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The Aberrant Immune System in Bipolar Disorder

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15.1 Introduction

Bipolar disorder (BD) [1] is a mood disorder characterized by episodic pathologic disturbances in mood: (hypo)manic episodes and depressive episodes which alternate with euthymic periods, i.e., with normal mood. BD has to be distinguished from (unipolar) major depressive disorder (MDD), which is characterized by depressive episodes only.

According to DSM-5, the core criterion of a (hypo)manic episode is the occurrence of pathologic elated (euphoria), expansive or irritable mood and increased energy or activity lasting at least 1 week. In addition to these core criteria, there are other symptoms, of which three or more need to be present to a significant degree – namely, inflated self-esteem or grandiosity, decreased need for sleep, being more talkative than usual, flight of ideas, distractibility, increase in goal-directed activity

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or psychomotor agitation, and excessive involvement in pleasurable activities that have a high potential for painful consequences. A depressive episode consists of at least one of the core symptoms: depressed mood and loss of interest or pleasure, completed with symptoms such as sleep problems, psychomotor changes, fatigue or loss of energy, feelings of worthlessness or excessive feelings of guilt, difficulty concentrating or making decisions, and recurrent thoughts of death [1].

Two types of BD are recognized: bipolar I disorder (BD-I) and bipolar II disorder (BD-II). Both types are characterized by the occurrence of extreme high and low mood episodes. Their main difference is the severity of manic episodes. Patients with BD-I experience full-blown manic episode(s), while BD-II patients experience only hypomanic episode(s). Manic, depressive, and mixed episodes can also be complicated by the presence of concurrent psychotic symptoms. Besides the mood symptoms, many patients with BD also show cognitive dysfunctions which may persist during euthymic periods, and which involve disturbances in various domains such as attention, verbal memory, and executive functioning [2, 3].

Worldwide, BD affects about 45 million people [4]. The lifetime prevalence of BD is about 2% across different countries, women being affected as frequently as men [5, 6]. Across the world, the disorder ranks sixth among all health conditions in terms of causing disability [7] with poor clinical and functional outcome [8], increased risk for suicidality [9], and significant societal costs [10].

Historically, treatment options for MDD, schizophrenia and partly BD, have focused on medications that modify the activity of monoamine neurotransmitter systems (i.e., dopamine, serotonin, and noradrenalin systems). Monoamines do play a role in the pathophysiology of these disorders, but the monoaminergic theory of illness has failed to deliver novel agents beyond the limited treatment options currently available.

The aim of this chapter is to provide an overview of various perspectives of the aberrant immune system in BD in light of the search of new therapy options. Nationwide epidemiologic analyses established a link between autoimmune liability, lifetime infections, psychosocial factors, and the presences of psychiatric disorders [11]. The “macrophage theory of mood disorders” postulates an aberrant pro-inflammatory state of monocytes/macrophages in patients with mood disorder and considers this aberrant state of the cells as a driving force behind the illness [12]. The theory was founded on the discovery in the 1980s and 1990s of increased serum or plasma levels of pro-inflammatory macrophage and T cell cytokines in patients. Also raised frequencies of auto-immune diseases and various T cell abnormalities were found in patients with BD [13], together with an aberrant expression of pro-inflammatory genes in circulating monocytes [11]. Moreover, although genome studies have linked BD to hundreds of variations, the stronger associations were found in the MHC immune region, such as the rs3130297 SNP, located in the NOTCH4 gene29.

The aberrant immune system is thought to have its effect on BD illness progression, via the tryptophan catabolic pathway and via glial cells, such as microglia and oligodendrocytes [14]. Therapeutic interventions targeting the immune system directly have thus far been mainly focused on non-steroid anti-inflammatory drugs

(NSAID), omega-3-fatty acids, and N-acetylcysteine (NAC) [15]. More recently, scientific attention has been given to the gut-brain-axis in BD, with emphasis on increased intestinal permeability and microbiome disturbances driving immune system dysregulation [16]. Based on the research that is becoming more extensive and global, this field seems promising for potential treatment options.

15.2 The Aberrant Immune System

15.2.1 Pro-Inflammatory Cytokines

The discovery of the various signal compounds (cytokines and growth factors) between the cells of the immune system in the 1980s and 1990s of the last century and the development of easy detection ELISA methods for their determination in serum and plasma made it possible to carry out extensive investigations to, e.g., interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, their receptors, and BDNF in mood disorders. Increased levels were found in BD patients when compared to controls, although not in all studies [17, 18]. Initially, these seemingly contradicting results were not well understood. In 2018 Rowland et al. performed an extensive meta-analysis of cytokines, neurotrophins, and oxidative stress mediators in BD, including 53 studies comprising more than two thousand cases and controls. In this meta-analysis, a combination of high-sensitivity C-reactive protein (hsCRP)/IL-6, brain-derived neurotrophic factor (BDNF)/TNF-α, and soluble TNF-α receptor 1 (sTNFR1) alterations was found to be associated with specific mood phases in BD [19]. During depression BDNF and TNF-α were found to be decreased, while sTNFR1 and hsCRP/IL-6 were found to be normal. In euthymia hsCRP/IL6 were increased, while sTNFR1, TNF-α, and BDNF were found to be normal. During mania hsCRP/IL-6 remained high as in euthymia, but sTNFR1 and TNF-α were also increased; BDNF was decreased in mania. Apparently, the activity and phase of the disease is a determinant for alterations in the cytokine and growth factor serum levels.

It is also important to consider that aberrations in cytokine concentrations are a cross-diagnostic feature of severe mental illnesses, demonstrated by a recent meta-analysis [20]. In this analysis, comparing cytokine profiles in patients with schizophrenia, BD and MDD, manifest alterations in blood cytokine levels were demonstrated, which are consistent with an inflammatory and T-cell activation profile shared between the mental illnesses.

15.2.2 Autoimmune Thyroiditis

Considering the cytokine profile consistent with an inflammatory profile, it is not surprising that patients with BD have a raised prevalence of autoimmune diseases. We here focus as an example on Hashimoto's autoimmune thyroiditis [21–23], also because this is a frequent autoimmune complication of BD. Autoimmune thyroiditis

is a chronic disease in which the body interprets components of the thyroid gland such as thyroid peroxidase (TPO) and thyroglobulin (Tg) as foreign (non-self). The body therefore mounts a specific destructive immune reaction toward its own thyroid cells. Although the attack is primarily orchestrated by inflammatory and cytotoxic T cells, the body also produces antibodies to TPO and Tg, which are used as easy-to-determine serum markers of the disease [24]. Autoimmune thyroiditis is considered an endophenotype of BD [13]. Not only BD patients but also their offspring (affected as well as non-affected) and their monozygotic (affected and non-affected) and dizygotic (affected, but not as much unaffected) co-twins have a raised prevalence of autoimmune thyroiditis [13, 25]. The intrinsic disturbances of monocytes and T cells in BD patients and their first degree family members are thought to be instrumental in the higher prevalence of autoimmune thyroiditis.

15.2.3 Monocyte Inflammatory Gene Expression

Stemming from the increased prevalence of autoimmune thyroiditis, it was hypothesized that an activated inflammatory response system in monocytes constitutes the shared susceptibility factor for both BD and thyroid autoimmunity. To investigate the pro-inflammatory state of monocytes in a more precise and robust manner, a quantitative polymerase chain reaction (q-PCR) analysis of purified monocytes was performed in which a signature of 22 discriminative mRNAs for inflammatory, chemokinesis/motility, cell survival/apoptosis, and mitogen-activated protein kinases (MAPKs) pathway molecules was detected and found to be increased in expression in monocytes in BD patients compared to that in controls [26]. In a subsequent study, this increased gene expression was found to be only present during mood episodes and not or hardly during euthymia [27]. The inflammation-related signature was also found to be associated with increased psychomotor symptoms [28]. In a follow-up study on well-controlled and euthymic relatively old bipolar patients, the inflammatory signature was even found to be decreased in expression in the patient monocytes, while a vascular repair factor (HGF) was found increased. This profile of gene expression is reminiscent of that of the vascular repair monocytes (so-called circulating angiogenic cells) seen in atherosclerotic disease and fitted well with the high prevalence of the metabolic syndrome seen in this relatively older patient group. Atherosclerotic diseases are nowadays also considered as partly belonging to the group of auto-inflammatory conditions.

15.2.4 T Lymphocytes

Important regulators of the inflammatory response are not only the cells belonging to the myeloid lineage (e.g., the monocytes, macrophages, and dendritic cells), but also the cells of the lymphoid lineage of the immune system (e.g., the different sets of T cells). T cells are generated in the thymus and all T cell are positive for an antigen-specific CD3+ T cell receptor. The CD3+ T cell population differentiates in

the thymus into either the CD8+ T cytotoxic cells (with the capacity to kill, e.g., virus-infected cells and cancer cells) or CD4+ T helper cells (with the capacity to help other immune cells functioning). In the last decades, it was discovered that the latter CD4+ T helper population contains cells with the capacity to develop into 4 main types of T helper cells: the Th1 cells with the capacity to produce pro-inflammatory IFN-γ, the Th2 cells with the capacity to produce the anti-inflammatory, but B cell stimulating cytokine IL-4, the Th17 cells which produce IL-17, and the T regulatory cells which dampen all sorts of inflammatory responses by virtue of their production of IL-10 and TGF-β.

In BD, the different sets of T cells and T helper cells have not been examined as extensively as in MDD. However, many of the studies carried out by us on different cohorts have found slightly reduced levels of the total population of CD3+ T cells in euthymic BD patients [29], their children at risk for BD, and in affected and non-affected co-twins of BD patients [30]. In the latter group, the slight reduction in the total population of circulating CD3+ T cells was found to be associated with the familial liability to develop BD.

Despite these reduced levels of total T cells, a higher activation state (as measured by strong CD25 positivity) of the T cells has been demonstrated in both euthymic and symptomatic BD patients, compared to healthy controls [31]. We consider this activation as a compensatory reaction to counteract the slight T cell deficiency state of BD patients. Also circulating levels of T helper cells were found to be higher in euthymic BD as compared to healthy controls, but in particular to patients with active MDD [32]. Other investigators examining subpopulations of T cells also found reduced levels of T cells (particularly of T cytotoxic cells), but again in the presence of higher percentage of activated ($CD25^+$) T helper cells. In older euthymic BD patients, we found higher levels of IL-4-producing Th2 and IL-17-producing Th17 cells [29], and we again interpreted these findings of a higher production reactivity of the cells as a compensation for the reduced number of total T cells. With regard to children of a bipolar parent who are at risk for BD, we found next to the earlier mentioned slight reduction in T cells in general, an age-dependent change in the levels of the Th1, Th2, Th17, and T regulator populations [30]: In the bipolar offspring Th1, Th2, Th17, and the T regulatory cells followed a dynamic course over time with significantly reduced levels of Tregs in adolescence and reduced numbers of Th1 and Th17 cells in young adulthood. In post hoc analysis, the T regulatory cells were inversely associated with the pro-inflammatory monocyte state, which also occurred in adolescence in bipolar offspring irrespective of current psychopathology [33].

With regard to the T regulatory cell population, reduced percentages have in general been described in BD: Barbosa et al. described a lower percentage of IL-10 expressing T regulatory cells [34] and del Prado et al. also found lower levels of T regulatory cells in BD patients as compared to healthy controls [35]. We found the T regulatory cells to be dependent on age and significantly higher T regulatory cells were only found in BD patients under 40 years of age as compared to healthy controls; this was not the case in BD patients of over 40 years of age [36].

15.2.5 Conclusion on the Aberrant Immune System

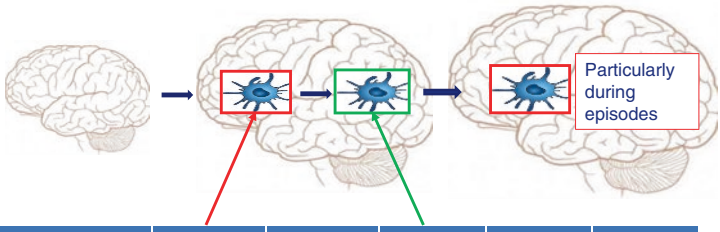
Taken together, the immune system findings suggest a basic slight numerical T cell deficiency in BD patients irrespective of the phase of the disease and associated with the familial liability to develop BD in twins and offspring. Despite this numerical deficiency (or better probably due to the numerical deficiency), there are signs of a higher functional activation of the T system (high CD25 expression) and the capacity of T helper cells to produce higher levels of particularly IL-17 and IL-4. T regulatory cells are in general found to be reduced in BD patients, opening the gateway to a higher inflammatory state. We indeed found an inverse relationship of the level of T regulatory cells and the monocyte inflammatory state. However, it must be noted that age dependency, particularly also at teenage time, plays an important role in fluctuations of the populations of functional T helper cells and chronic monocyte inflammation patterns. The latter occurred particularly during active phases of the disease, something that has also been noted for the pro-inflammatory cytokine levels in serum and in plasma (Fig. 15.1).

15.3 Tryptophan Metabolism as an Intermediary Mechanism

Abnormal interactions between the immune system and the HPA-axis, as well as abnormal interactions between the immune system and the neuronal system acting via tryptophan catabolites and interacting with glial cells, have been suggested to result in mood disorder symptomatology.

In the tryptophan breakdown, several enzymes are of importance. Tryptophan hydroxylase is the enzyme that metabolizes the amino acid tryptophan down the pathway to the neurotransmitters serotonin and melatonin; both monoamines play an important role in emotion regulation and cognition. In addition, tryptophan is also metabolized down the kynurenine pathway via an alternative route. Two enzymes play a role in the first and rate-limiting step in this oxidative degradation of tryptophan to kynurenine: indoleamine-pyrrole 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). IDO is particularly expressed in monocytes/macrophages and the IDO activity is enhanced by pro-inflammatory cytokines, e.g., by IFN-α, during viral infections. TDO is expressed in the liver and TDO activity is enhanced when there is physical or mental stress [37]. Under mentioned circumstances, tryptophan breakdown along the kynurenine branch is increased, while the availability of tryptophan for serotonin synthesis is decreased. Along the kynurenine pathway, tryptophan is first metabolized into kynurenine [38]. Subsequently, kynurenine is broken down via (1) a neuroprotective, kynurenic acid, NMDA receptor antagonist pathway, or (2) a neurotoxic, 3-hydroxy kynurenine, and quinolinic acid, NMDA receptor agonist pathway [39]. In the brain, the catabolism occurs in the astrocytes and microglia, where astrocytes produce mainly neuroprotective kynurenic acid while macrophages produce mainly neurotoxic metabolites, like quinolinic acid. Normally, formation of quinolinic acid is faster, while kynurenic acid has a counteractive protective role against quinolinic acid [40]. Based on the above, it

A MODEL OF THE DYNAMIC IMMUNE PATHOGENESIS OF BIPOLAR DISORDER



	17 years	21 years	28 years	30-50 years	> 50 years
	Euthymic children of a bipolar parent			Bipolar patients	
Tendency to monocytosis/lymphopenia, especially shortage of CD3+ T cells and CD3+CD4+T helper cells	+	+	+	+	+
CD3+ CD4+ CD25+ FOXP3+ T regulatory cells and serum sCD25 levels	decreased	normal	normal	increased in age >40 years	increased
CD3+ CD4+ IL17+ T cells	normal	decreased	normal	increased	increased
Pro-inflammatory monocyte genes	increased	slightly increased	normal	increased in episodes	decreased, increased in episodes
Serum CCL2 levels	normal	increased	increased	increased	not tested
Pro-inflammatory serum compounds (PTX3, hsCRP and IL-6)	increased	increased	not tested	increased, particularly in episodes	not tested

Fig. 15.1 The figure shows the immune aberrancies found in the peripheral blood mononuclear cell (PBMC) preparations of the bipolar or bipolar-related cohorts studied in the EU-MOODINFLAME studies. These cohorts comprise established bipolar patients, but also euthymic offspring of a bipolar parent who are at high risk to develop bipolar disorder. Remarkable are the dynamic changes over time in the cell-mediated immune system, and we assume that these changes are driven by inborn abnormalities, environmental (microbial, stress) influences, and aging of the immune system. See for details text and listed references. In all bipolar (related) subjects, we found a tendency to have reduced percentages of circulating lymphocytes, particularly of CD3+ T cells and CD3+ CD4+ T helper cells (with increased percentages of monocytes). In a twin study this reduced percentage of CD3+ T cells was found to be associated with the familial inborn liability to develop bipolar disorder. We assume that this minor T cell defect has an influence on hippocampal neogenesis and mood regulation, since T cells are known to be essential for these processes. Within the reduced T and T helper cell populations, we found in the offspring a proneness to have reduced T regulatory cells at adolescence. These low T regulatory cells correlated to a high pro-inflammatory state, as measured by a high expression of inflammatory genes in circulating monocytes and high serum inflammatory compounds at that age. We assume that at that time (adolescence) also the microglia is pro-inflammatory activated in the offspring, and has negative effects on hippocampal development and function. As time passes into adulthood in the offspring, the pro-inflammatory aberrancies largely disappear and normalize in the bipolar offspring, yet the CD3+ T cell lymphopenia remains. In episodic bipolar patients (and in postpartum mood disorders), pro-inflammatory aberrancies are clearly evident (monocyte gene expression, circulating serum inflammatory compounds), against the background of the minor CD3+ T cell lymphopenia. It is tempting to speculate that environmental microbial influences (alterations in the microbioma?) trigger the pro-inflammatory state in individuals with a proneness to develop bipolar disorder, such as the bipolar offspring. In the euthymic phases of bipolar patients the minor CD3+ T cell abnormalities stayed visible, while we found an abnormal apportioning of the T helper cell subsets (high T regulatory cells, high Th17 cells). We assume that the high T regulatory cells represent a controlled inflammatory state, and although high Th17 cells are present, pro-inflammatory monocytes were not present in the euthymic phase. Even an anti-inflammatory pro-angiogenic state of monocytes was found in senior bipolar patients with a high prevalence of the metabolic syndrome; we assume that this depended on the vascular problems occurring in these older bipolar patients

was hypothesized that an imbalance between the neurodegenerative and neuroprotective pathways leads to neurodegeneration and brings a person to a chronically depressive episode. This imbalance might either be due to a highly increased neurodegenerative pathway activity or due to a lack of sufficient neuroprotective factor activity [41].

Several studies have shown an involvement of the tryptophan to kynurenine pathway degradation in BD, which seems to be shifted toward its neurotoxic branch [42]. The plasma kynurenine/tryptophan ratio, defined as the tryptophan breakdown index, was found to be increased in BD, together with a reduction of the plasma kynurenic acid concentration, thus decreasing its neuroprotective effects [43]. More recently, similar data of decreased kynurenic acid levels were reported in a BD sample compared to healthy volunteers [44]. Finally, kynurenine breakdown has also been related to white matter microstructure in BD. In particular, BD patients show reduced concentrations of kynurenic acid and 5-Hydroxyindoleacetic acid (5-HIAA), a measure of serotonin levels. This was positively associated with diffusion tensor imaging (DTI) measures of white matter integrity [45].

15.4 Immune System and Glial Cell Aberrations

Neuroglia, consisting of glial cells, are the other predominant portion of the brain, next to neurons [46]. Glial cells were long thought to be mainly of use as structural supportive cells for the neurons, holding them in place, supplying them with nutrients and oxygen, and destroying pathogens. However, starting at the turn of the century, research demonstrated glial cells to have important functions in neurodevelopment and synaptic function [47, 48] and they are now known to be important regulators of neuroimmune interactions in the central nervous system [14, 49].

The glial cell population consists mainly of oligodendroglia, astrocytes, and microglia. In humans, astrocytes perform a multitude of functions such as, but not limited to, providing metabolic support as a lactate and glycogen energy buffer, vasomodulation by regulating blood flow [50], promoting myelinating activity of oligodendroglia [51, 52], regulating nervous system repair [53], facilitating long-term memory potentiation [54], and several kinds of signal transmission modulation, including modulation of synaptic transmission [55] and regulation of ion concentration in the extracellular space [56].

Microglia are the resident macrophages of the brain and spinal cord and thus act as the first and main form of active immune defense in the CNS, constantly scavenging the CNS for plaques, damaged neurons, and infectious agents. Besides functions relating to the immunoresponse, microglia play an important role in maintaining homeostasis. As with peripheral macrophages, microglial activation could be in an inflammatory sense (M1 macrophages), an anti-inflammatory sense (M2 macrophages), and a regenerating/tissue support sense (M2b macrophages). Animal models demonstrated that microglia are also involved in tissue regeneration and play an active role in neuronal support, i.e., the development of mature synapses during

embryogenesis [57], pruning synapses postnatally [58], regulating neurogenesis [59], and inducing apoptosis [11]. It may well be the case that some microglial cells induce apoptosis, while others actively facilitate neurogenesis.

Activation of microglia has been studied in PET imaging studies, with tracers binding to the translocator protein (TSPO, previously known as peripheral benzodiazepine receptor (PBR)), since TSPO expression has been associated with a pro-inflammatory state [60]. Current tracers used to visualize TSPO expression are [^{11}C]PK11195, [^{11}C]-PBR28 and [^{18}F]-FEPPA.

In psychotic disorders, an increase in microglia activation was demonstrated after a first psychotic episode [61]. During a psychotic episode, this inflammation was found to "condense" in the hippocampus [62]. The first TSPO study in MDD, using [^{11}C]-PBR28, did not demonstrate an increase in binding between 10 MDD patients and 10 healthy controls [63]. However, subsequent studies, including studies with [^{11}C]-PBR28 and [^{18}F]-FEPPA, demonstrated microglia activation quite robustly in MDD patients, with varying duration of illness and age [64–66]. Interestingly, treatment with antidepressants and cognitive behavioral therapy had an ameliorating effect on this activation [67, 68].

With regard to BD, increased [^{11}C]PK11195 binding has been demonstrated in the hippocampus of 14 euthymic BD type I patients, compared to 11 healthy controls [69].

The immune system may also exert its effect on the brain via oligodendrocytes. Oligodendroglia create myelin sheaths around neuronal axons for support and to increase the axonal transmission speed. In addition they provide trophic support by producing glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and insulin-like growth factor-1 (IGF-1) [70]. Oligodendrocyte function can be visualized in vivo using DTI. Using this technique, microstructural white matter aberrations involving all the major tracts have been demonstrated quite robustly in BD [71, 72]. Kynurenine catabolites, produced by cells of the immune system and derived from the serotonin precursor tryptophan, are known to affect oligodendrocyte function in vitro and inflammation-related cytokines, such as TNF-α, IFN-ɣ, and IL-10, have been found to be inversely associated with DTI-measured white matter microstructural integrity [73].

15.5 Potential Immune-Mediating Treatment Strategies

Randomized controlled trails (RCTs) investigating celecoxib, a cyclooxygenase-2 (COX-2) inhibiting non-steroidal anti-inflammatory drug (NSAID), demonstrated positive effects in BD. In BD, improvement of manic [74] and depressive symptoms was found [74–76]. In schizophrenia, treatment with this medication yielded improvement of positive symptomatology (hallucinations, delusions), negative symptomatology (passivity, apathy), and generally improved functioning [77]. These transdiagnostic and multi-dimensional effects of celecoxib support a common immune pathway model for severe mental illnesses and indicate that treatments, influencing the immune system, hold promise.

Omega-3 fatty acids have been extensively investigated for their antidepressant effects, but have failed to show overall treatment effectiveness in a meta-analysis [15]. Add-on treatment using N-acetyl cysteine, a glutathione precursor antioxidant, initially showed success for alleviating depression in BD [78]; however, a follow-up study failed to demonstrate a significant effect as maintenance treatment [79] and a recent replication study also was not able to show benefit over placebo [80].

Treatment with aspirin has also been suggested to be beneficial in BD. In a study testing the efficacy of aspirin and minocycline as an augmentation therapy for bipolar depression [81], a main effect of aspirin on depressive symptoms was observed. In a large pharmaco-epidemiological study related to BD [82], in which medication histories on subjects who had been prescribed lithium were collected using health care registry data, low-dose aspirin was found to be associated with a reduction in the relative risk of clinical deterioration in subjects, whereas other NSAIDs and glucocorticoids did not. In another study assessing the effect of 240 mg of aspirin on lithium-related sexual dysfunction [83], patients in the aspirin group showed significantly greater improvement in total sexual function scores than the placebo group (14.4% and 19.7% improvement respectively), while mood symptoms remained stable over the course of the study. However, to date no RCT has been performed investigating the direct effect of aspirin on mood symptoms or mood stability.

15.6 The Gut-Brain Axis

Recent investigations have pointed to the gut-brain axis as a new target for treatment to affect brain functioning in a significant subset of patients [84]. In this approach the chronic low-grade inflammation stems from increased intestinal permeability, associated with gut microbiome disturbances.

Recently, two papers elaborately reviewed the evidence for the contribution of increased intestinal permeability to the pathophysiology of BD in this rapidly developing field of research [84, 85]. Numerous studies have reported that BD patients have abnormal reactions to food-derived antigens, indicative of increased intestinal permeability. In support of this view, BD patients were also found to have elevated serum concentrations of immunoglobulin G (IgG) to gliadin and deamidated gliadin in comparison to controls [86]. In a follow-up study, patients with manic symptoms had increased baseline IgG to gliadin, which normalized after 6 months of treatment [87]. In the same study, re-hospitalized patients during a 6-month follow-up period were more likely to have increased IgG to gliadin at the beginning of the follow-up.

It has been hypothesized that BD can originate from early exposure to microbial infections, contributing to the etiology, through chronic neuro-inflammatory and autoimmune processes [88]. *Anti-Saccharomyces cervisiae* IgG antibodies (ASCA), typically increased in Crohn's disease or ulcerative colitis, is a marker of intestinal inflammation. Patients with BD were found to have increased levels of ASCA along with IgG to casein and gluten, and ASCA correlated with IgG to these food antigens

compared to controls [89]. ASCA also correlated to IgG to *T. gondii* and measles in patients who experienced a recent onset of psychosis in the course of BD.

It is also interesting that an imbalance of the intestinal microbiota is associated with BD [90], as this may offer a non-invasive and relatively simple strategy to improve symptoms and the condition of the brain. One study found that a lower abundance of a strain of *Faecalibacterium* was associated with improved physical health, better depression scores, and sleep quality scores, thereby providing support for the hypothesis that targeting the microbiome may be an effective treatment paradigm for BD [91]. Another study also found a decrease in abundance of *Faecalibacterium* in the BD group in comparison to non-psychiatric subjects [92]. Besides this, investigators found a decrease in abundance in *Ruminococcaceae* and both the phylum *Actinobacteria* and the class *Coriobacteria* as significantly more abundant in BD patients as compared to healthy controls.

Coello et al. [93] found that not only the gut microbiota composition of BD patients but also that of their unaffected first-degree relatives differed from that of healthy controls. This observation is interesting in the light of the slight T cell deficiencies also found in unaffected first degree relatives of BD patients (see before) and the monocyte inflammatory gene activation in first degree relatives (twins) linked to common environmental influences [94].

As described above, increased intestinal permeability causes translocation of bacterial material and food-derived antigens. The translocation of these substances results in hyper-activation of the intestinal immune response through the interaction of, e.g., lipopolysaccharides (LPS), glycolipids derived from the outer membrane of gram-negative bacteria, with toll-like receptor 4 (TLR4) in immune cells, e.g., monocytes/macrophages. This interaction with the TLR4 activates the inflammatory NFkB pathway, over-production of pro-inflammatory cytokines, and disruption of the tryptophan catabolic pathway with a reduction of levels of serotonin [84]. Moreover, hyper-activation of the intestinal immune system may also result in the activation of the hypothalamic–pituitary–adrenal (HPA) axis, which in addition has a direct implication on BD [95].

In a large study in humans with schizophrenia and BD, *C. albicans* seropositivity was associated with gastro-intestinal (GI) disturbances as well as cognitive deficits [96]. In a study in patients with diabetes mellitus type 2, probiotics were found to cause a decrease in LPS and CRP, and a positive effect on cardiometabolic profile [97, 98]. In another study in postmenopausal women, a similar cardiometabolic effect was found [99].

Given the accumulating evidence for abnormal immune responses which are seen in BD patients, and the observation that the intestinal epithelial barrier and intestinal microbiota can play a role in both diseases, probiotic therapy can be viewed as a promising candidate for treatment in these patients [90, 100]. Probiotics were associated with a significantly lower rate of re-hospitalization in 66 patients [101]. The probiotic's effect was increased in individuals with elevated levels of systemic inflammation at baseline based on IgG class antibodies to the NR2 peptide fragment of the NMDA receptor, IgG class antibodies to gliadin, IgG class antibodies to the Mason-Pfizer monkey virus gag protein, and IgM class antibodies to

Toxoplasma gondii. In another recent study, a significant improvement in performance concerning attention and psychomotor processing speed was found in BD patients, supporting the hypothesis that probiotic might be beneficial to improve cognitive functioning [102].

Summarizing, in multiple studies increased intestinal permeability in BD has been demonstrated by translocation of food and bacterial antigens, as well as intestinal microbiome disturbances. These aberrancies are associated with a dysregulation of the immune system and the precipitation and exacerbation of psychiatric symptomatology, metabolic complications, and increased cognitive impairment.

15.7 Concluding Remarks

Over the last few decades, insight in the immune disturbances associated with BD has expanded greatly. Starting off with serological and epidemiological studies, molecular biological and imaging techniques have elucidated various aspects of the aberrant immune system, encompassing alterations in serum cytokines, chemokines, and tryptophan catabolites, alterations in the T cell and monocyte/macrophage-mediated immune reactions, and the cerebral processes linked to these immune and biochemical alterations. However, studies remain typically small in size and cross-sectional in design, complicating the exploration of these dynamic processes in detail and over time, and larger multi-modal longitudinal studies are needed.

New treatment approaches targeting the immune system directly or indirectly, via the gut, have also emerged, although limited in size and number, compared to pharmaceutical company–driven trials. Effect sizes of existing studies are typically not more than modest, and this is probably attenuated by general study methodologies on heterogeneous patient groups. A more personalized treatment approach toward the status of the immune state is a promising strategy to increase the impact of immune system targeting medication, while keeping adverse effects acceptable.

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