CHARLES UNIVERSITY IN PRAGUE
FACULTY OF PHYSICAL EDUCATION AND SPORT

Presence and Influencing Factors of Motor Fatigue during Six-Minute Walk Test in Multiple Sclerosis

Master's Thesis

Promoter:
PhDr. Kamila Řasová, Ph.D.

Author:
Vendula Doležalová

Prague, April 2014

DECLARATION

I hereby declare that all content of my Thesis is my own individual work and all the literature sources I have used are mentioned in the Literature section. I also declare that this Thesis was not used to obtain any other or the same academic title.

Prague, April 2014 Vendula Doležalová ___________________

Evidenční list / Evidence of Borrowings

Souhlasím se zapůjčením své diplomové práce ke studijním účelům. Uživatel svým podpisem stvrzuje, že tuto diplomovou práci použil ke studiu a prohlašuje, že ji uvede mezi použitými prameny.

I hereby agree that this Thesis can be used for study purposes. The user confirms by his/her signature that the Thesis was used for study purposes and declares that the Thesis will be quoted in the literature list.

Jméno a příjmení:	Fakulta / katedra:	Datum vypůjčení:	Podpis:
Name:	Faculty / Department:	Date of Borrowing:	Signature:

ACKNOWLEDGMENT

I would like to thank to my supervisor PhDr. Kamila Řasová, Ph.D. for all help, valuable professional feedback and all the time she spent on guiding me during writing my Thesis.

Further I would like to thank to Prof. Peter Feys for opportunity to spend eight months internship in research in his REVAL research team in Hasselt, Belgium. There I have gained, in addition to the data that I used for my Thesis, also the general overview of the principles of data processing, statistical analyses, manuscript writing, as well experience on data collection, coordination of the research project and guidance of the students. This internship has largely enriched my existing expertise and encouraged me into considering my further researcher carrier. I really appreciate that I could cooperate with such an expert in Multiple Sclerosis as Prof. Peter Fey is.

SOUHRN

Název práce: Přítomnost a ovlivňující faktory motorické únavy během šestiminutového testu chůze u roztroušené sklerózy mozkomíšní.

Vymezení problému: Poruchy chůze omezují každodenní aktivity pacientů s roztroušenou sklerózou mozkomíšní (pRS). Toto omezení je ještě důraznější při součastném výskytu motorické únavy. Předchozí studie poukázaly na průběžné zpomalování rychlosti chůze během vytrvalostního Šestiminutového testu (6MWT) u pacientů s mírnou nebo těžkou poruchou. Doposud však není známo, zda je motorická únava přítomna u všech pRS, a jak souvisí s charakteristikou pacienta (se stupněm postižení, typem roztroušené sklerózy-RS, či délkou onemocnění).

Cíl práce: Identifikace motorické únavy u pRS během Šestiminutového testu chůze a vyhodnocení jejího výskytu ve vztahu k pacientově charakteristice.

Metoda řešení: K výzkumu přítomnosti motorické únavy byla použita data celkem 208 chodících pRS z průřezové RIMS (organizace Rehabilitace Roztroušené Sklerózy – Rehabilitation in Multiple Scelrosis) multicentrické studie. Této studie se účastnilo 10 evropských a 1 americké výzkumné centrum. Všichni probandi byli svým neurologem ohodnoceni jako schopní chůze – tj. v rozsahu 0 – 6.5 Kurtzkeho škály. Pacienti byli vyšetřeni následujícími testy chůze: 6MWT, Timed Up and Go testem (TUG), Měřeným 25 stop dlouhým testem (T25FW), Měřeným 10 metrů dlouhým testem (T10MW), Měřítkem chůze u lidí s RS (Multiple Sclerosis Walking scale – MSWS 12). Dále bylo provedeno vyšetření dopadu celkové únavy na každodenní aktivity pomocí Modifikované škály dopadu únavy (MFIS). Pacienti poté byli rozděleni do dvou skupin – s motorickou únavou a bez motorické únavy. Motorická únava byla definována jako 20% pokles vzdálenosti ušlé v první a poslední minutě 6MWT (skupina s Motorickou únavou = 47, skupina bez Motorické únavy = 161). Na základě rozdělní pacientů do dvou skupin, byla vypočítána prevalence motorické únavy dle stupně postižení a typu RS. Pro výpočet rozdílů mezi skupinami byly použity T-test, Mann/Whitney test a Chi-square test. Dále byly vypočítány korelační koeficienty mezi 2 skupinami a charakteristikami pacientů (věk, pohlaví, délka onemocnění, Index tělesné hmotnosti), testy chůze (Šestiminutový test chůze, Timed Up and Go test, měřeným 25 stop dlouhým testem, měřeným 10 metrů dlouhým testem, Měřítkem chůze u lidí s RS) a Modifikovanou škálou dopadu únavy (MFIS).

Výsledky: Motorická únava byla přítomna u 22.6% pacientů s roztroušenou sklerózou mozkomíšní. Prevalence motorické únavy se signifikantně zvyšovala se zvyšujícím se stupněm postižení (dle Kurtzkeho škály 0-2.5, 4%; 3-4, 9.3%; 4.5-5.5, 32.1%; 6, 36.6%; > 6, 45.7%; $p < 0.01$). U progresivního typu onemocnění byla prevalence výskytu motorické únavy vyšší ve srovnání s relaps-remitentním typem RS (sekundárně progresivní RS 20.5%, primárně progresivní RS 30.8%, relaps-remitentní forma RS 10.8%; $p < 0.01$). Výsledky všech testů chůze se signifikantně lišily mezi 2 skupinami s a bez motorické únavy. Signifikantní korelace byly také nalezeny mezi 2 skupinami a všemi testy chůze, typem RS a Kurtzkeho škálou. Nesignifikantní rozdíly a korelace mezi 2 skupinami byly pro věk, pohlaví, délku onemocnění, Index tělesné hmotnosti a Modifikovanou škálu dopadu únavy.

Závěr: Pouze u jedné čtvrtiny pacientů s roztroušenou sklerózou mozkomíšní se vyskytla motorická únava (dle použitého kritéria 20% poklesu vzdálenosti ušlé v první a poslední minutě Šestiminutového testu chůze). Prevalence motorické únavy se zvyšuje se zvyšujícím se postižením (dle Kurtzkeho škály a dalších testů chůze) a je závislá na typu RS.

Klíčová slova: Roztroušená skleróza mozkomíšní (RS), Motorická únava, chůze, Šestiminutový test chůze (6MWT)

ABSTRACT

Title: Presence and Influencing Factors of Motor Fatigue during Six-Minute Walk Test in Multiple Sclerosis.

Background: Ambulation impairment limits daily activities in persons with Multiple Sclerosis (pwMS), even more pronounced in the presence of motor fatigue. Previous studies reported a continuous slowing down of the walking pace during the Six-Minute Walk test (6MWT) in persons with moderate to severe ambulatory dysfunction. However, it is not known whether motor fatigue during walking is present in all pwMS and how it relates to person characteristics such as disability level, type of MS or disease duration.

Methods: Data from the cross-sectional RIMS multi-centre study with 208 ambulatory pwMS from 10 European and 1 US centres were used. Expanded Disability Status Scale (EDSS) ranged from 0 to 6.5. PwMS were evaluated with the 6MWT as well as other walking measures (Timed Up and Go - TUG, Timed 25 Foot Walk - T25FW, Timed 10 Meter Walk Test – T10MW, Multiple Sclerosis Walking Scale-12 - MSWS-12) and the Modified Fatigue Impact Scale (MFIS) which assesses overall fatigue impact on daily life. Subjects were stratified into two subgroups with and without motor fatigue, defined as 20% threshold decline of distance walked during first compared to last minute of the 6MWT (Motor Fatigued Group, n=47; Non Motor Fatigued Group, n=161). Prevalence of motor fatigue according to disability level and type of MS was reported. T-test, Mann/Whitney test and Chi-square test were used to investigate difference between the subgroups. Correlation coefficients between motor fatigue subgroups and patient characteristics (age, gender, disease duration, Body Mass Index - BMI), walking measures (6MWT, TUG, T25WT, T10MW, MSWS-12) and MFIS were calculated.

Results: Motor Fatigue occurred in 22.6% of pwMS. Prevalence of motor fatigue increased significantly with increasing disability level (EDSS 0-2.5, 4%; EDSS 3-4, 9.3%; EDSS 4.5-5.5, 32.1%; EDSS 6, 36.6%; EDSS > 6, 45.7%; $p < 0.01$). Moreover prevalence of motor fatigue was significantly higher in progressive MS compared to relapsing remitting (RR) MS (secondary progressive MS 20.5%, primary progressive MS 30.8% RR 10.8%; $p < 0.01$). Results of all waking measures showed significant differences within two subgroups ($p < 0.01$). Significant correlations were found between motor fatigue, as determined during the 6MWT, walking measures, type of MS and EDSS. Correlations were non-significant for age, gender, disease duration, BMI and MFIS.

Conclusion: One quarter of the pwMS showed motor fatigue during 6MWT according to our 20% decline criterion. Motor fatigue prevalence is associated with increasing disability level (EDSS and walking ability/capacity) as well as with type of MS.

Key words: Multiple Sclerosis, Motor Fatigue, Ambulation/Walking/Gait, 6MWT

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	ABBREVIATED WORDS
2MWT	Two-Minute Walk Test
6MWT	Six-Minute Walk Test
12MWT	Twelve-Minute Walk Test
DI	Deceleration Index
EDSS	Expanded Disability Status Scale
FI	Fatigue Index
FS	Functional Systems
FSMC	Fatigue Scale for Motor and Cognitive Functions
FSS	Fatigue Severity Scale
HADS-D	Hospital Anxiety and Depression Scale
HAI	Hauser Ambulation Index
HR	Heart Rate
ICC	Intra-Class Correlation coefficient
IQR	Inter-Quartile Range
MFIS	Modified Fatigue Impact Scale
MI	Motricity Index
MS	Multiple Sclerosis
MSWS-12	Multiple Sclerosis Walking Scale-12
N	Number, frequency
PDDS	Patient Determined Disease Steps
PP	Primary Progressive type of MS
RIMS	Rehabilitation in Multiple Sclerosis
RR	Relapsing-Remitting type of MS
SD	Standard Deviation
SP	Secondary Progressive type of MS
SF-MPQ	McGill Pain Questionnaire
T10MW	Timed 10 Meter Walk Test
T25FW	Timed 25 Foot Walk Test
T100WT	Timed 100 Meter Walk Test
T500MW	Timed 500 Meter Walk Test
TUG	Timed Up and Go Test
VO_2	Volume of the oxygen

1 INTRODUCTION

Multiple Sclerosis (MS) is autoimmune neurological disease affecting central nervous system. The clinical manifestations/symptoms can be very variable and have diverse impact in the life of the persons with MS (pwMS). Among functional dysfunctions belong: muscle tone disruption, decreased muscle force, spasticity, coordination problems, impaired sensitivity, proprioception problems, visual and cognitive problems. Patients are very often complaining about the feeling fatigued especially at the end of the day, after physical/mental activity or after stay in the hot environment. Psychological problem such as depression, anxiety or just luck of confidence or motivation are also often related to this disease. All these above mentioned dysfunctions lead to the impaired balance and walking abilities. Next to the fatigue are walking or balance problems one of the most often patient reported dysfunction negatively influencing their quality of life.

When we are talking about the fatigue in pwMS we have to specify the type of it. Feeling fatigued can be caused by multiple reasons. Fatigue in general is the state of exhaustion distinct from depressed mood or physical weakness. It can be evaluated by self-report scales or performance-based measures. Physical induced fatigue is called as a motor fatigue, which is specific for its occurrence after the prolonged or repetitive muscle work/contractions.

Several experimental studies evaluated the motor fatigability in pwMS. Despite these performed researches the measuring of the motor fatigue in clinical practice remains unexplored and complicated. There are already some authors who are dealing with this problematic and who are in the meantime mainly trying to describe the relations between the patient characteristics and results of long walking tests. For example multiple studies already investigated the pacing patterns during long walking tests in different disability level subgroups, in different type of MS or according the results of the questionnaires evaluated by patients focused on fatigue or walking abilities. Aerobic intensity, oxygen consumption or walking pattern related to the long walking tests were reported as well. As it was already mentioned all performed studies are mainly describing the relations between results of the long walking tests and patient characteristics or other outcomes measures. The point is that there is not yet established the test, criterion or cut off score which could be used in the clinical practice to detect the MS patients with the motor fatigue.

The aim of my Master´s Thesis is to determine and justify the criterion of the motor fatigue in pwMS by using the Six-Minute Walk test. Next describe the relation of the motor fatigue criterion and the other tests commonly used by clinicians for investigating the MS patients. Further goal is to define the prevalence of the motor fatigue in pwMS and create a clear take home message useable in clinical (rehabilitation) practice.

2 MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is a chronic autoimmune demyelinising disease of the central nervous system with the prevalence in the Europe 83 per 100 000 cases the incidence 4.3 cases per 100 000 [Pugliatti *et al.* 2006]. Due to the affected central nervous system the clinical manifestation can be very variable. Nevertheless the most often patient reported symptoms are walking/balance problems and feeling fatigued [Krupp *et al.* 1988]. General fatigue in MS is usually described by patients as a generalized sensation of bodily and mental lack of energy. Other influences on fatigue in pwMS are motivation, depression, general physical impairment/disability, type of the activity/task, sleepiness, weakness, exercise intolerance etc. [Scheidegger *et al.* 2010]. From this enumeration of the possible components of the fatigue is obvious that it has multifactorial causes. General fatigue in MS during the within one-day repeated 6MWT was not confirmed, despite the fact that patients evaluated themselves as a feeling fatigued [Feys *et al.* 2014, Goldman *et al.* 2008]. Couple of studies [Burschka *et al.* 2012, Dalgas *et al.* 2014, Goldman *et al.* 2008, Phan-Ba *et al.* 2012] reported on deceleration tendency during 6MWT measured minute by minute. Authors mostly agreed on conclusion that the possible explanatory cause of this deceleration is the occurrence of the motor fatigue.

2.1 Literature search

The literature search concerning the articles investigating the motor fatigue in MS was performed. For the search were used the databases PubMed and PEDro. Following MeSH and Key–terms were used: Multiple Sclerosis, motor fatigue, walking/gait/ambulation, and 6MWT. Double articles were excluded. Remaining articles were briefly screened based on the title and the abstract. The articles with not available abstract, with the lack of information or the articles in another then English language were excluded. The full text of the final ten research papers were then analyzed and served as a baseline for the methodology. Contents and main take home messages of these key articles are described in the following two chapters.

2.2 Motor fatigue in MS

There are various definitions for the motor fatigue. From the physiological point of view is the motor fatigue defined as a loss of force during sustained muscle work [Edwards *et al.* 1977]. It is distinct from sleepiness (physiological state between the wakefulness and overt sleep, satisfied by sleep) or tiredness (lack of energy and initiative, improved by rest but not by sleep) [Mathis and Hess 2009].

Walking is an important bodily function that is highly valued by persons with MS independent disease stage [Heesen *et al.* 2008]. Typically, in clinical trials, it is assessed by the Timed 25 Foot Walk (T25FW), which is part of the MS functional composite score and measures the fastest walking speed. However the introduction of the MS Walking Scale-12 (MSWS-12) has led to increased awareness of the multi-dimensionality of walking including also aspects such as walking distance, endurance and mental effort of walking that is not captured by the T25FW. The Six-Minute Walk test (6MWT) is accepted as a golden standard that also incorporates walking endurance and walking effort, as reflected by increased in heart rate and oxygen consumption, mainly during the first three minutes of the test [Bosnak-Guclu *et al.* 2012, Paltamaa *et al.* 2007]. The performance of the 6MWT is considered as performed at moderate intensity based on a report of approximately 67% of the maximal heart rate. Walking speed is mainly related to muscle strength while walking distance may also be determined by motor or muscle fatigue, also referred to as fatigability [Dobkin 2008]**.**

Clinically, the 6MWT also allows to investigate the pacing pattern per minute which is of interest as it may indicates or not motor fatigue is clinically manifesting. There are several reports on the pacing pattern minute by minute in MS, with differentiation of groups with different severity of ambulatory impairment [Burschka *et al.* 2012, Dalgas *et al.* 2014, Goldman *et al.* 2008, Phan-Ba *et al.* 2012]. Overall, all studies indicated similarly that walking distance is decreasing during the first two minutes of the 6MWT. Goldman et al (2008) published the first study with disability differentiation indicating that patients with mild disability could increase walking distance again towards the end of the test whereas persons with severe disability showed a consistent decrease throughout the 6MWT. However, no statistical values between minutes were provided while the severe subgroup with EDSS > 4 only consisted of six participants. While part of the studies could not replicate this pattern of consistently decreased walking distance in larger samples [Dalgas *et al.* 2014], there are indications that more severely disabled subjects show decreased walking performance during the 6MWT. Interestingly, the study of Phan-Ba calculated ‘deceleration indexes’ calculated as ratio between the walking speed during the last 100 m of a Timed 500 Meter Walk Test (T500MW) and maximal speed during T25FW test.

The present study analysed data from a large dataset [Dalgas *et al.* 2014] to investigate the prevalence of motor fatigue, featured as continuously slowing down of walking speed during the 6MWT according to disability level. The underlying hypothesis was that motor fatigue may be considered as a symptom that is not equivalent present in every person with MS, similar to the heterogeneous appearance of other symptom in a MS population.

Authors Feys *et al.* [2013] and Pilutti *et al.* [2013] used the GAITRite walkway system (for measuring the spatio-temporal gait parameters) as objective motor fatigue investigation option. The results from the GAITRite were compared to the results of the 6MWT. Differences in 6MWT performance and spatio-temporal parameters occurred to be dependent on the disability level.

Kinematic gait analysis was used by Sehle *et al.* [2011] as another objective assessment option of the motor fatigue in MS. Patients underwent a physical exertion test while walking usual speed on the treadmill until they reached complete exhaustion. Motor fatigue was then defined by the differences in the gait patterns from which the Fatigue Indexes were calculated.

In MS, motor fatigue has been also quantified for leg and arm muscles by static and dynamic muscle contractions. First publication investigating the associations among the motor fatigue, strength and ambulatory impairment in MS patients versus healthy control was performed by Schwid *et al.* [1999]. According to results MS patients experienced more fatigue then the healthy control subjects during the sustained maximal contractions, repetitive maximal contractions and ambulation. In addition motor fatigue appeared to be distinct from weakness. The reason was because the degree of fatigue was not associated with the degree of the individual muscles weakness.

Surakka *et al.* [2004] has calculated ‘motor fatigue indexes’ based on the sustained isometric 30 seconds contractions and 5 seconds lasting isometric maximal torque.

A recent study indicated that muscle fatigue or endurance indexes are highly related to the outcome of longer walking tests [Broekmans *et al.* 2013].

2.3 How to test the motor fatigue in MS?

In the following pages are summarized the outcome measures used in ten studies dealing with the motor fatigue in MS included in the literature review.

2.3.1 Disability measures

Following measures are widely used when determining the disability level in pwMS. Evaluation of both measures (Expanded Disability Status Scale and Hauser Ambulation Index) is mainly dependent on the walking abilities of MS patients.

2.3.1.1 Expanded Disability Status Scale

The Kurtzke Expanded Disability Status Scale (EDSS) is the most widely used measure of impartment in pwMS regarding the disease severity [Balcer 2001, Goodkin *et al.* 1992, Kurtzke 1983, Noseworthy *et al.* 1990]. It is an ordinal non-continuous scale with emphasis on ambulatory function. The rage of the scale is from 0 to 10 with 0.5 point scoring system. The rating system is described in the following table.

Table 1: Kurtzke Expanded Disability Status Scale

SCORE	STATUS
0	Normal result of neurologic examination
1.0	No disability, minimal signs in one functional system
1.5	No disability, minimal signs in more than one functional system
2.0	Minimal disability in one functional system
2.5	Minimal disability in two functional systems
3.0	Moderate disability in one functional system, or mild disability in three or four functional systems though fully ambulatory
3.5	Fully ambulatory but with moderate disability in three or four functional systems
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance, characterized by relatively severe disability; able to walk without aid or rest for some 300 meters
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to preclude full daily activities (e.g. to work full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond about 5 meters even with aid. Essentially restricted to a wheelchair; wheels self in standard wheelchair and transfers alone; active in wheelchair about 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid to transfer; wheels self but cannot carry on in standard wheelchair a full day; may require a motorized wheelchair
8.0	Unable to walk at all, essentially restricted to bed, chair or wheelchair but may be out of bed much of the day; retains many self-care functions; generally has effective use of the arms
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s) ; retains some self-care functions
9.0	Helpless bed patient; can communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/ swallow
10	Death due to Multiple Sclerosis

Rating of the disability till level 4.0 is based on eight Functional Scores (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, other function) in fully ambulatory patients. Scores above value 4.0 are then highly dependent on ambulation status of the pwMS. Based on distance that pwMS is able to walk without resting and on the need of assistive device use [Kurtzke 1983].

Despite often criticisms about the difficulties with reliability and sensitivity the EDSS remains standard clinical measure of the disease severity in pwMS [Kurtzke 1983, Rudick *et al.* 1996, Whitaker *et al.* 1995, Willoughby and Paty 1988, Wingerchuk *et al.* 1997].

In the studies describing the motor fatigue in pwMS are the EDSS scores divided to two (mild = 0 - 4, moderate = 4.5 – 6.5, [Broekmans *et al.* 2013, Burschka *et al.* 2012]) or three (mild = 0 – 2.5, moderate = 3 - 4, severe = 4.5 -6. 5, [Dalgas *et al.* 2014, Phan-Ba *et al.* 2012]) categories.

2.3.1.2 Hauser Ambulation Index

The Hauser Ambulation Index (HAI) was developed by Hauser *et al.* [1983] to quantify changes in the gait. It is performance measure based on speed and the degree of assistance needed during the walking 25 feet. The mobility is scored by the scale from 0 (fully active) to 9 (patient is restricted to the wheelchair or unable to transfer himself/herself independently).

Table 2: Hauser Ambulation Index

SCORE	STATUS
1	Walks normally, but reports fatigue that interferes with athletic or other demanding activities
2	Abnormal gait or episodic imbalance; gait disorder is noticed by family and friends; able to walk 25 feet (8 meters) in 10 seconds or less
3	Walks independently; able to walk 25 feet in 20 seconds or less
4	Requires unilateral support (cane or single crutch) to walk; walks 25 feet in 20 seconds or les
5	Requires bilateral support (canes, crutches, or walker) and walks 25 feet in 20 seconds or less; or requires unilateral support but needs more than 20 seconds to walk 25 feet
6	Requires bilateral support and more than 20 seconds to walk 25 feet; may use wheelchair* on occasion
7	Walking limited to several steps with bilateral support; unable to walk 25 feet; may use wheelchair* for most activities
8	Restricted to wheelchair; able to transfer self independently
9	Restricted to wheelchair; unable to transfer self independently

*The use of a wheelchair may be determined by lifestyle and motivation. It is expected that patients in Grade 7 will use a wheelchair more frequently than those in Grades 5 or 6. Assignment of a grade in the range of 5 to 7, however, is determined by the patient's ability to walk a given distance, and not by the extent to which the patient uses a wheelchair.

The HAI demonstrated a good test-retest variability and inter-rater reliability. However recently is not very often used in clinical practice nor for research purposes and was replaced by Timed 25 Foot Walk Test [Hauser *et al.* 1983].

Authors Feys *et al.* [2013] used in their study the HAI as well as EDSS for evaluation of the functional level.

2.3.2 Muscle strength and sustained/repetitive contractions measurement

One of the possibilities how to objectively quantify the motor fatigue in MS is to measure the maximal muscle strength or repetitive muscle contractions. These tests are used mainly for the research purposes to determine and investigate muscle fatigability. They were not yet classified as an outcome measures with the utility in daily rehabilitation practice. What we can see more often used is the testing of the uscle strength by Motricity Index.

2.3.2.1 Motricity Index

The Motricity Index (MI) is the simple measure of motor loss in the upper and lower extremities evaluated by the experienced investigator. This test is not in the true sense of motor fatigue investigation, but it can tell us something about the general muscle weakness in pwMS. The full version of the test contains three tests for upper limbs (pinch grip, elbow flexion and shoulder abduction) and three tests for lower limbs (ankle dorsiflexion, knee extension and hip flexion). The scoring system is different for the upper and lower extremities. For the arms patient can get 0, 11, 19, 22, 26 and 33 points for each of the three items. For the legs the scoring is 9, 14, 19, 25 and 33 points. When the patient scores 33 points in all three items the total score is then 99 + one point in addition.

The test was considered as valid and reliable when testing on the stroke population [Collen *et al.* 1990, Collin and Wade 1990]. The MI was included to battery of the tests evaluating the clinical features in MS patients. The battery of the tests containing the MI showed the internal consistency [Rasova *et al.* 2012].

Evaluation of the muscle strength by using the Motricity Index for the lower limbs was included in the study design of Feys *et al.* [2013].

2.3.2.2 Dynamometry, myometry

The dynamometer (myometer) is an easy use device for measuring force, moment of the force or power. In the investigation of the motor fatigue linked to the walking abilities in pwMS two main designs were applied: measuring of the isometric and isokinetic strength. Both measurements models were considered as a reliable for testing MS patients [Armstrong *et al.* 1983, Schwid *et al.* 1999, Surakka *et al.* 2004].

Most of the authors in addition to the isokinetic and repetitive muscle contractions investigated the muscle fatigability by using the isometric contractions, while the diverse testing protocols were applied (sustained contractions, maximal sustained contractions or maximal torque during 5 seconds) [Broekmans *et al.* 2013, Schwid *et al.* 1999, Surakka *et al.* 2004].

2.3.3 Walking measures

Walking measures are easy to perform tests often used in the clinical practice to investigate the walking abilities in pwMS.

2.3.3.1 Short walking tests

The Timed 25 Foot Walk Test, Timed 10 Meter Walk Test and Timed Up and Go Test are the most often used tests suitable for the clinical practice while investigating the pwMS [Tyson and Connell 2009].

Timed 25 Foot Walk Test

The Timed 25 Foot Walk Test (T25FW) was considered as reliable waking measure which can be used as a standard measure in Multiple Sclerosis [Gijbels *et al.* 2012]. The intra-class coefficient is ICC = 0.991 [Learmonth *et al.* 2013]. Test retest reliability and internal consistency was also evaluated and confirmed [Rasova *et al.* 2012] and the test was considered as one of the characterized objective measure of walking disability in pwMS [Kieseier and Pozzilli 2012].

The T25FW was used in the study of Phan-Ba *et al.* [2012] where was performed in two models: with the dynamic and static start. Patients walked faster during the T25FW with the dynamic start. These data then Phan-Ba used to calculate the Deceleration Index. Authors Broekmans *et al.* [2013] and Feys *et al.* [2013] used T25FW among the other tests for the testing of walking capacity.

Timed 10 Meter Walk Test

In the study of Paltamaa *et al.* [2007] was the T10MW considered as valid test strongly associated with dependence in mobility and domestic life. The test is recommended to use for clinical settings for measuring overall walking disability [Kieseier and Pozzilli 2012, Tyson and Connell 2009]. The test can be measured in the usual or fastest speed with dynamic or static start.

The Timed 10 Meter Walk Test walked in the usual speed was not used in the previous studies for evaluation of the motor fatigue in MS, but regarding the methodology of this Thesis is the test included the introduction section.

Timed Up and Go Test

Timed Up and Go Test (TUG) is not true walking test assessing only the walking ability. The test gives us the information also about the balance and general mobility [Bethoux and Bennett 2011]. It is mainly used and tested in older adults population, where the test was considered as reliable and valid measure for quantifying functional mobility [Podsiadlo and Richardson 1991]. Time to time is also use in the MS patients. The reproducibility of the test was in the moderate MS patients very high. The intra-class correlation was 0.98 and the authors suggested to use only one attempt while evaluating people with moderate MS [Nilsagard *et al.* 2007].

The test was used as one of the walking capacity tests in the study of Broekmans *et al.* [2013], where the results of the walking measures and the upper legs muscle strength were compared.

2.3.3.2 Long/endurance walking tests

The long walking measures often serve as an suitable outcome measures for evaluating the walking endurance.

Two-Minute Walk Test

The Two-Minute Walk Test (2MWT) was considered as reliable test which can be used as a standard walking measure in Multiple Sclerosis [Gijbels *et al.* 2012]. It is valid test for testing of walking distance in MS, but with poor intrarater and interrater reliability [Gijbels *et al.* 2010]. According to authors Gijbels *et al.* [2011] can be 2MWT used instead of 6MWT to test walking endurance. This conclusion was based on the results of the 6MWT where patients walked constant distance during the last four minutes of the test. However the recent studies dealing with the pacing pattern during 6MWT refuses this conclusion [Burschka *et al.* 2012, Dalgas *et al.* 2014], because the results did not confirmed the findings of Gijbels *et al.* [2011].

Despite the discussion about the insufficiency to detect the motor fatigue by using 2MWT, was the test included together with T25FW and TUG in the study of Broekmans *et al.* [2013] for evaluating the walking capacity in pwMS. Feys *et al.* [2013] used the 2MWT together with the 6MWT and spatiotemporal gait analysis on the GAITRite carpet.

Six-Minute Walk test

According to Goldman *et al.* [2008] is the 6MWT feasible, reproducible, and reliable measure in pwMS, intra-class correlation coefficient (ICC = 0.95) and inter-rater reliability = 0.91. Within-day variability of 6MWT in pwMS was tested in the study of Feys *et al.* [2014] and was considered as constant. Plenty of studies confirmed that 6MWT is a suitable endurance/fatigability walking test in pwMS feasible to use in clinical practice or for research purposes. [Baert *et al.* 2014, Bethoux and Bennett 2011, Burschka *et al.* 2012, Gijbels *et al.* 2010, Motl *et al.* 2012, Tyson and Connell 2009].

The minute by minute measured 6MWT was used as a in the studies of Burschka *et al.* [2012], Dalgas *et al.* [2014] and Goldman *et al.* [2008] as a main outcome measure assessing the occurrence of the motor fatigue in pwMS. Total distance walked during the 6MWT was measured in the study of Feys *et al.* [2013] and Pilutti *et al.* [2013].

Twelve-Minute Walk Test

The 12-Minute Walk Test (12MWT) was developed by Cooper [1968] for assessing the cardiovascular fitness in healthy people. The test initially examined in patients with respiratory dysfunction [Butland *et al.* 1982, McGavin *et al.* 1976]. Reliability and validity of the test was investigated only the stroke patients population [Kosak and Smith 2005].

The 12MWT was included as one of the walking outcome measures in the study of Burschka *et al.* [2012] in order to compare results of the pacing patterns in healthy controls and MS patients during the 6MWT and 12MWT.

Timed 100 Meter Walk Test

In the study of Belachew [2009] the Timed 100 Meter Walk Test (T100MW) showed an excellent intra-class correlations. Next in comparison with the T25FW was the T100MW considered as a more sensitive measure for estimation the maximal walked distance in pwMS. Authors Kieseier and Pozzilli [2012] concluded that the long walking tests (T100MW, 2MWT and 6MWT) are better for the assessment of walking fatigability, distance limitations and functional capacity in pwMS.

The test was included in the study design of the motor fatigue measurement in MS by authors Phan-Ba *et al.* [2012].

Timed 500 Meter Walk Test

Despite the fact that the Timed 500 Meter Walk Test (T500MW) is a component of the EDSS, this walking test is not often used in clinical trials for evaluating the walking endurance. Usually the 6MWT is preferred measure while testing the long distance walking abilities, because it provides more sensitive information about the walking performance then the T500MW [Goldman *et al.* 2008]. The main difference between the 6MWT and T500MW are the instructions given to the patient before he/she begins with walking. For the 6MWT is patient asked to walk as far as possible while in the T500MW the recommended instruction is to walk as fast as possible. During the 6MWT the examiner note the walked distance, during the T500MW is the outcome the time.

In two studies describing the motor fatigue in MS was the T500MW chosen as a main endurance walking measure [Phan-Ba *et al.* 2012, Schwid *et al.* 1999].

2.3.4 **Self reported measures**

To get the information about the patient´s perception of the walking abilities or the fatigue, the self-reported measures are often included in the clinical trials.

2.3.4.1 Multiple Sclerosis Walking Scale-12

The Multiple Sclerosis Walking Scale-12 (MSWS-12) is a 12-item scale specifically designed for pwMS asking the patient how much the MS influenced their walking abilities during the last two weeks. Total score range from 12 – 60 points with the following Likert-type scale in each item: 1 = “No at all”, 2 = “A little”, 3 = “Moderately”, 4 = “Quite a bit”, 5 = “Extremely”. The higher total score is the higher impact of MS is [Tyson and Connell 2009].

The item test-retest reproducibility of this test is high (test-retest=0.78) as well as reliability (reliability=0.94), internal consistency (int. consistency = 0.94) and responsiveness (effect size=1.12) [J. C. Hobart *et al.* 2003, Holland *et al.* 2006, McGuigan and Hutchinson 2004, Motl and Snook 2008]. Further research findings suggest that this test is related to aspects of walking quality (assessed as spatiotemporal parameters of gait), walking speed and endurance (measured by 6MWT) [Pilutti *et al.* 2013]. The MSWS-12 also provides additional information about the related aspects of walking (such as running or climbing stairs) in comparison with objective walking tests [Kieseier and Pozzilli 2012].

The MSWS-12 questionnaire was used as one of the walking measures in the study of Dalgas *et al.* [2014] and Feys *et al.* [2013] investigating the motor fatigue in pwMS.

2.3.4.2 Patient Determined Disease Steps

The Patient Determined Disease Steps (PDDS) was developed for the self-assessment of the disease status in pwMS. The questionnaire contains one question to evaluate the walking abilities (with the scoring from 0 to 8) and then eleven performance specific questions (with the scoring system range from 0 to 5 and 0 to 6). Among the eleven performance specific questions are the questions about the mobility, hand function, vision, fatigue, cognitive symptoms, bladder/bowel problems, sensory symptoms, spasticity symptoms, pain, depression, tremor and coordination.

Plenty of studies confirmed and reported validity of the PDDS questionnaire in MS population [Learmonth *et al.* 2013, Motl and Snook 2008, Schwartz *et al.* 1999].

Only one author dealing with the motor fatigue problematic in MS used this questionnaire as one of the outcome measure [Pilutti *et al.* 2013].

2.3.4.3 Modified Fatigue Impact Scale

The Modified Fatigue Impact Scale (MFIS) is a modified form of Fatigue Impact Scale (FIM) from authors Fisk *et al.* [1994]. The questionnaire is focused on pwMS-rated evaluation of how fatigue impacts their lives during last four weeks. It contains 3 subscales regarding effects of fatigue in physical, cognitive and psychosocial functioning. The MFIS is a 21-item long questionnaire (derived from 40-item FIS questionnaire) which has been recommended by the Multiple Sclerosis Council for Clinical Practice Guidelines. The questionnaire is one of the components of the Multiple Sclerosis Quality of Life Inventory, which is a battery consisting of 10 individual scales providing a quality of life measurement [Fischer *et al.* 1999].

The total score range from 0 to 84 points, 0 – 36 for physical subscale (items 4, 6, 7, 10, 13, 14, 17, 20, 21), 0 – 40 for cognitive (items 1, 2, 3, 5, 11, 12, 15, 16, 18, 19) and 0 – 8 for psychosocial functioning (items 8, 9). Higher total score corresponds with the greater self-evaluated perception of the fatigue. The questions are asking how often fatigue influenced your activities during last two weeks. Scoring of each item is provided by Likert-type scale with following answers: 0 = ”Never”, 1 = “Rarely”, 2 = “Sometimes”, 3 = “Often” 4 = “Almost always”.

MFIS has shown excellent test-retest reliability (ICC = 0.85), internal consistency and it is a valid measure of impact of fatigue in pwMS [Amtmann *et al.* 2012, Kos *et al.* 2005, Rietberg *et al.* 2010, Tellez *et al.* 2005].

In the study of Dalgas *et al.* [2014] score of 38 served as a cut-off score for differentiation the fatigued and non-fatigued MS patients. Feys *et al.* [2013] used the total score of the MFIS questionnaire in their study.

2.3.4.4 Fatigue Scale for Motor and Cognitive Functions

The Fatigue Scale for Motor and Cognitive Functions (FSMC) serves for the subjective evaluation of the mental and physical fatigue in pwMS. A Likert-type 5-point scale (ranging from 1 to 5) in 20 questions is used. The final score can range from 20 to 100, while the lower score indicates the lower impact of the fatigue.

The validation of the FSMC was done on the large sample of MS and healthy controls. Height sensitivity and specificity were found as well [Penner *et al.* 2009].

Fatigue was defined according to the FSMC questionnaire in motor fatigue investigating study of Sehle *et al.* [2011]

2.3.5 Other experimental measures

Next to the muscle strength assessments, walking tests or self-reported measures we can find in the literature also the other tools which were used or which could be used for investigating and describing the motor fatigue in pwMS.

2.3.5.1 GAITRite

GAITRite Walkway System is a 5.18 m long and 90 cm wide carpet with the pressure-activated sensors. The walkway is connected to the computer and the special software is analyzing the foot prints and spatiotemporal data of walking/running. [Webster *et al.* 2005]. Several studies described the GAITRite system to be valid and reliable tool [Givon *et al.* 2009, Remelius *et al.* 2012, Sosnoff *et al.* 2011, Webster *et al.* 2005].

According to the previous studies is the GAITRite technology an applicable tool to evaluate the motor fatigue in pwMS [Feys *et al.* 2013, Pilutti *et al.* 2013].

2.3.5.2 Kinematic gait analysis

The kinematic gait analysis using the three line-scanning camera systems with 11 active infrared markers (attached to the patient´s body) was used in the study of Sehle *et al.* [2011]. In addition the system was synchronized with the standard video camera. He researchers let the patient walk at comfortable speed until he/she reached the exhaustion and recorded the gait kinematic parameters.

The kinematic gait analysis is complicated specialized device demanding possibility to the investigate the motor fatigue.

2.3.5.3 Heart rate

Heart rate (HR) monitoring during the endurance induced activities is one of the possible tools how to investigate and quantify the occurrence of the motor fatigue in MS [Dalgas *et al.* 2014]. The values are usually expressed as a percentage of the maximal HR, because as it is known HR is age dependent [Cleary *et al.* 2011]. The moderate relative intensity (69% of the maximal HR) in mild to severely impaired MS patients was reported by Savci *et al.* [2005].

In the publication of Dalgas *et al.* [2014] the heart rate of every minute of the 6MWT for three EDSS subgroups was measured. Results of the HR in the moderate and severe group (EDSS = 3 - 6.5) were significantly lower than in mild disabled group.

Measuring of the HR is easy to perform and the results are usable to define the individual or relative aerobic intensity, which is closely related to occurrence of the motor fatigue.

2.3.5.4 Deceleration Index

Phan-Ba *et al.* [2012] has quantified the level of the motor fatigue in MS by calculation of so-called Deceleration Index (DI). Patients performed four walking tests (T25FW with dynamic and static start, T100MW and T500MW). Te tests walked by the fastest and slowest speed were recruited. The fastest speed occurred during the T25FW with the dynamic start and the slowest speed during the last 100 m of the T500MW. The equation for the calculation of the DI was the ratio between the mean walking speed of the last 100 m of the T500MW and the mean walking speed of the T25FW with the dynamic start.

2.3.5.5 Fatigue Indexes

Two publications tried to express the level of the motor fatigue in pwMS by calculation of the Fatigue Index (FI).

In the study report of Sehle *et al.* [2011] was the walking pattern of pwMS evaluated by using the kinematic gait analysis on treadmill. Patients walked in their usual speed until they reached complete exhaustion. The FI was then defined as the number of significant mean and standard deviation changes from the beginning to the end of the exertion test relative to the total number of gait kinematic parameters. The FI ranged from 0.33 – 0.92. However no threshold for distinguishing the patients with and without motor fatigue was determined.

Another outcomes measures and equation were used by the authors Surakka *et al.* [2004] for calculation of FI in pwMS. As an outcome measures served the 5 seconds lasting isometric torque of the knee flexors and 30 s lasting isometric contraction of the knee extensors. The FI was based on the calculated area under the force versus time curve. The starting point for the calculation of the FI was the time point of maximum torque achieved by the subject. Authors considered the new FI as a reliable model of measuring the motor fatigue in pwMS. From the clinical point of view is this way of detection of the motor fatigue in pwMS unpractical and hardly useable in daily rehabilitation practice.

3 RESEARCH OBJECTIVES, RESEARCH QUESTIONS AND HYPOTHESIS

3.1 Research objectives

Identification of the motor fatigue and its relation to patient characteristics (age, gender, BMI, EDSS, type of MS, disease duration) walking measures (6MWT, TUG, T25FW, T10MW, MSWS-12) and subjective evaluation the impact of the fatigue on physical, cognitive, and psychosocial functioning (evaluated by MFIS questionnaire). Evaluation and calculation of the differences in pacing strategies during 6MWT in groups with and without motor fatigue.

3.2 Research questions

1) What is the percentage occurrence of the motor fatigue in patients with MS?
2) What are the patient characteristics in the Motor Fatigued Group?
3) What are the differences in the walking measures between the two subgroups (groups with and without motor fatigue)?
4) What are the differences in pacing strategy during the 6MWT in two subgroups?
5) What is the more relevant outcome measure of motor fatigue, MSWS-12 or MFIS questionnaire?

3.3 Hypothesis

1) Occurrence of the motor fatigue will be less than 50% in total group of the patients.
2) Percentage occurrence of the motor fatigue will be dependent on disability level, disease duration and type of MS.
3) Results of all walking measures (6MWT, MSWS-12) will vary between the subgroups except short walking tests (T25FW, T10MW and TUG).
4) Motor Fatigued Group of pwMS will show slowing down during 6MWT. Non Motor Fatigued Group of pwMS will walk constant distance each minute of the 6MWT.
5) MFIS questionnaire evaluating the impact of the fatigue on physical, cognitive, and psychosocial functioning will be more appropriate to detect the pMS with

motor fatigue then MSWS-12 questionnaire evaluating impact of MS on the individual´s walking abilities.

3.4 Reason and importance of the research

Walking is an important bodily function that is highly valued by persons with MS independent disease stage. Ability to walk longer distances influences the participation level in pwMS [Heesen *et al.* 2008]. Motor fatigue influence the endurance demanding activities and can have highly impact on above mentioned psycho-social aspects of pwMS life. The aim of this study is to identify the patients with the motor fatigue and capture the prevalence of having motor fatigue based on the possible influencing factors. Further investigation will be focused on determination of the suitable walking measures that could be used in clinical practise for detecting the motor fatigued patients. This study can later on serve as a baseline for the future research of motor fatigue in pwMS.

4 METHODOLOGY

4.1 Subjects

The participants were recruited according to inclusion criteria from 10 European and 1 US centres to the multicentre-study organized by RIMS (Rehabilitation in Multiple Sclerosis) in years 2009-2012.

Inclusion criteria:

1) A clinical definitive diagnosis of MS.
2) EDSS in range 1.0 – 6.5
    a. EDSS 1.0 = no disability, minimal signs of one of the 8 functional systems (FS).
    b. EDSS 6.5 = the ability to walk at least 20 meters independently with or without the use of an assistive device.

Exclusion criteria:

1) No MS relapse or relapse-related treatment with glucosteroids in the month prior to the study.
2) Other exclusion criteria-contraindications such as severe orthopaedic or cardiovascular dysfunction, or the presence of other neurological diseases.

4.2 Experimental design, outcomes measures

A cross-sectional multi-centre study design was applied. General data such as age, gender, disease duration, type of MS height and weight were recorded. Disability level was evaluated by Expanded Disability Status Scale (EDSS) by patient´s neurologists. Performed walking measures were Timed Up and Go (TUG), Timed 25 Foot Walk at fast speed (T25FW), Timed 10 Meter Walk Test (T10MW), Six-Minute Walk test (6MWT) and Multiple Sclerosis Walking Scale-12 (MSWS-12). The Modified Fatigue Impact Scale (MFIS) questionnaire was used for evaluation the impact of the fatigue on physical, cognitive, and psychosocial functioning. All centres used the same standardized instruction booklet, including details on test procedures, verbal instructions and level of encouragement. Subjects were permitted to use habitual assistive devices during testing. All the questionnaires and verbal or written instructions were translated to the mother language of the country where the study took place. Each of 11 participating centres had their approval of the Ethical committee (Annex 1) and all patients signed the inform consent (Annex 2).

4.2.1 General data

As mentioned above the general data such as date of the birth (age in years), gender (male/female), height (m) and weight (kg) about every patient were collected. Information about disease duration (years), type of MS (primary progressive - PP, secondary progressive - SP, relapsing-remitting - RR) and drug use (name of the drug) from the official record of the patient´s neurologist were gathered as well.. Later on the Body Mass Index was calculated from patient´s weight (kg) / height^2 (m) equation.

The scoring sheet for the general data is in Annex 3

4.2.2 Disability Expanded Status Scale

The Kurtzke Disability Status Scale measures the disability level with emphasis on ambulatory function in pwMS. Level of disability (range from 0 to 6.5) was evaluated and determined by patient´s neurologist.

4.2.3 Walking measures

Participants were evaluated by five walking measures in following order.

4.2.3.1 Timed Up and Go test (TUG)

Timed Up and Go test is used to assess mobility, balance, walking ability, and fall risk.

Equipment needed for the examination is the chair with the armchairs (chair´s height = 46 or 47 cm), tape or cone placed 3 m far away from the chair, stopwatch and assistive device (if needed).

Instructions:

Patient should wear regular footwear and use his/her customary walking aid. The starting position is sitting on the chair with back resting on the back of the chair and with arms resting on the chair´s arms. The upper extremities should not be on the assistive device (if used for walking), but it should be nearby. Aim of the test is stand up from the starting position, walk 3 meters to marked line/cone, make a turn, walk 3 m back to the armchair and sit down. Explain and show to the patient how to perform the test. The instruction is: *"Walk at your comfortable and safe walking speed."* Ask if he/she is ready to start. Start the test by counting: *"3, 2, 1, GO",* and stop the time (in seconds) needed to perform the test. The stopwatch should start when you say go, and should be stopped with the patient's buttocks touch the seat [Podsiadlo and Richardson 1991]. The time should be rounded with 0.1 second accuracy.

4.2.3.2 Timed 25 Foot Walk Test (T25FW)

The Timed 25 Foot Walk Test is walking measure commonly used in the clinical practice to evaluate the maximal walking speed.

Equipment needed for the examination is stopwatch, marked 25-foot distance in the walkway without obstacles, tape and assistive device (if needed).

Instructions:

Patient should wear regular footwear and use his/her customary walking aid. Examiner clearly marks on the floor with the tape the 25-foot (7.62 metres) long course. The patient is standing just behind the starting line and the instruction is: *"Walk the 25 foot long hallway as quickly as possible, but safely. So not slow until after you have passed the finish line. Ready? GO."* Running is not allowed. Timing starts when the lead foot crosses the starting line. The examiner can walk just behind the patient as he/she completes the task (for safety reasons). Timing is stopped when the lead foot crosses the finish line. The subject's walk time is recorded within 0.1 second, rounded as needed. Round up to the next tenth if hundredth's place is > = .05, round down if hundredth's place is < .05 (e.g., 32.45" would round to 32.5" but 32.44" would round to 32.4"). After completing the first timed walk, position the patient just behind the line where s/he is now standing, repeat the same instructions, and have the patient complete the walk again. The time limit is set to 3 minutes (180 seconds) per trial. [Fischer *et al.* 1999]

4.2.3.3 Timed 10 Meter Walk Test (T10MW)

The Timed 10 Meter Walk Test in usual walking speed with the “flying start” on 14- meters long walkway was used as another short distance walking test.

Equipment needed: stopwatch, objects free 14-meters walkway, tape and assistive device (if needed).

<u>Instructions:</u>

Patient should wear regular footwear and use his/her customary walking aid. Examiner on the object free walkway clearly marks on the floor with the tape four lines in distances 0, 2, 12 and 14 meters. Time of the 10 m Walk Test is measured when the patient past line in 2 and 12 meters distance. First and last two meters of the test are here to avoid measuring the acceleration and deceleration phase of the gait.

The patient is directed to the starting line (line marking 0 meters of the 14 meters long course) and is instructed to walk 14 meters at usual pace. Point where the 14-metre course ends and then instruct the patient as following: *“I would like you to walk 14 meters at your own comfortable/usual speed. Do not slow down until after you have passed the finish line. Ready? GO.”* Before the examiner starts testing the patient he/she can demonstrate the test. The timing begins when the lead foot crosses the 2-metre line and stops when the lead foot crosses the 12-metre line. Time is recorded within 0.1 second, rounding as needed. The examiner can walk just behind the patient as he/she completes the task (for safety reasons).

4.2.3.4 Six-Minute Walk test (6MWT)

The 6MWT is the test assessing the sub-maximal aerobic capacity/endurance during 6 minutes walking on 30 m long walkway [Enright 2003]. Ideal place for the walkway is object free, straight smooth surface corridor with marked endpoints in distance of 30 m. The endpoints are taped lines on the ground. Examiner marks to the scoring sheets distance walked every minute of the 6MWT.

Equipment needed is stopwatch, 30 m walkway, tape and assistive device (if needed).

<u>Instructions:</u>

Patient should wear regular footwear and use his/her customary walking aid.

"Walk as fast as possible and as far as possible, but safely for 6 minutes. You will walk back and forth on this walkway. Consider that 6 minutes is a long time to walk, so you will be exerting yourself. You should pivot briskly at the end of the 30 m long hallway on the marked line and continue back the other way without hesitation. Now I am going to show you." Examiner demonstrates walking one lap with pivot turning on the marked lines.

"Are you ready to do that? I am going to use this stop watch and clip board to keep track of the time and number of laps you complete. I will notify you of your time at 1 minute and every minute after that. Remember that the object is to walk AS FAR AS POSSIBLE, but safely for 6 minutes, but don't run or jog. Start now or whenever you are ready." If you need to walk close to the patient because of the safety reasons, walk behind him, to avoid influence his walking pace by yours. Patient should wear regular footwear and the assistive devices can be used while performing the 6MWT.

When the timer shows 4 minutes remaining, tell the patient the following: "*2 minutes have passed. You have 4 minutes to go."*

When the timer shows 3 minutes remaining, tell the patient the following: *"3 minutes have passed. You have 3 minutes to go."*

When the timer shows 2 minutes remaining, tell the patient the following: *"4 minutes have passed. You have 2 minutes to go."*

When the timer shows only 1 minute remaining, tell the patient: "*5 minutes have passed. You only have 1 minute left."*

Do not use other words of encouragement (or body language to speed up). If the patient stops walking during the test, say this: *"You are doing well. You should keep walking if you are able."* Do not stop the timer.

If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk and note on the worksheet the distance, the time stopped and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: *"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."* When time is up, say this: "*Stop!*" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped and mark the distance to the scoring sheet.

4.2.3.5 Multiple Sclerosis Walking Scale-12 (MSWS-12)

Multiple Sclerosis Walking Scale-12 (MSWS-12) is a 12-items patient-rated questionnaire evaluating the impact of MS on walking during past two weeks.

Equipment needed for the examination is 12-items MSWS-12 questionnaire and pen.

Instructions:

Patient gets the questionnaire with 12 items regarding the impact of MS on walking abilities during last two weeks. *"Please read each statement carefully and circle one of the five offered numbers that best describes state of your degree of limitation."* In case patient needs a help with marking the responses, the interviewer can help with the marking the answers according to patient response. The interviewer can explain any words or phrases that patient doesn´t understand. After completing the test, evaluator checks if the patient answered all 12 questions.

Scoring sheets for all walking measures are in Annexes 3 and 4.

4.2.4 Modified Fatigue Impact Scale (MFIS)

The Modified fatigue Impact Scale is a 21-item long questionnaire evaluating the effects of fatigue in terms of physical, cognitive, and psychosocial functioning.

Equipment needed for the examination is MFIS questionnaire and pen.

Instructions:

Patient gets the questionnaire with 21 items regarding the impact of fatigue in pwMS. *"Please read each statement carefully and circle one of the five offered numbers that best describes how often fatigue has affected you in this way during the past 4 weeks."* After completing the test, evaluator checks if the patient answered all 21 questions. In case patients need a help with marking the responses, the interviewer can help with the marking the answers according to patient responses. The interviewer can explain any words or phrases that patient doesn´t understand. In case patient is not sure which answer to select, investigator can ask him: *"Choose the one answer that comes closest to describing you."* After completing the test, evaluator checks if the patient answered all 12 questions.

Scoring sheet of the MFIS questionnaire is in Annex 5.

4.3 Motor fatigue criterion

To define motor fatigue during the 6MWT, was calculated the percentage decline by dividing the distance walked during the 6th minute by the distance walked during the 1st minute, and multiplying the result by 100. A 20% threshold decline of distance was then used as criterion to stratify subjects into a Motor Fatigued Group (decline > 20%, n = 47) and a Non Motor Fatigued Group (decline ≤ 20%, n = 161).

4.4 Statistical analyses

Descriptive statistics were used to describe the total sample and subgroups of motor fatigue. Independent variables were patient characteristics (age, gender, disease duration, BMI), disability level according EDSS subgroups ((1) EDSS = 0-2.5, (2) EDSS = 3-4, (3) EDSS = 4.5-5.5, (4) EDSS = 6, (5) EDSS > 6), walking measures (6MWT, TUG, T25FW, T10MW, MSWS-12) and MFIS. Prevalence of motor fatigue (frequency and percentage of subjects in two subgroups – with and without motor fatigue) were reported and illustrated, this according to disability level and type of MS respectively. Differences between subgroups of motor fatigue for the above mentioned variables were investigated by T-test, Mann/Whitney test and Chi-square test, as appropriate. Spearman correlations coefficients between motor fatigue groups and patient characteristics (age, gender, BMI, disease duration, type of MS and EDSS), walking measures (T25FW, T10MW, TUG, 6MWT, MSWS-12) and MFIS were calculated as well.

Distances walked during each minute of the 6MWT were evaluated by using ANOVA repeated measures and Tukey HSD Pos-Hoc test. For comparison the distances walked during first and last minute of the 6MWT for total group paired t-test was used. Data of 6MWT minute by minute (distance in each minute expressed as a percentage of 1st minute) in each subgroup was compared by using two-way repeated ANOVA with Tukey HSD Post-Hoc test. In all analyses, p-value ≤ 0.05 was considered significant.

The frequency and the percentage of the patients with and without motor fatigue within five EDSS categories were calculated and illustrated by using frequency tables. The same calculation and illustration was made combining numbers of the patients in two subgroups and type of MS.

Finally the Spearman/Pearson correlations of the 6MWT and the others walking measures (TUG, T25FW, T10MW, MSWS-12) in total group and in subgroups was calculated as appropriate.

Data were analysed with statistical software STATISTCA 8.

5 RESULTS

5.1 Total group and subgroups characteristics

Descriptive statistics results of participants characteristics in total group (n = 208) and in subgroups of motor fatigue (Non Motor Fatigued Group = 161, Motor Fatigued Group = 47) are summarized in Table 3. The units of each continuous variable (age, BMI, disease duration) are mentioned next to the variable in the brackets and the values are given in mean and standard deviation. In case of the categorical variables (gender, type of MS or EDSS 5 categories) are the groups/categories listed below each categorical variable and the values are given in frequency (numbers of the quantity) and percentage. The results of the interval variable (EDSS with the interval from 0-10) are given in median and inter-quartile range.

The average age in total group was 47.9 (SD = 10.67) years with more than half representation of the women (58.65%). The value of BMI 25.4 with the SD 5.32 tells us that the tested group was borderline normal – overweight population [Eknoyan 2008]. Mean of the disease duration was calculated for 11.32 years with 7.8 years SD. Relapsing – remitting (RR) type of disease was the most often type of MS (50.96%), followed by secondary progressive (SP – 31.73%) and primary progressive type (PP - 17.31%). EDSS IQR ranged from 3 till 6 with the median 4.5. The 5 EDSS categories with the number of the patients in percentages were following:

1) Very Mild EDSS = 0 – 2.5 (24.4%)
2) Mild EDSS = 3 – 4 (25.96%)
3) Moderate EDSS = 4.5 – 5.5 (13.46%)
4) Severe EDSS = 6 (19.71%)
5) Very severe EDSS ≥ 6.5 (16.83%)

Values for the same variables in the two subgroups are also displayed in the Table 3. For comparison of each variable within the two subgroups the p-values (by using T-test, Mann-Whitney test, Chi-square test according to distribution and type of the variable) and Pearson/Spearman correlations coefficients were calculated. We can see that the subgroups were comparable in age, gender, BMI and disease duration. On the other hand the subgroups significantly differed in type of MS distributions, EDSS (higher in Motor Fatigued Group – median = 6) and 5 EDSS categories. The lower EDSS category was the higher percentage of pwMS was in the category in Non Motor fatigued Group. The opposite relationship was found in the Motor Fatigued Group – the number of participants is increasing with the raising EDSS category (see Figure 3). Progressive types of MS are more represented in Motor Fatigued Group (see Figure 4).

5.2 Walking measures and MFIS results for total group and subgroups

Summary of the results for total group and for the subgroups are illustrated in the Table 4. The distance walked during the 6MWT showed large variability in total group (median 361.23 meters with SD 169.81 meters). The similar results were found for TUG (14.64 seconds with SD 15.57), T25FW (1.32 m/s with SD 0.56), T10MW (1.32 with SD 0.56) and MSWS-12 (median 41 with IQR 28-48). Only results of the MFIS questionnaire were not markedly scattered since the total score can range from 0 to 84 points (median 40 with IQR from 30 till 50).

Comparison of the walking measures results between the subgroups were in all performed tests significantly different (p-value < 0.001). These significant results are supported also by correlation coefficients (see the Table 4). Despite these all differences between the subgroups, results of the evaluated MFIS questionnaire did not show any difference in the scores in two subgroups (p-value = 0.53).

Table 3: Participant characteristics for total group and for subgroups

Participant Characteristics	*MS Total Group*	Motor fatigue (based on percentual change during 6MWT)			
		Non Motor Fatigued Group *<20% decline*	*Motor Fatigued Group* *>20% decline*		
	(n = 208)	*(n = 161)*	*(n = 47)*	*p - value †*	*correlation ‡*
Age (years), mean ±SD	47.9 (10.67)	47.21 (10.85)	50.23 (9.77)	0.09	0.13
Gender, n (%)				1.0	-0.05
Male	86 (41.35)	64 (39.75)	22 (46.81)		
Female	122 (58.65)	97 (60.25)	25 (53.19)		
BMI (kg/m^2), mean ± SD	25.4 (5.32)	25.11 (4.89)	26.43 (6.56)	0.24	0.09
Disease duration (years), mean ± SD	11.32 (7.8)	10.85 (7.77)	12.98 (7.63)	0.06	0.09
Type of MS, n (%)				0.00*	0.24*
RR	106 (50.96)	92 (57.14)	14 (29.79)		
SP	66 (31.73)	49 (30.43)	17 (36.17)		
PP	36 (17.31)	20 (12.43)	16 (34.04)		
EDSS (0-10), median (IQR)	4.25 (3-6)	4 (2.5-6)	6 (5-6.5)	0.00*	0.39*
EDSS 5 categories, n (%)				0.00*	0.39*
(1) EDSS 0-2,5	50 (24.4)	48 (29.81)	2 (4.26)		
(2) EDSS 3-4	54 (25.96)	49 (30.44)	5 (10.64)		
(3) EDSS 4,5-5,5	28 (13.46)	19 (11.80)	9 (19.15)		
(4) EDSS 6	41 (19.71)	26 (16.15)	15 (31.91)		
(5) EDSS >= 6,5	35 (16.83)	19 (11.80)	16 (34.04)		

† T- test, Mann-Whitney test and Chi-square test as appropriated
‡ Correlation coefficients between motor fatigue subgroups and variables
* Significant results

Table 4: Results of walking measures and MFIS questionnaire in total group and in subgroups of motor fatigue

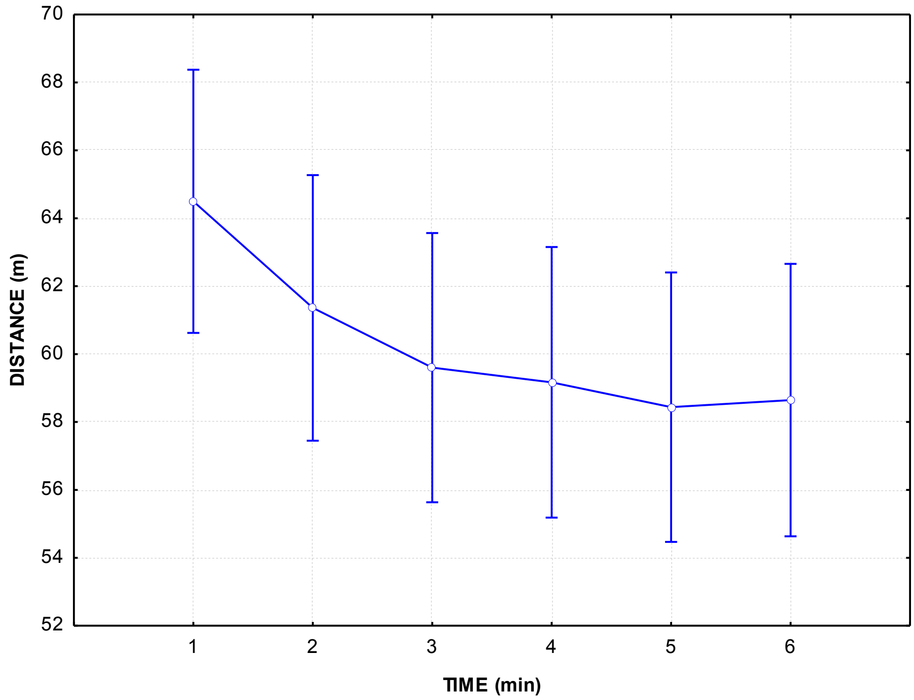
Walking measures and MFIS	*MS Total Group*	Motor fatigue (based on percentual change during 6MWT)			
		Non Motor Fatigued Group *<20% decline*	*Motor Fatigued Group* *>20% decline*		
	(n = 208)	*(n = 161)*	*(n = 47)*	*p - value* †	*correlation* ‡
6MWT (m), mean ±SD	361.23 (169.81)	407.61 (153.55)	202.36 (120.18)	0.00*	-0.53*
TUG (sec.), mean ±SD	14.64 (15.57)	12.5 (13.73)	22.03 (19.11)	0.00*	0.40*
T25FW - fast speed (m/s), mean ±SD	1.20 (0.53)	1.32 (0.50)	0.80 (0.40)	0.00*	-0.44*
T10MW - usual speed (m/s), mean ±SD	1.32 (0.56)	1.44 (0.53)	0.89 (0.45)	0.00*	-0.44*
MSWS-12 total score, median (IQR)	41 (28-48)	36 (27-46)	48 (42-54)	0.00*	0.35*
MFIS total score, median (IQR)	40 (30-50)	41 (29-50)	39 (31-48)	0.53	0.05

† T- test, Mann-Whitney test and Chi-square test as appropriated
‡ Correlation coefficients between motor fatigue subgroups and variables
* Significant results

5.3 Pacing pattern during 6MWT in total group and in subgroups

The pattern of walking pace during the 6MWT for the total sample is presented in Figure 1. As you can see from the graph, the longest distance was walked during the 1st minute of 6MWT, followed by pronounced decline in walking speed (distance/minute) during the 2nd and 3rd minute and ended by shortest distances walked during the 5th and 6th minute. Therefore the 20% decline between 1st and 6th minute was chosen as a criterion of the motor fatigue.

Figure 1: Results of 6MWT minute by minute for total group



For the more detailed analysis of the distances during each minute the Tukey HSD Post-Hoc test was calculated (Table 5). From the results we can conclude that the pacing strategy of pwMS has tendency to mainly decline during the first 3 minutes of the test. Last 3 minutes of the 6MWT did not significantly differed from each other, but from the values of the distances we can see that decline in walking speed continued. Except the last minute of the test, where a small speeding up occurred.

Table 5: Tukey HSD Post-Hoc test for each minute of 6MWT for total group

Distance per minute	1st min. (64.5m)	2nd min. (61.4m)	3rd min. (59.6m)	4th min. (59.2m)	5th min. (58.4m)	6th min. (58.6m)
1st min. (64.5m)		0.00*	0.00*	0.00*	0.00*	0.00*
2nd min. (61.4m)	0.00*		0.04*	0.00*	0.00*	0.00*
3rd min. (59.6m)	0.00*	0.04*		0.98	0.36	0.59
4th min. (59.2m)	0.00*	0.00*	0.98		0.82	0.95
5th min. (58.4m)	0.00*	0.00*	0.36	0.82		1.00
6th min. (58.6m)	0.00*	0.00*	0.59	0.95	1.00	

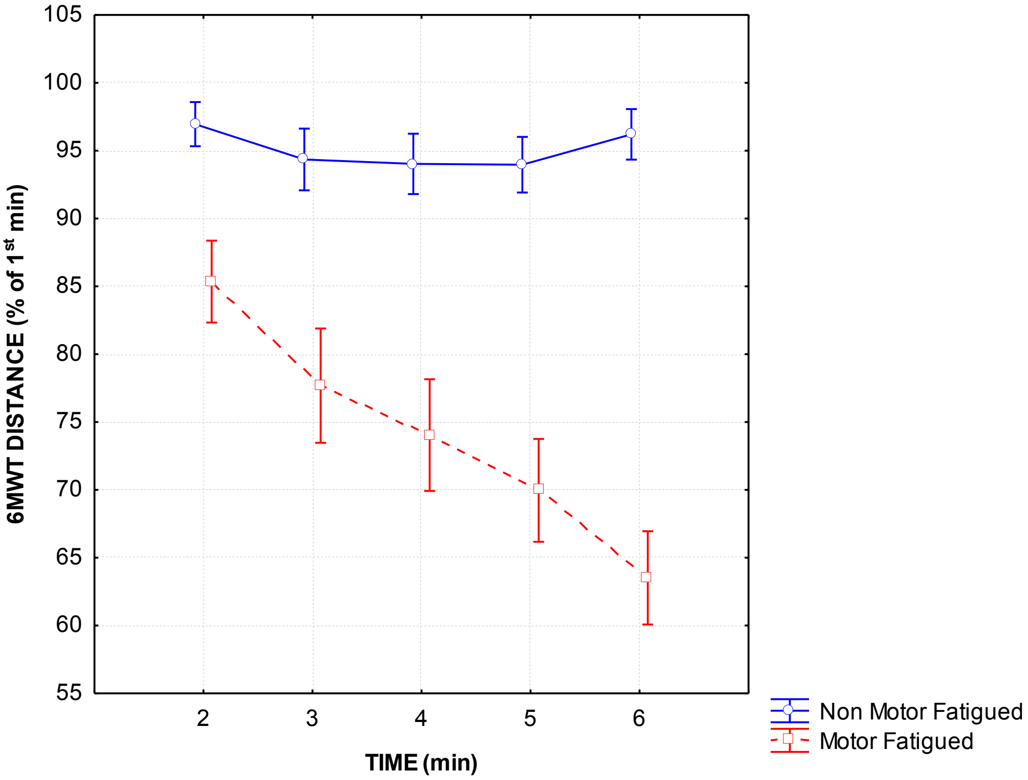
* Significant results

According the results of the 6MWT for the total group the first minute of the test served as a 100% (the longest distance walked during the test) for the calculation of the percentual decline in the rest of the minutes. Each minute distance as a percentage of the 1st minute in two subgroups is displayed in the Figure 2. The previously mentioned results of the walking measures, specifically the results of total distance during the 6MWT varied between the groups with and without motor fatigue (since longer distance was walked by patients in Non Motor Fatigued Group – see Figure 2). Minute by minute comparison was needed to get to know more about the walking pattern during the test in each group.

As we can see in the Figure 2, the percentage of distance walked in each minute significantly differed between the subgroups. Patients allocated in the Non Motor Fatigue Group walked approximately 94 – 97% distance of the 1st minute. The comparison within the minutes by using Tukey Posh-Hoc test did not show significant differences. Despite this fact we can observe in this subgroup tendency of slowing down in the first three minutes followed by constant distance walked from third to fifth minute and ended by speeding up during the last minute of the test. But as it was already mentioned the minute by minute comparison in this group was not significantly different.

In the Motor Fatigue Group we can find another result. First of all the total distance was significantly lower than in Non Motor Fatigued Group (202.36 meters – see the Table 4). The significant differences were found between all minutes beyond 3-4 and 4-5 minutes combinations. Distinctive attribute of the walking pattern in this group is continuous slowing down accentuated in the beginning and at the end of the 6MWT (between 1-2 and 5-6 minutes).

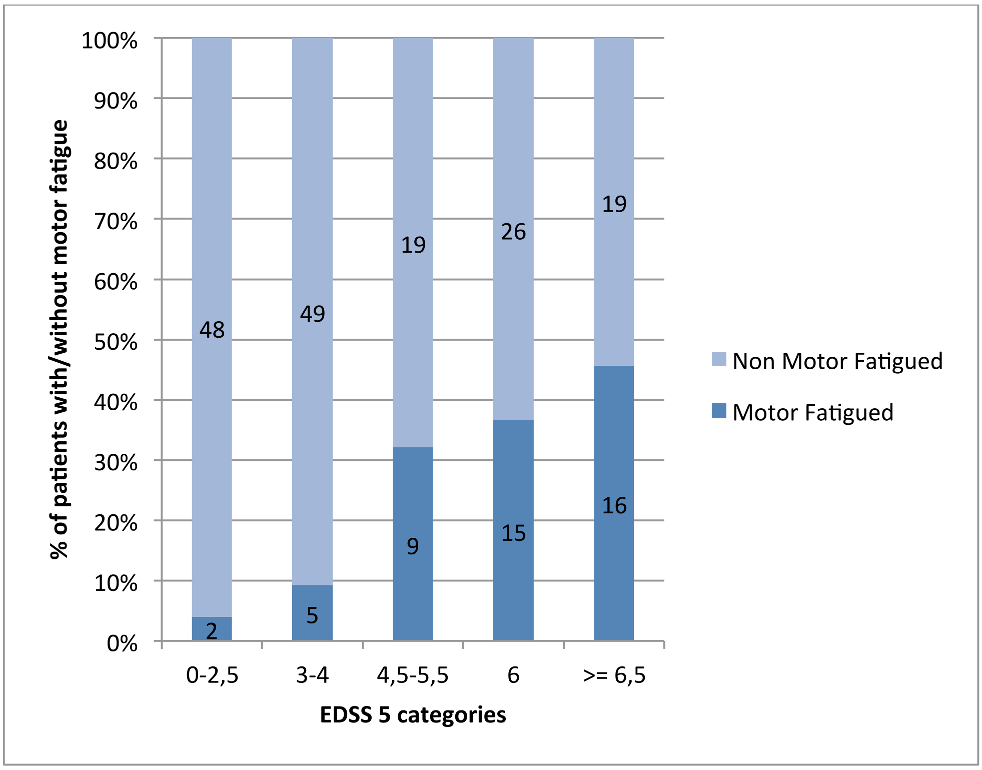
Figure 2: Distance during 6MWT as a percentage of 1st minute in two subgroups



5.4 Prevalence of motor fatigue

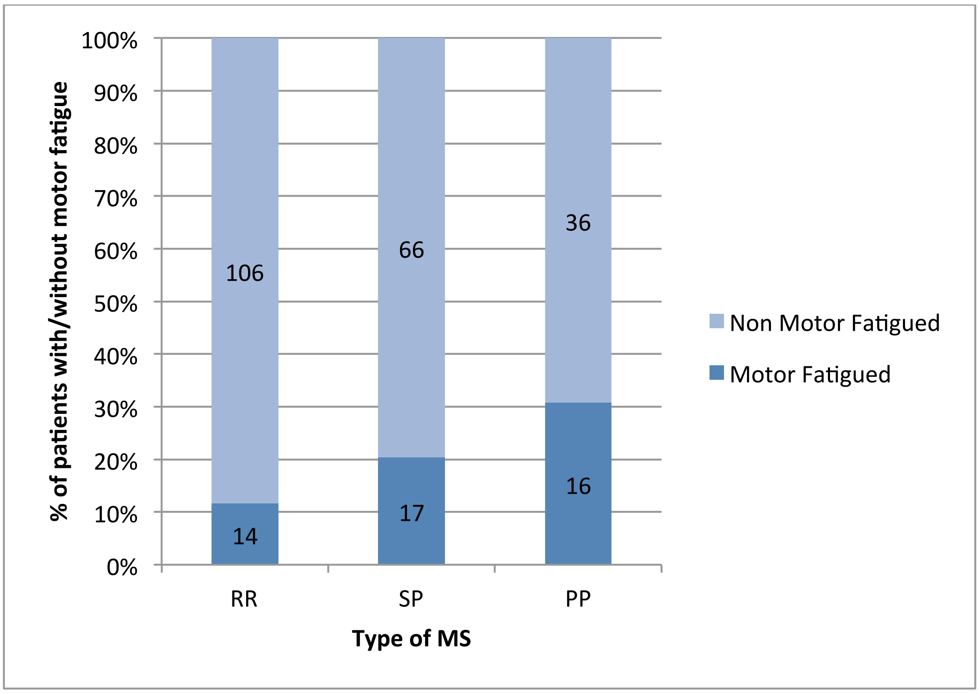
As is displayed in the Figure 3 and 4 – the EDSS and type of MS significantly differed between the groups with and without motor fatigue. These findings indicates that the motor fatigue is associated to disability level (EDSS) and type of MS. Figure 3 illustrates that the prevalence of motor fatigue is significantly increasing already from EDSS 4.5 (EDSS 0-2.5, 4%; EDSS 3-4, 9.3%; EDSS 4.5-5.5, 32.1%; EDSS 6, 36.6%; EDSS > 6, 45.7%; $p < 0.01$). In the Non Motor Fatigued group is on the contrary decreasing percentage of probability of motor fatigue with increasing disability level (EDSS 0-2.5, 96%; EDSS 3-4, 90.7%; EDSS 4.5-5.5, 67.9%; EDSS 6, 63.4%; EDSS > 6, 54.3%; $p < 0.01$).

Figure 3: Percentage and frequency of patients with and without motor fatigue in 5 EDSS categories



Regarding the type of MS and occurrence of the motor fatigue is the main finding that in the progressive type of MS is the prevalence of the motor fatigue higher than in relapsing remitting type (PP 30.8%, SP 20.5%, RR 10.8%; $p < 0.01$), (see Figure 4). When we look to the percentages of the occurrence of motor fatigue in each type of MS, we can see that the highest prevalence is in primary progressive type – 30.8%. That means that approximately every third patient with PP type of MS have chance to be motor fatigued. In the other types of MS is the probability of having motor fatigue much lower. In the secondary progressive type it is every fifth patient and in the relapsing remitting type only every tenth patient.

Figure 4: Percentage and frequency of patients with and without motor fatigue according Type of MS



5.5 Characteristics of the Motor Fatigued subgroup

All person characteristics such as age, gender, Body Mass Index (BMI) and disease duration were comparable between the subgroups. The correlation coefficients between the subgroups and the walking measures (6MWT = -0.53, T25FW = -0.44, T10MW = -0.40, TUG = 0.40, MSWS-12 = 0.35), EDSS (EDSS = 0.39, EDSS 5 categories = 0.39) and type of MS (type of MS = 0.24) were all significant ($p < 0.01$), (see Figure 1). Only the results of MFIS questionnaire did not correlate and did not show the significant difference between the subgroups (MFIS = 0.05, $p = 0.53$).

In the Table 6 are the correlation coefficients of the 6MWT and walking measures in total group and in the subgroups. All the combinations in all groups were significant (with p-value < 0.05). The strongest correlations were found between the 6MWT and T25WT (for total group and Non Motor Fatigued Group = 0.95, for Motor Fatigued Group = 0.93) and T10MW (for total group and Non Motor Fatigued Group = 0.95, for Motor Fatigued Group = 0.94). The greatest differences in correlations were in

6MWT and TUG. Were the strongest correlation was in Motor Fatigued Group = -0.92, followed by total group = -0.90 and Non Motor Fatigue Group = -0.85. MSWS-12 questionnaire showed the weakest link to the 6MWT, but still significant (total group = -0.73, Non Moto Fatigued Group = -0.68, Motor Fatigued Group = -0.70).

Table 6: Correlations of the walking measures for total group and for the subgroups

	MS Total Group (n=208)	*Non Motor Fatigued Group <20% decline (n = 161)*	*Motor Fatigued Group >20% decline (n = 47)*
Variables	*correlation ‡*	*correlation ‡*	*correlation ‡*
6MWT/T25FW	0.95*	0.95*	0.93*
6MWT/T10MW	0.95*	0.95*	0.94*
6MWT/TUG	-0.90*	-0.85*	-0.92*
6MWT/MSWS-12	-0.73*	-0.68*	-0.70*

‡ Spearman/Pearson correlations as appropriate
* Significant results with p-value < 0.05

6 DISCUSSION

The aim of this study was to detect the motor fatigue in pwMS and find its influencing factors. The 6MWT have been chosen to examine the motor fatigue in pwMS. The test measures walking endurance and reflects the best habitual walking performance [Gijbels *et al.* 2010]. According to the results of the 6MWT the two subgroups with and without motor fatigue were created (the criterion of the motor fatigue will be explained in detail later) and influencing factors were examined. Age, gender, BMI and disease duration were comparable in subgroups, but we can find the significant differences in EDSS and type of MS within the subgroups. The prevalence of being motor fatigued significantly raises with raising EDSS level already from EDSS 4.5. The similar results were found also in the previous studies [Burschka *et al.* 2012, Dalgas *et al.* 2014, Gijbels *et al.* 2010, Goldman *et al.* 2008, Motl and Snook 2008, Phan-Ba *et al.* 2012]. Another influencing factor is type of MS. In progressive MS is prevalence of having motor fatigue higher in comparison with RR type (similar results were in the study Dalgas *et al.* [2014]). This fact is probably due to lower level of neuroplasticity in progressive types of MS [Hampton *et al.* 2013].

The subjective evaluation of walking abilities and overall fatigue impact on daily life evaluated by MSWS-12 and MFIS questionnaires showed different results in comparison within the subgroups. The total scores of the MSWS-12 showed significant differences between the subgroups and also the correlations were significant. Total scores of the MFIS questionnaire did not significantly varied within the subgroups. According to these results we can assume that the use of MSWS-12 is more appropriate in relation to occurrence of motor fatigue in pwMS (similar comparison was made in the study of Goldman *et al.* [2008]).

6.1 Pacing strategy during 6MWT in Motor Fatigued and Non Motor Fatigued Group

As it is seen from the results, the pacing strategies between the groups with and without motor fatigue were different. While the Non Motor Fatigued Group patients showed tendency walk the same distance during entire test, in the second subgroup where were allocated patients with motor fatigue were participants significantly slowing down and walked significantly shorter distances. The similar results were published by

Burschka *et al.* [2012], only with the difference that the patients were stratified to two subgroups according to their disability level (continuous slowing down at the group of patients with EDSS = 4-5). Another study of Dalgas *et al.* [2014] and Phan-Ba *et al.* [2012] confirmed the continuous slowing during whole test in more disabled group of pwMS (EDSS = 4-6.5).

6.2 20% threshold justification

As a criterion of the motor fatigue the 20% decline between 1st and last minute of the 6MWT was used. The decision of selection of 20% threshold was based on the clinical meaningful change, where the change of 20% is often interpreted by clinicians and researchers as being clinically significant [Bosma *et al.* 2009, J. Hobart *et al.* 2013, Schwid *et al.* 1999].

The significant differences in all walking measures and the subgroups imply that the selected cut-off criterion of 20% decline of distance between first and last minute of 6MWT is an applicable threshold of motor fatigue.

Another comparison for justification of the selected 20% decline criterion was calculated – correlation between the 6MWT and the walking measures in two subgroups. All results were significant, that means that the stratification of the patients to the Motor and Non Motor Fatigued Group according to the chosen criterion of the 20% decline between the 6th and 1st minute of the 6MWT was appropriate.

6.3 Other influencing factors of motor fatigue

The disease duration, BMI, age, gender, level of disability, type of MS was considered and examine as the influencing factor of the motor fatigue in pwMS. There are still other influencing factors of the motor fatigue that need further exploration. Some of them were already described in the literature – for example heart rate during the 6MWT as an indicator of the physical fitness [Dalgas *et al.* 2014], depression (evaluated by Hospital Anxiety and Depression Scale – HADS-D), fatigue (evaluated by Fatigue Severity Scale - FSS) or pain (evaluated by McGill Pain Questionnaire – SF-MPQ) [Motl *et al.* 2013]. By authors Dalgas *et al.* [2014] was also reported no influence of the time of the day on performance during 6MWT. Experimental measurements of the lower extremities repetitive muscle contractions influence the walking capacity can be used to quantify the changes in motor functions [Broekmans *et al.* 2013, Dobkin 2008, Schwid *et al.* 1999, Surakka *et al.* 2004]. Evaluation of the spatio-temporal gait parameters with the GAITRite carpet was tested as well [Feys *et al.* 2013, Pilutti *et al.* 2013]. Pulmonary function and respiratory muscle strength also distinctly influence the functional exercise capacity (tested by the 6MWT) [Bosnak-Guclu *et al.* 2012, Savci *et al.* 2005].

There are still some influencing factors such as level of confidence during walking, motivation, balance, spasticity, VO_2 max. consumption which were not yet investigated and which can interfere the motor fatigue. Further research taking into account all above mentioned influencing factors still need to be done to get more complex view about the motor fatigue in MS problematic.

6.4 Clinical use

Working as a clinician is needed to keep in mind that the motor fatigue can occurs in every fourth pwMS. Be on the alert also when working with the patient with progressive type of MS or with moderately to severe impaired patient. Then the 6MWT can serve as an appropriate walking endurance measure to quantify the motor fatigue and control it during the time.

The question is how to deal with the motor fatigue and how can patients with MS eliminate it? The answer can be found in the studies dealing with endurance improving interventions. Recent findings report the improvement of the walking endurance after variable rehabilitation methods such as: treadmill walking training, repetitive gait training, endurance exercise and isometric strength exercise, robot assisted gait training or even practicing of yoga had positive influence on the walking endurance tested by 6MWT [Ahmadi *et al.* 2013, Broekmans *et al.* 2013, Dettmers *et al.* 2009, Lo and Triche 2008, Romberg *et al.* 2004, Straudi *et al.* 2013].

7 CONCLUSION

Only one quarter of the pwMS showed motor fatigue during 6MWT according to our 20% decline criterion. Prevalence of the motor fatigue is associated with increasing disability level (significant increase already from EDSS ≥ 4.5) and with type of MS, (where higher prevalence is in the progressive types). The hypothesis that the Motor fatigue will depend on the disease duration was not confirmed.

Results of all walking measures significantly varied between subgroups no matter if it was short (T25WT, T10MW, TUG), long (6MWT) walking tests or questionnaire (MSWS-12).

Different walking pattern occurred between the subgroups. Non Motor Fatigued Group walked constant distance every minute of the 6MWT without any sign of the motor fatigue. On the other hand the patients allocated to the Motor Fatigued Group were slowing down during entire test.

The MSWS-12 questionnaire evaluating individual walking ability is more appropriate to detect the motor fatigue than the MFIS questionnaire. Further the criterion of 20% decline between 6^{th} and 1^{st} minute during 6MWT is according to the results of other walking measures in subgroups appropriate test to detect the pwMS with the motor fatigue.

Finally as it was mentioned in discussion part the motor fatigue is influenced by multiple factors. Beside the level of disability and type of MS we have to consider also level of physical fitness of the patient, muscle strength/weakness, general fatigue, pain, balance, depression, confidence during walking and motivation.

LITERATURE

AHMADI, A., ARASTOO, A. A., NIKBAKHT, M., ZAHEDNEJAD, S. and RAJABPOUR, M. Comparison of the Effect of 8 weeks Aerobic and Yoga Training on Ambulatory Function, Fatigue and Mood Status in MS Patients. *Iranian Red Crescent medical journal* 15, 6 (Jun 2013), 449-454.

AMTMANN, D., BAMER, A. M., NOONAN, V., LANG, N., KIM, J. and COOK, K. F. Comparison of the psychometric properties of two fatigue scales in multiple sclerosis. *Rehabilitation psychology* 57, 2 (May 2012), 159-166.

ARMSTRONG, L. E., WINANT, D. M., SWASEY, P. R., SEIDLE, M. E., CARTER, A. L. and GEHLSEN, G. Using isokinetic dynamometry to test ambulatory patients with multiple sclerosis. *Physical therapy* 63, 8 (Aug 1983), 1274-1279.

BAERT, I., FREEMAN, J., SMEDAL, T., DALGAS, U., ROMBERG, A., KALRON, A., CONYERS, H., ELORRIAGA, I., GEBARA, B., GUMSE, J., HERIC, A., JENSEN, E., JONES, K., KNUTS, K., MAERTENS DE NOORDHOUT, B., MARTIC, A., NORMANN, B., EIJNDE, B. O., RASOVA, K., SANTOYO MEDINA, C., TRUYENS, V., WENS, I. and FEYS, P. Responsiveness and Clinically Meaningful Improvement, According to Disability Level, of Five Walking Measures After Rehabilitation in Multiple Sclerosis: A European Multicenter Study. *Neurorehabilitation and neural repair* (Feb 6 2014).

BALCER, L. J. Clinical outcome measures for research in multiple sclerosis. *J Neuroophthalmol* 21, 4 (December 2001), 296-301.

BELACHEW, S. C., P. DELVAUX, V. The timed 100-meter walk test: an easy-to-use sensitive tool to detect and evaluate restricted walking capacities in multiple sclerosis. . *Neurology* (2009), 242-243.

BETHOUX, F. and BENNETT, S. Evaluating walking in patients with multiple sclerosis: which assessment tools are useful in clinical practice? *International journal of MS care* 13, 1 (Spring 2011), 4-14.

BOSMA, L. V., KRAGT, J. J., BRIEVA, L., KHALEELI, Z., MONTALBAN, X., POLMAN, C. H., THOMPSON, A. J., TINTORE, M. and UITDEHAAG, B. M. The search for responsive clinical endpoints in primary progressive multiple sclerosis. *Multiple sclerosis* 15, 6 (Jun 2009), 715-720.

BOSNAK-GUCLU, M., GUNDUZ, A. G., NAZLIEL, B. and IRKEC, C. Comparison of functional exercise capacity, pulmonary function and respiratory muscle strength in patients with multiple sclerosis with different disability levels and healthy controls. *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine* 44, 1 (Jan 2012), 80-86.

BROEKMANS, T., GIJBELS, D., EIJNDE, B. O., ALDERS, G., LAMERS, I., ROELANTS, M. and FEYS, P. The relationship between upper leg muscle strength and walking capacity in persons with multiple sclerosis. *Multiple sclerosis* 19, 1 (Jan 2013), 112-119.

BURSCHKA, J. M., KEUNE, P. M., MENGE, U., HOFSTADT-VAN OY, U., OSCHMANN, P. and HOOS, O. An exploration of impaired walking dynamics and fatigue in multiple sclerosis. *BMC neurology* 12 (2012), 161.

BUTLAND, R. J., PANG, J., GROSS, E. R., WOODCOCK, A. A. and GEDDES, D. M. Two-, six-, and 12-minute walking tests in respiratory disease. *British medical journal (Clinical research ed.)* 284, 6329 (May 29 1982), 1607-1608.

CLEARY, M. A., HETZLER, R. K., WAGES, J. J., LENTZ, M. A., STICKLEY, C. D. and KIMURA, I. F. Comparisons of age-predicted maximum heart rate equations in college-aged subjects. *Journal of strength and conditioning research / National Strength & Conditioning Association* 25, 9 (Sep 2011), 2591-2597.

COLLEN, F. M., WADE, D. T. and BRADSHAW, C. M. Mobility after stroke: reliability of measures of impairment and disability. *International disability studies* 12, 1 (Jan-Mar 1990), 6-9.

COLLIN, C. and WADE, D. Assessing motor impairment after stroke: a pilot reliability study. *Journal of neurology, neurosurgery, and psychiatry* 53, 7 (Jul 1990), 576-579.

COOPER, K. H. A means of assessing maximal oxygen intake. Correlation between field and treadmill testing. *JAMA : the journal of the American Medical Association* 203, 3 (Jan 15 1968), 201-204.

DALGAS, U., KJOLHEDE, T., GIJBELS, D., ROMBERG, A., SANTOYO, C., DE NOORDHOUT, B. M., KNUTS, K. and FEYS, P. Aerobic intensity and pacing pattern during the Six-Minute Walk test in patients with multiple sclerosis. *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine* 46, 1 (Jan 2014), 59-66.

DETTMERS, C., SULZMANN, M., RUCHAY-PLOSSL, A., GUTLER, R. and VIETEN, M. Endurance exercise improves walking distance in MS patients with fatigue. *Acta neurologica Scandinavica* 120, 4 (Oct 2009), 251-257.

DOBKIN, B. H. Fatigue versus activity-dependent fatigability in patients with central or peripheral motor impairments. *Neurorehabilitation and neural repair* 22, 2 (Mar-Apr 2008), 105-110.

EDWARDS, R. H., HILL, D. K., JONES, D. A. and MERTON, P. A. Fatigue of long duration in human skeletal muscle after exercise. *The Journal of physiology* 272, 3 (Nov 1977), 769-778.

EKNOYAN, G. Adolphe Quetelet (1796-1874)--the average man and indices of obesity. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 23, 1 (Jan 2008), 47-51.

ENRIGHT, P. L. The Six-Minute Walk test. *Respiratory care* 48, 8 (Aug 2003), 783-785.

FEYS, P., SEVERIJNS, D., VANTENDERLOO, S., KNUTS, K., HANNES, D., GIJBELS, D. and WENS, I. Spatio-temporal gait parameters change differently according to speed instructions and walking history in MS patients with different ambulatory dysfunction. *Multiple Sclerosis and Related Disorders* 2, 3 (2013), 238-246.

FEYS, P., BIBBY, B., ROMBERG, A., SANTOYO, C., GEBARA, B., DE NOORDHOUT, B. M., KNUTS, K., BETHOUX, F., SKJERBAEK, A., JENSEN, E., BAERT, I., VANEY, C., DE GROOT, V. and DALGAS, U. Within-day variability on short and long walking tests in persons with multiple sclerosis. *Journal of the neurological sciences* (Jan 9 2014).

FISCHER, J. S., RUDICK, R. A., CUTTER, G. R. and REINGOLD, S. C. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Multiple sclerosis* 5, 4 (Aug 1999), 244-250.

FISCHER, J. S., LAROCCA, N. G., MILLER, D. M., RITVO, P. G., ANDREWS, H. and PATY, D. Recent developments in the assessment of quality of life in multiple sclerosis (MS). *Multiple sclerosis* 5, 4 (Aug 1999), 251-259.

FISK, J. D., RITVO, P. G., ROSS, L., HAASE, D. A., MARRIE, T. J. and SCHLECH, W. F. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 18 Suppl 1 (Jan 1994), S79-83.

GIJBELS, D., ALDERS, G., VAN HOOF, E., CHARLIER, C., ROELANTS, M., BROEKMANS, T., EIJNDE, B. O. and FEYS, P. Predicting habitual walking performance in multiple sclerosis: relevance of capacity and self-report measures. *Multiple sclerosis* 16, 5 (May 2010), 618-626.

GIJBELS, D., EIJNDE, B. O. and FEYS, P. Comparison of the 2- and 6-minute walk test in multiple sclerosis. *Multiple sclerosis* 17, 10 (Oct 2011), 1269-1272.

GIJBELS, D., DALGAS, U., ROMBERG, A., DE GROOT, V., BETHOUX, F., VANEY, C., GEBARA, B., MEDINA, C. S., MAAMAGI, H., RASOVA, K., DE NOORDHOUT, B. M., KNUTS, K. and FEYS, P. Which walking capacity tests to use in multiple sclerosis? A multicentre study providing the basis for a core set. *Multiple sclerosis* 18, 3 (Mar 2012), 364-371.

GIVON, U., ZEILIG, G. and ACHIRON, A. Gait analysis in multiple sclerosis: characterization of temporal-spatial parameters using GAITRite functional ambulation system. *Gait & posture* 29, 1 (Jan 2009), 138-142.

GOLDMAN, M. D., MARRIE, R. A. and COHEN, J. A. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. *Multiple sclerosis* 14, 3 (Apr 2008), 383-390.

GOODKIN, D. E., COOKFAIR, D., WENDE, K., BOURDETTE, D., PULLICINO, P., SCHEROKMAN, B. and WHITHAM, R. Inter- and intrarater scoring agreement using grades 1.0 to 3.5 of the Kurtzke Expanded Disability Status Scale (EDSS). Multiple Sclerosis Collaborative Research Group. *Neurology* 42, 4 (Apr 1992), 859-863.

HAMPTON, D. W., SERIO, A., PRYCE, G., AL-IZKI, S., FRANKLIN, R. J., GIOVANNONI, G., BAKER, D. and CHANDRAN, S. Neurodegeneration progresses despite complete elimination of clinical relapses in a mouse model of multiple sclerosis. *Acta neuropathologica communications* 1, 1 (2013), 84.

HAUSER, S. L., DAWSON, D. M., LEHRICH, J. R., BEAL, M. F., KEVY, S. V., PROPPER, R. D., MILLS, J. A. and WEINER, H. L. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. *The New England journal of medicine* 308, 4 (Jan 27 1983), 173-180.

HEESEN, C., BOHM, J., REICH, C., KASPER, J., GOEBEL, M. and GOLD, S. M. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. *Multiple sclerosis* 14, 7 (Aug 2008), 988-991.

HOBART, J., BLIGHT, A. R., GOODMAN, A., LYNN, F. and PUTZKI, N. Timed 25 Foot Walk: direct evidence that improving 20% or greater is clinically meaningful in MS. *Neurology* 80, 16 (Apr 16 2013), 1509-1517.

HOBART, J. C., RIAZI, A., LAMPING, D. L., FITZPATRICK, R. and THOMPSON, A. J. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology* 60, 1 (Jan 14 2003), 31-36.

HOLLAND, A., O'CONNOR, R. J., THOMPSON, A. J., PLAYFORD, E. D. and HOBART, J. C. Talking the talk on walking the walk: a 12-item generic walking scale suitable for neurological conditions? *Journal of neurology* 253, 12 (Dec 2006), 1594-1602.

KIESEIER, B. C. and POZZILLI, C. Assessing walking disability in multiple sclerosis. *Multiple sclerosis* 18, 7 (Jul 2012), 914-924.

KOS, D., KERCKHOFS, E., CARREA, I., VERZA, R., RAMOS, M. and JANSA, J. Evaluation of the Modified Fatigue Impact Scale in four different European countries. *Multiple sclerosis* 11, 1 (Feb 2005), 76-80.

KOSAK, M. and SMITH, T. Comparison of the 2-, 6-, and 12-minute walk tests in patients with stroke. *Journal of rehabilitation research and development* 42, 1 (Jan-Feb 2005), 103-107.

KRUPP, L. B., ALVAREZ, L. A., LAROCCA, N. G. and SCHEINBERG, L. C. FAtigue in multiple sclerosis. *Archives of neurology* 45, 4 (1988), 435-437.

KURTZKE, J. F. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 33, 11 (Nov 1983), 1444-1452.

LEARMONTH, Y. C., DLUGONSKI, D. D., PILUTTI, L. A., SANDROFF, B. M. and MOTL, R. W. The reliability, precision and clinically meaningful change of walking assessments in multiple sclerosis. *Multiple sclerosis* 19, 13 (Nov 2013), 1784-1791.

LEARMONTH, Y. C., MOTL, R. W., SANDROFF, B. M., PULA, J. H. and CADAVID, D. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. *BMC neurology* 13, 1 (Apr 25 2013), 37.

LO, A. C. and TRICHE, E. W. Improving gait in multiple sclerosis using robot-assisted, body weight supported treadmill training. *Neurorehabilitation and neural repair* 22, 6 (Nov-Dec 2008), 661-671.

MATHIS, J. and HESS, C. W. Sleepiness and vigilance tests. *Swiss medical weekly* 139, 15-16 (Apr 18 2009), 214-219.

MCGAVIN, C. R., GUPTA, S. P. and MCHARDY, G. J. Twelve-minute walking test for assessing disability in chronic bronchitis. *British medical journal* 1, 6013 (Apr 3 1976), 822-823.

MCGUIGAN, C. and HUTCHINSON, M. Confirming the validity and responsiveness of the Multiple Sclerosis Walking Scale-12 (MSWS-12). *Neurology* 62, 11 (Jun 8 2004), 2103-2105.

MOTL, R. W. and SNOOK, E. M. Confirmation and extension of the validity of the Multiple Sclerosis Walking Scale-12 (MSWS-12). *Journal of the neurological sciences* 268, 1-2 (May 15 2008), 69-73.

MOTL, R. W., SUH, Y., BALANTRAPU, S., SANDROFF, B. M., SOSNOFF, J. J., PULA, J., GOLDMAN, M. D. and FERNHALL, B. Evidence for the different physiological significance of the 6- and 2-minute walk tests in multiple sclerosis. *BMC neurology* 12 (2012), 6.

MOTL, R. W., BALANTRAPU, S., PILUTTI, L., DLUGONSKI, D., SUH, Y., SANDROFF, B. M., LANE, A. and FERNHALL, B. Symptomatic correlates of six-minute walk performance in persons with multiple sclerosis. *European journal of physical and rehabilitation medicine* 49, 1 (Feb 2013), 59-66.

NILSAGARD, Y., LUNDHOLM, C., GUNNARSSON, L. G. and DCNISON, E. Clinical relevance using timed walk tests and 'timed up and go' testing in persons with multiple sclerosis. *Physiotherapy research international : the journal for researchers and clinicians in physical therapy* 12, 2 (Jun 2007), 105-114.

NOSEWORTHY, J. H., VANDERVOORT, M. K., WONG, C. J. and EBERS, G. C. Interrater variability with the Expanded Disability Status Scale (EDSS) and Functional Systems (FS) in a multiple sclerosis clinical trial. The Canadian Cooperation MS Study Group. *Neurology* 40, 6 (Jun 1990), 971-975.

PALTAMAA, J., SARASOJA, T., LESKINEN, E., WIKSTROM, J. and MALKIA, E. Measures of physical functioning predict self-reported performance in self-care, mobility, and domestic life in ambulatory persons with multiple sclerosis. *Archives of physical medicine and rehabilitation* 88, 12 (Dec 2007), 1649-1657.

PENNER, I. K., RASELLI, C., STOCKLIN, M., OPWIS, K., KAPPOS, L. and CALABRESE, P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Multiple sclerosis* 15, 12 (Dec 2009), 1509-1517.

PHAN-BA, R., CALAY, P., GRODENT, P., DELRUE, G., LOMMERS, E., DELVAUX, V., MOONEN, G. and BELACHEW, S. Motor fatigue measurement by distance-induced slow down of walking speed in multiple sclerosis. *PloS one* 7, 4 (2012), e34744.

PILUTTI, L. A., DLUGONSKI, D., SANDROFF, B. M., SUH, Y., PULA, J. H., SOSNOFF, J. J. and MOTL, R. W. Further validation of multiple sclerosis walking scale-12 scores based on spatiotemporal gait parameters. *Archives of physical medicine and rehabilitation* 94, 3 (Mar 2013), 575-578.

PILUTTI, L. A., DLUGONSKI, D., SANDROFF, B. M., SUH, Y., PULA, J. H., SOSNOFF, J. J. and MOTL, R. W. Gait and six-minute walk performance in persons with multiple sclerosis. *Journal of the neurological sciences* 334, 1-2 (Nov 15 2013), 72-76.

PODSIADLO, D. and RICHARDSON, S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society* 39, 2 (Feb 1991), 142-148.

PUGLIATTI, M., ROSATI, G., CARTON, H., RIISE, T., DRULOVIC, J., VECSEI, L. and MILANOV, I. The epidemiology of multiple sclerosis in Europe. *European journal of neurology : the official journal of the European Federation of Neurological Societies* 13, 7 (Jul 2006), 700-722.

RASOVA, K., MARTINKOVA, P., VYSKOTOVA, J. and SEDOVA, M. Assessment set for evaluation of clinical outcomes in multiple sclerosis: psychometric properties. *Patient related outcome measures* 3 (2012), 59-70.

REMELIUS, J. G., JONES, S. L., HOUSE, J. D., BUSA, M. A., AVERILL, J. L., SUGUMARAN, K., KENT-BRAUN, J. A. and VAN EMMERIK, R. E. Gait impairments in persons with multiple sclerosis across preferred and fixed walking speeds. *Archives of physical medicine and rehabilitation* 93, 9 (Sep 2012), 1637-1642.

RIETBERG, M. B., VAN WEGEN, E. E. and KWAKKEL, G. Measuring fatigue in patients with multiple sclerosis: reproducibility, responsiveness and concurrent validity of three Dutch self-report questionnaires. *Disability and rehabilitation* 32, 22 (2010), 1870-1876.

ROMBERG, A., VIRTANEN, A., RUUTIAINEN, J., AUNOLA, S., KARPPI, S. L., VAARA, M., SURAKKA, J., POHJOLAINEN, T. and SEPPANEN, A. Effects of a 6-month exercise program on patients with multiple sclerosis: a randomized study. *Neurology* 63, 11 (Dec 14 2004), 2034-2038.

RUDICK, R., ANTEL, J., CONFAVREUX, C., CUTTER, G., ELLISON, G., FISCHER, J., LUBLIN, F., MILLER, A., PETKAU, J., RAO, S., REINGOLD, S., SYNDULKO, K., THOMPSON, A., WALLENBERG, J., WEINSHENKER, B. and WILLOUGHBY, E. Clinical outcomes assessment in multiple sclerosis. *Annals of neurology* 40, 3 (Sep 1996), 469-479.

SAVCI, S., INAL-INCE, D., ARIKAN, H., GUCLU-GUNDUZ, A., CETISLI-KORKMAZ, N., ARMUTLU, K. and KARABUDAK, R. Six-minute walk distance as a measure of functional exercise capacity in multiple sclerosis. *Disability and rehabilitation* 27, 22 (Nov 30 2005), 1365-1371.

SEHLE, A., MUNDERMANN, A., STARROST, K., SAILER, S., BECHER, I., DETTMERS, C. and VIETEN, M. Objective assessment of motor fatigue in Multiple Sclerosis using kinematic gait analysis: a pilot study. *Journal of neuroengineering and rehabilitation* 8 (2011), 59.

SCHEIDEGGER, O., HESS, C. W. and RÖSLER, K. M. General features of motor fatigue – a review. *SCHWEIZER ARCHIV FÜR NEUROLOGIE UND PSYCHIATRIE* 161, 5 (2010), 150-153.

SCHWARTZ, C. E., VOLLMER, T. and LEE, H. Reliability and validity of two self-report measures of impairment and disability for MS. North American Research Consortium on Multiple Sclerosis Outcomes Study Group. *Neurology* 52, 1 (Jan 1 1999), 63-70.

SCHWID, S. R., THORNTON, C. A., PANDYA, S., MANZUR, K. L., SANJAK, M., PETRIE, M. D., MCDERMOTT, M. P. and GOODMAN, A. D. Quantitative assessment of motor fatigue and strength in MS. *Neurology* 53, 4 (Sep 11 1999), 743-750.

SOSNOFF, J. J., WEIKERT, M., DLUGONSKI, D., SMITH, D. C. and MOTL, R. W. Quantifying gait impairment in multiple sclerosis using GAITRite technology. *Gait & posture* 34, 1 (May 2011), 145-147.

STRAUDI, S., BENEDETTI, M. G., VENTURINI, E., MANCA, M., FOTI, C. and BASAGLIA, N. Does robot-assisted gait training ameliorate gait abnormalities in multiple sclerosis? A pilot randomized-control trial. *NeuroRehabilitation* 33, 4 (Jan 1 2013), 555-563.

SURAKKA, J., ROMBERG, A., RUUTIAINEN, J., VIRTANEN, A., AUNOLA, S. and MAENTAKA, K. Assessment of muscle strength and motor fatigue with a knee dynamometer in subjects with multiple sclerosis: a new fatigue index. *Clinical rehabilitation* 18, 6 (Sep 2004), 652-659.

TELLEZ, N., RIO, J., TINTORE, M., NOS, C., GALAN, I. and MONTALBAN, X. Does the Modified Fatigue Impact Scale offer a more comprehensive assessment of fatigue in MS? *Multiple sclerosis* 11, 2 (Apr 2005), 198-202.

TYSON, S. and CONNELL, L. The psychometric properties and clinical utility of measures of walking and mobility in neurological conditions: a systematic review. *Clinical rehabilitation* 23, 11 (Nov 2009), 1018-1033.

WEBSTER, K. E., WITTWER, J. E. and FELLER, J. A. Validity of the GAITRite walkway system for the measurement of averaged and individual step parameters of gait. *Gait & posture* 22, 4 (Dec 2005), 317-321.

WHITAKER, J. N., MCFARLAND, H. F., RUDGE, P. and REINGOLD, S. C. Outcomes assessment in multiple sclerosis clinical trials: a critical analysis. *Multiple sclerosis* 1, 1 (Apr 1995), 37-47.

WILLOUGHBY, E. W. and PATY, D. W. Scales for rating impairment in multiple sclerosis: a critique. *Neurology* 38, 11 (Nov 1988), 1793-1798.

WINGERCHUK, D. M., NOSEWORTHY, J. H. and WEINSHENKER, B. G. Clinical outcome measures and rating scales in multiple sclerosis trials. *Mayo Clinic proceedings* 72, 11 (Nov 1997), 1070-1079.

LIST OF ANNEXES