CURRICULUM VITAE

Tzu-Yun C. McDowell

Education

2005- Ph.D. Department of Epidemiology and Preventive Medicine
University of Maryland, Baltimore (expected graduation date: May, 2010)

2003 M.A. Kinesiological Sciences
University of Maryland, College Park, MD

2000 B.S. School of Physical Therapy, College of Medicine
National Taiwan University, Taipei, Taiwan

Certifications

2003, Dec. Sensory Integration and Praxis Test Certification, U.S.A.

2000, Nov. Physical Therapy License by the Department of Health, Taiwan, R.O.C.

Professional Experience

Research

2007 - Research Analyst/Programmer, full-time position
Under grants:
Examining Healthcare Patterns and MS Outcomes with VHA and Medicare Data
A National Survey of Veterans with Multiple Sclerosis
Department of Epidemiology and Preventive Medicine
University of Maryland, Baltimore

Responsibilities: Develop, collect and manage the national survey for the Multiple Sclerosis Surveillance Registry (MSSR) under the Multiple Sclerosis Center of Excellence East, Baltimore VAMC (MSCoE); analyze MSSR survey data for presentation and publication; perform statistical consulting, analysis and programming (SAS) for projects using Veteran Health Administrative database; work with MSCoE personnel to design and implement MS related research and to establish quality indicators and benchmarkers for MS care; present research and represent the MSCoE at national and international meetings.

2003 - 2007 Study Coordinator/Research Analyst, full-time position
Under grants:
Adaptive sensorimotor control in children with developmental coordination disorder
Bilateral arm training in patients with chronic stroke
Bilateral vs. Unilateral arm training in chronic stroke
Department of Physical Therapy and Rehabilitation Science
University of Maryland, Baltimore

Responsibilities: Coordinate personnel and testing schedule for multi-site studies for children with developmental coordination disorder (DCD) and patients with stroke; serve as primary contact for parents of children with DCD regarding recruitment, testing and seminar; serve as primary tester for the sensory integration and praxis test; setup and collect data with various laboratory equipment; perform programming, data analysis (Matlab) and statistical analysis (SAS); provide technical assistant and statistical consulting; develop agendas and instruct at the DCD parent seminar; perform administrative tasks related to the day-to-day operation of the laboratory. Other duties include: serve as primary trainer for intervention studies for patients with chronic stroke, assist various performance tests related to arm function and balance; and support functional MRI and transcranial magnetic stimulation tests.

2001 - 2003 Graduate School Fellowship
Under grant: *Posture development and perception-action coupling*
Department of Kinesiology
University of Maryland, College Park

Responsibilities: Assist with data collection, reduction, and analysis; train undergraduate assistants for lab related activities; participate and present projects at national meetings.

2000 - 2001 Research Assistant, full-time position
Under grant: *Kinematic analysis of treadmill walking in pre- and full-term infants*
Infant Development Research and Motion Analysis Laboratory
School of Physical Therapy
National Taiwan University, Taipei, Taiwan, R.O.C.

Responsibilities: Assist with data collection, support writing grant applications; and perform administrative tasks related to the day-to-day operation of the laboratory

Clinical
2000 Physical Therapist, part-time position
National Taiwan University Hospital, Taipei, Taiwan, R.O.C.

Responsibilities: Evaluate, treat, and design training programs for patients at an outpatient clinic

Teaching Experience

2007 - 2008 Teaching Assistant for Graduate Course –
Survival Analysis (2007)
Longitudinal Analysis (2008)
Department of Epidemiology and Preventive Medicine
University of Maryland, Baltimore, MD
Responsibilities: Grade weekly assignments; assist and advise students on their questions related to SAS programming, assignments, and projects; evaluate and generate questions for students' final presentations.

2008 Guest Lecturer for Graduate Course – Longitudinal Analysis
Topic: Covariance Structures
Department of Epidemiology and Preventive Medicine
University of Maryland, Baltimore, MD
Responsibilities: Prepare and organize lecture materials with the course instructor; give two lectures and demonstrate related SAS programs in class; Stimulate questions and discussion from students

2002 - 2003 Teaching Assistant for Undergraduate Course
Laboratory Instructor – Motor Development
Department of Kinesiology
University of Maryland, College Park, MD
Responsibilities: Develop and prepare materials for the lab; instruct weekly lab class to students; grade students' exams, assignments and lab performance; stimulate discussions and assist students' understanding of course materials.

2002 - 2003 Guest Lecturer for Undergraduate Course
Laboratory – Topical Investigations: Introduction to Kinesiology
Department of Kinesiology
University of Maryland, College Park, MD

Responsibilities: Demonstrate research related to Kinesiology

Fellowships/Grants/Awards

2009	Service Recognition Award, School of Medicine, University of Maryland, Baltimore
2008	Young Investigator Travel Award, from the Americas Committee for Treatment and Research in Multiple Sclerosis
2008	Scholarship, from the Consortium of Multiple Sclerosis Center
2001 – 2003	Graduate School Fellowship award, University of Maryland, College Park
2000	Highest Class GPA & Scholarship, National Taiwan University, Taipei

Journal Publications

- Olugemo OA, Desai T, Krumholz A, **McDowell T-Y**, Zhan M, Royal W, Wallin M, Bever C, Culpepper WJ. Sleep Disorders in Multiple Sclerosis (submitted).

- Viswanathan P, **McDowell T-Y**, Kagerer F, Contreras-Vidal JL, Whitall J. Modulation of bilateral finger tapping to subliminal and perceptible auditory change in the phasing of sensorimotor coupling (submitted).

- Culpepper WJ., Cowper-Ripley DC., Litt ER, **McDowell T-Y**, Hoffman, PM. Using GIS tools to improve MS specialty care access in the Veterans Health Administration. Journal of Rehabilitation Research and Development 2010 (in press).

- **McDowell T-Y,** Amr S, Langenberg P, Royal W, Bever C, Culpepper WJ, Bradham DD. Time of birth, residential solar radiation and age at onset in multiple sclerosis. Neuroepidemiology 2010; 34:238-244

- Whitall J, **Chang T-Y**, Horn CL, Jung-Potter J, McMenamin S, Wilms-Floet A, Clark JE. Auditory-motor coupling of bilateral finger tapping in children with and without DCD compared to adults. Hum Mov Sci. 2008 Dec;27(6):914-31

- Chen L-C, Metcalfe JS, **Chang T-Y**, Jeka JJ, Clark JE. The development of infant upright posture: sway less or sway differently? Exp Brain Res. 2008 Mar;186(2):293-303.

- Metcalfe JS, McDowell K, **Chang T-Y**, Chen L-C, Jeka JJ, Clark JE. Development of somatosensory-motor integration: an event-related analysis of infant posture in the first year of independent walking. Dev Psychobiol. 2005 Jan;46(1):19-35.

- Metcalfe JS, Chen L-C, **Chang T-Y**, McDowell K, Jeka JJ, Clark JE. The temporal organization of posture changes during the first year of independent walking. Exp Brain Res. 2005 Mar;161(4):405-16.

Published Reports

- Cowper Ripley DC, Culpepper WJ, Hoffman PM, Litt ER, **McDowell T-Y**.
  Geographic Access to Treatment for VHA Patients with Multiple Sclerosis: MSCoE-East.
  Management Report, Rehabilitation Outcomes Research Center REAP, Gainesville, FL, 2008.

- **Chang T-Y**. The relationship between touch and infants' upright posture during the first year of walking. University of Maryland, College Park, Master thesis. 2004

Presentations

- **McDowell T-Y,** Amr S, Langenberg P, Royal W, Bever C, Culpepper WJ, Bradham DD. Past sun exposure, vitamin D intake and age at onset in multiple sclerosis. Consortium of Multiple Sclerosis Center, San Antonio, TX 2010.

- Culpepper WJ, **McDowell T-Y,** Wallin MT, Royal W, Bever CT. Therapy-related Acute Leukemia in Mitoxantrone-treated Veterans with MS. Consortium of Multiple Sclerosis Center, San Antonio, TX 2010.

- **McDowell T-Y,** Culpepper WJ, Bever C, Royal W, Bradham DD. Timing of Birth, Residential Solar Radiation and Age at Onset in Veterans with Multiple Sclerosis. Consortium of Multiple Sclerosis Center, Atlanta, GA, 2009

- Culpepper WJ, **McDowell T-Y,** Wallin MT, Bever CT, Bradham DD. Cardiac Disease After Mitoxantrone in Veterans with MS. Consortium of Multiple Sclerosis Center, Atlanta, GA, 2009

- Cowper Ripley DC, Culpepper WJ, Hoffman PM, Litt ER, **McDowell T-Y**. Geographic Access to Treatment for VHA Patients with Multiple Sclerosis. HSR&D, Baltimore, Maryland, 2009.

- **McDowell T-Y**, Culpepper WJ, Bever C, Bradham DD. Osteoporosis in Veterans with Multiple Sclerosis. the Americas Committee for Treatment and Research in Multiple Sclerosis, Montreal, Canada, 2008

- Culpepper WJ, Bever C, **McDowell T-Y**, Bradham DD. DMT Compliance in the VHA MS Surveillance Registry. the Americas Committee for Treatment and Research in Multiple Sclerosis, Montreal, Canada, 2008

- **McDowell T-Y**, Culpepper WJ, and Bradham DD. Age and Comorbidity in Veterans with Multiple Sclerosis. Consortium of Multiple Sclerosis Center, Denver, CO, 2008.

- Ajayi OF, **McDowell T-Y**, Culpepper WJ, Bever C, Royal W. High Prevalence of Sleep Disorders in Veterans with Multiple Sclerosis. American Academy of Neurology, 2008

- Whitall J, McComber-Waller S, Liu W, **Chang T-Y**. Changing motor control and coordination in persons with chronic stroke. Motor Control and Human Skill. Australia, 2007.

- Metcalfe JS, Chen L-C, **Chang T-Y**, McDowell K, Jeka JJ, Clark JE. The structure of postural sway in the first year of independent walking: Effects of experience and somatosensory cues. International Conference on Infant Study, Chicago, IL, 2004.

- Viswanathan P, **Chang T-Y**, Horn C, Roche R, Whitall J. Adaptation to gradual and abrupt changes in sensorimotor coupling: Auditory cues and bilateral finger tapping. North American Society for the Psychology of Sport and Physical Activity, Vancouver, British Columbia, 2004.

- Roche R, Horn C, **Chang T-Y**, Viswanathan P, Whitall J. Auditory motor processing in typically developing children: A cross-sectional study. North American Society for the Psychology of Sport and Physical Activity, Vancouver, British Columbia, 2004.

- **Chang T-Y** and Clark JE. The relationship between touch and infants' upright posture during the first year of walking. North American Society for the Psychology of Sport and Physical Activity, Savannah, GA. 2003.

Computer Skills

Standard Windows-Based Word-processing, Spreadsheet and Illustration Programs. Programming level use of Matlab and SAS. Operational level use of Labview and SPSS. Microsoft Office Access and AutoData (a software package used to design questionnaires/surveys and automates data entry via scannable/faxable forms).

ABSTRACT

Title of Dissertation: Ultraviolet Radiation, Vitamin D Intake and Multiple Sclerosis

Tzu-Yun McDowell, Doctor of Philosophy, 2010

Dissertation directed by: Sania Amr, MD, MS, Associate Professor
Department Epidemiology and Preventive Medicine
University of Maryland, Baltimore

Background: Multiple Sclerosis (MS), an inflammatory and neurodegenerative disease, has an elusive etiology that is thought to be an interaction between genetic and environmental risk factors. Ultraviolet Radiation (UVR) and/or vitamin D have been consistently shown to be protective against MS development; however, their roles in modulating the clinical course of this disease remain unclear.

Objectives: The overall objective of this dissertation was to examine the effects of UVR and vitamin D related exposures on the ages of disease onset and progression to disability among a national cohort of Veterans with MS.

Methods: We conducted a cross-sectional study, using a questionnaire designed to assess the different parameters that contribute to UVR exposure and vitamin D synthesis. We examined the dual influence of (1) timing and geographical location of birth and (2) sun exposure and vitamin D-related intakes from childhood to MS onset on the clinical course of this disease. All the analyses were conducted by disease subtype (Relapsing vs. Progressive MS). Multiple linear regression and Cox proportional hazard models were used to analyze the data.

Results: Among Veterans with Relapsing MS (N=731), those born in winter and in low solar radiation areas, had their disease symptom onset on an average 2.8 years earlier (p = 0.02) than those born during other seasons in areas with medium to high solar radiation. Among 948 veterans with Relapsing MS, we found that low sun exposure in fall/winter seasons during childhood and early adolescence was also associated with early MS onset (p = 0.01); whereas regular use of cod liver oil in childhood was associated with later disease onset (p = 0.01). Among Veterans with progressive MS (N=151), low average fall/winter sun exposure before symptom onset was associated with an increased risk of disability (p = 0.01); while regular intake of cod liver oil during childhood and early adolescence decreased the risk (p = 0.04).

Conclusions: Our findings suggest that environmental exposures before MS onset, primarily related to UVR and/or vitamin D status, early in life and during childhood and early adolescence have significant effects on the clinical course of MS.

Ultraviolet Radiation, Vitamin D Intake and Multiple Sclerosis

by

Tzu-Yun McDowell

Thesis submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2010

Dedication

To all the patients who suffer with multiple sclerosis, their families, and all those dedicated to helping overcome this disease.

Acknowledgments

I would like to extend my gratitude to all the participants for contributing their time and effort for this study.

My deep appreciation goes to my committee members: Dr. Sania Amr, Dr. Chris Bever, Dr. Douglas D. Bradham, Dr. William J Culpeper, Dr. Patricia Langenberg, and Dr. Walter Royal for their guidance and valuable input into this dissertation. I would like to especially thank Dr. Sania Amr, the chair of the dissertation committee, for her time, patience and constructive advice that sharpened my scientific thinking and writing; Dr. Douglas Bradham for the opportunities and support he has given me and Dr. William J Culpeper for sharing his experience in survey research and friendship during my research.

I would like to thank Dr. Jill Whitall for her early support and encouragement that helped me to join the graduate program at University of Maryland, Baltimore.

I would like to extend my thanks to many staff of the Cooperative Studies Program Coordinating Center of the VA Maryland Health Care System at Perry Point, Maryland for their assistances and hard work on the survey production. I would like to thank Josh Moore and Shan Jin for their assistance on survey data entry and reduction.

My deepest gratitude goes to my dear and loving family and friends in Taiwan and the United States for their endless support, especially my husband Kaleb, for his slave-driving (encouragement) to complete this long journey.

Table of Contents

List of Figures

List of Tables

CHAPTER I: LITERATURE REVIEW

1.1 Multiple Sclerosis

1.1.1 Introduction to Multiple Sclerosis

Multiple Sclerosis (MS), a chronic, immune-mediated inflammatory and neurodegenerative disease, is the most common neurological disorder as well as the leading non-traumatic cause of disability among young adults. The signs and symptoms of MS occur as the consequence of underlying neuropathologic changes within the central nervous system (CNS). Acute inflammatory demyelination initiated by autoimmune attacks, and axonal loss that results from chronic demyelination are the mechanisms underlying CNS damage and neurodegeneration. They can lead to either slowing of neural conduction or complete disruption of conduction[1]. Demyelination resulting from acute focal inflammation is often what causes MS symptoms to appear at early stages of the disease. When inflammation subsides, partial or complete recovery of the clinical symptoms (remission) often occurs with repair of the axonal structure (re-myelination), especially in the early phases. However, once a pathological threshold is reached (chronic demyelination and accumulated axonal loss), disease progresses under the primary mechanism of neurodegeneration that aggregates the clinical disease and results in irreversible neurological disability [2]. Brain atrophy, in addition to cortical lesions, is another major contributor to disease burden in patients with MS; causing a variety of signs and symptoms that depend on the size, number, and location of the CNS lesions. The most common symptoms include: optic neuritis, nystagmus, weakness, sensory loss, fatigue, ataxia, bowel dysfunction and cognitive impairment [1, 3].

Figure 1.1 illustrates a natural history of MS clinical presentation and disability (Black line), underlying mechanism (Blue shaded areas on the bottom of the diagram) and neurological disability measured from MRI (gadolinium enhancing [GD] or 'active' lesions – Green; T2 lesions – Purple; and brain volume – Blue). During the inflammatory phase, which is the dominant disease process in the early stage of the disease, relatively frequent relapses (black line) and GD lesions (green line) occur. During this phase, varying degrees of recovery can take place as depicted by the stepped pattern in black and green line representing decrease of disability along with reduction of GD lesions, respectively. As time progresses, there is an accumulation of axonal loss (neurodegeneration) with fewer and fewer relapses and GD lesions, a plateau in the number of T2 lesions and an ever increasing loss of total brain volume. Once neurodegeneration becomes the dominant disease process, patients transit their MS from relapsing-remitting (RRMS) type of disease to secondary progressive (SPMS) type associated with constant worsening of the symptoms and functions.

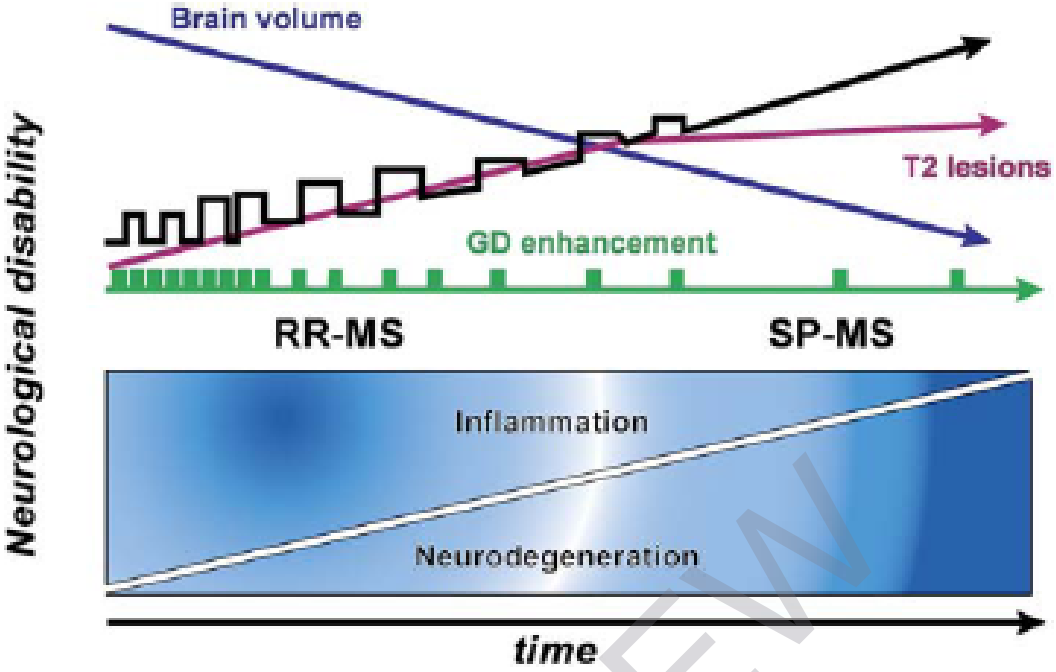

Figure 1.1 Natural history of MS in terms of clinical presentation, underlying mechanism and neurological disability measured from MRI. [2]

The unpredictable pattern in type, frequency, and severity of symptoms as well as progression to disability is the hallmark characteristic of MS. As a consequence of these clinical characteristics, MS presents as a complex disease that is very difficult to manage [3, 4]. MS patients, not only have to deal with current symptoms and the resulting disability, but also live with fear about progression of the disease. To date, there is still no cure for MS. Most pharmacotherapy is for symptom management (e.g., fatigue, spasticity), except for a subgroup of patients for whom there are medications, such as interferon- β (INF- β), which are approved by the FDA as primary disease modifying therapies (DMT). However, the long-term effect and impact of DMT on MS progression has yet to be determined.

1.1.2 Clinical Course of MS: Subtype and Disease Progression

The clinical course of MS consists of two forms: (1) relapses of acute neurological symptoms followed by a partial or complete remission, and (2) progression with irreversible worsening of symptoms and signs [3-5]. Four main subtypes for MS are defined based on whether clinical symptoms are relapsing or progressive in nature: (1) relapsing-remitting (RRMS), (2) secondary progressive (SPMS), (3) primary progressive (PPMS) and (4) progressive relapsing (PRMS) (see Figure 1.2)[1]. RRMS, the most common subtype that affects about 85% of MS cases, is characterized by relapses (symptom exacerbations) followed by varying degrees of recovery with a stable course between relapses. Approximately 50-80% of RRMS patients progress to SPMS within 10 years. SPMS is characterized by relapses with incomplete recovery and a progressive course (e.g. increasing disability) between relapses.

The primary distinction between RRMS and SPMS is what happens between relapses. There is a stable course (little if any worsening) between relapses in RRMS; whereas there is observable progression of disability between relapses in SPMS. In contrast to the relapsing forms of MS, about 10-15% of new MS cases have a steady progression of symptoms from onset without any exacerbation and remission, termed PPMS. A small number of PPMS patients will go on to develop PRMS, which is characterized by a progressive disease course from onset with appearance of relapses[1], which are usually rare and occur earlier in the disease history.

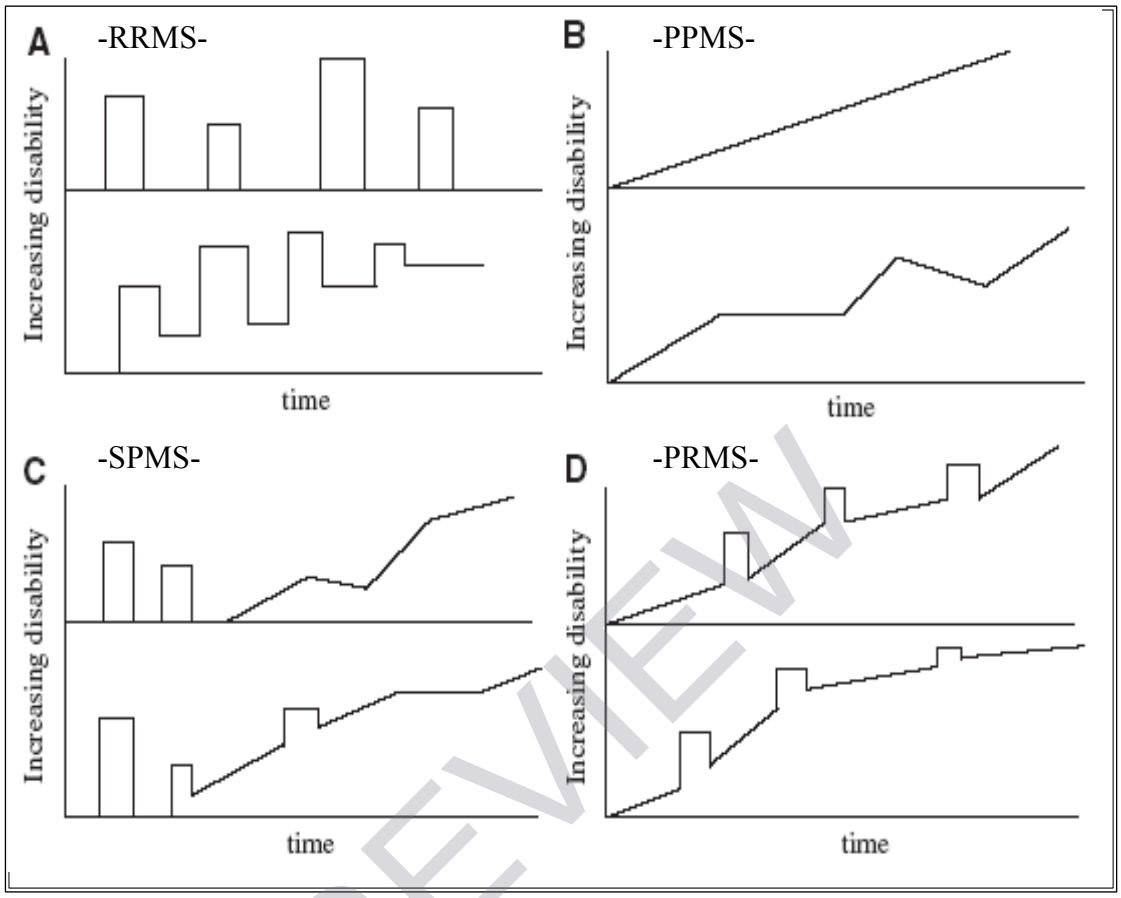

Figure 1.2 Graphical summary of MS subtype A: Relapsing-remitting MS (RRMS), B: Primary-Progressive MS (PPMS), C. Secondary-Progressive MS (SPMS), and D. Progressive-Relapsing MS (PRMS)[1]

Because the clinical course of MS is variable between and within patients, identifying reliable prognostic factors has been challenging. Lubin [1] summarized the broad clinical guidelines for favorable and unfavorable indicators in MS (Table 1.1). Characteristics of relapses in the first year (low number, little residual disability after each relapse and long time between first and second relapse), early age of onset, female sex, and monosymptomatic onset with optic neuritis or sensory symptoms have consistently been associated with a better prognosis. On the other hand, a

progressive course from onset is associated with the worst outcome [1, 6]. Although these indicators have been widely accepted for clinical applications, whether or not they are actual predictors for progression of MS is debatable.

In a recent systematic review, Langer-Gould et al. reported that early disease characteristics (degree of remission after relapses, frequency of relapses) but not age of onset nor patient gender, are the most consistent predictors of long-term disability in RRMS patients[6]. Other investigators examined the age at which patients reached disability milestones according to their clinical subtypes. They found that patients, with either RRMS or PPMS, were comparable with respect to the age at which they reached an assigned disability milestone, especially a more severe one [5, 7-10]. They suggested that clinical subtype and course of MS may be mainly age-dependent. The degree of long-term disability increases with age, which reflects an age-related degenerative process that is independent of previous relapses and age at onset [5, 7-11]. Their findings also support the concept that MS should be viewed as a single disease with different clinical phenotypes, rather than several distinct diseases.

Although the course of MS is very difficult to predict, there are important clinical stages associated with disease progression that can be recognized by neurologists and patients, such as physical disability. Various studies show that 50 to 80% of MS patients are unable to perform work tasks and usual housework after 10 years of disease. Approximately 32 to 76% of MS patients require a walking aid; and 11 to 29% are bedridden after 15 years of illness [12-16]. Patient Determined Disease Steps (PDDS) is a simple and reproducible assessment of functional disability in MS[17, 18]. It primarily evaluates ambulation of MS patients on a scale of 1 to 9 (from a

stage of normal motor function to bedridden, see Appendix A); a broad scale of disability categories that is particularly useful for studies targeting long-term outcomes of MS.

Table 1.1 Favorable and Unfavorable prognostic indicators in MS

Favorable indicators	Unfavorable indicators
Early age of onset	Later age of onset
Female sex	Male sex
Optic neuritis as presenting episode	Progressive course from onset
Sensory symptoms as presenting episode	Involvement of cerebellar or motor function
Little residual disability after each exacerbation (i.e. Excellent recovery)	Poor recovery from exacerbations
Long inter-exacerbation period	Frequent exacerbations
Acute onset of symptoms	

1.1.3 Epidemiology and risk factors of MS

The prevalence of MS is approximately one per 1000 with female to male ratio of 1.5 to 2.5 [19]. MS symptoms generally appear in early adulthood with the diagnosis peaking between the ages of 20 and 45 [3, 4, 12, 20-22]. Because of the chronic nature of this disorder, there are 250,000 to 350,000 cases of MS in the United States at any point in time, with 45% of these being older than 55 [23]. The disease contributes to about 92,000 hospitalizations per year with an estimated annual medical cost of $2.5 billion in the U.S. [4, 24].

The etiology of MS remains elusive and is thought to be a complex interaction between genetic and environmental risk factors [25-27] . It is acknowledged that there is a strong genetic component in development of MS. This is supported by evidence of

increased MS incidence in immediate family members, and association with certain HLA allotypes [28-30]. Further, Caucasians, particularly of European/Scandinavian descent, are more likely to develop MS compared to people of African and Oriental descent [12, 24, 31]. However, monozygotic twin and familial studies consistently show that genetic factors contribute to approximately 30% of the risk [12, 32, 33]; the remainder is thought to be associated with non-inherited factors.

Parallel to the ongoing research on the genetic risk for MS, research for possible environmental risks has investigated various infectious agents, toxins, and vaccinations. Infectious agents have been suggested to be the most plausible candidates among non-inheritable factors [26, 34]. Many latent viruses, certain herpes and influenza viruses, which have antigens close to the structure of myelin basic protein (MBP), can trigger an autoimmune process by activating T-cells specific to MBP[35]. Infection with a certain common viruses in late childhood and adolescence is associated with increased risk of MS when compared to the same infection in early childhood[36, 37].

In this context, "hygiene hypothesis" was originally proposed [38]. According to the hygiene hypothesis, lack of intense infections (not a specific agent) in industrialized countries due to improved hygiene and advanced medicine may alter the human immune system and leads to autoimmunity or allergy. It was postulated that exposure to several infectious agents early in life is protective against the development of MS in susceptible individuals. On the other hand, there is compelling evidence from epidemiological and biological research implicating Epstein-Barr virus (EBV) as a specific infectious agent that triggers MS[26, 27, 36, 37, 39, 40]. Higher EBV