Chronic Fatigue and Depression due to Multiple Sclerosis: immune-inflammatory pathways, tryptophan catabolites and the gut-brain axis as possible shared pathways

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Abstract/summary

Chronic fatigue and major depression (MDD)-like symptoms are common manifestations of multiple sclerosis (MS), both with huge impact on quality of life. Depression can manifest itself as fatigue, and depressive symptoms are often mistaken for fatigue, and vice versa. The two conditions are sometimes difficult to differentiate, and their relationship is unclear. Whether chronic fatigue and depression occur primarily, secondarily or coincidentally with activated immune-inflammatory pathways in MS is still under debate. We have carried out a descriptive review aiming to gain a deeper understanding of the relationship between chronic fatigue and depression in MS, and the shared pathways that underpin both conditions. This review focuses on immune-inflammatory pathways, the kynurenine pathway and the gut-brain axis. It seems likely that proinflammatory cytokines, tryptophan catabolites (the KYN pathway) and the gut-brain axis are involved in the mechanisms causing chronic fatigue and MDD-like symptoms in MS. However, the evidence base is weak, and more research is needed. In order to advance our understanding of the underlying pathological mechanisms, MS-related fatigue and depression should be examined using a longitudinal design and both immune-inflammatory and KYN pathway biomarkers should be measured, relevant clinical characteristics judiciously registered, and self-report instruments for both fatigue and depression should be used.

1.0 Introduction

Multiple sclerosis (MS) is an inflammatory disease with onset in young adults causing secondary neurodegeneration within the central nervous system (CNS) (Filippi et al., 2018). Common MS symptoms are sensory, visual and motor symptoms, cognitive difficulties, chronic fatigue, depression and bowel- and bladder symptoms. Fatigue, cognitive problems and bowel and bladder symptoms have the most impact on quality of life and the ability to work (Filippi et al., 2018). The disease course is highly variable. The majority of patients present with a relapsing-remitting disease course driven primarily by an inflammatory component for years. With time, neurodegeneration dominates with a progressive disease course. A small proportion of patients have a progressive disease course from onset (Filippi et al., 2018; Lublin et al., 2014). Although the etiology of the disease is still elusive, there is agreement that an interplay between genes and environmental factors is involved (Sawcer et al., 2011; Waubant et al., 2019). Moreover, MS is considered an autoimmune inflammatory disorder known to affect both white and grey matter, mediated by immune cells (IMSGC, 2019).

Chronic fatigue and MDD-like symptoms are common manifestations in patients with multiple sclerosis (MS), but their causes and inherent relationship remains to be explained. Both fatigue and depression are correlated to smaller cortical surface area and volumes on brain MRI in MS (Nygaard et al., 2015). Fatigue is also common in the general population, especially following infections (Loge, Ekeberg, & Kaasa, 1998). Evidence suggests that activated immune-inflammatory pathways play a role in the onset of fatigue and depression in MS, and cytokine-hypotheses of MS-associated fatigue (Patejdl, Penner, Noack, & Zettl, 2016) and depression (Hurley & Tizabi, 2013) have been postulated. The Kynurenine pathway (KP) of tryptophan metabolism is an important regulator of the production of neuroactive compounds, both neuroprotective and neurotoxic. The fact that the KP is induced by proinflammatory cytokines and interplays with both macrophages and microglia (innate immunity) and T-cells (adaptive immunity), makes it plausible that this “producer” of neuroactive compounds is a required factor involved in the disease progression, as well as in fatigue and depression. There is increasing interest in the role of gut dysbiosis and gut permeability across a host of medical conditions (Mangalam et al., 2017), and recent data suggests that alterations in the gut may be important in the etiology of MS. It is also of note that alterations in the gut are linked to both depression (Anderson, Maes, & Berk, 2012) and fatigue (Maes & Leunis, 2008), whilst elevations in pro-inflammatory cytokines can increase gut permeability (Vanuytsel et al., 2014). As such, alterations in gut dysbiosis/permeability may be important to the emergence of depressive and fatigue symptoms in MS patients.

2.0 Multiple Sclerosis (MS) - possible pathogenic mechanisms

MS pathology is characterized by demyelinated areas, so-called plaques, in the white and grey matter of the brain as well as in the spinal cord , indicating a loss of myelin sheaths and oligodendrocytes (Popescu & Lucchinetti, 2012).

In the last 25 years we have seen the introduction of increasingly more potent disease modifying drugs aiming at suppressing active inflammation. With increasing age and more progressive disease the efficacy is reduced or lost (Signori, Schiavetti, Gallo, & Sormani, 2015).

2.1. MS and the role of the immune system

Although inflammation is present at all stages of MS, it is more prominent in acute phases than in chronic phases (Dendrou, Fugger, & Friese, 2015; Grigoriadis & van Pesch, 2015). The extent of inflammation seems to decline with age and disease duration. Studies in MS patients have shown that peripheral immune responses targeting the CNS drive the disease during early phases, while neurodegeneration dominates in the progressive phase (Correale, Gaitan, Ysrraelit, & Fiol, 2017; Kaufmann et al., 2020).

The inflammatory process comprises the interaction of a diversity of immunological cells (Grigoriadis & van Pesch, 2015). Early lesions show leakage of the blood–brain barrier (BBB) and invading peripheral immune cells, predominantly macrophages and CD8+ T cells, but CD4+ T cells, B cells and plasma cells can also be found. As the disease progresses, infiltration of T cells and B cells, activation of microglia and astrocytes, as well as myelin reduction and axonal injury are apparent, resulting in a more distinct atrophy of the grey and white matter (Dendrou et al., 2015) (Popescu & Lucchinetti, 2012). Memory T cells are activated in the periphery by a process thought to involve an interplay between genetic and environmental factors. Proinflammatory T cells then penetrate the CNS by crossing the BBB and are re-activated in response to CNS antigens. This induces an inflammatory response in the CNS (Dendrou et al., 2015). Proinflammatory cytokines induce macrophage and microglial activation that, in turn, produces other proinflammatory mediators and oxygen and nitric oxide radicals, finally leading to demyelination and axonal loss (Das Sarma et al., 2009; Murphy, Lalor, Lynch, & Mills, 2010). Microglia and macrophages remain in a chronic state of activation throughout the disease. Successful clinical trials in MS targeting immune molecules or specific cell types provides strong evidence for the involvement of particular immune effector and regulatory cells. Studies suggest that B cells and different T effector cell populations of the adaptive immune system, together with natural killer (NK) and microglial cells of the innate immune system, play

unique roles in contributing to MS (Baecher-Allan, Kaskow, & Weiner, 2018). Studies of immune cells in patients with MS, as compared with healthy donors, showed their functional dysregulation in MS. The role that distinct populations of T effector cells, T regulatory cells, and B cells might play in MS, will not be further describes in this paper. For further reading, this topic is thoroughly highlighted in (Baecher-Allan et al., 2018).

Several studies have reported elevated levels of proinflammatory cytokines in the CSF and plasma of patients with MS, including IL-1β, TNFα and IL-6 (Al-Omaishi, Bashir, & Gendelman, 1999; Argaw et al., 2006; Dujmovic et al., 2009; Frei, Fredrikson, Fontana, & Link, 1991; Hauser, Doolittle, Lincoln, Brown, & Dinarello, 1990; Martins et al., 2011; Sharief & Hentges, 1991). Moreover, the cytokine pattern observed in the CSF of patients with active MS varies according to the disease stage. In a comprehensive study, Martins and co-workers analyzed a broad range of cytokines in serum samples from 833 patients with multiple sclerosis and 117 healthy controls (Martins et al., 2011). They found significantly increased levels of IFN-γ, IL-2, IL-1β, TNF-α, IL-4, IL-10, and IL-13, that are both proinflammatory and anti-inflammatory cytokines in the patients with MS. Morris et al (Morris et al., 2018) postulate that the characteristic pattern of deviations in the cytokine profile seen in patients in the active phase of MS differs from that observed in patients who are in remission (Morris et al., 2018). In general, elevated levels of the anti-inflammatory cytokines TGF-β1 and IL-10 are characteristic in patients in remission, while elevated levels of the proinflammatory cytokines TNF-α, IL-1β and IFN-γ are characteristic in patients following a relapse (Morris et al., 2018). Increased levels of TNF-α has been found to correlate with clinical disability estimated by EDSS scores, and to predict relapse (Hauser et al., 1990; R. Li et al., 2015).

2.2. The Kynurenine pathway (KP) and the link to the immune system

Over the past decade, the Kynurenine pathway (KP) of tryptophan metabolism has arisen as perhaps the most important regulator of the production of both neuroprotective and neurotoxic compounds. The essential amino acid tryptophan (TRP) is degraded to numerous neuroactive compounds in an enzymatic cascade known as the kynurenic acid (KA) or the TRP catabolite (TRYCAT) pathway. This includes KA, 3-hydroxykynurenine (3-OH-KYN), and quinolin acid (QA). TRP is converted to Kynurenine (KYN) in the initial and rate-limiting step of the KP (Bender & McCreanor, 1985), catalyzed by either indoleamine 2,3-dioxygenase (IDO) or TRP dioxygenase (TDO). TDO, which is expressed in the liver, uses mainly TRP as a substrate and is induced by glucocorticoids, TRP, and nicotinamide shortage. IDO may be ubiquitously expressed after induction by proinflammatory cytokines and has broad substrate specificity. Many metabolites of the serotonin, or 5-hydroxy-tryptamine (5-HT) pathway, may act as substrates, including TRP, hydroxytryptophan, serotonin,

tryptamine, and melatonin (Yamazaki, Kuroiwa, Takikawa, & Kido, 1985). KYN may subsequently be metabolized in two separate ways. The first one results in the formation of the neurotoxic metabolites 3- OH-KYN, 3-hydroxyanthranilic acid (3-HAA), and QA (Alberati-Giani & Cesura, 1998). These neurotoxic metabolites act via special mechanisms; 3-OH-KYN induces neuronal apoptosis, 3-OH-KYN and 3-HAA induce oxidative stress (Okuda, Nishiyama, Saito, & Katsuki, 1998), and QA activates the N-methyl-D-aspartate (NMDA) receptors (Stone & Perkins, 1981). The second way KYN can be metabolized is through conversion to the neuroprotective metabolite KA, which counteracts the action of QA by being an antagonist of the NMDA receptor (Swartz, During, Freese, & Beal, 1990).

The KP can be active both in the peripheral and in the central nervous system. KA, 3-HAA, and QA cannot cross the BBB, while KYN and TRP can be transported across the BBB via the large neutral amino acid transporter system (Fukui, Schwarcz, Rapoport, Takada, & Smith, 1991). Brain KYNs are linked to, and influenced by, the peripheral KP (Kita, Morrison, Heyes, & Markey, 2002). Serotonin is synthesized within the brain from the essential amino acid TRP. Activation of the KP thus results in lowering of the brain availability of TRP for serotonin synthesis and disturbances in the amounts of neuroprotective and neurotoxic catabolites.

In peripheral organs, steroid hormones, growth factors and cytokines regulate levels of KP enzymes by stimulating both IDO (O'Connor et al., 2009; Prendergast, Chang, Mandik-Nayak, Metz, & Muller, 2011) and TDO (Liao et al., 2007). IDO is induced by proinflammatory cytokines, including interferon (IFN)-γ, interleukin (IL)-1β, and tumor necrosis factor-α (TNF-α) (Maes, Leonard, Myint, Kubera, & Verkerk, 2011; Oxenkrug, 2007). Systemic and central immune stimulation, including cytokine-induced IDO activation, may result in hyper- or hypofunction of essential active metabolites, and is associated with several neurological disorders (Schwarcz, Bruno, Muchowski, & Wu, 2012).

KYN can have excitotoxic and neurotoxic effects, and induce symptoms of depression or anxiety (Maes & Rief, 2012; Wichers et al., 2005). Conversely, KA has anxiolytic (Lapin, Mutovkina, Ryzov, & Mirzaev, 1996) and neuroprotective (Swartz et al., 1990) effects. The KYN/TRP ratio reflects IDO activity (Maes et al., 2011), whereas both the KYN/KA and QA/KA ratios reflect the neurotoxic potential. It is also important to note that TRP depletion and Tryptophan catabolites (TRYCATs) may render the immune system phenotypically more tolerogenic (Maes et al., 2011).

The fact that the KP interplays with both macrophages and microglia (innate immunity) and T-cells (adaptive immunity) (Mandi & Vecsei, 2012) makes it plausible that this “producer” of neuroactive compounds is an entailing factor involved in MS progression.

2.3. The KP and possible involvement in MS

As argued above, the KP may have a role in MS progression by potentially linking inflammation to excitotoxic neurodegeneration, via cytokine-induced IDO activation.

In experimental autoimmune encephalitis (EAE), an animal model of MS, IDO activation has been found to suppress the autoimmune process, while IDO inhibition exacerbates it (Mittal, 2015). Furthermore, results from clinical MS studies demonstrate a correlation between disease activity and changes in KP metabolites (Mittal, 2015; Watzlawik, Wootla, & Rodriguez, 2016). However, the significance of these findings and the exact role of the KP remain unclear (Mittal, 2015; Watzlawik et al., 2016).

As early as in the late seventies, Manaco reported that the level of TRP was decreased in the plasma and CSF of MS patients during a relapse, indicating IDO activation (Monaco, Fumero, Mondino, & Mutani, 1979). A better understanding of the KP in the past decade, as well as the introduction of more efficient methods of measuring the KP metabolites, could potentially have led to more research into the areas of KP in MS. However, there are few studies on TRP levels and IDO activity in MS patients, the results have been inconsistent, and evidence regarding IDO activation in MS has been controversial (Fakan, Szalardy, & Vecsei, 2019), most likely due to the variable course of the disease. A recent review indicates that baseline IDO activity may be downregulated in stable MS, probably contributing to the disease pathogenesis, whereas it is relatively upregulated during an acute inflammatory relapse (Fakan et al., 2019). In addition to IDO activity, studies indicate increased downstream kynurenine metabolism during an acute inflammatory exacerbation in MS (Fakan et al., 2019).

A recent study (Lim et al., 2017) showed that the KYN/TRP ratio (reflecting increased IDO activity) was elevated in MS patients, indicating that KP metabolism is deviant in MS, which is in agreement with previous findings (Aeinehband et al., 2016; Mancuso et al., 2015). Increased IDO activity is known to suppress the T-cell mediated response in MS (Mancuso et al., 2015; Mellor & Munn, 2004). It is argued that the findings of increased levels of neuroprotective metabolites is only observed in active MS, not in progressive MS, and increased toxic metabolites in progressive MS demonstrate a role for neurotoxic KP metabolites in mediating neurodegeneration in MS (Lim et al., 2017). Furthermore, it has been suggested that induction of the KP (that is, up-regulation of IDO) may initially be beneficial as IDO mediates an immunomodulatory effect, but that chronic IDO activation may change the excitotoxic balance by increasing QA production and also disturb the synthesis of serotonin and melatonin in the brain. This may again have implications for, and thereby mechanistically connections to, fatigue and depression in MS.

2.4. The gut-brain axis in MS

There is a growing interest in the role of alterations in the gut microbiome in MS, and the etiological and treatment implications that may arise as a consequence (Anderson, Rodriguez, & Reiter, 2019; Schepici, Silvestro, Bramanti, & Mazzon, 2019). A decrease in the production of short-chain fatty acids, butyrate, acetate and propionate, by the gut microbiome are common in gut dysbiosis, and mediate many of the changes associated with gut dysbiosis. A decrease in butyrate may be of particular relevance, given that butyrate decreases demyelination and increases remyelination (Chen, Noto, Hoshino, Mizuno, & Miyake, 2019), key features of MS pathophysiology. Butyrate is also a powerful epigenetic regulator, being a histone deacetylase inhibitor (HDACi), as well as dampening immune inflammation optimizing mitochondrial function and decreasing ceramide levels (Anderson et al., 2019). Butyrate also helps to maintain the gut barrier, for instance by increasing the melatonergic pathway in intestinal epithelial cells (Jin et al., 2016). As such, variations in butyrate can have central and systemic effects that are relevant to MS pathophysiology (Morris et al., 2017).

An increase in gut permeability is common across a diverse array of medical conditions, including psychological stress and raised levels of pro-inflammatory cytokines (Rodriguez, Wootla, & Anderson, 2016). The slackening of tight junctions between intestinal epithelial cells leads to a 'leaky gut', and thereby to an increase in circulating lipopolysaccharide (LPS). LPS acts on toll-like receptor (TLR) 4 to modulate the activity of many cells, including immune and glia cells. As such, increased gut permeability can modulate systemic and central immune/glia responses and contribute to their dysregulation in MS.

It is also of note that gut dysbiosis/permeability are evident in depression (Maes & Leunis, 2008), depression-associated neuro-immune conditions (Anderson & Maes, 2017) and in fatigue (Maes, Coucke, & Leunis, 2007). Consequently, variations in gut dysbiosis/permeability may be an important aspect of how MS pathophysiology becomes associated with an increased risk of depression and fatigue.

3.0. Fatigue and Depression in MS

Chronic fatigue and MDD-like symptoms are both common and challenging manifestations of MS. Fatigue is one of the most commonly reported symptoms in MS, affecting up to 90% of individuals with MS at some point during the course of the disease (Lerdal, Celius, Krupp, & Dahl, 2007; Lerdal, Celius, & Moum, 2003) (Colosimo et al., 1995; Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Hadjimichael, Vollmer, & Oleen-Burkey, 2008; Krupp, Alvarez, LaRocca, & Scheinberg, 1988). Together with cognitive decline, fatigue is the major cause of unemployment and problems in social

and family interactions (Fisk et al., 1994; Lerdal et al., 2007). It is also one of the most difficult symptoms to manage. The prevalence rate of depression in MS is somewhat lower, but still high, ranging from 40 to 50% (Joffe, Lippert, Gray, Sawa, & Horvath, 1987; Lerdal et al., 2007; Minden, Orav, & Reich, 1987; Sadovnick et al., 1996). Some studies have shown correlation between these two symptoms (Ford, Trigwell, & Johnson, 1998; Greeke et al., 2017; Lerdal et al., 2007), whereas others have shown no correlation (Krupp et al., 1988; Vercoulen et al., 1996). Even though the two clearly share many common clinical and pathophysiological features, it has been suggested that chronic fatigue and major depression in general can be separated by their course (Maes et al., 2012). Both chronic fatigue and depression may lead to chronic impairments and disabilities, whereas sickness behavior is a reversible and adaptive condition. The inherent relation and causes of the two are, however, still under debate (Maes et al., 2012).

3.1. Fatigue in MS

According to the 1998 Multiple Sclerosis Council for Clinical Practice Guidelines, fatigue in MS is a "subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" ("Fatigue And Multiple Sclerosis: Evidence-Based Management Strategies For Fatigue In Multiple Sclerosis," 1998). In these guidelines, chronic fatigue was distinguished from acute fatigue. Chronic persistent fatigue was defined as fatigue present more than 50% of the days during a 6 week period, limiting functional activities or quality of life. Acute fatigue was defined as a new or significant increase in fatigue compared to the previous 6 weeks. Finally, the Council hypothesised fatigue as either primary (intrinsic to the MS disease process) or secondary to chronic illness factors, such as medication, depression or poor sleep. Fatigue has later been defined by Krupp et al., (Krupp, Serafin, & Christodoulou, 2010) as "an overwhelming sense of tiredness, a lack of energy, or feeling of exhaustion, distinct from sadness or weakness, which is perceived by the individual or the caregiver to interfere with usual or desired activity". Fatigue in MS can be differentiated from fatigue in other conditions as it typically worsens with increasing temperature. Fatigue may also be subdivided in physical and mental fatigue (Penner & Paul, 2017).

There are several self-report instruments aiming at assessing fatigue. In a review from 2016 (Newland, Starkweather, & Sorenson, 2016), three questionnaires were identified as frequently used to quantify fatigue in MS populations; The Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989), the Modified Fatigue Impact Scale-21 (MFIS-21) (Larson, 2013) and The Neurological Fatigue Index for MS (NFI-MS) (Mills, Young, Pallant, & Tennant, 2010). FSS was by far the most frequently used scale. The authors of the review conclude that future research on MS-related fatigue may consider a longitudinal design with a carefully selected self-report instrument to

advance understanding of the underlying pathological mechanisms (Newland et al., 2016). Like MFIS, the Fatigue Scale Motor Cognition (FSMC) is also used to quantify fatigue as it allows for differentiation of motor and cognitive fatigue (Penner et al., 2009).

Several pharmacological treatments have been trialed to treat fatigue in MS. However, no treatments have so far shown sustained efficacy. A recent meta-analysis study concluded that amantadine seems to be the only drug that has some efficacy in the treatment of fatigue due to MS, but the data is very limited (Yang, Wang, Deng, & Yu, 2017). Furthermore, the impact of psychological changes in reducing fatigue in MS has been examined. A Cochrane group reviewed forty-five trials, including 69 exercise interventions and 2250 people with MS in order to determine the effectiveness and safety of exercise therapy on fatigue (Heine, van de Port, Rietberg, van Wegen, & Kwakkel, 2015)**.** Self-reported questionnaires were used. Even though the authors conclude that exercise therapy may reduce self-reported fatigue, and seems to cause no harm, they emphasize that the studies have several methodological weaknesses. Most trials did not include people who clearly experienced fatigue, did not target the therapy on fatigue specifically, and did not use validated measures of fatigue as the primary outcome (Heine et al., 2015).

3.1.1. Pathological mechanisms

It has been postulated that there is remarkable phenomenological and neuroimmune overlaps between MS and Chronic Fatigue Syndrome (CFS) (Morris & Maes, 2013). The affected all try to cope by energy conservation strategies in order to meet the energy demands day by day (Morris & Maes, 2013). Both disorders show a relapsing-remitting or progressive course, while infections and psychosocial stress largely worsen the fatigue symptoms. Activated immunoinflammatory, oxidative and nitrosative (O+NS) pathways and autoimmunity occur in both conditions illnesses.

The role of neuroinflammatory pathways, focusing on cytokines and KP, will be further described herein.

3.1.2. Role of inflammation and cytokines

Proinflammatory cytokines may influence neuronal and neuroendocrine functions and induce behavioral symptoms referred to as sickness behavior, the symptoms being fever and fatigue, loss of appetite, sleepiness, withdrawal from normal social activities, aching joints, and cognitive deficits (Dantzer & Kelley, 2007). Studies examining whether inflammation itself is associated with fatigue in MS have, however, produced somewhat inconsistent results. Immune cells of MS patients with

fatigue have been found to release significantly less IFN-γ upon nonspecific stimulation, that is, a stress-inducing task, than the cells from MS patients without fatigue, while TNF-α and IL-10 production did not differ between the groups (Heesen et al., 2005). C-reactive protein, neopterin and ICAM-1, typical markers of inflammation, have been found to correlate with disease activity, but not with fatigue severity in MS patients (Giovannoni, Thompson, Miller, & Thompson, 2001; Kraus et al., 1998). TNF-α and IFN-γ have been found to be significantly increased in fatigued vs. non-fatigued MS patients in studies using cytokine stimulation (phytohaemagglutinin) of whole blood cells (Heesen et al., 2006). Furthermore, the concentration of TNF-α mRNA has been found positively correlated to the presence of fatigue in MS patients in one study (Flachenecker et al., 2004). Finally, a study compared the concentrations of a broad range of both proinflammatory cytokines (IL-1β, IL-2, IL-6, IL-8, IL-12p70, IL-17, TNFα, and IFN-γ) and anti-inflammatory cytokines (IL-4, IL-5, IL-10, and IL-13) in fatigued and non-fatigued MS patients (Malekzadeh, Van de Geer-Peeters, De Groot, Teunissen, & Beckerman, 2015). Only IL-6 was found to be moderately correlated with the presence of fatigue. A review from 2016 on this topic concluded that no study has yet provided empirical data to support the hypothesis that elevated cytokine concentrations are responsible for fatigue in MS (Patejdl et al., 2016). It has been emphasised that inconsistency in results across studies might be associated with differences in sample-size and in the patients' characteristics. Levels of pro- and anti-inflammatory markers can fluctuate during the disease course and disease-modifying therapies can affect cytokine expression (Akcali, Zengin, Aksoy, & Zengin, 2017). Interestingly, in two recent studies on drug-naïve MS patients (Alvarenga-Filho et al., 2016; Alvarenga-Filho et al., 2017) , higher IL-6 and TNF-α levels were observed among fatigued patients, compared to non-fatigued. In addition, the fatigue scores correlated with IL-6 and TNF-α levels. It has been suggested that future large-scale studies would benefit from comparing the relationship between fatigue and immune characteristics in patients with different disease phenotypes after controlling for use of disease-modifying drugs (Chalah & Ayache, 2018).

3.1.3. Role of TRP metabolism/KP

As mentioned above, chronic IDO activation may change the excitotoxic balance and disturb the synthesis of serotonin and melatonin in the brain, which again may have implications for fatigue and depression in MS (Lim et al., 2017). It has been suggested that inflammation can influence the pathway which enhances some downstream metabolites in the KP (such as 3-Hydroxykynurenine (3-HK), Anthranilic acid (AA) and 3-Hydroxyanthranilic acid (3-HAA)), but not others (KA, picolinic acid and nicotinamide adenine dinucleotide (NAD+)), in patients with MS when compared to healthy controls. The abnormal KP in MS can potentially lead to mood/behavioural and sleep abnormalities,

excitotoxicity-induced neurodegeneration and energy depletion related to cognitive fatigue in MS. There is significant research data indicating a causative relationship between the activation of the KA and the development of pathological fatigue in different populations (Morris, Carvalho, Anderson, Galecki, & Maes, 2016). As far as we know, however, no previous research has investigated the association between KYN metabolites and severity of fatigue in MS patients.

3.1.4. Role of gut-brain axis

As noted above, gut dysbiosis and increased gut permeability can be evident in MS, depression and fatigue (Anderson et al., 2019; Maes et al., 2007). The loss of butyrate will contribute to the demyelination and suppressed remyelination that are core features of MS pathophysiology, whilst also contributing to an increase in immune inflammatory activity, altered epigenetic regulation, suboptimal mitochondrial function and increased gut permeability. These are also features of depression and fatigue, suggesting that alterations in the gut in MS pathophysiology may be an important aspect of any emerging depression and fatigue, as well as to MS pathophysiology per se. An increase in ceramide is often evident in MS, with ceramide contributing to demyelination MS (Anderson et al., 2019). Butyrate leads to the conversion of ceramide to glucosyl-ceramide, thereby lowering the apoptotic effects of ceramide, whilst also increasing the production of ganglioside, which is an important treatment target in MS (Qin et al., 2017). Ceramides are also increased in depression, where they are a significant treatment target (Dinoff, Herrmann, & Lanctôt, 2017). Increased ceramides are also evident in medical presentations associated with high reporting of fatigue (Nagy-Szakal et al., 2018).

Interestingly, the increase in gut permeability may contribute to changes in ceramide across MS, depression and fatigue, with LPS via TLR4 raising levels of inducible nitric oxide synthase (iNOS) and superoxide, which readily combine to form peroxynitrite, the major inducer of acidic sphingomyelinase and ceramide (Anderson et al., 2019). As such, alterations in the gut microbiome and gut permeability may contribute to the detrimental effects of ceramide in MS patients, including depressed mood and fatigue.

3.2. Depression in MS

Depression is common in MS, experienced by around 50% of patients (Patten, Marrie, & Carta, 2017). The prevalence estimates are generally 2–3-times higher than those of the general population.

General risk factors for depression, such as (younger) age, (female) sex, and family history of depression are less consistently associated with depression due to MS than they are in the general population (Patten et al., 2017). In spite of the high prevalence, research on treatment strategies for depression in MS is scarce. There is evidence, however, that cognitive behavioral therapies and antidepressant medications may have some efficacy (Patten et al., 2017).

Depression occurring early in the disease course is thought to be related to the psychological impact of being diagnosed with a chronic disease, but depression may occur throughout the disease course (Landro, Celius, & Sletvold, 2004). Inflammatory changes are implicated in the etiology of depression (Miller & Raison, 2016), logically providing a candidate mechanism linking depression to MS. Evidence from animal models suggests that some aspects of depression and fatigue in MS may be linked with inflammatory markers (Gold & Irwin, 2009). Furthermore, both TNF-α and interleukin-1β have been reported positively correlated with depression scores (Rossi et al., 2017). Depression itself can manifest as fatigue, and studies have also identified a correlation between fatigue and depression in MS (Kaynak et al., 2006; Patrick, Christodoulou, & Krupp, 2009).

3.2.1. Pathological mechanisms

As thoroughly and recently reviewed (Morris et al., 2018), a wide range of biological deviations are shared between patients with major depressive disorders (MDD) and patients with MS, including peripheral inflammation, neuroinflammation, chronic oxidative and nitrosative stress, mitochondrial dysfunction, gut dysbiosis, increased intestinal barrier permeability with bacterial translocation into the systemic circulation, neuroendocrine abnormalities and microglial pathology. Accumulating evidence suggests that there may be some common mechanisms behind the pathogenesis and pathophysiology of depression and MS, i.e. neuroinflammation and neurodegeneration (Hurley & Tizabi, 2013; Maes et al., 2012).

3.2.2. Role of inflammation and cytokines

A mentioned above, numerous studies have shown abnormal levels of proinflammatory cytokines in MS patients. However, there are only a few studies on the association between cytokines and the severity of depression in MS patients. In one study, mRNA expression of TNF-α and IFN-γ correlated significantly with the severity of depression during acute MS attacks (Kahl, Kruse, Faller, Weiss, & Rieckmann, 2002). Another study reported the finding of significant and positive correlation between IFN-γ production by stimulated Th1 lymphocytes and depression in MS patients (Pokryszko-Dragan et al., 2012). Finally, levels of IL-6, CRP and other markers of systemic inflammation have been found to

be higher in MS patients reporting symptoms of depression compared with patients who did not (Kallaur et al., 2016). The authors conclude that the expression of depression in MS is primed by peripheral inflammation. Interestingly, no significant associations between depression and type of MS, duration of illness, age, sex, nicotine dependence, and body mass index were found.

It is noteworthy that elevated levels of IL-6 have been shown to be associated with increased symptoms and severity of disease in MS patients exposed to protracted periods of extreme psychosocial stress (Sorenson, Janusek, & Mathews, 2013). Furthermore, it is worth noting that depression in MS is related to treatment with some immunomodulatory drugs, such as IFN-β, leading to reluctance to provide interferons to patients with pre-existing depression. A recent systematic review aimed at examining the impact of IFN-β treatment on depression in MS patients (Alba Pale, Leon Caballero, Samso Buxareu, Salgado Serrano, & Perez Sola, 2017). They found that the 10 included studies had heterogeneity regarding samples, methodology and results. Only three studies supported a relationship between IFN-β and depression, while the remaining articles reviewed did not find such an association. The authors conclude that there is no clear relationship between IFN-β treatment and depression in MS.

3.2.3. Role of TRP metabolism/KP

It has been suggested that the development of depressive symptoms as a result of cytokine therapy is attributable to cytokine-induced elevated activity of the KP (Myint & Kim, 2014). Nevertheless, studies of KP in patients with MDD have, however, produced varying results (Dahl et al., 2015; Elovainio et al., 2012; Gabbay et al., 2010; Hughes et al., 2012; Myint et al., 2013; Myint et al., 2007; Quak et al., 2014). The inconsistencies seen could be due to low sample size, different recruitment procedures and patient characteristics, or patients not being drug-naive at the start of treatment. Thus the involvement of KP in MDD is still under debate.

To the best of our knowledge, only one study has examined KP in relation to depression in MS patients. In a group of 71 MS patients, no significant correlation was observed between TRP and depression. However, when stratifying for those who were depressed among the MS patients, they found that the best predictors for depression were low levels of TRP, and consequently, a high KYN/TRP ratio (Aeinehband et al., 2016). KYNA showed no correlation with depression. Interestingly, the mentioned correlations were found significant only when the psychiatrist's ratings of depression were used, and not when the patients' self-reported symptoms were used.

3.2.4. Role of gut-brain axis

As highlighted above, gut dysbiosis and increased gut permeability may contribute to important pathophysiological changes in MS that will raise the likelihood of depressive and fatigue symptoms. The increased pro-inflammatory cytokines and their induction of IDO will not only increase activation of the kynurenine pathway, but also attenuate serotonin and melatonin production. As some of the effects of butyrate seem mediated via its induction of the melatonergic pathway, as shown in intestinal epithelial cells (Jin et al., 2016), a decrease in melatonin may further exacerbate the lost effects of suppressed butyrate levels. This may be of some importance as there is an increasing interest in the role of the melatonergic pathway, including within mitochondria, in immune cell regulation.

Recent work indicates that night-time, pineal melatonin dampens activated immune cells via its induction of the circadian gene, Bmal1, leading to the suppression of pyruvate dehydrogenase kinase, and therefore the disinhibition of the pyruvate dehydrogenase complex (PDC). In mitochondria, PDC leads to the conversion of pyruvate to acetyl-CoA, with acetyl-CoA increasing ATP production from the tricarboxylica acid cycle and from oxidative phosphorylation, thereby shifting mitochondrial metabolism and dampening immune cell inflammatory activity (Anderson & Maes, 2020). Interestingly, acetyl-CoA also acts as a necessary substrate for the initial enzyme in the melatonergic pathway, aralkylamine N-acetyltransferase (AANAT), suggesting that important effects of pineal melatonin may be via its induction of the mitochondrial melatonergic pathway in immune cells. In such circumstances, the suppression of melatonin synthesis by pro-inflammatory cytokine-induced IDO will be contributing to alterations in immune and glia reactivity (Anderson & Maes, 2020). It will be important to determine how changes in circadian melatonin modulates immune cells and glial mitochondria in driving depression and fatigue in MS.

The induction of IDO leads to the production of kynurenine and other TRYCATs, which mediate some of their effects by activating the aryl hydrocarbon receptor (AhR). The AhR is an important regulator of the immune system, generally increasing innate immune pro-inflammatory activity, whilst suppressing natural killer cells and CD8+ T cells (Anderson, Carbone, & Mazzoccoli, 2020; Quintana & Sherr, 2013). The AhR modulates mitochondrial function, including in immune cells, and therefore has significant impacts on metabolism that is relevant to both fatigue and depression (Anderson & Maes, 2017). Single nucleotide polymorphisms in the AhR are associated with MS (Zorlu, Hoffjan, Haghikia, Deyneko, & Epplen, 2019), fatigue (Morris et al., 2016) and the regulation of the gut microbiome (Scott, Fu, & Chang, 2020) (Scott et al., 2020), highlighting the role that the IDO/TRYCAT/AhR pathway has on the many aspects of MS and its association with fatigue and depression (S. Li et al., 2020).

Recent work has also highlighted a role for alterations in the opioid system in MS, depression and fatigue (Anderson et al., 2019) [Anderson et al., 2019; Anderson and Maes, in press]. Such work has highlighted an important role for the μ/κ-opioid receptor ratio in the regulation of MS and fatigue, as well as depression (Al-Hakeim et al., 2019). Alterations in butyrate, LPS and melatonin have significant impacts on the opioid system, suggesting that changes in the opioid system in immune, glia and neurons are important to the emergence of depression and fatigue in people presenting with MS.

4.0. Conclusions

Inflammation is present at all stages of MS, but is most prominent in the early, active phases. Even though inflammation in the brain and spinal cord is present in both active and progressive MS, predominance of the cell types involved varies between different phases. Evidence suggests that peripheral immune responses targeting the CNS drive the disease during early phases, while immune reactions within the CNS dominate progressive phases. The inflammatory process includes many different immunological cell types, including macrophages, CD8+ T cells, CD4+ T cells, B cells, plasma cells, microglia and astrocytes. An inflammatory response is induced in the CNS as a result of activation of proinflammatory T memory cells in the periphery. These cells subsequently penetrate the CNS by crossing the BBB and are re-activated in response to CNS antigens. Several studies have reported elevated levels of proinflammatory cytokines in the CSF and plasma of people with MS, including IL-1β, TNFα and IL-6. It seems likely that the cytokine pattern in active MS varies depending on the stage of the disease. In an experimental animal model of MS, IDO activation has been found to suppress the autoimmune process, while IDO inhibition exacerbates it. In addition, a correlation between disease activity and changes in KP metabolites has been found in some MS studies. Despite this, the significance and exact role of KP in MS remains uncertain. There are implications, however, that changed KP activity may have a role in the detrimental effects in MS progression.

Chronic fatigue and MDD-like symptoms are both common and challenging symptoms of MS, and clearly share clinical and pathophysiological features. Although there is some evidence of a strong association between the two, it has been suggested that chronic fatigue and major depression can sometimes be separated by their course. This view is based on a model for sickness behavior and depression, signifying that sickness behavior is a reversible and adaptive condition, whereas depression is maladaptive and leads to chronic impairment. Proinflammatory cytokines may influence neuronal and neuroendocrine functions, thereby inducing behavioral symptoms including symptoms reminiscent of chronic fatigue and major depression.

So far, however, studies examining whether inflammation itself is associated with fatigue in MS have produced inconsistent results. Moreover, abnormal KP in MS can hypothetically lead to mood/behavioral and sleep abnormalities, excitotoxicity-induced neurodegeneration and energy depletion related to fatigue in MS. Although there is data indicating a causative relationship between the activation of the KP and the development of fatigue in several populations, there is a lack of similar research in MS. As indicated above, gut dysbiosis and gut permeability can play a significant role in driving MS pathophysiological and overlaps with emerging depression and fatigue.

Even if numerous studies have shown abnormal levels of proinflammatory cytokines in MDD as well as in MS patients, there are surprisingly few studies on the association between cytokines and the severity of depression in MS patients. There are indications that the expression of depression in MS is primed by peripheral inflammation, but the evidence base is weak. The same yields for research on KP in relation to depression in MS patients; surprisingly little research has been performed. However, one study points in the direction that low levels of TRP, and consequently, a high KYN/TRP ratio, predict depression in MS. The gut is emerging as an important site in the regulation of a host of diverse medical conditions, and may be linked to the pathophysiology of MS. The importance of gut-related factors in the emergence of depression and fatigue from MS pathophysiology will be important to determine, including how this acts to regulate immune, glia, ceramide, mitochondria and the melatonergic pathway, as well as integrate the effects of pro-inflammatory cytokines and the kynurenine pathway.

Figure 1 summarizes the findings of the current review.

In conclusion, it is likely that both inflammation/ proinflammatory cytokines, KYN pathway and the gut-brain axis are involved in the mechanisms causing chronic fatigue and MDD-like symptoms in MS. Some evidence supports this notion: however, more research is needed. Future research on MS-related fatigue and depression should consider a longitudinal design in which both inflammatory markers and TRYCATs are measured, relevant clinical characteristics are judiciously registered, and finally, self-report instruments for both fatigue and depression are used after careful selection. Such studies would most likely advance our understanding of the underlying pathological mechanisms of fatigue and depression due to MS, hopefully leading to better treatment options.

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