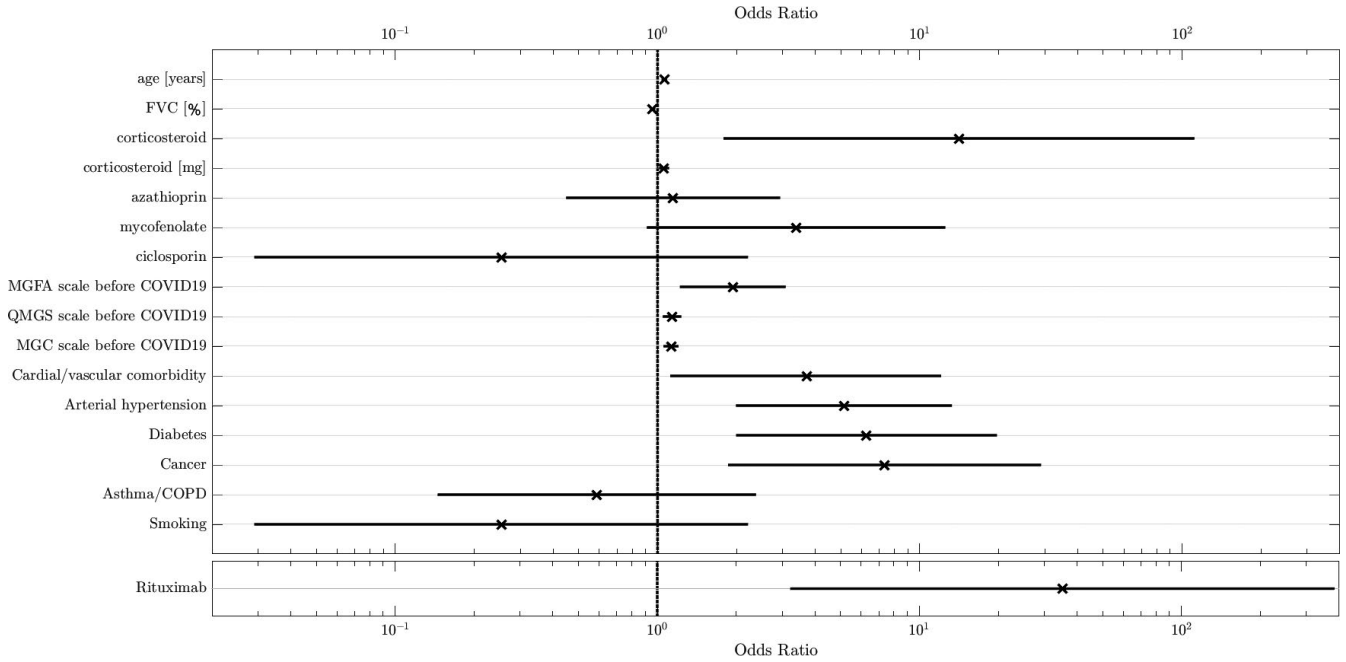

FIGURE 2 Odds ratio and confidence interval for severe pneumonia for different parameters and in the case of rituximab odds ratio of death for COVID-19 infection

CS increased the odds of severe pneumonia (OR 1.059, 95% CI 1.014–1.107, $p = 0.01$), but the p value exceeded the level of significance. To clarify the dependence of the severity of COVID-19 infection on a dosage of CS, we calculated the logistic regression for two categories, namely severe COVID-19 pneumonia and a mild course of COVID-19 infection (OR 1.093, 95% CI 1.027–1.1164, $p = 0.005$).

We tested whether any type of immunosuppressive treatment (azathioprine, mycophenolate mofetil, ciclosporin) caused more severe COVID-19. For every immunosuppressive drug, the median of the COVID-19 severity scale was 4 for treated as well for non-treated patients ($p = 0.24$). We observed similar results for individual types of immunosuppressives, namely azathioprine (OR 1.147, 95% CI 0.448–2.935, $p = 0.8$), mycophenolate mofetil (OR 3.375, 95% CI 0.91–12.515, $p = 0.1$) and ciclosporin (OR 0.255, 95% CI 0.029–2.212, $p = 0.3$).

The corresponding values in patients treated with rituximab for death caused by COVID-19 were OR 35.143, 95% CI 3.216–383.971 and $p = 0.004$.

Patients with an unsatisfied condition of MG status described using MGFA, Myasthenia Gravis Composite (MGC) and Quantitative Myasthenia Gravis (QMG) scales were at higher risk of severe pneumonia: OR MGFA status 1.936, 95% CI 1.217–3.081, $p = 0.005$; OR QMG 1.136, 95% CI 1.047–1.232, $p = 0.002$ and OR MGC 1.125, 95% CI 1.053–1.202, $p < 0.001$.

Finally, we tested the association of COVID-19 pneumonia with six different categories of comorbidities (cardiovascular diseases, arterial hypertension, diabetes mellitus type 2, cancer, bronchial asthma, and smoking). The majority of comorbidities increased the odds of severe pneumonia: (1) cardiovascular diseases: OR 3.669, 95% CI 1.117–12.057, $p = 0.04$, which exceeds the level of significance for multiple comparisons; (2) arterial hypertension: OR 5.136, 95% CI 1.99–13.257, $p < 0.001$; (3) diabetes mellitus type 2: OR 6.264, 95% CI 1.993–19.682, $p = 0.001$ and (4) cancer: OR 7.333, 95% CI 1.856–28.978, $p = 0.004$. Conversely, in asthma/COPD (OR 0.586, 95% CI 0.145–2.374, $p = 0.5$) as well as in smoking (OR 0.255, 95% CI 0.029–2.212, $p = 0.3$) we did not demonstrate any effect. The OR results are plotted in Figure 2.

The specific treatment of COVID-19 pneumonia did not pose a risk in MG (11 patients were treated using remdesivir, one with favipiravir, one with inosine pranobex and four with convalescent plasma). We did not register any adverse effects and treatment did not affect MG exacerbation (OR 3.1019, 95% CI 0.885–10.87) but $p = 0.1$ exceeded the level of significance and we also did not find significant changes in the ADL scale level during COVID-19 treatment (OR 1.709, 95% CI 0.590–4.953, $p = 0.4$). We observed a change in MGFA during infection, but MGFA status also increased due to respiratory insufficiency and general weakness.

DISCUSSION

Our research is, to the best of our knowledge, the largest cohort of 93 MG patients with COVID-19, and as the most important predictors of severe COVID-19 infection we identified unsatisfied condition of MG with lower FVC and previous long-term CS treatment especially in higher doses, older age, the presence of cancer, and recent rituximab treatment.

Similar smaller groups, but with only descriptive statistics of the cohort of patients with MG and COVID-19, were also reported by neurologists from the USA [22,23] and Brazil [24].

As demonstrated in our results, a significant finding was that higher FVC before COVID-19 in MG is associated with a lower risk of severe COVID-19 course (OR 0.957) and that the outcome of MG patients during COVID-19 is related to their premorbid MG status according to MGFA classification (OR 1.936), the values on the QMG scale (OR 1.136) and the MGC scale (OR 1.125). There are already many studies evaluating the long-term consequences of COVID-19, and FVC is considered to be a basic indicator of the outcome because shortness of breath is one of the persistent predominating symptoms in 43% of post-COVID-19 patients [25,26]. Since we measured FVC in MG patients by default as part of scoring their condition, we had this indicator available before infection and it clearly is an important predictive factor of the patients' outcome after COVID-19 disease.

Oral CS treatment was associated with severe pneumonia and an increase in CS dosage by 5 mg led to a 56% higher chance of severe COVID-19 pneumonia in MG patients. Patients with unsatisfactory control of MG before infection were also at a higher risk of severe pneumonia incidence. This result is related to the fact that patients with a worse MG score usually take a higher dose of CS. The reason may be faster deterioration of respiratory parameters in unstable MG patients during COVID-19 infection and faster progression of pneumonia in the field of impaired cellular immunity due to chronic CS therapy. It is known that long-term oral CS treatment clearly increases the risk of serious infections as a result of short-term lymphopenia due to suppressing T-cell activation and differentiation [27]. Equally, the use of CS seemed to protract SARS-CoV-2 viral clearance, and in MERS-CoV-infected patients (also from the group of beta coronaviruses related to SARS) the use of systemic CS was found to be one of the most significant factors that contributed to increased mortality [28].

Patients with immune-mediated inflammatory diseases in New York, USA who were treated with chronic CS were more likely to require hospitalization for COVID-19 than patients who were not receiving CS [29] as is also evidenced by our conclusions. However, these two parameters are strongly associated with each other, and from our statistical analysis we are not able to distinguish exactly what has a greater influence on the course of COVID-19 in MG patients, whether it is the severity of MG before infection or the dose of CS.

This is followed by the question of how to use CS in MG COVID-19 patients, at which disease stage, and at which dosage [21]. As reported by the World Health Organization (WHO) regarding COVID-19, steroids should not be routinely given for the treatment of viral pneumonia outside of clinical trials [30]. There is no conclusive evidence to support the use of CS in the treatment of viral respiratory infection and their use remains controversial in COVID-19. Analysis has revealed no beneficial effects and, in some cases, harmful effects [31] especially in the case of long-term oral CS treatment before COVID-19 as is also evidenced by our results. Other additional risk factors for infection during chronic treatment with CS are higher doses, longer durations of therapy and older age [32]. In our cohort, older MG patients had a slightly higher chance

of suffering from severe COVID-19 pneumonia, so age can be considered a significant risk factor for the severity of COVID-19 in myasthenic patients. Based on our observations, we suggest not increasing CS during COVID-19, even in the case of exacerbation of MG, and rather choosing the route of IVIG therapy.

None of the immunosuppressants we used (azathioprine, mycophenolate mofetil, ciclosporin) had a statistically significant effect on the course of COVID-19 in our MG patients, which means we did not prove that these immunosuppressants increased the likelihood of COVID-19 complications, affected the course of COVID-19 in our MG patients or worsened their outcome. Camelo-Filho et al. [24] support this hypothesis since in their observed group of 15 MG patients with COVID-19 infection, the previous use of immunosuppressive therapy did not seem to result in an unfavorable outcome. Previous smaller cohorts of MG and COVID-19 have also shown a favorable outcome in patients receiving low-dose prednisone combination immunosuppressive therapy [23,33]. In our study group, a total of 47% of 93 MG patients used immunosuppressive therapy, only a low number of MG patients exacerbated their underlying disease during COVID-19 infection (15%), as this treatment affects the long-term stabilization of their myasthenic state, and at the same time, as shown by various studies [34], it probably plays a certain protective role in COVID-19 infection, because it reduces the immune response that leads to inflammatory cytokine storm and clinical deterioration. Some drugs recently used to treat MG (e.g., tocilizumab) are being investigated as a possible anti-inflammatory treatment for cytokine storm caused by COVID-19 [19].

Based on our observations, we do not recommend reducing or even discontinuing these immunosuppressants in MG patients with COVID-19 infection.

A completely different situation occurred in our MG patients who became infected while on biologic therapy. COVID-19 and concomitant biologic therapy with rituximab in patients with MG resulted in a more severe course of COVID-19 infection with a high risk of death (OR 35.143, 95% CI 3.216–383.971). In the cohort, four patients were treated with rituximab before COVID-19 infection. One of them survived, but his course of COVID-19 was calculated to be grade 5 on our scale with the need for hospitalization and oxygen therapy for pneumonia. Yatsuda et al. [13] point out that patients undergoing recent rituximab therapy are likely to fail to develop anti-SARS-CoV-2 antibodies, which may lead to severe and prolonged COVID-19, as is also evidenced by the case of our only surviving MG patient who had no antibodies IgG and IgM SARS-CoV-2 presented several weeks apart and severe course of COVID-19. Rituximab, an anti-CD20 monoclonal antibody, targets CD20-positive B lymphocytes, which are a prominent component of these disorders (COVID-19 and MG). Immunopathogenetic background is related to B-cell depletion, which could compromise antiviral immunity including the development of SARS-CoV-2. The European Academy of Neurology and MG expert panel came to the consensus that it may be better to hold off on B-cell depleting agents (such as rituximab) under such conditions [14,35]. Convalescent serum could be a potential therapeutic option for patients with immunodeficiency secondary to rituximab who develop severe COVID-19. Nevertheless, pausing rituximab therapy carries a risk of destabilizing MG control and might increase the requirement for CS, which could conversely worsen outcomes in MG patients with COVID-19. In multiple sclerosis patients, outcomes of COVID-19 during B-cell-depleting therapy range from mild disease to death, but rates of critical illness and death do not seem to be increased dramatically relative to the wider population [18]. Based on our results we recommend caution in myasthenic patients shortly after rituximab treatment. But due to the limited number of our patients on this therapy, the effect of rituximab on severity of COVID 19 infection needs to be assessed in a larger patient cohort.

Of all the comorbidities observed in myasthenic patients – pulmonary, cardiovascular, metabolic and oncologic – the course of COVID-19 is most adversely affected by cancer (OR 7.333). Similar findings have also been published in non-myasthenic patients [36]. Surprisingly, in our MG patients we did not prove that asthma/COPD or smoking affected their course of COVID-19 (95% CI 0.145–2.374 and 95% CI 0.029–2.212, respectively).

Only 14 patients (15%) from all the MG patients with COVID-19 had an exacerbation of MG during COVID-19 infection; three of these aggravated myasthenic patients died and all three were receiving biologic therapy with rituximab. We explain this mainly by the fact that these patients may experience a reduction in the production of antibodies to COVID-19 and the risk of a more serious course of this infection precisely because they become infected immediately or a few weeks after receiving rituximab. Statistically, the course of infection in MG worsened patients was not different from patients who did not worsen in MGFA or ADL (OR 1.821, 95% CI 0.578–5.721, $p = 0.373$). Of all the deceased patients, 30% were also worsened in their underlying disease; and of all the MG COVID-19 patients, 11% died as a result of COVID-19 infection. Different results were reported by the CARE-MG group [22], where worsening of myasthenic symptoms with the need for rescue therapy with IVIG or plasma exchange was documented in 40% of MG patients, unlike in our cohort where this figure was only 15%. In our seven MG patients whose condition worsened, we used IVIG treatment as the first option rescue therapy also due to this treatment being recommended for its positive impact on concomitant COVID-19 infection [3,14,15]. There is some evidence to suggest that IVIG might increase the risk of thrombosis including multifocal stroke in COVID-19 [17], so it is good to have these patients covered by anticoagulant therapy. Specific treatment of COVID-19 with remdesivir, favipiravir and convalescent plasma was not associated with MG exacerbation (95% CI 0.885–10.87). We documented persisting myasthenic worsening even after recovery from COVID-19 infection in six patients only.

In conclusion, based on our observations, long-term use of CS before COVID-19 infection in myasthenic patients predicts a worse course of COVID-19 infection that in all likelihood is also due to the instability of MG, which requires higher doses of CS. Conversely, immunosuppressive treatment in stable MG patients does not affect the course of COVID-19 infection and could lower the risk of exacerbation of MG during COVID-19. Therefore, based on our results, we do not recommend discontinuing chronically used

immunosuppressants or reducing their doses rapidly. CD20 antibody treatment during the COVID-19 pandemic in MG patients is very risky and we recommend initiating it only in severe refractory forms of MG in suitable patients with no comorbidities, those of younger age, and in smaller doses than usual. IVIG and possibly tocilizumab appear to be the optimal treatment for exacerbations of MG during COVID-19 infection.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Michala Jakubíková: Conceptualization (lead); Data curation (equal); Investigation (equal); Methodology (equal); Project administration (lead); Writing-original draft (lead); Writing-review & editing (lead). **Michaela Týblová:** Conceptualization (equal); Data curation (equal); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project administration (equal). **Adam Tesař:** Formal analysis (lead); Methodology (equal); Software (lead); Validation (lead); Visualization (equal). **Magda Horáková:** Data curation (supporting); Funding acquisition (equal); Investigation (supporting); Project administration (supporting). **Daniela Vlažná:** Data curation (supporting); Investigation (supporting). **Irena Ryšánková:** Data curation (supporting); Investigation (supporting). **Iveta Nováková:** Data curation (supporting); Investigation (supporting). **Kristýna Dolečková:** Data curation (supporting); Investigation (supporting). **Pavel Dušek:** Formal analysis (supporting); Software (supporting). **Jiří Piťha:** Supervision (equal). **Stanislav Voháňka:** Funding acquisition (equal); Supervision (equal). **Josef Bednařík:** Resources (equal); Supervision (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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4.5 Horáková M, Horák T, Parmová O, Bednařík J, Voháňka S. Quantitative myotonia assessment with a commercially available dynamometer in myotonic dystrophy types 1 and 2.

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The idea of this project arose from the need for myotonia quantification in our centre. One patient with MD1 pointed out the beneficial side effect of an unrelated treatment and we wanted to quantify its effect (the case will be mentioned later : The Association of methylprednisolone dosing to cessation of myotonia in a patient with myotonic dystrophy type 1.) We were unable to reproduce the methodology of measuring handgrip relaxation time (RT) described in 2007[152], despite contacting the authors, mainly because of the unavailability of a dynamometer that could produce an analog signal. Finally, we decided to develop a method using a commercially available dynamometer.

Twenty patients with MD1, 25 patients with MD2, and 35 healthy controls were included in this study. The protocol was quite similar to the previous approach (3 trials with 10-minute interval rest) but to reduce the inter-trial variability (that was expressed as coefficient of variation of 33.2% in MD1 in the original method), the target forces were established prior to RT measurement. Patients were encouraged to perform a maximal voluntary contraction in real-time mode, and the actual force after 3 s was recorded. The target force was then defined as 75% of the previously recorded maximal force. In the course of all attempts, patients were asked to exceed the target force for 3 s in visual response to an arrow on the display of dynamometer. Relaxation time was then automatically measured (by using a built-in feature of the dynamometer, Endurance test), from target force to 10% of target force. Data from the last test can be directly displayed on the device, otherwise the data are stored in a non-volatile memory archive and can be transferred to a computer by using a USB connector and downloaded via automated software (provided freely by the manufacturer) as a simple spreadsheet of RT in relation to 10% steps in the target force. Therefore, it enables to analyse all phases of the muscle relaxation separately, as can be seen on the Figure 15:

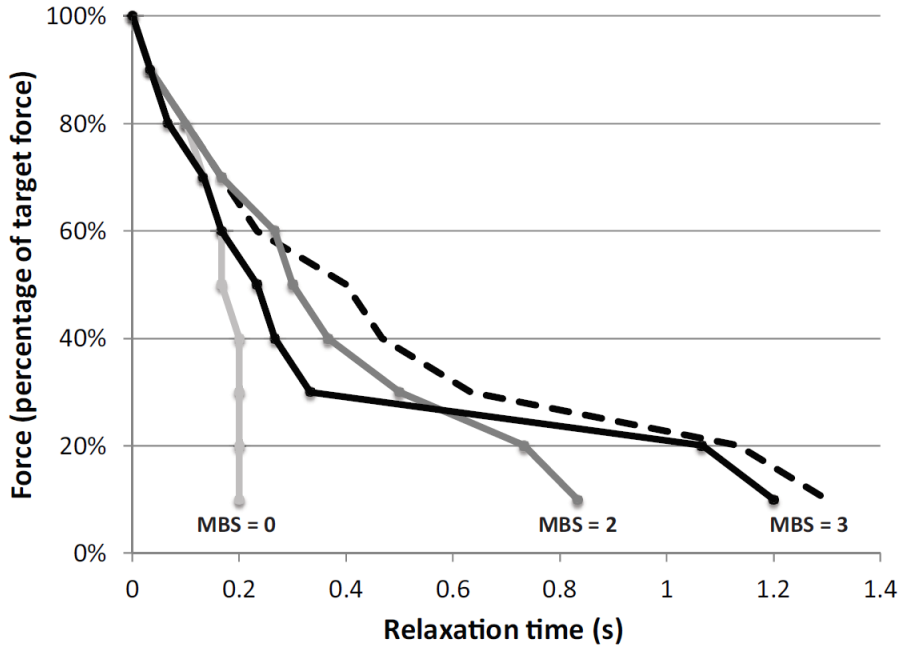

Figure 15: Relation between relaxation time and current percentage of target force showing the course of muscle relaxation in MD1 patient. (MBS = Myotonia Behaviour Scale)

The intraclass correlation coefficients (ICCs) were excellent, 0.945 for MD1 and 0.931 for MD2. The coefficient of variation (for comparison to previous method) was reduced to 22% in MD1. The validity of the method was determined by correlations with Myotonia Behaviour Scale questionnaire (0.627 for MD1 and 0.581 for MD2).

Further, this method can be used for analysis of warm-up phenomenon, if 6 squeezes are performed each trial. We demonstrated the warm-up phenomenon in both MD1 and MD2, though more profound in MD1. Differences in relaxation times between first and second voluntary contractions were 1.54 s in MD1 and 0.14 s in MD2. The differences between second and sixth contractions were still significant in MD1 (0.77 s), there was no further decline in MD2.

The simplicity of the method enabled its routine use in our centre not only for myotonic dystrophy but also for myotonia congenita (mutation in CLCN1 gene) and paramyotonia congenita (mutation in SCN4A gene). The difference between myotonia and paramyotonia can be easily demonstrated by employing the 6-squeezes method.

QUANTITATIVE MYOTONIA ASSESSMENT WITH A COMMERCIALLY AVAILABLE DYNAMOMETER IN MYOTONIC DYSTROPHY TYPES 1 AND 2

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ABSTRACT: *Introduction*: The objective of this study was to develop a simple method for quantitative assessment of myotonia in patients with myotonic dystrophy type 1 (DM1) and DM2, to compare the myotonia severity, and to correlate this objective outcome with a subjective scale, the Myotonia Behaviour Scale (MBS). *Methods*: A commercially available dynamometer was used for all measurements. The relaxation time after voluntary contraction was measured in 20 patients with DM1, 25 patients with DM2, and 35 healthy controls. *Results*: The average relaxation time was 0.17 s in controls, 2.96 s in patients with DM1, and 0.4 s in patients with DM2. The correlation between relaxation time and MBS score was significant, 0.627 in patients with DM1 and 0.581 in patients with DM2. *Discussion*: Our method provides a valid and reliable quantitative measure of grip myotonia suitable as an outcome measure in clinical trials and as part of routine examinations to gather data on the natural history of myotonic disorders.

Muscle Nerve **59**:431–435, 2019

Myotonia is an abnormal delay in muscle relaxation after contraction. It is caused by increased excitability of the muscle fibers, leading to repetitive action potentials in response to stimulation. It is a cardinal symptom of myotonic disorders, including myotonic dystrophies and the nondystrophic myotonias. Although the most typical symptom of myotonia is difficulty in releasing a forceful handgrip, facial muscles, tongue, and other bulbar muscles may also be affected, resulting in problems with talking, chewing, and swallowing. Myotonia can vary from mild to severe and may constitute a substantial disability, leading to significant deterioration in quality of life.[1]

Development of a safe and effective drug treatment for myotonia that might be routinely employed remains the subject of current research. A Cochrane review[2] and its most recent amendment from 2009 concluded that trials reported as of 30 July 2009 were generally small and of poor quality. One aspect crucial to any clinical trial is reliable determination of the treatment effect; among the issues identified in the studies covered by the Cochrane review was the lack of a conclusive method for the quantitation of myotonia.

Relaxation time (RT) after maximum voluntary contraction is currently the variable most frequently employed in the assessment of myotonia. It may be measured by stopwatch or, more accurately, by specialized equipment and computerized protocols. Because repeated contraction and relaxation may temporarily improve myotonia (the "warm-up phenomenon"), it may influence results, depending on the duration and frequency of muscle contraction set for the test.

A computerized approach to the quantitation of myotonia in patients with myotonic dystrophy type 1 (DM1) employing a handgrip dynamometer was published in 2007.[3] The dynamometer produced an analog signal that was sent to a computer via an analog-to-digital transducer, and, subsequently, the RT was analyzed by customized software. This method was then used by the same authors to demonstrate the effect of mexiletine in a clinical trial[4] and tested in nondystrophic myotonias.[5] A later study (with lamotrigine) employed the Myotonia Behaviour Scale (MBS),[6] which consists of 6 statements from which the patient has to choose 1, ranging from asymptomatic (score 0) to severe (score 5) myotonia. This study used a stopwatch to measure the duration of myotonia.[7] In 2017, the authors of an open-label trial with ranolazine similarly chose stopwatch and subjective grading of stiffness severity by participants.[8] The computerized approach[3] requires special equipment that is not available in most centers, possibly explaining the choice of subjective questionnaires and less accurate measurement using stopwatches by other authors.

We sought to develop a simple method of quantitating myotonia using a commercially available dynamometer and to prove it suitable as an outcome measure in clinical trials and as part of routine examinations. Our objectives were to assess the reliability of the method, strength of correlation between RT and MBS, and differences of both RT and MBS between patients with DM1 and DM2.

MATERIALS AND METHODS

Study Participants. All study participants gave written informed consent, and all study procedures received approval

Abbreviations: C, healthy controls; DM, myotonic dystrophy; ICC, intraclass correlation coefficient; MBS, myotonia behavior scale; RT, relaxation time; $RT_{100–10}$, relaxation time from 100% to 10% of target force

Key words: muscle relaxation; muscle strength dynamometer; myotonia; myotonic dystrophy; outcome measure; warm-up

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from the institutional review board at the University Hospital, Brno. In total, 80 participants were enrolled, 20 patients with DM1, 25 patients with DM2, and 35 healthy controls (C). All patients were recruited from the Neuromuscular Centre of the University Hospital, Brno during routine visits in the period July 2017–March 2018. All patients were over 18 years, and all diagnoses had been genetically confirmed. Healthy controls were free of any known muscle disease and had no acute medical problems. Their recruitment was targeted at an equal distribution of age groups. All patients completed a Czech version of the MBS questionnaire.[9]

Measurements. The protocol of myotonia measurement was based on the approach described by Moxley *et al.*[3] in 2007. A commercially available handgrip dynamometer (DynX; MD Systems, Westerville, Ohio) was used for all measurements.

Patients were seated upright in a chair that permitted standardized arm positioning with the forearm in a neutral position and the wrist extended. Relaxation time after voluntary contraction was measured from the dominant hand for all participants. Patients were asked to perform a contraction at a previously defined force, hold it for 3 s, and then release the grip as fast as possible. They were asked to keep their fingers on the handles of the dynamometer throughout the measurement to eliminate the use of finger and wrist extensors to release grip. Three sets of measurements (trials) were performed with 10-min intervals of rest between trials. Each trial consisted of 6 voluntary contractions with an approximately 10-s rest period between each contraction.

The strength of voluntary contraction was set close to maximum, but target forces were established to ensure that each attempt was based on the same value. Prior to RT measurement, patients were encouraged to perform a maximal voluntary contraction in real-time mode, and the actual force after 3 s was recorded. The target force was then defined as 75% of the previously recorded maximal force. The 75% level (a figure selected after repeated testing among healthy volunteers) established the highest possible force that each participant was able to exert throughout. In the course of all attempts, patients were asked to exceed the target force for 3 s in visual response to an arrow on the display of dynamometer. Relaxation time was then automatically measured (by using a built-in feature of the dynamometer), from target force to 10% of target force.

Statistical Analysis. Data were analyzed in SPSS version 23 (IBM, Armonk, New York). Severity of myotonia was calculated as the mean RT from 100% to 10% of target force ($RT_{100–10}$) of the first squeeze in each trial. The same value was used to correlate the severity of myotonia with MBS score by using the Spearman correlation coefficient. Additional contractions were collected to analyze warm-up phenomenon, determined as a difference between the mean RT for the first squeeze and subsequent squeezes, and tested by using the Wilcoxon signed-rank test. Intraclass correlation coefficients (ICC; two-way random, average measures) were used to assess the inter-trial variability of the first squeezes in each group. Coefficients of variation (the ratio of standard deviation to the mean of 3 trials) were calculated to allow comparison of our simplified method to the original method because these variables had been used in previous studies.[3,5] In consideration of the lack of data normality, a Kruskal–Wallis test with a *post hoc* series of Mann–Whitney tests with Bonferroni corrections were employed to analyze the differences in RT and maximal force among DM1, DM2, and healthy controls. All other differences between DM1 and DM2 were assessed with Mann–Whitney tests. Data obtained from healthy controls were used to determine the upper limit of normal RT, calculated as a 0.95 quantile of the values.

Table 1. Comparison of basic characteristics, relaxation time, and maximal force in study participants.*

Variable	Controls	DM1	DM2
Age, y	46.8 (24, 89)	38.9 (24, 59)	53.1 (18, 74)
Sex, %	60 W, 40 M	70 W, 30 M	80 W, 20 M
Age of onset, y	na	21.1	35.9
Duration of disease, y	na	17.8	17.1
$RT_{100–10}$, s	0.17 (0.07, 0.27)	2.96 (0.33, 9.00)	0.40 (0.10, 1.80)
$RT_{100–10}$, SD	0.05	2.41	0.35
Maximal force, kg	21.9 (8.2, 37.1)	9.4 (3.3, 22.0)	15.0 (3.3, 41.3)
Maximal force, SD	7.7	2.4	8.7

DM, myotonic dystrophy; W, women; M, men; na, not applicable; $RT_{100–10}$, relaxation time from 100% to 10% of target force.

*Values are mean (minimum, maximum), except when indicated as SD.

RESULTS

Study Participants. Basic descriptive characteristics of the study participants are presented in Table 1. No age difference appeared between healthy controls and each group of patients, but a significant difference between DM1 and DM2 ($P < 0.0001$) emerged. Sex did not differ among groups. The mean age of onset differed significantly ($P < 0.0001$), whereas the mean duration of disease did not differ ($P = 0.451$).

Myotonia Quantitation. The results of $RT_{100–10}$ are presented in Table 1 and Figure 1. Significant differences were found among all groups. The upper limit of normal as well as the maximum in the control group was 0.27 s. All DM1 patients exceeded this limit (the minimum in DM1 group was 0.33 s). In the DM2 group, 13 patients (52%) were below this limit; nevertheless, only 5 of them reported having myotonia.

Intertrial Variability. The variability of $RT_{100–10}$ in each of the 3 trials is illustrated in Figure 2. The ICCs were 0.945 (DM1), 0.931 (DM2), and 0.437 (C). The intertrial variation coefficients of $RT_{100–10}$ were 22% (DM1), 29% (DM2), and 28% (C).

Myotonia Behaviour Scale. All but 4 patients (all of them DM1) completed the MBS questionnaire. The mean MBS scores were 2.6 (DM1) and 1.6 (DM2). The minimum (score 0) and maximum (score 4) were the same in both myotonia groups. The difference between MBS in the 2 groups was statistically significant ($P = 0.043$), even though Figure 3 clearly shows that patients with DM1 generally reported lower MBS than those with DM2 in relation to value of $RT_{100–10}$. For example, the mean $RT_{100–10}$ in

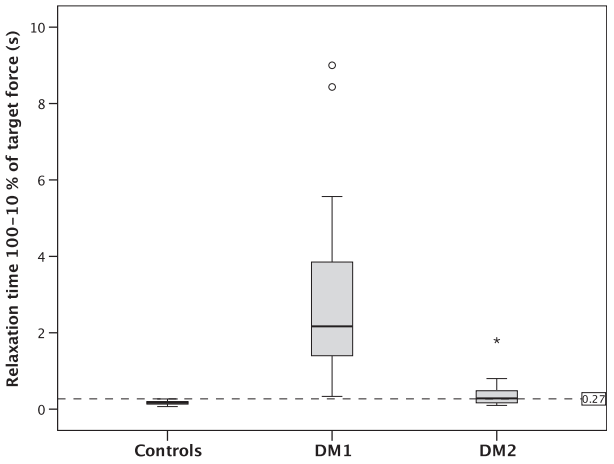

FIGURE 1. Relaxation time in healthy controls and patients with DM1 and DM2. The box plot indicates the 25th percentile, median, and 75th percentile. The circles represent outliers, and the asterisk represents extreme outliers. The dashed line represents the upper limit of normal calculated as a 0.95 quantile of the values in healthy controls. DM, myotonic dystrophy.

patients with an MBS score of 3 was 3.0 s in DM1 and 0.5 s in DM2 (both groups consisted of 7 patients). There was a significant correlation between MBS score and $RT_{100–10}$, with Spearman correlation coefficients of 0.627 (P = 0.001) in DM1 and 0.581 (P = 0.003) in DM2 (Fig. 3A,B).

Warm-up Phenomenon. An analysis of the warm-up phenomenon is presented in Figure 4. Differences in $RT_{100–10}$ were at their greatest between first and second voluntary contractions in both DM1 and DM2 (1.54-s decline in DM1, with $P < 0.0001$; 0.14-s decline in DM2, with $P = 0.02$). Although the differences between second and sixth voluntary contractions were still significant in DM1 (0.77 s, with P = 0.004), there was no further decline in DM2 (−0.02 s). Relaxation time from 100% to 10% of target force remained unchanged with consecutive contractions in the control group.

Maximal Force. The results for maximal force are presented in Table 1. Significant differences in maximal force emerged among all groups.

DISCUSSION

This study introduces a quantitative measure of hand-grip myotonia suitable both for clinical trials and routine examination. It exhibited low intertrial variability and significant correlation with a subjective scale assessing myotonia. More pronounced myotonia with more extensive warm-up phenomenon was demonstrated for the DM1 subgroup compared with the DM2 subgroup.

The main advantage of this method is the commercial availability of the dynamometer and the ease of postacquisition processing of data. Data are stored in a nonvolatile memory archive and can be transferred to a computer by using a USB connector and downloaded via automated software (provided freely by the manufacturer) as a simple spreadsheet of RT in relation to 10% steps in the target force. Data from the last test can be also directly displayed on the device.

The use of target force is also a considerable departure from the original method, which employed relaxation time after maximum voluntary contraction, a variable that might change from squeeze to squeeze. The force of maximal voluntary contraction might be affected by the motivation of the patient, particularly in consecutive measurements, so the results might be less consistent. This study examined RT in terms of a target force that remained the same throughout testing. In addition, the patients in the current study were asked to maintain grip for 3 s above the line of target force from which the RT was to be measured, thus eliminating any fluctuation in maximal force and also eliminating the requirement to choose a starting point for decline. Only 1 patient was unable to exert the required force repeatedly and, because

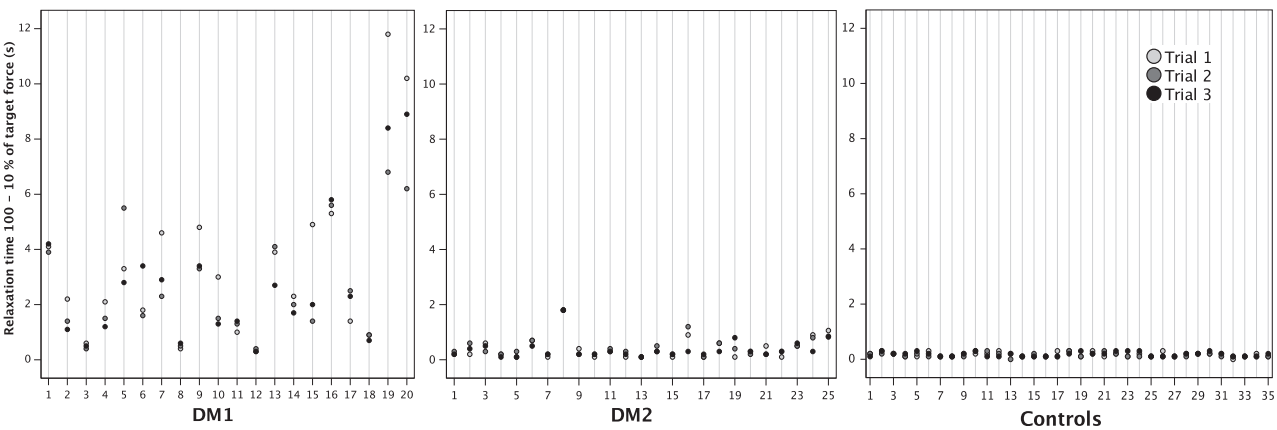

FIGURE 2. Intertrial variability of relaxation time of first squeezes in DM1, DM2, and healthy controls. Each number on the x-axis represents 1 participant from each group. DM, myotonic dystrophy.

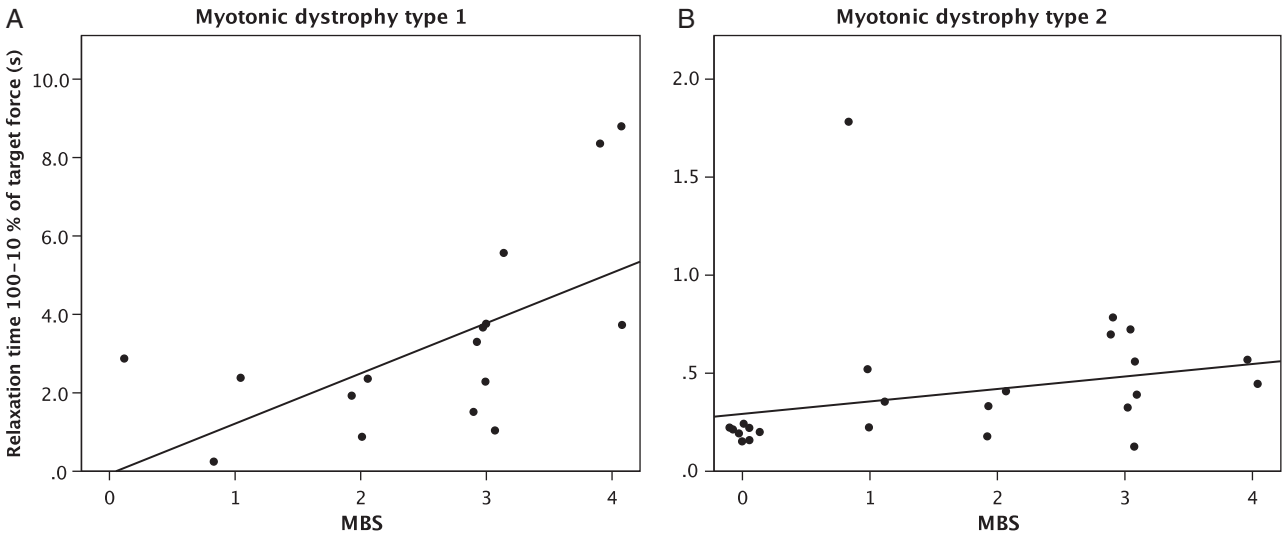

FIGURE 3. Correlation between relaxation time and MBS in patients with DM1 **(A)** and DM2 **(B)**. DM, myotonic dystrophy; MBS, Myotonia Behaviour Scale.

it occurred during the first trial, we simply reset the target force and repeated the measurement.

Even though we studied only intertrial variability, ICC for both DM1 and DM2 groups proved to be extremely high (0.945 and 0.931, respectively). The low ICC for healthy controls (0.437) can be explained by the very homogeneous values of $RT_{100–10}$ in this group. The coefficient of variation in this study was very similar to that obtained by the original method[3] (23.1% in controls and 33.2% in DM1 in the original method vs. 28% in controls and 22% in DM1 here), even though the patients were not fasting and a pegboard was not used to stabilize the arm as was the case in original study. Furthermore, the mean relaxation time from 90% to 5% of maximal force was quite similar (0.37 s in controls and 2.42 s in DM1) compared with our results for $RT_{100–10}$ (0.17 s in controls and 2.96 s in DM1). In the method that was employed here, the upper limit of normal was able to distinguish all DM1 patients, whereas, in the original method, 4 of the 25 patients with DM1 remained below the limit.

Simultaneous objective and subjective evaluation of myotonia severity also proved an advantage of this study. The correlation between $RT_{100–10}$ and subjective MBS was significant. Only 1 DM1 patient rated MBS at 0, even though his $RT_{100–10}$ was 2.8 s. The patient said explicitly that the current severity of his myotonia was nothing compared with that of a year ago. The study also demonstrated that MBS cannot be compared across different diseases because patients with DM1 generally reported lower MBS compared with those with DM2.

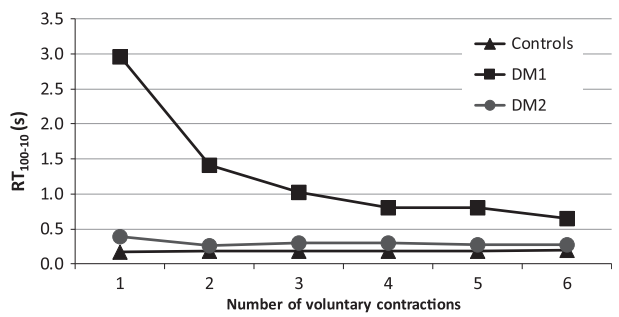

FIGURE 4. Warm-up phenomenon in healthy controls and patients with DM1 and DM2. DM, myotonic dystrophy; $RT_{100–10}$, relaxation time from 100% to 10% of target force.

The prevalence of DM2 in the Czech population is much higher than that of DM1.[10] This is in agreement with several other studies,[11,12] suggesting that DM2 might be underdiagnosed because the symptoms frequently occur in the elderly population. Myotonic dystrophy 2 is generally milder, with proximal weakness. This study confirmed that the average muscle force in patients with DM2 was significantly higher than that in patients with DM1 and demonstrated that the myotonia is less severe and the warm-up phenomenon less pronounced in DM2.

This study has some limitations. As previously discussed, a fixed target force was set throughout testing, which renders analysis of peak force and warm-up phenomenon of peak force impossible. All time values are rounded to one-tenth of 1 s, and the apparatus must be manually set to target force for each squeeze, which is not easy to accomplish when analyzing warm-up phenomenon (in the 10 s between squeezes). No group of nondystrophic myotonias was included, so it can only be assumed that the method described here may also be used for such a group.

In conclusion, the method detailed above provides a valid and reliable quantitative measure of grip myotonia in patients with DM1 and DM2. It is simple, requiring only a commercially available dynamometer and no other special equipment. Each trial takes about 1 min, but, after taking into consideration the

10-min intervals between the 3 trials, it takes about 35 min of a patient's time. We propose that it could be used as an outcome measure in clinical trials investigating drug treatments for myotonia. Its simplicity may also permit it to be used as a routine examination in gathering data on the natural history of myotonic disorders.

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Myotonia Behaviour Scale (MBS) was selected as a patient-reported outcome assessing myotonia severity based on its employment in few clinical trials. Apart from cross-cultural adaptation of the questionnaire we also performed analysis of validity and reliability on 15 MD1 and 25 MD2 patients.

The test-retest reliability was excellent, correlation coefficients of 0.965 in MD1 and 0.991 in MD2. The average MBS score was 2.5 in MD1 and 1.7 in MD2. Interestingly, there were significant correlations with handgrip relaxation times (RT) in both MD1 and MD2, yet the MD1 patients generally scored lower than MD2. For example, the average RT of patients scoring MBS as 3 was 3.3 s in MD1 and only 0.5 s in MD2. It can be explained by the fact, that myotonia in MD1 presents a relatively mild symptom compared to the other symptoms they suffer, thus causing different perception of myotonia severity. Further, one MD1 patient rated MBS at 0, even though his relaxation time was 2.8 s. The patient said explicitly that the current severity of his myotonia was nothing compared with that of a year ago. This finding implies that MBS cannot be compared across different diseases. However, while the RT was above the upper normal limit in all MD1 patients, 6 MD2 patients subjectively reporting myotonia were below this limit. Therefore, the MBS scale can be advantageously used in patients with mild myotonia as a more sensitive marker.

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Validace dotazníku pro pacienty s myotonií – česká verze Myotonia Behaviour Scale

Validation of questionnaire for patients with myotonia – Czech version of Myotonia Behaviour Scale

Souhrn

Úvod: Myotonie je základní symptom myotonických poruch. Jejím typickým projevem je obtížné povolení ruky po silném stisku. Myotonie snižuje kvalitu života pacientů a těžší stupeň je i velmi invalidizující. Proto je v terapii myotonie zkoušena celá řada léků. Jedním z hlavních problémů lékových studií byla absence spolehlivého stanovení tíže myotonie. Cílem naší práce byl překlad a validace škály Myotonia Behaviour Scale (MBS), která byla vytvořena k subjektivnímu hodnocení tíže myotonie. *Metodika:* Český překlad byl schválen profesionálním překladatelem a validován metodou zpětného překladu. Opakovatelnost a reprodukovatelnost byla ověřena na vzorku 15 pacientů s myotonickou dystrofií typu 1 (MD1) a 25 pacientů s myotonickou dystrofií typu 2 (MD2), kteří vyplnili formulář MBS v rámci rutinní kontroly a dále s odstupem 2 dnů. *Výsledky:* Průměrné skóre MBS bylo 2,5 ve skupině MD1 a 1,7 ve skupině MD2. Korelační koeficient mezi prvním a druhým zodpovězením byl 0,965 u MD1 a 0,991 u MD2. Korelační koeficient mezi relaxačním časem stisku ruky a hodnotou MBS byl 0,672 u MD1 a 0,627 u MD2. *Závěr:* Škála MBS je velmi jednoduchá a rychlá a může být použita pro dlouhodobé sledování pacientů. U obou skupin pacientů byla signifikantní korelace mezi hodnotou MBS a relaxačním časem stisku ruky.

Abstract

Background: Myotonia is a cardinal symptom of myotonic disorders. The most typical symptom of myotonia is a difficulty in releasing a forceful handgrip. It significantly deteriorates the quality of life to a degree that is disabling. Therefore, many drugs have been tested in myotonia therapy. One of the main issues of clinical trials has been the lack of a conclusive method for the quantification of myotonia. The aim of our study was translation and validation of the Myotonia Behaviour Scale (MBS). This scale was designed for subjective assessment of myotonia severity. *Methods:* Czech translation was approved by a professional translator and then validated through forward-backward translation. Repeatability and reproducibility were tested on a sample of 15 patients with myotonic dystrophy type 1 (MD1) and 25 patients with myotonic dystrophy type 2 (MD2). All patients completed one MBS form during a routine visit and a second one two days later. *Results:* The average MBS score was 2.5 in MD1 group and 1.7 in MD2 group. Correlation coefficients between the first and second completion were 0.965 in MD1 and 0.991 in the MD2 group, respectively. Correlation coefficients between relaxation time of handgrip and MBS score were 0.672 in MD1 and 0.627 in the MD2 group, respectively. *Conclusion:* MBS is a simple and quick scale suitable for long-term monitoring of patients with myotonia. We reported a significant correlation between MBS score and relaxation time of a forceful handgrip in both groups.

Práce byla podpořena projektem institucionální podpory FN Brno MZ ČR – RVO (FNBr – 65269705) a projektem specifického výzkumu č. MUNI/A/1072/2017 podpořeného z prostředků účelové podpory na specifický vysokoškolský výzkum, kterou poskytlo MŠMT v roce 2018.

Autoři práce děkují pacientům, kteří podstoupili vyšetření.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.
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myotonická dystrofie – myotonie – škála – dotazník

Key words

myotonic dystrophy – myotonia – scale – questionnaire

Úvod

Myotonie je základní symptom myotonických poruch, mezi které řadíme myotonické dystrofie typu 1 (MD1), myotonické dystrofie typu 2 (MD2) a heterogenní skupinu poruch chloridového nebo sodíkového kanálu, které se také označují jako ne-dystrofické myotonie. Myotonií označujeme zpomalení svalové relaxace po volní nebo vyvolané kontrakci. Jde o stav patologicky zvýšené excitability svalové membrány, kdy reakcí na stimulaci vzniká série dalších akčních potenciálů. Korelátem na EMG jsou myotonické výboje – repetitivní výboje jednoho svalového vlákna, které mění frekvenci i amplitudu.

Typickým projevem myotonie je obtížné povolení ruky po silném stisku. Postiženy ale bývají také svaly obličeje, jazyka a dalších bulbárních svalů, což může působit obtíže s mluvením, kousáním i polykáním. Myotonie snižuje kvalitu života pacientů [1] a těžší stupeň myotonie je i velmi invalidizující.

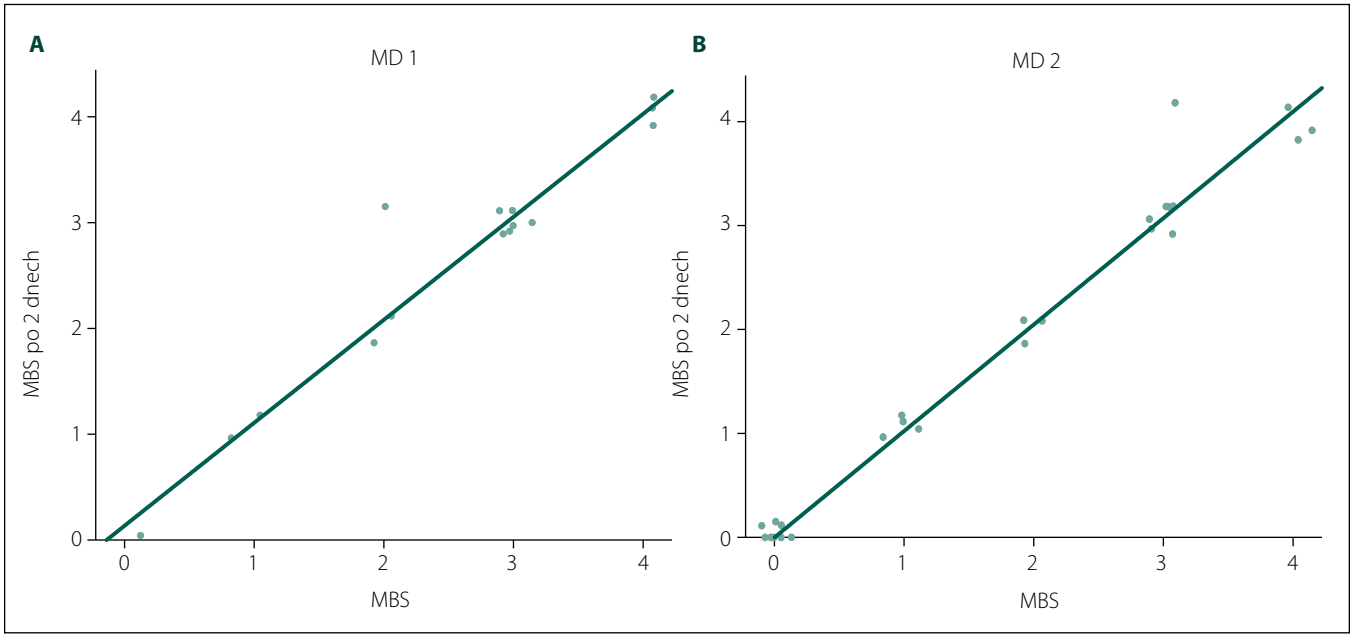
V terapii myotonie zatím není rutinně využíván žádný lék, ačkoliv první práce o terapeutickém ovlivnění myotonie byla publikována již v roce 1936, kdy byli čtyři pacienti s kongenitální myotonií léčeni chininem [2]. V terapii myotonie byla vyzkoušena celá řada dalších léků – antiarytmika, tricyklická antidepresiva, antiepileptika, benzodiazepiny a mnoho dalších, ale systematický přehledový článek z roku 2006 poukázal na celkově špatnou kvalitu publikovaných prací [3]. Jedním z hlavních problémů studií byla absence spolehlivého stanovení tíže myotonie. V lékové studii s mexiletinem z roku 2010 byl jako primární outcome použit relaxační čas po max. svalové kontrakci ruky měřený ručním dynamometrem a poměrně složitým post-processingem dat (převádění analogového signálu na digitální, identifikace začátku svalové relaxace speciálně vyvinutým softwarem). Metoda se zřejmě pro svoji komplikovanost neuchytila a v další lékové studii s lamotriginem byl jako primární outcome použit subjektivní dotazník s názvem Myotonia Behaviour Scale (MBS) [4], zatímco objektivní testování myotonie bylo prováděno pouze za pomocí stopek.

Dotazník MBS je velmi jednoduchá škála, která se skládá z šesti tvrzení, z nichž pacient vybírá to, se kterým se nejvíce ztotožňuje (tab. 1). Škála vznikla pro pacienty s kongenitální myotonií v roce 2005 [5] modifikací škály původně určené k hodnocení bolesti [6]. Hodnocena může být 0 (= žádná myotonie) až 5 body (= velmi těžká myotonie).

Validace české verze MBS vznikla v rámci projektu Kvantitativní testování myotonie u pacientů s myotonickou dystrofií, jehož cílem bylo vytvoření jednoduché metodiky k objektivnímu měření míry myotonie pomocí ručního dynamometru. Využití škály MBS umožnilo srovnání naší objektivní metodiky se subjektivním hodnocením pacientů.

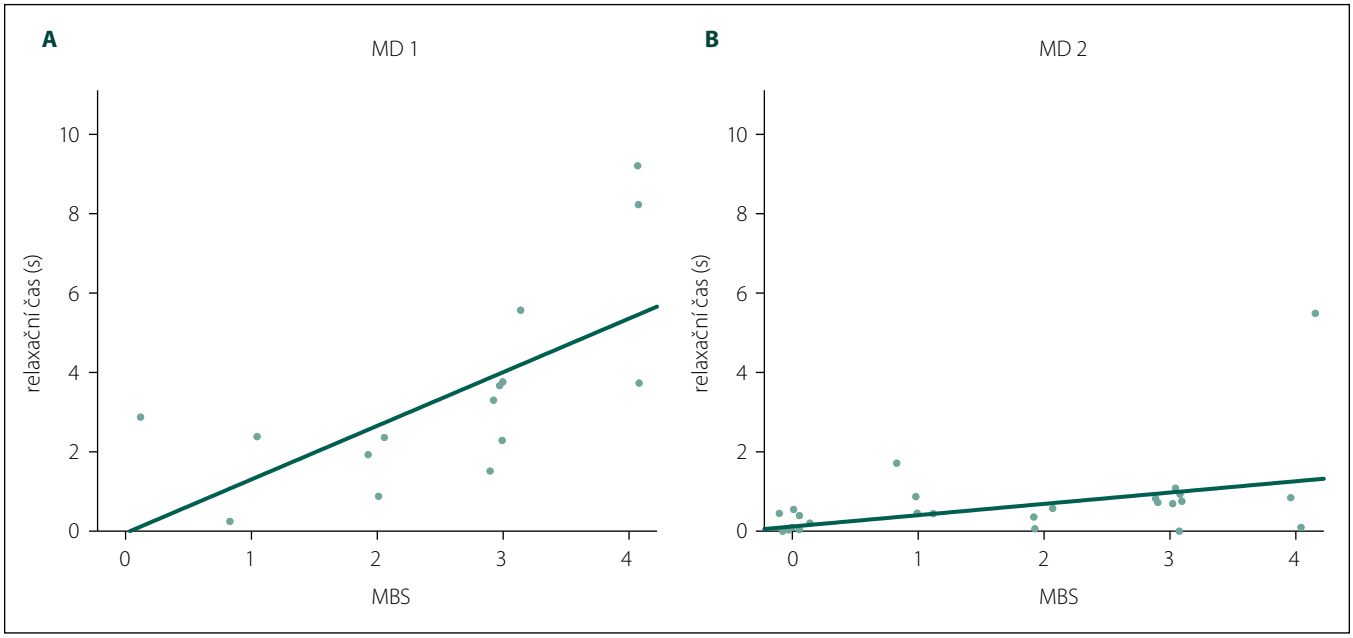
Tab. 1. Behaviorální škála myotonie.

0	není žádná svalová ztuhlost
1	je přítomna určitá svalová ztuhlost, ale lze ji ignorovat
2	je přítomna určitá svalová ztuhlost, kterou lze občas ignorovat, ale nenarušuje každodenní činnosti
3	je přítomna svalová ztuhlost, která vyžaduje vyšší soustředěnost při vykonávání některých povinností a činností
4	je přítomna těžká svalová ztuhlost, která narušuje všechny povinnosti a činnosti
5	je přítomna taková svalová ztuhlost, která vyžaduje neustálý pohyb, aby nedošlo k úplnému znehybnění



Obr. 1. Korelace mezi prvním (A) a druhým (B) zodpovězením MBS.
MBS – Myotonia Behaviour Scale; MD1 – myotonická dystrofie typu 1; MD2 – myotonická dystrofie typu 2

Fig. 1. Correlation between the first (A) and the second (B) completion of MBS.
MBS – Myotonia Behaviour Scale; MD1 – myotonic dystrophy type 1; MD2 – myotonic dystrophy type 2



Obr. 2. Korelace mezi subjektivním hodnocením pacientů (MBS) a objektivním měřením relaxačního času s pomocí dynamometru u MD1 (A) a MD2 (B).

MBS – Myotonia Behaviour Scale; MD1 – myotonická dystrofie typu 1; MD2 – myotonická dystrofie typu 2

Fig. 2. Correlation between subjective patient evaluation (MBS) and relaxation time measured objectively using a dynamometer in MD1 (A) and MD2 (B) group.

MBS – Myotonia Behaviour Scale; MD1 – myotonic dystrophy type 1; MD2 – myotonic dystrophy type 2

Soubor a metodika

Český překlad byl schválen profesionálním překladatelem. Ke zhodnocení jednoznačnosti překladu byl originál porovnán se zpětným překladem rodilým mluvčím. K vyhodnocení opakovatelnosti a reprodukovatelnosti české verze MBS bylo použito opakované testování (test-retest).

Všichni účastníci studie před testováním podepsali informovaný souhlas se studií. Informovaný souhlas i projekt byly schváleny etickou komisí FN Brno. Do studie bylo zařazeno celkem 15 pacientů s MD1 a 25 pacientů s MD2 z Neuromuskulárního centra FN Brno v období od července 2017 do března 2018. K účasti ve studii byli dotazováni všichni pacienti s geneticky potvrzeným onemocněním v rámci jejich rutinní kontroly v uvedeném období. Pacienti dostali k vyplnění formulář MBS a současně byla objektivně měřena tíže myotonie ručním dynamometrem. Všichni pacienti dostali další prázdný formulář MBS a byli telefonicky kontaktováni s odstupem 2 dnů a dotázáni na aktuální hodnocení MBS.

Objektivní kvantifikace myotonie byla měřena ručním dynamometrem DynX® (MD Systems, Westerville, OH, USA). Ve stručnosti, přístrojem byl měřen relaxační čas (doba do poklesu síly ze 100 % na 10 %) po 3s silném stisku ruky. Síla stisku byla předem kalibrována pro každého pacienta jako 75 % jeho max. síly ve 3. vteřině. Měření byla opakována celkem 3× s 10min intervalem kvůli potlačení warm-up fenoménu. Průměrná hodnota všech tří měření byla použita ke korelaci se skóre MBS.

Z 15 pacientů s MD1 bylo 12 žen (80 %) a 3 muži (20 %). Věkový průměr byl 38 (24–59) let. Průměrný věk v době prvních příznaků byl 36 (12–70) let. Doba trvání nemoci byla v průměru 18 (3–31) let.

Z 25 pacientů s MD2 bylo 20 žen (80 %) a 5 mužů (20 %). Věkový průměr byl 53 (24–59) let. Průměrný věk v době prvních příznaků byl 21 (10–56) let. Doba trvání nemoci byla v průměru 17 (0–49) let.

Data byla statisticky zpracována v programu SPSS version 23 (IBM Corp, Armonk, NY, USA). Jako koeficient opakovatelnosti (test-retest coefficient) a ke korelaci MBS s relaxačním časem byl použit Spearmanův korelační koeficient. Na srovnání skupin pacientů byl použit Mann-Whitneyho U test.

Výsledky

Průměrné skóre MBS bylo 2,5 ve skupině MD1 a 1,7 ve skupině MD2. V obou skupinách bylo min. i max. stejné (0–4). Rozdíl mezi skupinami nebyl statisticky významný ($p = 0,1$).

Korelace mezi prvním a druhým zodpovězením je znázorněna na obr. 1. Spearmanův korelační koeficient byl 0,965 u MD1 a 0,991 u MD2. Pouze jeden pacient ze skupiny MD1 a jeden pacient ze skupiny MD2 při druhém hodnocení udali skóre o 1 bod vyšší.

Průměrná hodnota relaxačního času u skupiny MD1 byla 3,4 (0,33–9,0) s a 0,6 (0,1–5,7) s u skupiny MD2. Korelace mezi relaxačním časem a hodnotou MBS je znázorněna na obr. 2. Spearmanův korelační koeficent byl 0,672 ($p = 0,006$) u MD1 a 0,627 ($p = 0,001$) u MD2. Z obrázku je patrné, že pacienti s MD1 se obecně hodnotili nižším skóre MBS ve srovnání s pacienty MD2. Například průměrná hodnota relaxačního času u pacientů s MBS 3 byla 3,3 s u MD1 a 0,5 s u MD2.

Diskuze

Myotonická dystrofie 1. typu je způsobena CTG trinukleotidovou expanzí v genu Dystrophia Myotonica Protein Kinase (*DMPK1*) [7], MD2 je způsobena tetranukleotidovou expanzí CCTG v komplexním motivu $(TG)_n(TCTG)_n(CCTG)_n(NCTG)_n(CCTG)_n$ v intronu 1 genu Cellular Nucleic

Acid Binding Protein, dříve Zinc Finger Protein 9 (*CNBP*) [8]. Příčinou myotonie u myotonické dystrofie není primární mutace v genu chloridového kanálu ClC-1 (gen nese označení *ClCN1*), ale jeho posttranskripční alternativní sestřih [9,10].

Škála MBS je velmi jednoduchá a rychlá a může být použita pro dlouhodobé sledování pacientů. U obou skupin pacientů byla signifikantní korelace mezi hodnotou MBS a relaxačním časem povolení stisku ruky. Z našich výsledků je ale zřejmé, že hodnota MBS může být srovnávána pouze mezi pacienty se stejnou diagnózou, protože pacienti s MD1 při stejném hodnocení MBS měli výrazně delší relaxační čas než pacienti s MD2.

Zatímco ve skupině MD1 prokázalo objektivní měření u všech pacientů myotonii (horní hranice normy naší metodiky je 0,3 s), ve skupině MD2 bylo 6 pacientů subjektivně udávajících myotonii pod tímto limitem. Proto může být MBS škála s výhodou použita u pacientů s mírnou myotonií jako citlivější marker.

V souhrnu, česká verze MBS je subjektivní škála pro pacienty s myotonií, která je velmi dobře použitelná v běžné praxi pro dlouhodobé sledování pacientů a porovnávání skupin pacientů se stejnou diagnózou. Naopak není vhodná pro srovnání skupin pacientů s jinou diagnózou. Ačkoli MBS byla využita i v lékových studiích jako primární outcome [4], domníváme se, že pro podrobnější sledování pacientů v rámci studií je výhodná kombinace s objektivní kvantifikací myotonie, např. pomocí měření relaxačního času po stisku dynamometru.

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We reported the case of a patient suffering from myotonic dystrophy type 1 whose myotonic symptoms repeatedly improved on methylprednisolone prescribed for unrelated flares of ulcerative colitis. We found that myotonia disappeared with a delay of four weeks after starting methylprednisolone with the effect lasting for at least a month after discontinuation.

The patient was being treated for a flare in June 2017, starting with 32 and immediately dropping the dose by 4 mg a week. Myotonia severity was measured by means of relaxation time (RT) and Myotonia Behaviour Scale (MBS) score that were validated in previously mentioned papers. MBS was completed every week during the followed period, and RT was measured at specific timepoints. First assessment of myotonia severity took place just 11 days prior to the initiation of methylprednisolone, with RT of 1.3 s and MBS score 3.

The symptoms of myotonia began to wear off three weeks after starting methylprednisolone (MBS of 1) and totally disappeared by four weeks after starting methylprednisolone (MBS of 0), as reported by the patient. The RT was measured for the first time seven weeks after the initiation of the treatment and the values were normal. The first symptoms of myotonia returned about a month after the last dose of methylprednisolone and reached a peak of severity more than two months after the last dose (coming back to MBS of 3 and RT 1 s). In this case, we were also able to follow the responsiveness of both RT and MBS score, though in only one patient.

The molecular mechanism is unclear. We searched the literature for any mention of corticosteroid efficacy on myotonia symptoms and the evidence was scarce. Only one trial was conducted in 1959 and it tested quinine, prednisone, and procainamide for 3 weeks, without a wash-out period. Therefore, it could not detect the delayed effect of the drug that we have observed. We hypothesised the stabilization of muscle membrane, alteration of chloride and sodium channels, however, the delay and prolongation of the effect indicate changes in gene expression.

Side-effects of corticosteroids clearly contradict routine use of such high dose to treat myotonia. Yet the case suggests that a much lower dose might be effective as well. Anyway, future open-label or placebo-controlled studies are warranted to confirm our finding and to find the least possible dose that would remain effective.

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Case Report

The Association of methylprednisolone dosing to cessation of myotonia in a patient with myotonic dystrophy type 1

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Abstract

We report the case of a patient suffering from duplicity of myotonic dystrophy type 1 and ulcerative colitis whose treatment for ulcerative colitis included repeated administrations of descending doses of methylprednisolone and in whom we found an association between methylprednisolone dosing and cessation of myotonia. Myotonia severity was expressed as relaxation time after voluntary contraction and as a patient-reported outcome using the Czech version of the Myotonia Behavior Scale. The patient was being treated for a flare of ulcerative colitis, starting with 32 mg of methylprednisolone and reducing the dose by 4 mg a week. The symptoms of myotonia began to wear off three weeks after starting methylprednisolone and had totally disappeared by four weeks after starting methylprednisolone. The first symptoms of myotonia returned about a month after the last dose of methylprednisolone and reached a peak of severity more than two months after the final dose.

Keywords: Myotonia; Myotonic dystrophy; Methylprednisolone; Corticosteroids; Muscle relaxation; Therapy.

1. Introduction

Myotonic dystrophy type 1 (DM1) is a rare, hereditary, multi-system disorder, the most prominent symptoms of which are muscle weakness and myotonia. According to a prospective study in patients with DM1 [1], published in 2017, myotonia has a very severe impact on quality of life, second only to muscle weakness. We report the case of a patient suffering from duplicity of DM1 and ulcerative colitis (UC) whose treatment for UC included, among other drugs, repeated administrations of descending doses of methylprednisolone and in whom we found an association between initiation of methylprednisolone dosage and cessation of myotonia.

2. Case report

A 40-year-old woman with a 10-year history of genetically confirmed (Triplet-Primed PCR) DM1 spontaneously reported, at a routine visit in May 2016, that her myotonia symptoms disappeared while taking methylprednisolone for flares of UC. UC had been diagnosed in 1998 and its treatment at the time comprised a stable dose of mesalamine and periods of descending doses of methylprednisolone overlaid with maintenance treatment with azathioprine. Since then, she has undergone several withdrawals and re-initiations of methylprednisolone and reported that her fluctuations in the myotonia were always the same: in each cycle, myotonia completely disappeared within 2–3 weeks of taking methylprednisolone and returned about a month after the last dose of it. Apart from DM1 and UC she suffered from mild depression, treated with a stable dose of escitalopram since 2015. There was no abnormality in serum levels of glucose, potassium and fT4 in available blood tests (Table 1).

The measured and reported values herein are derived from the cycle that took place from June to November 2017.

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Table 1
Relation of RT and MBS to current treatment.

Time points	RT (s)	MBS	Dose of Methylprednisolone (mg)	Dose of Azathioprine (mg)	Dose of Escitalopram (mg)	Lab results
Baseline (Week 0 - 11 days)	1.3	3	0	0	10	Serum glucose: 5.1 mmol/L*; Serum potassium: 3.73 mmol/L*
Week 0**	-	3	32	0	10	
Week 1	-	3	28	0	10	
Week 2	-	1	24	0	10	
Week 3	-	0	20	0	10	
Week 4	-	0	16	0	10	
Week 5	-	0	12	0	10	
Week 6	0.2	0	8	0	10	
Week 7	-	0	4	50	10	
Week 8	-	0	0	50	10	Serum glucose: 5.1 mmol/L; Serum potassium: 3.74 mmol/L
Week 9	-	0	0	0	10	
Week 12	-	1	0	0	10	
Week 15	0.8	2	0	0	10	
Week 16	0.9	3	0	0	10	
Week 18	1.2	3	0	0	10	
Week 23	1.0	3	0	0	10	Serum glucose: 4.9 mmol/L***; Serum potassium: 4.41 mmol/L***; Serum fT4: 13.1 pmol/L****

RT, relaxation time; MBS, Myotonia Behaviour Scale.
* The blood tests were performed 80 days prior Baseline.
** The exact date of Week 0 was July 5, 2017.
*** The blood tests were performed 22 days after Week 23.
**** The blood tests were performed 34 days after Week 23.

Myotonia severity was expressed as relaxation time (RT) after voluntary contraction, measured by a commercially-available hand-grip dynamometer as described previously [2], and as a patient-reported outcome using the Czech version of the Myotonia Behaviour Scale (MBS) [3]. In brief, the patient was asked to perform a contraction of the hand for 3 s at a previously-defined force (target force), established as 75% of her maximal force, followed by release of the grip as quickly as possible. The patient's target force was set to 5.2 kg for all measurements. Relaxation time was then automatically measured from target force to 10% of target force. Three sets of measurements were taken, with 10-min intervals of rest between them. The outcome RT was calculated as the mean RT from 100% to 10% of target force. The results of RT in relation to MBS and current treatment appear in Table 1. The patient was being treated for a flare of UC, starting with 32 mg of methylprednisolone and dropping the dose by 4 mg a week, with the last week overlaid with azathioprine. The symptoms of myotonia began to wear off three weeks after starting methylprednisolone and totally disappeared by four weeks after starting methylprednisolone, as reported by the patient. This was verified by measuring RT seven weeks after the initiation of treatment. The first symptoms of myotonia returned about a month after the last dose of methylprednisolone and reached a peak of severity more than two months after the last dose. Fig. 1 shows the relaxing phases of muscle contractions at four different time points. Fig. 2 shows the variability of three trials.

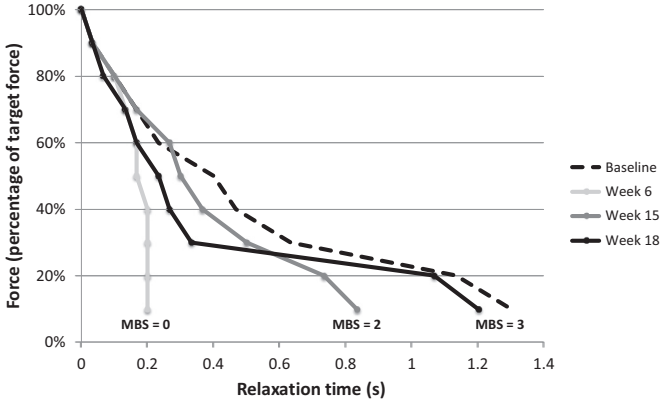

Fig. 1. Relaxation phases of muscle contractions at various time points. The broken line represents the first measurement, without methylprednisolone treatment. The light grey line represents the measurement 6 weeks after initiation of treatment (while still taking 8 mg of methylprednisolone). The dark grey and black lines represent the measurements 7 and 10 weeks after discontinuation of the treatment, respectively.

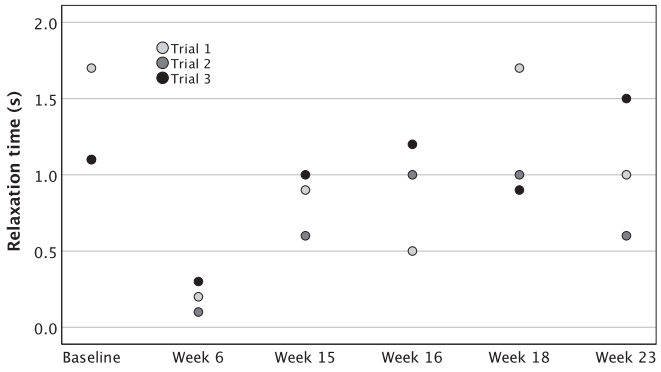

Fig. 2. Variability of RT measurements. Three trials were performed at each time point. The value from trial 2 overlaps with trial 3 at baseline.

3. Discussion

To the best of our knowledge, the only trial to employ corticosteroids in the treatment of myotonia (20 mg of prednisone per day) was of a cross-over design testing quinine, prednisone and procainamide for 3 weeks, without a wash-out period [4]. The number of patients was low and it was conducted in 1959. Taking into account the fact that the molecular basis of DM1 was not discovered until 1992 [5], the groups of patients could not be reliably defined. Furthermore, our case disclosed the delayed effect of the drug, something that could not have been covered by the design of the 1959 study. There also exist a few case reports suggesting that corticosteroids might ameliorate myotonia [6–10]. With one exception, these were also published prior to 1992. The most recent report, presented in 2002, described a patient with myotonia congenita whose myotonic symptoms improved on prednisone prescribed for an unrelated facial palsy [10]. The disadvantage of all these studies was a lack of conclusive methods for quantification of myotonia, rendering impossible the determination of treatment effect.

The molecular mechanism underlying methylprednisolone efficacy is unclear. It may be mediated by stabilization of muscle-fibre membrane [11], alteration of the function of chloride or sodium channels [12,13] or changes in electrolytes, however, the delay and prolongation of the effect indicate changes in gene expression.

Several limitations of the report need to be acknowledged. We present a single case report of a patient who was not blinded from the results and purpose of myotonia measurement. The diagnosis of DM1 was made by Triplet-Primed PCR method and no advance techniques were performed. Each measurement was conducted at a different time of year, yet Table 1 shows that myotonia symptoms were worse during June without methylprednisolone than in October, more than a month after the last dose of methylprednisolone. Furthermore, the patient reported the same cessation of myotonia in the cold winter months while on methylprednisolone. The methylprednisolone effect could also be biased by other drugs and comorbidities; however, the influences of escitalopram and mesalamine appear highly unlikely in the light of the stability of their doses, while azathioprine is also unlikely to be involved in view of its time relation to myotonia disappearance. Moreover, the patient has never reported a cessation of myotonia when not related to corticosteroids. Side-effects dictate that the starting dose of methylprednisolone in this case is undoubtedly too high to be used as a routine treatment, yet the illustration also suggests that a very low dose might also be effective and we believe that an open-label trial is needed to determine the lowest dose of the drug that is still effective.

In conclusion, our case presents an association between a medium dose of methylprednisolone and the disappearance of myotonia symptoms in a DM1 patient, with a delay of three weeks and the effect lasting for at least a month after discontinuation. Future open-label or placebo-controlled studies are warranted.

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5 Conclusion

The thesis summarizes the outcome measures currently being used in myasthenia gravis and myotonic dystrophy type 1 and type 2. The outcomes in myasthenia gravis are well established and since 2018, Quantitative Myasthenia Gravis Score (QMG), Myasthenia Gravis Activities of Daily Living (MG-ADL), Myasthenia Gravis Composite (MGC), Myasthenia Gravis Quality of life 15 (MG-QOL15) and steroid sparing effect are the only myasthenia-specific outcome measures used in randomized clinical trials. Therefore, we have validated and adapted the MGC and MG-QOL15 for use in Czech Republic. The outcomes in myotonic dystrophy have not been well established yet, but the Myotonic Dystrophy Health Index (MDHI) and Myotonia Behaviour Scale (MBS) seem to be very promising and MBS scale is now also validated in Czech. Further, we established a quantitative assessment of myotonia using a commercially available dynamometer and employed this method in routine monitoring of our patients.

Apart from the patient-reported outcomes, questionnaires, composite scales, force measurements and functional tests, the role of imaging methods is being emphasized in neuromuscular disorders. Even though the manual segmentation and subjective grading of each muscle is very time-consuming, there is an extensive research of automated muscle segmentation and quantitative fat proportion measurement with advance MRI techniques. As mentioned in introduction, a parameter such as fat proportion could not be used as a primary outcome (due to regulatory requirements for approval) until a clear correlation with functional tests is confirmed. Therefore, MRI will never substitute for functional outcomes. However, with the expanding knowledge in gene therapy, a universal outcome for multiple neuromuscular disorders sounds very promising.

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List of Abbreviations

6mWT = 6-Minute Walking Test
9HPT = Nine-Hole Peg Test
10mWT = 10-Meters Walking Test
AChR = Acetylcholine Receptors
ACTH = Adrenocorticotropic Hormone
ASRS = Autism Spectrum Rating Scales
BDI = Beck Depression Inventory
BIN1 = Bridging Integrator-1
BMD = Becker Muscular Dystrophy
BPI = Brief Pain Inventory Score
CC-CDM1-RS = Caregiver Completed Congenital DM1 Rating Scale
CDM1-RS = Clinician-Completed Congenital DM1 Rating Scale
CGI = Clinical Global Impressions Scales
CNBP = Cellular Nucleic Acid-Binding Protein
COVID-19 = Coronavirus Disease of 2019
CPAP = Continuous Positive Airway Pressure
DEXA = Dual Energy X-ray Absorptionmetry
DMD = Duchenne Muscular Dystrophy
DMPK = Dystrophia Myotonica Protein Kinase
DSS = Daytime Sleepiness Scale
ESS = Epworth Sleepiness Scale
EQ-5D = EuroQol- 5 Dimension
FSHD = facioscapulohumeral muscular dystrophy
FSS = Fatigue Severity Scale
FVC = Forced Vital Capacity
GSRS = Gastrointestinal Symptom Rating Scale
HRQOL = Health-Related Quality of Life
IBSIS = Irritable Bowel Syndrome Impact Scale
ICC = Intraclass Correlation Coefficient
ICIQ-B = International Consultation on Incontinence Questionnaire Anal Incontinence Symptoms and Quality of Life Module
ICIQ-FLUTS = International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms Modules
INQoL = Individualized Neuromuscular Quality of Life Questionnaire
I-PSS = International Prostate Symptom Score
IVIG = Intravenous Immunoglobulins
LGMD = Limb-Girdle Muscular Dystrophy
LRP4 = Lipoprotein Receptor-Related Protein 4
MBNL = Muscleblind-like
MBS = Myotonia Behaviour Scale
MD1 = Myotonic Dystrophy type 1
MD2 = Myotonic Dystrophy type 2
MDHI = Myotonic Dystrophy Health Index scores
MGC = Myasthenia Gravis Composite Score
MG-ADL = Myasthenia Gravis Activities of Daily Living
MG-DIS = Myasthenia Gravis Disability Scale
MGFA = Myasthenia Gravis Foundation of America
MGII = Myasthenia Gravis Impairment Index

MG-QOL = Myasthenia Gravis Quality of Life
MG-QOL15 = Myasthenia Gravis Quality of Life 15
MG-QOL15r = Myasthenia Gravis Quality of Life 15 revised
MID = Minimal Clinically Important Difference
MMT = Manual Muscle Test
MRC = Medical Research Council's scale
MRI = Magnetic Resonance Imaging
MSLT = Mean Sleep Latency Test
MuSK = Muscle-Specific Tyrosin Kinase
MYH14 = Non-Muscle Myosin Heavy-chain Gene
MYOM1 = Myomesin 1 gene
M-VAS = Myotonia Visual Analog Scale
NIH = National Institutes of Health
OMMYD = Outcome Measure in Myotonic Dystrophy working group
PGI = Patient Global Impression Scales
POMS = Profile of Mood States Questionnaire
PPT = Purdue Pegboard Test
PPVT = Peabody Picture Vocabulary Test
PRO = Patient-Reported Outcomes
QMA = Quantitative Muscle Test
QMG = Quantitative Myasthenia Gravis Score
RNA = Ribonucleic Acid
ROC = Receiver Operating Characteristic
RT = Relaxation Time
SART = Sustained Attention to Response Task
SD = Standard Deviation
SF-36 = Short Form 36
SIP = Sickness Impact Profile
SMA = spinal muscular atrophy
Top 3 CC VAS= Top 3 Caregiver Concerns Visual Analog Scale
VAS = Visual Analog Scale
VGCC = Voltage-Gated Calcium Channels
VGKC = Voltage-Gated Potassium Channels

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List of original publications

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