MONOGENIC DISEASES MASQUERADING AS MULTIPLE SCLEROSIS:
A SYSTEMATIC REVIEW

by

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LIST OF ABBREVIATIONS

ALA   delta-aminolevulinic Acid
ALD/AMN  X-linked Adrenoleukodystrophy/Adrenomyeloneuropathy
APBD   Adult Polyglucosan Body Disease
CADASIL  Cerebral Autosomal Dominant Arteriopathy with Subcortical
         Infarcts and Leukoencephalopathy
CMT    Charcot Marie Tooth
CNS    Central Nervous System
CSF    Cerebral Spinal Fluid
CTX    Cerebrotendinous Xanthomatosis
EM     Electron Microscopy
EMG    Electromyography
FA     Friedreich Ataxia
FXTAS  Fragile-X Associated Tremor Ataxia Syndrome
LHON   Leber Hereditary Optic Neuropathy
LM     Light Microscopy
HMSN   Hereditary Motor and Sensory Neuropathies
HSP    Hereditary Spastic Parapareses
MELAS  Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like
        Episodes
MERRF  Myoclonic Epilepsy with Ragged Red Fibers
MLD    Metachromatic Leukodystrophy
MRI    Magnetic Resonance Imagining
**LIST OF ABBREVIATIONS (con’t)**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>MS</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>NCV</td>
<td>Nerve Conduction Velocity</td>
</tr>
<tr>
<td>PM</td>
<td>Pelizaeus-Merzbacher</td>
</tr>
<tr>
<td>PNS</td>
<td>Peripheral Nervous System</td>
</tr>
<tr>
<td>PPMS</td>
<td>Primary Progressive Multiple Sclerosis</td>
</tr>
<tr>
<td>RRMS</td>
<td>Relapsing Remitting Multiple Sclerosis</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischemic Attack</td>
</tr>
<tr>
<td>TRAPS</td>
<td>TNF Receptor-Associated Periodic Syndrome</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cell</td>
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</table>
Monogenic Diseases Masquerading as Multiple Sclerosis: A Systematic Review

Abstract

by

MEGHAN JO MARINO

Multiple sclerosis (MS) is a neurodegenerative disease with highly variable phenotypic expression and neuroradiological findings, which can lead to making an accurate diagnosis difficult at times. The monogenic disease differential diagnosis list has not been extensively reviewed in over fifteen years. The purpose of this research was to identify monogenic diseases that can masquerade as MS in order to create tools to aid clinicians in the differential diagnostic process. A systematic literature review was performed using PubMed and CINAHL databases. From this review, a total of twenty-two monogenic diseases were identified and examined for similarities and differences with MS. Analyses of the data generated four tables: 1) comparison of clinical similarities, 2) clinical differences from MS, 3) common MRI findings, and 4) additional screening and testing options. Knowledge of these rare diseases is important for avoiding diagnostic mistakes and use of inappropriate treatment approaches.
INTRODUCTION:

Multiple sclerosis (MS) is a disease with highly variable expression, making it a difficult diagnosis to correctly identify. Recent medical literature raises doubts about the reliability of published prevalence rates of MS, and many are thought to be inflated. For example, some studies have shown that relying on clinical information and magnetic resonance imaging (MRI) interpretation leads to one-third of the diagnoses of MS to be incorrect (Poser & Brinar, 2007). A lack of specific phenotypic features further complicates the diagnostic process; moreover, there is no pathognomonic sign or symptom nor is there a specific diagnostic test for MS. Similar signs and symptoms can occur in patients who have other diseases, just as tests such as MRI, spinal fluid examination, and evoked potential readings are sensitive for MS, but not specific (Scolding, 2007).

The differential diagnosis of MS can be divided into several pathophysiological categories: inflammatory/autoimmune diseases, infectious diseases, genetic disorders, neoplastic diseases, and other demyelinating diseases (Fadil et al, 2007). In order to provide optimal medical care, it is imperative that an appropriate diagnosis be made, as this not only has implications for the patient, but also for the patient’s family and the patient’s clinicians. Medical management for the patient and his/her family members, accurate recurrence risks, and natural history knowledge, such as anticipation of additional medical risks all depend on the diagnosis. As many genetic diseases, which may be rare and less well known, can masquerade as MS, outlining a list of differential diagnoses can be difficult at best. Additionally, clinicians may lack the diagnostic
expertise to discriminate genetic disorders from MS. Common tools, such as a family history, may not always be useful, especially in the cases of autosomal recessive diseases, de novo mutations, or patients who have been adopted or simply lack the knowledge regarding this type of information about their relatives. Thus, lack of a family history does not negate the possibility of an underlying genetic cause for an individual’s symptoms.

The most recent published review that described genetic disorders that masquerade as MS was Natowicz and Bejjani, 1994. However, due to the advances of MRI and the constant growing field of genetics, this reference may no longer be comprehensive. New genes and genetic syndromes have been found and described, and technology has improved to help aid in missing obvious misdiagnoses of MS (i.e. tumors or structural abnormalities). To my knowledge, no recent studies have thoroughly investigated the genetic disease differential of MS.

**SIGNIFICANCE FOR GENETIC COUNSELING:**

As the discipline of genetics continues to grow and encompass a broader scope of diseases, genetic counselors and geneticists are being asked to provide healthcare professionals with information about and approaches to genetic disorders. However, one important barrier to providing optimal counseling to a patient is absence of a clear diagnosis. Many diseases share similar features/clinical findings which make them difficult to distinguish from each other. Furthermore, not all diseases have a specific genetic test that can be performed in order to confirm a suspected diagnosis.
Making the appropriate diagnosis can be crucial to patient care. Having a specific diagnosis allows for appropriate treatment and/or management plans to take place, provides families with accurate information regarding recurrence risks and risks to other family members, and may provide a patient with an answer or explanation as to “why” he or she is affected. Conversely, not having the appropriate diagnosis can do potential harm to a patient—both physically and psychologically. For example, being treated for a disease one does not have, especially in regard to certain medications, could be both harmful and expensive. Coming to terms with a diagnosis can be a challenge for any patient, regardless of the condition. The period of time surrounding receiving a diagnosis can be either one of emotional instability and insecurity, or it can be a time of relief. Clinical observations and anecdotal descriptions suggest that for an individual to receive a diagnosis, have it negated, and then be rediagnosed with another condition can adversely impact the patient, with the largest impact being on the physician-patient relationship (Kuzel et al, 2004).

While MS is a common neurological disease, it also is one which has a broad range of clinical findings, making it a difficult disease to diagnosis. The purpose of this research project was to identify genetic diseases that can be misdiagnosed as MS in order to develop a set of tables which can assist both clinicians and genetic counselors in facilitating the diagnostic process. The tools produced as a result of this review may aid in differentiating those who truly have MS from those who may have a monogenic disease.
PURPOSE OF STUDY:
The purpose of this systematic review of the literature was to identify monogenic diseases whose findings overlap with those of multiple sclerosis (MS) in order to develop a set of tools for clinicians and genetic counselors to aid in the differential diagnostic process.

SPECIFIC AIMS:
1. Identify monogenic disorders that present with an MS-like phenotype from a systematic review of the literature
2. Describe the disorders identified in Aim 1 to include:
   - Disease name
   - Disease summary
     - Genetic defect
     - Inheritance pattern
     - Prevalence
     - Age-of-onset (average)
     - Key clinical findings
     - Disease prognosis and management
3. Compare and contrast the identified disorders with the features of MS by developing a set of tables with:
   - Clinical similarities and differences
   - Neuroimaging findings
   - Screening and diagnostic testing
BACKGROUND:

MULTIPLE SCLEROSIS SUMMARY

MS is the most common demyelinating disease of the central nervous system (CNS) and is estimated to affect approximately 400,000 Americans and more than 2.5 million worldwide. The general population risk in the United States to develop MS is 1 in 750 and affects women twice as often as it affects men. It is typically a disease that affects people of Northern European heritage, while African Americans, Southeast Asians, and Inuits are less likely to develop the disease. It has also been seen with an increased prevalence in Northern latitudes.

The onset of this degenerative neurological disease is usually in mid-adulthood, commonly between the ages of 20 and 40 years (Fadil et al, 2007). Although it is less common, there have been cases of adolescents being affected. Current understanding of the pathogenesis indicates that it is an autoimmune disease. Dysregulation of cellular and humoral immune responses with loss of regulatory T cell function cause lymphocytes and macrophages to infiltrate the CNS, leading to inflammation and progressive destruction of myelin sheaths around the neurons of the CNS (Compston & Coles, 2008). Demyelination causes a reduction of neuronal impulses, which leads to a range of clinical symptoms. A wide range of variability exists among the onset of symptoms, severity, and disease progression. Thus, MS has been divided into four classes, and each class can have a mild, moderate, or severe disease course. The classes are identified and summarized as follows (Hurwitz, 2009):
1. Relapsing-Remitting (RRMS)

This type of MS is identified in about 85% of individuals who are initially diagnosed with the disease. It is characterized by periods of time in which there is a severity or worsening of symptoms, known as a relapse or exacerbation, which is then followed by a complete recovery of function and reduction in symptoms known as remission.

2. Primary-Progressive (PPMS)

MS characterized by progression of symptoms, without any periods of remission, from the onset of disease.

3. Secondary-Progressive (SPMS)

Characterized by RRMS at the onset of the disease, eventually leading into a PPMS form. About 90% of individuals with RRMS develop this type after 25 years (Ebers, 2001).

4. Progressive-Relapsing (PRMS)

This rare form of MS occurs in approximately 5% of individuals with MS. It is distinguished from other forms of MS by disease progression with clear worsening of symptoms/neurological function periodically throughout.

Common presenting symptoms of MS include monocular visual impairment with pain (optic neuritis), paresthesias, weakness, and impaired coordination. Frequent accompanying signs and symptoms include bladder urgency or retention, constipation, sexual dysfunction, fatigue, depression, diplopia, gait and limb ataxia, and Lhermitte’s
sign (shock-like sensation in the arms, legs, or trunk) (Calabresi, 2004). In most patients, clinical manifestations indicate the involvement of motor, sensory, visual, and autonomic systems, but many other symptoms can occur, and few of the clinical features are disease-specific. Virtually any symptom associated with the CNS can present itself in MS. In addition, periods of exacerbation can occur. MS is frequently overlooked during the onset of disease because initial symptoms resolve spontaneously in most patients. Relapses typically occur within months, but may occur over years if the disease is the relapsing-remitting type of MS.

Approximately eighty-five percent of patients present with an acute episode affecting one (or occasionally several) areas of the body (Hurwitz, 2009). This phenomenon has been termed the clinically isolated syndrome and represents individuals who have experienced a first attack and been found to have lesions consistent with MS on their MRI. The chance of a second attack of demyelination subsequently occurring increases from fifty percent at 2 years to eighty-two percent at 20 years (Fisniku et al, 2008). This sequence of events fulfills the diagnostic criteria for RRMS.

**MS Diagnostic Criteria**

There is no diagnostic test for MS (Scolding, 2004). The diagnosis of MS is based on clinical evidence and supplemented by laboratory investigations. MS diagnostic criteria, originally devised for research protocols, have expanded to include clinical characteristics, cerebrospinal fluid (CSF) findings, and brain/spinal MRI features (Palace 2009). While MRI, CSF exam, and evoked potential recordings are sensitive tests for
MS, they lack specificity. Thus, a diagnosis of MS also requires exclusion of the other
diseases that could better explain the clinical and paraclinical findings (Miller, 2008).

The most recent diagnostic criteria for MS were developed during an international
collaborative group meeting of researchers. They set out to create diagnostic criteria that
could be used by the practicing physician and that could be adapted, if necessary, for
clinical trials (Appendix 1). The panel also reviewed definitions used in previous
diagnostic criteria. They defined an “attack” (exacerbation or relapse) as an episode of 1)
neurological disturbance of the kind seen in MS, 2) when clinicopathological studies
established that the causative lesions were inflammatory and demyelinating in nature, 3)
the episode lasted for at least 24 hours, and 4) no change in core body temperature
occurred or infection was identified. The panel also determined that in order to consider
the onset of one attack separate from the onset of another the time between attacks should
be at least 30 days (McDonald et al., 2001).

**Clinical Examination**

Clinical examination of MS is subjective and difficult because physicians must rely on
patient report for descriptions of symptoms. A thorough neurological examination is
performed on all patients to assess gait speed, balance and coordination, tremor, muscle
spasticity, and weakness.
Neuroimaging Findings

A brain/spinal MRI is the most useful test for confirming the diagnosis of MS. Strict criteria have been set for MRI findings which require evidence of at least three of the following (Barkhof et al, 1997; Tintore et al, 2000):

1. one gadolinium-enhancing lesion or nine T2 hyperintense lesions if gadolinium-enhancing lesions are not present
2. one or more infratentorial lesion
3. one or more juxtacortical lesion (i.e. involving the subcortical u-fibers)
4. three or more periventricular lesions

Lesions are ordinarily larger than 3 mm in cross section and one spinal cord lesion can be substituted for one brain lesion. Lesions are defined as sclerotic plaques in the brain or spinal cord visible on MRI, which represent the end state of a process involving inflammation, demyelination and remyelination, oligodendrocyte depletion and astrocytosis, and neuronal and axon degeneration (Peltonen, 2007).

MS is characterized pathologically by multifocal areas of demyelination in the white matter; however, there is increasing evidence suggesting that the disease process may include damage of the gray matter and the axons as well. In a 3-year longitudinal study, 31 patients with early relapsing remitting MS were examined and found to have larger decreases in global gray matter but small increases in global white matter brain volume (Dalton et al, 2004). These authors suggested that “progressive grey matter, but not white matter, atrophy is seen in the earliest clinically observable stages of relapse onset
multiple sclerosis” (Dalton et al, 2004). The limitation with brain/spinal MRI is that the readings can be subjective and can vary from radiologist to radiologist.

Biochemical/Laboratory Findings

Most patients with MS have normal appearing cerebral spinal fluid (clear and colorless) with normal cell counts and total protein levels (no more than 11mg/dL) (Rammohan, 2009). In approximately 90% of patients with confirmed MS, however, the CSF immunoglobulin G concentration is increased relative to other CSF proteins, and CSF gel electrophoresis reveals oligoclonal IgG bands that are not present in a matched serum sample (Calabresi 2004). The oligoclonal IgG bands are the result of a heterogeneous charge pattern of the immunoglobins (Rammohan, 2009); however, an increased CSF IgG and the presence of oligoclonal bands are not specific for MS and, therefore, not diagnostic of the disease. Other diseases such as Lyme disease, neurosarcoidosis, systemic lupus erythematosus, and CADASIL can all exhibit these. It is recognized that the quality of CSF analysis is not uniform among laboratories, regions, or countries. “Therefore, CSF analysis probably is most useful for ruling out infections or neoplastic conditions that mimic MS” (Calabresi 2004).

Molecular Findings

Since MS is a multifactorial disease, and thus far only candidate genes have been identified, clinical molecular genetic testing for MS is currently not available.
MS Prognosis and Management

While there is no cure for MS, due to continuing advances in research and technology, there are now a number of pharmacological treatment options available. Drug treatment can be divided into two kinds—treatment of disease progression and treatment of exacerbations. Pharmacological approaches to MS have different effects on the underlying disease, but the primary goal of treatment with these drugs is to prevent disease progression by slowing the growth of existing lesions and preventing new lesions from forming. The disease modifying drugs, all of which are immunosuppressant drugs, most commonly used to treat MS include interferons (Avonex, Betaseron, and Rebif); glatiramer acetate (Copaxone) used in treatment of RRMS; and natalizumab (Tysabri), a monoclonal antibody that blocks adhesion molecules on the surface of immune cells. Tysabri is an immunomodulator that works by preventing the body from damaging its own myelin.

The majority of drugs used to treat MS are from the beta interferon family, a naturally occurring protein in the body. Beta interferon is produced by fibroblasts, macrophages, and epithelial cells, and provides antiviral protection. While the exact mechanism of action is unknown, it is thought that beta interferon acts in MS by reducing both inflammation and the body's autoimmune reaction that is responsible for the inflammation and consequent destruction of myelin.
The treatment of exacerbations involves the use of drugs with anti-inflammatory properties such as corticosteroids. They shorten the length of exacerbations and aid in recovery by reducing the inflammation on the brain and spinal cord.

A new drug, Gilenya (fingolimod) was recently approved as the first oral medication for the treatment of MS. Gilenya is a sphingosine 1-phosphate receptor (S1PR) modulator that works by retaining lymphocytes within the lymph nodes, which reduces the number able to migrate to the blood and spinal cord and worsening the disease.

Additionally, supportive or symptomatic treatments using other medications and/or physical therapy and rehabilitation are available for managing weakness, spasticity, bladder and bowel dysfunction, sexual dysfunction, pain, tremor and ataxia, depression, and heat intolerance.

**Genetics of MS**

Both genetic and environmental factors appear to play a role in the development of MS, which makes it a complex disease with multifactorial inheritance. While the general population risk to develop MS is 1 in 750, epidemiologists have determined that if an individual’s parent is affected with MS, the risk increases to approximately 1 in 40 (Compston & Coles, 2008). It is thought that individuals inherit a genetic susceptibility and then are exposed to environmental factors that lead to disease.
The environmental causes have not been clearly identified, although it is hypothesized that the Epstein-Bar virus plays a role (Compston & Coles, 2008). In addition, geographic location, seasonal allergens, and other infections are all thought to be possible environmental triggers. There is extensive evidence that supports the connection between a genetic susceptibility to MS and environmental triggers.

Population studies have shown an increased risk of developing MS among relatives of affected individuals compared to those of unaffected individuals (Sadovnick et al., 1988; Robertson et al., 1996; Carton et al., 1997). Moreover, studies of families have been conducted in which MS occurs more frequently than chance alone would predict. No single gene has been identified that solely predisposes to MS. It is believed that MS is a polygenic disease, with some studies associating the \textit{HLA-DRB1} gene (Oksenberg et al; 2004, International Multiple Sclerosis Genetics Consortium, 2007), and the \textit{IL2RA} and \textit{IL7RA} genes (IMSGC, 2007; Peltonen, 2007).

Other factors further refine the risk of developing MS. These include the parent-of-origin, age-of-onset, and gender. A study group from the Canadian Collaborative Project on Genetic Susceptibility to MS examined parental MS status and age of MS onset to determine if and how these variables influence sibling recurrence risks. Their study consisted of 1083 MS index cases, 2166 of their parents, and 3112 of their siblings. The authors found that sisters of index cases had over a 2-fold risk to develop MS compared to brothers. They also noted that the “sib risk to develop MS decreases as the age of MS onset increases for index cases,” and an index case whose parent also had MS is almost
doubled the sib risk for MS (Sadovnick et al., 2000). They concluded from their results that “gender, age of MS onset, and having one parent with MS may individually and interactively alter sib risk for MS” (Sadovnick et al., 2000).

**MULTIPLE SCLEROSIS DIFFERENTIAL DIAGNOSIS**

Multiple authors have identified “red flags” for the diagnosis of MS. Rudick and colleagues (Rudick et al, 1986) developed a list of the following features that should cast doubt on a diagnosis of MS: absence of eye findings (optic nerve involvement or oculomotor abnormalities); absence of clinical remission (more worrisome in a young patient); localized disease (posterior fossa, craniocervical junction, or spinal cord); atypical clinical features (absence of sensory findings and/or absence of bladder involvement); and absence of cerebrospinal fluid abnormalities. Additionally, Ratchford and Calabresi (2008) identified the following atypical clinical features: onset after age 60 or before adolescence, family history of a similar disease, early cognitive signs, cortical signs, a progressive course from onset in a young patient, and the presence of symptoms not attributed to the CNS (e.g. peripheral neuropathy). The same authors noted a number of radiological findings as “red flags”: symmetric lesions, peripheral white matter lesions rather than periventricular lesions, lack of ovoid lesions, lack of involvement of the inner corpus callosum, areas of mass effect, and longitudinally extensive cord lesions.

While the identification of these “red flags” is useful, they do not provide a comprehensive list of alternate diagnoses. The individuals who have come closest to
doing so are Miller and colleagues (Miller et al, 2008). They presented clinical and paraclinical “red flags” and suggested alternative diagnoses to MS. However, their recommendations were largely consensus-based, and the “sensitivity, specificity, and accuracy of these “red flags” has not been investigated” (Miller et al, 2008). They considered each “red flag” as an individual variable and did not consider the differential diagnoses if more than one co-existed. Additionally, the value of each “red flag” was not assessed.

In summary, MS is a complex disorder which can be misdiagnosed because of its variable phenotype. Some of the genetic diseases that are part of the differential diagnosis of MS are X-linked adrenoleukodystrophy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and several of the lysosomal storage diseases. The purpose of this systematic review of the literature is to identify all the known monogenetic diseases, which can be misdiagnosed as multiple sclerosis (MS) and to develop a set of reference tables for clinicians and genetic counselors to use in formulating a differential diagnosis.

**SYSTEMATIC LITERATURE REVIEWS**

A systematic review is defined as a method of comprehensively identifying and obtaining all available literature regarding a specific topic (Green, 2005). Such reviews are “systematic in identification and evaluation of research, objective in interpretation, and reproducible in its conclusions” (Green, 2005, pg 271). This methodology allows researchers to summarize large amounts of information, and because it encompasses
multiple studies and all available data, it is “generally considered to be the best form of evidence” in scientific research (Glaszjal et al, 2004, pg 39). Moreover, systematic reviews “overcome some of the bias associated with small single trials and the lack of generalizability inherent in studies conducted in one particular population” (Green, 2005, pg 271).

METHODS:

PART 1) In order to identify the monogenic diseases that mimic an MS-like phenotype, a systematic review of literature was performed (specific aim 1). The search was conducted in July and August, 2010. Studies were included in the review if they met the following criteria: 1) they identified a monogenic disease in the MS differential diagnosis or 2) mentioned a monogenic disease as having MS-like symptoms; 3) were published in a peer-reviewed journal; and 4) were published in the English language.

Because of rapid advances in technologies and with the completion of the Human Genome Project, only literature published from 2000 onward was included in the review.

Titles, abstracts, and key words in the databases PubMed and CINAHL were searched using the following key word combinations:

- ‘Multiple sclerosis’ & genetic
- “ “ & genetics
- “ “ & mutation
- “ “ & mutations
- “ “ & syndrome
- “ “ & syndromes
References identified during the search were imported into Endnote, a software tool designed for managing bibliographies, and duplicate references were eliminated. Each reference was read and grouped into one of three categories based on its likely relevance: 1) the title appeared relevant to the research topic—meaning that it provided information about one or more genetic diseases being listed as a differential diagnosis for MS; 2) the relevance of the title was unknown; and 3) papers that did not appear to be relevant to the research topic.

Recurring themes were used to group the titles into the appropriate categories:

Category 1) diagnosing MS; misdiagnosis of MS; name of a genetic disease; MS review articles; pediatric MS

Category 2) case reports; MRI review articles; MS variants; MS symptoms
Category 3) MS treatments or therapies; MS research (example: research on drug trials); other autoimmune diseases

Articles from category 1 were then obtained and evaluated for content. Abstracts from articles in the second category were read to determine the utility of the paper, and if deemed appropriate, were obtained and evaluated for content. For those articles that did not have an abstract available, the article was retrieved and briefly read through to determine its relevance.

Bibliographies from the articles chosen were scanned for additional articles significant to the research topic not obtained through the original search. The title of each reference was read and a determination was made as to its relevance based on the previously defined criteria; however, no date restriction was placed on this part of the search. Every article assigned to group 1 was given an identifier (i.e. A1, A2, B13, etc) as a way for tracking articles/references (these identifiers are used in Table 1 and in Appendix 3). Appendix 2 lists all the category 1 articles.

As each article was read, a list of monogenic diseases mentioned as being a differential diagnosis or mimic of MS was compiled. This list included the disease name and the number of articles that made reference to it (Table 1).
<table>
<thead>
<tr>
<th>Disease Name</th>
<th>Articles Referenced</th>
</tr>
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<tbody>
<tr>
<td>Adrenoleukodystrophy</td>
<td>B6 B8 B11 B14 C4 C13 C30 D10 F6 F7 G1 G3 H1 H5 K2 L6 M5 M7 M8 M10 M20 P19 R5 R10 R12 R14 S6 T3 T5 W7 W8 RO1 RO2 RV2</td>
</tr>
<tr>
<td>Adult polyglucosan body disease (APBD)</td>
<td>R14</td>
</tr>
<tr>
<td>Alexander disease</td>
<td>C12 J2 M5 T3 RH2 RO1 RS1 RV2</td>
</tr>
<tr>
<td>Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)</td>
<td>B2 B6 B11 C4 C13 C14 C20 C30 E1 F4 F5 F6 F7 G3 H1 H5 J4 K11 M5 M7 N6 O3 P24 R4 R14 S6 S12 T3 T5 W8 RF1</td>
</tr>
<tr>
<td>Cerebrotendinous Xanthomatosis (CTX)</td>
<td>B13</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>C12 C14 C23 F9 H1 I1 M5 R14 S3 T3 T5</td>
</tr>
<tr>
<td>Fragile-X tremor/ataxia syndrome (FXTAS)</td>
<td>C8 P7 Z3 RG1 RH1</td>
</tr>
<tr>
<td>Friedreich Ataxia</td>
<td>B5 B6 M5 M7 Q1</td>
</tr>
<tr>
<td>Hereditary ataxias</td>
<td>B6 C27 C30 D11 M5 N6 R12 R14 S13</td>
</tr>
<tr>
<td>Hereditary motor sensory neuropathy (HMSN)</td>
<td>A1 B6 P6</td>
</tr>
<tr>
<td>Hereditary spastic paraparesis (HSP)</td>
<td>B6 C20 C30 M4 M5 M7 N3 N6 R12 S12 RM1</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>H1 M2 O4</td>
</tr>
<tr>
<td>Krabbe syndrome</td>
<td>B6 C13 H1 K2 M7 R14 T5 RO1</td>
</tr>
<tr>
<td>Leber hereditary optic neuropathy (LHON)</td>
<td>B6 B10 C7 C13 C30 D10 F4 F5 G3 G7 G9 H1 K7 K9 L5 M6 N6 O4 P4 P10 R12 S6 S12 T3 T4 T5 RB1 RH4 RJ1</td>
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<tr>
<td>Friedreich Ataxia</td>
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<tr>
<td>Hereditary ataxias</td>
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<tr>
<td>Hereditary spastic paraparesis (HSP)</td>
<td>B6 C20 C30 M4 M5 M7 N3 N6 R12 S12 RM1</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>H1 M2 O4</td>
</tr>
<tr>
<td>Krabbe syndrome</td>
<td>B6 C13 H1 K2 M7 R14 T5 RO1</td>
</tr>
<tr>
<td>Leber hereditary optic neuropathy (LHON)</td>
<td>B6 B10 C7 C13 C30 D10 F4 F5 G3 G7 G9 H1 K7 K9 L5 M6 N6 O4 P4 P10 R12 S6 S12 T3 T4 T5 RB1 RH4 RJ1</td>
</tr>
<tr>
<td>Friedreich Ataxia</td>
<td>B6 C27 C30 D11 M5 N6 R12 R14 S13</td>
</tr>
<tr>
<td>Hereditary ataxias</td>
<td>B6 C27 C30 D11 M5 N6 R12 R14 S13</td>
</tr>
<tr>
<td>Hereditary motor sensory neuropathy (HMSN)</td>
<td>A1 B6 P6</td>
</tr>
<tr>
<td>Hereditary spastic paraparesis (HSP)</td>
<td>B6 C20 C30 M4 M5 M7 N3 N6 R12 S12 RM1</td>
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<tr>
<td>Kearns-Sayre syndrome</td>
<td>H1 M2 O4</td>
</tr>
<tr>
<td>Krabbe syndrome</td>
<td>B6 C13 H1 K2 M7 R14 T5 RO1</td>
</tr>
<tr>
<td>Leber hereditary optic neuropathy (LHON)</td>
<td>B6 B10 C7 C13 C30 D10 F4 F5 G3 G7 G9 H1 K7 K9 L5 M6 N6 O4 P4 P10 R12 S6 S12 T3 T4 T5 RB1 RH4 RJ1</td>
</tr>
</tbody>
</table>

**ALD** = Adrenoleukodystrophy  
**APBD** = adult polyglucosan body disease  
**CADASIL** = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy  
**CTX** = Cerebrotendinous Xanthomatosis  
**FXTAS** = Fragile-X tremor/ataxia syndrome  
**HMSN** = hereditary motor sensory neuropathy  
**HSP** = hereditary spastic paraparesis  
**Krabbe** = hereditary motor sensory neuropathy  
**Leigh syndrome** = Leber hereditary optic neuropathy  
**MLD** = metachromatic leukodystrophy  
**TRAPS** = TNF receptor associated periodic syndrome  

**Table 1:** Monogenic disease name with article identifiers referencing it
Table 2 notes if the article referencing each disease was a review article or a case report. For those that were case reports, they were then subdivided between those that distinguished a genetic disease from true MS (based on specified criteria) or those that were possible/probable MS. Ultimately, any article that did not identify a genetic disease as being a differential diagnosis of MS or exhibiting MS-like features was excluded.

<table>
<thead>
<tr>
<th>Disease Name</th>
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<th>Possible MS</th>
<th>Review Article</th>
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<td>FXTAS</td>
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<td>3 *CNS</td>
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<td>0</td>
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<td>Krabbe</td>
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<td>LHON</td>
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<td>12</td>
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<tr>
<td>MERRF</td>
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<td>0</td>
<td>0</td>
<td>6</td>
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<td>MLD</td>
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<td>0</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>PM</td>
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<td>Wilson disease</td>
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</tbody>
</table>

ALD = Adrenoleukodystrophy
APBD = adult polyglucosan body disease
CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CTX = Cerebrotendinous Xanthomatosis
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HMSN = hereditary motor sensory neuropathy
HSP = hereditary spastic paraparesis
LHON = Leber hereditary optic neuropathy
MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes
MERRF = myoclonic epilepsy with ragged red fibers
MLD = metachromatic leukodystrophy
PM = Pelizaeus-Merzbacher
TRAPS = TNF receptor associated periodic syndrome
*CNS = criteria not specified

Table 2: Type of articles referencing the monogenic diseases
To further delineate the reliability of each article, the impact factor was obtained for each of the journals that had a relevant article used. This was performed by checking each journal’s website, or by e-mailing a contact person for the journal. A comprehensive list of all journals used and their corresponding impact factors, as well as the article identifiers that came from each can be found in Appendix 3.

PART 2) Each of the genetic disorders identified in the review was researched and summarized (specific aim 2). Information for each was retrieved from reviewing a number of resources including PubMed, CINAHL, Online Mendelian Inheritance in Man (OMIM), and GeneReviews. The articles found during the literature review were also used.

PART 3) Each monogenetic disorder identified in Aim 1 was examined for similarities and differences with MS based on the information obtained in part 2 and from the literature extracted from the search. This was performed in order to develop tables comparing and contrasting the diseases. A total of four tables were created—one examining the monogenic diseases that share common MS clinical signs/symptoms; one displaying clinical differences between each of the diseases and MS; one representing a list of common MRI findings for each of the monogenic diseases; and one providing details on screening and diagnostic testing for each of the diseases.
RESULTS:

PART 1) The initial literature search yielded a total 33,701 results. Table 3 lists the number of articles generated from each keyword search for both databases.

<table>
<thead>
<tr>
<th>Keyword(s)</th>
<th>PubMed</th>
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<th>Total</th>
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</thead>
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<td>Multiple sclerosis and genetic</td>
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<td>Multiple sclerosis and mimic</td>
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<td>Multiple sclerosis and misdiagnosis</td>
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<td>143</td>
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</table>

TOTAL = 31341  2360

GRAND TOTAL = 33,701

Table 3: Systematic literature review search results based on keyword and database
These were all imported into ENDNOTE, and the duplicates were automatically searched for and eliminated. After the duplicates were eliminated, the remaining total of unique references was 13,970. This total was sorted first alphabetically, and then divided among the three categories as described in the Methods section. Initially, 212 references were identified as being relevant and were assigned to category 1; 1140 were assigned to category 2; and 12,441 were deemed not relevant and assigned to category 3. The remaining 177 articles were additional repeat references found manually as the titles and bibliography information were examined. Of the 1140 category 2 references, 114 had abstracts that made them appear useful and were added to the category 1 references. Thus, the grand total of articles retrieved and read for data analysis was 326. Table 4 lists the number of articles initially assigned to each category (grouped by author’s last initial), as well as how many were then assigned from category 2 to category 1. The last row of the table is a sum of category 1 references.
<table>
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<td>1140</td>
<td>12441</td>
<td>177</td>
<td>114</td>
<td>326</td>
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</tbody>
</table>

**Table 4: Category totals.** Grouped by author’s last name including total of Category 2 articles that were assigned to Category 1. Category 1 = title appeared relevant; Category 2 = title relevance unknown; Category 3 = title irrelevant

Not all the category 1 references provided information relevant to the research topic.

Articles that did not specifically list or discuss a monogenic disease as being part of the MS differential diagnosis or compare features to MS were eliminated. Figure 1 illustrates the algorithm for identifying articles assigned to Category 1. References listed in the articles used were examined which yielded an additional fifty-six articles not obtained through the initial search. Sixteen of these were found useful and retrieved.
13,970 total results retrieved

177 additional repeats found

Group 1
= 212

Group 2
= 1140

Group 3
= 12441

= 114

= 1026

Total Group 1 = 326

171 not used
(did not provide a monogenic disease as an MS differential)

62 not retrieved
(unable to locate article)

= 93 Articles

Articles' References Searched

= 56 references retrieved

14 not used (did not provide a monogenic disease as an MS differential)

26 not retrieved
(unable to locate article)

= 16 Articles

Total Group 3 = 13467

GRAND TOTAL ARTICLES USED = 109

Figure 1: Illustrates the algorithm for assigning articles to Category 1.
PART 2) After all the articles were read, a list of the monogenic diseases with similarities to MS was compiled. A total of twenty-two monogenic diseases were found in the literature to be considered in the differential diagnosis of MS based on similar clinical features, MRI characteristics, or both. These include adrenoleukodystrophy/adrenomyeloneuropathy, adult polyglucosan body disease (APBD), Alexander disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebrotendinous xanthomatosis (CTX), Fabry disease, Friedreich ataxia, fragile-X tremor/ataxia syndrome (FXTAS), hereditary spastic parapareses, hereditary sensory motor neuropathies, Kearns-Sayre, Krabbe disease, Leber hereditary optic neuropathy (LHON), Leigh syndrome, metachromatic leukodystrophy, mitochondrial encephalopathy lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), Pelizaeus-Merzbacher, porphyria, Refsum disease, TNF receptor-associated periodic syndrome (TRAPS), and Wilson disease.

Each of the above genetic diseases was researched in order to create tables for clinical use in comparing and contrasting them with MS in order to aid in the differential diagnostic process. The following are brief summaries of each of the diseases including information regarding the genetic defect, natural history and clinical symptoms, prognosis, and treatment. Many of these diseases have a variable phenotype and complex genetic etiologies. Additionally, only certain forms of some of these diseases are considered part of the MS differential, and it is these forms that are the focus of this research paper. The summaries presented as part of this research of each disease are in no
way comprehensive—they merely provide general information most relevant to the research topic.

1. X-linked Adrenoleukodystrophy/adrenomyeloneuropathy

X-linked adrenoleukodystrophy (X-ALD) is an inherited peroxisomal disorder that affects the white matter of the nervous system and the adrenal cortex. The prevalence is estimated between 1:20,000 and 1:50,000, with approximately a seven percent de novo mutation rate.

Genetic Cause

X-ALD is caused by a defect in the $ABCD1$ (ATP-binding cassette, subfamily D, member 1) gene located on chromosome Xq28. Mutations in this gene result in defective peroxisomal beta-oxidation and the accumulation of very long chain fatty acids in all tissues of the body.

Major Clinical Findings

Both the phenotype and the age of onset vary with no apparent genotype-phenotype correlation. Additionally, carrier females can display a wide range of symptoms. Briefly, the phenotypes can be summarized as follows based on Kemp et al (2001): 1) childhood cerebral: onset at 3-10 years with progressive behavioral, cognitive, and neurological deficit, with inflammatory brain demyelination, often leading to total disability, or end stage disease, within 3 years. This type represents about 31-35% of phenotypic males. 2) adolescent: similar to childhood cerebral, but with a later age of
onset and slower progression. Four to seven percent of males have this type. 3) adrenomyeloneuropathy (AMN): mainly involves the spinal cord with distal axonopathy, mild or absent inflammatory response, and forty percent have cerebral involvement with more rapid progression. Stiffness, muscle weakness in the lower extremities, abnormalities of sphincter control, and sexual dysfunction are additional features seen in AMN. This phenotype affects both males (40-46%) and carrier females (~20%) with onset in late twenties for males and increases with age in females. 4) adult cerebral: characterized by dementia, behavioral disturbances, white matter inflammatory response, and rapid progression. This type is seen in two to five percent. 5) olivo-ponto-cerebellar: primarily cerebellar and brainstem involvement in adolescence or adulthood in approximately one to two percent of males. 6) addison-only: adrenal insufficiency with no apparent neurological involvement. Most individuals with this type eventually develop AMN. The incidence for this type varies with age. 7) asymptomatic: no adrenal or neurological deficits.

Treatment

Treatment of ALD involves treating the manifestations of the disease. Corticosteroid replacement therapy is used for those with adrenal insufficiency, and physical therapy is helpful in those who have AMN.

Similarities to MS

Clinical features of X-ALD/AMN that may pose diagnostic difficulty are urinary incontinence, weakness, impotence, and depression. "In approximately 85% of affected
individuals with adrenoleukodystrophy, MRI shows a characteristic pattern of symmetric enhanced T2 signal in the parieto-occipital region with contrast” (Moser et al, 2006). Thus, ALD/AMN can mimic not only clinical features of MS, but also MRI features.

*Differences from MS*

Diagnostic differences lie in nerve conduction velocity testing and in very long chain fatty acid assays. Patients with ALD/AMD have slower nerve conduction velocities and have elevated VLCFA’s in serum. Neither of these is typical for someone with MS.

**2. Adult Polyglucosan Body Disease**

APBD is a rare autosomal recessive disease that affects both the central and peripheral nervous systems. Less than fifty individuals have been reported to be affected (Klein et al, 2004).

*Genetic Cause*

It is caused by mutations in the *GBE1* gene located on chromosome 3p12. *GBE1* encodes the 1, 4-alpha-glucan-branching enzyme, which is involved in the production of glycogen. Most *GBE1* mutations lead to decreased GBE activity which results in the accumulation of abnormally branched glycogen molecules within the cells (Massa et al, 2008). Polyglucosan bodies are found in many tissues of the body; however, APBD only affects the nervous system.
**Major Clinical Findings**

Most patients present with symptoms in their fifth or sixth decade, the most common being peripheral neuropathy, gait disturbance, distal sensory impairment, and neurogenic bladder (Klein et al, 2004). The disease slowly progresses and about half of the patients develop some degree of cognitive impairment (Massa et al, 2008).

**Treatment**

Treatment of APBD involves symptomatic intervention with the use of gait aids as well as urologic assessment and management.

**Similarities to MS**

A number of the clinical features of APBD resemble those of MS. They include gait disturbances, limb weakness, spasticity, urinary incontinence, sensory deficits, and cognitive impairment.

**Differences from MS**

Distinguishing features that may aid in differentiating APBD from MS are peripheral neuropathy, absent oligoclonal bands on CSF analysis, and dementia.

**3. Alexander Disease**

Alexander disease is a leukodystrophy, pathologically characterized by the presence of Rosenthal fibers (eosinophilic inclusions localized in astrocyte cytoplasm) (Pareyson et
al, 2008). While Rosenthal fibers are the hallmark for this disease, they are not specific to it.

**Genetic Cause**

Alexander disease is caused by mutations in the *GFAP* gene on chromosome 17q21, and it exhibits autosomal dominant inheritance. The exact prevalence is unknown. The infantile and juvenile forms are caused by *de novo* mutations, while individuals with the adult form may have an affected parent.

**Major Clinical Findings**

Symptoms usually manifest themselves in infancy with progressive macrocephaly, spasticity, seizures, and ataxia. Death usually occurs within a few years after onset. However, juvenile and adult cases have been reported with clinical features including bulbar/pseudobulbar signs, ataxia, gradual loss of intellectual function, seizures, megalencephaly, and breathing problems. Other individuals with the adult form are asymptomatic and have only been diagnosed due to evaluation for other conditions or autopsy.

Clinically, the presentation of Alexander disease is nonspecific. The diagnosis is established by MRI findings and/or molecular testing. Van der Knaap et al (2001) suggest that the presence of four of the following five criteria are sufficient for an MRI-based diagnosis. These findings include: extensive cerebral white matter abnormalities with a frontal preponderance, a periventricular rim of decreased signal intensity on T2-
weighted images and elevated signal intensity on T1-weighted images, abnormalities of the basal ganglia and thalami, brain stem abnormalities, and contrast enhancement of one of more of the following—ventricular lining, periventricular rim, frontal white matter, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, or brain stem. CSF studies show increased levels of αβ-crystallin and heat shock protein 27, as well as increased levels of glial fibrillary acidic protein. Lower brainstem involvement is the most characteristic finding (Pareyson et al, 2008).

**Treatment**

There is no unique therapy for Alexander disease. Treatment involves symptomatic intervention and management. Antiepileptic drugs, physical and occupational therapy, and nutritional intervention are all methods of supportive care used.

**Similarities to MS**

The adult form is the most variable, can exhibit incomplete penetrance, and symptoms can resemble multiple sclerosis (Schwankhaus et al, 1995) such as ataxia and bulbar/pseudobulbar signs. Additionally, symptoms of Alexander disease can fluctuate, resembling the relapsing-remitting pattern of MS. Neuroimaging findings can also resemble those of MS.

**Differences from MS**

The abundance of Rosenthal fibers in Alexander disease is much greater than would be seen in MS. Family history is another tool that could be helpful. An elevation of β-
crystallin and heat shock, protein 27 in the CSF has been reported in Alexander disease
which may be a differentiating finding between it and MS. Molecular testing to rule out
Alexander would be the most sensitive way of differentiating these two diseases if doubt
arises.

4. CADASIL

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and
Leukoencephalopathy (CADASIL) is the most common genetic cause of strokes and
vascular dementia in adults.

**Genetic Cause**

CADASIL is caused by mutation in the *NOTCH3* gene on chromosome 19p13. While
the exact prevalence is unknown, it is estimated to affect approximately 4 per 100,000
individuals. Additionally, the *de novo* mutation rate is unknown. Some individuals with
CADASIL lack a family history of the disease because family members have not been
appropriately assessed.

**Major Clinical Findings**

Clinical findings of CADASIL vary depending on the age of onset. The most common
manifestation in the early form, affecting individuals younger than 30 years old, is
migraine with aura. Focal neurological deficits due to lacunar infarcts and behavioral
symptoms are most common in the later form. (Andre, 2010). Depression, dementia,
cognitive decline, and epilepsy are also observed.
There are no diagnostic criteria for CADASIL as the features and age of onset vary so greatly. Molecular genetic testing is available.

**Treatment**

Management of CADASIL is supportive care based on each individual’s symptoms.

**Similarities to MS**

Symptoms of CADASIL can both progress and have time periods of improvement, resembling a relapsing-remitting pattern similar to MS. Shared symptoms between the two diseases include depression and cognitive decline. Imaging similarities are also present between CADASIL and MS.

**Differences from MS**

Certain specific imaging markers allow a differentiation between these two entities. They include hyperintensities in the white matter of the anterior temporal loves and frequent involvement of the external capsules (Pandey & Abubacker, 2006). Contrast enhancement is often seen in MS, but not in CADASIL. Thus, the presence of contrast enhancement can differentiate MS from CADASIL, but the absence of it does not help (Pandey & Abubacker, 2006). Additionally, family history of stroke, vascular dementia, migraine headaches, and an absence of optic neuritis and spinal cord involvement may aid in ruling out MS.
5. Cerebrotendinous Xanthomatosis

CTX is an autosomal recessive lipid storage disease. The prevalence is estimated to be one per 50,000 among Caucasians.

Genetic Cause

It is caused by mutations in the \textit{CYP27A1} gene located on chromosome 2q33-qter. \textit{CYP27A1} mutations result in deficiency of the mitochondrial enzyme sterol 27-hydroxylase which impairs the primary bile acids synthesis and leads to accumulation of cholestanol and cholesterol in bodily tissues, especially in the nervous system (Bartholdi et al, 2004).

Major Clinical Findings

Individuals may notice symptoms at various ages with the most common being infantile-onset diarrhea, childhood-onset cataracts, adolescent- to young adult-onset tendon xanthomas, and adult-onset progressive nervous system involvement. The latter three findings are considered the classical triad of the disease (Bartholdi et al, 2004). Neurological manifestations include dementia, psychiatric disturbances, pyramidal signs, cerebellar signs, seizures, and sensory-motor neuropathy. Other findings may include dystonia and atypical parkinsonism. A spinal phenotype has also been described in which spastic paraparesis is the main clinical sign (Verrips et al, 1999).

Treatment

Treatment of CTX is aimed at reducing cholestanol concentration to improve clinical
signs. Inhibitors of HMG-CoA reductase are one option. Cataract removal is typically required, and symptomatic treatment is available through additional pharmacological agents such as anti-epileptic medications.

**Similarities to MS**

Shared symptoms between CTX and MS include gait disturbance, cognitive decline, depression, weakness, spasticity, and sensory disturbances. The neurological involvement is progressive resembling primary progressive multiple sclerosis.

**Differences from MS**

Typically, CTX presents with the triad of cataracts, tendon xanthomas, and progressive nervous system involvement. CTX also can cause chronic diarrhea, which is not common in MS. Neuroimaging shows leukencephalopathy in the dentate nuclei, which is another feature uncommon for MS.

6. **Fabry Disease**

Fabry disease is an X-linked recessive lysosomal storage disorder.

**Genetic Cause**

Fabry is caused by mutations in the GLA gene located on chromosome Xq22. *De novo* mutations are rare. Abnormalities in this gene cause a deficiency in the activity of α-galactosidase A, an enzyme that hydrolyses the terminal alpha-galatosyl moieties from glycolipids and glycoproteins. Thus, lack of this enzyme causes a build-up of
glycosphingolipids in many tissues of the body that leads to cellular dysfunction, inflammation, and/or fibrosis (Zarate & Hopkin, 2008).

**Major Clinical Findings**

The clinical presentation of Fabry disease is variable, including the age-of-onset, rate of progression, and organ manifestations (Zarate & Hopkin, 2008). The disease process begins early in life, and symptoms typically manifest themselves in childhood with acroparesthesias, angiokeratomas, hypohidrosis, and corneal/lenticular opacities. Cardiac involvement and cerebrovascular manifestations present in middle age; and proteinuria and renal insufficiency usually occur in the third to fifth decade of life. Heterozygous females may also exhibit symptoms with a range in severity from asymptomatic to severe.

**Treatment**

Enzyme replacement therapy with the use Fabrazyme® is recommended for males with Fabry. Additionally, prophylaxis of renovascular disease, heart disease, and cerebrovascular disease is available as it is for the general population. Pharmacological and other therapeutic interventions for symptoms are used based on the symptoms present in each patient.

**Similarities to MS**

Neurological involvement in Fabry disease is well recognized. This includes “painful neuropathy, cerebrovascular disease, and aggressive forms with multifocal relapsing
central symptoms and progressive disability (multiple sclerosis-like)” (Salviati et al, 2010). Symptoms of Fabry that may mimic those of MS include transient or permanent weakness, hemiparesis, numbness and paresthesias, urinary incontinence, dysarthria, and ataxia.

**Differences from MS**

Peripheral nerve involvement is seen in Fabry disease and is not typically observed in MS. Additionally, oligoclonal bands are not found on CSF analysis in patients with Fabry. A careful physical exam should also be performed to look for angiokeratomas and corneal dystrophy as these are also not seen in MS.

**7. Friedreich Ataxia**

Friedreich ataxia (FA) is an autosomal recessive ataxia syndrome that affects approximately one per 50,000 Caucasians (Pandolfo, 2009).

**Genetic Cause**

FA is caused by a GAA trinucleotide repeat expansion (typically 70 - > 1000 repeats) in the *FXN* gene which is located on chromosome 9q13. This expansion causes reduced expression of frataxin which reduces mitochondrial function and increases oxidative damage (Pandolfo, 2009). The majority of affected individuals are compound heterozygotes for this expansion.
**Major Clinical Findings**

FA has a variable age of onset ranging from 10 – 25 years. Most individuals present with gait instability. Other common symptoms are intention tremor, dysarthria, dysphagia, muscle weakness, spasticity, scoliosis, bladder dysfunction, absent lower limb reflexes, and sensory peripheral neuropathy. Approximately two-thirds of individuals have cardiomyopathy and one-third develop diabetes mellitus. Optic atrophy, with or without vision loss, is present in thirty percent of those with FA, and twenty percent have sensorineural hearing loss. An “atypical” FA presentation occurs in twenty-five percent of individuals who have a later onset or retained deep tendon reflexes.

**Treatment**

Treatment of FA involves a multidisciplinary approach as multiple organ systems can be affected. Thorough evaluations are recommended to assess for cardiomyopathy, hearing loss, diabetes mellitus, bladder function, swallowing, and speech. Intervention depends on symptoms present and may include physical, occupational, and/or speech therapy, walking aids, hearing aids, and pharmacologic agents. FA is a progressive disease; however, the rate of progression is variable. Death is often related to cardiomyopathy.

**Similarities to MS**

Symptoms common in both FA and MS are ataxia, weakness, optic atrophy and sensory disturbances. A patient presenting with these may pose diagnostic difficulty, especially those with the late-presenting phenotype.
Differences from MS

Cardiomyopathy and diabetes are not common in MS, but are observed in patients with FA. Therefore, a thorough medical and family history is important to aid in differentiation between these diseases.

8. Fragile X-Associated Tremor Ataxia Syndrome

Carriers of the permutation of the fragile X mental retardation 1 gene who are older than 50 years are at a risk of developing neurological symptoms. This phenomenon has been termed fragile X-associated tremor ataxia syndrome (FXTAS). This fragile X permutation has a prevalence of approximately 1 in 100-300 females and 1 in 300-800 males (Zhang et al, 2009).

Genetic Cause

FXTAS results from a CGG trinucleotide expansion (typically 59-200 CGG repeats) in the FMR1 gene located on Xq27. This repeat causes neurological symptoms due to the toxic effects of the excess amount of FMR1 mRNA.

Major Clinical Findings

Penetrance of FXTAS varies based on gender. Male carriers have a 40% risk of developing FXTAS, while female carriers have a 5-10% risk. There is variability in the severity of symptoms, disease progression, and MRI findings in individuals affected with FXTAS (Paul et al, 2010). The most common clinical signs are intention tremor and gait
ataxia. Other features include parkinsonism, moderate to severe working memory deficits, or executive cognitive function deficits.

**Treatment**

No specific treatment is available for FXTAS. Intervention of symptoms and utilization of gait aids may assist those with the disease.

**Similarities to MS**

Symptoms shared by these two disorders include intention tremor, ataxia, spasticity, and sensory disturbances. Like RRMS, symptoms in FXTAS may resemble a relapsing-remitting pattern.

**Differences from MS**

Neuroimaging is helpful in differentiating these two entities. FXTAS cerebral white and subcortical alterations generally involve the subependymal, deep, and subcortical white matter and are usually more confluent than seen in typical MS. Additionally, family histories of fragile X, mental retardation, or premature ovarian failure (another FMR1 permutation carrier associated syndrome) are all clues to consider FXTAS in the differential diagnosis of MS.

**9. Hereditary Spastic Parapareses**

The hereditary spastic parapareses (HSP) are a heterogeneous group—both clinically and genetically—of inherited disorders.
**Genetic Cause**

Thirty-five different genes have been found to be associated with HSP; however, the four most common genes associated with it are LICAM, PLP, paraplegin, and spastin (McDermott et al, 2000). Mutations in PLP (located on chromosome Xq22) cause X-linked spastic paraplegia type 2 (SPG2) and also cause Pelizaeus-Merzbacher disease (see below for disease summary).

**Major Clinical Features**

Progressive lower limb spasticity is the main feature seen in all the forms. They can be characterized according to their inheritance pattern or by HSP type. The two types described are pure and complicated. Pure HSP is characterized by gait disturbance, stiffness in the legs, and urinary disturbances. The age of onset ranges from infancy to the eighth decade, and up to twenty-five percent are asymptomatic (McDermott et al, 2000). Additional features that have been described in the pure form are spasticity, hyperreflexia and extensor reflex plantar responses, weakness in the lower limbs, paresis in the lower limbs, loss of ankle jerks, pes cavus, and mild dorsi column disturbance. The other type of HSP is called complicated HSP. Spastic paraparesis in this type is variable. Other features seen are optic atrophy, retinopathy, extrapyramidal disease, amyotrophy, dementia, ataxia, mental retardation, deafness, ichthyosis, peripheral neuropathy, and epilepsy.

SPG2 characteristics are optic atrophy, pes cavus, muscle atrophy, weakness, spasticity, ataxia, dysarthria, hyperreflexia, upper limb involvement, and cerebellar signs. Onset is
typically in childhood, although the phenotype is highly variable.

*Treatment*

Treatment of HSP, regardless of type, is aimed at reducing spasticity though the use of physical and occupational therapy, as well as pharmacological agents such as benzodiazepines or baclofen.

*Similarities to MS*

Complicated HSP would not typically pose diagnostic difficulty with MS. The only exception would be if optic atrophy was present in a rare autosomal dominant type.

Pure HSP, however, may be mistaken for MS since both diseases may cause spasticity, hyperreflexia, and urinary incontinence.

*Differences from MS*

A family history and MRI findings are useful tools in differentiating HSP from MS. HSP typically lacks the neuroradiological findings common in MS.

**10. Hereditary Sensory Motor Neuropathies**

The hereditary sensory and motor neuropathies are a genetically and clinically heterogeneous group of diseases. They include Refsum disease (see below for disease summary) and Charcot Marie Tooth (CMT). CMT is also a genetically heterogeneous
group of conditions affecting the peripheral nervous system. It is a disease of the nerves that affects the muscles, not a disease of the muscles themselves.

**Genetic Cause**

CMT can be divided into groups based on nerve conduction velocities (NCV). CMT1 encompasses those that are demyelinating, while CMT2 are those that are axonal. These two groups can then further be divided according to inheritance pattern and underlying genetic cause. There are multiple genes that lead to CMT with PMP22 being the most common for CMT1, and MFN2 as being the most common for CMT2. Two other forms of CMT have been also described—CMT 4 and CMT X. CMT 4 is a rare form with autosomal recessive inheritance, and exhibits either axonopathy or myelinopathy. CMT X is an X-linked form and shows axonopathy with secondary myelin changes. CMTX type 1 is caused by mutations in the gap-junction beta-1 protein (GJB1) gene located on chromosome Xq13. Mutations in this gene produce proteins with impaired glial/neuronal interactions and signal transduction. Loss of function can result in both peripheral and central demyelination (Sargiannidou et al, 2009).

**Major Clinical Features**

Common clinical features of CMT are high arches, hammertoes, muscle wasting in the lower legs and feet, foot drop leading to poor balance, abnormal sensations in the extremities, chronically cold hands and/or feet, fatigue, sleep apnea, scoliosis, hearing loss, and vision loss. Individuals affected by CMT do not necessarily exhibit all of these symptoms. There is variability, even within families.
Treatment

Treatment of CMT is symptomatic intervention. Ankle/foot orthoses and other gait aids are commonly used. Surgery for pes cavus and hip dysplasia is also sometimes required.

Similarities to MS

Features shared between MS and the hereditary neuropathies include sensory disturbances, weakness, vision loss, and poor balance. CMTX has been found to have signs and symptoms of CNS involvement, which may resemble the clinical presentation of primary progressive MS (Isoardo et al, 2005).

Differences from MS

Muscle wasting in the lower extremities, pes cavus, and hammertoes are not observed in MS. Family history may be useful, and peripheral neuropathy is seen in CMT and not typical for MS.

11. Kearns-Sayre Syndrome

Kearns-Sayre (KSS) is a rare mitochondrial deletion syndrome characterized by central nervous system, muscle, and endocrine involvement (Chu et al, 1999).

Genetic Cause

As with other mitochondrial diseases, the deletions in KSS can vary in abundance, as well as in size. The majority of individuals of KSS have large-scale mtDNA deletions. The KSS phenotype can also be seen in individuals who have mutations in the MTTL1
gene (mitochondrial tRNA leucine-1), however, the prevalence of this unknown.

Major Clinical Findings

Disease onset usually presents in childhood with eye involvement—external ophthalmoplegia, pigmentary retinopathy, and/or ptosis. Other common features include short stature, microcephaly, sensorineural hearing loss, renal tubular acidosis, muscle weakness, and cardiac conduction block. Central nervous system involvement includes cerebellar ataxia, seizures, and dementia. Endocrinopathies include diabetes mellitus, hypoparathyroidism, and growth hormone deficiency.

Treatment

Treatment of KSS first involves complete neurologic, cardiologic, ophthalmologic, and endocrinologic evaluations, after which treatment of manifestations is the only intervention available. Coenzyme Q and L-carnitine supplements are used in the treatment of mitochondrial disorders, including KSS.

Similarities to MS

KSS and MS both can cause spasticity, weakness, and ataxia. These two features alone would not normally pose diagnostic difficulty. However, given the nature of mitochondrial diseases and the large amount of variability in their clinical presentation, challenges may arise in making a diagnosis.
**Differences from MS**

Typically, patients with KSS have a number of other clinical features that would distinguish them from MS. These include cardiac involvement, renal acidosis, hearing loss, growth retardation, diabetes, and seizures.

**12. Krabbe**

Krabbe disease is one of the inherited leukodystrophies that leads to demyelination of the central and peripheral nervous systems. It is estimated to occur in approximately one in 100,000 individuals, and it displays autosomal recessive inheritance.

**Genetic Cause**

Krabbe can be caused by mutations or a deletion of the GALC gene located on chromosome 14q31. Pathogenic mutations cause deficient enzyme activity of galactosylceramidase (GALC) — which is abundant in the myelin sheath. Deficient GALC activity results in the lack of accumulation of galactosylceramide in the brain and demyelination. Pathological hallmarks of the disease include rapid and complete myelin and oligodendrocyte loss, reactive astrocytic gliosis, and infiltration of globoid cells (cells with more than one nucleus) (Suzuki, 2003).

**Major Clinical Findings**

Krabbe is divided into 4 forms, depending on the age-of-onset which ranges from infancy to adulthood. Juvenile krabbe is characterized by vision loss, hemiparesis, ataxia, and psychomotor regression. The later onset form has a more variable phenotype with most
of the adults developing slowly progressive spastic paraparesis and slow, unsteady, stiff, and wide-based gait. Vision problems may also occur.

*Treatment*

There is no specific treatment for the late-onset forms of Krabbe. Treatment involves supportive care and management of symptoms.

*Similarities to MS*

Due to their variable clinical presentation, the atypical and late onset forms of Krabbe may be difficult to distinguish from MS based on limb weakness, tremor, ataxia, dysarthria, and bulbar signs.

*Differences from MS*

Peripheral nerve involvement is a key differentiator in making the diagnosis of Krabbe vs MS.

**13. Leigh Syndrome**

Leigh syndrome is a rare neurometabolic disorder that affects the central nervous system.

*Genetic Cause*

Leigh syndrome is due to deficiency of cytochrome c oxidase. There is genetic heterogeneity in Leigh syndrome. Mutations have been identified in both nuclear and
mitochondrial genes involved in energy metabolism, including the mitochondrial respiratory chain complexes I, II, III, IV, and V genes and the genes involved in the pyruvate dehydrogenase complex. There is also a form of Leigh’s disease (called X-linked Leigh's disease) which is the result of mutations in a gene that produces another group of substances that are important for cell metabolism. The X-linked Leigh's disease is caused by a mutation in the PDHA1 gene, part of the pyruvate dehydrogenase complex, located on the X chromosome.

**Major Clinical Findings**

Onset is usually in infancy or early childhood with multiple organ involvement. It is characterized by psychomotor retardation, feeding/swallowing difficulties, vomiting, respiratory problems, cranial nerve palsies hypo/hypertonia, generalized seizures, increased reflexes, spasticity, ataxia, and eye involvement (nystagamus, progressive external ophthalmoplegia, and/or optic atrophy) (Lerman-Sagie, 2005). The juvenile and adult forms are more benign and more variable. A clinical diagnosis of Leigh syndrome is based on the following criteria: progressive neurological disease with motor and intellectual deterioration, signs and symptoms of brainstem and basal ganglia disease, raised lactate levels in blood and CSF, and hyperintense lesions on T2-weighted MRI (Malojcic et al, 2004).

**Treatment**

Various therapeutic agents have been suggested to improve the signs and symptoms of Leigh syndrome. These include sodium dichloroacetate, flunarazine, soybean oil,
coenzyme-Q, and ketogenic diet; however, none of these have been tested in clinically controlled trials (Malojcić et al, 2004). None of these, though, have been shown to help. Other supportive management is based on the symptoms present in a given patient.

**Similarities to MS**
Clinical features shared between Leigh syndrome and MS are diplopia, dysarthria, tremor or clonic jerks, ataxia, optic atrophy and cognitive impairment.

**Differences from MS**
High lactate levels in blood and CSF are observed in Leigh syndrome, but not in MS.

**14. Leber Hereditary Optic Neuropathy**
LHON is a mitochondrial disease characterized by bilateral, painless, visual failure. It is the most common mitochondrial disorder affecting vision.

**Genetic Cause**
There are 18 allelic variants that can cause the disease, but the majority of patients have one of three mtDNA point mutations—G3460A, G11778A, or T14484C (Lerman-Sagie et al, 2005). It is maternally inherited, and the phenotype is variable, with those harboring the 14484 mutation have a better visual prognosis.

**Major Clinical Findings**
The common eye characteristics are visual blurring/clouding, centrocecal scotoma,
central retinal vessel vascular tortuosity, cicumpapillary telangiectatic microangiopathy, swelling of retinal nerve fibers, optic and optic atrophy and vision loss in the chronic phase. Other clinical features may include cardiac arrhythmia, nonspecific myopathy, tremor, ataxia, spastic dystonia, and peripheral neuropathy. Onset is during the second or third decades of life, and males are more likely to be affected than females (Lerman-Sagie et al, 2005).

A multiple sclerosis-like illness has been described in some patients with LHON. The 11,778 mtDNA mutation has been associated with demyelinating disease and optic neuritis in a mother and her son whose clinical and paraclinical evidence was indistinguishable from MS (Jansen et al, 1996). There has also been an association described between the 3460 mutation and periventricular white matter changes, and between the 14484 mutation and demyelinating disease (Bhatti and Newman, 1999; Horvath et al, 2000).

**Treatment**

There is currently no treatment to improve the visual outcome in individuals with LHON. Management is done by supportive care.

**Similarities to MS**

LHON may especially pose diagnostic challenges when the patient has the “multiple-sclerosis-like” phenotype. Both diseases demonstrate ataxia, optic atrophy, spasticity, and hyperreflexia.
Differences from MS

Family history and DNA analysis of the mitochondrial genome are the tools most useful in distinguishing MS-like LHON from MS.

15. Metachromatic Leukodystrophy

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disease resulting from deficiency of arylsulfatase A, which leads to accumulation of sulphatide in the white matter of the CNS and peripheral nerves (Chebel et al, 2009).

Genetic Cause

MLD is caused by mutations in the arylsulfatase A (ARSA) gene located on chromosome 22q13.3-qter. More than 150 mutations have been described and there is a genotype-phenotype correlation with the splice-site mutations, insertions, and deletions resulting in no active enzyme. Other mutations changing a single amino acid are associated with a low level of ARSA enzyme activity and often result in the juvenile or adult onset forms of MLD.

Major Clinical Findings

There are three forms of the disease—infantile, juvenile, and adult—with the juvenile and adult forms being the most likely to be part of an MS differential diagnosis. The adult form can present as two different types. One is predominantly motor disease with pyramidal and cerebellar signs such as weakness, dystonia, loss of coordination, spasticity, incontinence, seizures, and peripheral neuropathy. The other type is
characterized primarily by behavioral and/or psychiatric problems which are followed by dementia and spastic paresis (Fernandes et al, 2006). The course of the disease can vary, with periods of stability occurring between periods of decline.

_Treatment_

Treatment of MLD involves the use of antiepileptic drugs for seizures, physical therapy, and psychosocial support and counseling.

_Similarities to MS_

The late onset adult form of MLD may look like the clinical and radiological picture of MS. Both have incoordination, urinary incontinence, depression, cognitive deficits, optic atrophy, and gait disturbances. Both also show CNS white matter pathology on MRI.

_Differences from MS_

Distinguishing signs and symptoms of MLD from MS include peripheral nerve involvement and symmetrical CNS findings.

16. **Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes**

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a mitochondrial, multisystem disease.

_Genetic Cause_

MELAS is caused by mutations in multiple genes within the mitochondrial genome.
**Major Clinical Findings**

Onset of MELAS is typically in childhood. Common presenting signs include seizures, weakness, recurrent headaches, and recurrent vomiting. Other clinical features may include stroke, dementia, hemiparesis, short stature, hemianopsia, optic atrophy, congestive heart failure, pigmentary retinopathy, progressive external ophthalmoplegia, cardiac conduction block, diabetes mellitus, nephropathy, and hearing loss. The typical age of death ranges from ten to 35 years.

**Treatment**

There is no specific treatment for MELAS. Administration of coenzyme-Q and L-carnitine have been reported to provide some benefit, as they have with other mitochondrial diseases. Supportive care of symptoms is the only other intervention available.

**Similarities to MS**

MELAS has a variable phenotype due to its mitochondrial pathogenesis. It may sometimes exhibit a relapsing-remitting course similar to the one observed in RRMS.

**Differences from MS**

Seizures, recurrent vomiting, stroke, heart involvement, diabetes, and hearing loss are all features that may be observed in a patient with MELAS that would not be typical for MS.
17. Myoclonic Epilepsy with Ragged Red Fibers

Myoclonic epilepsy with ragged red fibers (MERRF) is a genetic disease of maternal mitochondrial inheritance.

Genetic Cause

MERRF is caused by mutations in the MT-TK gene with the m.8344 A>G mutation accounting for approximately 80% of cases. Because it is a mitochondrial disease, all children of an affected woman will have some degree of mutant mitochondria in their cells (heteroplasmy). However, the number of mutant mitochondria received and the tissues involved can vary from person to person.

Major Clinical Findings

Onset of disease is usually in childhood. A clinical diagnosis of MERRF is based on the following four features: myoclonus (usually the first symptom), generalized epilepsy, ataxia, and ragged red fibers on muscle biopsy. Other features commonly associated with MERRF are sensorineural hearing loss, short stature, optic atrophy, cardiomyopathy, dementia, peripheral neuropathy, myopathy, weakness, and exercise intolerance.

Treatment

While there is no cure for MERRF, the disease can be treated by treating the manifestations. Additionally, coenzyme Q10 and L-carnitine are often used to help improve mitochondrial function.
Similarities to MS

MERRF has a variable phenotype, but optic atrophy, fatigue, spasticity, and cognitive decline are all features that may be seen in both MERRF and MS.

Differences from MS

Epilepsy, hearing loss, cardiomyopathy, and peripheral neuropathy are features that may be seen in MERRF but not typical for MS.

18. Pelizaeus-Merzbacher

Pelizaeus-Merzbacher disease (PMD) is a PLP1-related disorder of the central nervous system with a US prevalence of approximately one per 200,000 to 500,000.

Genetic Cause

PLP1 encodes for an integral membrane protein that, along with DM20, forms fifty percent of the protein content in the CNS myelin. Mutations in the PLP1 gene, which is located on chromosome Xq22, result in defective central nervous system myelination. A genotype-phenotype correlation has somewhat been identified. PLP1 duplication is the most common mutation associated with classical PMD. Point mutations are associated with a severe form of PMD, and other mutations are associated with a milder form of PMD. Female heterozygotes for PLP1 gene mutations sometimes develop neurological signs and symptoms (Garbern, 2007).
Major Clinical Findings

The common clinical features of classical PMD—the type that is part of the MS differential—are: nystagmus in the first two months, hypotonia, spastic quadriparesis, ataxia, dystonia, and cognitive impairment. Other findings may include weakness, nocturia, dysarthria, optic atrophy, and hyperreflexia. Age of onset is typically in childhood, but later onset has been reported.

Treatment

Symptom management is the only intervention for individuals with PMD. Antiepileptic drugs and medications for spasticity may be used. Physical therapy and gait aids are also generally necessary.

Similarities to MS

The features of PMD may be mistaken for primary progressive MS based on the ataxia, spasticity, hyperreflexia, optic atrophy, weakness, and cognitive impairment. Like MS, PMD may also show oligoclonal bands and increased proteins on CSF analysis. Neuroimaging studies may also appear similar.

Differences from MS

Family history may be useful. Neuroimaging abnormalities are typically symmetric in PMD, unlike in MS.
19. Porphyria

The porphyrias are a group of both clinically and genetically heterogeneous diseases caused by the dysfunction of enzymes involved in heme biosynthesis which results in the pathological accumulation and excretion of porphyrins (Poblete-Gutierrez et al, 2006). The type of porphyria that can be part of the MS differential is acute intermittent porphyria (AIP). It exhibits autosomal dominant inheritance and is the most common acute porphyria in the world with a prevalence of approximately one-to-two per 100,000 (Poblete-Gutierrez et al, 2006).

Genetic Cause

AIP is caused by mutations in the porphobilinogen deaminase (HMBS) gene on chromosome 11q23.3.

Major Clinical Findings

There are no cutaneous symptoms in AIP. Common clinical symptoms include abdominal pain, mental disturbances, constipation, diffuse pain, vomiting, muscle weakness, sensory loss, tachycardia, fever, convulsions, and respiratory paralysis. The disease typically begins to manifest itself at puberty with periods of acute attacks. Often times these attacks are triggered by porphyrinogenic drugs, alcohol, hormones, infection, or reduced caloric intake.

Treatment

Treatment of AIP involves identifying and then avoiding precipitators of attacks. Some
individuals may need assistance with feeding in order to restore energy. Intravenous hemin preparations are also a recommended intervention to reduce ALA and PBG accumulation.

**Similarities to MS**

Clinical features shared between these two entities include muscle weakness and sensory disturbances. The time periods of acute attacks may resemble the relapsing-remitting pattern of RRMS.

**Differences from MS**

MS should be easily distinguished from porphyria if the patient displays the other common symptoms such as abdominal pain, constipation, vomiting, fever, and convulsions. None of these are typical for MS.

**20. Refsum Disease**

Refsum disease is a type of hereditary motor and sensory neuropathy with an unknown prevalence.

**Genetic Cause**

It is caused by mutations in either the *PHYH* (on chromosome 10pter-p11.2) or *PEX7* (on chromosome 6q22-q24). Mutations in these genes cause defective alpha oxidation of phytanic acid which causes toxic accumulation of phytanic acid and impaired myelin function (Wills et al, 2001).
**Major Clinical Findings**

Refsum disease has a variable age of onset ranging from infancy to the fifth decade. The most common, and often presenting symptom, is retinitis pigmentosa. Juvenile and late-onset Refsum may display symptoms such as ataxia, weakness, and neuropathy, hearing loss, anosmia, ichthyosis, and cardiac arrhythmias.

**Treatment**

Management and treatment of Refsum involves dietary restriction of phytanic acid, avoidance of sudden weight loss, and follow-up care with cardiologists and ophthalmologists.

**Similarities to MS**

Juvenile and late-onset Refsum may have MS-like symptoms such as ataxia, weakness, and neuropathy, as well as increased CSF protein concentration.

**Differences from MS**

Anosmia, ichthyosis, and cardiac involvement are not observed in MS. Individuals with Refsum also have increased serum/plasma phytanic acid, which would not be seen in an MS patient.

**21. Tumor Necrosis Factor-Receptor Associated Periodic Syndrome**

Tumor necrosis factor-receptor-associated periodic syndrome (TRAPS) is an auto-inflammatory disorder first termed familial Hibernian fever in 1982 and described an
Irish-Scottish family with episodic fever, abdominal pain, and myalgia (Kumpfel et al, 2008). It exhibits autosomal dominant inheritance, genetic heterogeneity, as well as incomplete penetrance (Rezaei, 2006).

**Genetic Cause**

TRAPS is due to mutations in the \textit{TNFRSF1A} gene on chromosome 12p13. More than 50 different mutations have been described and a genotype-phenotype has been identified with the P46L, R92Q, and T61I variants being low penetrant variants (Rezaei, 2006). The R92Q mutation is the most common mutation found in individuals with TRAPS, has a less typical phenotype with milder clinical symptoms, and later age-of-onset (Kumpfel et al, 2004).

**Major Clinical Features**

The typical TRAPS phenotype has an age of onset at around 10 years and characterized by periodic, recurrent fever; painful, migratory rashes; myalgias; muscle stiffness; arthralgias; recurrent abdominal pains; and ocular involvement (periorbital edema and/or conjunctivitis) (Kumpfel et al, 2004). Other features that may be observed include ataxia, gait disturbances, neuropsychiatric disorder, and personality changes. The episodes can vary in length from a few days up to weeks. Oligoclonal bands may be present on CSF and white matter lesions are seen on conventional T2 MRI.

**Treatment**

Treatment involves symptomatic management and administration of etanercept.
Similarities to MS

Clinical features shared between TRAPS and MS include fatigue, muscle stiffness and spasticity, gait disturbances, ataxia, and cognitive impairment. The periodic fluctuation in symptoms resembles relapsing-remitting MS. Oligoclonal bands are seen in both entities. Additionally, the white matter lesions may resemble MS.

Differences from MS

Detailed family history, paying close attention to TRAPS-associated symptoms is one tool of considering TRAPS has an MS differential. Other features that may be present in TRAPS, but uncommon in MS, include recurrent symptoms of unexplained fever, urticarial rash, and arthralgia/arthritis.

22. Wilson Disease

Wilson disease is an autosomal recessive disorder of copper metabolism.

Genetic Cause

It is caused by mutations in the \( ATP7B \) gene located on chromosome 13q14-q21. Abnormal gene product causes toxic accumulation of copper in the body (Lorincz, 2010). Clinical manifestations vary and can include hepatic, neurologic, or psychiatric disturbances.

Major Clinical Findings

The neurological symptoms of Wilson’s include variable dysarthria, dystonia, tremor,
and choreoathetosis, gait disturbances, seizures, insomnia, headaches, and pseudobulbar palsy. These symptoms may be accompanied by psychiatric disturbances such as personality and behavior changes to depression and psychoses (Gouider-Kjouja, 2009). Hepatic manifestations include chronic hepatitis, cirrhosis, and liver failure. Kayser-Fleischer rings are a common ophthalmic finding in Wilson’s. These rings are caused by copper deposition on the inner surface of the cornea in Descemet’s membrane.

*Treatment*

Treatment of Wilson’s involves the use of chelating agents and zinc salts for medical therapy. Penicillamine and Trientine are two copper-chelators used for Wilson’s (Goider-Khouja, 2009). Liver transplantation is also an option and recommended for those with progressive hepatic insufficiency. Additional supportive care based on symptoms present is available.

*Similarities to MS*

Features shared between Wilson disease and MS include dysarthria, incoordination, cognitive decline, and behavioral abnormalities. Individuals with the “cerebellar syndrome” type of Wilson’s are more likely to cause diagnostic challenge.

*Differences from MS*

The hallmark Kayser-Fleischer rings seen in Wilson’s are not observed in MS. Other diagnostic differences include the hepatic manifestations of Wilson’s and seizures.
PART 3) The similarities and differences between each of the above described diseases was compared to MS in order to develop a set of tools for clinical use. Multiple tables were designed with the intent that they be utilized as a group. Table 5 represents the clinical features shared between the 22 selected monogenic diseases and MS. The most common MS features were used and each monogenic disease was then checked for similarities of these features. Spasticity, weakness, and ataxia are the symptoms most commonly shared between all the diseases. Optic neuritis is fairly specific to MS. Only LHON and TRAPS are monogenic diseases that may cause this. Interestingly, CADASIL is a strong MS mimic, but when glancing at this table alone, one may not think so. Contrarily, Refsum disease is least likely of these diseases to pose diagnostic difficulty, but when looking at this table it appears to share quite a few symptoms with MS.
## CLINICAL FEATURES OF MS SHARED WITH MONOGENIC DISEASES

<table>
<thead>
<tr>
<th>Disease Name</th>
<th>ataxia</th>
<th>bowel/bladder disturbances</th>
<th>cognitive impairment</th>
<th>depression</th>
<th>dysarthria</th>
<th>dysphagia</th>
<th>diplopia</th>
<th>fatigue</th>
<th>gait disturbances</th>
<th>incontinence</th>
<th>incoordination</th>
<th>intention tremor</th>
<th>optic atrophy</th>
<th>optic neuritis</th>
<th>paresthesias</th>
<th>sensory disturbance</th>
<th>sexual dysfunction</th>
<th>spasticity</th>
<th>vision loss</th>
<th>weakness</th>
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| Multiple Sclerosis                       | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X
Table 6 represents clinical features that are found in the monogenic diseases that are uncommon in MS. Table 7 is a list of each monogenic disease with their corresponding typical MRI features. An entire research project could be spent on neuroimaging findings for these diseases and MS and is beyond the scope of this study. Finally, table 8 is a screening and diagnostic testing table that illustrates what the common CSF, biochemical, and molecular findings are for each of the diseases. While genetic testing is available for all the genetic diseases, other tests may aid in determining whether genetic testing is necessary. This table also demonstrates that other than CSF analysis, no other biochemical screening or diagnostic testing is available for MS.
<table>
<thead>
<tr>
<th>Disease Name</th>
<th>Constitutional</th>
<th>Cardiovascular</th>
<th>Endocrine Metabolic</th>
<th>Gastrointestinal</th>
<th>Genitourinary</th>
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<td>X-ALD/AMN</td>
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<td>primary adrenal insufficiency</td>
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<td>renal failure; isothenuria</td>
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<td>MI, congestive heart failure; vessel ectasia</td>
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<td>HMSN (eg. CMTX)</td>
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<td>HSP (eg. SPG2)</td>
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<td>Kearns-Sayre</td>
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<td>lactic acidosis</td>
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<td>nausea, vomiting, diarrhea, constipation, paralytic ileus; abdominal pain</td>
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<td>hypertension</td>
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<td>renal dysfunction</td>
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<td>cardiomegaly, heart failure</td>
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<td>hypoparathyroidism hemolytic anemia</td>
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<td>renal tubular dysfunction renal calculi</td>
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<p>| Table 6: Clinical features in monogenic diseases that are uncommon in MS |
| Note: Only positive findings are noted…a blank does not mean a shared finding |</p>
<table>
<thead>
<tr>
<th>Disease Name</th>
<th>Integumentary</th>
<th>Musculoskeletal</th>
<th>CNS</th>
<th>PNS</th>
<th>Psychiatric</th>
<th>Respiratory</th>
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<tr>
<td>X-ALD/AMN</td>
<td>hyperpigmentation</td>
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<td>eyes = blindness ears = cognitive hearing loss</td>
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<td>AFSO</td>
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<td>peripheral neuropathy</td>
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<tr>
<td>CADASIL</td>
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<td>eyes = optic nerve infarction; ischemic optic neuropathy recurrent subcortical infarcts, seizures; microbleeds migraine; lacunar infarcts</td>
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<td>psychiatric disturbances; mood disorders</td>
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<td>CTX</td>
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<tr>
<td>Fabry Disease</td>
<td>hypohidrosis; angiokeratoma</td>
<td>muscle cramps; fasciculations lymphedema; limited extension of terminal joints</td>
<td>TA's; stroke; seizures</td>
<td>trophic anesthesia</td>
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<td>mild obstructive lung disease</td>
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<td>Leigh Syndrome</td>
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Table 6 (con't).
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<thead>
<tr>
<th>Disease Name</th>
<th>MRI Finding(s)</th>
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<tbody>
<tr>
<td>Adrenoleukodystrophy/Adrenomyeloneuropathy</td>
<td>characteristic pattern of symmetric enhanced T-2 signal in the parieto-occipital region with contrast enhancement at the advancing margin; Atrophy of pons and cerebellum; symmetric lesions</td>
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<tr>
<td>Adult Polyglucosan Body Disease</td>
<td>Paraventricular, subcortical, and deep white matter changes that may include involvement of the upper pons, superior cerebellar peduncles, dentate nuclei, and anterior medulla (including the olives) often extending to the level of the cervical-medullary junction; No gadolinium enhancement; Cerebral, cerebellar, and spinal cord atrophy</td>
</tr>
<tr>
<td>Alexander Disease</td>
<td>Extensive cerebral white matter abnormalities with a frontal preponderance; A periventricular rim of decreased signal intensity on T2-weighted images and elevated signal intensity on T1-weighted images; Abnormalities of the basal ganglia and thalami; regional atrophy of the brain stem; Contrast enhancement of one or more of the following: ventricular lining, periventricular rim, frontal white matter, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, brain stem</td>
</tr>
<tr>
<td>CADASIL</td>
<td>Hemorrhages; involvement of anterior temporal and inferior frontal lobe; lacunar infarcts; T2 hyperintensities of U-fibers at vertex</td>
</tr>
<tr>
<td>Cerebrotendinous Xanthomatosis</td>
<td>bilateral hyperintensity of the dentate nuclei and cerebral and cerebellar white matter</td>
</tr>
<tr>
<td>Fabry Disease</td>
<td>T1 hyperintensities of pulvinar</td>
</tr>
<tr>
<td>Friedreich Ataxia</td>
<td>Dentate nucleus severely affected</td>
</tr>
<tr>
<td>FXTAS</td>
<td>Subependymal, deep, &amp; subcortical region involvement; more confluent than MS lesions; generalized atrophy; T2 hyperintensities in middle cerebellar peduncles</td>
</tr>
<tr>
<td>Hereditary Spastic Paraparesees</td>
<td>Usually normal; mild-mod atrophy of intracranial structures</td>
</tr>
<tr>
<td>Hereditary Sensory Motor Neuropathies</td>
<td>nerve root hypertrophy on spinal MRI</td>
</tr>
<tr>
<td>Kearns-Sayre</td>
<td>Basal ganglia calcifications; diffuse signal abnormality of central WM</td>
</tr>
<tr>
<td>Krabbe Disease</td>
<td>Diffuse cerebral atrophy; T2 hyperintensities</td>
</tr>
<tr>
<td>Leber Hereditary Optic Neuropathy</td>
<td>Myelin loss (spongy myelin); periventricular changes</td>
</tr>
<tr>
<td>Leigh Disease</td>
<td>Symmetric lesions; no gadolinium enhancement</td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy</td>
<td>increased T2 signal, typically involving the posterior cerebrum and not conforming to the distribution of major arteries</td>
</tr>
<tr>
<td>MELAS</td>
<td>brain atrophy and basal ganglia calcification. Bilateral putaminal necrosis and atrophy of the brain stem and cerebellum have been reported</td>
</tr>
<tr>
<td>MERRF</td>
<td>symmetric and widespread abnormality of the white matter of cerebrum, brain stem, and cerebellum</td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher</td>
<td>Lesions are bioccipital and partially or totally reversible</td>
</tr>
<tr>
<td>Porphyria</td>
<td>symmetrical signal changes involving the corticospinal tracts, cerebellar dentate nuclei, and corpus callosum</td>
</tr>
<tr>
<td>Wilson Disease</td>
<td>bilateral abnormalities in putamen, globus palidus caudate, thalamus, midbrain, pons, cerebellum; Hyper T2 and hypo T1 intensities; cortical atrophy</td>
</tr>
</tbody>
</table>

Table 7: Neuroimaging findings common for each of the monogenic diseases
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
<td>↑ protein (often) ↑ Immunoglobulin (often) oligoclonal bands present (often)</td>
<td></td>
<td></td>
<td>↑ serum/plasma VLCFA’s</td>
<td>evidence of adrenal insufficiency (often)</td>
</tr>
<tr>
<td>X-linked Adrenoleuodystrophy/Adrenomyeloneuropathy</td>
<td>↑ protein oligoclonal bands</td>
<td></td>
<td>↑ serum/plasma VLCFA’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult Polyglucosan Body Disease</td>
<td>↑ protein (common)</td>
<td></td>
<td>↓ fibroblast glycoegen branching enzyme activity</td>
<td>mutation analysis of GBE1 gene</td>
<td>EM of peripheral nerve EM of skin biopsy</td>
</tr>
<tr>
<td>Alexander Disease late onset form</td>
<td>↑ protein (often)</td>
<td></td>
<td></td>
<td>mutation analysis of GFAP gene</td>
<td></td>
</tr>
<tr>
<td>Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy</td>
<td>↑ protein (often)</td>
<td></td>
<td></td>
<td>mutation analysis of NOTCH3 gene</td>
<td>EM of skin biopsy</td>
</tr>
<tr>
<td>Cerebrotendinous Xanthomatosis</td>
<td></td>
<td>low plasma cholesterol (occasional)</td>
<td>↑ plasma/serum cholesterol ↑ bile alcohols in urine &amp; plasma</td>
<td>↑ serum cholestrol mutation analysis of CYP27 gene</td>
<td>EM/EM of peripheral nerves</td>
</tr>
<tr>
<td>Fabry Disease</td>
<td>↑ protein (sometimes)</td>
<td>Proteinuria (frequent) unc serum BUN/creatinine (occasional)</td>
<td>↓ WBC α-galactosidase A activity</td>
<td>↓ WBC α-galactosidase A activity (males only)** fibroblast mutation analysis of GLA gene</td>
<td>LM/EM peripheral nerve biopsy; slit lamp ophthalmologic exam</td>
</tr>
<tr>
<td>Fragile-X Tremor/Ataxia Syndrome</td>
<td>↑ protein (sometimes)</td>
<td>CGG repeat analysis of FMR1 gene</td>
<td>CGG repeat analysis of FMR1 gene</td>
<td></td>
<td>high serum FSH (females)</td>
</tr>
<tr>
<td>Friedreich Ataxia</td>
<td>↑ serum glucose</td>
<td>GAA repeat analysis of FXN gene</td>
<td>GAA repeat analysis of FXN gene</td>
<td></td>
<td>abnormalities of ECG and echo, NCV</td>
</tr>
<tr>
<td>Hereditary Motor &amp; Sensory Neuropathies (e.g. CMT1X)</td>
<td></td>
<td></td>
<td></td>
<td>mutation analysis of GJB1 gene</td>
<td>EMG/NCV EM/EM of peripheral nerve biopsy</td>
</tr>
<tr>
<td>Hereditary Spastic Parapareses (SPG2)</td>
<td>↑ protein (often)</td>
<td>↑ serum lactate &amp; pyruvate, and serum glucose (sometimes)</td>
<td>blood lactate and blood pyruvate deletion analysis of mt genome</td>
<td>deletion analysis of mt genome</td>
<td>LM/EM muscle biopsy; hypoparathyroidism (occasional)</td>
</tr>
<tr>
<td>Kearns-Sayre</td>
<td>↑ protein (often)</td>
<td>↑ serum lactate &amp; pyruvate, and serum glucose (sometimes)</td>
<td>blood lactate and blood pyruvate deletion analysis of mt genome</td>
<td>deletion analysis of mt genome</td>
<td>LM/EM muscle biopsy; hypoparathyroidism (occasional)</td>
</tr>
<tr>
<td>Krabbe</td>
<td>↑ protein (often)</td>
<td>↓ WBC galactosylceramidase activity</td>
<td>↓ WBC galactosylceramidase activity</td>
<td>↓ WBC galactosylceramidase activity</td>
<td>LM/EM peripheral nerve biopsy; EMG/NCV</td>
</tr>
<tr>
<td>Leber Hereditary Optic Neuropathy</td>
<td>↑ blood lactate</td>
<td>mutation analysis of mt genome</td>
<td>mutation analysis of mt genome</td>
<td></td>
<td>diluted ophthalmologic evaluation; VEP and/or ERG</td>
</tr>
<tr>
<td>Leigh Syndrome</td>
<td>↑ lactate (often) ↓ glucose (often)</td>
<td>↑serum lactate and pyruvate ↓ glucose</td>
<td>inclusion plasma alanine mutation analysis of mt genome</td>
<td>mutation analysis of mt genome analysis of nuclear DNA genes (BCS1L, COX10, NDUFA1, NDUFAF2, NDUFS4, NDUFS7, NDUFS9, SCO1, SCO2, SDHA, SURF1, and NDUFS8)</td>
<td>EMG/NCV</td>
</tr>
</tbody>
</table>

Table 8: Screening and diagnostic testing recommended for differentiating monogenic diseases from MS

** Some carrier females have α-galactosidase A activity in the normal range so this may not always be reliable for females
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like Episodes</td>
<td>↑ protein (sometimes) ↑ lactate (common)</td>
<td>↑ serum CK (sometimes) ↑ plasma alanine</td>
<td>↑ resting serum lactate ↑ serum CK (sometimes) ↑ plasma alanine</td>
<td>mt mutation analysis</td>
<td>LM/EM muscle biopsy</td>
</tr>
<tr>
<td>Myoclonic Epilepsy with Ragged Red Fibers</td>
<td>↑ protein ↑ lactate (common)</td>
<td>↑ serum CK (often); ↑ lactate, pyruvate (sometimes)</td>
<td>↑ serum CK (often); ↑ lactate, pyruvate (sometimes);inc plasma alanine</td>
<td>mutation analysis mt genome</td>
<td>LM/EM muscle biopsy; EMG/NCV</td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy late onset form</td>
<td>↑ protein (sometimes)</td>
<td>↑ WBC arylsulfatase A activity</td>
<td>↑ WBC and fibroblast arylsulfatase A activity</td>
<td>mutation analysis of ARSA gene</td>
<td>LM/EM peripheral nerve biopsy abnormal NCV</td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher late onset form</td>
<td>oligoclonal bands (sometimes)</td>
<td>↑ plasma and urine PBG and ALA</td>
<td>↑ plasma &amp; urine PBG</td>
<td>mutation analysis of PLP1 gene</td>
<td>EMG/NCV</td>
</tr>
<tr>
<td>Porphyria cute intermittent type</td>
<td>↑ protein (usually)</td>
<td>↑ serum/plasma phytanic acid</td>
<td>↑ serum/plasma phytanic acid</td>
<td>mutation analysis of PHYH &amp; PEX7 genes</td>
<td>NCV</td>
</tr>
<tr>
<td>Refsum Disease late onset form</td>
<td>oligoclonal bands (common)</td>
<td>↑ Sed rate serum crp??</td>
<td>↑ serum urinary copper; ↑ serum cereuloplasmin</td>
<td>mutation analysis of TNFRSF1A gene</td>
<td>slit lamp ophthalmologic exam</td>
</tr>
<tr>
<td>TNF-Receiver Associated Periodic Syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Only positive findings are noted**

EM = electron microscopy
EMG = electromyography
LM = light microscopy
NCV = nerve conduction velocity
↑ = increased or high
↓ = decreased or low
ALA = delta-aminolevulinic acid

Table 8 (con’t).
DISCUSSION:

The Review Process

One of the most important aspects of performing a systematic literature review is that no discrimination is made; meaning, all relevant articles regardless of study type or journal in which they are published are included for data extraction. It is this aspect of a systematic literature review which provides reliability and validity to the topic under investigation. In this study every article that mentioned a monogenic disease as being part of the MS differential diagnosis was utilized. Nonetheless, it is important for clinicians and counselors to realize that not all of the identified monogenic diseases should necessarily be considered in the differential diagnosis for every patient with nonspecific neurological symptoms. This review included all those disorders with the potential to be misdiagnosed as MS. Impact factors for each journal were obtained (Appendix 2); however, no articles were eliminated based on the impact factor alone. While impact factors provide some information on the strength of the research in a specific journal, it is only one criterion of such judgment. Journals of a specialty field are likely to have lower impact factors than broad-range or well-renowned journals; however it does not mean that the research published in those journals are not valid or important.

Additionally, authors in a given field who publish in well known journals are more likely to be cited as well as researchers who are well known in their specific areas of expertise are likely to cited more frequently. In this review however, many articles were case reports. Therefore, the names of the author(s) or the journal(s) are not as important as the details of the case itself.
The review process itself was a limitation for this study. Due to the large amount of titles that had to be read, it could not be helped that the reviewer considered titles differently as more and more titles were read and categorized. As titles were categorized and the list of genetic diseases that were part of the MS differential began to materialize in the reviewers mind, more attention was paid to titles with those disease names.

After the genetic disease list was compiled and the systematic review process of this study was over, the reviewer took a second glance at all the original titles as a way of checking for personal validity. Two additional monogenic diseases were found during this process. Due to time restraints, they were not incorporated into this research; however, it is important to mention them. The first is autosomal dominant optic atrophy caused by OPA1 mutations on chromosome 3q28-3q29. The second is autosomal dominant leukodystrophy caused by lamin B1 mutations and duplications on chromosome 5q31.

**The Genetic Diseases**

This study utilized the available literature and identified 22 monogenic diseases that can be misdiagnosed as MS. This list of diseases was developed by combining case reports of misdiagnoses and previous authors’ differential diagnosis lists for MS. These genetic diseases, however, are not all equal in their likelihood of being misdiagnosed as MS. Table 1 lists the identified monogenic diseases with the number of the references in which they were identified.
CADASIL, CMT1X, Fabry, FXTAS, LHON, Pelizaeus-Merzbacher, and TRAPS have all been misdiagnosed as “definite” MS based on case reports and clinical studies (Pandey & Abubacker, 2006; O’Riordan et al, 2002; Callegaro et al, 2006; Saip et al, 2007; Invernizzi et al, 2008; Carmosino et al, 2005; Zhang et al, 2009; Greco et al, 2008; Hall et al, 2005; Isoardo et al, 2005; Warshawsky et al, 2005; Hoffmann et al, 2008;). While the diagnostic criteria on which these MS diagnoses were based were not always specified, they illustrate the notion that these diseases all have phenotypic variability and can present diagnostic challenges.

**Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)**

Pandey and Abubacker (2006) presented two cases in which these patients were first diagnosed with multiple sclerosis based on neuroimaging. However, further investigation of their family histories, revealing recurrent infarctions in other family members, prompted genetic testing for CADASIL. Both cases were found to have a *NOTCH3* mutation. “CADASIL can mimic MS both clinically and on MRI because of the presence of recurrent, remitting episodes of focal neurological deficits in both conditions, their occurrence in relatively young individuals, and intervening symptom-free periods for many years” (Pandey & Abubacker, 2006). Both conditions can show lesions similar in morphology and location.

O-Riordan, Nor, and Hutchinson (2002) reported a family with CADASIL in which the index case and her daughter were both initially diagnosed as MS. T2-weighted magnetic
resonance imaging scans in both CADASIL and MS may show diffuse periventricular
white matter hyperintensities, leading to diagnostic confusion in this family (O’Riordan et al, 2002). This case further demonstrates the potential pitfalls in distinguishing these
two entities. Thus, careful attention to family histories and MRI findings, especially
those typical for CADASIL, is sometimes necessary to distinguish between the two.

Charcot Marie Tooth Disease (CMT)

A case published in Neurology by Isoardo et al (2005) describing a patient who showed
CNS demyelinating disease that satisfied diagnostic criteria for primary progressive MS, actually had CMT1X. A second patient with CMT1X who fulfilled diagnostic criteria
for relapsing-remitting MS was published in Journal of Neurology. Other cases of CNS
involvement in CMT1X have been published (Panas et al, 2001). These cases have all
raised the question of the association between the GJB1 gene with MS. Did these
patients truly have MS-like disease due to their CMT disease-causing mutations, or did they have CMT and MS concurrently? This question is unable to be answered at this
time.

The MPZ gene on chromosome 1q22 is responsible for causing various forms of CMT—
CMT1B (demyelinating type), CNT2I (axonal), and CMT2J (axonal). Mutations in these
genes have been reported in kindreds who have both CMT and at least one member with
an MS diagnosis. Whether or not the individual with MS has a chance association of both
CMT and MS or has a CMT phenotype that mimics MS and satisfies MS diagnostic
criteria has not been determined (Kilfoyle et al, 2006; Rajabally and Abbott, 2005).
**Fabry**

Two case reports were found in which patients were diagnosed with MS, and then later a diagnosis of Fabry was made. One case was a woman with recurrent neurological deficits secondary to multifocal small vessel involvements with hyperintense lesions located in bilateral thalamus, supratentorial areas, and left cerebellum. She later presented with skin lesions and proteinuria which lead to enzyme assays, which confirmed a diagnosis of Fabry (Saip et al, 2007).

The other case was a male who presented in right hemiparesis and motor aphasia with several T2-weighted hyperintense lesions in the periventricular areas. Eight years later the diagnosis of MS was ruled out based on renal function abnormalities, normal optic discs, and a prematurely implanted pacemaker. Upon re-examination and another medical history review, proteinuria, renal dysfunction, and gastrointestinal symptoms lead to the consideration of Fabry. DNA analysis confirmed an L131P mutation. This patient had initially satisfied criteria for an MS diagnosis set by both Poser and McDonald.

**Fragile-X Tremor/Ataxia Syndrome (FXTAS)**

In a study investigating the initial diagnoses of individuals with FXTAS, Hall et al (2005) found that two out of fifty-six patients with FXTAS were initially diagnosed with MS (one had clinically definite MS, and the other had probable MS). MRI of FXTAS shows generalized atrophy, white matter abnormalities, and distinctive T2 hyperintensities in the middle cerebellar peduncles and/or brain stem (Hall et al, 2005). The white matter abnormalities in FXTAS are usually more confluent than seen in typical MS (Greco et al,
Due to the clinical and MRI similarities between MS and FXTAS, screening individuals for an FMR1 premutation, especially if the family history contains developmental delay, autism, ovarian insufficiency (another FMR1 associated disorder in permutation carriers) intention tremor, ataxia, or neuropathy is a logical step.

**TNF-Receptor Associated Periodic Syndrome (TRAPS)**

TRAPS with CNS involvement, leading to diagnostic confusion with MS, has been described by Hoffmann et al 2008, Kumpfel et al 2004, and Minden et al 2003. Kumpfel et al performed a prospective study where twenty-five out of 200 patients with MS (clinically definite) reported symptoms associated with TRAPS. Of these twenty-five patients, six were found to carry the R92Q mutation. Part of the same study tested 365 unrelated patients with MS without known TRAPS-associated symptoms for the R92Q mutation. Of these, 17 were R92Q heterozygotes. They concluded from their study that “TRAPS should be considered in MS patients with unexplained recurrent symptoms such as myalgia, arthralgia/arthritis, urticarial rash, and severe fatigue, even when there is no history of fever flares.” Additionally, careful evaluation of medical and family histories may aid in differentiating CNS-TRAPS from MS, with careful attention to TRAPS-associated symptoms and a family history of similar characteristics. Making the distinction between CNS-TRAPS from MS is especially important because of the method of treatment for each disease. Anti-TNF therapy used in the treatment of TRAPS can actually exacerbate MS.
**Hereditary Spastic Parapareses (HSP)**

A report of a frame shift mutation in the spastin gene (SPG4) in a large family with HSP was written in 2001. Two sisters in this family had a diagnosis of MS. It is still undetermined if they had concurrence of MS and HSP, HSP alone with an MS-like phenotype, or if mutations in this gene may predispose to the acquisition of MS (Mead et al, 2001).

This SPG4 case demonstrates a common problem when considering any of these diseases vs. MS. It is always possible that an individual may actually have two diseases. While the chances of this would vary depending on each disease’s incidence, it is something to be aware of. With the availability of genetic testing, it has become rather straightforward in being able to confirm to refute a genetic diagnosis. The problem lies with the MS diagnosis. No such testing is available.

**Others**

Porphyria and Refsum disease were mentioned in a review article as being a differential diagnosis of MS. However, this research study did not identify any case reports of a misdiagnosis ever being made. Additionally, both of these diseases would typically present with other clinical findings that would make a diagnosis of MS unlikely. While a few clinical features may be shared between them and MS, an experienced clinician would likely not have difficulty distinguishing between these diseases.
**Pediatric vs. Adult MS**

Not all of these genetic diseases would be considered in the differential diagnosis of MS due to their common ages-of-onset. Thus, certain of these would be more likely to be considered in a pediatric MS case rather than an adult MS case. Krabbe, the leukodystrophies (MLD and ALD), and Pelizeaus-Merzbacher are more likely to be part of the pediatric MS differential.

**RRMS vs. PPMS**

As with the age-of-onset, not all of these genetic diseases would be considered in every MS case because of the different courses of MS. The mitochondrial diseases, CADASIL, LHON, CMT type 2, HSP (due to SPG4 mutations), adult Alexander’s, Fabry, FXTAS, and Wilson disease are all more likely to be part of the relapsing-remitting MS differential.

ALD/AMN, adult MLD, hereditary parapareses or ataxias (including Friedreich Ataxia), CMT1X, and adult polyglucosan body disease exhibit a progressive pattern more like primary progressive MS.

**MRI**

MRI is the most useful diagnostic test in making a diagnosis of MS. However, the white matter abnormalities seen on MRI are not always specific to MS. “Non-specific white matter abnormalities on MRI scans and the large number of disorders associated with such continue to pose diagnostic difficulty” (Charil, 2006). CADASIL, adult
polyglucosan body disease, Alexander disease, the leukodystrophies, and many of the mitochondrial diseases are all monogenic diseases that have been shown to display similar MRI characteristics. Table 4 represents a list of all the monogenic diseases identified in this review with their corresponding “typical” MRI presentations. Hopefully, this is useful as it provides clinicians with a quick reference when confronted with an abnormal MRI presentation for MS. For example, in a patient being evaluated for MS who displays abnormalities in the dentate nuclei, the clinician should also consider cerebrotendinous xanthomatosis and Friedreich’s ataxia in the differential as this is a common finding in these diseases. Of course, the MRI picture must be considered in conjunction with the clinical picture. Expanding on the previous example, dentate nuclei abnormalities on MRI along with early-onset cataracts in a patient would make the diagnosis of cerebrotendinous xanthomatosis much more likely than Friedreich’s ataxia.

**Limitations**

As with all research, this systematic review is not without limitations. One of which is that the article selection in the search was performed by only one reviewer. Effort was made to err on the side of caution and to include rather than exclude a questionable article; it is possible that some relevant titles were missed. While every attempt was made to make this an exhaustive list, it is possible that there are remaining genetic diseases part of the MS differential that were not identified due to this study design and structure. Two of these diseases were already mentioned in this paper.

Another limitation is that monogenic diseases are only one small fraction of the number
of alternative diagnoses to MS. This review and the tables created from it are only useful for monogenic disease comparison and not for aiding in differentiating MS from other common masqueraders such as systemic lupus erythematosus.

**Conclusions**

Caution must be taken when considering any of these monogenic diseases as they all have a variable phenotype. These tables include information reflecting the most common characteristics. Unlike MS, though, many of these diseases have additional diagnostic testing options to aid in making it more or less likely. When utilized as a group, the tables created in this research allow for identification of alternative diagnoses to MS by both MRI characteristics and clinical features. They also provide guidance on additional diagnostic testing that may be useful when considering one of these monogenic diseases as a diagnosis.

The differential diagnosis of MS is vast, and it has long been known that genetic diseases are included in it. Certain genetic diseases can mimic the clinical features, the radiological findings, or both. However, no recent study has comprehensively identified these diseases, nor have clear comparisons and differences been identified. Review articles do not necessarily provide the details needed for one to know how to differentiate one disease from another. This study has attempted to conquer both of those limitations. Through systematically reviewing the literature, all possible monogenic diseases that can imitate MS were strived to be identified; and through the development of multiple tables, the similarities and differences of these diseases were examined.
Appendix 1

The Diagnostic Scheme for MS (adapted from McDonald et al, 2007):

1. A clinical presentation of two or more attacks and objective clinical evidence of 2 or more lesions. –or—

2. Two or more attacks and objective clinical evidence of 1 lesion –and—
   Additional data of dissemination in space (demonstrated by MRI) or
   Two or more MRI-detected lesions consistent with MS plus positive CSF*
   or Await further clinical attack implicating a different site –or—

3. One attack with objective clinical evidence of 2 or more lesions –and—
   Dissemination in time (demonstrated by MRI) or
   Second clinical attack –or—

4. One attack with objective clinical evidence of 1 lesion (monosymptomatic presentations; clinically isolated syndrome) –and—
   Dissemination in space (demonstrated by MRI) or
   Two or more MRI-detected lesions consistent with MS plus positive CSF
   and Dissemination in time (demonstrated by MRI) or
   Second clinical attack –or—

5. Insidious neurological progression suggestive of MS –and—
   Positive CSF and
   Dissemination in space demonstrated by either
   Nine or more T2 lesions in brain or 2 more lesions in spinal cord
   or four-to-eight brain plus one spinal cord lesions –or—
   Abnormal VEP** associated with four-to-eight brain lesions, or
   with fewer than four brain lesions plus one spinal cord lesion
   demonstrated by MRI –and—
   Dissemination in time, demonstrated by MRI –or—continued progression for 1 year

* positive CSF = increased IgG concentration relative to other CSF proteins
**VEP = abnormal visual evoked potential of the type seen in MS (delayed with a well-preserved wave form)
Appendix 2


O’Riordan S, Nor AM, Hutchinson M. CADASIL imitating multiple sclerosis: the importance of MRI markers. *Multiple Sclerosis* 2002; 8: 430-432.


Quan D, Kleinschmidt-De Masters BK. A 71-year old male with 4 decades of symptoms referable to both central and peripheral nervous system. *Brain Pathology* 2005; 15: 369-370, 373.


Rolak L. Multiple sclerosis: It’s not the disease you thought it was. *Clinical Medicine and Research* 2003; 1: 57-60.


Sriram S. TRAPS and MS: two diseases or an MS mimic? *Neurology* 2008; 70: 1077-1078.


## Appendix 3: Journals’ Impact Factors and Articles from Each

<table>
<thead>
<tr>
<th>Journal Title</th>
<th>Impact Factor</th>
<th>References</th>
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<tr>
<td>New England Journal of Medicine</td>
<td>47.050</td>
<td>B11; N6</td>
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<tr>
<td>JAMA</td>
<td>31.700</td>
<td>M10</td>
</tr>
<tr>
<td>Lancet Neurology</td>
<td>18.126</td>
<td>C14; M7</td>
</tr>
<tr>
<td>Brain</td>
<td>9.490</td>
<td>K7; Y1</td>
</tr>
<tr>
<td>Annals of Neurology</td>
<td>9.317</td>
<td>W4</td>
</tr>
<tr>
<td>Neurology</td>
<td>8.170</td>
<td>C7; E1; F7; F9; H1; R14; S21; V3; RH1; RH3; RI2; RS1</td>
</tr>
<tr>
<td>Annals of Rheumatic Disease</td>
<td>8.111</td>
<td>RM2</td>
</tr>
<tr>
<td>Archives of Neurology</td>
<td>6.310</td>
<td>C8; RG1</td>
</tr>
<tr>
<td>Brain Pathology</td>
<td>5.903</td>
<td>G1</td>
</tr>
<tr>
<td>Current Opinion in Neurology</td>
<td>5.430</td>
<td>RO2</td>
</tr>
<tr>
<td>The Journal of The American Society for Experimental NeuroTherapeutics</td>
<td>5.381</td>
<td>C12</td>
</tr>
<tr>
<td>Journal of Neurology, Neurosurgery, and Psychiatry</td>
<td>4.869</td>
<td>K1; M4; S6; Z3; RM1</td>
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<tr>
<td>Drugs</td>
<td>4.732</td>
<td>H4</td>
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<tr>
<td>Journal of Neuropathology and Experimental Neurology</td>
<td>4.564</td>
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<td>Arthritis and Rheumatism</td>
<td>4.152</td>
<td>RK1</td>
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REFERENCES


O’Riordan S, Nor AM, Hutchinson M. CADASIL imitating multiple sclerosis: the importance of MRI markers. *Multiple Sclerosis* 2002; 8: 430-432.


