LITHUANIAN UNIVERSITY OF HEALTH SCIENCES

Faculty of Medicine

Department of Neurology

Immunological and genetic factors and their effect on multiple sclerosis prognosis: Systematic review

MASTER'S THESIS

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1. SUMMARY

Author: Anastasia Semionov

Title: Immunological and genetic factors and their effect on multiple sclerosis prognosis.

Introduction: Multiple sclerosis is the most common disease of the CNS to cause permanent disability in young adults. Many causative factors were investigated during the last decade to determine prognosis of the disease, when genetic factors and immunological factors were the leading subjects to study as showed strong correlation to disease prognosis. In this study I am going to systematically review and discuss the most recent studies provided the information regarding various factors influencing MS outcomes, as well as their effect on treatment strategies of multiple sclerosis.

Research aim: To systematically review, compare and analyze the latest research work in order to determine correlation between immunological and genetic factors and their effect on multiple sclerosis prognosis.

Objectives:

1. Genetic factors (HLA gene region, microRNA) of multiple sclerosis and their effect on disease course and disability.
2. Immunological factors (IgG oligoclonal bands, intrathecal IgM oligoclonal bands, CD4+ and CD8+ T cells, interleukins) effect on multiple sclerosis and disease course and disability.
3. Immuno-genetics factors effect on treatment strategies and prognosis of multiple sclerosis.

Methodology: Systematic review that analyzed and compared research work and publication in the last 10 years in the English language. Using PubMed Medline research engine and including exclusion and inclusion criteria.

Results and conclusion: In this study analysis and comparison of articles from the last 10 years was done in order to present the latest development in the field of multiple sclerosis prognosis in relationship with immunological and genetic factors. The different subtypes of MS were presented first, and later the discussion of main known genetic factors as HLA genes and mic-RNA and their correlation on disease prognosis. Immunological factors were discussed as well with latest studies regarding their effect on possible disease progression. As last part were presented studies about new treatment strategies focusing on immune-genetic factors.

2. ACKNOWLEDGMENT

I would like to thank my supervisor.

I would like to dedicate this thesis to all my colleagues who are fighting COVID-19 worldwide.

3. SANTRAUKA

Autorius: Anastasia Semionov

Pavadinimas: Imunologiniai ir genetiniai veiksniai bei jų reikšmė išsėtinės sklerozės prognozei.

Įvadas:Išsėtinė sklerozė yra labiausiai paplitusi CNS liga, sukelianti nuolatinį jaunų suaugusiųjų negalią. Per pastarąjį dešimtmetį buvo ištirta daugybė priežastinių veiksnių, siekiant nustatyti ligos priežastis ir galimą jos prognozę, genetiniai ir imunologiniai veiksniai buvo kaip vieni pagrindinių galinčių įtakoti ligos išsivystimą ir galinčių turėti reikšmės ligos prognozei. Šiame tyrime sistemingai apžvelgsiu ir aptarsiu naujausius tyrimus, kuriuose buvo pateikta informacija apie imunologinius ir genetinius veiksnius, galinčius turėti reikšmės išsėtinei sklerozei, taip pat apie galimą jų poveikį išsėtinės sklerozės gydymui.

Tyrimo tikslas: Sistemingai peržiūrėti, palyginti ir analizuoti naujausius tyrimus, siekiant nustatyti sąsajas tarp imunologinių ir genetinių veiksnių ir jų reikšmę išsėtinės sklerozės prognozei.

Uždaviniai:

1. Išsėtinės sklerozės genetiniai veiksniai (HLA geno sritis, mikroRNR) ir jų poveikis ligos eigai ir negaliai.
2. Imunologiniai veiksniai (oligokloninės juostos, intratekalinės IgM, CD4 + ir CD8 + T ląstelės, interleukinai) reikšmė išsėtinės sklerozės ir ligos eigai bei negaliai.
3. Imunogenetinių veiksnių galima reikšmė išsėtinės sklerozės gydymo taktikai ir prognozei.

Metodika: sisteminė apžvalga, kurioje buvo analizuojami ir palyginami moksliniai tyrimai ir publikacijos per pastaruosius 10 metų anglų kalba, kurie buvo rasti naudojant „PubMed Medline“, įtraukiant straipsnius, kurie atitiko įtraukimo kriterijus.

Rezultatai ir išvada: Atliekant šį tyrimą buvo analizuojami ir palyginami pastarųjų 10 metų straipsniai, siekiant pateikti naujausius išsėtinės sklerozės prognozės pokyčius atsižvelgiant į imunologinius ir genetinius veiksnius. Pirmiausia buvo pristatyti skirtingi IS potipiai, vėliau aptarti pagrindiniai žinomi genetiniai veiksniai, kaip HLA genai ir mikrRNR, bei jų ryšys su ligos prognoze. Imunologiniai veiksniai taip pat buvo aptarti remiantis naujausiais tyrimais apie galimč jų reikšmę ligos prognozei ir gydymui. Paskutinėje dalyje buvo pristatyti tyrimai apie naujas gydymo strategijas, daugiausia dėmesio skiriant imunogenetiniams veiksniams.

4. CONFLICT OF INTEREST

I declare that there is no conflict of interest.

5. CLEARANCE ISSUED BY THE ETHICS COMMITTEE

No clearance issued by the Ethics Committee is needed in this study.

6. ABBREVIATIONS

- Ag-antigen
- AID -autoimmune disease
- ANOVA-One-way analysis of variance
- APC- antigen presenting cell
- BBB-blood brain barrier
- BCR- B cell receptor
- BDNF-brain-derived neurotrophic factor
- CCL2-C-C motif chemokine ligand 2
- CDMS-clinically definitive multiple sclerosis
- CHI3L1-chitinase-3-like protein 1
- CI-Confidence interval
- CIS-clinically isolated syndrome
- CLR-C-type lectin receptors
- CNS-central nervous system
- CSF-cerebrospinal fluid
- DAMP- danger associated molecular pattern
- DC-dendritic cell
- DMTs- disease-modifying therapies
- EAE-experimental autoimmune encephalomyelitis
- ECM-extra cellular matrix
- EDSS -expanded disability status scale.
- ER-endoplasmic reticulum
- FMC- fast migrating cerebroside
- FO-follicular
- Foxp3-forkhead box protein
- GalCer- galactosylcermide
- GL-glycolipid;
- HI- healthy individual
- IFN-β-interferon β
- IFN-γ-interferon γ
- Ig-immunoglobulin
- IL-interleukin

- iNKT cells-invariant natural killer T cells
- iTregs-induced regulatory T cells
- mAb- monoclonal antibody
- MAIT- mucosal-associated invariant T cells
- MHC-major histocompatibility complex
- MMP- matrix metalloproteinase
- MOG-myelin oligodendrocyte glycoprotein
- MS-multiple sclerosis
- MSSS- multiple sclerosis severity score
- MZ- marginal zone
- NCAM-neural cell adhesion molecule;
- NG2- neural/glial antigen 2
- NGF- nerve growth factor
- NKT-natural killer cells
- NLR- NOD-like receptors
- NMO- neuromyelitis optica
- NO-nitric oxide
- nTregs - natural regulatory T cells
- OPC-oligodendrocyte precursor
- PA-GC- polyacetylated β-GalCer
- PAMP-pathogen-associated molecular pattern
- PB- peripheral blood
- PBMCs – peripheral blood mononuclear cells
- PL-phospholipid
- POMS-pediatric onset multiple sclerosis
- PRR- pattern recognition receptor
- qPCR- quantitative polymerase chain reaction
- RLR- RIG-I-like receptor
- ROS- reactive oxygen species
- SL-sphingolipid
- SNP- single nucleotide polymorphisms
- RRMS-relapsing-remitting MS
- SPMS -secondary progressive MS
- TCR- T cell receptor

- TF – transcription factor
- TGF-β- transforming growth factor β
- Th- T helper
- TLR- Toll-like receptor
- TNF-α, tumor necrosis factor α
- Tregs- regulatory T cells
- tPA -tissue plasminogen activator
- VCAM-1- vascular-cell

7. TERMS

Clinically Isolated Syndrome (CIS): Prior to a diagnosis of MS, CIS is a solitary attack (or the event of one or few symptoms characteristic of MS), with a increasing risk of developing MS, when no other diseases or causes for symptoms are evident.

Demyelination: a damaging process in which the myelin that shields nerve fibers is taken off by a disease.

Expanded Disability Status Scale: 10-point scale (from 1 to 10 with half points) estimate degrees of disability, mainly in terms of mobility. Points 1 to 3 on the scale are primarily used to estimate function; points 4 to 9 measure mobility. Half points are used for higher clarity.

McDonald Criteria: diagnostic criteria for MS. The criteria includes combination of paraclinical tests, imaging, and clinical signs and symptoms.

Progression of MS: In numerous patients with MS the course is progressive, so that patients steadily exacerbate over months or years.

Primary progressive MS: a form of MS in which individuals don't experience periodically attacks, but rather have a gradually worsening disease over time.

Relapsing-remitting MS: refers to a form of the MS where patients undergo relapses of symptoms and indications (exacerbations), with absolute or incomplete improvement between attacks (remitting).

Remission: Reduction and stability in worsening of MS patients, or a complete reduction of symptoms.

Secondary progressive MS: a form of MS in which patients may resume to experience attacks, but as well manifest a gradually progressive worsening of their function over time. The progression of disease is separate from periodical attacks.

8. INTRODUCTION

Multiple sclerosis is a chronic autoimmune disorder of the central nervous system. The disease was originally reported in 1868 by Jean-Martin Charcot. MS refers to several scars known as “plaques” or “lesions” that occur in the white matter of the brain and spinal cord. MS is one of the most common neurological diseases in the world, affecting an estimated 2.3 million people worldwide (1). MS most commonly presents between the age of 20 and 50 years and is twice more frequent in women than men (2). Moreover, Multiple Sclerosis is the most common disease of the CNS to cause life long disability in young adults. When discussing pathogenesis, single causative event is unlikely to cause MS; instead, the disease seems to develop in genetically susceptible populations as a result of environmental exposures (3,4).

MS takes different clinical courses in patients The most common type is the relapsing–remitting course (progressive-relapsing MS) in which flare-ups of neurological disabilities occur periodically, accompanied by a complete or partial recovery. In some of the patients, neurological disabilities accumulate without proper recovery, that is when, MS takes a secondary progressive course (SPMS). In other individuals, the progressive form is taken from the start of clinically manifested MS, and this course is described as primary progressive MS (PPMS). Another form is a progressive course of MS that is integrated with sporadic relapses, that is, PRMS (5). Disease progression is characterized by plaque formation in the white matter, axonal injury, and demyelination, mostly in the spinal cord, optic nerve, brainstem, and periventricular regions. Chronic diseases such as MS can also cause massive emotional stress, which can lead to secondary symptoms such as fatigue and depression (2,6). Approximately 80% of patients undergo an initial clinical episode of demyelination, is a condition known as CIS (clinically isolated syndrome). Pathogenesis involves infiltration of inflammatory cells. Approximately 85%–90% of MS patients will present with initial CIS attacks with relapsing–remitting disease: acute inflammatory demyelinating reactions, also known as “flares” or “exacerbations”, followed by partial or complete recovery (2).

Regarding prognostic factors, it is generally assumed that the onset of a progressive course carries a poor prognosis. MS prognostic factors are complicated to prognose because disability accumulates slowly over decades and there is a lack of good factors of disability progression. Disease activity (rate of relapses and new MRI lesions) is thought to reflect inflammatory processes, whereas disease progression worsening of disability and brain and cord atrophy, can better correlate neuronal injury (7).

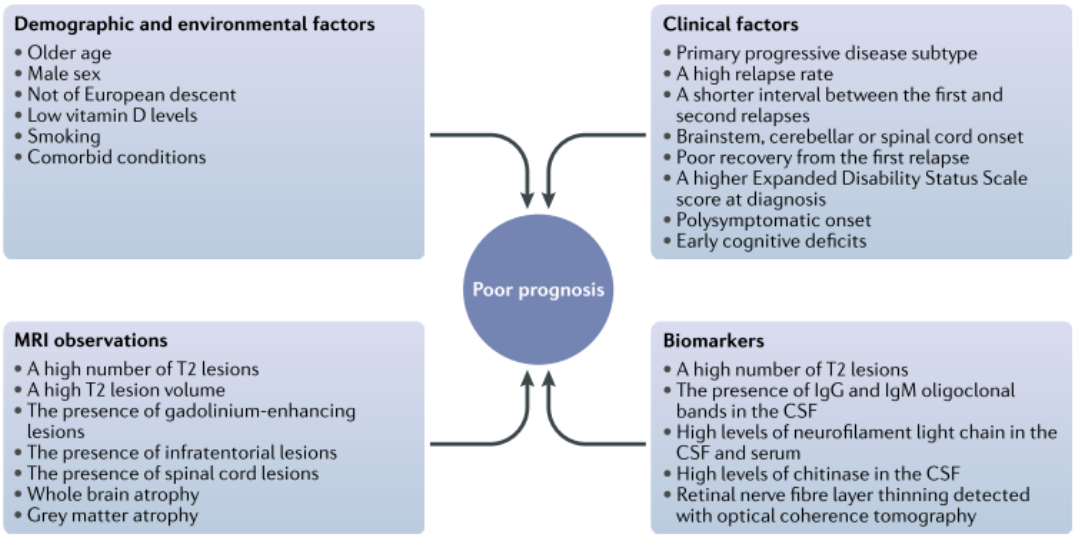

Figure 1 (8) presents overall poor prognostic factors.

(Taken from Rotstein D, Montalban X. Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis. Nat Rev Neurol 2019;15(5):287–300).

To assess MS progression and disability combined two methods of assessment. Progression on the Expanded Disability Status Scale (EDSS), is the most universally used measure of MS-related disability. The Multiple Sclerosis Severity Score (MSSS), combining the EDSS and disease duration, emerged over a decade ago as a way of distinguish MS patients based on their rate of progression (9,10).

The aim of this study is to systematically review the latest work done in the field of MS prognosis factors and its effect on the disease progression. I will present the latest studied done regarding genetic and immunological factors that might predict prognosis as well as relation to treatment strategies effected by immuno-genetics factors.

9. AIM AND OBJECTIVES OF THE THESIS

Research aim: To systematically review, compare and analyze the latest research work in order to determine correlation between immunological and genetic factors and their effect on multiple sclerosis prognosis.

Objectives:

1. Genetic factors (HLA gene region, microRNA) of multiple sclerosis and their effect on disease course and disability.
2. Immunological factors (IgG oligoclonal bands, intrathecal IgM oligoclonal bands, CD4+ and CD8+ T cells, interleukins) effect on multiple sclerosis and disease course and disability.
3. Immuno-genetics factors effect on treatment strategies and prognosis of multiple sclerosis.

10. RESEARCH METHODOLOGY AND METHODS

Data collection and search strategy:

In this systematic review PRISMA 2009 statement and check list were used as the main resource for research methodology. The main search engine was MEDLINE PubMed that yielded about 7116 research works. Randomized clinical trials, retrospective studies, systematic and literature reviews were used. Inclusion and exclusion criteria navigated which works should or shouldn't be used.

Information source:

- PubMed online research engine
- MEDLINE

Inclusion criteria:

Terms used: Multiple sclerosis, prognosis, relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis, secondary progressive multiple sclerosis, disability, oligoclonal bands, IgM, genome-wide association study , HLA gene, AHI gene ,interleukins, IL-6, IL-10, IL-17, CD4 T cells, CD8+ cells, microRNA, interferon gamma, interferon beta, immunogenicity, clinically isolated syndrome, biomarker, relapse, prognostic factors ,EDSS, MSSS, pharmacogenetics.

Sentences used:

- Immunological factors of multiple sclerosis
- Genetic factors of multiple sclerosis
- Factors effect multiple sclerosis prognosis
- Genetic factors and multiple sclerosis severity
- Genetic effect on multiple sclerosis prognosis

Exclusion criteria:

- Research work that wasn't published in the last 10 years
- Works written not in the English language
- Less than 80 research patients in a clinical trial
- Not relevant title or abstract
- Bias and low statistical power

Data collection process:

The initial search in PubMed yielded 7116 results, which were reduced to 300 after using filters such as published in the last ten years and only English language. Using the best match function in PubMed helped review the title and abstract of each work and select the most appropriate once which were 150 overall.

After full review of the text 40 research works were included into this systematic review.

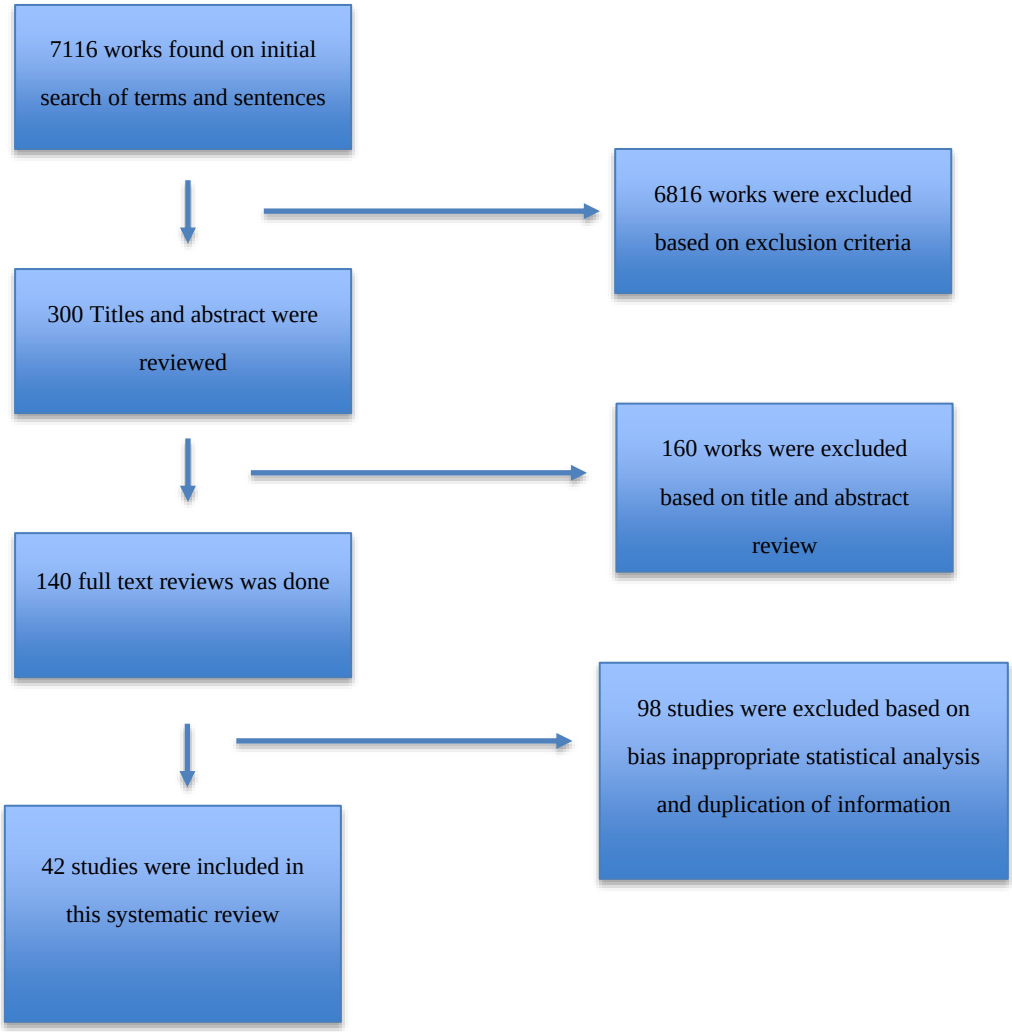

Figure 2. Inclusion and exclusion flow chart that describes the data collection process.

11. RESULTS

11. Genetic factors as HLA gene region and microRNA and of multiple sclerosis and their effect on disease severity.

11.1.1 Genetic factors as HLA gene region

MS is a multifactorial autoimmune disease with prominent genetic and non-genetic risk components. More then 100 loci have been strongly associated with susceptibility, when the leading signal genome-wide maps to the class II region of the human leukocyte antigen (HLA) gene cluster and explains up to 10.5% of the genetic variance underlying risk when HLA- DRB1*15:01 has the strongest effect (4,11). The primary genetic risk factor is the HLA-DRB1*15:01 allele of the HLA DR beta 1 gene, which resides within the major histocompatibility complex (12). More recent studies have showed that the genetic risk for MS is affected mostly by a series of class II risk alleles, while protective signals are mostly driven by class I alleles. Some of the class II risk alleles, the partially dominant HLA-DRB1*15:01 allele has been demonstrated to have the strongest association with MS, especially in Caucasian populations HLA class I alleles have been linked with either reduced (HLA-A*02:01, HLA-B*44:02) or increased (HLA-A*03, HLA-B*07) susceptibility to MS and the HLA- A*02:01 has been shown to drive the protective signal (3,13).

Important study was performed in Lithuanian, aiming to estimate the the impact of HLA-DRB1 alleles on the genetic susceptibility to multiple sclerosis in the Lithuanian population and results showed that HLA-DRB1*15 was present in 55.8% of the patients with MS and 10.0% of the controls. The protective alleles that were detected to be more prevalent of the control group when compered with the patients with multiple sclerosis were HLA- DRB1*01. HLA-DRB1*15 was more common among the female patients with multiple sclerosis than among the male patients. This study conclude that HLA-DRB1*15 was found to be correlated with MS in the Lithuanian population. Another finding was that HLA-DRB1*15 allele was more prevalent among the female patients with multiple sclerosis (14).

To understand the main and most important difference in prognosis we have to differentiate between 2 main types of MS. Most of the patients exhibit the relapsing-remitting (RR) form of disease, where acute attacks of neurological deterioration due to CNS inflammation and demyelination are followed by partial or total recovery of functions and remission. A minority of the patients experience progressive deterioration of disability due to demyelination and neuro-degeneration with infrequent neuro-radiological evidence of immune cell infiltration into the CNS, and are referred to as primary progressive MS patients (15).

Differences in clinical features and pathogenesis of PPMS and RRMS may be somewhat partially explained by the differences in their genetic background. Genome-wide association studies (GWAS) performed on more than 100,000 subjects showed 233 polymorphic variants corresponded with RRMS when compared with HI (healthy individual). To explore for genetic differences between two MS courses the comparison "PPMS vs RRMS" was performed. HLA-DRB1*09 allele was found to be significantly associated with high risk of PPMS. The associations of protective allele HLA- DRB1*07 and risk allele HLA-DRB1*04 with PPMS were just nominally significant (16).

Another aspect is showed in important study investigated pediatric onset of MS (POMS). This study comprehensively studied the genetic component in MS cases for whom first clinical disease symptoms expressed before age 18. HLA–DRB1*15 was associated with an effect estimate similar to previous smaller studies of this age group. Additional MHC variants have been showed in previous studies of adult MS patients, including a protective effect for HLA–A*02. Through fine mapping of the MHC region in the current study, they observed only modest evidence for HLA–A*02 effect in POMS. HLA–DRB1*15:01 was strongly associated with POMS (17). Moreover, 28 of 104 non–MHC variants studied (23%) were associated ($p<0.05$). Whether HLA–DRB1*15:01 is associated with earlier age of symptom onset in adult MS has been the subject of several investigations. Strong evidence supports the hypothesis that HLA– DRB1*15:01 is highly associated with an earlier onset in adults and pediatric population (18).

11.1.2 Genetic factors as microRNA

MicroRNAs are small non-coding RNA molecules that regulate gene expression at the post-transcriptional level, accompanied by mRNA degradation or translational repression. In general, miRNAs change, through a complex regulatory network, the expression of more than 60% of human genes. MiRNAs are main regulators of the immune response that influence maturation, proliferation, differentiation, and activation of immune cells, as well as antibody production and secretion of inflammatory mediators. Interruption of this regulation can lead to the development of various pathological conditions, including autoimmune inflammation (19).

Most MS-related miRNA studies are focused on miRNA expressions in blood mononuclear cells and various populations of T (CD4+ and CD8+) and B cells. In a study performed in Finland 2017 was performed a comprehensive study of circulating miRNAs in progressive forms of MS and found that their aberrant expressions were associated mostly with PPMS subtype, suggesting their involvement in immunopathogenesis of PPMS. Moreover, results from the correlation analyses among the validated miRNAs further support the important role of these miRNAs in PPMS, since the correlations were most prominent in the PPMS subtype (20).

Demyelination and failure of remyelination are the main mechanisms in the pathogenesis of multiple sclerosis (MS); the factors modulating these processes are still mostly unknown. A study performed in Italy 2015 was investigating MicroRNA 572 as deregulated in MS and is hypothesized to targets neural cell adhesion molecule, a glycoprotein taking part in CNS repair mechanisms. MiR-572 expression was reduced overall in MS patients compared to HI; this miRNA was significantly upregulated in SPMS and in RRMS throughout disease relapse, while it was downregulated in PPMS and in remitting phases of RRMS.

The results yield that this miRNA can be a tool that helps differentiate between PPMS and SPMS and between relapsing and remitting phases in RRMS. This suggestion was due to results showed that the lowest serum concentration of this miRNA was discovered in PPMS and in RRMS patients during the remitting phase of disease. Conversely, serum concentration of miR- 572 was significantly increased in SPMS compared to PPMS patients, and in RRMS patients during a disease relapse compared to those RRMS patients evaluated in a course of remission. Therefore, when comparing between groups results showed that serum levels of miR-572 were significantly different when the primary and secondary forms of progressive MS were compared, with significant increase in SPMS and significant decrease in PPMS. Similarly, in RRMS patients a significant increase of serum concentrations of miR-572 was detected in relapsing compared to remitting patients (21).

Another finding was done in a study in Russia 2015, showed correlation between microRNA genes and severity of MS. Study consisted of 464 patients who suffered from RRMS and 97 from SPMS, the control group consisted of 441 volunteers with no symptoms of neurological disorders. The study concluded that SNPs in miR-223 and mi-R146A are involved in MS susceptibility, whereas SNPs in mi-R499A and mi-R196A2 are involved in the MS course. But the most interesting and significant associations of miRNA genes variants were gender-specific, were identified in females, but not in males. Additionally to MIR223 by itself, the study discovered an association of biallelic combination (MIR223*T + MIR146A*G/G) with MS susceptibility in females. Especially, for the most significant association of miR499A*C/T + miR196A2*C) with MS severity in women. At the same time, no notable results were seen in men. This gender-dependent effects of polymorphisms of miRNA genes on disease susceptibility and clinical symptoms might be explained by differences in endocrine profiles between males and females (22).

11.2 Immunological factors as IgG oligoclonal bands, intrathecal IgM oligoclonal bands, CD4+ and CD8+ T cells, interleukins and their effect on multiple sclerosis and disease course and disability.

11.2.1 Immunological factors as IgG oligoclonal bands.

Part of the diagnostic criteria of multiple sclerosis is the presence of immunoglobulin G oligoclonal bands or a total increase of IgG immunoglobulin in the cerebrospinal fluid. OCB-negative patients were shown in multiple studies over the years to have a positive prognosis which is explained by the fact that these bands are correlates with increased intrathecal synthesis of antibodies of the IgG subclass produced by specific B-cell clones, which indicates inflammatory response within the central nervous system and consequently can indicate prognosis of ongoing disease. Moreover in study made in 2010 in UK was found significant difference in HLA-DRB1*04 and HLA-DRB1*15 carriage between OCB-negative and OCB-positive patients could be detected, with a significantly larger proportion of the OCB-negative patients carrying HLA-DRB1*04 and carriage of HLA-DRB1*15 being significantly more frequent among OCB-positive patients (23).

An important study was published by Oxford University in 2015 which studied the prognostic factors of MS in terms of disability, oligoclonal bans as one of them as compared to brain MRI. The IgG oligoclonal bands were taken within the first 3 months of disease onset. The presence of oligoclonal bands in CSF samples and a high number of brain T2 lesions were confirmed as prognostic risk factors for conversion to CDMS. CDMS was established when there was a second attack showing a new neurological abnormality that was confirmed via examination. Disability was evaluated according to the EDSS scale at each visit. 1051 patients were participate in the prospective cohort study which was conducted from January 1995 to February 2013. 686 (67.6%) were female and 329 (32.4%) were male. Of the total cohort, 792 (78.6%) underwent a CSF tap, among whom 453 (57.2%) exhibited positive oligoclonal bands. The brain MRI was analyzed in 951 (94%) of the patients. The presence of oligoclonal bands and, the appearance of 10 or more T2 lesions, strongly correlated with a great risk of conversion to CDMS.

As conclusion results categorized as follows: when compare the risk factors for developing further attacks and disability accumulation in CIS patients, the presence of oligoclonal bands is a medium- impact prognostic factor and brain MRI is a high-impact prognostic factor (24).

11.2.2 Immunological factors as intrathecal IgM oligoclonal bands.

It is very well established that both T and B cells are involved in MS pathogenesis. The significance of B cells explained by their presence in acute and chronic MS plaques, yet they are not directly involved in antibodies production rather then in antigen presenting antigen and cytokine secretion (25). They were found in meningeal follicles of secondary progressive patients, as well as in meningeal inflammation with T cells and plasma cells. In addition, there is evidence of the role of B cells in the presence of oligoclonal bands in the cerebrospinal fluid of the majority of MS patients , especially the IgG1 and IgG3 subclasses. These antibodies are directed against unknown antigens and do not recognize the major myelin proteins. A prognostic role of B cells in CSF has been shown, with an increased ratio of B cells to monocytes assessed by flow cytometry, correlated with a faster disease progression (26).

In the past few years, new studies were enrolled about the significance the IgM isotype in CSF. Moreover, not only the detection of IgG but as well as IgM OB at the time of diagnosis has been correlated to a worse prognosis (27). These are present in around 40% of MS patients not as a temporary phenomenon but as a constant presence when they recognize myelin lipids. Anti-lipid reactivity was confirmed in about 70% of IgM positive patients, and these antibodies correlate with the intrathecal synthesis of C3 and myelin basic protein concentration in CSF, supporting the role of IgM in demyelination and progression of the disease (28).

11.2.3 Immunological factors as CD4+ and CD8+ T cells.

The underlying pathogenesis is still somewhat unclear, but T lymphocytes, both CD4+ and CD8+ T cells, known to play a major roles in MS pathogenesis. The IL-17-producing T cells (CD4+or CD8+) have been present in both acute and chronic MS. At the presymptomatic stages of the disease, the autoreactive Th17 cells were detected in the peripheral blood mononuclear cells but not in the CNS. In addition, the count of Th17 cells was significantly increased in the cerebrospinal fluid of RRMS patients during relapse, when compared with same patients during remission or in patients with other noninflammatory neurological diseases. The detected count of IL- 17 correspond to the amount of active plaques as seen on magnetic resonance imaging studies and the severity of MS (29,30).

Pathogenesis mechanism explained by auto-reactive CD4+ T helper cells. On top of antigenic activation, naive CD4+ T cells activate, expand and differentiate into T cells that characterized by the production of different cytokines. The activation of myelin-specific T cells followed by dysregulation of Th1, Th2 and Th17 cytokines is consider to be a substantial event for MS initiation. CD4+ pro-inflammatory Th1 cells secrete mediators triggers a self-directed inflammatory attack which result in

myelin degeneration (31). Another study made in Norway 2019 (32) investigated the proteomic profiles of CD4+ and CD8+ T cells in RRMS patient compared to healthy individuals. In order to understand the T cell dysregulation at the protein level using electrospray liquid chromatography tandem mass spectrometry, they purified CD4 and CD8 cells and compared their proteomic profiles. The results showed dysregulation at the protein level in T cells from RRMS patients at an early stage of disease. To conclude, it has been progress understanding the importance of both types of the immune system and correlate them to different stages of the disease and its progression (Figure 3).

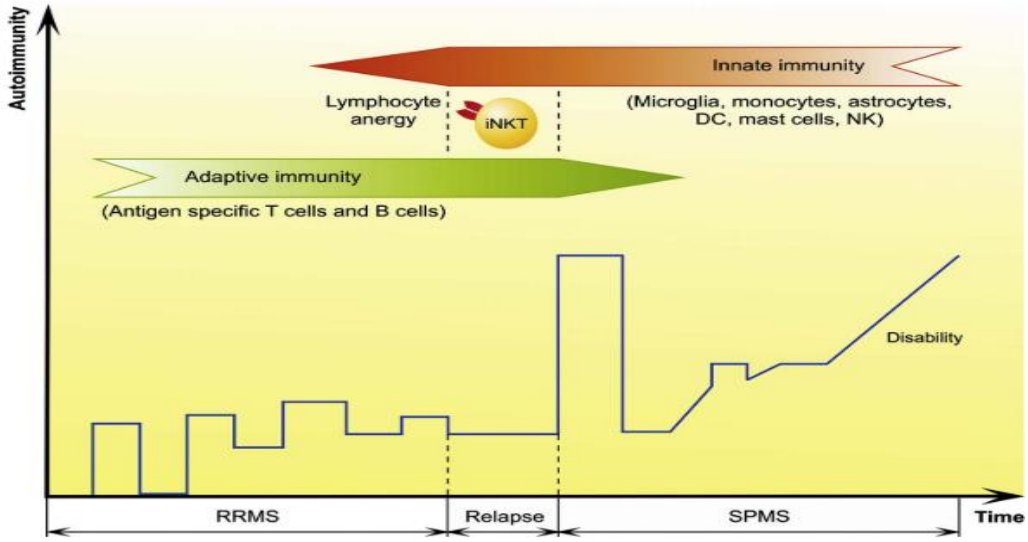

Figure 3 (31)- Difference of adaptive immune system which drives acute inflammatory events, when innate immunity drives progressive phase of MS.

(Taken from Podbielska M, O'Keeffe J, Hogan EL. Autoimmunity in multiple sclerosis: role of sphingolipids, invariant NKT cells and other immune elements in control of inflammation and neurodegeneration. J Neurol Sci. 2018;385:198–214).

11.2.3 Immunological factors as Interleukins.

In MS, T cells and antigen-presenting cells have a major role in the inflammatory process. As antigen-presenting cells provide T cells with their linked antigen and create a specific cytokine, T cells use cytokines to sustain their function and control immune responses of various cell types. This process eventually leads to specific cytokine associated with specific T cell subsets that destroy blood–brain barrier integrity, resulting in inflammation, demyelination, and neuronal damage. Table 1 demonstrates different interleukins and their contributing to the pathogenesis of multiple sclerosis (33,34).

Table 1 (33).

Interleukins	**Main producers**	**Levels in MS**
IL-2	Th 1	Increased
IL-6	Macrophages, microglia	Increased
IL-9	Th 9	Not reported
IL-10	Th 17, DC	Reduced
IL-12	DC, macrophages	Elevated in lesions, CSF
IL-17	Th 17	Increased
IL-21	Th 17, Th2, NKT	Increased or unchanged
IL-22	Th 17, Th 22	Increased
IL-23	DC, macrophages	Increased

Abbreviations: IL-interleukin, Th- T Helper cells, DC- dendritic cells, NKT- natural killer cells, CSF-cerebrospinal fluid.

IL-10 is a strong anti-inflammatory cytokine that leads to decrease secretion of TNF, IL-1β, IL-6, IL-8, IL-12, and IL-23, as well as lowers proliferation of TH1 and TH2 cells, minimize antigen presentation of monocytes and macrophages. Another important feature is the ability to act in a neuroprotective manner (33).

In a study made in China 2019, analyzed IL-10 serum levels during different stages of disease in order to determine if IL-10 has independent predictive ability in CIS. The results showed that serum IL-10 levels were remarkably decreased in CIS patients who relapsed when compared to patients who don't. Decreased serum IL-10 levels were corresponded with greater risk and shorter times to second events. In clinical association, a markedly increased CSF white blood cells count, number of T2 lesions, and gadolinium-enhancing lesions in baseline MRI were detected in the low serum IL-10 level group (35).

Interleukin-6, a powerful mediator of the acute phase response, is produced by T and B cells, macrophages, microglia, and also non-immune cells such as endothelial cells or neuron cells (33,36). Genome-wide association studies (37) have determined large numbers of MS-risk alleles in the IL-23/STAT3, IL-6/STAT3 and IL-12/STAT4 pathways involved in the differentiation of Th1 and Th17 cells which contributed to disease progression. Another late study analyzed correlation between levels of CSF inflammatory molecules as IL-6 and IL-8 at the time of diagnosis and both demographic and clinical characteristics of a large sample of 205 RRMS patients during a median follow-up of 3 years, as well as the prognostic characteristics of cytokine levels on their prospective disease course. Results showed that late diagnosis establishment and treatment initiation are correlated with increased CSF

levels of IL-6 and IL-8 in RR-MS, leads to worsening disease course and poor response to treatments (38).

IL-17 can be produced from both CD4+ T (Th17) cells and CD8+T cells. The clinical correlation between IL-17/Th17 and MS has been well documented and IL-17 has a major role in the development of experimental autoimmune encephalomyelitis. Moreover, it has been established that Th17 cells are markedly increased in the CSF and peripheral blood of patients with relapsing–remitting MS during relapse. In a another study (39), was evaluated the proportions of serum levels of IL-17 -secreted in the peripheral blood other cytokines in patients with either NMO or MS during relapse. Results showed significant increased levels of Tc17 cells in peripheral blood of MS patients as well as IL-17 as compared to healthy controls, in addition Tc17 cells were detected in active areas of acute and in chronic MS lesions together with IL- 17-producing CD4+ T cells, suggesting a contribution of to MS pathogenesis and severity (40).

11.3 Immuno-genetics factors effect on treatment strategies and prognosis of multiple sclerosis.

The clinical symptomatic variety of MS and the expanding selection of disease- modifying therapies for RRMS combine to make MS a leading example of importance for a personalized approach to medical therapy. Personalized medicine is defined as a strategy to treatment that accounts for an individual's characteristics, environment and disease features and biomolecular traits. Thus personalization of MS therapy require three main components: prediction of prognosis soon after diagnosis, an initial treatment decision based on risk–benefit trade-offs and patient preferences, and estimation of early treatment response. Prognostication is the foundation of personalized treatment and allows patients to be grouped on the basis of their demographic and environmental characteristics, clinical features, MRI measures and biomarkers (8). In the past few years more and more studies started investigate and moving towards treatments that limit or even stop the worsening of disability in patients with progressive disease (25). Some of the clinical studies in MS intended to predict prognosis, but subsequent large, prospective longitudinal cohort studies have integrated multivariate analyses and are likely to be more accurate. So far, DMTs that are effective in RRMS have been found not effective for PPMS and secondary progressive MS.

The genes that codify HLA cell proteins are extremely polymorphic and variable, with a few specific types associated with MS. Until now, no relationship was found between the HLA type and response to DMTs and the reason might be because of the alterations in the immunogenetic profiles of the populations studied and the different methods used in the HLA typing.

A recent study was aimed to examine the potential correlation between the human leukocyte antigen types-class I and II and the feedback to several disease-modifying therapies in patients with multiple sclerosis.They have inspected 87 patients with a diagnosis of relapsing-remitting MS based on the 2010 and 2013 revisions to the McDonald criteria. Data was taken at the beginning and end of each type of treatment, as well as the disease duration and EDSS score, which used for calculation of the Multiple Sclerosis Severity Score (MSSS) and correlation with the DMT used. DNA of the HLA system was analyzed with a high-resolution technique. Of the 87 patients studied, 79 were tested for HLA-DRB1, 79 for HLA-DPB1, 77 for HLA-DQB1, 54 for HLA-A, 58 for HLA-B and 78 for HLA-C. Since the analysis comprised 158 alleles of HLA-DRB1, 158 of HLA- DPB1, 154 of HLA-DQB1, 108 of HLA-A, 116 of HLA-B and 156 of HLA-C. Twelve different DMTs were used, and majority patients were treated with more than one DMT.

Results showed statistically significant decrease in the MSSS, suggesting improvement of the disability for the following alleles: HLA-DRB1*15:01 (7/7), DPB1*04:01 (13/16), DQB1*02:01 (5/5) and DQB1*03:01 (8/8) managed with Corticosteroids; HLA-DRB1*03:01 (5/5); HLA-DPB1*04:01 (6/7), DQB1*03:02 (7/7) and DQB1*06:02 (7/7), HLA- C*07:02 (5/5) treated with Azathioprine; HLA-DRB1*11:04 (6/6), DQB1*03:01 (5/5) and DQB1*03:02 (5/5) treated with Interferon β-1a 22 mcg; HLA-DPB1*02:01 (5/5); HLA- C*05:01 (5/5) treated with Interferon β-1a 30 mcg; HLA- DQB1*02:01 (5/6) treated with Interferon β-1b. For the other alleles, there was no statistically significant relationship.

Majority of the patients had a reduction in the MSSS regardless the type of HLA or DMT, presenting a beneficial effect of the therapy, but only few reached a statistically significant level (41). Another recent study analyzed the effect of first-line Interferon beta and second-line Natalizumab therapies on seven CSF biomarkers in RRMS and their relationship with clinical and radiological outcomes. The results showed that CSF biomarkers associated with different pathological processes taking part in MS effect both disease activity and DMT efficacy. Increased levels of these CSF biomarkers were observed in patients treated with Interferon beta compared to those treated with Natalizumab, propose that the efficacy of therapeutic intervention can be monitored by these biomarkers (42).

12. DISSCUSION

12.1 Genetic aspect:

In this study, I have found that more then 100 loci have been strongly associated with susceptibility, when the leading signal genome-wide maps to the class II region of the human leukocyte antigen (HLA) gene cluster. HLA- DRB1*15:01 has the strongest effect, earlier age of symptom onset, highly associated with an earlier onset in adults and pediatric population. HLA-DRB1*09 allele was found to be significantly associated with high risk of PPMS. Potective signals are mostly driven by class I alleles, another important gene with protective effect is HLA–A*02. HLA-DRB1*15 was found to be associated with multiple sclerosis in the Lithuanian population. HLA-DRB1*15 allele was more prevalent among the female patients with multiple sclerosis.

Circulating miRNAs in were found in progressive forms of MS that their aberrant expressions were associated mostly with PPMS subtype, suggesting their involvement in immunopathogenesis of PPMS. There is a significant correlation between microRNA genes and severity of multiple sclerosis. MiR-572 was significantly upregulated in SPMS and in RRMS throughout disease relapse, while it was downregulated in PPMS and in remitting phases of RRMS. MiR-572 possibly can be a tool that helps differentiate between PPMS and SPMS and between relapsing and remitting phases in RRMS.

12.2 Immunological aspect:

Regarding immunological factors mainly OCB-negative patients were shown in multiple studies over the years to have a positive prognosis which is explained by the fact that these bands are correlates with increased intrathecal synthesis of antibodies of the IgG subclass produced by specific B-cell clones**.** Significant difference in HLA-DRB1*04 and HLA-DRB1*15 carriage between OCB-negative and OCB-positive patients could be detected, with a significantly larger proportion of the OCB-negative patients carrying HLA-DRB1*04 and carriage of HLA-DRB1*15 being significantly more frequent among OCB-positive patients. When compare the risk factors for developing further attacks and disability accumulation in CIS patients, the detection of oligoclonal bands is a medium- impact prognostic factor and brain MRI is a high-impact prognostic factor.

The presence of of IgM OB at the time of diagnosis has been related to a worse outcome. Anti-lipid reactivity was confirmed in about 70% of IgM positive patients, and these antibodies correlate with the intrathecal synthesis of C3 and myelin basic protein concentration in CSF, supporting the role of IgM in demyelination and progression of the disease**.**

Low serum IL-10 levels were corresponded with greater risk and shorter times to second events and disease progression. MS-risk alleles in the IL-23/STAT3, IL-6/STAT3 and IL-12/STAT4 pathways involved in the differentiation of Th1 and Th17 cells which contributed to disease progression**.** Late diagnosis and treatment initiation are corelated with increased CSF levels of IL-8 and IL-6 in RRMS, leading to worsening disease progression and poor response to treatments. Tc17 cells were found in active areas of acute and in chronic MS lesions together with IL- 17-producing CD4+ T cells, suggesting a contribution of to MS pathogenesis and severity.

12.3 Therapeutic aspect:

Personalized medicine is defined as a strategy to treatment that accounts for an individual's characteristics, environment and disease features and biomolecular traits. Majority of the patients had a reduction in the MSSS regardless the type of HLA or DMT, presenting a beneficial effect of the therapy. CSF biomarkers associated with different pathological processes involved in MS effect both disease activity and DMT efficacy. Increased levels of these CSF biomarkers were observed in patients treated with interferon beta compared to those treated with Natalizumab, propose that the efficacy of therapeutic intervention can be monitored by these biomarkers. Personalized Multiple Sclerosis therapy is presently limited because of no evidence-based biomarkers. Newer biomarkers, for example neurofilament light chain, have great potential, but further standardization validation and validation of studies are need to be done.

13. CONCLUSIONS

In this systematic review, I analysed and compared different research works done in the last ten years, in order to present the most updated information about progress in scientific world regarding genetic and immunological factors that might predict prognosis as well as relation to treatment strategies effected by immuno-genetics factors. My conclusions are:

1. Genetic effect has a major and clear effect on disease progression. HLA- DRB1*15:01 has the most prominent effect on disease progression, known so far to medicine. Effect includes not only onset of symptoms but also progression and disability. Protective genes as highly investigated as well, when currently leading is HLA–A*02. Mic-RNA was found to have effect on disease progression. MiR-572 was found in many studies in correlation with flairs and disability progression.

2. Elevation of IgM and IgG OB in CSF and serum during diagnosis has been related to a worse outcome. Interluekin-10 is a protective factor, therefore its absence indicate worse prognosis. Compare to IL-6 and IL-,8 increased levels will lead to worsening disease course and poor response to treatments. CD4+and CD8+ T cells, was found to have a contribution to MS pathogenesis and severity.

3. Personalized medicine is the future of MS therapeutic strategies. CSF biomarkers were associated with different pathological processes involved in MS effect both disease activity and DMT efficacy, but but further validation and standardization of assays are required.

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