Designing a Decision Support Tool for Early Diagnosis and Intervention in Multiple Sclerosis

By

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ABSTRACT

Multiple Sclerosis (MS) is one of the most common neurological disorders that leads to disability at a younger age among people in North America and Europe[1]. It is a non-communicable disease with no cure, debilitated by physical and mental impairments[2]. Recent reports show an increase in the incidence of MS in United States that is twice more than the past estimate. The average period to diagnose MS still ranges from 6 months to 3 years. Studies suggest that early diagnosis and intervention can delay the progression of the disease and improve the quality of life[4-6]. Until today no clinical decision support exists that could be used to assist clinicians in diagnosing MS at early onset of symptoms. This study has been conducted to assess the need and explore the quantifiable predictors that could be used for helping clinicians in early detection of disease activity. A review of literature followed by a quasi-experimental approach has been done to collect predictors and analyze the trending incidence of MS in United States. A survey was also conducted to seek the expert opinions of neurologists and primary care physicians (PCPs) to analyze the existence and effectiveness of clinical decision support system in MS.

The literature review took into account various theories about the etiology of MS but found that some old theories are not relevant compared to the disease trends during the last two decades. The in-depth review found that some strong predictors do exist that could help clinicians in early diagnosis of the disease. The results obtained by analyzing HCUP data substantiate the rising incidence and prevalence of MS in United States and corroborates the higher incidence among young women getting diagnosed with MS. The survey analysis shows that currently no clinical decision support system (CDSS)

exists to diagnose MS early at the point of care. On a scale of 1 to 5 with 1 being strongly disagreed and 5 being strongly agreed, the neurologists have a response average of 1.6 and PCPs of 2.6 about the effectiveness of current techniques in the early diagnosis of MS. Among both groups 95% of clinicians haven't heard or used any CDSS at the point of care. Both groups agreed that a CDSS may help in early diagnosis, quality care and reducing unnecessary tests and costs with an average response rates of 3.9 and 4.0.

The predictors selected are weighted and used to design a clinical decision support system and tested on a sample population of MS patients who are diagnosed to have MS. On a weighted scale of 265 to 455 the average output is 341.6 with a 95% CI ranging between 325.94 and 357.26. Based on the outputs obtained from the expert system the study concludes that it is possible to use a clinical decision support system at the point of care to assist clinicians in diagnosing MS at an early stage. More testing needs to be done by a multi-centric research due to the variabilities and inconsistencies existing in the clinical manifestations as well as pathologic phenomena in MS.

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LIST OF ABBREVIATIONS

AI-Artificial intelligence

ANN-Artificial neural networks

BBB-Blood Brain Barrier

CIS-Clinically isolated syndrome

CNS-Central Nervous System

CDS-Clinical Decision Support

CDSS Clinical Decision Support System

CSF-Cerebrospinal Fluid

CT Computed tomography

DIS-Dissemination in Space

DIT-Dissemination in Time

DTI-Diffusion Tensor Imaging

EDSS-expanded disability status scale

EHR-Electronic Health Records

EMR Electronic Medical Records

FDA-Food and Drug Administration

Gd-Gadolinium

GWAS-Genome-Wide Association Screening

HIPAA-Health Insurance Portability and Accountability Act

HCUP-Healthcare Cost and Utilization Project

HRQoL-Health-Related Quality of Life

ICD-10-CM International Classification of Diseases, 10th Revision, Clinical Modification

MHC-Major Histocompatibility Complex

MRI-Magnetic resonance imaging

MRS-Magnetic Resonance Spectroscopy

MS Society-Multiple Sclerosis Society

MTR-Magnetisation Transfer Ratio

NARCOMS-North American Research Committee on MS

NIH-National Institutes of Health

NINDS-National Institute of Neurological Disorder and Stroke

NIS-Nationwide Inpatient Sample

PET-Positron Emission Tomography

PHI-Protected Health Information

PPMS-Primary Progressive MS

RRMS-Relapsing-Remitting MS

RAPD-Relative Afferent Pupillary Defect

SLE-Systemic Lupus Erythematosus

SPMS-Secondary Progressive MS

VDRE-Vitamin D Response Element

VZV-Varicella Zoster Virus

WHO-World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Introduction of the problem:

According to WHO Report in 2006, Multiple Sclerosis (MS) is one of the most common neurological disorders and cause of disability among 'young adults' in North America and Europe (WHO, 2006)[1]. It is a non-communicable disease with no cure, debilitated by physical and mental impairments[7]. The Multiple Sclerosis Foundation estimates that more than 400,000 people in the United States and about 2.5 million people around the world have MS. Recent studies from various corners of the world show that MS is increasing in prevalence world-wide[23-25]. Previously the lowest risk appears to be among Native Americans, Africans, and Asians. But that landscape of distribution has been changing with more new cases diagnosed around the world. A recent study conducted by the National Multiple Sclerosis Society and published in the February 15, 2019, estimated the prevalence to be closer to 1 million[140].

You can get MS at any age but most people are diagnosed between the ages of 20 and 40. The ratio of women with MS to men with the disease is 2 to 1. About 200 new cases are diagnosed each week in the United States. Rates of MS are higher farther from the equator. It's estimated that in southern states (below the 37th parallel), the rate of MS is between 57 and 78 cases per 100,000 people. The rate is twice as high in northern states (above the 37th parallel), at about 110 to 140 cases per 100,000. The incidence of MS is also higher in colder climates. People of Northern European descent have the highest risk of developing MS, no matter where they live.

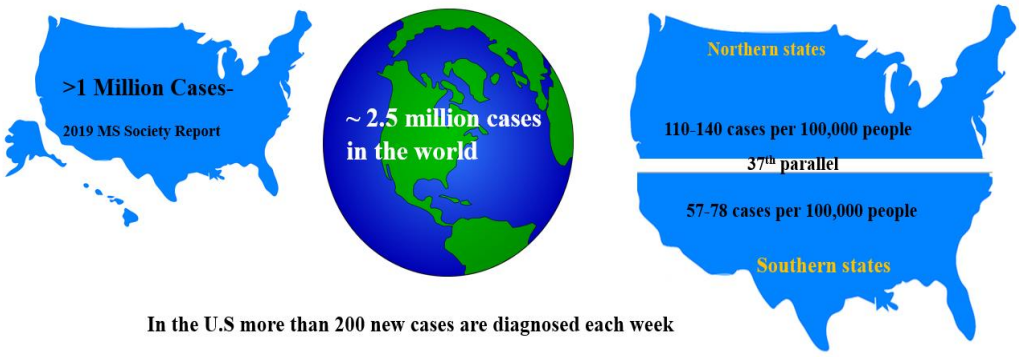


Figure 1.1: Incidence Rates of Multiple Sclerosis

MS is a disease of the brain with significant economic burden due to the high diagnostic cost and high drug cost further worsened by lost productivity and social cost[3, 4, 6]. Total all-cause healthcare costs for MS as reported by studies that included direct and indirect costs ranged from $8528-$54,244 per patient per year. On average, direct costs comprised 77% (range 64-91%) of total costs. Prescription medications accounted for the majority of direct costs. On average, indirect costs comprised 23% (range 9-36%) of total costs. Compared with direct all-cause medical costs for other chronic conditions reported in the literature, MS ranked second behind congestive heart failure[8].

A study in collaboration with the North American Research Committee on Multiple Sclerosis (NARCOMS) registry was conducted to estimate the indirect costs and health-related quality of life (HRQoL) (utilities) of multiple sclerosis (MS) patients in the United States (U.S), and to determine the impact of worsening mobility on these parameters. Indirect costs per participant per year, not including informal caregiver cost, were estimated at $30,601+/-31,184. The largest relative increase in indirect costs occurred at earlier mobility impairment stages, regardless of the measure used. These

results suggest that mobility impairment may contribute to increases in indirect costs and declines in HRQoL in MS patients. Costs associated with increasing disability and early retirement, and the potential impact of new treatments are yet to be known.

MS is not considered an inherited disorder. But researchers believe there may be a genetic predisposition to developing the disease. For example, about 15 percent of individuals with MS have one or more family members or relatives who also have MS, according to the National Institute of Neurological Disorders and Stroke. In the case of identical twins, there's a 1 in 3 chance for each sibling to have the disease. Researchers still aren't certain what causes MS. One leading hypothesis is that it's a genetic predisposition combined with an environmental or viral factor.

People with other autoimmune diseases, especially type 1 diabetes, thyroid disease, or inflammatory bowel disease, are at a slightly increased risk of developing MS. Researchers are also studying the relationship between MS and infections such as Epstein-Barr, herpes, and varicella-zoster, among others. However, MS itself is not contagious.

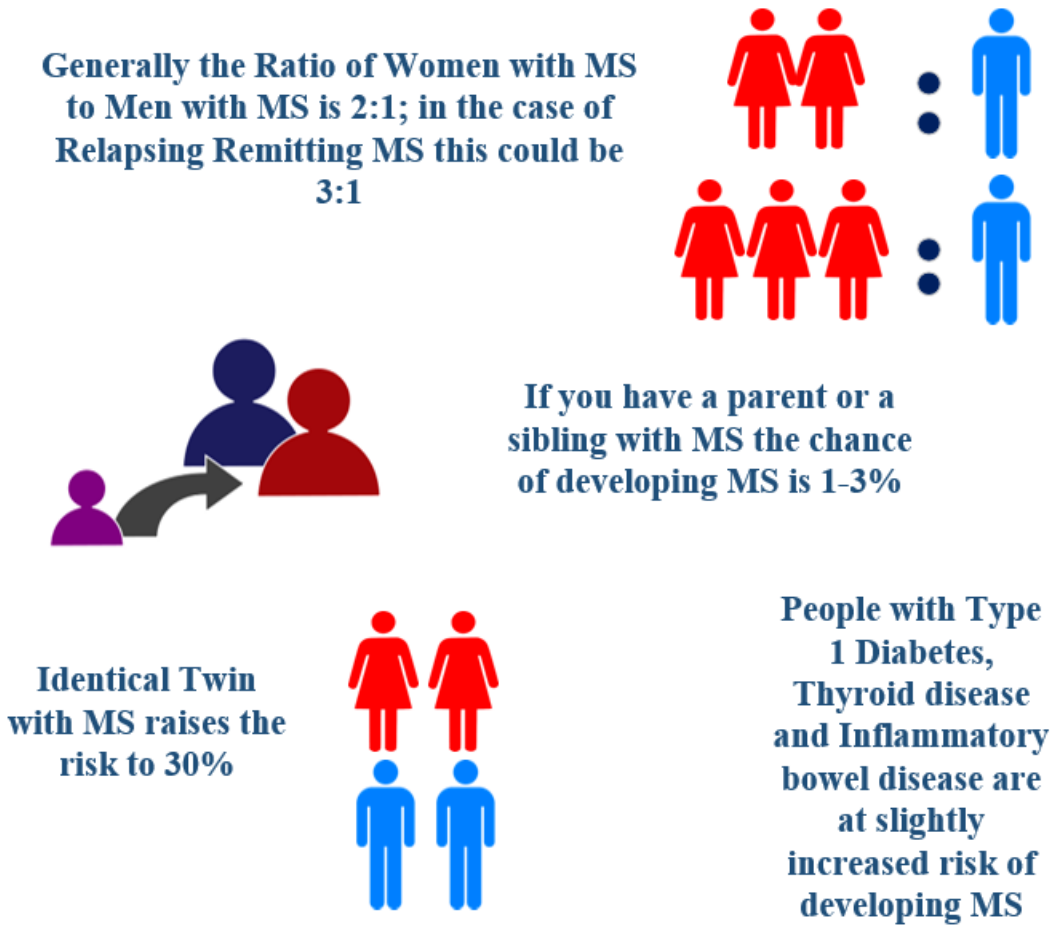


Figure 1.2: Gender and Genetic Factors Associated with Multiple Sclerosis.

1.1.1 Types of MS:

Based on the severity and progression of the disease activity and disability MS is classified into 4 types. Even though clinically isolated syndrome (CIS) is the term used for the initial presentation stage, it is not classifies as a type since it evolves into definite MS after a period of time that could vary from patient to patient.

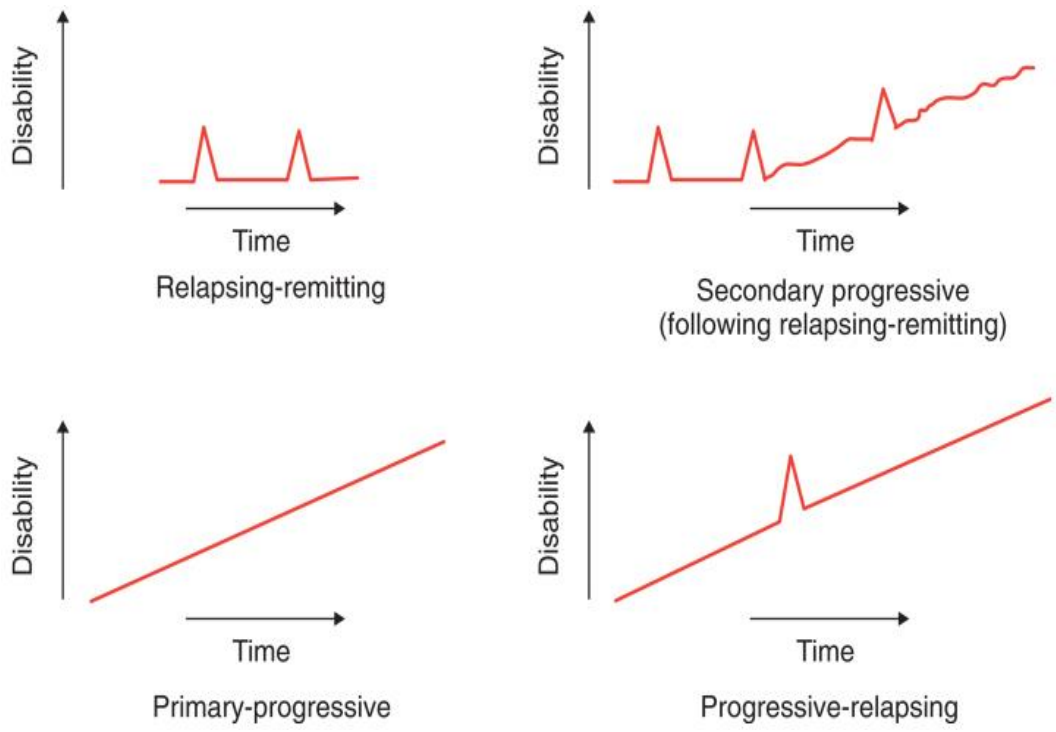


Figure 1.3 Types of MS

I. **Relapsing-remitting MS (RRMS):** is characterized by clearly defined relapses of increased disease activity and worsening symptoms. These are followed by remissions in which the disease doesn't progress. Symptoms may improve or disappear during remission. Approximately 85-90 percent of patients are diagnosed with RRMS at onset.

II. **Secondary Progressive MS (SPMS):** Untreated, about 50 percent of people with RRMS transition to secondary-progressive MS within a decade of the initial diagnosis.

III. **Primary-progressive MS (PPMS**) is diagnosed in about 10-15 percent of MS patients at onset. People with PPMS experience a steady progression of the disease with no clear relapses or remissions. The rate of PPMS is equally divided between men and women. Symptoms usually begin between the ages of 35 and 39.

IV. **Progressive-relapsing MS (PRMS)** is the rarest form of MS, representing about 5 percent of MS patients. People with PRMS have clear relapses combined with a steady progression of the disease.

Approximately 10 to 20 percent of people with MS have a benign course of the disease. This means they have only mild symptoms and little disease progression. However, long-term studies show that some of these people experience some progression after 10 to 20 years. About 1 percent of patients develop an aggressive form of MS that progresses very rapidly.

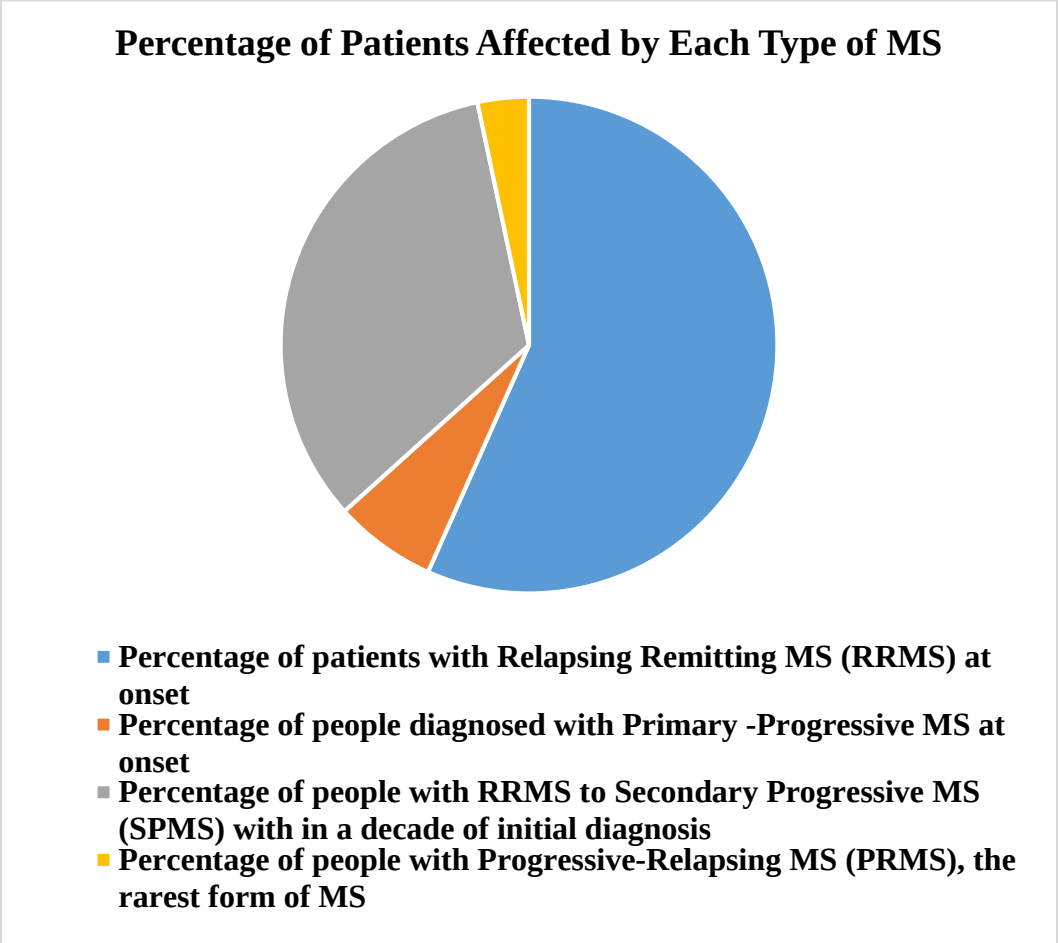


Figure 1.4: Percentage of Patients Affected by Each Type of Multiple Sclerosis

Symptoms vary a great deal from one patient to another — no two people have the same combination of symptoms.

Table 1.1: Clinical Symptoms of Multiple Sclerosis

Early Symptoms	Late Symptoms
Fatigue	Speech and swallowing problems
Vision problems	Cognitive dysfunction
Tingling and numbness	Difficulty with walking
Vertigo and dizziness	Bladder and bowel dysfunction
Muscle weakness and spasms	Sexual dysfunction
Problems with balance and coordination	Mood swings, depression

There is no cure for MS. Medications are designed to lessen frequency of relapses and slow the progression of the disease, but they don't address individual symptoms. They have been found through clinical trials to reduce the number of relapses, delay progression of disability, and limit new disease activity (as seen on MRI).There are currently 12 disease-modifying medications approved by the U.S. Food and Drug Administration as of 2017 (Table 1.2).

Table 1.2: Therapeutic agents for Multiple Sclerosis

Injectable Medications	Oral Medications	Infused Medications
Interferon beta-1a	Teriflunomide	Alemtuzumab
Interferon beta-1b	Fingolimod	Mitoxantrone
Glatiramer Acetate	Dimethyl Fumarate	Ocrelizumab
Peginterferon beta-1a		Natalizumab
Daclizumab		

All of these medications have demonstrated partial efficacy along with different side-effect profiles. Nevertheless, many patients continue to experience disease activity while on treatment, and recommendations have been made on how the success of therapy in an

individual patient can be assessed. The option of individualized optimal treatment is progressively more complicated due to the growth of our knowledge about the natural behavior of MS and its different types and stages, the variety of different therapies, their strength and weaknesses, and their serious and sometimes life-threatening side-effects. Lack of consensus in the current algorithms and treatment options make the clinical decision making difficult[10]. As our health care system has moved to value based care, the high cost of all these medications also create uncertainty in taking decisions to reduce cost of care.

1.2 Background and Statement of the Problem:

Multiple sclerosis is a chronic autoimmune disease of the central nervous system characterized by exacerbations of neurological dysfunction due to inflammatory demyelination. Neurologic symptoms typically present in young adulthood and vary based on the site of inflammation, though weakness, sensory impairment, brainstem dysfunction and vision loss are common. MS occurs more frequently in women and its development is complex-genetics, hormones, geography, vitamin D, and viral exposure all play roles. Early MS is characterized by relapsing-remitting course and inflammation of the white matter, though as patients age, the disease often transitions to a pathologically distinct secondary progressive phase with gradual disability accrual affecting gait, coordination and bladder function[15]. MS is characterized by a great inter-individual variability in disease course and severity. Some patients experience a rather mild course, controversially called 'benign MS' (BMS). The usefulness of this entity in clinical practice remains unclear[16]. Having a CDSS to support the clinicians and patients will mitigate the delay in the early diagnosis and early treatment decision process.

Progression of the disease is heavily weighted more on the worsening of physical disability measured by EDSS scoring[16]. EDSS appears to be a predictive factor for the progression of disease. Among other diagnostic biomarkers MRI plays a key role in the confirmation. Studies have shown evidence on the predictive value of MRI parameters. Magnetic resonance imaging (MRI) is the best biomarker of inflammatory disease activity in relapsing remitting Multiple Sclerosis (RRMS) so far but the association with disability is weak. High field MRI has improved image quality and resolution and new methods to measure atrophy dynamics have become available[17]. A CDSS algorithm using all these predictors will help the clinicians in taking treatment decisions to control the progression of the disease and thereby the disability.

1.3 Significance of the Study:

Diagnosis of MS has always been a clinical decision. Though many tests and criteria have assisted clinicians in arriving at conclusions, there is a high rate of misdiagnosis due to lack of systematic and evidence based decision support at the point of care. Patient's history of symptoms may be inadequate and inconclusive in most cases. Presenting symptoms of MS may be seen in other neurological disorders, and diagnostic tests and biomarkers have different levels of evidence and reliability. These challenges in the diagnosis shows how significant is the need of a clinical decision support for MS. Studies have shown that early diagnosis of MS helps in early intervention and hence can delay the progression of disease.

Treatment decisions in MS are affected by many factors and are made by the patient, doctor, or both. With new disease-modifying therapies (DMTs) emerging, the complexity surrounding treatment decisions is increasing, further emphasizing the importance of

understanding decision-making preferences[12]. Having a CDSS for MS will help in patient-centered decision making, shared decision making and physician-centered decision making. There is evidence that decision aids and shared decision-making can be valuable tools in the clinical care of multiple sclerosis patients[13]. Therefore having a CDSS at the point of care will benefit physician and patient in the decision making process. Since MS is a life-long disease and no complete cure exists the decision aids for physicians and patients will help in controlling the progression of disease and minimize disability. Since choosing DMTs is crucial and patient preference changes over time, having a CDSS will help in personalized decision making process and improve adherence to treatment[14].

1.4 Research Goals and Objectives:

The goal of the study is to develop a Clinical Decision Support (CDS) for early diagnosis of Multiple Sclerosis that can reduce the cost of care and improve the quality of life among MS patients. While the incidence and prevalence of MS is rising in United States, the number of misdiagnosed cases are also rising. One major source of misdiagnosis is misinterpretation of nonspecific clinical and imaging findings and misapplication of MS diagnostic criteria resulting in an over diagnosis of MS[11]. Since nonspecific white matter abnormalities on brain MRI and other imaging findings that may mimic MS, as well as MS-nonspecific lesions that are seen in people with MS, clinicians should be aware of all possibilities and should be able to interpret the clinical and MRI findings for proper diagnosis. An evidence based CDS can be utilized as a heuristic tool to minimize diagnostic errors. The differential diagnosis of MS includes MS variants and inflammatory astrocytopathies and other atypical inflammatory-demyelinating

syndromes, as well as a number of systemic diseases with CNS involvement. These differentials raises the odds of misdiagnosis in MS. A detailed history, a through neurological examination, MRI findings and cerebrospinal fluid study are essential for MS diagnosis. An evidence –based and optimized CDS can assist in filtering the differentials and arriving at correct diagnosis. With the implementation of Accountable Care Act (2010) our health care system has been evolved into a value-based care environment that emphasizes and oversees quality over cost. Therefore it is imperative to have the cost factor also added in the CDS to help clinicians in judiciously choosing the cost-effective diagnostic and therapeutic decisions at the point of care.

1.5. Research Hypotheses:

Having a clinical decision support tool for Multiple Sclerosis at the point of care can help clinicians in the early detection, avoid unnecessary tests and reduce the cost of care. The research hypotheses proposed are:

(i) If an evidence-based algorithm is designed using probabilistic signs and symptoms, then it can help clinicians in the early detection of Multiple Sclerosis.

The average time taken to diagnose MS is 6 months to 3 years. Studies have shown that early intervention can delay cognitive loss and progression of physical disabilities. Uncertainties in clinical presentations and etiology cause challenges to clinicians in making decisions. Until today no clinical decision support exists for early screening or early diagnosis of MS.

(ii) If the signs and symptoms are quantified by assigning weights and setting thresholds to determine the clinical need of advanced diagnostic tests, then it can help avoid unnecessary tests and delays in the diagnosis of Multiple Sclerosis.

Currently MRI is the only biomarker accepted as a standard for confirming diagnosis of MS. There are several studies that correlate association of MS with different etiological factors. Even though the exact cause of MS is not known it is possible to screen patients asking the history of possible etiological factors using an expert decision system and quantify the chances. This may help avoid several high cost tests that are done on patients empirically leading to waste of resources, time and money. An expert system can mitigate these losses to a great extent.

(iii) If the diagnostic algorithm is automated and used in electronic medical records then it can help clinicians in better decision making, in reducing the cost of care, improving the quality of care and the quality of life.

Investing money for artificial intelligence, machine learning and other advanced technological tools to diagnose MS is not feasible in current healthcare environment when cost regulations are strict and return of investment is not rewarding. A simple smart set that can be built and embedded in the EMR after testing the algorithm is affordable and feasible. Currently no such decision support system exist to flag possibility of MS and alert clinicians. This research study focuses on creating an evidence based model to make early detection and intervention happen at the point of care.

CHAPTER II

CLINICAL DECISION SUPPORT AND MULTIPLE SCEROSIS

2.1 Introduction

Computer based clinical decision support system (CDSS) has the potential to be truly transformative in health care. Despite considerable creativity and experimentation by enthusiasts over more than four decades, as well as convincing demonstration of effectiveness in particular settings, the adoption of CDS has been at a snail's pace. This slow progress has not accelerated significantly even with major recent national and international efforts to promote the use of the electronic health record (EHR), computerized physician order entry (CPOE), electronic prescribing (e-prescribing) and the personal health record (PHR). All of these are important substrates on which CDS can operate. Some capabilities have made their way into commercial health information system products. Examples include advice and warnings during CPOE to ensure proper doses, avoid harmful interactions, or warn about allergies, the provision of alerts to providers when abnormal laboratory results is found, and the use of order sets or grouping of orders for specific clinical problems and settings such as coronary care unit admission or postoperative care after hip replacement. The purpose of CDSS is to help clinicians in their decision making process and not to override their knowledge and expertise. CDS increases the probability and confidence in making the best decisions at the point of care utilizing the most relevant data in the electronic medical record or other databases to deliver evidence based quality care.

When it comes to chronic and complex disease conditions, the availability and progress of CDSS is limited and non-existent. Once such condition is multiple sclerosis which is

often called as the most expensive neurological disease condition that affects young men and women during their productive period of life. Developing a CDSS for a complex, multifaceted problem like multiple sclerosis needs consistent and coordinated efforts to bring evidence-based algorithms that would help clinicians to diagnose early and control the progression of disease that has no complete cure. The CDS should help clinicians at the point of care to avoid, errors, optimize quality, reduce cost and improve efficiency of care. As the healthcare delivery system in the U.S has recently changed from volume based to value based care most attention is given to quality over cost to deliver value.

2.2 History of Clinical Decision Support System:

The concept of CDSS is over six decades old and is traced back to 1950's when a mathematical model was presented by Ledley and Lusted in 1959 in their article titled "Reasoning foundations of medical diagnosis, symbolic logic, probability, and value theory aid our understanding of how physicians reason". This article has been called the first work in medical informatics. Since then over 25 CDSS models were released each having specific functions and purpose. In 2008 an extensive review of clinical decision support literature since 1959 was conducted by Wright A and Sitting DF who sequenced the systems and developed a four-phase model of the evolution of clinical decision support architectures[151]. The model developed consists of four phases: standalone decision support systems, decision support integrated into clinical systems, standards for sharing clinical decision support content and service models for decision support. These four phases have not heretofore been identified, but they track remarkably well with the chronological history of clinical decision support, and show evolving and increasingly

sophisticated attempts to ease integrating decision support systems into clinical workflows and other clinical systems.

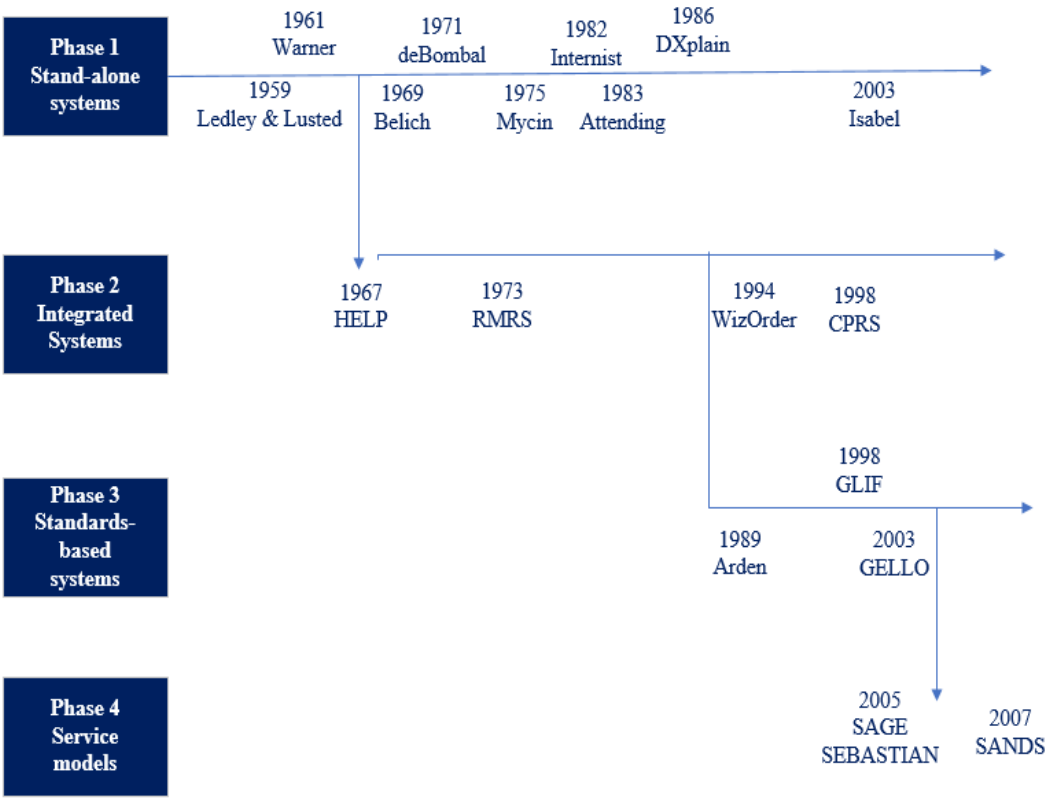


Figure 2.1 Schematic Drawing of the Four-Phase Model for Clinical Decision Support.

After all these years of evolution CDSS has become an integral application in health care technology. The HITECH Act 2009 followed by the Affordable Care Act 2010 promoted the use of technology by incentivizing adoption of EHR and other electronic databases and tools to improve the efficiency and quality outcomes. Today, almost all EHRs or EMRs have some type of CDSS integrated in the software as an application or interface. The tables (3.1 and 3.2) below show that the evolution of CDSS and since 2010 there has been an exponential growth of CDSS in all areas of healthcare management.

Table 2.1 Historic Timelines of the Evolution of CDSS

Historic Timelines of the Development of Clinical Decision Support Systems		
Architect/CDSS	**Timeline**	**Type and Purpose**
Ledley and Lusted	1959	A mathematical model for diagnosis
CASNET/Glaucoma	1960	Developed for the diagnosis and treatment of glaucoma
Homer Warner	1961	A mathematical model for diagnosing congenital heart disease
Morris Collen	1964	A system for automated multiphasic diagnosis
Howard Bleich	1969	A system to suggest therapy for acid-base disorders. It was the first decision support system to propose a management plan in addition to a diagnosis
PIP	1970	A system that gathered data and generated hypotheses about disease processes in patients with renal disease
F.T. de Dombal	1972	A probabilistic model to diagnose abdominal complaints
The Health Evaluation through Logical Programming (HELP)	1972	This system forms the basis of many research projects in clinical decision support
Micromedex	1974	System for medication safety, health and disease management, patient education, and toxicology. It also offers iPhone and iPad apps for its drug reference guide and medication interaction checker
INTERNIST I	1974	The first decision support system to span all of internal medicine
MYCIN	1976	An expert system for antibiotic dosing
Clem McDonald	1976	Protocol-based computer reminders

Table 2.2 Historic Timelines of the Evolution of CDSS (Continued)

Historic Timelines of the Development of Clinical Decision Support Systems (Contd)		
Architect/CDSS	**Timeline**	**Type and Purpose**
ABEL (Acid-Base and Electrolyte program)	1980	An expert system, employing causal reasoning, for the management of electrolyte and acid base derangements
QMR	1980	Designed as an electronic textbook, as an intermediate level spreadsheet for the combination and exploration of simple diagnostic concepts, and as an expert consultant program
PKC (problem-knowledge coupling)/Lawrence Weed	1980s	A problem-oriented medical record and the subjective, objective, analytical, and planning (SOAP) approach to clinical progress notes
ONCOCIN	Mid 1980s	A rule-based medical expert system for oncology protocol management
Perry Miller	1983	Attending system for anesthesia management, the first medical critiquing system
DXPlain	1987	A web version still available today
Elsevier	More than 25 years	A system divided into four categories: analytics and reporting; drug reference and decision support; evidence-based guidelines, clinical content, and tools; and learning and performance management
Brigham Integrated Computing System (BICS)/Jonathan Teich	1993	Provides nearly all clinical, administrative and financial computing services
Isabel	1999	A system that offers a Web-based checklist to help clinicians process symptoms and test results
Diagnosis One	2003	Includes components for clinical decision support, order sets, analytics, and public health recording and surveillance
ProVation	2006	Offers evidence-based clinical content and software for care plans
IndiGO	2007	Interfaces with electronic health records (EHRs)
Auminence	2010	Uses autonomy technology to retrieve diagnoses given fndings and organizes the diagnoses by body system

2.3 Types and Components of Clinical Decision Support System

CDSS is broadly classified into two types based on the advanced computing methodologies used in knowledge processing and generating decisions or outputs: (I) Knowledge based CDSS and (II) Non-knowledge based CDSS.

2.3.1 Knowledge Based CDSS: This consists of three parts—a knowledge base, an inference engine, and a mechanism to communicate. A rule-based reasoning and fuzzy logic are applied in this system. The knowledge base contains the rules that are evidence-based and associations of compiled data which most often take the form of IF-THEN rules. If this was a system for determining drug interactions, then a rule might be that IF drug X is taken AND drug Y is taken THEN alert user. Using another interface, an advanced user could edit the knowledge base to keep it up to date with new drugs. The inference engine combines the rules from the knowledge base with the patient's data. The communication mechanism allows the system to show the results to the user as well as have input into the system[143].

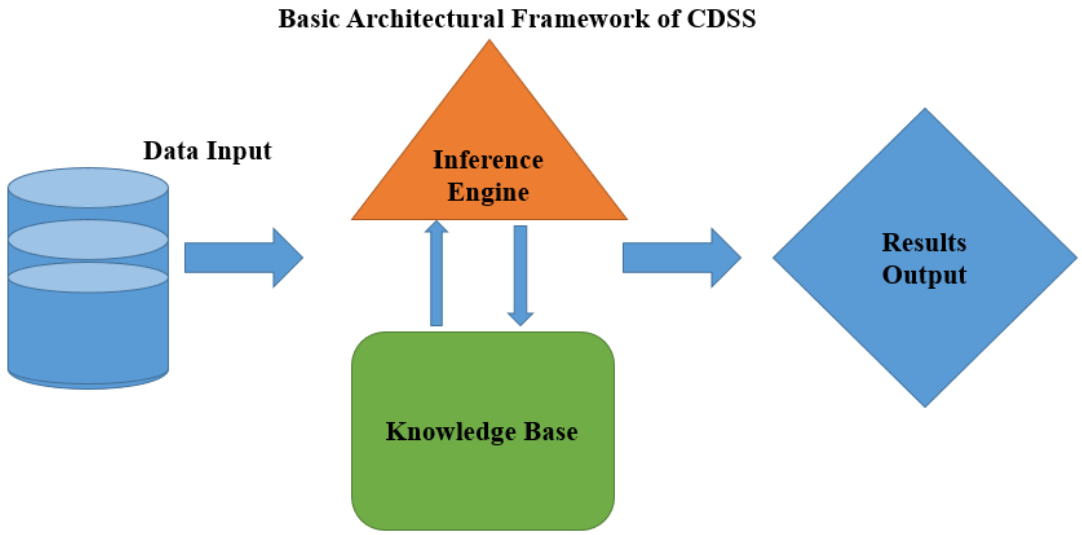


Figure 2.2 Basic Framework of Clinical Decision Support System

2.3.2 Non-Knowledge Based CDSS: This type of CDSS used artificial intelligence (AI) and machine learning (ML). AI and ML allow computers to learn from past experiences and/or find patterns in clinical data. This eliminates the need for writing rules and for expert input. However, since systems based on machine learning cannot explain the reasons for their conclusions, most clinicians do not use them directly for diagnoses, for reliability and accountability reasons. Nevertheless, they can be useful as post-diagnostic systems, for suggesting patterns for clinicians to look into in more depth[143].

There are three types of non-knowledge-based systems: **(I) Artificial neural networks** that use nodes and weighted connections between them to analyze the patterns found in patient data to derive associations between symptoms and a diagnosis. **(II) Genetic algorithms** are based on simplified evolutionary processes using directed selection to achieve optimal CDSS results. The selection algorithms evaluate components of random sets of solutions to a problem. The solutions that come out on top are then recombined and mutated and run through the process again. This happens over and over until the proper solution is discovered. They are functionally similar to neural networks in that they are also "black boxes" that attempt to derive knowledge from patient data. **(III) Support vector machines** that use a supervised learning technique similar to machine leaning but focuses on a narrow list of symptoms, such as symptoms for a single disease, as opposed to the knowledge based approach which cover the diagnosis of many different diseases[144].

2.4 Advantages of Clinical Decision Support Systems

There is growing recognition that CDSS, when well-designed and implemented, holds great potential to improve health care quality and possibly even increase efficiency and

reduce health care costs[145]. Improvement in the quality of care and efficiency in work flow are some of the reported benefits of CDSS in health care settings. The main purpose of CDSS is to provide timely information to clinicians, patients, and others to inform decisions about health care. Examples of CDS tools include order sets created for particular conditions or types of patients, recommendations, and databases that can provide information relevant to particular patients, reminders for preventive care, and alerts about potentially dangerous situations. CDSS can potentially lower costs, improve efficiency, and reduce patient inconvenience. In fact, CDS can sometimes address all three of these areas at the same time—for example, by alerting clinicians about possible duplicate tests a patient may be about to receive. A large body of evidence shows that CPOE which is one of the earliest decision supporting tool helped in improving patient safety.

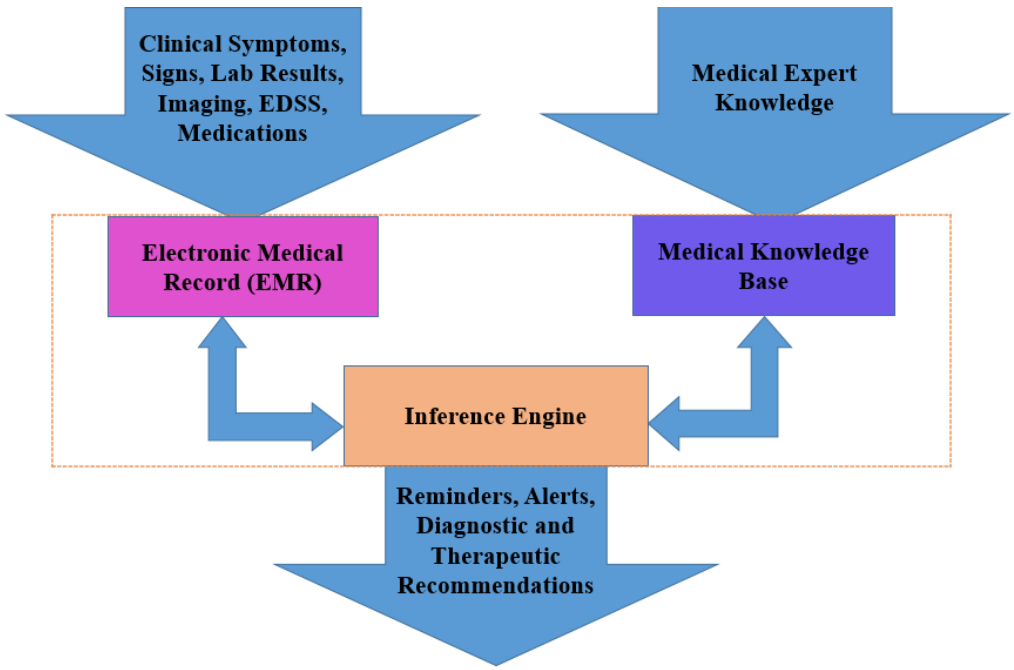


Figure 2.3 Architectural Frame Work of CDSS-EHR integration

A successful CDSS- EHR integration will enhance the provision of best practice and high quality care to the patient, which is the ultimate goal of healthcare. Errors always occur in healthcare, so trying to minimize them as much as possible is important in order to provide quality patient care. Three areas that can be addressed with the implementation of CDSS and EHR integration are: (i) medication prescription errors, (ii) adverse drug events, and (iii) other medical errors. During the last 10 years several studies have highlighted the effectiveness of CDSS as more advanced computing technology evolved and more integration of decision support tools being added to the clinical information systems. But still a mixed response exists about effectiveness due to lack of studies about effects on patient outcomes and cost control. In 2005 a systematic review concluded that CDSSs improved practitioner performance in 64% of the studies. The CDSSs improved patient outcomes only in 13% of the studies. Sustainable CDSSs features associated with improved practitioner performance was due to the automatic electronic prompts rather than requiring user activation of the system[146].

Table 2.3 Examples of CDS Interventions by Target Area of Care

Target Area of Care	Example
Preventive care	Immunization, screening, disease management guidelines for secondary prevention
Diagnosis	Suggestions for possible diagnoses that match a patient's signs and symptoms
Planning or implementing treatment	Treatment guidelines for specific diagnoses, drug dosage recommendations, alerts for drug-drug interactions
Follow up management	Corollary orders, reminders for drug adverse event monitoring
Hospital, provider efficiency	Care plans to minimize length of stay, order sets
Cost reductions and improved patient convenience	Duplicate testing alerts, drug formulary guidelines

(Clinical Decision Support System: State of the Art. AHRQ June 2009)

Another systematic review published in 2011 raised concerns about lack of evidence about the cost effectiveness of e-Health technologies which included CDSS[147]. Besides its uses in clinical practice, CDSSs are also widely used in clinical research; in medical education and training; to overcome problems in coding of data and to provide audit trail and decrease malpractice payments[148].

2.5 Weaknesses of Clinical Decision Support Systems

There are several challenges and barriers in adopting and sustaining CDSS. After the initial cost, additional cost needed for maintenance, support and training. As healthcare organizations are struggling to control healthcare cost in the U.S, implementation of CDSS is not an easy process. Resistance from clinicians is another barrier. There are still clinicians who think CDSS may threaten their clinical judgement and limit their freedom to think. Some clinicians think that CDSS leads to longer encounter time and force them to do extra work spending more time on computers than with patients. No study has ever found that CDSS reduces mortality. There is one systematic review that concluded that CDSS might moderately improve morbidity outcomes[149]. Lack of randomized control studies about the effectiveness of CDSS is also a drawback.

Since medical science is an ever changing science the CDSS will require updating on a consistent basis to meet the changing guideline and protocols.

Complexity of CDSS is another barrier that discourage clinicians who are not experts in computers and software programs. Alert fatigue due to excessive alerts and reminders lead to burn out and inefficiency, according to the reports from medical organizations like American Medical Association. User acceptance of CDSS takes longer period after installation. Ignoring or overriding recommendations from CDSS can also do more harm

than good. Taking users into confidence and training them is a challenging task. Attitude of clinicians and patients need to change for good acceptance rate. Those responsible for implementation need to recognize that CDS requires careful integration into the clinical workflow, which will take effort and involvement on the part of clinician users. The high frequency of failure to attend to the CDS alerts and recommendations represents a challenge for both clinicians and patients.

Some other challenges are interoperability and ease of integration with EHRs[150]. Some legacy systems may not be compatible for integrating the CDSS. This may require huge capital investment to change the hardware and applications of the legacy systems. There are also cases of semantic errors caused by differences in the terminology and ontology used in CDSS and EHRs. This can lead to failures in the operations and potential errors causing legal and ethical issues. Finally lack of evaluation standards and oversight make users skeptical in the adoption process and sometimes cause delays in implementation. Fortunately the opportunities in the current environment hold promise for increased use of CDSS. These include growing concerns about quality of care at the national level, calls for better cognitive support for clinicians, and incentives at the Federal level for meaningful use of health IT. In addition, the new generation of clinicians has trained in academic medical centers and other environments with advanced IT systems and is likely to be comfortable with technology, as will many of their patients. All of these factors are likely to lead to a more receptive environment for use of health IT[145]. At this point in time, the appropriate decision is not whether to design and implement CDS, but how to design and implement it so that, as the Institute of Medicine report says, we "make it easy to do the right thing."

2.6 Clinical Decision Support in Managing Multiple Sclerosis:

Clinical and demographic predictors of Multiple Sclerosis are scattered with varying probabilities. The etiology of MS is still unknown but a wide range of studies exist that correlate association of MS with environmental factors, genetic factors and infections. Recent rise in incidence of MS is causing concern and until today no screening tool or clinical decision support exist to identify risk or make disease predictions. Even diagnosis of MS takes an average 6 months to 3 years. In this research study the clinical and demographics factors are selected and quantified to help clinicians in early diagnosis and intervention. The expert system designed in this study is a start to apply evidence based approach to identify all clinical and demographic predictors and recommend advanced testing or follow ups in a systematic way to detect cases at early stage and start clinical management to delay disabilities and cognitive deterioration.

CHAPTER III

LITERATURE REVIEW

3.1 Epidemiology of Multiple Sclerosis:

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) characterized by inflammatory and degenerative changes in the brain and spinal cord. MS is the most common cause of non-traumatic disability in young adult and therefore extensive research has been performed in order to clarify the etiology and pathogenesis of this disease[18]. Studies report that MS is the most common chronic progressive neurologic disease of young adults, affecting individuals in their most productive years, and placing a heavy burden on affected persons, their family members, and the health care system. Unlike some other world regions, considerable gaps exist in knowledge regarding the incidence and prevalence of MS in the United States because there is no robust method for estimating either epidemiologic statistic on a national basis.

In MS, a multifactorial interplay of genetic and environmental factors leads to a chronic activation of the immune cells and cerebral tissue injury[19]. A study conducted by the National Multiple Sclerosis Society and published in the February 15, 2019, online issue of Neurology®, the medical journal of the American Academy of Neurology, shows more than twice as many people in the U.S. are living with multiple sclerosis than previously thought. The previous studies estimated the prevalence to be 400,000, but this new study shows that number is closer to 1 million[140]. In the last 4 decades, 4 studies have estimated the prevalence of MS in the United States by using methods intended to provide representative samples of the US population (Table 2.1).

Table 3.1 Epidemiologic Studies of MS prevalence in the U.S

Epidemiologic Studies of Multiple Sclerosis (MS) Prevalence in the U.S using Probability Sample Surveys					
Reference Authors (Year)	**Study Years**	**Case Definition**	**Population**	**National MS Prevalence Per 100,000 Population**	**Number of Persons with MS in the U.S (95% CI)**
Baum and Rothschild(1981)	1976	Survey of physicians and hospitals, asked to report patients meeting uniform criteria for probable and possible MS	National sample of 8,800 physicians and 725 hospitals, a probability sample of the 1976 US population	58 per 100,000 (all ages)	123,000
Collins(1997)	1990-1992	Patients or family members reporting physician-diagnosed MS	NHIS, a household probability sample of US population	70 per 100,000(all ages)	180,000
Noonan et al. (2002)	1982-1996	Patients or family members reporting physician-diagnosed MS	NHIS, a household probability sample of US population	85 per 100,000(all ages)	211,000 (191-231,000)
Campbell et al. (2014)	2008-2009	Patients having 1 or more medical claims with MS diagnostic code 340 during a single year	MEPS-HC, a household probability sample of US population	191 per 100,000 (≥ 18 years)	572,312 (397,004-747,619)
Abbreviations: CI=confidence interval; MEPS-HC= Household Component of the Medical Expenditure Panel Survey; NHIS=National Health Interview Survey					

(Nelson et al, Neurology Mar 2019, 92 (10) 469-480)

Population based MS Registries have been found to be useful to estimate MS prevalence in some countries like Denmark, Sweden, Norway, and Poland. However, a similar US population-based MS registry does not exist. In the United States, there are several voluntary MS registries for conducting outcomes research; however, none of these

registries attempts the near-complete case ascertainment in a defined geographic region that would enable the estimation of MS prevalence.

3.1.1 Temporal Trends and Latitudinal Gradient Effect: MS has been traditionally considered to be more frequent in women and in regions more distant from the equator. The most comprehensive review of MS prevalence to date, has confirmed a statistically significant positive association between MS prevalence and latitude globally[27]. High frequency areas of the world (prevalence of 60 per 100,000 or more) include all of Europe (including Asian Russia), southern Canada, northern United States, New Zealand, and southeast Australia. In many of these areas, the prevalence is more than 100 per 100,000; the highest reported rate (300 per 100,000) is in the Orkney Islands. In the United States, the estimated prevalence is 100 to 150 per 100,000, for a total of 300,000 to 400,000 persons with MS[29-30]. Confidence in these prevalence estimates is limited by inconsistent registration, tracking, and reporting of MS cases[28]. Considerable gaps exist in knowledge regarding the prevalence of neurologic diseases, such as multiple sclerosis (MS), in the United States[134].

However, the universal association between latitude and risk of MS has been challenged by findings from a 2010 systematic review and meta-analysis of epidemiologic studies of MS[31]. The results showed that, while the prevalence of MS increased with geographic latitude in Western Europe, North America, and Australia/New Zealand, the incidence of MS increased with latitude only in Australia/New Zealand, and not in Western Europe or North America. Thus, there was no latitudinal gradient for MS incidence in the northern hemisphere. In the absence of association with incidence, the observed latitudinal-

gradient of MS prevalence could be explained by other factors, such as survival time, diagnostic accuracy, and ascertainment probability.

3.1.2 Gender and Race: Recent reports suggest that the latitude gradient could be disappearing and that the female-to-male ratio among patients with MS has increased in the last five decades[26]. A systematic review of 28 epidemiologic studies found that, from 1955 to 2000, the estimated female to male ratio of MS incidence increased from 1.4:1 to 2.3:1[26]. Subsequent studies have also found that the female-to-male incidence ratio is increasing, mainly due to an increasing incidence of MS in females[31-34]. The reasons are unclear but a new study published in 2014 found that females susceptible to MS produce higher levels of a blood vessel receptor protein, S1PR2 (Sphingosine-1-phospahte receptor 2), than males and that the protein is present at even higher levels in the brain areas that MS typically damages[153]. But the enhanced expression of this receptor protein is found in other autoimmune conditions also.

The geographic variance in MS prevalence was previously thought to be explained in part by racial differences; white populations, especially those from Northern Europe, appeared to be most susceptible, while people of Asian, African, or American Indian origin appeared to have the lowest risk, with other groups intermediate. But, subsequent studies in the United States demonstrated and increased incidence of MS in Blacks, Hispanics and Children suggesting that racial susceptibility is also changing[35-36].

3.1.3 Sunlight and Vitamin D: Another explanation for the possible association of MS with latitude was that exposure to sunlight might be protective, either because of an effect of ultraviolet radiation or of vitamin D. A number of studies have found an inverse relationship between sun exposure, ultraviolet radiation exposure, or serum vitamin D

levels, and the risk or prevalence of MS[37-44]. At the same time some studies have shown that sunlight and vitamin D levels are inversely related to MS disease activity in established cases leading to the belief of protective benefits of these factors. The three prominent studies are: (1) Analysis of data from Nurses' Health Study II found that the risk of developing MS was significantly reduced among women taking >/= 400 IU/day of Vitamin D (relative risk 0.59, 95% CI 0.38-0.91)[43]. (2) A longitudinal cohort study of 469 subjects with MS found that vitamin D levels were inversely associated with the risk of new T2 weighted or gadolinium enhancing T1-weighted lesions on Brain MRI[45]. (3) A prospective report of over 450 patients with a clinically isolated syndrome suggestive of MS showed that serum 25-hydroxyvitamin D levels, measured in the first 12 months delayed the risks of conversion to clinically definite MS and the progression of the disease[46].

3.1.4 Viral Infections: Epidemiological studies have identified several viruses as factors that may influence MS risk including Epstein-Barr virus, Herpes simplex virus types 1 and 2, Human herpes virus 6, measles, mumps and rubella. Although several viruses have been associated with MS, no specific evidence linking viruses directly to the development of MS has been reported[46]. Recently increasing attention has been given to Epstein-Barr virus (EBV), which causes infectious mononucleosis as a possible cause or trigger of MS[48]. In a meta-analysis of 14 case-control and cohort studies, the risk of MS was increased after infectious mononucleosis (relative risk 2.3, 95% CI 1.7-3.0)[49]. A prospective nested case-control study of women and another nested case-control study found that higher antibody titles of EBV complex and EBV viral capsid antigen were

associated with an increased risk of MS[50-51]. There is also a conflicting evidence of EBV in brain tissue of MS patients[52-55].

There is also a virus reported as having protective action against MS, like Cytomegalovirus[57]. It is not clear if the association is causal or spurious, nor is it known precisely how such an infection would be protective[56].

Varicella zoster virus (VZV) has also been implicated to MS in some studies. A case-control study found viral particles identical to VZV, and DNA from VZV, in cerebrospinal fluid (CSF) samples from patients with acute relapses of MS[58-59].

Two recent observational studies suggests that the humoral immune response that is poly-specific and not exclusively directed against a particular virus may be involved in MS pathogenesis[20-21].

3.1.5 Vaccinations: Since the pathogenesis of MS is thought to involve the immune system, it has been hypothesized that a stimulus of the immune system (e.g. vaccine) may trigger the disease. However, several studies have failed to show any association between vaccines and MS[65-69]. Although a later study, a well-designed case-control study, found an increased risk of MS in patients who had received hepatitis B vaccination the indisputable large benefit of this vaccine far outweighs the possible and still unproven risk of developing MS that the vaccine may carry [70-71]. Two well-designed studies seemingly refuted the possible link: one finding no association between hepatitis B vaccination and the development of MS, and the other finding no association between several different vaccines and disease relapse in patients with MS[73-74].

A 2006 systematic review of nine case-control studies found a negative association between tetanus vaccination and the risk of MS (odds ratio 0.67; 95% CI 0.55-0.81)[66]. A summary of published evidence (through January 2001) supported the safety of vaccination in patients with MS. A subsequent case-control study found no association between several different vaccines and the development of MS and/or optic neuritis[67-68].

Another study that analyzed the vaccination against the human papillomavirus has been shown not to increase the risk of MS[72].

3.1.6 Genetic Factors: There are various studies published since 2005 finding association of over 100 polymorphisms with MS. Among the strongest association is that the risk of developing MS is related to certain class I and class II alleles of the major histocompatibility complex (MHC), particularly the HLA-DRB1 locus[75-80]. Growing body of evidence suggests that the risk of MS is associated with multiple non-MHC susceptibility genes of modest effect (e.g. CD6, CLEC16A, IL2RA, IL7R, IRF8, and TNFRSF1A) [78-79, 81-83]. In addition, polymorphisms in the IL-7R gene may slightly increase the risk of MS[76, 84, 85]. It has been found in one study that the presence of a vitamin D response (VDRE) element located in the promoter region of many but not all HLA-DRB1 alleles suggests that environmental differences in vitamin D might interact with HLA-DRB1 to influence the risk of MS[86]. However, other factors related to HLA variation may have more impact on MS risk than vitamin D regulation of HLA-DR expression. In one study of Australian Caucasians that compared 466 MS cases and 498 controls, the risk of developing MS varied more than 10-fold according to HLA-DRB1 allele type and associated sequence variation in the promoter region, with odds ratios ranging from 0.28 to 3.06[87]. A protective effect was associated with HLA-DRB1*04,

*07, and *09 (DR53 group) alleles, while DRB1*15 and *16 (DR51 group) and *08 (DR8 group) were associated with a higher risk. However, VDRE sequence variation itself was not independently associated with MS risk. Most of the Caucasian HLA-DRB1 alleles expressed a functional VDRE sequence, including alleles that had no apparent effect on MS risk. Moreover, in a study from Sardinia, where the prevalence of MS is high, the VDREs associated with several of the HLA-DRB1 variants linked to MS risk in Sardinians were often mutated and nonfunctional[88]. These results suggest that, at least in Sardinia, the effect of vitamin D on HLA-DRB1 expression as mediated by VDRE is quite limited. Instead, among Sardinians, polymorphisms in B-cell activating factor (BAFF) regulatory elements has a very high relationship to the development of MS.

In a population-based twin studies of 1993, the risk of developing MS for dizygotic twin pairs is the same as that for siblings (3 to 5 percent); however, the risk for monozygotic twins is at least 20 percent and may reach close to 39 percent[89]. For purposes of genetic counseling, the sibling risk of MS is 3 to 5 percent. But, MRI studies of unaffected family members that have noted abnormalities on scanning suggest that the risk may be even higher.

The frequency of familial MS varies from 3 percent to 23 percent in different studies. One well-designed population study of 8205 Danish patients with MS found that the relative lifetime risk of MS was increased sevenfold (95% CI 5.8-8.8) among first-degree relatives (n = 19,615). The excess familial lifetime risk for first-degree relatives was 2.5 percent (95% CI 2.0-3.2) in addition to the sporadic absolute risk of MS in Danish women and men of 0.5 and 0.3 percent, respectively. These sporadic rates from the Danish population are among the highest in the world[90].

Table 3.2: Familial Risks for Multiple Sclerosis

Relationship to patient	Recurrent Risk (%)	Risk Relative to Population	Proportion of Genetic Sharing
Adopted first-degree relative	0.2	Identity	0
Sibling with MS	3.0-5.0	15-25 fold increase	50
Dizygotic Twin	3.0-5.0	15-25 fold increase	50
Monozygotic Twin	34	170 fold increase	100
One parent with MS	3.0-5.0	15-25 fold increase	50
Two parents with MS	6.0-10.0	30-50 fold increase	50 with each parent
Assumes lifetime population prevalence of 0.2% (Ebers et al., Dyment et al, 2004a)			

3.1.7 Sex of affected parent: There is also accumulating evidence about the susceptibility of MS linked to the sex of the affected parent. Some studies have found a maternal parent-of-origin effect, with an excess of maternal inheritance of MS susceptibility. In contrast, studies of parent-child pairs with MS have found that paternal transmission is equal to or greater than maternal transmission. The explanation for this discrepancy is unclear, but epigenetic mechanisms (e g., DNA modifications such as histone acetylation and DNA methylation that do not modify the DNA sequence) transmitted through cell division may be involved in direct transmission from an affected parent[91-97].

As genome-wide association studies increase in size, the ability to detect risk alleles conferring even very small increases in MS susceptibility increases. In a report published in 2013 that focused on genetic variants associated with immune function, the number of genetic variants linked to MS risk was >100[82]. Although the precise functional effects of these variants are mostly unknown, they are over-represented in regulatory as opposed to coding regions of genes associated with immunologic function, and many of the variants are associated with other autoimmune conditions as well[98]. For example, a genome-wide association study focused on a population from Sardinia, where there is a high prevalence

of MS and systemic lupus erythematosus (SLE) [99]. A variant in the TNFSF13B gene, encoding B-cell activating factor (BAFF), was associated with both MS and SLE. The proposed mechanism is that the TNFSF13B variant causes higher production of soluble BAFF, leading to enhanced humoral immunity and an increased risk of autoimmunity. The authors of this study suggested that among this group, there is an inverse relationship between susceptibility to malarial diseases and autoimmunity. This relationship clearly would not be as important in Northern Europe and United States.

3.1.8 Genomic Linkage Screens and Association Screens: The first series of genomic-wide screens using several hundred microsatellite DNA markers in 100 affected sibling pairs (pairs of non-twin siblings in which one was affected by MS and the other was not) was undertaken in the 1990s. Follow up studies using multiple affected families adding more microsatellite markers to the initial genome screens also were done. But all these studies failed to detect any convincing new MS susceptibility loci nor produce new MS-associated genes. Pooling data for meta-analysis also didn't help in identifying loci other than MHC. It became clear that identification of the other effects of genetic variations impacting MS susceptibility would require not only better markers but also a substantially higher number of families to reach necessary statistical power. Thus the International Multiple Sclerosis Genetics Consortium (IMSGC) was founded in 2003 which took the initiative for the first large-scale linkage study with sufficient statistical power to detect loci that had similar effects to that of the MHC across the genome came from populations in Australia, Scandinavia, the United Kingdom and the United States. However this study could only identify the well-known association between MHC and MS susceptibility.

Further technological innovation led to identification of genetic variants that occur at a single base pair position within the genome called single nucleotide polymorphisms (SNPs) throughout the genome. Unlike linkage analysis SNP-based technology was capable of detecting smaller individual genetic effects by mapping the SNP variants from thousands of individuals. MS was one of the first disease to be studied using genome-wide association screening (GWAS). The IMSGC conducted the first GWAS in 2007 using 334,923 SNPs in 930 MS trio families (a trio family is a MS patient and both parents) with replication datasets consisting of another 609 family trios and an additional 2322 case subjects and 789 unrelated controls[76]. As anticipated, the MHC was definitively associated with MS susceptibility; however, beyond the MHC only two other loci were identified with a statistically significant level of confidence. These loci (the first non-MHC loci that were definitely associated with MS risk) encoded genes involved in immune regulation: the interleukin-2 receptor (IL2Rα) and the interleukin-7 receptor (IL7Rα).

Associations with MS susceptibility for both loci were subsequently validated in other populations[108-109]. However, variations at these two alleles, along with those of the MHC, could not account for all of MS heritability. For example, the IL2Rα variant was present in 88% of patients and 85% of controls. Similarly, the MS-associated IL7Rα variant was present in 78% of patients and 75% of controls.

3.1.9 Other factors: Another recently recognized environmental risk factor for MS is smoking. Smoking is reported to affect a number of biological mediators of inflammation

through its action on immune-inflammatory cells, leading to an immunosuppressant state[22]. The Nurses' Health Study showed that the relative incidence rate of MS in current smokers compared to never smokers was 1.6, with a dose response dependent on pack years smoked.

Birth month has been implicated as a possible risk factor for MS, though the literature is conflicting. A 2013 meta-analysis and systematic review found that the risk of MS was increased for those born in April and May and decreased for those born in October and November[60]. This study suggested that the gestational or neonatal environment influences the risk of MS later in life. But a subsequent study found that the birth effects are actually false positive results that result from confounding caused by seasonal variation in birth rates, with data from Europe and North America showing excess births in March, April, or May, and reduced births in November, December, and January[61].

Obesity in childhood or adolescence may also be a risk factor for MS, as suggested by several studies[62-64].

3.2 Pathology:

MS pathology and pathogenesis are apparently much more complex than originally anticipated. A major challenge in the field of pathology in MS came from recent developments in magnetic resonance imaging (MRI) and spectroscopy technique (MRS). Neuroimaging studies helped neuropathologists to identify profound alterations in the so-called normal appearing white matter as well as gray matter. MRS data confirmed earlier pathologic observations that not only myelin, but also axons and neurons, are affected by the disease activity and illustrated the magnitude of neurodegenerative events in brain.

All these new insights gave rise to the concept that in MS neurodegeneration may occur independently of the inflammatory process.

The characteristic neuro-pathologic feature of MS is the presence of focal demyelinated plaques within the central nervous system(brain and spinal cord) accompanied by varying degrees of inflammation and gliosis, with partial preservation of axons[104]. The lesions can occur in the optic nerves, spinal cord, brainstem, cerebellum and the juxta-cortical and periventricular white matter[105]. Axonal injury is a prominent feature of MS plaque but may not be present in acute phase.

Although MS has been traditionally considered as a disease of focal white matter lesions, the spectrum of MS pathology is now understood to encompass a broader array of abnormalities. This includes diffuse damage of so-called normal appearing white matter 9NAWM) and normal-appearing gray matter (NAGM) on MRI, both of which are associated with a progressive loss of brain volume[100]. Widespread confluent and plaque-like demyelination with oligodendrocyte destruction is the unique pathological hallmark of the disease, but axonal injury and neurodegeneration are additionally present and in part extensive. Re-myelination of existing lesions may occur in MS brains; it is extensive in a subset of patients, while it fails in others. Active tissue injury in MS is always associated with inflammation, consistent with T-cell and macrophage infiltration and microglia activation. Recent data suggest that oxidative injury and subsequent mitochondrial damage play a major pathogenesis-role in neurodegeneration. Inflammatory cortical demyelination has been found in 38 percent of biopsy-proven cases of early MS[101].

The two main MS phenotypes are those of relapsing and progressive disease. However, the pathology of brain injury in both relapsing and progressive forms of MS is not fundamentally different, though some studies have suggested that progressive forms of MS are marked by reduced or absent inflammation[102]. More convincing evidence suggests that primary progressive MS is part of the clinical spectrum of MS and is not pathophysiologically different from relapsing MS that has evolved into a secondary progressive phase[103].

3.3 Pathogenesis:

MS is a heterogeneous disorder reflecting different pathways to brain tissue injury. Inflammation, demyelination and axonal degeneration are the major pathologic mechanisms that cause the variable clinical and pathological features. However the cause of MS remains unknown[106-107]. The most widely accepted theory is that MS begins as an inflammatory immune-mediated disorder characterized by autoreactive lymphocytes and later the disease is dominated by microglial activation and chronic neurodegeneration.

3.3.1 Immunopathology:

In recent years the insight into the role of innate immune system in MS changed. The old hypothesis based on animal models that MS was driven by T cell activity is now supplemented with B cell activity also as more in depth view of the complexity of the disease has been revealed by immunological studies. Focal white-matter lesions in MS, the classical plaques, are defined by a triad of inflammation, primary demyelination, and reactive astrocytic scar formation. The pathological finding that inflammatory response mediated by cells leading to tissue injury and blood-brain barrier (BBB) damage reflected

as T2 lesions (plaques) in brain MRI has been supported by several studies. Mononuclear cells consisting of T lymphocytes and macrophages accumulate in the active lesion sites and connective tissue spaces of brain and spinal cord confirmed the immune-mediated inflammatory process. The dominant T-cell populations in the lesions are MHC Class I restricted CD8+ T lymphocytes (80%) and Class II restricted CD4+ T cells (20-30%). In line with these cells, expression of pro-inflammatory cytokines, in particular interleukins 17 and 21, were found in the infiltrating T cells in MS lesions[80]. Migration of these cells through the BBB in the course of immune surveillance and brain inflammation need pre activation of cells. Migration of leukocytes through the wall of cerebral vessels requires the expression and activation of adhesion molecules and the interaction of chemokines with their specific receptors. Much less is currently known about how B lymphocytes and monocytes enter the CNS. It has also been found that inflammation in MS lesions may be downregulated by the local action of regulatory T cells like HLA-G-positive T Cells and Fox-P3 positive T cells[110-112].

Another interpretation of the role of T cells in lesion pathogenesis in MS is that leukocytes may not necessarily be harmful. Several studies convincingly demonstrate that T cells, B cells, and monocytes can produce neurotrophins and leukocytes that are immunoreactive for brain derived neurotrophic factor. These factors have been found in the active MS plaques. Thus autoreactive T cells also have neuroprotective functions stimulating remyelination and repair[112-113].

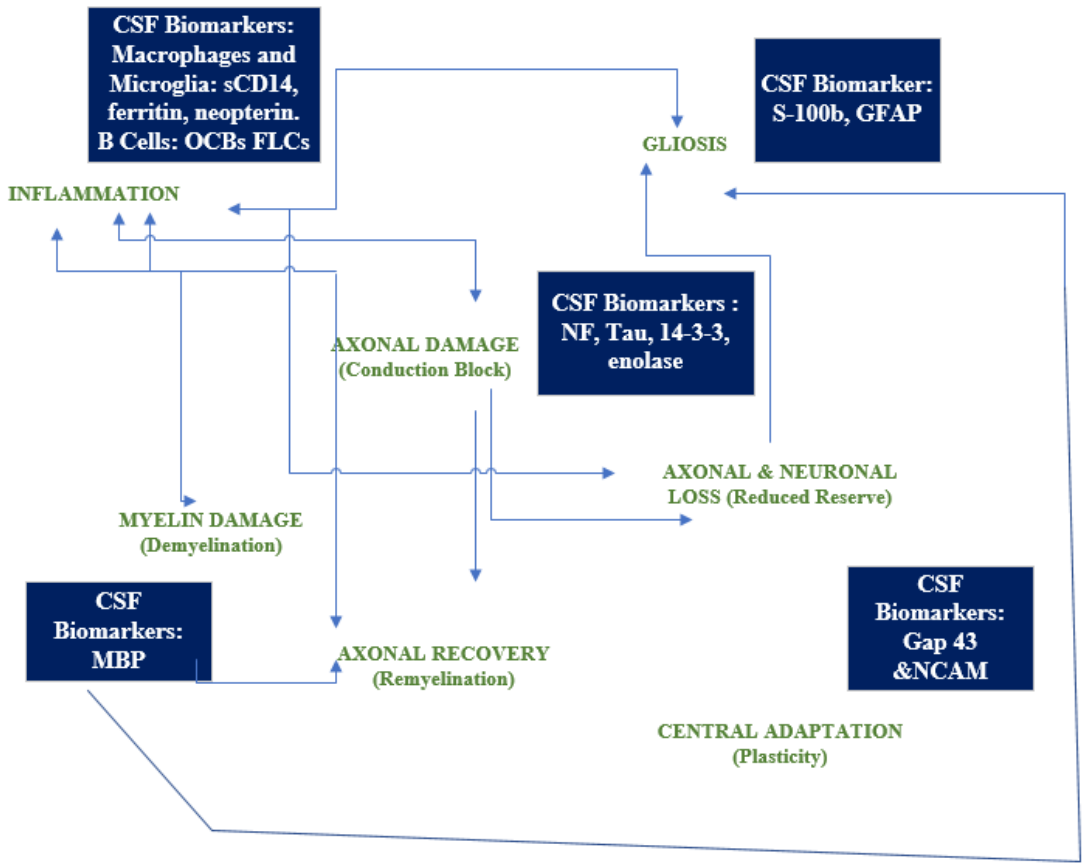


Fig: 3.1 Key Pathogenic Changes (CSF, cerebrospinal fluid; OCBs, oligoclonal immunoglobulin G bands; FLCs, Free Light Chains; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; NCAM, neural cell adhesion molecule)

Besides T lymphocytes, macrophages and activated microglia cells are abundant in active MS lesions. Autoreactive T cells, both of CD4+ and CD8+ phenotype, can be isolated from peripheral blood of MS patients and macrophages or microglia cells within MS lesions may express antigenic peptides from CNS proteins on their surface. Furthermore, clonal expansion of T cells within the lesions suggests their antigen-driven proliferation. Despite these advances it is not known whether autoreactive T cells in MS lesions are an exception to the rule.

Phagocytes in MS lesions can express a large number of molecules, which are engaged in migration, phagocytosis, antigen presentation, and tissue injury. They include adhesion molecules, chemokine receptors, scavenger receptors, Fc receptors, MHC molecules, costimulatory molecules, proteases, Toll-like receptors and inducible nitric oxide synthase. Which of these molecules are dominantly upregulated appears to depend upon the type of tissue damage, the stage of the individual lesion and the disease state, although in most of these studies an exact lesion is missing[106]. The local microenvironment determines the pattern of macrophage and microglia activation in MS lesions. In some very aggressive and fulminant MS lesions the inflammatory infiltrates also contain granulocytes and even eosinophils.

The presence of inflammation in active MS lesions, the association of MS susceptibility with gene polymorphisms related to inflammatory genes and the therapeutic effects of anti-inflammatory or immunomodulatory treatments strongly suggest that inflammation drives demyelination and neurodegeneration in MS.

3.3.2 Inflammation and Blood Brain Barrier (BBB) damage in MS:

Contrast enhancement in T1-weighted MRI scans following systemic application of gadolinium (diethylene triamine penta-acetic acid-DTPA) is a well-established biomarker for BBB damage in brain. In MS, gadolinium (Gd) enhancement frequently precedes the formation of new focal white-matter lesions. Studies have shown profound inflammation within and around blood vessels in Gd-enhancing lesions. Gd enhancement is a very reliable surrogate marker for the inflammatory activity of MS lesions and used routinely for diagnosis and clinical studies. Studies in the past have shown that changes in the BBB permeability are not strictly related to inflammation and are present in both active and

inactive lesions. Early studies using post mortem perfusion of the brain with organic dyes showed widespread changes in the BBB permeability in MS patients in active and inactive lesions. This led to a dogma that presence of Gd enhancement in MRI equates to the presence of inflammation in MS and, conversely, that the absence of enhancement excludes inflammation.

In recent year more genetic studies postulated the role of both T cells and B cells in the damage to BBB. In genetically susceptible individuals, through immune dysregulation and probably mistaken antigen identity, CD4 T cells become primed in the peripheral blood and cross the blood–brain barrier, where they recognize components of the myelin sheath. The subsequent release of cytokines, such as interferon-γ (IFN-γ) and tumor necrosis factor-alpha, activates macrophages and B cells; local inflammation ensues, resulting in destruction of oligodendrocytes with demyelination of axons[131]. Disruption of the myelin sheath leads to reduced saltatory conduction and reduced conduction velocities along nerve fibers. In some cases, this results in the focal neurological symptoms known as ‘relapses’. Although local inflammation generally resolves and remyelination occurs, the underlying nerve fibers can accumulate damage over time, resulting in progressive axonal loss and brain atrophy.

In multiple sclerosis it is postulated that the CD4 T cells specific for certain microbial antigens are able to cross-react and recognize proteins on the surface of the myelin sheath. In genetically susceptible individuals who lack immune-regulatory mechanisms, these autoreactive cells are allowed to persist. They eventually recognize and destroy myelin after crossing the blood-brain barrier. APC-antigen presenting cell; TH- T helper cell.

3.3.3 Myelin and oligodendrocyte pathology in MS:

Myelin is affected in MS lesions by segmented demyelination at the node of Ranvier and traverse the plaque area as denuded axons. In active lesions myelin sheaths are destroyed in close association with activated macrophages and microglia. The macrophages take up myelin fragments and gradually degrade the myelin proteins and lipids within their lysosomes. This degradation process takes several days to weeks and the presence of myelin fragments within macrophages is a very reliable marker for active lesions[114]. Minor myelin proteins such as myelin-associated glycoproteins are degraded within a few days and myelin lipids are degraded into cholesterol esters and triglycerides, which may persist within macrophages in the lesions for several months. Lipid degradation products can be detected in the magnetic resonance spectroscopy, which helps to classify the age of a lesion by neuroimaging.

The fate of oligodendrocytes in MS lesions was controversial for many years. The issue was resolved only when electron microscopy was performed and specific markers of oligodendrocytes and their progenitor cells became available. It was originally believed that oligodendrocytes are completely lost with remyelination, but the specific markers revealed the presence of abundance of oligodendrocytes in lesions. A systematic study on a large sample of MS patients revealed that the oligodendrocyte density is highly variable between different lesions[115]. In the early stages of lesions oligodendrocytes are destroyed in parallel to demyelination, although the degree to which this damage occurs varies between lesions. Mature oligodendrocytes which survive the demyelinating attack are still present in the lesions[116].

At the top of the proposed cascade of events that lead to axonal loss is the production of reactive-oxygen species (ROS) and nitric oxide (NO) from activated microglia and infiltrated macrophages. ROS and NO can induce neuronal mitochondrial dysfunction, which might contribute to demyelination, apoptosis of oligodendrocytes, and degeneration of axons. Specifically within axons, the reduced production of ATP caused by mitochondrial dysfunction might lead to increased calcium concentrations, with consequent neuronal death. Acidosis and glutamate-mediated excitotoxicity contribute to increased intracellular concentrations of calcium. mGluR=metabotropic glutamate receptor. NCX=sodium-calcium exchanger. ASIC=acid-sensing ion channel.

3.3.4 Pathophysiology of Nerve Conduction in Myelinated and Demyelinated axons:

Nerve conduction in myelinated axons occurs faster, called salutatory manner, with the nerve impulse jumping from one node of Ranvier to the next without depolarization of the axonal membrane underlying the myelin sheath between nodes (Fig.2.8). Myelin helps in producing considerably faster conduction velocities (approximately 70m/s) than in unmyelinated nerves (approximately 1m/s) where continuous propagation is very slow. Conduction block occurs when the nerve impulse is unable to traverse the demyelinated segment. This can happen when the resting axon membrane becomes hyperpolarized due to the exposure of voltage-dependent potassium channels that are normally buried underneath the myelin sheath. A temporary conduction block often occurs following a demyelinating event. Later, redistribution of sodium channels ultimately allows continuous propagation of action potential through the demyelinated segment.

3.3.5 Demyelination:

Although multiple sclerosis is generally believed to be a T-cell mediated inflammatory disease of the central nervous system, recent experimental and neuropathological studies show that additional pathogenetic factors are required to induce widespread primary demyelination and secondary tissue damage. The pathogenetic heterogeneity of multiple sclerosis suggests that immunomodulatory treatment of this disease may be more complex. Another theory of demyelination in multiple sclerosis is that it may be activation of myelin-reactive T cells in the periphery, which then express adhesion molecules, allowing their entry through the blood-brain barrier (BBB).

T cells are activated following antigen presentation by antigen-presenting cells such as macrophages and microglia, or B cells. Perivascular T cells can secrete proinflammatory cytokines, including interferon gamma and tumor necrosis factor alpha. Antibodies against myelin also may be generated in the periphery or intrathecally. Ongoing inflammation leads to epitope spread and recruitment of other inflammatory cells (i.e., bystander activation). The T cell receptor recognizes antigen in the context of human leukocyte antigen molecule presentation and also requires a second event (i.e., co-stimulatory signal via the B7-CD28 pathway, not shown) for T cell activation to occur. Activated microglia may release free radicals, nitric oxide, and proteases that may contribute to tissue damage.

3.3.6 Remyelination:

Besides mature oligodendrocytes the brain tissue also contains glial progenitor cells and most experimental data suggest that these cells are responsible for remyelination[117]. Glial

progenitor cells are abundant in some lesions. Systematic studies on this issue provided clear evidence that remyelination within MS plaques is much more frequent and extensive than previously anticipated[118-119]. Prineas et al provide convincing electron microscopic evidence for myelin repair, by showing the appearance of very thin myelin sheaths with shortened internodes. He also documented the abundance of activated remyelinating oligodendrocytes by using specific myelin protein markers. He further concluded that remyelination in MS lesions starts at very early stages, even when myelin-containing macrophages were still abundantly present in active lesions. Besides he also showed that remyelinated lesions sometimes became a target for new demyelinating attacks, indicating that repeated episodes of de and re-myelination can occur within the same brain lesion[120-121].

Several processes are thought to be involved in disease pathogenesis. Lymphocyte-driven inflammation induces conduction blocks in structurally intact axons, drives demyelination, and induces transection of axons (with consequent conduction block) within acute lesions. Activated microglial cells might contribute to the repair mechanisms that lead to remyelination or to the degeneration of axons. Redistribution of sodium channels along demyelinated axons could restore conduction. Astrocytic activation and proliferation (gliosis) might impede repairs[122]. In addition there is a heterogeneity in the extent of remyelination between different patients. In the majority of patients completely demyelinated plaques dominate and remyelination is sparse and restricted to small lesions or lesion areas. In contrast, in other patients, extensive myelin repair leads to remyelination of more than 80% of plaques and plaque areas[123-124]. However, when the focus of study was shifted to areas of completed remyelination and to the shadow

plaques, extensive remyelination is found to be presenting about 20-30% of patients, while in the others remyelination was sparse or absent[123].

A longitudinal MRI study correlated changes of lesion hypointensity over time with initial histopathological features in 14 biopsied MS lesions. The extent of hypointensity increased in initially demyelinated plaques and decreased in remyelinating lesions. The initial axonal loss determined the increase of hypointensity over time. In conclusion, both axonal loss and demyelinating activity determine the evolution of hypointensity over time[125]. Conventional MRI sequences have limited specificity for myelination. A recent study published in 2014 evaluated the imaging modalities which are potentially more specific to myelin content in vivo, such as magnetisation transfer ratio (MTR), restricted proton fraction f (from quantitative magnetisation transfer measurements), myelin water fraction and diffusion tensor imaging (DTI) metrics, in addition to positron emission tomography (PET) imaging. The study conformed to the fact that MTR is strongly affected by myelin, but may also be influenced by water content and inflammation, and axonal density. Lesion MTR is lower in the presence of demyelination, with significantly higher MTR observed in remyelinated lesions, although still lower than in NAWM, which may be due to incomplete remyelination, morphological differences in the newly formed myelin and a degree of axonal loss. Similar findings were reported in another postmortem MRI and histopathological study performed in 36 MS patients [126].

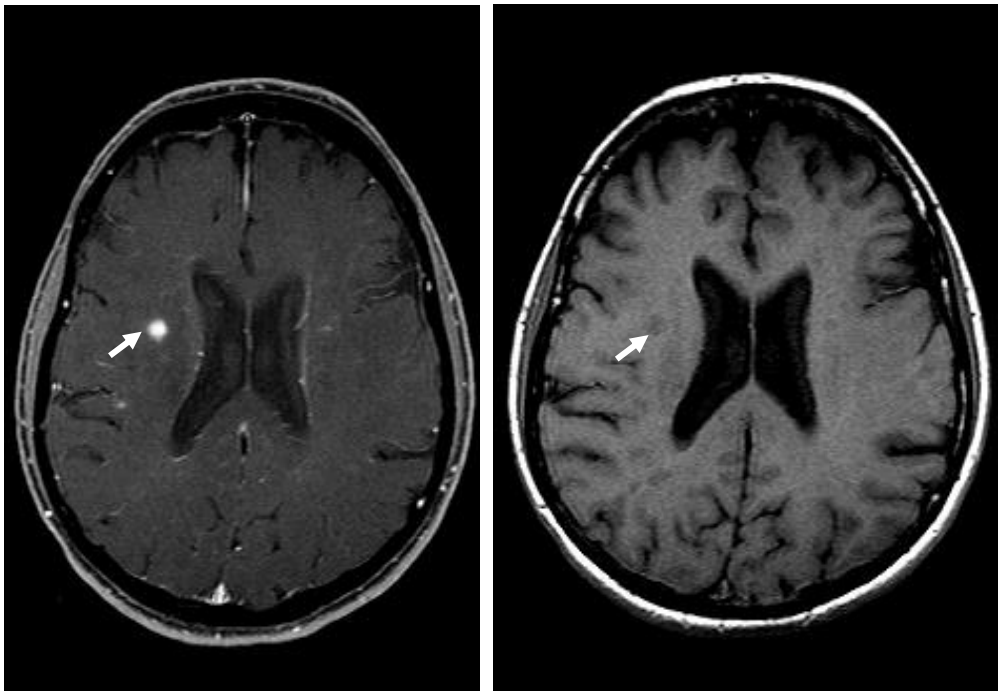


Figure 3.2: Axial View of Brain Slices of a MS Patient: Demonstrating Demyelination.

Cadavid, D**., Cheriyan, J.,** Skurnick, J., Lincoln, J. A., Wolansky, L. J., & Cook, S. D. (2009). New acute and chronic black holes in patients with multiple sclerosis randomised to interferon beta-1b or glatiramer acetate. *J Neurol Neurosurg Psychiatry, 80*(12), 1337-1343. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19687024. doi:10.1136/jnnp.2008.171090

Since most of the lesions of multiple sclerosis are not remyelinated, enhancement of remyelination is a possible therapeutic strategy that could perhaps be achieved with the transplantation of oligodendrocyte-producing cells into the lesions. In a 2002 study forty-eight chronic lesions obtained at autopsy from 10 patients with multiple sclerosis were examined immunocytochemically for oligodendrocytes and oligodendrocyte progenitor cells[127].

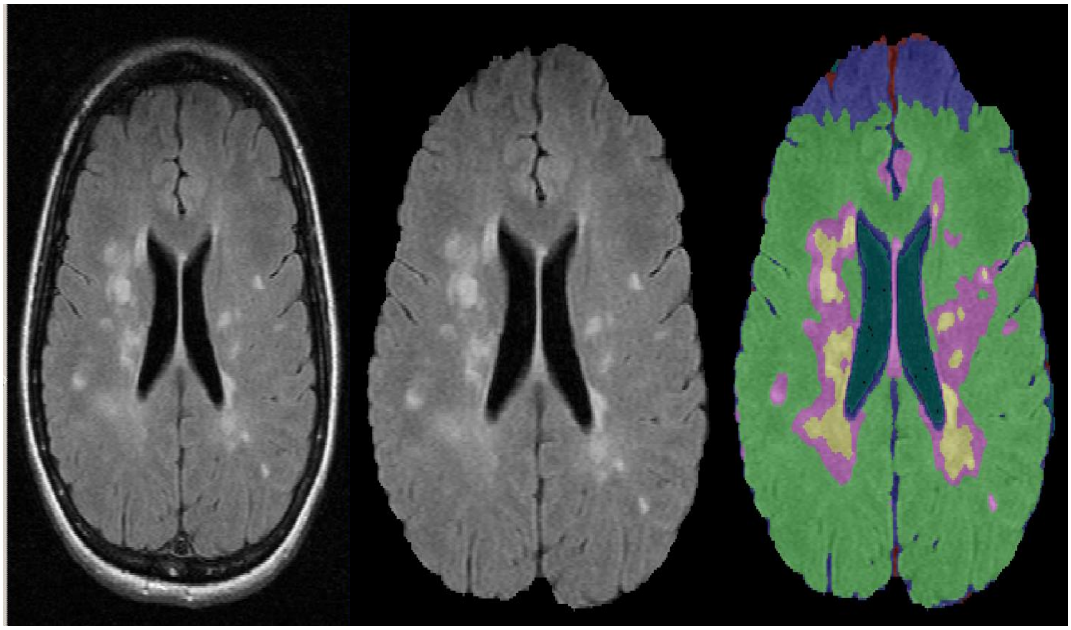


Figure 3.3: Impact of Inflammation on brain volume in Multiple Sclerosis.

Cheriyan, J., Kim, S., Wolansky, L. J., Cook, S. D., & Cadavid, D. (2012). Impact of inflammation on brain volume in multiple sclerosis. *Arch Neurol, 69*(1), 82-88. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22232347. doi:10.1001/archneurol.2011.674

3.4 Pathophysiology of MS:

***3.4.1 Introduction*:** The underlying pathophysiology of MS is widely believed to be autoimmune in nature targeting the central nervous system 9CNS). It is mediated by autoreactive lymphocytes that cross the blood-brain barrier (BBB) and enter the CNS where they cause local inflammation that results in demyelination, gliotic scarring and axonal loss. The plaques of demyelination inside central nervous system detected by MRI remains the classical biomarker for the clinical diagnosis. Typical clinical course of the disease is classified based on the MRI activity and progression of disability (Figure 2.13). However, advances in the understanding of genetics of MS and discovery of the importance of variants in HLA genes of the major histocompatibility complex (MHC)

opened up new influences of genetic and epigenetic factors in the pathophysiology of MS.

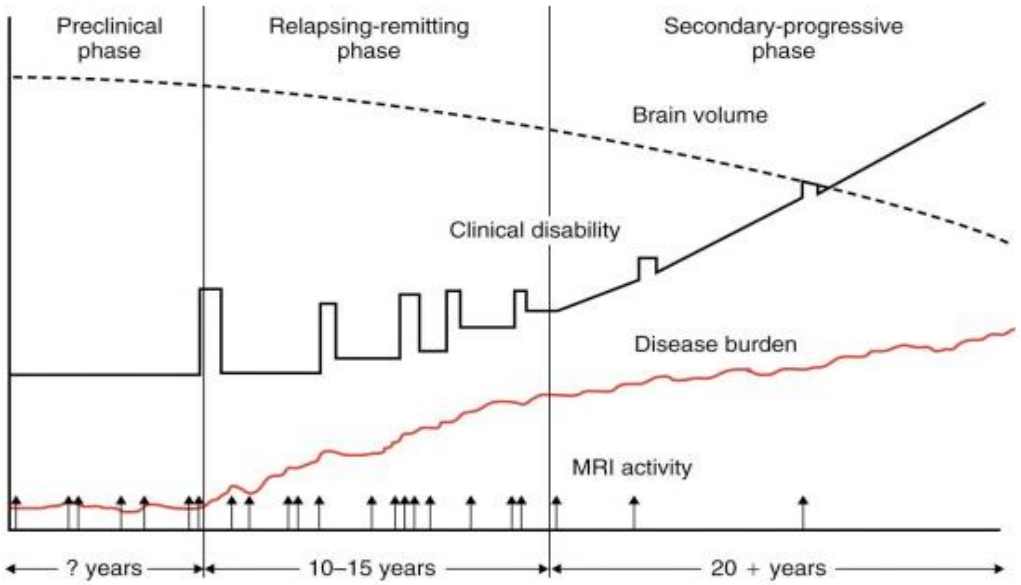


Figure 3.4: Typical Clinical and Magnetic resonance imaging (MRI) Course of Multiple Sclerosis.

MRI activity (vertical arrows) indicates an inflammatory process as measured on brain MRI by gadolinium enhancement or new T2 hyperintense brain lesions. MRI activity typically is more frequent than clinical relapses (spikes in clinical disability), which indicates that more disease activity is taking place than is clinically apparent. Loss of brain volume and increase in disease burden (total volume of lesions), both measured on MRI, indicate permanent tissue damage, which is present early in the disease and gradually progresses over time.(Adapted from Fox RJ, Cohen JA: Multiple sclerosis: the importance of early recognition and treatment. Cleve Clin J Med 2001; 68:175 - 171.)

3.5 Signs and Symptoms:

The onset of MS may be abrupt or insidious. Symptoms may be severe or seem so trivial that a person may not seek medical attention for months or years. Sometimes MRI scan

obtained for an unrelated reason may show evidence of asymptomatic MS. Symptoms of MS are extremely varied and depend on the location and severity of lesions within the CNS. Because MS can affect any area of the brain, optic nerve, or spinal cord, MS can cause almost any neurologic symptom. Initial symptoms of MS is shown in Table 2.3 below.

Table 3.3 Initial Symptoms of MS

Initial Symptoms of MS			
Symptom	**Percentage of Cases**	**Symptom**	**Percentage of Cases**
Sensory Loss	37	Lhermitte	3
Optic Neuritis	36	Pain	3
Weakness	35	Dementia	2
Paresthesia	24	Visual Loss	2
Diplopia	15	Facial Palsy	1
Ataxia	11	Impotence	1
Vertigo	6	Myokymia	1
Paroxysmal Attacks	4	Epilepsy	1
Bladder	4	Falling	1

(WB Mathews et al: McAlpines Multiple Sclerosis. New York, Churchill Livingstone, 1991)

A patient may present with symptoms in one leg but signs in both. Weakness of the limbs may manifest as loss of strength, speed, or dexterity, as fatigue, or as a disturbance of gait. Exercise-induced weakness is a characteristic symptom of MS.

Typical relapses of MS involve episodes of numbness, weakness, or dyscoordination affecting an arm, a leg, or both. Disease localized to the spinal cord can cause sensory or motor changes involving one side of the body or below a certain spinal cord level (i.e., hemiparesis or paraparesis). Brainstem involvement can manifest as diplopia, altered sensation in the face, or ataxia. Inflammation of the optic nerve (optic neuritis) usually manifests as blurry vision with painful eye movements.

Of all the lesions in MS, cerebral lesions are most common, but they cause the fewest symptoms. Very large cerebral lesions can manifest with weakness or numbness and rarely cause aphasia or other cortical dysfunction. Most cerebral lesions are not in eloquent regions and so are clinically silent and identified only by brain MRI. Lhermitte's sign is a nonspecific sign, whereby flexion of the neck causes an electric shock–like shooting sensation extending into the arms or down the back. Lhermitte's sign is believed to arise from partially demyelinated tissue, whereby mechanical stimulation leads to axonal activation.

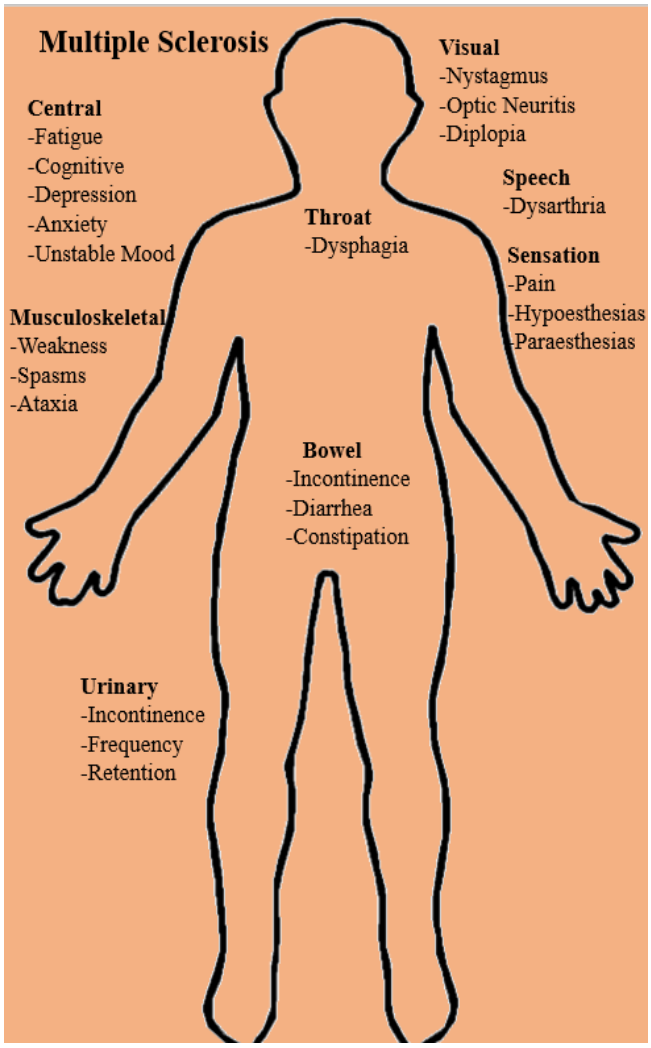


Figure 3.5 Main Symptoms of Multiple Sclerosis.

A web-based survey of patients and caregivers conducted by MultipleSclerosis.net from November 2012 until January 2013 reported the most common initial MS symptoms based on the responses by 3,132 patients. Among these symptoms the most significant initial symptoms are numbness and tingling, walking difficulty, vision problems and fatigue.

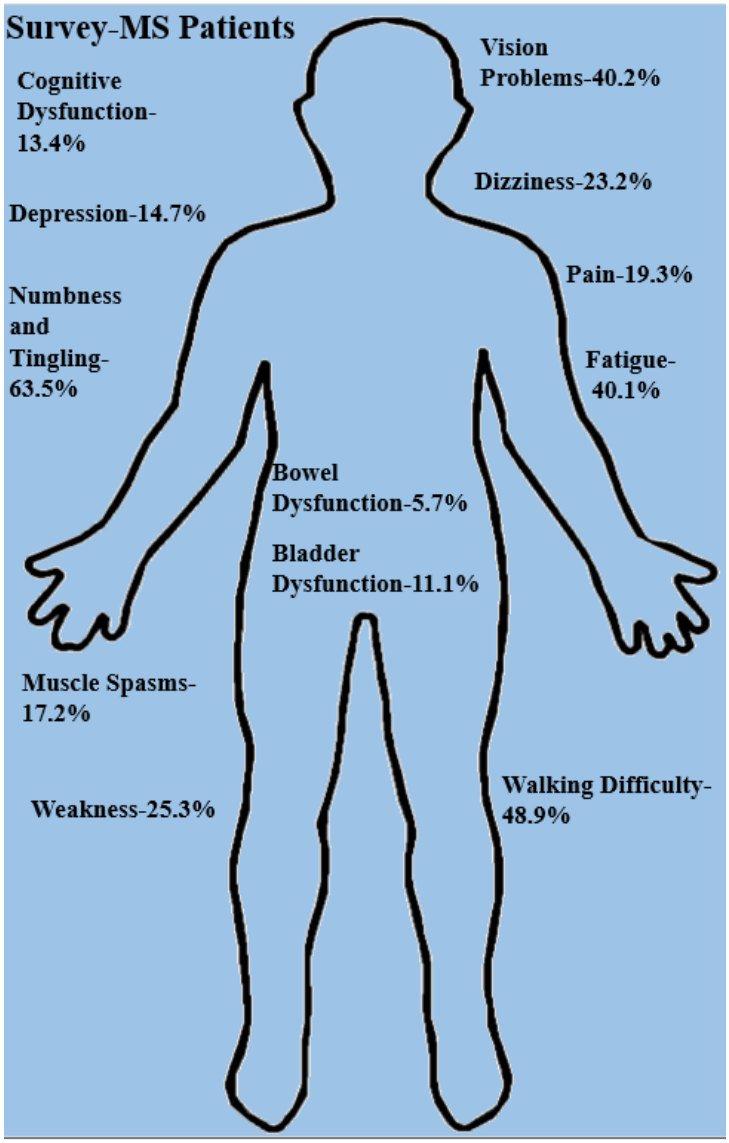


Figure 3.6 Most Significant Initial Symptoms Web-based survey 2013. Retrieved from Multiplesclerosis.net on March 12, 2019

Other common symptoms of MS include bladder and bowel dysfunction, decreased memory, fatigue, and affective disorders such as depression. Although these symptoms are not uncommon at the diagnosis of MS, they are also nonspecific and can be seen in a multitude of disorders.

3.6 DIAGNOSIS:

In 1982 a new diagnostic criteria for the diagnosis of MS was formally released for clinical research protocols[130]. At that time degrees of diagnostic certainty were identified by categories ranging from clinically definite diagnosis to laboratory-supported definite MS, clinically probable MS, and laboratory-supported probable MS. Since then no formal review of criteria was done until 2000. In July 2000, the International Panel on the Diagnosis of Multiple Sclerosis presented a new diagnostic criteria for multiple sclerosis (MS) that have come to be known as the "McDonald Criteria" after the chair of that group, Dr. W. Ian McDonald. The Criteria was meant for practicing physicians and was adopted internationally by the MS community[128]. This criteria integrated magnetic resonance image (MRI) assessment with clinical and other para-clinical methods like Cerebrospinal fluid (CSF) findings and Visual Evoked Potential (VEP). Emphasis was given to objectively-determined clinical evidence supported by clinical signs, radiological findings and laboratory findings. Some subcategory terms used previously like, "clinically definite", "laboratory supported" etc., were eliminated. It redefined what constitutes an 'attack'; how "abnormality" is determined in MRI and CSF analysis; what constitutes "dissemination of clinical events and lesions in time and space" (Tables I and II)

In 2005 this criteria was again revised to incorporate evidence-based data obtained since the publication of the original McDonald criteria. The 2005 criteria liberalized the requirements for imaging and Cerebrospinal fluid (CSF) findings making it more data driven. The panel made changes in the use and interpretation of imaging criteria for dissemination in time and space, and added spinal cord lesions into the imaging criteria. A new criteria to simplify the diagnosis of primary progressive multiple sclerosis was also added[129].

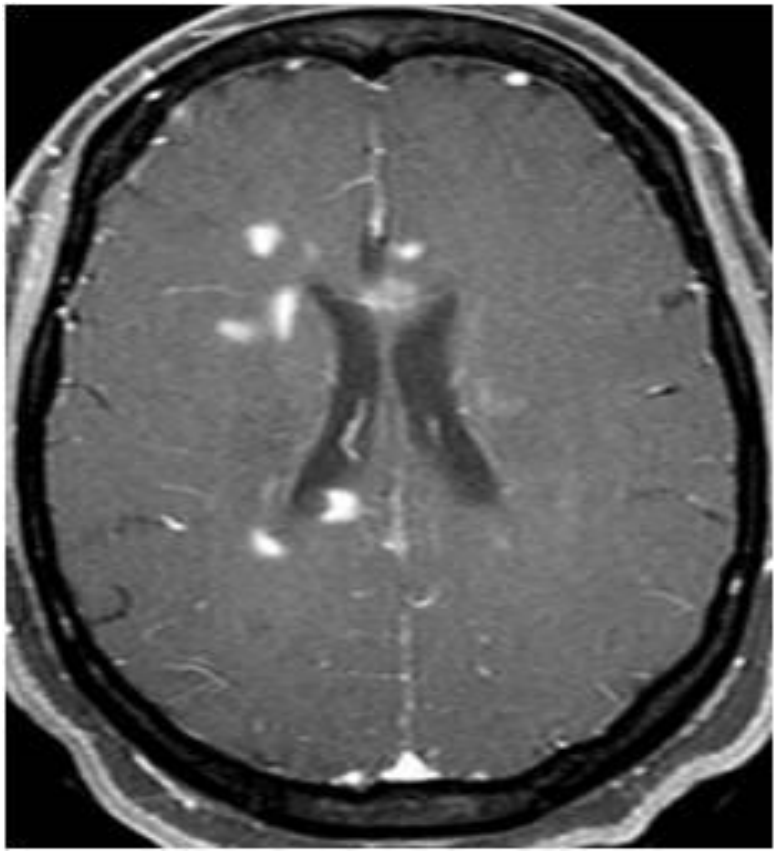


Fig 3.7: Axial Flair MRI Showing Periventricular Plaques

Cheriyan J.,Kim S, Cook S., Wolansky L.,Cadavid D., Enhancement volumes in MS patients randomized to Interferon beta 1b and Glatiramer acetate imaged by montly 3 tesla MRI with triple dose gadolinium in the BECOME study, AAN 2009, Seattle, Washington.

3.7 Diagnostic criteria:

The diagnosis of MS requires CNS damage that is disseminated both in time (damage at different dates) and in space (damage to at least two different parts of the CNS). The Schumacher Criteria (1965) was the first official method for diagnosing MS and it was purely based on clinical findings. Later, the Poser Criteria (1983) standardized the use of diagnostics tests such as Evoked Potentials (EP) and a spinal tap, allowing confirmation of damage disseminated in space and disseminated in time. Poser criteria could distinguish among "possible", "probable" and "definite" MS in a patient. In 2001 McDonald Criteria was adopted by the International Panel for on MS Diagnosis which incorporated clinical evaluation with MRI scans in establishing diagnosis. This also required dissemination in time and space. McDonald criteria endorsed in 2001 was revised in 2005, 2010 and 2017 depending on the scientific advances in diagnostic testing. In 2017 the International Panel reviewed the 2010 McDonald Criteria and recommended revisions based on the advances in the past 7 years to demonstrate CNS injury disseminated in time and space, mainly through clinical history, clinical examination, laboratory findings and MRI findings. 2017 McDonald Criteria continue to be applied to patients experiencing a typical Clinically Isolated Syndrome (CIS), redefined what is needed to fulfill dissemination in time and space of lesions in the CMS and stress the need for no better explanation for the presentation[133].

Research to further refine the criteria should focus on optic nerve involvement, validation in diverse populations, and incorporation of advanced imaging, neurophysiological, and body fluid markers.

Table 3.4: 2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis

2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis	
Clinical Presentation	**Additional Data Needed To Make MS Diagnosis**
……..in a person with a typical attack /CIS at onset	
≥ 2 attacks and objective clinical evidence of ≥ 2 lesions ≥ 2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemination in space **(DIS)** and dissemination in time **(DIT)** have been met.
≥ 2 attacks and objective clinical evidence of 1 lesion	One of these criteria: **-DIS:** additional clinical attack implicating different CMS site **-DIS:** ≥ 1 **Symptomatic or asymptomatic MS**—typical T2 lesions in ≥ 2 areas of CNS: Periventricular**, juxta cortical/cortical,** infratentorial or spinal cord.
1 attack and objective clinical evidence of ≥ 2 lesions	One of these criteria: **-DIT:** additional clinical attack **-DIT:** simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic MS**—typical MRI lesions **-DIT:** new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) **-CSF-Specific (i.e. not in serum) oligoclonal bands**

Colored text= revisions compared to previous Mc Donald Criteria (2010). KEYs:

CIS: clinically isolated syndrome; **CNS:** central nervous system; **CSF:** cerebrospinal fluid;**DIS:** dissemination in space; **DIT:** dissemination in time; **T2 lesion**: hyper intense lesion on T2-weighted MRI **(The Lancet Neurology 17(2) 162-173)**

Table 3.4 Continued: 2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis

2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis	
Clinical Presentation	**Additional Data Needed To Make MS Diagnosis**
1 attack and objective clinical evidence of 1 lesion	One of these criteria: -**DIS:** additional attack implicating different CNS site -**DIS**: ≥ 1 MS- typical **symptomatic or asymptomatic** T2 lesions in ≥ 2 areas of CNS: periventricular**, juxta cortical/cortical**, infratentorial or spinal cord **AND** **One** of these criteria : -**DIT:** additional clinical attack -**DIT:** simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions -**DIT:** by new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) -**CSF—specific (i.e. not in serum) oligoclonal bands**
Progression from onset	-1year of disability progression (retrospective or prospective) **AND** **Two** of these criteria : **≥ 1 symptomatic or asymptomatic** MS-typical T2 lesions (periventricular, **juxta cortical/cortical** or infratentorial) ≥ 2 T2 spinal cord lesions CSF-specific (i.e. not in serum) oligoclonal bands.

Colored text= revisions compared to previous Mc Donald Criteria (2010). KEYs: CIS: clinically isolated syndrome; **CNS:** central nervous system; **CSF:** cerebrospinal fluid; **DIS:** dissemination in space; **DIT:** dissemination in time; **T2 lesion**: hyper intense lesion on T2-weighted MRI **(The Lancet Neurology 17(2) 162-173)**

3.8 Diagnostic Investigations:

3.8.1 Imaging: MRI remains the most important diagnostic tool in MS**.** Gadolinium contrast can identify active lesions. Brain volume loss correlates with disease

progression. The presence of periventricular and callosal lesions is reasonably specific for MS.

3.8.2 Expanded Disability Status Scale (EDSS) Clinical Rating: A patient may be rated according to several clinical disability scales, on the basis of findings on the history and physical examination. The most widely accepted of these is the 10-point Kurtzke Expanded Disability Status Scale (EDSS), which was developed originally in 1955 as the Disability Status Scale and has been revised over the years[152]. The EDSS assigns a severity score to the patient's clinical status that ranges from 0–10 in increments of 0.5. The scores from grades 0–4 are determined using functional systems (FS) scales that evaluate dysfunction in the following 8 neurologic systems:

- Pyramidal
- Cerebellar
- Brainstem
- Sensory
- Bladder and bowel
- Vision
- Cerebral
- Other

EDSS grades are as follows:

- 0 - Normal neurologic examination (all grade 0 in FS, cerebral grade 1 acceptable)

- 1.0 - No disability, minimal signs in 1 FS (i.e., grade 1 excluding cerebral grade 1)

- 1.5 - No disability, minimal signs in more than 1 FS (more than 1 grade 1 excluding cerebral grade 1)
- 2.0 - Minimal disability in 1 FS (1 FS grade 2, others 0 or 1)
- 2.5 - Minimal disability in 2 FS (2 FS grade 2, others 0 or 1)
- 3.0 - Moderate disability in 1 FS (1 FS grade 3, others 0 or 1) or mild disability in 3 or 4 FS (3/4 FS grade 2, others 0 or 1) though fully ambulatory
- 3.5 - Fully ambulatory but with moderate disability in 1 FS (1 grade 3) and 1 or 2 FS grade 2, or 2 FS grade 3, or 5 FS grade 2 (others 0 or 1)
- 4.0 - Fully ambulatory without aid; self-sufficient; up and about some 12 hours a day despite relatively severe disability, consisting of 1 FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk approximately 500 m without aid or resting
- 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, usually consisting of 1 FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk approximately 300 m without aid or rest
- 5.0 - Ambulatory without aid or rest for approximately 200 m; disability severe enough to impair full daily activities (e.g., to work full day without special provisions; usual FS equivalents are 1 grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)

- 5.5 - Ambulatory without aid or rest for approximately 100 m; disability severe enough to preclude full daily activities (usual FS equivalents are 1 grade 5 alone; others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0)
- 6.0 - Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk approximately 100 m with or without resting (usual FS equivalents are combinations with more than 2 FS grade 3+)
- 6.5 - Constant bilateral assistance (canes, crutches, or braces) required to walk approximately 20 m without resting (usual FS equivalents are combinations with more than 2 FS grade 3+)
- 7.0 - Unable to walk beyond approximately 5 m even with aid; essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about approximately 12 hr./day (usual FS equivalents are combinations with more than 1 FS grade 4+; very rarely, pyramidal grade 5 alone)
- 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair (usual FS equivalents are combinations with more than 1 FS grade 4+)
- 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair but may be out of bed itself much of the day, retains many self-care functions; generally has effective use of arms (usual FS equivalents are combinations, generally grade 4+ in several systems)

- 8.5 - Essentially restricted to bed much of the day; has some effective use of arms; retains some self-care functions (usual FS equivalents are combinations, generally 4+ in several systems)
- 9.0 - Helpless bedridden patient; can communicate and eat (usual FS equivalents are combinations, mostly grade 4+)
- 9.5 - Totally helpless bedridden patient; unable to communicate effectively or eat/swallow (usual FS equivalents are combinations, almost all grade 4+)
- 10.0 - Death due to MS

Advantages of the EDSS are that it is widely used clinically, is easy to administer, and requires no special equipment. Its limitations are as follows:

- It is heavily dependent on mobility
- It is somewhat subjective in certain areas (e.g., bowel and bladder function)
- It is insensitive to small changes
- It does not present an accurate picture of the patient's cognitive abilities and functional abilities in performing activities of daily living (ADLs)
- It is nonlinear in terms of the time spent at various ranges of the scale

Despite its limitations, the EDSS is often used as a standardization measure for clinical trials.

Other useful scales include the Ambulation Index, which is based solely on the ability to walk 25 feet, and the Multiple Sclerosis Functional Composite (MSFC), which includes

the Ambulation Index, the 9-hole peg test, and the PASAT attention test. The MSFC is reported as z scores, which have been difficult to translate into clinical significance. In addition, the Scripps Neurologic Rating Scale, developed by Sipe in 1984, has been used by some investigators. This scale has a finer incremental scale than the Kurtzke scale, but it is not widely accepted and does not consider cognitive involvement.

3.8.3 Lumbar puncture: cerebrospinal fluid (CSF) examination is helpful in MS although is not always performed as part of the diagnostic work-up. Oligoclonal immunoglobulin G (IgG) bands are present in 90% of patients but can be absent in early disease. Identical oligoclonal bands in the serum and CSF indicates a systemic rather than intrathecal response, so other infectious inflammatory or paraneoplastic causes should be considered.

3.8.4 Neurophysiology: 80–90% of patients with MS have delayed visual evoked potentials (VEPs), and detecting these is less invasive than a lumbar puncture. Visual EPs are examined by flashing lights across the subject's visual fields and detecting electrical activity in the visual cortex using an electroencephalogram. This test detects loss of vision from optic nerve damage. The patient is seated in front of a screen and focuses on the center, where a checkboard pattern is shifting. One eye is tested at a time and each eye is tested twice. In an audit study of 273 MS patients 92.5% of patients who eventually received a diagnosis of multiple sclerosis were found to have VEP abnormalities[141]. When the procedure was first introduced it was found to detect abnormality in 85–95% of individuals who would eventually receive a diagnosis of clinically definite multiple sclerosis[142].

3.8.5 Blood Tests: although there is no specific blood test for MS, the absence of other autoimmune markers (antinuclear antibodies, extractable nuclear antigen, anti-neutrophil cytoplasmic antibodies, anti-double-stranded DNA antibodies, antiphospholipid antibodies) can be helpful. The serum NMO-IgG/aquaporin-4 titer is important if considering Devic's disease, as is Lyme disease antibody to exclude previous Lyme exposure.

Table 3.5: Routine Imaging and Laboratory Tests

Imaging and Laboratory Tests	
MRI Brain ± Spinal Cord	Hypointensities (non-Gad) or Gad enhanced lesions
Cerebrospinal Fluid	Cell Count
	Protein
	Oligoclonal IgG
Blood Tests	Oligoclonal IgG
	ESR, ANA, ENA, ANCA, RF, C', Vitamin B12
	Anti-dsDNA, Antiphospholipid, Anticardiolipin antibodies
	NMO-IgG
	Lyme disease IgM/IgG
Visual Evoked Potentials	
ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; anti-dsDNA, anti-double-stranded DNA; C′, complement; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; IgG, immunoglobulin G; IgM, immunoglobulin M; RF, rheumatoid factor.	

3.9 Management:

Nowhere is the multidisciplinary team approach more appropriate than in MS, particularly at disease onset, during relapses and in the later stages of progression. Treatment is either symptomatic or, with relapsing–remitting disease, directed towards

preventing relapses. Patients benefit from a holistic multi-professional therapy program, which can be instituted either as an inpatient or increasingly in community-based services.

3.9.1 Symptomatic Management:

Acute exacerbations or relapses of MS are managed with corticosteroids. Typically, methylprednisolone (0.5–1.0 g/day) is given orally or intravenously over 2–5 days. Although symptom duration is reduced, there is no overall effect on disease progression or subsequent relapse rate.

Table: 3.6 Common Symptoms and Therapeutic Agents Used for Management

Symptomatic Management	
Fatigue	Anantadine, Modafinil
Depression	SSRI (Citalopram), SSNRI (Venlafaxine), TCA (Amitriptyline)
Pain	Amitryptiline, Pregabalin, Gabapentin, Cannabis extract (Nabiximols)
Spasticity	Baclofen, Dantrolene, Diazepam,Tizanidine, Cannabis extract (Nabiximols) Botulinum toxin, Physiotherapy.
Bladder Disturbance	Oxybutynin, Tolterodine, Cannabis Extract (Nabiximols), Catheterization, Intravesical Botulinum toxin.
Erectile Dysfunction	Sildenafil
Tremor	Clonazepam, Primidone, Beta-adrenoreceptor blockers
Walking	Fampridine
SSRI- Selective Serotonin Reuptake Inhibitor; SSNRI-Selective Serotonin and Noradrenaline Reuptake Inhibitor; SSRI-Selective Serotonin Reuptake Inhibitor; TCA-Tricyclic Antidepressant	

Fatigue, depression, pain, weakness, spasticity, bladder disturbance and erectile dysfunction commonly occur with disease progression and are often amenable to

symptomatic treatment. Recently, cannabis extract (also known as nabiximols, a cannabinoid oromucosal mouth spray, has been used for the treatment of neuropathic pain, spasticity and bladder overactivity in MS patients. Dalfampridine, an acetylcholine-release enhancer, improves walking in over a third of MS patients by an average of 25%. Tremor is less common and particularly difficult to treat in MS, and can occasionally require neurosurgical interventions such as deep brain stimulation.

3.10 Disease Modifying treatments:

Immunomodulatory and immunosuppressive agents play an important role in reducing relapses and MRI activity in MS. Their effect on slowing disease progression can be modest, but many clinicians believe that prompt treatment tailored to a patient's disease activity is crucial to limit long-term accumulation of disability. 5 Newly diagnosed patients with RRMS may be offered first-line medication, such as an injectable IFN-β or glatiramer acetate preparation (Table 2.3). IFN-β and glatiramer acetate are not currently recommended by NICE (TA32) but are commonly prescribed and reimbursed as part of the MS Risk Sharing Scheme. Problems with injection sites and flu-like symptoms are common, and injectable medications prove unacceptable to some patients; however, they offer the best characterized safety profile, especially in pregnancy. Neutralizing antibodies develop in up to 30% of patients after 2 years of treatment. Newer oral medications such as teriflunomide and dimethyl fumarate are increasingly offered as first-line, and are recommended by NICE as first-line treatments, as is alemtuzumab for those with recent relapses and MRI activity. All immunosuppressive agents also increase the risk of infection to a variable extent. Patients with CIS are sometimes offered these treatments, as they reduce the risk of a second relapse and MS diagnosis.

Table 3.7: Disease Modifying Treatments

Currently Available Disease Modifying Therapies for MS-2018		
Drug Class	**Trade Name**	**Dosing/Route of Administration**
Interferon β (IFN)	Avonex	1xWeek, i.m
	Betaferon/Extavia	Alternate days, s.c
	Rebif	3x Week, s.c
	Plegridy	Fortnightly, s.c
Glatiramer Acetate	Copaxone	Daily , s.c
Dimethyl fumarate	Tecfidera	2 x Daily, p.o
Teriflunomide	Aubagio	1 x Daily, p.o
Natalizumab	Tysabri	1x Month, i.v
Alemtuzumab	Lemtrada	Induction Therapy, i.v
Fingolimod	Gilenya	1 x Daily, p.o
i.m-intramuscular; i.v-intravenous; p.o- orally; s.c-subcutaneously		

Second-generation medications provide more effective disease control, albeit with more significant adverse effects, for those with active disease or who fail first-line treatment. The monoclonal antibody natalizumab (anti-alpha-4 integrin) prevents lymphocytes from crossing the blood–brain barrier; it reduces relapses by 68% when given as a monthly infusion. This compares favorably to IFN-β and glatiramer acetate, with a reduction of only around 35%. Natalizumab treatment increases the risk of progressive multifocal leucoencephalopathy, a rare disease in which JC virus damages the CNS white matter, which can lead to significant morbidity and mortality. Fingolimod is an oral disease-modifying drug that acts by sequestering lymphocytes in lymph nodes; it reduces relapses by approximately 54%. Adverse effects include macular edema, symptomatic but reversible cardiac conduction defects with the first dose, serious herpetic reactivation (herpes simplex virus-1/2 and varicella-zoster) and interstitial pneumonitis. Alemtuzumab is a monoclonal antibody against CD52 that destroys mature lymphocytes, allowing new non-autoimmune lymphocytes to be generated; the relapse rate is decreased

by 50% compared with IFN-β. Possible adverse effects include the development of new autoimmune disease such as thyroid disease and idiopathic thrombocytopenic purpura. Natalizumab, fingolimod and alemtuzumab (and indeed all disease-modifying medications) are thought to slow the progression of disability in MS in part by targeting the focal inflammatory activity of RRMS.

For those patients with active disease, starting effective disease-modifying treatment should be an urgent priority. Treatment decisions should be made by MS specialists, such is the increasing complexity of therapeutic options in MS. Unfortunately there are still no disease-modifying medications available that are effective during the progressive phase of disease, although clinical trials are ongoing.

Ocrelizumab (ant-CD20) targets B cells and is more effective than IFN-β at reducing the relapse rate. It is awaiting approval from the regulatory authorities. The results of a primary progressive MS Ocrelizumab trial are currently awaited, after promising interim results. Hemopoetic bone marrow transplants have been used to 'reset' the immune system and can stop relapses in some cases. Although desirable, preventing relapses does not necessarily stop disease progression as there seems to be a neurodegenerative component to MS. The use of mesenchymal stem cells to repair brains with MS is under investigation but does not reverse disability in patients with established secondary progressive disease. Other approaches that aim to manipulate inflammation, neurodegeneration and remyelination are being tested in clinical trials. Until the advent of effective neuroprotective agents, we can only offer partial stabilization of disease progression with current therapies.

3.11. Economic Burden of Multiple Sclerosis

National health expenditures in the U.S are projected to grow at an average annual rate of 5.5 percent for 2018–27 and represent 19.4 percent of gross domestic product in 2027. On a per capita basis, health spending has increased over 30-fold in the last four decades, from $355 per person in 1970 to $10,739 in 2017. In constant 2017 Dollars, the increase was almost 6-fold from $1,797 in 1970 to $10,739 in 2017 (National Health Expenditure Accounts Data 2017). By 2000, health expenditures had reached about $1.4 trillion, and in 2017 the amount spent on health had more than doubled to $3.5 trillion. As shown in the Figure 2.13, hospital care and physician/clinical services combined account for half (53%) of the nation's health expenditures.

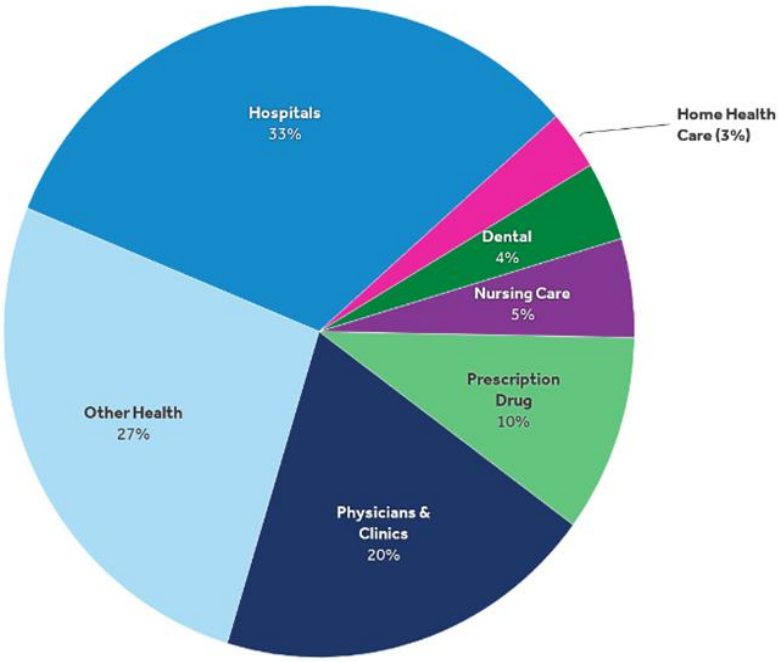


Figure 3.8 National Health Expenditures Data 2017 (Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group)

In the United States RRMS affects about three times as many women as men. Some patient groups, such as African Americans, experience a more rapid and severe clinical course. The annual cost of MS in United States is estimated to be $28 billion[139].

Management of MS has changed dramatically in recent years as the popularity of disease-modifying therapies rises and their associated costs soar[135]. One example is the cost of first-generation disease-modifying therapies for MS that was shown to increase annually at a rate of 5–7 times higher than that of prescription drug inflation. Although the surging cost of drugs in recent years has contributed greatly to the cost of managing MS, the largest per capita expenditure of caring MS before 2000 was hospitalizations. The cost of hospitalization accounted for 30% of the total costs and as MS progresses there is an increased use of emergency care that often results in hospitalization due to worsening of existing symptoms and onset of new symptoms. Lack of a study in the United States providing a broad overview of the cost and the usage of medical resource by MS patients is a major drawback.

A study published in 2017 tried to attain an estimated cost of MS management by investigating the trends of medical care use and of the cost and charge structure changes using the National Inpatient Sample (NIS) which is part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ) [136]. This study found an annual growth rate of approximately 540,000 new MS admissions, a decreased percentage of routine discharge, and an increased percentage of discharging patients to other institutions. These changes reflected an increased burden of direct and indirect medical and nonmedical expenses. This study also observed that the annual total charges and costs of managing MS in 2013 were $755

million and $198 million, respectively, and were growing at astounding annual rates of $40 million and $8 million, respectively. Since the NIS database only estimates approximately 20% of the admissions in U.S. hospitals in 44 states, the total national bill for the managing MS can be extrapolated to approximately $4.3 billion in 2013. This would amount almost 50% of the estimated MS drug expenditure, which is around $9 billion annually[137].

Another cost-utility analysis published by Institute for Clinical and Economic Review in 2017 aimed at systematically comparing cost effectiveness of all relevant Disease Modifying Therapies (DMTs) for first-line treatment of RRMS, second line treatment of RRMS, and first line treatment of PPMS. This study used a Markov Model with health states based on Expanded Disability Status Score categories and supportive care. Outcome measures included total costs, quality-adjusted-life years (QALYs) and incremental cost-effectiveness ratios (ICERs) [138]. The analysis found that the total cost for care among patients with RRMS which included discounted costs for DMT therapy, Serious Adverse Events (SAEs), and other MS-related healthcare cost over a projected lifetime were approximately$333,300 for supportive care and $572,000 to $1.5 million for DMTs. Discounted life expectancy from age of DMT initiation was 21.4 years for supportive care and projected discounted QALYs were 5.7 for supportive care and 12.6 for DMTs.

Among patients with PPMS, projected discounted costs, life years and QALYs for supportive care were approximately $264,300, 15.6 years and 2.7QALYs, respectively. The results for base-case analysis of this study is shown in Table 2.8.

Table 3.8: Results for Base-Case Analysis.

Drug	Cost	Relapses	Life-Years	QALYs
RRMS				
Supportive Care	$333,273	16.4	21.4	5.7
Teriflunomide 7 mg	$951,141	14.8	21.9	7.8
Interferon β-1a 22 mcg (Rebif)	$1,088,892	14.6	21.9	7.9
Interferon β-1a 30 mcg (Avonex)	$1,069,959	15.6	22.0	7.9
Teriflunomide 14 mg	$968,663	14.8	22.0	8.4
Glatiramer acetate 20 mg (Copaxone)	$1,160,237	14.3	22.0	8.4
Glatiramer acetate 20 mg (Glatopa)	$862,912	14.3	22.0	8.4
Interferon β-1a 44 mcg (Rebif®)	$1,114,885	14.5	22.1	8.5
Dimethyl fumarate	$1,023,958	14.3	22.2	9.0
Fingolimod	$1,114,879	13.5	22.2	9.0
Interferon β-1b 250 mcg (Betaseron)	$1,057,932	14.8	22.2	9.1
Interferon β-1b 250 mcg (Extavia)	$959,939	14.8	22.2	9.1
Peginterferon β-1a	$1,142,597	14.8	22.2	9.1
Natalizumab	$1,261,612	12.3	22.4	10.2
Daclizumab	$1,480,080	13.0	22.7	10.9
Ocrelizumab	-	12.8	22.7	11.0
Alemtuzumab	$571,971	10.8	23.1	12.6
PPMS				
Supportive Care	$264,334	N/A	15.6	2.7
Ocrelizumab	-	N/A	16.1	3.3

(Institute for Clinical and Economic Review 2017. Evidence Report: DMTs for RRMS and PPMS)

This study also calculated the cost per additional QALY, cost per additional life-year, and cost per relapse avoided for each DMT compared to supportive care and compared to generic glatiramer acetate 20 mg (Table 2.5). DMTs were ordered according to the projected QALYs. When compared to supportive care for RRMS, costs per additional QALY ranged from approximately $34,700 per QALY for alemtuzumab to $341,400 for interferon β-1a 22 mcg; costs per additional life year ranged from approximately $141,600 per year for alemtuzumab to $1.5 million for interferon β-1a 22mcg; and costs

per relapse avoided ranged from approximately $43,200 for alemtuzumab to $954,900 for interferon β-1a 30 mcg.

Table 3.9: Pairwise Results for DMTs Compared to Supportive Care for RRMS

Drug	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
Teriflunomide 7 mg	$289,970	$1,346,566	$410,754
Interferon β-1a 22 mcg (Rebif)	$341,359	$1,536,810	$430,998
Interferon β-1a 30 mcg (Avonex)	$331,381	$1,412,036	$954,935
Teriflunomide 14 mg	$236,954	$1,083,312	$400,198
Glatiramer acetate 20 mg (Copaxone)	$303,302	$1,346,923	$407,877
Glatiramer acetate 20 mg (Glatopa)	$194,253	$862,653	$261,230
Interferon β-1a 44 mcg (Rebif)	$284,135	$1,261,603	$418,760
Dimethyl fumarate	$211,444	$964,152	$332,580
Fingolimod	$238,970	$1,089,957	$276,100
Interferon β-1b 250 mcg (Betaseron)	$214,355	$908,578	$468,100
Interferon β-1b 250 mcg (Extavia)	$185,369	$785,715	$404,801
Peginterferon β-1a	$238,321	$1,036,909	$514,656
Natalizumab	$208,987	$929,821	$228,597
Daclizumab	$222,782	$916,425	$344,719
Alemtuzumab	$34,659	$141,639	$43,178

(Institute for Clinical and Economic Review 2017. Evidence Report: DMTs for RRMS and PPMS)

The cost analysis studies reported from other countries of the world also substantiate the high direct and indirect costs of Multiple Sclerosis. Recent research in the UK has shown that most people with MS are in employment at the time of diagnosis, but that employment loss starts shortly after diagnosis and 80% of people with MS are unemployed within ten years of diagnosis. Thereby early diagnosis and occupational rehabilitation plays an important role in the rehabilitation of MS patients to improve the functional status and reduce the productivity loss. Some studies conducted in U.S during late 1990s and early 2000s also highlighted the considerable health care costs, social costs and productivity loss of MS. Table 2.5 shows cost analysis of previous studies conducted in the U.S and other European countries.

High diagnostic cost and drug cost are the main reasons for high cost in MS care. Prevention is not a realistic option and no curative treatments are available for MS. A number of disease modifying drugs have been developed in the past 20years which can reduce the number of attacks and progression to some extent. Even though drug treatment options are relatively limited, significant improvements in the quality of life of people with MS can be supported by early diagnosis, value based care and improved rehabilitation approaches.

Table 3.10: Cost Analysis of MS

COST ANALYSIS OF MS			
Countries	**Direct Cost***	**Indirect Cost****	**Total Cost**
USA(Bourdette,1991) (Whetten,Goldstien,1998) (Kobelt,2006)			$35,000 /MS patient /year $2.2 million per case for life time. $47215/patient/year (19 billion for 400,000)
UK (Kobelt,2006)			Avg. $18000-$94000 (based on EDSS < 4to >/=7)
France			$59,500 per patient per year with mean EDSS 4.4
Italy (Amato 2002)	$1487 per 3 months	$5418 per 3 months	$27620 per patient per year
Germany(Reese,2011)	$29468	$26132	$55600
Austria (Kobelt,2006			$21000 to$85000 per patient per year(based on EDSS 0 to >/=7)
Sweden(Berg,2006)			$16 billion annual cost(MS population)
Spain (Casado,2006)			Avg. $32750 /patient/year.(R 19000-71300)
*Direct Cost- Drug Cost, Hospital Care. **Indirect Cost- Productivity cost for patient and care givers like loss of employment, absenteeism from work, rehabilitation equipment. Total Cost = Direct Cost + Indirect Cost			

CHAPTER IV

RESEARCH METHODOLOGY

4.1 Introduction

This research is based on a multi modal approach that includes quantitative and quasi-experimental analysis. Quantitative analysis was done to measure the disease burden and the economic burden of Multiple Sclerosis using data from the National Inpatient Sample (NIS) of the Health Care Cost and Utilization Project (HCUP). A large body of evidence has been collected from systematic reviews and meta-analysis from pre appraised sources that are related to the hypotheses. Real patient cases have been collected from published peer-reviewed sources to test the hypotheses. The quasi experimental approach basically involved the development of a Clinical Decision Support System (CDSS) with simulated tests to discover the possibilities of using it for early diagnosis and reducing the cost by rationally choosing diagnostic tests to prove the research hypothesis. The architecture of the CDSS and the logic used are discussed in this manuscript. The rationale of using the multi-modal research is to ensure that the CDSS designed is knowledge-based, and incorporate all the necessary evidence to substantiate diagnostic criteria used in making right decisions at the point of care. Using a knowledge-based algorithm can increase the credibility and reliability of the results, reminders and alerts generated from the CDSS. The decisions suggested from the system will help clinicians in their decision-making process and would lead to an early and accurate diagnosis to initiate early intervention, control the progression of disease and reduce cost burden. As the U.S. health care system has transitioned from volume-based to value-based care this CDSS can also help in controlling the cost by avoiding unnecessary and expensive tests.

4.2 Research Design

A review of literature from 2000 to date was conducted on Multiple Sclerosis. EndNote X9.1 reference management software was used to do an open-dated global search for relevant peer reviewed articles. The key terms and phrases used for the search are shown in Table 3.1 with the number of hits in parenthesis. Some manuscripts that were revised versions of older manuscripts published before 2000 were traced back to review the initial findings to collect evidence and understand the evolution of the related topics. Pub Med and Medline databases were searched separately whenever there was difficulty in accessing reference sections of some relevant articles. Reference sections of accepted articles were reviewed to identify any additional relevant studies. Websites of MS based medical organizations and social organizations were also reviewed using the search engines of Google Scholar, Yahoo and Bing. Excluded were Newspaper articles, Social Media posts, individual blogs and other non-scholarly sources (Table 4.2). Peer reviewed manuscripts form foreign journals were also reviewed to analyze the global distribution and impact of Multiple Sclerosis. NIS data from HCUP was analyzed to assess the disease pattern and trends to quantify the disease burden and cost burden at population level in the United States. To filter the MS patients from the national inpatient sample, the International Classification of Diseases (ICD) codes version 9 and 10 were used. Cases were filtered for the years 2010 to 2014 using ICD 9 codes and for 2016 using ICD 10 codes. Data from year 2015 was excluded due to data issues caused by transition from ICD 9 to ICD 10. A longitudinal analysis has been done using the demographics and regional distribution of cases across the U.S.

Table 4.1: Terms and Phrases Used to Search Articles Using EndNoteX9.1Software

Terms and Phrases used to search articles using EndNoteX9.1software	
Terms	***Phrases***
Multiple Sclerosis (50560)	**Mental well-being and Multiple Sclerosis (221)**
Multiple Sclerosis and physical rehabilitation(787)	**Neuro cognitive rehabilitation in MS(8)**
Drug cost and Multiple Sclerosis (452)	**Health care cost of MS in United States(135)**
Multiple Sclerosis and Public Health (15216)	**MS and public health issues (0)**
Public Health and Neurology(1372)	**Multiple Sclerosis and productivity loss (28)**
Politics and Multiple Sclerosis (11)	**Mental health of MS patients (236)**
Health Economics and Neurology(1061)	**Surveillance system for Multiple sclerosis(679)**
Inequities and Multiple Sclerosis (0)	**Surveillance system for neurological disorder(1713)**
Multiple Sclerosis and United States(5692)	**Home-based care for Multiple Sclerosis (9)**
Multiple Sclerosis and Canada(1751)	**Telemedicine for Multiple Sclerosis(26)**
Multiple Sclerosis and Italy(2762)	**Complementary and Alternative Medicine for Multiple Sclerosis(0)**
Multiple Sclerosis and Europe(2768)	**Legislation for Neurological disease surveillance(21)**
Multiple Sclerosis and Germany(2321)	**Multiple Sclerosis registries in the world (9)**
Multiple Sclerosis Registry (340)	**Danish Registry for MS(49)**
Multiple Sclerosis Surveillance(4673)	**Italian Registry for MS (15)**
Burden of Multiple Sclerosis(534)	**United States National Registry for MS (12)**
Health policy and Multiple Sclerosis (111)	**Prevalence of MS in United States (91)**
Norway Multiple Sclerosis Registry (19)	**Health Disparities in Multiple Sclerosis (10)**
Multiple Sclerosis societies (84)	**Psychosocial impact on Cognitive functioning in Multiple sclerosis (6)**

Table 4.2: Criteria Used for Literature Review

Inclusion Criteria	Exclusion Criteria
1. Peer reviewed scholarly manuscripts with RCTs, meta-analysis and scientifically sound models. **2.MS society Website** **3.MS Registries of European Countries** **4.Neurology Journals** **5.Neurology organizations' websites** **6.Published Books** **7.WHO Publications** **8.Government Publications**	**1.Printed News papers** **2.Online Newspapers** **3.Poster Sessions** **4.Blogs** **5. Podcast interviews.** **6. Webinar print outs.** **7.Emails**

4.3 Development Stages and Architecture of CDSS

The development of CDSS for Multiple Sclerosis (MS) was decided after thorough review of literature and case studies published in leading peer-reviewed medical journals and publications of MS organizations. The design of the study has been done in two stages.

4.3.1 Stage1 comprised several steps of extensive review of literature and data collection from real case studies. During this stage different types of variables were selected based on evidence and clinical significance gathered from published manuscripts and guidelines. An expert opinion survey was included to assess the need and current diagnostic techniques available to neurologists and primary care physicians. HCUP data collected was limited to multiple sclerosis patients using the ICD 10 codes.

4.3.2 Types of Variables: The variables used in the study are:

Static list variables: This is a variable that has a specific list of possible values. The possible values always remain the same for each user of the system. They automatically divide up the logic into the possible values for consideration. They are one of the most commonly used types of variables in the Expert Knowledge System.

Numeric value variable: This is a variable that is assigned a numeric value. The value may be asked of the end user, calculated from other rules, obtained from external sources, etc.

String Value Variable: This is a variable that will be assigned a value that is a text string. The value of a String variable can be parsed and tested in various ways to build test conditions, but generally they are used as identifiers for external data sources or text to use in reports.

Advice and Recommendations variables: These variables form the THEN part of the rule. End user provides the values for these variables. Their values are set by the rules that fire when the system is run, based on the input provided by the end user for other variables these are sub classified as:

(i) ***Collection variables***: used in complex reports which have many independent rules that contribute to the system results. Collection variables have a value that is a list of strings. This is used to build reports, notes or advice to the end user. They are used in many ways, especially in systems that that build complex reports, or which may have many independent rules that contribute to the system results.

(ii) ***Confidence Variables:*** These variables have a value that is a confidence, probability or certainty score, typically the text of the variable. Like a numeric variable, the value is a number, but in this case it is a measure of how likely it is that the variable applies to a particular situation. The value would be set by end user input causing various rules to fire that would increase or decrease the probability that this is a correct diagnosis for the particular end user. A single confidence variable can be assigned values by various rules in a system, and the Expert Knowledge System will automatically combine the values to arrive at single overall confidence value. Various formulas in the Expert System can be selected to combine the assigned values in various ways. Confidence variables are never directly asked of the end user, but are always set by the rules in a system. Confidence variables are used most effectively in systems where there are multiple possible recommendations based on how likely they are. Each recommendation is a separate Confidence variable, and each is given a confidence value by the rules in the system. The one(s) with the highest confidence value are the ones that will be displayed in the system run results. However, there are many other ways to use Confidence variables in systems that do not use uncertain reasoning or "fuzzy logic".

4.3.3 Stage II: This stage involved several steps involving validation and analysis of data collected from various sources narrated in stage 1. This stage included qualitative and quantitative analysis of data collected. Variables selected were defined and categorized into groups to create questions, display results and describe the decision making logic in the Expert Knowledge System used for building the CDSS. Variables that are non-specific and clinically irrelevant were excluded.

4.3.4 Stage III: This stage involves creating logic rules to build logic blocks and command blocks to run the inference engine of the Expert Knowledge System. Figure 4.1 shows the illustration of the two phases in the development process of CDSS in the research study.

4.3.5 Logic Blocks: They are made up of IF/THEN rules, often called heuristic rules. These rules describe the individual steps a clinician could use in making a decision. A heuristic is simply an individual "rule of thumb" that is part of overall decision making process. An overall decision is normally based on the combination of many rules which address different parts of the decision. The individual rules may be at a high level and quite general, or very detailed and specific. The various rules are structured and organized using Logic Blocks which make it easy to build and maintain sets of rules that completely describe a decision making process.

Since the rules are processed by the inference engine of the Expert System, the rules can be structured in many different ways that will all produce correct results. As long as all relevant rules in a system are described by the Logic Blocks, the inference engine will find and use them. An IF condition is a Boolean test of the value of the expression made up of variables, which can be true or false depending on the end user's input. A THEN condition is an assignment of a value to a variable. The assignment will be made if, and when, the rule "fires"—which means that the IF conditions are determined to be true. The assignment will add to the information that the system has to work with. THEN conditions always have one or more associated IF conditions that determine under what situation the THEN assignment should be made. IF conditions always evaluate to TRUE or FALSE. THEN conditions assign a value to a variable.

4.3.6 Command Blocks: Command blocks provide the rules to the inference engine on WHAT to do while logic blocks provide rules on HOW to do things. The Expert System used in this study requires a Command Block to run the system. Command Blocks may contain a few commands to many commands. The goal of the command block is to separate the logical flow of the system, asking questions because the inference engine needs the data for its immediate calculations from the procedural flow of the system. Command Blocks allow procedural operations to be specified in a procedural way, leaving the Logic and Action Blocks to define the rules and logic of the system.

4.3.7 Action Blocks: Action blocks provide another way to easily describe logic that is largely procedural, and which does not require the more powerful tree structures of a Logic Block. The most typical application for Action Blocks is to build smart questionnaires that ask a series of questions, but skip some questions based on answers that indicate they are not needed and may ask more detailed questions in other cases. In addition, an Action Block driven questionnaire can build and display reports dynamically and provide the end user with immediate feedback and advice. Action blocks can be combined with Logic Blocks, using the logic blocks to derive the value for variables used in Action Block. While Action Block is always run with forward chaining, it can use all options in the Expert System for backward chaining, external interfaces and user interfaces to run the rules.

4.3.8 Inference Engine: This expert system has a special program called an "Inference Engine" that is used to analyze and combine individual rules to solve a larger problem. The Inference Engine determines: (1) What possible answers there are to the problem, (2) What data is needed to determine if a particular answer is appropriate, (3) If there is a

way to derive or calculate the needed data from other rules, (4) When enough data is available to eliminate a possible answer, and stop asking unnecessary questions related to it, (5) How to differentiate between remaining answers (6) Which answer(s) is most likely based on the rules.

It is the Inference Engine that makes IF/THEN rules in this Expert System very different from IF/THEN commands in computer languages such as Visual Basic or C++. Rules are not equivalent to lines of code; they are facts that are automatically combined in various ways by the Inference Engine. This makes the Corvid Expert System approach far more powerful, effective and maintainable for knowledge delivery than traditional programming techniques. This ability for the Inference Engine to find and use rules as they are needed and relevant to the problem allows a much more "unstructured" approach to the heuristics. The Corvid Inference Engine processes both procedural commands (usually in Command Blocks) along with the logical rules in Logic Blocks and Action Blocks. The rules can be run using either Backward or Forward Chaining.

4.3.9 Backward Chaining / Forward Chaining: There are 2 primary ways for the Inference Engine (Corvid Runtime) to test and use rules – backward chaining and forward chaining. Forward chaining means "in order" and Backward Chaining means "when needed".

In Forward Chaining, the Inference Engine uses the rules in order - with no consideration of the usefulness of the values that might be set by the THEN conditions. When rules are run in Forward Chaining, they are run in order. The first rule is tested first. If the system does not have enough data to determine whether the IF conditions are true or false, it will ask the end user questions to get the specific data it needs to test those conditions.

In Backward Chaining the Inference Engine can use the rules, where rules are not used in order, but rather based on the need to achieve a particular goal. “Goals” are specific items of data that the system needs. In Backward Chaining, the inference engine would look through the rules to find one that was relevant to the Goal.

The CDSS developed for this research study is based on the knowledge- based model in Figure 3.2 in the previous chapter. This is enhanced by the evidence based approach and knowledge of a clinician to make the best decision at the point of care for early diagnosis and timely intervention.

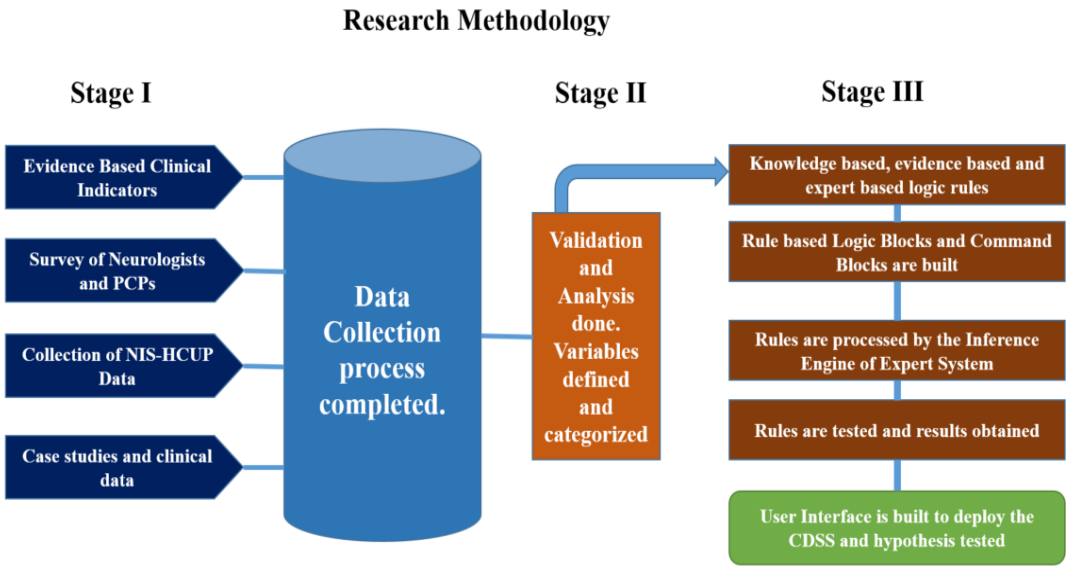


Figure 4.1 Stages of the Research Study

4.4 Clinical Decision Making Algorithm for Early Diagnosis of MS

Currently no algorithm exists for early diagnosis of MS. Lack of decision support has resulted in delays, redundancies and misdiagnosis resulting in higher cost, poor quality of life and lost productivity. Early diagnosis and early intervention help to control the disease activity, delay the progression of disease and disabilities. After extensive review

of literature and compiling evidence based guidelines this study proposes an algorithm that would support all clinicians in early diagnosis of the disease. All clinically significant manifestations are weighted based on the evidence extracted from peer reviewed manuscripts, patient surveys and diagnostic criteria used by MS organizations across the United States as well as internationally. The flow diagram (Figure 4.3) below shows the design and order of eliciting the signs and symptoms at the point of care. Signs and symptoms are selected based on the probabilistic basis and reported by patient surveys and clinical studies. Careful attention has been given to keep the accepted standards of clinical examination and to use the gold standard of McDonald's criteria in confirming the diagnosis using the MRI biomarker. Only clinically significant signs and symptoms that have at least 10% chance of getting manifested when there is actual disease activity are included in this study. Some rare signs and symptoms that are not classical in early stages of disease are excluded. The demographic factors which are predisposing factors for the disease and epidemiologically connected to the disease are also weighted based on the literature review. All scores are assigned in a range to 10 to 100 and displaced in Table 4.3 below.

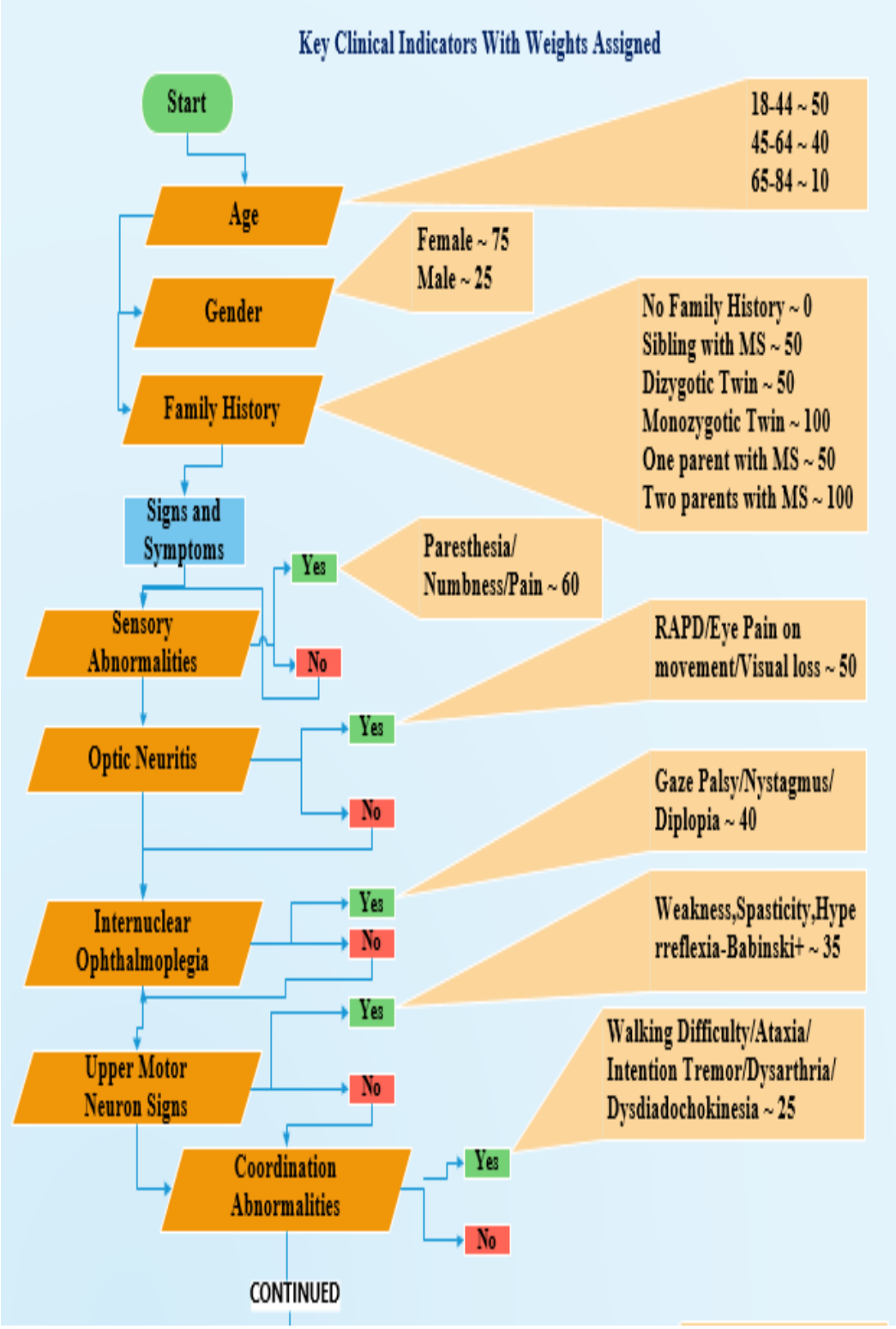


Figure 4.2a Key Clinical Predictors with Weights Assigned

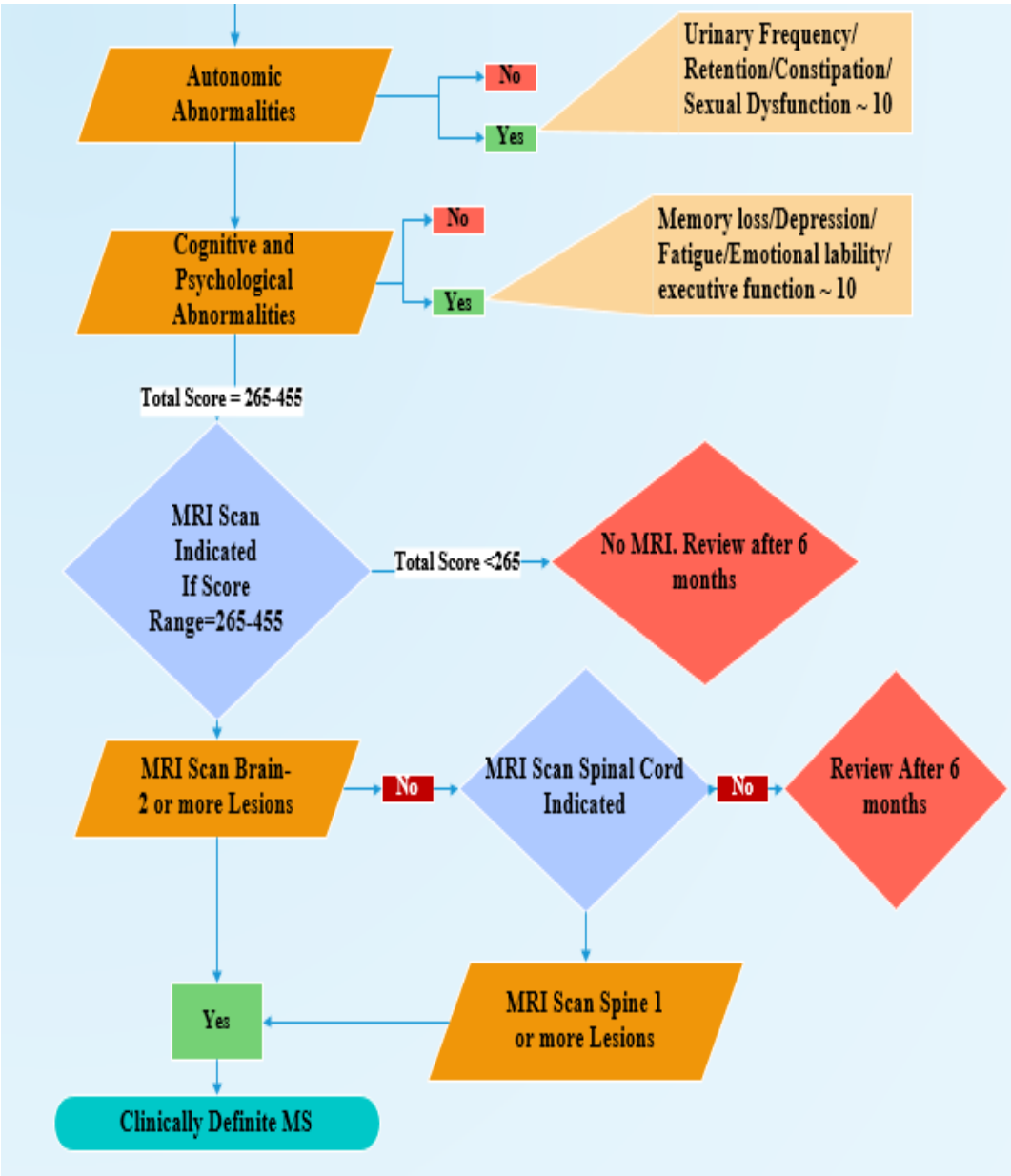


Figure 4.2b Key Clinical Predictors with Weights Assigned

A systematic approach that involves assessment of demographic factors, epidemiological factors and genetic factors followed by a detailed neurological examination is necessary for the diagnosis of MS. The CDSS designed in this study is a tool that assist clinicians to reach at a diagnostic decision and intervention at the earliest. This is not a tool to replace

clinician judgement or clinical tests that are deemed necessary for confirming diagnosis. This CDSS model is tested using a clinical decision support software named Corvid Exsys on real patient case scenarios and simulated scenarios collected from published literature.

4.5 Demonstration of Expert System Designed for the Study

The decision support designed is applied in two stages for screening and definitive diagnosis. Stage 1 uses a screening logic and command, and Stage 2 uses a definitive diagnosis logic created using the McDonald's diagnostic criteria.

4.5.1 Selection of variables:

Variables were selected based on evidence and extensive reviews. For the screening logic only those variables that are clinically relevant and found to have objective evidence to predict onset of disease activity were listed. Figure 4.3 shows the list of variables.

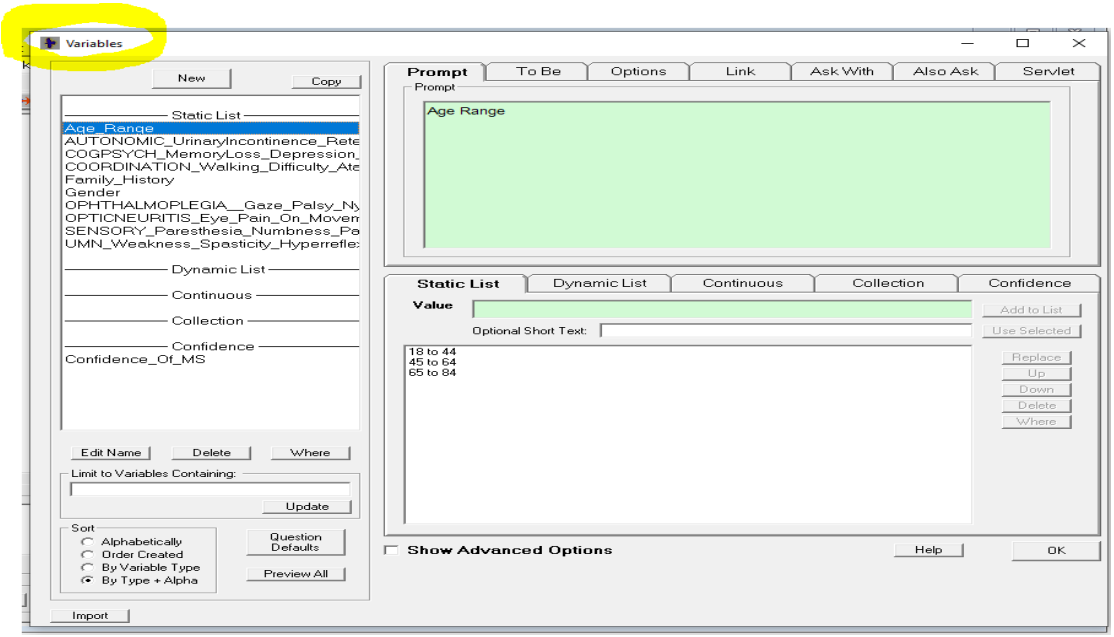


Figure 4.3 List of Variables for Screening Logic

4.5.2 Screening Logic Block:

Figure 4.4 shows the screening logic block created to apply the Boolean Logic on the selected variables. After that a command block was created (Figure 4.5) to run the logic and test as an end-user to get recommendation on the probability of the disease condition.

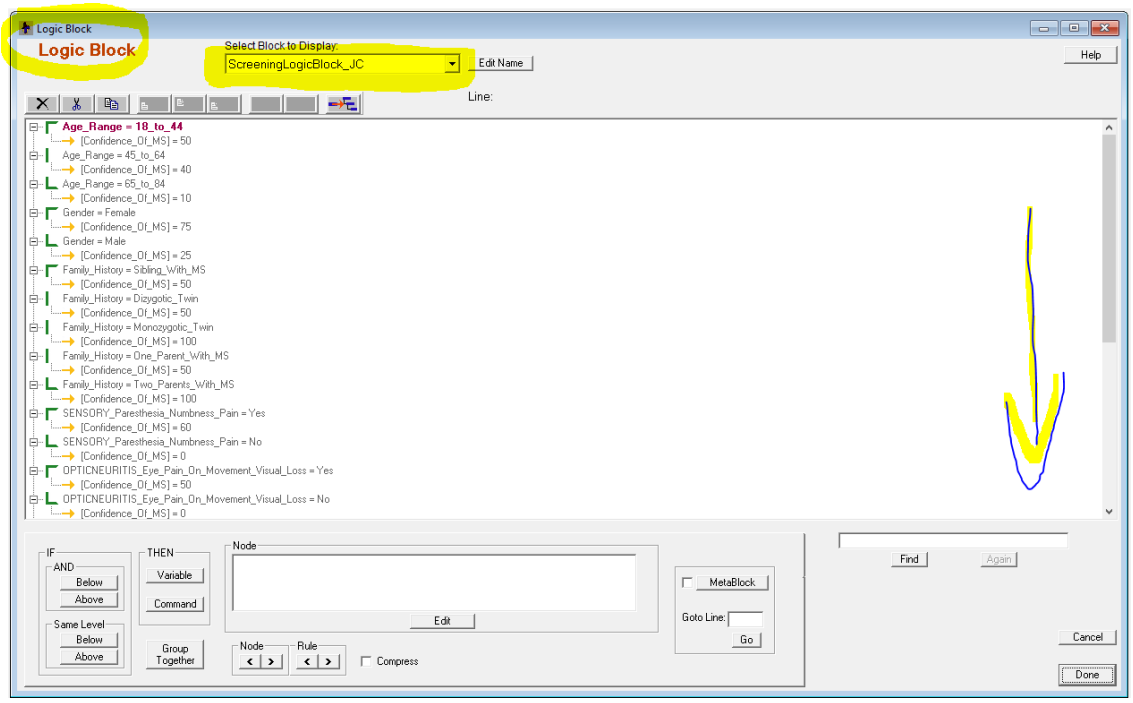


Figure 4.4 Screening Logic Block

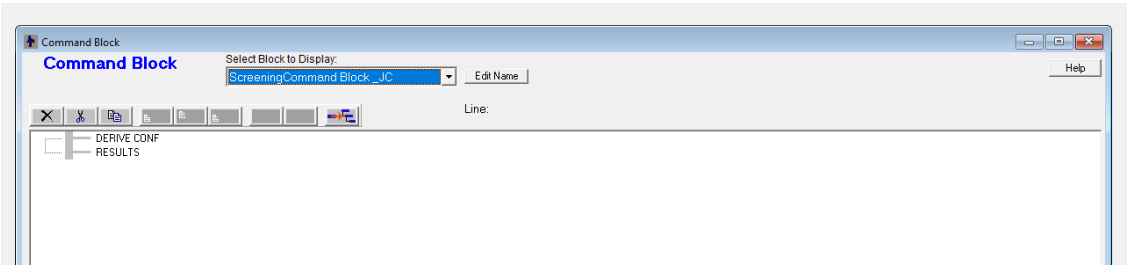
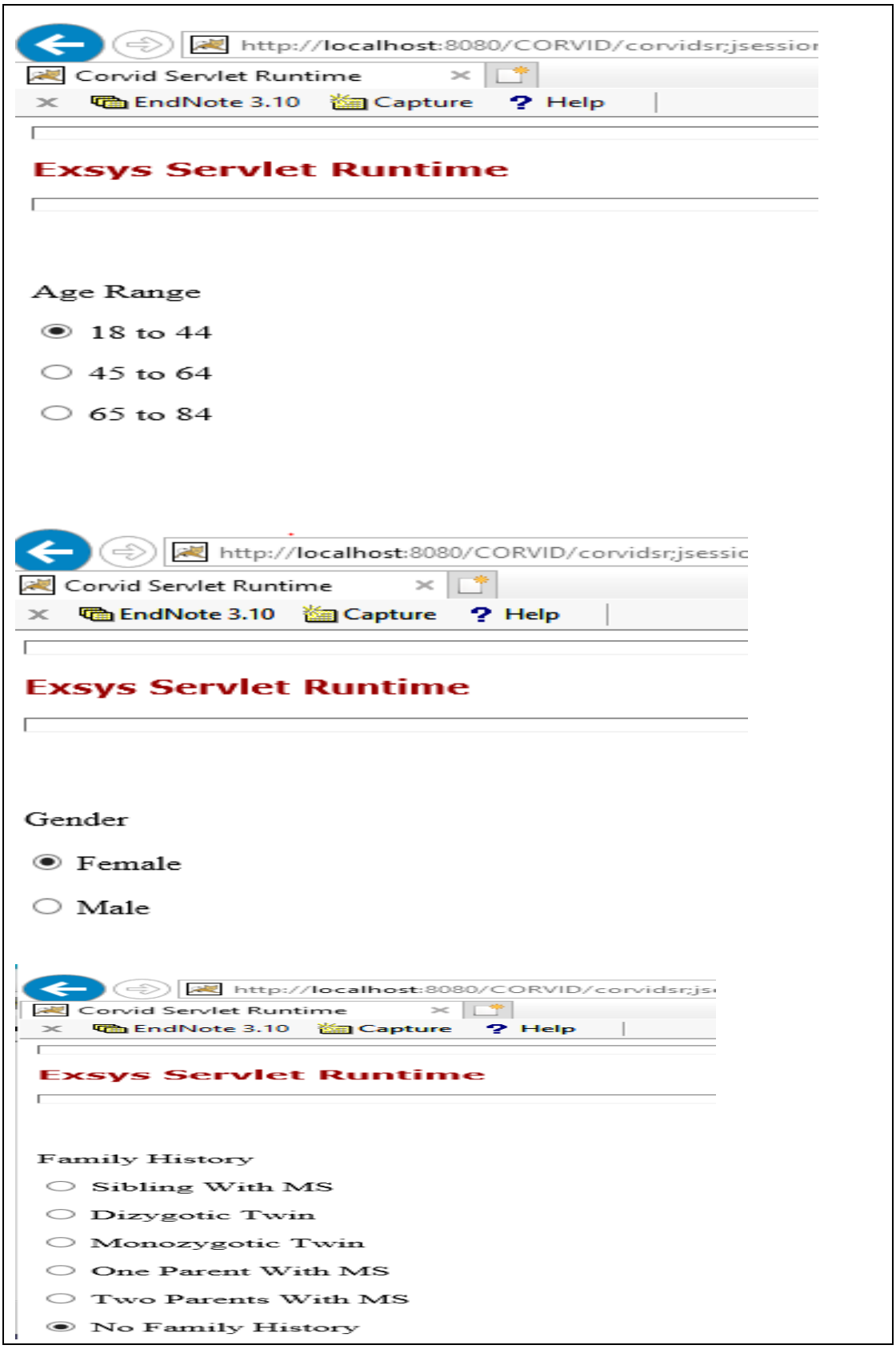
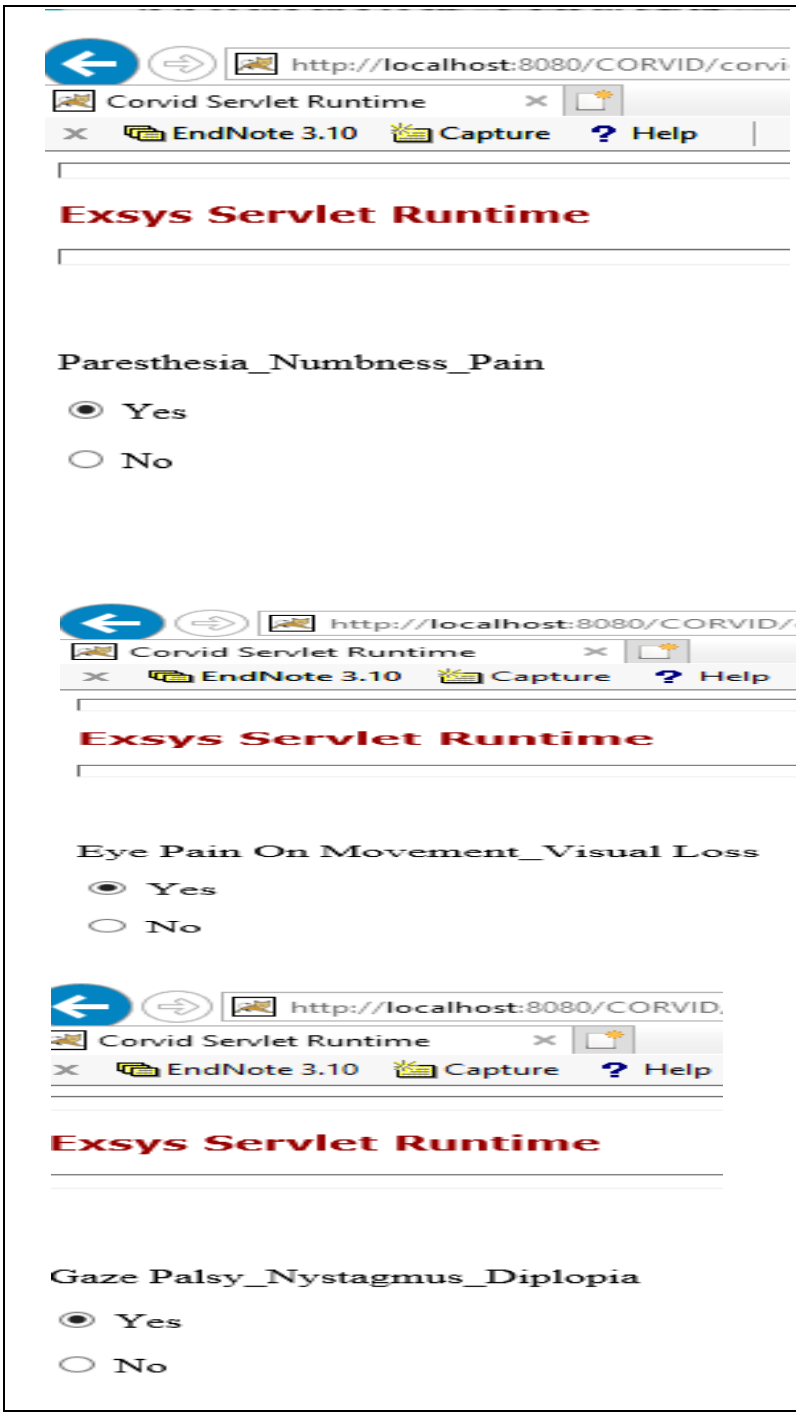
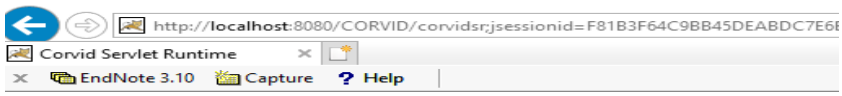


Figure 4.5 Screening Command Block


http://localhost:8080/CORVID/corvidsr;jsessior
Corvid Servlet Runtime
EndNote 3.10
Capture
Help
Exsys Servlet Runtime
Age Range
18 to 44
45 to 64
65 to 84
http://localhost:8080/CORVID/corvidsr;jsessic
Corvid Servlet Runtime
EndNote 3.10
Capture
Help
Exsys Servlet Runtime
Gender
Female
Male
http://localhost:8080/CORVID/corvidsr;js
Corvid Servlet Runtime
EndNote 3.10
Capture
Help
Exsys Servlet Runtime
Family History
Sibling With MS
Dizygotic Twin
Monozygotic Twin
One Parent With MS
Two Parents With MS
No Family History

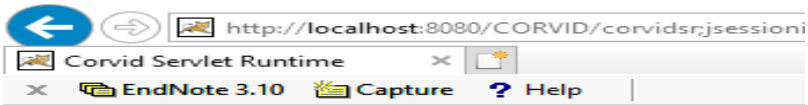

http://localhost:8080/CORVID/corvi
Corvid Servlet Runtime
EndNote 3.10
Capture
Help
Exsys Servlet Runtime
Paresthesia_Numbness_Pain
Yes
No
http://localhost:8080/CORVID/
Corvid Servlet Runtime
EndNote 3.10
Capture
Help
Exsys Servlet Runtime
Eye Pain On Movement_Visual Loss
Yes
No
http://localhost:8080/CORVID
Corvid Servlet Runtime
EndNote 3.10
Capture
Help
Exsys Servlet Runtime
Gaze Palsy_Nystagmus_Diplopia
Yes
No



Exsys Servlet Runtime

Walking Difficulty_Ataxia_Intention Tremor_Dysarthria_Dysdiadochokinesis

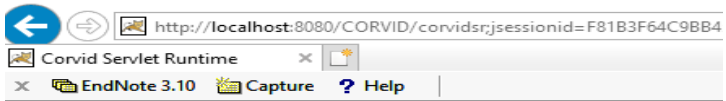
- (•) Yes
- ( ) No



Exsys Servlet Runtime

Weakness_Spasticity_Hyperreflexia_BabinskiPlus

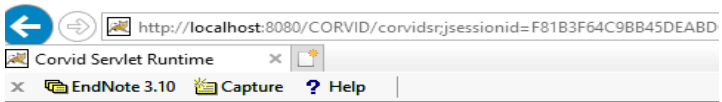
- (•) Yes
- ( ) No



Exsys Servlet Runtime

UrinaryIncontinence_Retention_Constipation_SexualDysFunction

- (•) Yes
- ( ) No



Exsys Servlet Runtime

MemoryLoss_Depression_Fatigue_EmotionalLability_ExecutiveFunction

- (•) Yes
- ( ) No

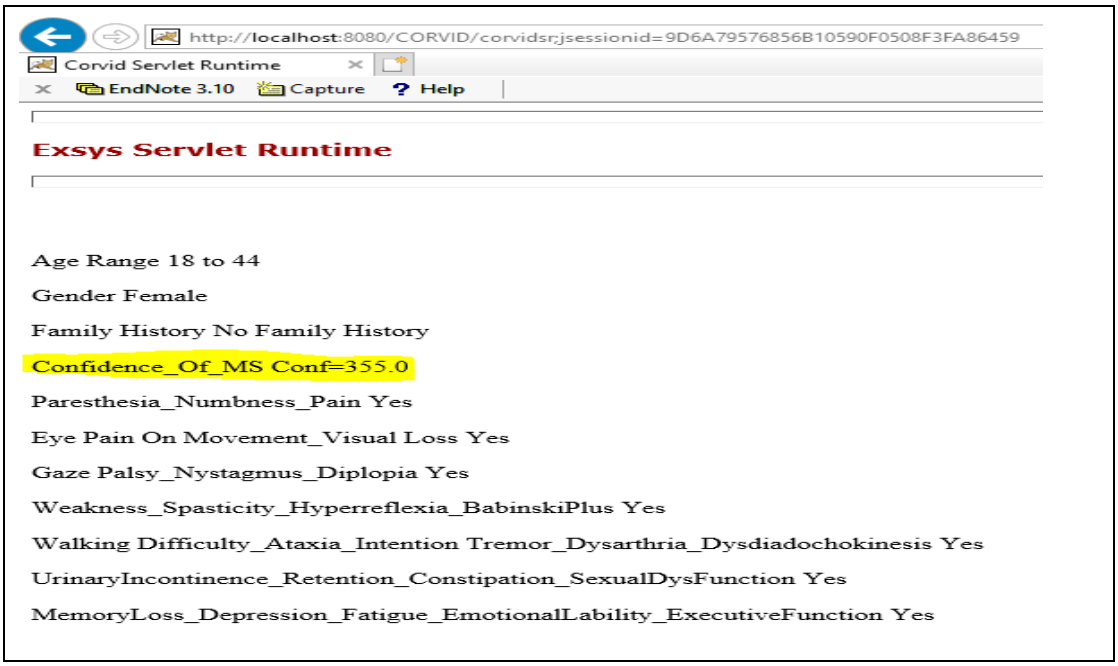


Figure 4.6 Demonstration of Stage 1, executing screening logic and recommendation obtained from the expert system by summing up the confidence value of variables.

If the score is 265 or more (with maximum attainable score 455) the patient is a candidate for MRI Scanning and Diagnostic Logic Block Needs to be run to confirm diagnosis by the decision support tool using the MRI results and McDonald's Criteria. If the summing of confidence value is less than 300 the patient is unlikely to have MS and can be reviewed at 6 months or after a year at the discretion of the clinician.

4.5.3 Diagnostic Logic Block:

This has been designed according to the 2017 McDonald's criteria of definitive diagnosis of MS. This is the final step of diagnostic decision making using the most important biomarker, MRI, for confirming definitive diagnosis. The step takes into account the McDonald's Criteria 2017 updated version to determine the dissemination of lesions in time and space which is key is diagnosing clinically isolated syndrome (CIS) and relapsing remitting MS. The results obtained by using case scenarios show that this

CDSS will help in early diagnosis and intervention to control the disease. If the expert system recommends Definite MS with confidence value of 10 the patient is diagnosed with MS. This logic uses number of MRI lesions in the brain and spinal cord along with number of clinical attacks.

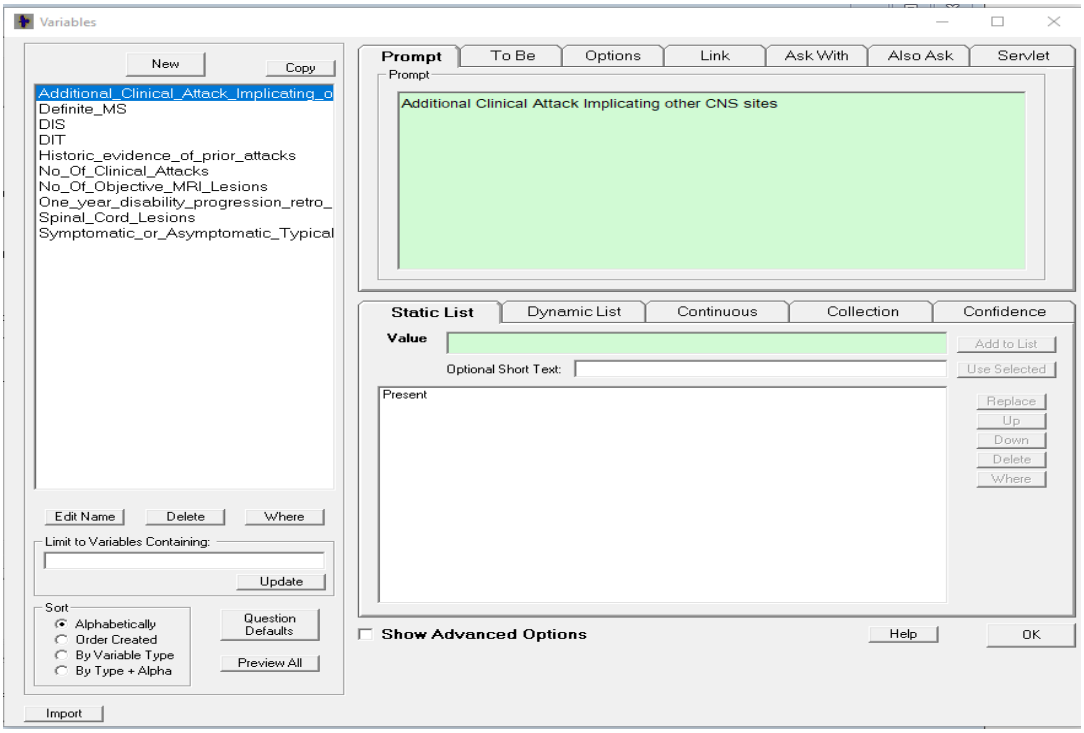


Figure 4.7 List of Variables in Diagnostic Screening Logic.

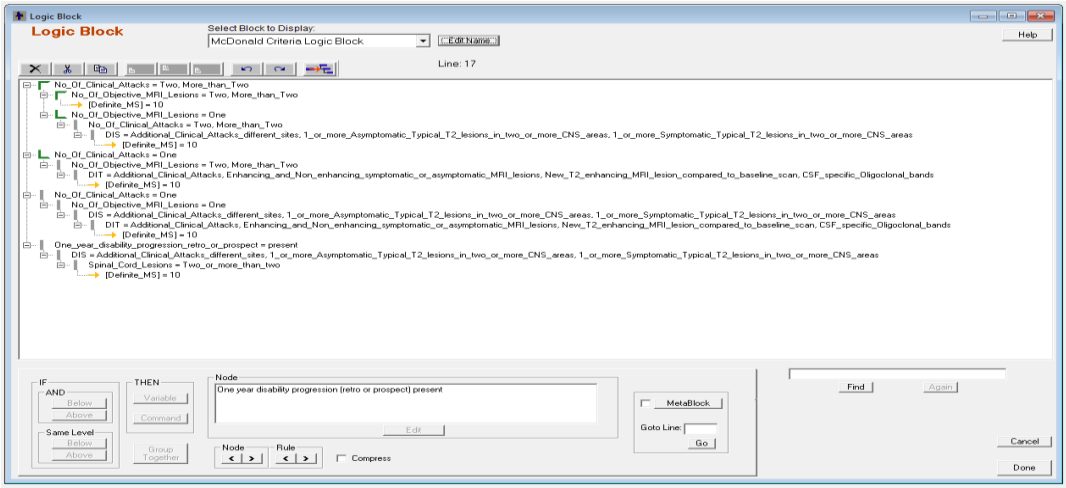


Figure 4.8 Diagnostic Logic Block built using McDonald's criteria of diagnosis 2017

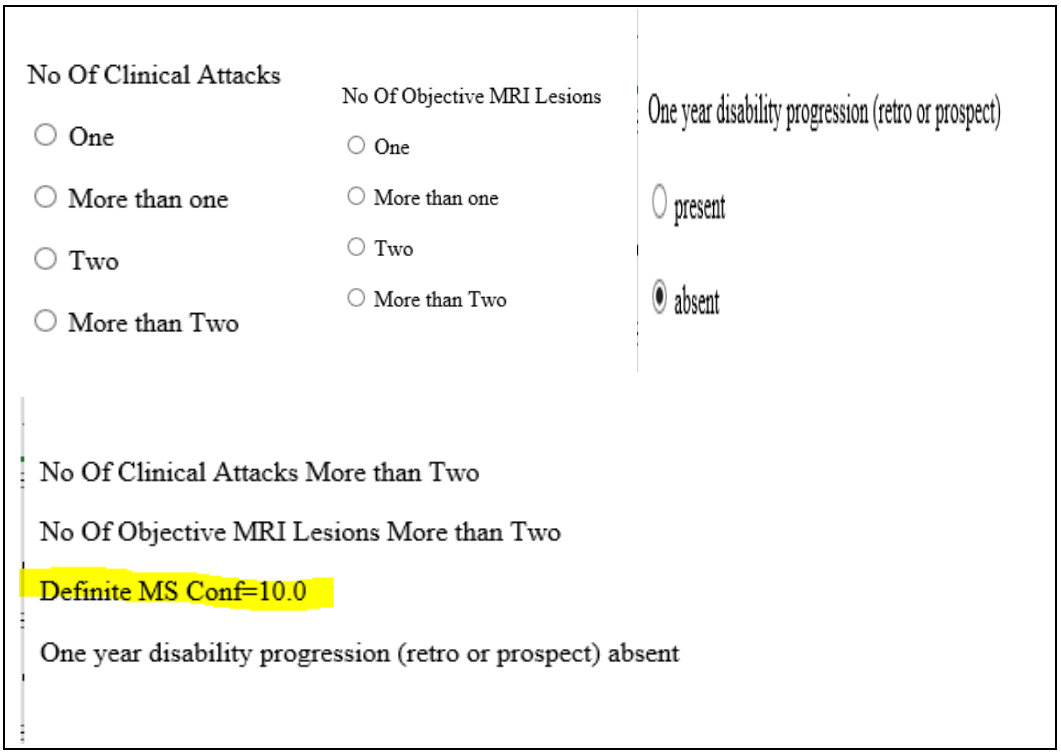


Figure 4.9 Command Blocks Run Using McDonald's Diagnostic Criteria

4.5.4 Case Studies:

The cases have been selected from various sources that include organizational websites, peer publications and patient case study series for educational purposes. Availability of live cases in Multiple Sclerosis is limited and time consuming process. Only RRMS cases were selected due to the easy access and commonality compared to other types of Multiple Sclerosis. Both male and female patients were selected. Appendix 2 shows the summary of patient cases selected for testing the expert system.

CHAPTER V
RESEARCH RESULTS

5.1 Introduction

This chapter describes the observations and findings obtained in the study. The results presented are graphical illustrations of the analysis done at various stages of the study using different data sources, analytical tools and the Expert Knowledge system. The analytical reports created for distribution of MS patients by demographic features in the U.S were derived from complex data sources used by National Inpatient Sample datasets. The CDSS was tested to simulate real-life case scenarios and clinical findings as per the guidelines of Neurological sciences organizations and MS Society standards. The CDSS screen shots in this chapter are illustrations of the development stages and the testing stages.

5.2 Data Analyses

A longitudinal descriptive analysis has been done to identify the current status of distribution of diagnosed cases in the U.S. The weighted national estimates from HCUP National Inpatient Sample (NIS) have been used to analyze the incidence and distribution of MS, based on various demographic factors across the nation. Definite cases of MS were filtered from the NIS database using the categorization filter of ICD-9 CM codes. The principal diagnosis code 340: Multiple Sclerosis was used to extract diagnosed and discharged cased from the NIS. The transition of ICD-9 CM to ICD-10 CM in 2015 has led to technical difficulties in identifying all cases in 2015. Therefore the year 2015 is excluded due to incomplete data.

5.2.1 Trend Analysis of Incidence of MS in the U.S using HCUP-NIS Data

Figure 5.1 below confirms the fact that the incidence rate of MS is increasing over the last two decades. Even though the biomarker for definite diagnosis, MRI, has been available since 1980's more cases have been reported since 2000. However, the review of literature done for this study couldn't find an exact cause for this phenomenon. Some researchers opined that this increase in number of cases could be due to increased awareness and better diagnostic tools (like high Tesla MRI machines) for diagnosing the disease. The increasing trend of incidence is seen in the data analysis done using the inpatient sample data.

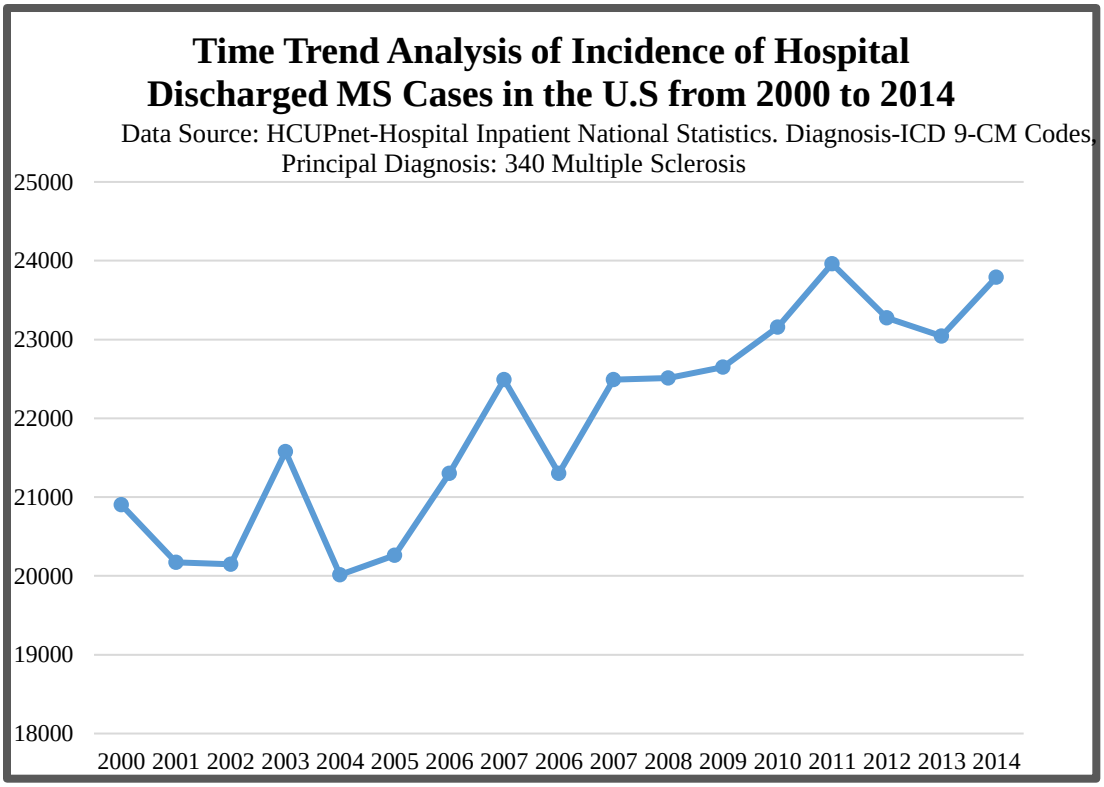


Figure 5.1 Time Trend Analysis of Incidence of MS cases in the U.S

5.2.2 Distribution of MS Cases in the U.S by region and year

Figure 5.2 below shows the geographic distribution of MS cases in the U.S. The chart shows that cases are more when the patients are away from the Earth's equator. Studies show that there is a significantly higher incidence of the disease is found in the northern most latitudes of the northern hemisphere and the higher southern hemispheres compared to southernmost latitudes. The chart below shows higher incidence in northeast, northwest and south than the western area. U.S lies in the high risk zone area in the global distribution map of MS.

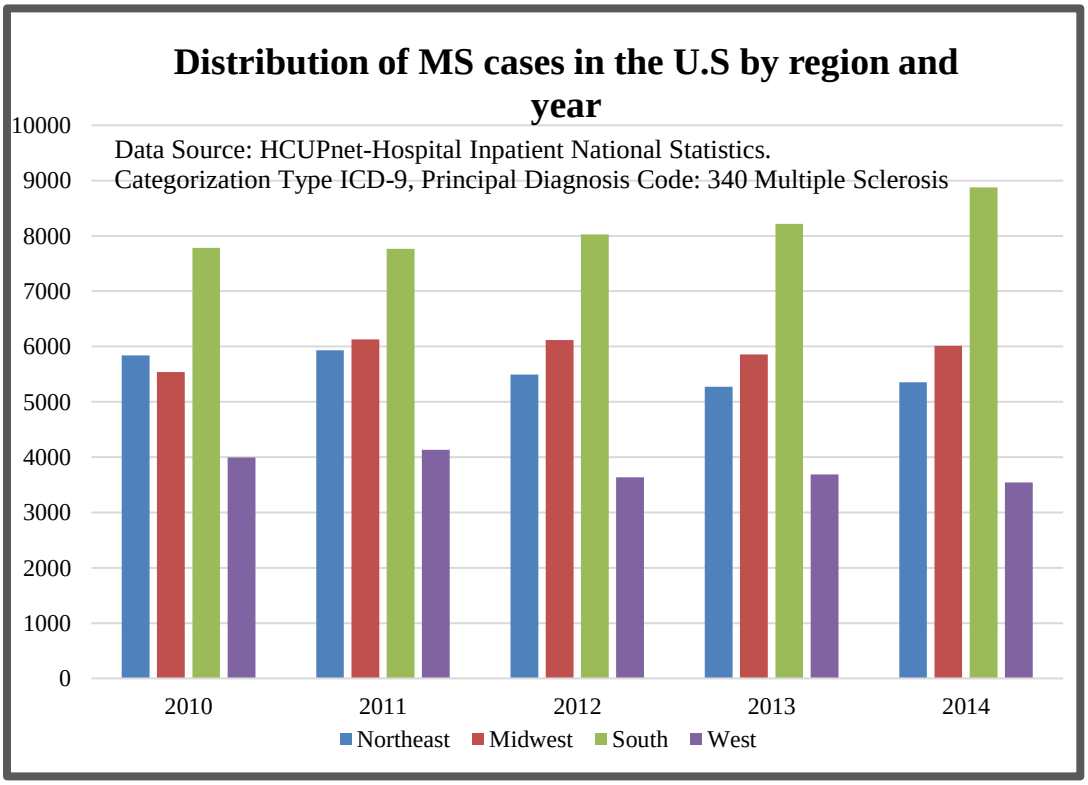


Figure 5.2 Geographic Distribution of MS cases in the U.S

5.2.3 Distribution of MS Cases by Gender in the U.S

Figure 5.3 below shows the distribution of MS cases by gender. MS is much more common in females than males, about 2-3 times more in women than in men. The analysis done here does not differentiate MS into its subgroups. But most of the cases, about 85%, are relapsing-remitting type. In recent years, the diagnosis of MS has increased more rapidly among women but the reasons are unclear.

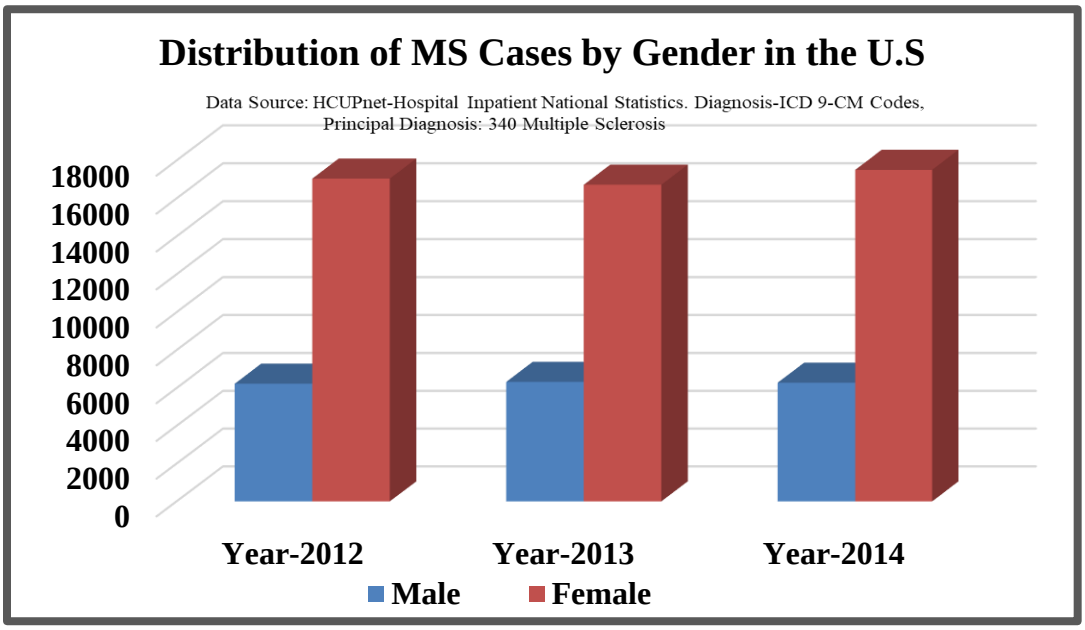


Figure 5.3 Distribution of MS Cases by Gender in the U.S

5.2.4 Distribution of MS Cases by Age Groups in the U.S

Figure 5.4 below shows the distribution of MS by age. In this analysis we can see that age group 18-44 has the highest number of cases. The fact that MS affects people during the most productive period of life is substantiated by this analysis of in-patient sample.

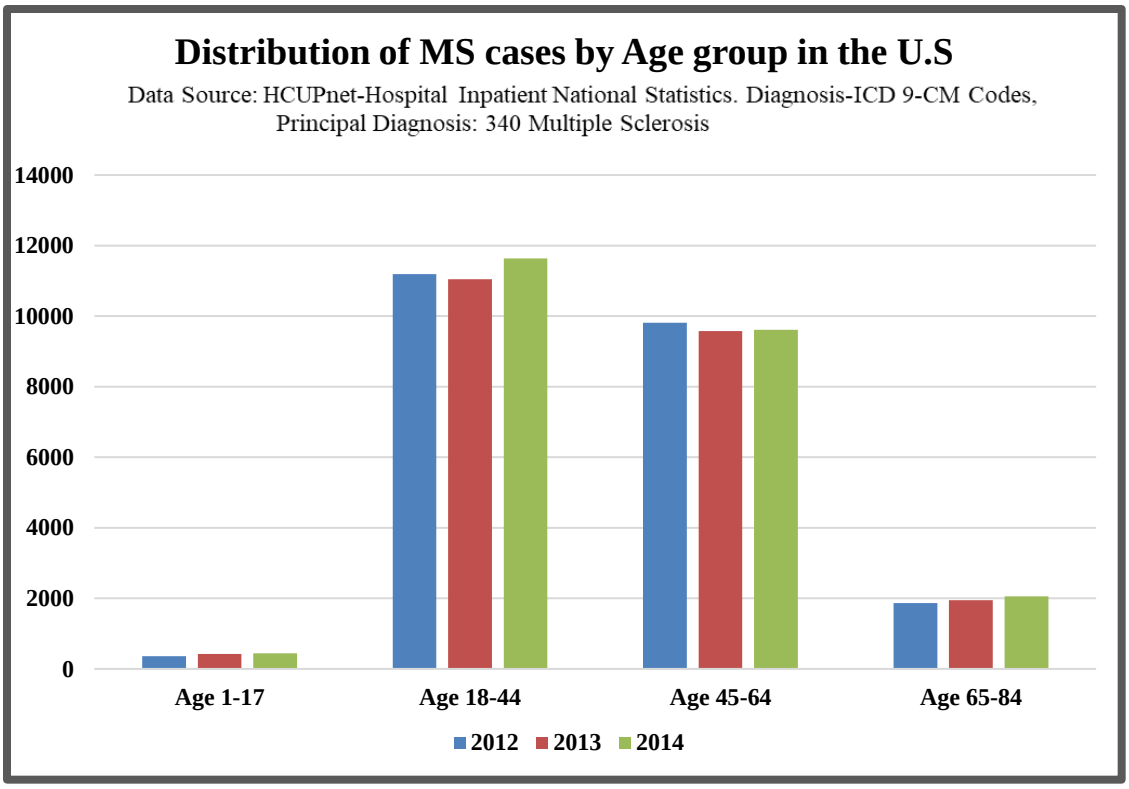


Figure 5.4 Distribution of MS Cases by Age Group in the U.S

5.3 Survey Analysis of Neurologists and Primary Care Physicians

As part of the fact check and collect evidence on current diagnostic techniques and need assessment, a survey was conducted among experts like neurologists and primary care physicians. 16 neurologists and 6 primary care physicians took part in the survey from United States, Canada and UAE. The survey contained 7 questions (see Appendix 1). Three questions in the survey used a scale of 1 to 5 to quantify the expert opinion. Feedback from 20 experts were collected and analyzed (Table 5.1). A quantitative analysis of 3 questions were done to make inferences about the need and advantages of CDSS.

Table 5.1 CDSS Survey Analysis of Neurologists and Primary Care Physicians

	Neurologists	PCP	Row Total	
Specialty	**14**	**6**	**20**	
Percent	70%	30%	100%	
Knowledge of CDSS for MS				
Yes	1	0	1	
Percent	7%	0%	5%	
No	13	6	19	
Percent	93%	100%	95%	
Use any Diagnostic tool (Not CDSS)				
Yes	2	0	2	
Row Percent	14%	0%	10%	
No	12	6	18	
Row Percent	86%	100%	90%	
Is current technique effective for early diagnosis				**Percentage**
Strongly Disagree (1)	3	0	3	15%
Disagree (2)	4	2	6	30%
Neither-Nor (3)	6	4	10	50%
Agree (4)	1	0	1	5%
Strongly Agree (5)	0	0	0	0%
Time to Diagnose MS				
6-12 Months	3	0	3	15%
1-2 Years	9	2	11	55%
2-3 Years	2	4	6	30%
3-4 Years	0	0	0	0%
4-5 Years or More	0	0	0	0%
CDSS will Improve early diagnosis and quality				
Strongly Disagree (1)	1	0	1	5%
Disagree (2)	0	0	0	0%
Neither-Nor (3)	2	0	2	10%
Agree (4)	10	6	16	80%
Strongly Agree (5)	1	0	1	5%
CDSS helps avoiding unnecessary tests and costs				
Strongly Disagree (1)	0	0	0	0%
Disagree (2)	0	0	0	0%
Neither-Nor (3)	2	0	0	0%
Agree (4)	11	6	17	85%
Strongly Agree (5)	1	0	1	5%

The survey analysis found significant need of CDSS in early diagnosis of MS and majority of experts disagreed with the current diagnostic techniques. The average time taken to diagnose MS varied from 6 months to 3 years among the surveyed experts conforming to the findings in the review of literature. Some survey questions were quantified using a scale of 1 to 5 with 1 being strongly disagree and 5 being strongly agree.

Quantitative analysis of key survey questions found that experts disagree with the current techniques and agree that a CDSS would help in early diagnosis, improve quality of care and reduce cost and unnecessary tests.

5.3.1 Analysis of Survey Question 4: Is current technique effective for early diagnosis of MS?

The response to the question about the effectiveness of current technique showed the disagreement among both groups. Table 5.2 and Figure 5.5 illustrate the response analysis.

Table 5.2 Analysis of Effectiveness of Current Technique for Early Diagnosis. (On a scale of 1=Strongly Agree and 5= Strongly Disagree)

Measures	Neurologists	PCPs
Response Averages	1.6	2.6
Standard Error	0.248	0.211
1.96 x Standard Error	0.487	0.413
95% Confidence Mean Upper Value	2.13	3.01
95% Confidence Mean Lower Value	1.15	2.19

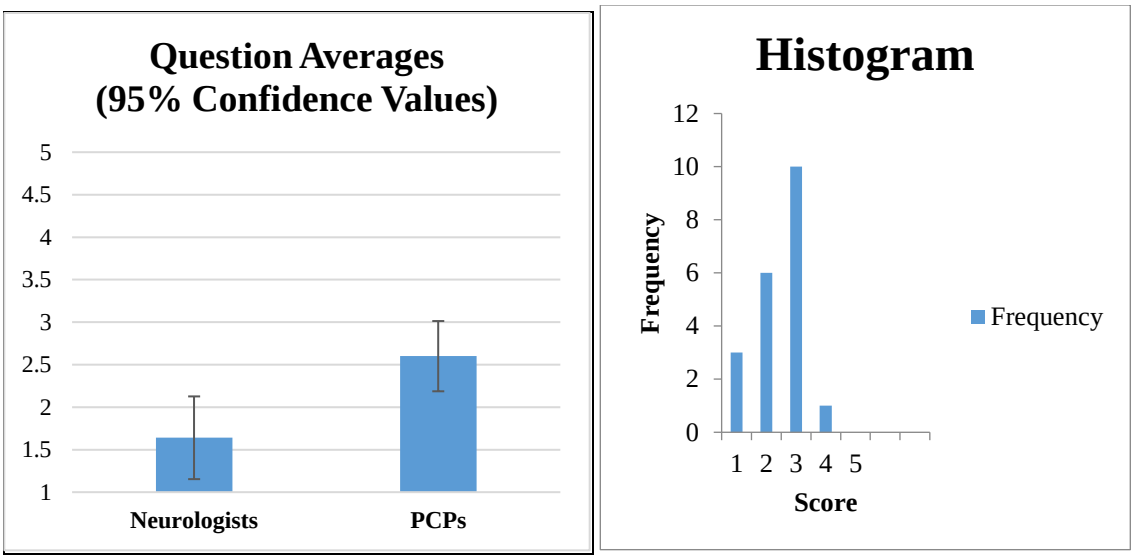


Figure 5.5 Confidence values and Histogram for Survey Question 4

5.3.2 Analysis of Survey Question 6: Does CDSS improve early diagnosis and quality?

Though no effective CDSS currently exists, both groups responded that such a system would help in early diagnosis and to improve quality of care.

Table 5.3 CDSS for early diagnosis and to improve quality of care. (On a scale of 1=Strongly Agree and 5= Strongly Disagree)

Measures	Neurologists	PCPs
Response Averages	3.7	4.0
Standard Error	0.244	0.000
1.96 x Standard Error	0.479	0.000
95% Confidence Mean Upper Value	4.18	4.00
95% Confidence Mean Lower Value	3.22	4.00

Table 5.3 and Figure 5.6 illustrate the analysis of response from both groups.

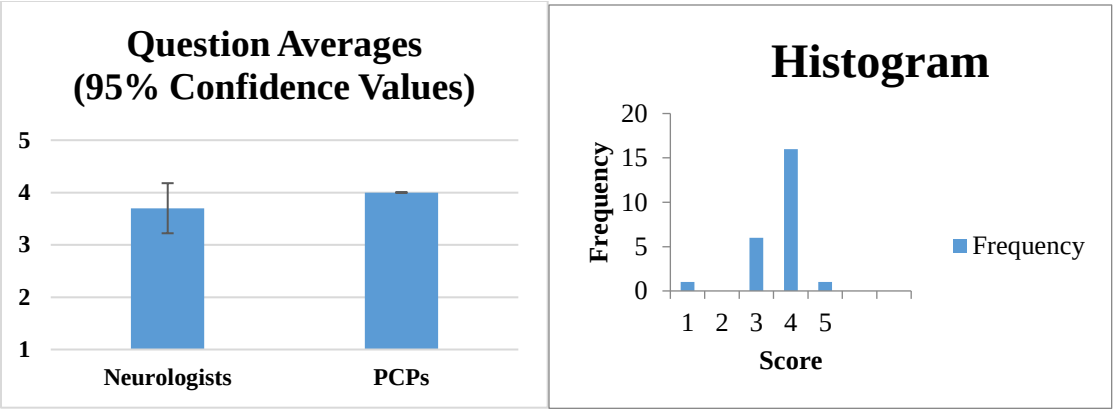


Figure 5.6 Confidence values and Histogram for Survey Question 6

5.3.3 Analysis of Survey Question 7: Does CDSS reduce unnecessary tests and costs?

Table 5.4 and Figure 5.7 illustrates the analysis of the question about other advantages.

Table 5.4 CDSS to reduce unnecessary tests and reduce costs. (On a scale of 1=Strongly Agree and 5= Strongly Disagree)

Measures	Neurologists	PCPs
Response Averages	3.9	4.0
Standard Error	0.127	0.000
1.96 x Standard Error	0.249	0.000
95% Confidence Mean Upper Value	4.18	4.00
95% Confidence Mean Lower Value	3.68	4.00

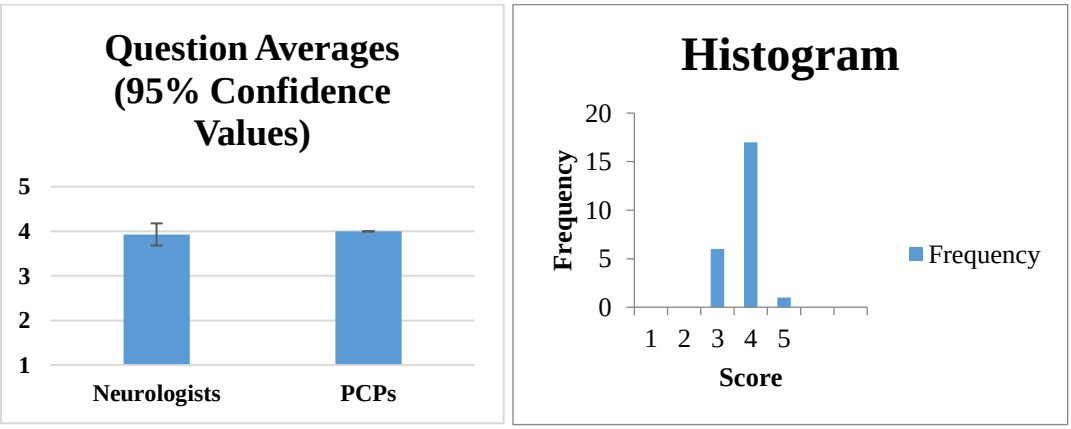


Figure 5.7 Confidence values and Histogram for Survey Question 7

5.4 Testing Expert System Using Patient Case Studies.

Twenty two patient cases were extracted from published case studies to test the decision support system. The initial signs and symptoms of patients at the time of initial diagnosis were compiled and used for testing the reliability and validity of the expert system. The table below shows the summary of cases selected for the testing and analysis.

5.4.1 Sample Case Study1:

39 year old female presented with weakness of right leg and blurring of vision last 6 months. She developed pain and watering from eyes 2-3 times over last one year which subsided on taking acetaminophen. On clinical examination she was found to have motor weakness lower limbs, paresthesia, mild nystagmus right side, hyperreflexia, Babinski + on right side. No ataxia, fine tremor+ on both hands and dysdiadochokinesia +. No urinary incontinence, but constipation was present. Her mental functional were normal but reported disappointment and failure to attend work. She had a warning from the employer for absence and missing deadlines for project. Her Mother was diagnosed with some neurological problem at the age of 65 but not sure if it was MS.

The expert system was used to test the signs and symptoms of this patient at the time of initial presentation.

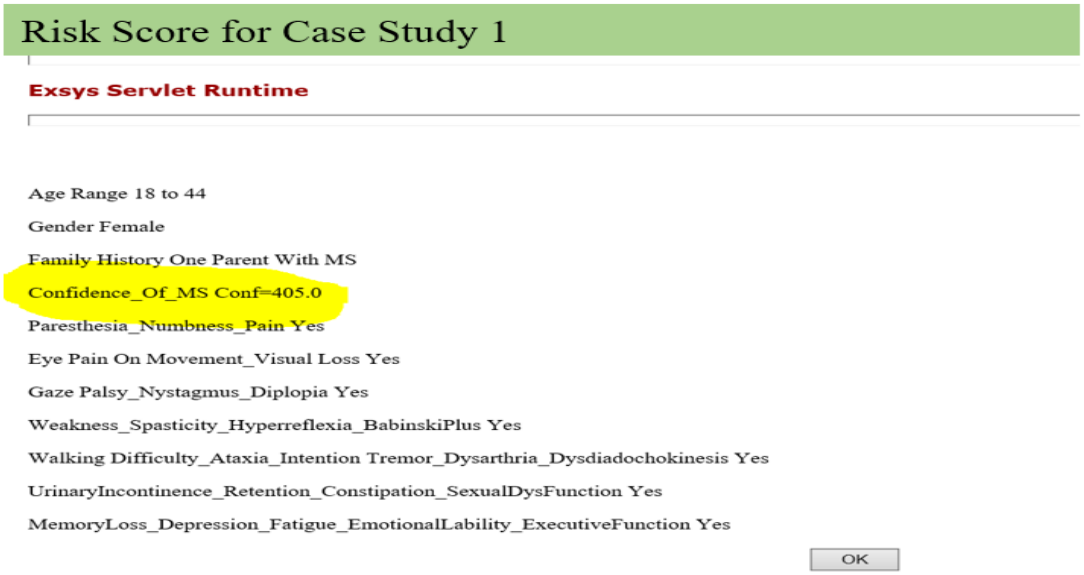


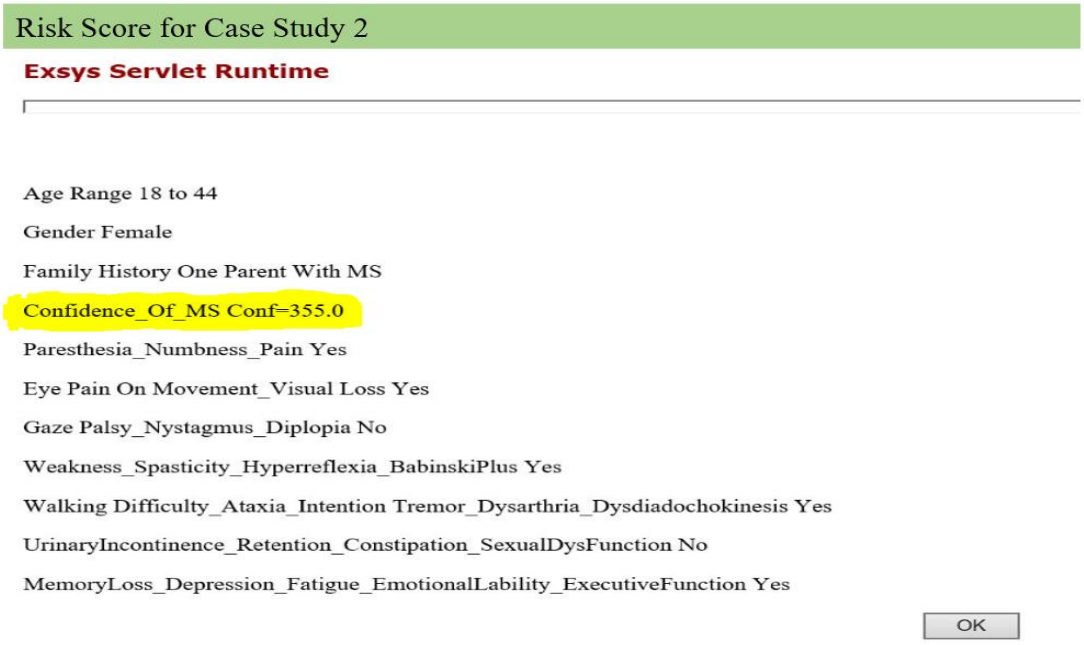
Figure 5.8 Risk score analysis by expert system using the Screening Logic

A patient with a score between 265 and 455 is a candidate for MRI scanning to confirm the diagnosis. This patient is recommended MRI scan and the results of MRI scan are analyzed using the Diagnostic logic in the expert system as the second stage of decision making and confirmation.

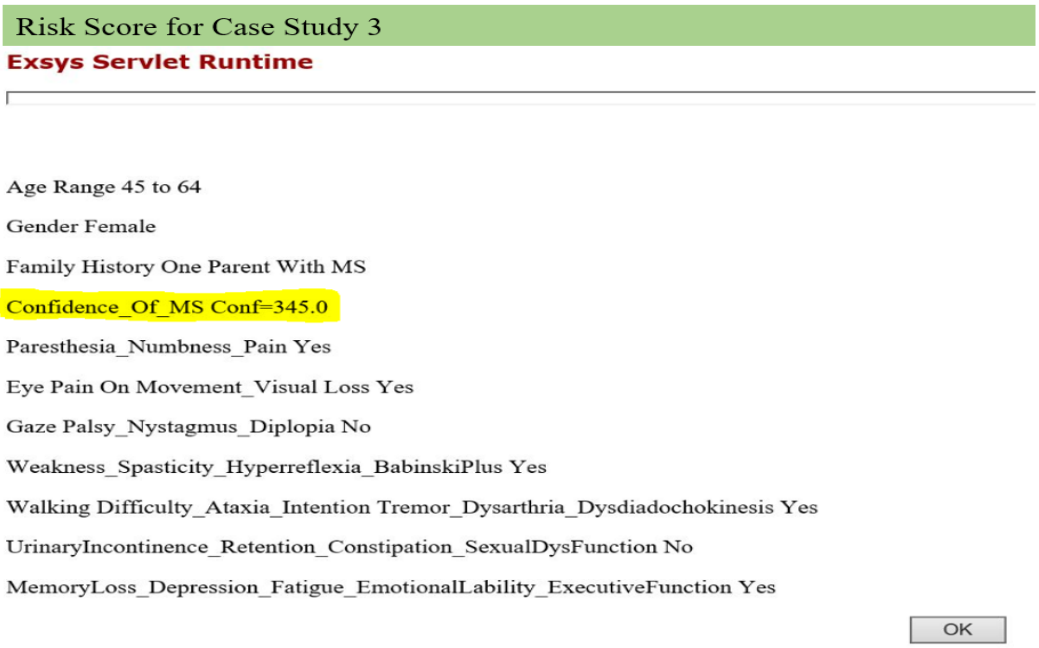
The scan results of this patient shows multiple T2 lesions in the periventricular areas of the brain. This patient also had episodes of clinical attacks in the past that went unnoticed. Findings in the MRI scan are entered in the McDonald Diagnostic logic to confirm the diagnosis.

Figure 5.9 Diagnostic Decision based on McDonald's Diagnostic Criteria

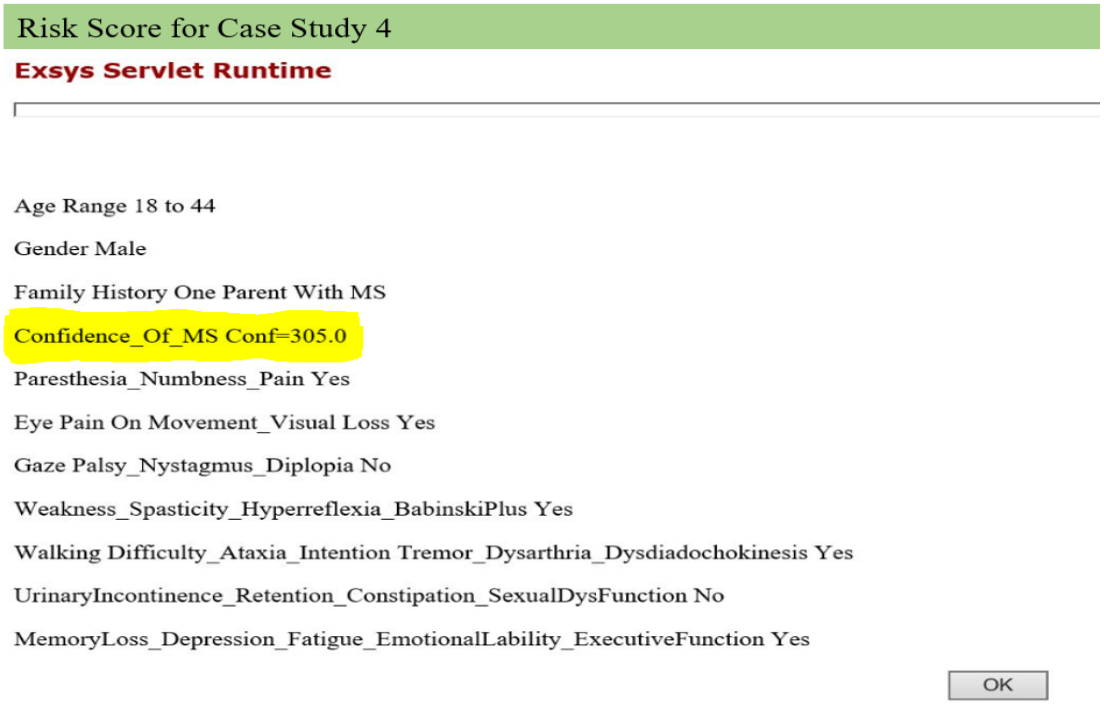
5.4.2 Sample Case Study 2:



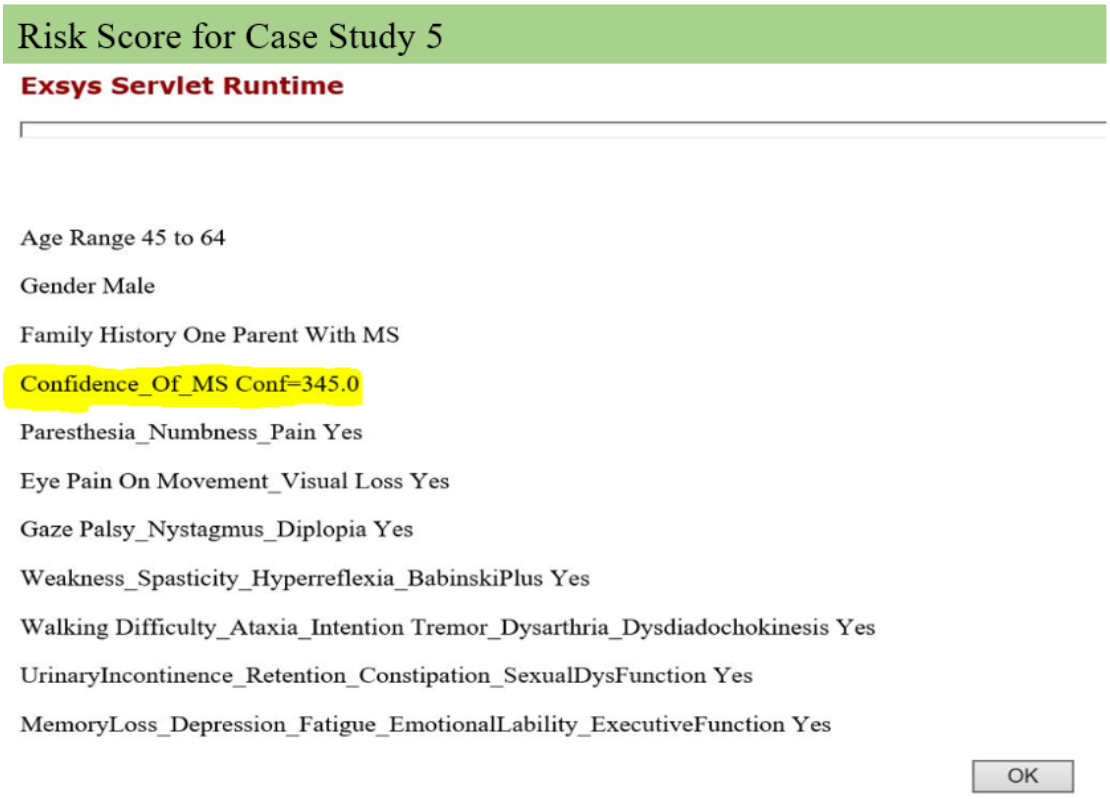
5.4.3 Sample Case Study 3:



5.4.4 Sample Case Study 4:



5.4.5 Sample Case Study 5:



5.5 Aggregate Analysis of Case Studies tested in Expert System

All scores obtained from the case studies were analyzed to find the average score and confidence limits. The average score was 341.6 and the 95% confidence intervals were 357.26 as upper limit and 325.94 as lower limit.

Table 5.5 Aggregate Analysis of Scores Obtained from Case Studies

Aggregate Scores of Case Studies	
Averages	341.6
Maximum Possible Score	455
Minimum Possible Score	265
Standard Error	7.989
1.96 x Standard Error	15.659
95% Confidence Mean Upper Value	357.26
95% Confidence Mean Lower Value	325.94

5.6 Future Work:

The model designed and tested in this research study needs to be tested on real patients at the point of care. Future plan is to use this approach in out-patient MS clinics of institutions by creating a smart-set that can be embedded in the Electronic Medical Record to test suspected cases of Multiple Sclerosis and predict the possibility and keep surveillance for early diagnosis. The algorithm created in this study can also be applied automatically to identify cases in EMR database and filter eligible cases that could progress to clinically definite MS. This can also be used as a predictive analytic tool in analyzing patient records to identify susceptible cases and alert them for early diagnosis. The survey conducted as part of this study substantiate the fact that the current techniques are not adequate and a CDSS is necessary for early diagnosis and quality care. All the experts were of the opinion that currently it takes 6 months to 3 years to make a definite diagnosis of MS. The survey analysis of physicians mainly neurologists done as part of this study sheds light to the need of a CDSS at point of care and confirms that the current diagnostic techniques are not effective for early diagnosis.

CHAPTER VI

DISCUSSION AND CONCLUSIONS

6.1 Introduction

Incidence and prevalence of Multiple Sclerosis is rising in the United States and across the world. Even though the exact etiology is not known, several theories exist that correlate the disease to latitudinal gradient, viral infections, vitamin D, cigarette smoking and genetic factors. Previous theories of latitudinal gradient has been questioned with rising number of cases which some researchers attribute to improved and advanced diagnostic tools and access to care. But still the average time period to diagnose a case varies from 6 months to 3 years.MS is the most common immune-mediated inflammatory demyelinating disease of the central nervous system and most common debilitating neurological disease among young people during the most productive years of their lives. The cost of illness of MS is higher than any other neurological diseases when you add up direct costs, indirect costs and intangible costs. Unpredictable course of the disease, variability in clinical presentations and long term disabilities create challenges in managing the disease and contribute to the high economic and social burden. Studies have shown that early diagnosis and treatment can delay the progression of disease and improve quality of life. The advent of newer drugs called Disease Modifying Therapies (DMTs) have given hope but the adverse effects and high cost of these drugs are drivers of the cost of illness.

MS is a heterogeneous disease with variable clinical and pathologic features. At this time there are no classical symptoms, physical findings or laboratory tests that can, by themselves, diagnose MS. Several strategies have to be used to determine the long established-criteria for diagnosis, and to rule out other possible causes since the

symptoms and signs of MS overlap with other neurological diseases. These strategies include a careful medical history, a family history, a neurologic exam and various tests including MRI, spinal fluid analysis and blood tests to rule out other conditions. Studies have shown that early diagnosis and intervention can control the disease activity and prevent the progression of disease. Making the diagnosis of MS as quickly and accurately as possible is important for several reasons. As we know that permanent neurologic damage can occur even in the earliest stages of MS, it is important to confirm diagnosis so that treatment can be started early and appropriately. The best way to achieve this is empowering clinicians with a clinical decision support system that will act as a tool to assist in making a definitive diagnosis. This study has been done to develop a CDSS that can be used by clinicians to assess the signs and symptoms and make decisions based on evidence based probabilities. Currently no CDSS exists to assist clinicians at the point of care to diagnose or rule out MS. The use of a CDSS proposed in this study is significant for early diagnosis and treatment initiation. There is enormous body of evidence exist in literature to suggest that a CDSS can improve the clinical work flow, reduce medical errors, improve quality of care and reduce the healthcare cost by eliminating unnecessary tests and treatments. As far as this CDSS is concerned it could reduce the delays in diagnosis and reduce the disease activity by early detection and treatment.

The review of literature suggests that there is no consensus exists in managing MS due to the variabilities and inconsistences existing in the clinical manifestations as well as pathologic phenomena in MS. Several studies highlight the delays in making the diagnosis and higher cost involved in treatment. In-depth review has been done to explore all theories in the epidemiology of MS. Though attempt has been made to limit to recent

studies dated from year 2000, some old manuscripts prior to 2000 have also been reviewed to compare and contrast the inferences illustrated in epidemiological studies.

Prevalence and incidence of MS have been reviewed in a chronological order and found significant variations compared to older theories. Worldwide distribution of MS has taken a new turn with more cases being diagnosed due to the imaging techniques and access to care.

Traditional theories of temporal trends and latitudinal gradient have been reviewed and compared with recent studies that correlated the etiology more to other factors. The influence of risk factors like gender and race have been demonstrated by doing a separate analysis using the NIS data. While global studies were reviewed in detail, special attention was given to the studies done in the U.S. Recent studies demonstrate increasing female to male ratio which is also reflected globally and in the U.S. Only a very few studies were found to support theories of Vitamin D deficiency, sunlight exposure, vaccinations and smoking. Viral infections mainly EBV have been found to have strong association in some large clinical studies but failed to prove the causation.

Genetic factors and familial linkage have been found to be significant with advances in genomic linkage screen and association screen. More studies need to be done in this area to understand the exact etiology of MS.

Review of literature has also been done to dig deep into the pathogenesis and pathophysiology of MS. Illustrations found from major studies have been examined in depth to quantify the variables for the CDSS development. Advances in the molecular imaging and radiological imaging have revealed new information and knowledge in

understanding the immune-pathogenesis and disease progression in MS. The use of new protein markers have helped in understanding the demyelination and re-myelination processes involved in MS. Literature substantiate the fact that the use of MRI as the principal biomarker has improved the diagnostic and therapeutic interventions.

Literature review has been done to research the signs and symptoms that manifest frequently and selected as variables based on the supporting evidence found in the peer reviewed journals and organizational guidelines. The history of MC Donald's criteria for radiological diagnosis has been studied and applied as the confirmatory logic in the CDSS designed in this study. Imaging and laboratory tests that are used commonly to assess the progress of disease activity have also been reviewed in detail to finalize the logic and command blocks used for the CDSS development.

To understand the burden of disease a review of literature has been done to assess the economic cost, social cost and productivity losses associated with MS. The fact that most cases of MS are diagnosed during the productive years of life (18-44 yrs.) makes it a priority to diagnose early and initiate therapeutic intervention to control the progression and limit the disabilities.

This study has utilized a multimodal approach by conducting both a quantitative study and a quasi-experimental study. A thorough review of literature has been done by limiting the search of peer-reviewed manuscripts from the year 2000 to select the most recent and evidence based resources. Resources searched for literature review included summaries and guidelines from neurological organizations, pre-appraised resources, non-pre-appraised resources, and federated searches. Data published in systematic reviews and meta-analysis have been used to give weights and quantify the variables used in

developing the CDSS algorithm. Additional data analyses were done using the HCUP-NIS data to confirm the disease distribution and burden in the United States. The preliminary results of the study using patient case scenarios show that it is feasible to develop a CDSS for early diagnosis and intervention for managing MS. More studies are necessary to measure the impact of CDSS in reducing the time to diagnose MS and improving the rates of early intervention and cost reduction.

6.2. Limitations of the Study

This study has been focused on clinically isolated syndrome and relapsing remitting MS (RRMS) since these are the most common clinical categories of MS encountered by clinicians. RRMS constitutes 85% of MS cases. The CDSS proposed in the study may be useful in these two clinical scenarios and may not be helpful in other categories of MS which are rare, like secondary progressive MS, primary progressive MS and progressive relapsing MS. Pediatric cases are excluded in this study due to the rarity of cases and lack of adequate literature published. The CDSS designed has been tested on patient cases retrieved from the published case studies that sometimes lack certain fine details needed for prioritizing the variables. Lack of clinical details may compromise the diagnostic accuracy. The CDSS proposed is intended for the use of clinicians at the point of care to assist in diagnostic decision making. This is not recommended for laymen use. Only 20 cases have been selected for testing the proposed CDSS. More cases need to be tested at different sites of the country and on different populations categorized by demographic factors. No test has been done by incorporating this CDSS algorithm in any electronic medical records. This needs to be done to validate the accuracy and reliability of the CDSS and these steps takes longer time.

The average time taken to diagnose a case of MS is 6 months to 3 years. 85% of the cases are RRMS cases which manifest initially as clinically isolated syndrome (CIS). The early diagnosis of MS should happen at the window period of CIS, but most of the times a definitive diagnosis is not made at the point of care. Patients have to wait for several months to years to get definitive diagnosis and by that time significant damage and disabilities would have occurred. The variability in clinical presentations makes it challenging for clinicians to make diagnosis. MS is a chronic neurological disorder that has no complete cure. The disease is characterized by repetitive attacks of neurological deficits with varying degrees of recovery. These attacks or relapses occur at different locations of CNS at different times. Clinically each attack is visualized as a lesion in the MRI of brain or spinal cord. In this study we found that recent epidemiological studies have reported an increase of MS among young patients and predicted to increase up to 10 folds in some countries. In the United States also some recent studies have shown more cases being reported and young women are affected two to three times more than men. Our knowledge of MS has progressed according to our knowledge in medicine and biology. Technological advances in the recent times especially in molecular genetics and immunology have identified new patterns and triggers that control the disease activity in MS. Although the disease course for most patients usually start of CIS or RRMS, it typically transitions into aggressive forms with more relapses, degenerations and disabilities. For diagnosing MS, three different finding s are required, multiplicity of lesions in the CNS, i.e., dissemination in space (DIS); recurrent disease flare ups during the course of illness, i.e., dissemination in time (DIT); and immunological disturbance. These criteria in addition to demographic factors are used in designing the CDSS in this

study. Enormous body of evidence shows that early therapeutic interventions, pharmacological and neurocognitive, can control and delay the progression of disease and improve the quality of like. The CDSS designed in this study is expected to provide a tool to make probabilistic determination and diagnose real cases at the earliest.

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APPENDICES

Appendix 1:

Need Assessment for a Clinical Decision Support for Early Diagnosis of Multiple Sclerosis

This survey is exclusively for primary care providers and neurologists. (Acronyms: CDSS-Clinical Decision Support System; MS-Multiple Sclerosis)

Note: PLEASE CHOOSE ONLY ONE ANSWER

1. What is your medical specialty?
    1. Neurology
    2. Internal Medicine
    3. Family Medicine
    4. General Medicine
    5. Other----------

2. Do you know any Clinical Decision Support currently in use for diagnosing Multiple Sclerosis?
    1. Yes
    2. No

3. Do you currently use any diagnostic tool for diagnosis of Multiple Sclerosis at the point of care?
    1. Yes
    2. No

4. Do you agree the current diagnostic technique for MS is effective for early diagnosis of MS?
    1. Strongly disagree
    2. Disagree
    3. Neither agree nor disagree
    4. Agree
    5. Strongly agree

5. How long do you think currently it takes to diagnose Definite MS?
    1. 6-12 months
    2. 1-2 years
    3. 2-3 years
    4. 3-4 years
    5. 4-5 years or more

6. Do you agree that a Clinical Decision Support will improve early diagnosis and the quality of care for MS patients?
   1. Strongly disagree
   2. Disagree
   3. Neither agree nor disagree
   4. Agree
   5. Strongly agree

7. Do you think that a CDSS can help avoid unnecessary tests and reduce cost of care in managing MS?
   1. Strongly disagree
   2. Disagree
   3. Neither agree nor disagree
   4. Agree
   5. Strongly agree

   PS: THANK YOU SO MUCH FOR SHARING YOUR EXPERT OPINION. YOUR NAME AND IDENTITY ARE NEVER DISCLOSED AND WILL REMAIN ANONYMOUS.

Appendix 2: Patient Cases Part 1

Cases	Age	Gender	Family History	Sensory Deficits	Optic Neuritis	Hyperreflexia
1	39	F	Mother +	3+	1+	1+
2	41	M	NA	1+	1+	1+
3	30	M	Aunt+	3+	1+	1+
4	44	F	NA	1+	1+	1+
5	37	F	Mother +	3+	1+	1+
6	45	F	Mother +	4+	1+	1+
7	50	M	NA	1+	1+	1+
8	55	F	NA	1+	1+	1+
9	59	M	NA	1+	1+	1+
10	40	F	Aunt+	3+	1+	1+
11	44	F	Aunt+	3+	1+	1+
12	58	F	NA	1+	1+	1+
13	32	F	Mother +	3+	1+	1+
14	30	F	Mother +	3+	1+	1+
15	35	F	Aunt+	3+	1+	1+
16	27	F	Grandmother+	2+	1+	1+
17	40	F	Mother +	3+	1+	1+
18	30	F	Grand Aunt+	3+	1+	1+
19	36	F	NA	1+	1+	1+
20	41	F	Aunt+	3+	1+	1+
21	47	M	Mother +	3+	1+	1+
22	55	M	NA	1+	1+	1+

Appendix 3: Patient cases Part 2

Cases	Spasticity	Nystagmus	Diplopia	UMN	Coordination	Autonomic	CogPsych
1	1+	1+	NA	4+	1+	NA	Yes
2	NA	1+	NA	4+	1+	NA	Yes
3	1+	1+	1+	4+	1+	NA	Yes
4	1+	1+	1+	4+	1+	1+	Yes
5	1+	1+	1+	3+	1+	NA	Yes
6	1+	1+	1+	3+	1+	1+	Yes
7	1+	1+	1+	4+	1+	1+	Yes
8	1+	1+	1+	4+	1+	1+	Yes
9	1+	1+	1+	4+	1+	1+	Yes
10	1+	1+	1+	4+	1+	1+	Yes
11	1+	1+	1+	4+	1+	NA	Yes
12	1+	1+	1+	4+	1+	1+	Yes
13	1+	1+	1+	4+	1+	NA	Yes
14	1+	1+	1+	2+	1+	NA	Yes
15	1+	1+	1+	2+	1+	NA	Yes
16	1+	NA	NA	1+	1+	NA	Yes
17	1+	1+	1+	1+	1+	NA	Yes
18	1+	1+	1+	2+	1+	NA	Yes
19	1+	1+	NA	4+	1+	NA	Yes
20	1+	NA	1+	4+	1+	NA	Yes
21	1+	1+	1+	4+	1+	1+	Yes
22	1+	1+	1+	4+	1+	1+	Yes