



Inflammasomes as a Prognostic Marker and Possible Therapeutic Target in Multiple Sclerosis: A Rapid Review of the Literature

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Abstract

Introduction: Inflammasomes are multiprotein complexes innate to the immune system that, upon activation, initiate a chain reaction culminating in the production of cytokines IL-1 and IL-18. Recent studies have suggested a connection between inflammasome activation and neurological diseases such as multiple sclerosis (MS). In this review, we aimed to evaluate the role of inflammasomes as potential therapeutic agents and prognostic markers of MS.

Methods: Through a database search, 156 articles were identified. Of these, we selected articles focusing on observational and interventional studies that either directly measured the expression of inflammasomes or the levels of cytokines or interleukin as outcomes. After applying a snowball sampling strategy, this review ultimately included nine studies.

Results: Our search yielded nine studies published between 2010 and 2022—9 observational studies included case-control and cohort designs. All studies comprised adult populations, 20–72 years of age. All studies incorporated a control group. We selected studies that utilized surrogate measures to evaluate outcomes such as inflammasome expression of NLRP3 or similar genes and assess cytokine levels such as IL-1 β , IL-18, IL-23, and TNF.

Discussion: Overall, the revised studies suggest a possible role for inflammasomes components, including ASC and caspase-1, which have been evaluated as potential prognostic markers in MS. Therapeutic strategies have focused on the inhibition of NLRP3, which is one of the most prominent and studied inflammasomes, by IFN- β .

Introduction

Inflammasomes are complex proteins of the innate immune system that include a sensor Nod-like receptor (NLR) molecule, the adaptor protein ASC, and caspase-1 (Piancone et al., 2021; Piancone et al., 2018). These protein complexes can be triggered by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), and have the ability to sense various stimuli such as bacteria, fungi, extracellular ATP, amyloid- β , uric acid, and environmental irritants (Malhotra et al., 2015; Piancone et al., 2018). The activation of inflammasomes leads to the amplification of CD4 T helper

Type 1 (Th1) and CD4 T helper type 17 (Th17) responses, with IL-1 β and gamma playing key roles in this process.

This activation process sets up a positive feedback loop for Th17 cells, ultimately resulting in the disruption of the blood-brain barrier (BBB); this disruption leads to an increased accumulation of Th1 and Th17 cells in the central nervous system (CNS), subsequently triggers the release of granulocyte and macrophage-colony stimulating factor (GM-CSF), interferon-gamma, and tumor necrosis factor (TNF), which activate microglia and oligodendrocytes, these cells release IL-8, an immune system amplifier, which recruits neutrophils and produces proteolytic enzymes that target the extracellular matrix of myelinating cells (McGinley et al., 2018; Govindarajan et al., 2020). NLRP3, the most studied inflammasome, seems to contribute to Th1 and Th17 cell responses and their migration to the CNS and subsequent demyelination (Guo et al., 2015). Several

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diseases are related to the deregulation of NLRP3, including degenerative diseases, such as Multiple sclerosis (MS). MS is a progressive, autoimmune disorder of the central nervous system characterized by inflammation, oligodendrocyte damage, and demyelination (Cotsapas et al., 2018)

MS is not uniformly distributed worldwide, and its prevalence varies significantly across different regions. The highest prevalence is in North America, with a prevalence rate of 140/100,000, and in Europe, with a prevalence rate of 108/100,000. On the other hand, the lowest rates are found in East Asia, with a prevalence rate of 2.2/100,000, and in Sub-Saharan Africa a prevalence rate of 2.1/100,000. (Kanai & Rees, 2016; Oh et al., 2018) Therefore, there is significant variation in the prevalence of this condition across different regions, including Asia, where Hong Kong has a rate of 0.77/100,000. In contrast, Iran has a much higher rate of 85.80/100,000. (Oh et al., 2018). The global median prevalence of MS increased from 30/100,000 in 2008 to 33/100,000 in 2013 (Kanai & Rees, 2016).

The diagnosis of MS is clinical; however, the combination of lumbar puncture, magnetic resonance imaging (MRI), and serological analysis are helpful for the prediction of disease prognosis (Oh et al., 2018). Clinically, in the symptomatic phase of the disease, the patient usually presents with cognitive impairment, optic neuritis, brainstem, spinal cord syndromes, or dominant parietal lobe syndromes (Dobson & Giovannoni, 2019). The disease has been categorized into four clinical phenotypes: Relapsing-Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS) (Oh et al., 2018).

The exact role of inflammasomes in MS pathogenesis and their potential as prognostic markers and therapeutic targets are still debated; a review of the literature is necessary to weigh the evidence.

Materials and Methods

Study Design

A rapid review of studies was conducted, a limited version of a formal systematic literature review.; the Cochrane guidelines for rapid review were adopted (Garritty et al., 2020). This rapid review does not aim to substitute a comprehensive systematic review; instead, it seeks to complement it by providing a temporary literature synthesis. This Rapid review offers a snapshot of the present understanding of the MS, the current evidence, and the research trends providing insights to guide subsequent comprehensive reviews.

Eligibility Criteria

Eligible studies were selected based on the following criteria: (1) observational studies or clinical trials; (2) adult patients (≥ 18 years of age) with a diagnosis of MS in any of the variants; (3) intervention if the level of inflammasomes was evaluated, or the clinical prognosis and disability progression were measured using laboratory tests, including blood, Cerebrospinal Fluid (CSF), MRI, or scales; and (4) articles published after 2010. Studies were excluded if they involved: (1) animal, in vitro, postmortem, or ex vitro intervention; (2) patients < 18 years, or if age was not reported; (3) not related to MS; (4) did not mention inflammasomes; (5) were systematic reviews or reviews; (6) were expert opinions and/or book chapters; (7) ongoing studies; and (8) unpublished studies.

Search Strategy

The search was conducted by two authors on October 1, 2022, using PubMed MESH terms and the following combinations: (((("Inflammasomes"[Mesh]) OR "Interleukin-1"[Mesh]) OR "NLR protein, human" [Supplementary Concept]) AND ("Multiple Sclerosis"[Mesh] OR "Multiple Sclerosis, Relapsing-Remitting"[Mesh] OR "Multiple Sclerosis, Chronic Progressive"[Mesh])).

Study Selection

The PubMed search using the mesh mentioned above terms returned 156 articles. The initial screening involved two researchers, followed by a secondary screening conducted by six researchers. Two researchers independently repeated the second screening to ensure consistency and compared their findings. After the first screening by title and abstract, 106 articles were obtained; Subsequently, the second screening was performed based on content, applying the predefined inclusion and exclusion criteria. Additionally, the snowballing technique was utilized, and duplicate articles were eliminated. Ultimately, this process led to the selection of 9 articles (See Figure 1).

Data Extraction

A standard table format was used to extract the link to the study, author and year of publication, type of study, characteristics of the subjects (age and gender), sample size, country, multiple sclerosis variant, type of intervention, and the surrogate outcomes (See Table 1).

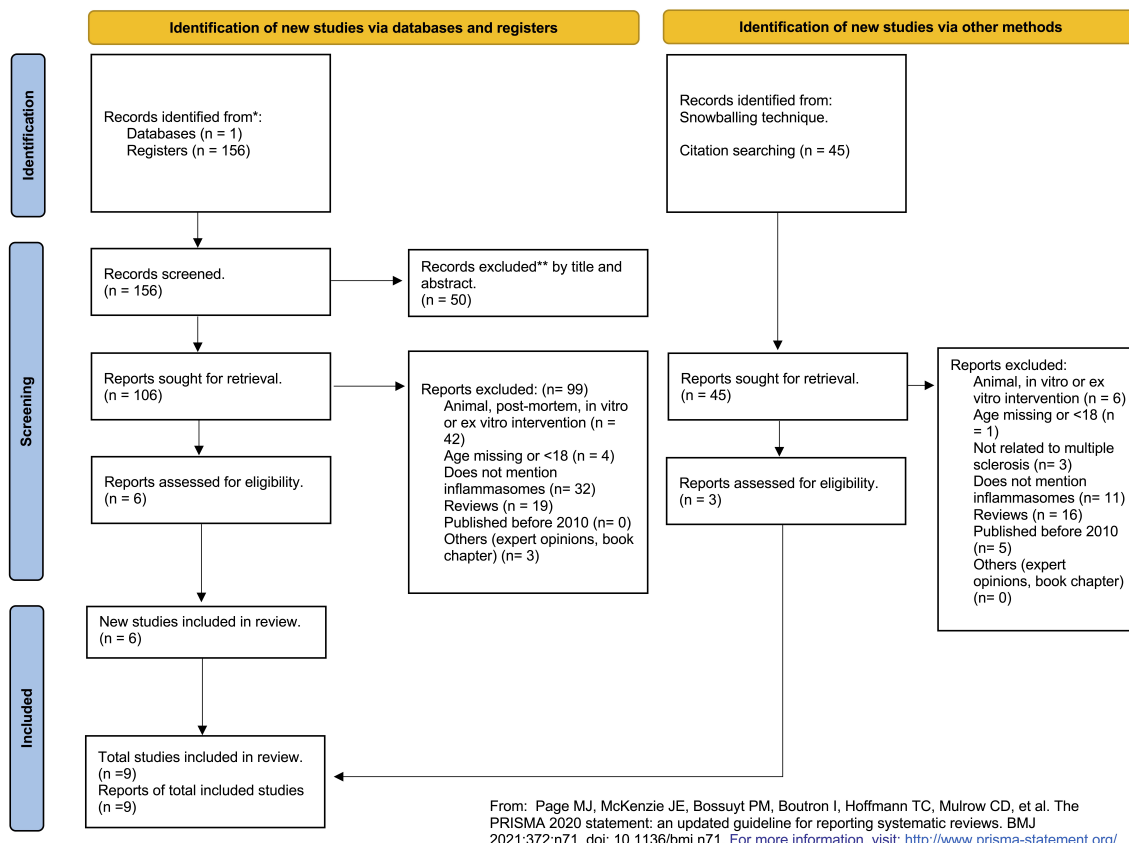


Figure 1: PRISMA Flowchart.

Risk of Bias

The quality assessment was conducted using the NIH Study Assessment Tools. Each study underwent an evaluation based on a set of twelve to fourteen questions, depending on its specific study type. The studies were rated good, fair, or poor quality. A "good" study indicates the lowest risk of bias, a "fair" study suggests some susceptibility to bias that does not sufficiently invalidate its results, and a "poor" study indicates significant bias. (National Heart, Lung, and Blood Institute., 2021) All the studies included in the table were good to fair (See Figure 2).

Results

Our search yielded nine studies published between 2010 and 2022—nine observational studies included case-control and cohort designs. All studies comprised adult populations, 20–72 years of age. All studies incorporated a control group. We selected studies that utilized surrogate measures to evaluate outcomes such as inflammasome expression of NLRP3 or similar genes and assess cytokine levels such as IL-1 β , IL-18, IL-23, and TNF. One specific article focuses on the inflammasomes NLRP1/NLRP3 gene pane.



Figure 2: Risk of Bias.

Author (year)	Study Design	Age	Gender	Sample Size	Country	MS Variant	Intervention	Surrogate outcomes
D'Angelo et al. (2018)	Cohort study	36-55 years	20 females 10 males	60 (30 RRMS treated and 30 RRMS untreated)	Spain	RRMS	IFN- β	levels of the cytokines TNF- α , IL-1 β , IL-12/23p40, IL-18, IL-18BP, and (TGF)- β 1.
Imani et al. (2018)	Case-control study	Mean age: 34.2 \pm 9.2	88 females 62 males	250 (150 MS patients and 100 healthy controls)	Iran	RRMS	No intervention	NLRP3 gene expression level using real-time PCR.
Malhotra et al. (2015)	Cohort study	Mean age 34-36	65 females 32 males	109 (97 RRMS patient 12 controls)	Spain	RRMS	IFN- β	changes on EDDS and levels of IL1 and Genotyping of NLRP3 polymorphism.
Malhotra et al. (2020)	Cohort study	>18 years	34 females 10 males	56 (44 MS patients and 12 healthy controls)	Spain	RRMS, SPMS and PPMS	No intervention	IL1 β ,NLRP3, IL6, and TNF expression levels.
Noroozi et al. (2017)	Analytic Observational study	>18 years	22 females 8 males	30 RRMS patients before treatment (controls). 30 RRMS patients after treatment	Iran	RRMS	IFN- β 1 α	Expression of NLRP3, NLRP1, NLRP4, and AIM2 and carboxy-terminal CARD (ASC), caspase-1, IL-1 β , and IL-18.
Piancone et al. (2018)	Descriptive Observational study	26-72 years	23 females 18 males	51 (41 MS patients , 10 healthy controls)	Italy	PPMS, SMS, AMS, and benign MS	No intervention	IL-1 β , IL-18, caspase-1, and caspase-8 concentration by ELISA, uric acid concentration.
Keane et al. (2018)	Descriptive Observational study	24-64 years	22 females 10 males	152 (32 MS patients, 120 healthy controls).	USA	RRMS, SPMS	No intervention	Caspase-1, ASC, and IL-18.
Soares et al. (2019)	Cohort study	25-52 years	161 females. 49 males	497 (264 MS patients and neuromyelitis Optica; and 233 healthy controls).	Brazil	RRMS, PPMS and SPMS	IFN- β	IL-1 β and IL-18 levels.
Vidmar et al. (2019)	Cohort study	Mean age 43	Sex ratio of 1.6:1, female to male	319 subjects categorized into 3 cohorts. The MSFAM cohort included 86 MS The sporadic (MSS) cohort included 89 MS and healthy controls 144.	Slovenian, Croatian and Serbian population	Any type of MS	No intervention	Inflammasome gene panel of NLRP1/NLRP3.

Table 1: Characteristics of included articles.

Discussion

Overall, the revised studies suggest a possible role for inflammasomes components, including ASC and caspase-1, which have been evaluated as potential prognostic markers in MS. Therapeutic strategies have focused on the inhibition of NLRP3, which is one of the most prominent and studied inflammasomes, by IFN- β .

The revised studies provide insights into the high prevalence of multiple sclerosis (MS) in females, with approximately 63% of the patients diagnosed with MS being females. Furthermore, around 55% of the studies were conducted in Europe, highlighting the elevated prevalence of MS in these populations. Additionally, 22% of the studies were conducted in Iran, indicating a notable prevalence in this region. In contrast, only one study was conducted in South America and the United States, suggesting a need for more research in these regions.

Inflammasomes as Prognostic Markers in Multiple Sclerosis

Although multiple sclerosis (MS) is not considered an inherited disease, emerging evidence suggests that NLRP3 polymorphisms, gene expression variations, and the secretion of IL-1 β and IL-18 may have a role in the development and progression of MS (Imani et al., 2018). Additionally, some authors suggest that the involvement of NLRP3, NLRC4, and AIM2 is crucial in the progression of MS through their mediation of Th1 and Th17 responses (Noroozi et al., 2016). Consequently, one study revealed a notable rise in rare protein-altering variants within genes associated with regulating inflammasomes in individuals with MS. (Vidmar et al., 2019).

In addition, studies have shown that the activation of NLRP3 and the production of IL-1 β are risk factors for both the development of MS and the progression to severe forms of the disease. In contrast, low IL-18 production and/or NLRC4 activation benefit patients with MS and are considered positive prognostic factors (Soares et al., 2019). In a particular study, the serum protein levels of caspase-1, ASC, and IL-18 were elevated in MS patients compared to the control group (Keane et al., 2018).

Consequently, some investigations have demonstrated that MS patients with detectable levels of IL-1 β are more likely to experience a higher progression index (PI) of disability and increased ambulatory limitations, as assessed by the Expanded Disability Status Scale (EDSS) and MS Functional Composite (MSFC). In contrast, patients with undetectable levels of IL-1 β in cerebrospinal fluid (CSF) exhibit significantly lower PI scores, Multiple Sclerosis Severity

Scores (MSSS), and a higher probability of presenting with a benign MS phenotype. Consequently, detecting IL-1 β in CSF is a potential negative prognostic factor for individuals with relapsing-remitting MS (RRMS) (Rossi et al., 2014; Heidary et al., 2014).

In summary, accumulating evidence suggests that NLRP3 polymorphisms, gene expression variations, and the production of IL-1 β and IL-18 may be involved in the development and progression of MS. Activation of NLRP3 and increased IL-1 β levels are associated with a higher risk of disease development and severity. In contrast, Low production of IL-18 was associated as a protective factor. Detectable IL-1 β levels in CSF are associated with a worse prognosis for patients with RRMS, indicated by higher disability progression indices.

Inflammasomes as Therapeutic Targets in Multiple Sclerosis

Several promising strategies in the treatment of MS exist. Interferon- β (IFN- β) currently represents one of the standard interventions to treat MS. Studies have shown that it decreases the levels of NLRP3 and NLRP1 (Piacone et al., 2018; D'Angelo et al., 2018). Additionally, other authors suggest that memory T cells from patients with MS exhibited a reduced ability to suppress NLRP3 inflammasome activation, which IFN- β restored. (Malholta et al., 2015) On the other hand, one study suggests that treatment with IFN- β 1a has a regulatory impact on the expression of specific inflammasomes such as NLRP3, NLRC4, and AIM2 (but not NLRP1). This suggests that IFN- β 1a, as an interferon therapy, may enhance clinical outcomes by blocking relapse in treated patients. (Noroozi et al., 2016).

In a separate study of patients with relapsing-remitting multiple sclerosis (RRMS), it was observed that those receiving IFN- β treatment had significantly higher levels of IL-10 compared to control groups, also other authors demonstrated that IL-10 inhibits the production of IL-1 β and the activation of NLRP3 in microglia, thereby preventing caspase-1-mediated maturation of IL-1 β . Which contributes to the clinical benefits of IFN- β in the treatment of MS. Additionally, recent advances have led to the development and testing of small molecule inhibitors targeting NLRP3 in animal models of MS. Such as MCC950, which directly acts on the NACHT domain of NLRP3. (Govindarajan et al., 2020). In addition, one study suggests that this type of therapy based on specific inhibition of the NLRP3 could be a better approach to treating progressive phases of MS. (Malholta et al., 2020).

In summary, the evidence suggests that NLRP3

plays a significant role in the response to IFN- β treatment. The overactivation or inability to suppress NLRP3 is implicated in the pathogenesis of MS, including the progress and severity. This emphasizes its potential as a future target for novel therapies.

Limitations

This rapid review is a limited version of a formal systematic literature review, and several limitations can be identified. Although PubMed is one of the top research databases, other databases were excluded because of time and access constraints, increasing the risk of missing articles. Therefore, a snowballing technique was employed to enhance the retrieval process. Nonetheless, the utilization of this technique restricts the generalizability of the findings. Additionally, unpublished and ongoing studies were excluded.

Conclusions

The role of NLRP3 in MS is complex and still under investigation. Therefore, studies have shown that inflammasomes that act as protein complexes can be activated by various stimuli, leading to the amplification of Th1 and Th17 responses mediated by IL-1 β and specific CD4 T cells. This activation process contributes to the disruption of the BBB and subsequent release of pro-inflammatory factors that further activate immune cells and promote the recruitment of additional immune cells to the CNS that promotes demyelination. Therefore the current evidence suggests that NLRP3 polymorphisms, gene expression variations, and the production of IL-1 β and IL-18 may be involved in the development and progression of MS.

Although several authors have identified inflammasomes as a possible therapeutic target, there needs to be more knowledge regarding the specific research focus. Future research should prioritize exploring novel therapeutic approaches and complementary therapies, emphasizing identifying the most effective inhibition of the inflammasomes for managing various variants of MS. Additionally, it is imperative to expand the range of studies to the countries where research in this field is currently limited. This expansion will enhance the applicability and generalizability of the findings.

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Data Availability Statement

Data found in this article can be traced to the academic article database using the search terms and strategies detailed previously.

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Conflicts of Interest

The authors declare no conflict of interest.

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