Multiple Sclerosis: What we know so far.

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Resumen

Este artículo revisará algunos de los avances en la patogénesis y factores de riesgo de la Esclerosis Múltiple (EM), así como los criterios diagnósticos de EM revisados por McDonald en 2017, los fenotipos revisados, los tratamientos disponibles y los distintos síntomas de la condición. La información actual sobre la EM es mucho más amplia que lo que se conocía hace 20 años, y aún existen aspectos que no se han esclarecido. No obstante, cada día se aprende algo nuevo sobre la condición, la cual puede ayudar a diagnosticar síntomas tempranos de esta. Con nuevos indicadores y criterios para analizar correctamente y observar el progreso de la condición del paciente y categorizar el fenotipo de EM, los médicos especializados en esta enfermedad pueden facilitar las recomendaciones y prescribir el tratamiento adecuado. Más aún, mediante la comprensión de los factores de riesgo y mecanismos de la patología, puede resultar en mejores opciones de tratamiento.

Palabras clave: Esclerosis Múltiple, Diagnóstico, Tratamiento

Abstract

This article, will review some of the advances in pathogenesis and risk factors of multiple sclerosis (MS), the 2017 revised McDonald criteria for diagnosing MS, revised phenotypes, currently available treatments and the different symptoms this disorder has. What we know about MS is vastly more than what we knew 20 years ago, and yet most of it is unclear, but every day, we learn something new about this disorder that can help diagnose early-onset symptoms of the disease. With new pointers and criteria for correctly analyzing and observing a patient's condition's progress and fittingly categorizing the MS phenotype, the MS-specialized physician can facilitate a recommendation and prescribe adequate treatment; furthermore, comprehending the risk factors and pathogenic mechanisms results in better treatment options.

Keywords: Multiple Sclerosis, Diagnosis, Treatment

Multiple Sclerosis (MS) is a demyelinating autoimmune disorder that affects the central nervous system (CNS) and, infrequently, the peripheral nervous system. The etiology of the immune disease still needs to be refined, despite the significant advances in this field. The etiology has multiple factors making it complex. The complicated nature is a typical depiction of the immunological and CNS systems. Marked contrast may exist between patients in connection to the severity of progression, response to medication, the onset of the condition, and histological patterns of damage to the tissue. Undoubtedly, immune mechanisms and inflammation are critical to the pathogenesis of MS. However, it is still questionable whether the inflammation is the first event in the cascade of pathophysiologic events or if it is a secondary response to an infectious agent that is unknown or primary CNS degeneration. Recent studies have developed compelling epidemiological and mechanistic evidence for the causal role of Epstein-Barr virus (EBV) in MS.

MS Risk Factors and Pathogenesis

Multiple sclerosis has a long subclinical period in most patients seen by silent lesions on MRI at the time of clinical onset, including subtle deficiencies in clinical testing years before the beginning of symptoms. The particular environmental factors that made susceptible a given person develop MS were most likely present many years before the clinical onset (Nourbakhsh & Mowry, 2019). Complicated interactions among genetic and environmental factors and random events affect the contingent probability of these pathogenic events and the strength of the CNS repair mechanisms, functional plasticity, and physical and cognitive reserve. Analysis gathered from preclinical and observational studies (including cohort and case-control studies) has resulted in the breakthrough of associations between many genetic loci and several environmental factors with the risk of developing MS. For many years, it was thought that there was no specific pathogen that would increase or develop MS, but in more recent years researchers have given light to EBV playing a significant role in the development of MS (Soldan & Lieberman, 2023). Multiple sclerosis can be caused by chronic/recurrent EBV infection. Models suggest that Relapsing-Remitting (RRMS) is caused by the repeated entry of EBV-transformed B cells to the CNS (Houen, Tier & Frederksen, 2020).

In contrast, Primary Progression (PPMS) is caused by the more chronic activity of EBV-transformed B cells in the CNS (Houen, et al., 2020). Even though there is no doubt that immune mechanisms and inflammation are crucial to the pathogenesis of MS, it is still debated whether the inflammation is the opening event in the torrent of pathophysiologic events or is an aftermath response to a yet unknown infectious agent or inherent primary CNS degeneration. Even if MS does not have some of the characteristics that are generally of autoimmune disease, most MS investigators believe that self-reactive immune cells obtaining access to and attacking the myelin sheath in the CNS are the primary pathogenic event.

MS Pathogenesis

Even though demyelination in the CNS is the primal characteristic of MS, axonal injury exists from the earliest stages of the disease. It is a significant contributor to

physical and cognitive disability. Lymphocytes that break through the blood-brain barrier unfold a pathogenic cascade — reaching a critical point in demyelination, neuroaxonal degeneration, synaptic loss, dying-back oligodendrogliopathy, and, in due course, tissue loss and astrogliosis (Nourbakhsh et al., 2019). Demyelination in MS is not limited to white matter. Pathologically, cortical and deep gray matter demyelination can be seen, which is also present even in the early stages of the disease. EBV-induced B cell immortalization or transformation is considered necessary in MS development, with molecular mimicry being a popular theory (Dobson & Giovannoni, 2018); however, more than 200 genetic variants have been discovered to be associated with modifying the risk of MS. The T lymphocytes, B lymphocytes, and innate immune mechanisms participate in MS pathogenesis.

Genetic Risk Factors

For more than 15 years, worldwide collaborations for genome-wide association research have studied thousands of MS patients and controls. This research has presented strong evidence for the association of almost 200 autosomal variants outside the major histocompatibility complex gene. With familial clustering of the disease, the increased risk is dependent on the degree of genetic similarity to the proband (a person serving as the starting point for the genetic study of a family; used especially in medicine and psychiatry) and higher prevalence of MS in some ethnic groups are strong evidence for a genetic basis of the disease. Many MS-associated genetic variants are located close to the genes that regulate innate or adaptive immunity and are shared by several other autoimmune diseases. These variants, however, only explain 20% to 30% of MS heritability. This proposes that the reminder of heritability is most likely related to epigenetic factors and gene-gene or gene-environment interactions. Data gathered involving family suggested that multiple frequent DNA variants in the population are the basis of MS heritability (Nourbakhsh et al., 2019). It is thought that these variants affect regulatory mechanisms and gene activity. Most of these variants are located in noncoding regions of the genome. Many of them are in intergenic areas. Carrying HLA-DRB1*1501 is associated with higher odds of developing MS. For years, only several variants of HLA antigen were known to affect MS risk. While having HLA-A*02 is associated with significantly reduced odds of developing MS.

Environmental Risk Factors

Multiple environmental factors have been considered to be risks of developing MS. However, only a few of these studies have been researched adequately and unbias. An even smaller amount is replicated with frequency. Some of the factors with the most substantial evidence of having a role in MS are low sunlight exposure, vitamin D deficiency/insufficiency, childhood obesity, smoking, and the Epstein-Barr virus.

Sun Exposure and Vitamin D

Higher serum vitamin D (vD) levels have been demonstrated to be related to a lower risk of developing MS. The impact of vD deficiency on a pregnant woman and the MS risk of the offspring is questionable. The relationship between serum vD levels and MS risk stays, notwithstanding when proportions of ultraviolet radiation (UVR) were incorporated into the models. Both UVR and vD are related to lower chances of

MS. However, not most of the impacts of UVR might be disclosed by its contribution to vD synthesis (Nourbakhsh et al., 2019). The UVR synthesizes vD in the skin, so it is difficult to analyze the independent impacts of these variants on the chances of developing MS. A few randomization studies have shown the relationship between genetic variations influencing serum vitamin D levels and the risk of MS. If the impact of UVR was utterly independent of vD, at that point oral administration of vD ought not to affect the risk of MS (Nourbakhsh et al., 2019). Numerous types of research have demonstrated the negative association between UVR exposure and MS when evaluated at the time of MS onset or diagnosis. A recent study in southern California (Langer-Gould et al., 2018) concluded that the relationship between serum vitamin D levels and MS has just appeared in whites and was not found in African Americans or Hispanics. However, research done in Argentina with 132 Hispanic patients revealed that, especially during an exacerbation, patients have reduced serum levels of vitamin D compared with healthy subjects (Correale, Ysrraelit & Gaitan, 2009). Correale et al. (2009) findings suggest that T cell regulation is essential in maintaining T cell homeostasis in a group of vitamin D-dependent patients.

Obesity

Demonstrating a correlation between hereditary variations influencing the weight record and the risk of MS, Mendelian randomization studies gave more grounded proof to the association of obesity, and MS. Just like adult-onset MS, obesity has been demonstrated to be related to pediatric-onset MS. In one investigation, obesity was a more grounded risk factor in people conveying HLA-DRB1*1501. Like other environmental risk factors, obesity in adolescence and young adults is, by all accounts, related to the consequent risk of MS. The risk increases in morbidly obese people; even an individual that is mildly overweight has a higher risk of MS (Nourbakhsh et al., 2019).

Epstein-Barr virus

EBV is a ubiquitous human lymphotropic herpesvirus virus with a well-established causal role in several cancers and recent evidence of the role of MS. How this type of virus that typically leads to benign latent infections can promote cancer and autoimmune is not fully understood (Soldan & Lieberman, 2023). Being truly EBV-negative protects from developing MS; symptomatic EBV infection (i.e., infectious mononucleosis) doubles the chances of getting MS (Dobson et al., 2018). In at-risk individuals, EBV infection of B cells promotes the development of MS through several possible mechanisms. These include molecular mimicry by EBV nuclear antigen 1 (EBNA-1), B cell transformation through latent membrane protein 1 (LMP1) and LMP2A, induction of B cell trafficking to the CNS, or other unknown mechanisms (Robison & Steinman, 2022).

MS Phenotype Classification

MS is partitioned into the accompanying categories, primarily based on clinical criteria, including the recurrence of clinical relapses, time disease progression, and lesion development on magnetic resonance imaging (MRI): Relapsing-Remitting MS (RRMS) (approximately 85% of cases); Secondary Progressive MS (SPMS); Primary progressive MS (PPMS); Progressive-Relapsing MS (PRMS) (Lublin, 2014). In May 2014, a revision of the MS phenotype was published, adding Clinically

Isolated Syndrome and eliminating RRMS (Kantarci, 2019). Now PPMS is not considered a separate entity but part of the spectrum of progressive disease. Clinically isolated syndrome (CIS) is viewed as a spectrum feature. It should be followed to determine subsequent disease, regardless of whether the definition for CIS has derived from different sources and has been utilized without alteration. CIS has been described as the first clinical neurological episode when a patient has symptoms and signs suggestive of MS. White matter lesions that match the criteria for multiple sclerosis in people without a history of demyelinating attack or an alternative origin are known as Radiologically Isolated Syndrome. So an MRI finding alone is not sufficient to diagnose MS. However, if new inflammatory activity is detected on a subsequent MR imaging, many neurologists would strongly consider initiating medication (Hosseiny, Newmen & Yousem, 2020).

2017 McDonald Diagnostic Criteria For MS

In 2017 McDonald's criteria for the diagnosis of MS were revised. The 2010 revision established the possibility of diagnosis at the first observation. Moreover, for the first time, a single MRI allowed the diagnosis of MS. This is because the dissemination of lesions in space (DIS) was evident without any better explanation. DIS was defined by one or more lesions in at least two of four typical areas of the CNS (periventricular, juxtacortical, infratentorial, and spinal cord). The presence of an asymptomatic gadolinium-enhancing lesion and a T2 lesion or a new T2 lesion at a follow-up MRI defined dissemination of lesions in time (DIT). The new 2017 revision furthers the implications for diagnosis. It aims to facilitate earlier diagnosis and to preserve the specificity of the 2010 criteria, reducing the frequency of misdiagnosis ("Guidelines for MS diagnosis…", n.d.).

Important Changes

The introduction of oligoclonal bands (OCBs) in the cerebral spinal fluid (CSF) to diagnose MS in a patient with evidence of DIS allows for the substitution of DIT. Symptomatic or asymptomatic gadolinium-enhancing lesions can be considered in determining DIS and DIT. Cortical lesions can be used in addition to juxtacortical ones to support DIS (Mantero, Abate, Balgera, La Mantia & Salmaggi, 2018).

Tools and procedures needed to diagnose MS

There is no unique or specific test for MS. The diagnosis of MS often depends on ruling out other conditions or disorders that may have similar symptoms. The doctor should start with a thorough medical history and examination (Mayo Clinic, n.d.).

1. Blood tests help rule out other conditions similar to MS, if the patient has had EBV and verify if the patient has low serum vitamin D levels that can worsen many immunological disorders. Biomarkers linked explicitly to MS are being developed to help significantly diagnose this immune disorder.
2. Lumbar puncture: Cerebral spinal fluid (CSF) can show the production of intrathecal antibodies that may be linked to MS, which are only present in the CNF.
3. MRI: An MRI can reveal brain and spinal cord lesions. On most occasions, intravenous gadolinium injection is required to give contracts and highlight any lesions that might be active.

4. Evoked potential tests (EPT): These record the electrical impulses generated by the nervous system in response to a stimulus. An EPT may be used for visual or electrical stimulation on the upper and lower extremities. For this, electrodes measure how fast the information travels through the nerves. While the MRI can show us the physiology of the brain and spinal cord, the EPTs can actually tell us more about the extent of the damage caused by MS.

Available Treatment for MS

So far, there is no cure for MS, mainly due to the "why?" of the disease. However, a treatment involves immunomodulatory therapy for underlying immune disorder and therapies to relieve or modifies symptoms. Most disease-modifying treatments for MS have been approved for use only in relapsing forms of MS, except for siponimod, ocrelizumab, and cladribine, which are approved for active secondary progressive disease (WebMD, n.d.). For RRMS and PPMS, new therapies based on monoclonal antibodies (MAbs) targeting B cells have demonstrated good efficacy in clinical trials. MAbs are thought to prevent B cells from mobilizing and entering the CNS by preventing chronic EBV infections (Houen et al., 2020). Without the negative effects of chemotherapy, MABs are among the most effective treatments for relapse MS. It is encouraging that new MABS are also being developed to assist in repairing the harm/disability that has already been done (Voge & Alvarez, 2019).

Treatment for acute relapses:

1. Methylprednisolone (Solu-Medrol) can fasten recovery from an acute exacerbation of MS.
2. Repository corticotropin (Acthar Gel) treats adults with acute relapses or flares of MS. Typically used when Solu-Medrol is no longer effective or tolerated.
3. Plasma exchange (Plasmapheresis) can be used in the short term for a severe attack if steroids are contraindicated or ineffective.

FDA approved:

1. Interferon (Avonex; Rebif)
2. Interferon β1b (Betaseron, Extavia)
3. Peginterferon β1a (Plegridy)
4. Glatiramer Acetate (Copaxone, the First to be available in its generic form)
5. Natalizumab (Tysabri, once a month IV)- Natalizumab was the first MAB approved by the FDA in 2004 for the treatment of MS.
6. Mitoxantrone (Novantrone, one of the oldest treatments. A chemotherapy)
7. Fingolimod (Gilenya, approved for children ten years and older. The first disease-modifying treatment for people younger than 20 years of age.)
8. Siponimod (Mayzent, is an improvement of Gilenya, with none of the required precautions before starting treatment. FDA approved 2019)
9. Teriflunomide (Aubagio)
10. Momomethyl fumarate (Bafiertam)
11. Dimethyl fumarate (Tecfidera)
12. Alemtuzumab (Lemtrada)
13. Ocrelizumab (Ocrevus, IV infusion every 6 months)- Targets the CD20 on circulating B-lymphocytes. The first anti-CD20 medication authorized for use in MS patients.

14. Cladribine (Mavenclad. FDA approved 2019)
15. Glatopa (First generic treatment approved by FDA. Produced by Sandoza, a Novartis division).
16. Rituximab (Rituxan, commonly prescribed off-label)- Is a chimeric MAB that binds to CD20 and lyses B cells via complement-dependent cytotoxicity (CDC) and ADCC.
17. Ofatumumab (Kesimpta, monthly subcutaneous injection)- It is an injection just under the skin, so it can target the B cells thought to play a role in relapsing MS (Novartis, n.d.).
18. Ubilituximab (Briumvi, IV infusion every 6 months)- The FDA recently approved ublituximab-xiiy for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults (AJMC, 2023).

Treatment for symptoms (Tobin, 2019):

(Symptoms and some treatment options)

1. Fatigue is the most common symptom associated with MS, with a prevalence of approximately 80% in any type of MS manifestation. Unlabeled treatments like amantadine, methylphenidate, and fluoxetine are used. Depression, medications, sleep disorders, and obesity may contribute to fatigue. A regular exercise plan and energy conservation measures may help.
2. Depression: Approximately 30% of prevalence is reported and is frequently associated with anxiety. All MS patients should be evaluated for depression and anxiety with adjacent screening tools. Treatment is also complex; medications such as SSRI or selective serotonin-norepinephrine reuptake inhibitors (SNRI) may help but should never be the only treatment. Psychological and psychiatric support is often needed. Cognitive-behavioral therapy and a regular exercise regimen are essential to a treatment plan.
3. Cognitive dysfunction: may affect 45% to 64% of patients. Prevalence is higher in progressive MS and may occur without brain MRI T2W lesions. Neuropsychological evaluation will help identify the factor affecting cognition. Regular social contact and physical activity may help select selected patients.
4. Spasticity is mainly associated with severe brainstem and spinal cord damage, often with painful leg spasms. Many muscle relaxants, such as baclofen and tizanidine, can be effective in most cases. Baclofen can be used as an intrathecal pump in severe spasticity.
5. Chronic Pain Syndrome: The estimated prevalence may vary between 30% to 90%. It may be central or peripheral, or combined. The etiology of pain should be identified and is fundamental for specific treatment. Spinal cord damage may produce a chronic central pain syndrome in which pregabalin and gabapentin may be effective in continuous use. Occasionally invasive treatment in nerve blocks or intrathecal devices and other forms may be effective in selected patients (Yada, et al., 2014). Oral cannabis extract and synthetic tetrahydrocannabinol may be

effective as a third-line option. It is crucial to keep in mind that the cannabis option is not FDA-approved, and exists concern regarding detrimental effects on cognition associated with chronic use.

6. Sexual dysfunction: May affect approximately up to 90% of patients. Erectile dysfunction, anorgasmia, reduced vaginal secretions, and libido reduction are expected. Structural damage to CNS may be associated with many MS patients, especially those severely impaired. It is essential to consider that fatigue, mood disorder, and anxiety may contribute to sexual dysfunction. Effective treatment of those conditions may help in some cases. Oral phosphodiesterase type 5 inhibitors and vaginal lubrication may help. Urological and gynecological evaluations are fundamental.
7. Optic neuritis: Intravenous methylprednisolone may speed recovery
8. Walking difficulties: Ampyra is the first and only brand drug indicated to help improve walking in adults with MS

Other symptoms related to MS are:

1. Pseudobulbar Affect: Inappropriate disproportionate and involuntary crying or laughing. Treated with dextromethorphan/quinidine tablets three times daily or tricyclic antidepressants, SSRI, or SNRI.
2. Paroxysmal symptoms: Trigeminal neuralgia, Lhetmitte's sign, and tonic spasms. Treated with antiepileptic medications such as carbamazepine or oxcarbazepine.
3. Temperature dysregulation: Most common in severely impaired patients. Treatment is limited to temperature control.
4. Bladder dysfunction: Urinary frequency, retention, or incontinence. It affects a significant quality of life. Urological evaluations are fundamental. Several treatment options are available.

Interaction of symptoms Affecting Activities of Daily Living and Quality of Life

Multiple symptoms may interact to worsen or complicate diagnosis and treatment. Fatigue, depression, anxiety, cognitive dysfunction, and sexual dysfunction may commonly coexist. Interaction in such a complicated way will cause a severe degree of impairment, physically and psychologically. Cognitive impairment, depression, and anxiety can be accurately evaluated through neuropsychological tests performed by a trained neuropsychologist. Often this information will help to treat in a more specific way and may reveal adjoined or hidden attention deficit disorder which may be responsive to adjacent therapy. Cognitive impairment in MS may affect speed processing and attentional domains, resulting in variable performance in an individual neuropsychiatric test over time. A single-point evaluation is insufficient; it is common to find significant variability in scores over time. Cognitive impairment is the most frequent reason to affect job performance and disability in young patients.

It has been seen that a diet low in sodium can minimize the risk of exacerbations. A recent study on the MS model proved that a fasting-mimicking diet (FMD) could reverse the symptoms and promote oligodendrocytes' regeneration (Choi et al., 2016). Dr. Choi also collected preliminary data from human subjects, which indicated that a controlled diet could modify the disease.

Conclusion

Multiple Sclerosis is a complex disease in the sense of systems complexity. It is an immunological dysfunction affecting immune regulation, causing a failure to recognize the self. Up to date, it is known that inadequate inflammation, causing damage to myelin and axons, including early in the disease, the brain cortex, is the leading cause of tissue damage. No treatment is fully effective in all individuals, nor effective through time in many others. In most cases, the selection of disease-modifying therapy is done in a trial and observe mode. Following effectivity and potentials adverse effects. Brain MRI, a magnetic and radiofrequency tool for imaging the brain and spinal cord, is essential in diagnosing and following up with patients. The same medications in a particular patient may induce clinical remission for decades, but others will fail multiple treatment options. Thus, multiple sclerosis patients should always be treated as an individual to have better efficacy and a chance of a normal life. MS inflammation may be minimally active in a subclinical intensity, but nevertheless, follow-up visits should be consistent. Holistic treatment emphasizing the human being suffering from MS is the gold standard. Interactions of symptoms should always be in mind to be effective in minimizing brain and spinal cord damage and improving quality of life. Remember, is not as simple as to treat MS; it is critical to realize that we should treat the human being that has Multiple Sclerosis.

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