

Immuno- inflammatory markers of bipolar disorder: a review of evidence

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1. ABSTRACT

Bipolar is a severe psychiatric disorder which ethiopathogenesis remains unclear. Despite a clearly established heritability, genetic studies have failed to elucidate the underlying mechanism of bipolar disorder, most likely due to the contributing role of environmental factors in the genesis of the disease.. Environmental factors have been consistently described to induce immuno-inflammation dysfunction, which are also known to play a role in the pathogenesis of bipolar disorders as due to the combined actions of small effects in many different genes interacting with environmental factors). Several mechanisms might explain the pro-inflammatory processes observed in bipolar disorder. Emerging evidence support the pathophysiological role of Human Endogenous Retroviruses, which reactivation (normally silenced), can be induced by infectious agents during pregnancy, early childhood and/or adolescence. ,Neurotoxic effects and inflammatory state are induced, which might in turn and after a prodromal phase, trigger acute mood episodes,. The present paper reviews the role of the immuno-inflammatory processes as key contributors to the bipolar disorders pathophysiology , the evidence supporting immuno-genetic predisposition,background, and the the possible implications of retroviruses reactivation in the pathogenesis of bipolar disorder.

2. INTRODUCTION

Bipolar disorder (BD) ranks at 4th leading cause of disability. Prevalence of classic BD is around 1%, while the full spectrum of BD accounts for 4%. It is classically described as a cyclical disease , with full blown manic or depressive episodes interspaced with normal euthymic periods; however, evidence now suggests that patients experience a more subtle chronic course, characterized by residual symptoms, emotional dysregulation, sleep and circadian rhythm disturbances, as well as cognitive impairment, with increased risk for psychiatric and medical comorbidity such as cardio-vascular diseases, diabetes mellitus, obesity and thyroid dysfunction (2). This revised perspective of bipolar disorders should promote development of improved diagnostic tools, including bio-signatures to allow for a comprehensive clinical assessment, but should also influence our understanding of the etio-pathology of bipolar disorder and support the identification of innovative therapeutic strategies. Along these lines, immunological abnormalities may well represent a significant component of the pathophysiology of the disorder. So far, attention has been focused on schizophrenia, which has been shown to be clearly associated with pre- and post-natal exposure to viral and parasitic antigens as well as cytokine dysregulation, and genome-wide association involving Human Leukocyte antigen (3). Evidence now suggests that pro-inflammatory cytokines may subserve manic and depressive episodes, as well as euthymic periods (4),

which we propose to further explore based on the literature. In addition, we will review the environmental and genetic risk factors that might be linked to these biological abnormalities. In order to start uncovering the mechanisms responsible for this acute and chronic inflammatory state), as well as immunological and inflammatory markers, immune-genetic findings. We will then provide insights into the possible implications of retroviruses and their reactivation by infections in bipolar disorder.

3. IMMUNO- INFLAMMATORY MARKERS IN BIPOLAR DISORDER

Despite heterogeneity of results which could be attributed to mood symptoms, of the disorder, effects of medication and/or comorbid medical disorders Pro-inflammatory markers have shown substantial evidence for increased inflammation during manic and depressive episodes, with particularly increase levels of C-Reactive Protein (CRP), cytokines and TNF- α (4).

3.1. Abnormalities of the innate and the adaptative system in bipolar disorder

Depressive bipolar patients display higher levels of interleukins, chemokines and cellular adhesion molecules which may induce alteration of the neurotransmitters turnover (of noradrenalin, 5-HT) and/or a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Elevated levels of cytokines increase HPA activity (14). Administration of IL-1 is associated with increased corticotrophin-releasing hormone, ACTH, and corticosteroids (15, 16), while IL-6, TNF α , and interferon stimulate the HPA axis both in rodents and in humans (17). In addition, cytokines have shown to favour neuronal survival along with actions on neurotransmitters, hormones and neurotrophins. Indeed, bipolar disorder patients experiment impairments in neuroplasticity and neuronal survival (18).

The association between manic and depressive episodes and a pro-inflammatory state involving both the innate and the adaptative immune system has been fully demonstrated (Table 1). In particular, Th1 cells are known to mediate cellular immune reactions and including production of the cytokines (IL-1, IL-6, IL-12) interferon- γ , and TNF α ; Th2 cells enhance antibody-mediated immune reactions and induce the production of cytokines IL-4 IL-5 and IL-10 while Th3 cells heighten the production of TGF- β .

Elevated levels of TNF- α have been reported in manic and depressive episodes (19-21) in bipolar disorder patients. High levels of IL-6 and TNF- α have also been reported during mania with IL-6 levels returning to baseline after treatment with mood stabilisers (22, 23) while TNF- α continued to be high. Reduced IL-2 levels in mania and depression and increased IL-6 and IL-8 have also been reported. During mania, IL-2, IL-4 and IL-6 were the only increased pro-inflammatory cytokines, while only IL-6 was found to be increased during depression. Conversely, no abnormalities were found during euthymia except elevated levels of IL-4 (24). This last study (24) suggests that mania

and to a lesser degree depression, is associated to a pro-inflammatory state.

Elevated IL-6 has been one of the most consistent findings in BD (25). IL-6 is a pleiotropic cytokine that is produced at sites of inflammation, secreted by T cells and macrophages. The role of the IL-6 is to stimulate the B and T lymphocytes and hepatocytes to produce acute inflammatory proteins such as CRP. Furthermore, IL-6 has potent anti-inflammatory and protective properties including inhibition of TNF and IL-1. Therefore, it has been suggested that cytokines such as IL-1, IL-6, and TNF act in a pro-inflammatory manner, augmenting the immune response to help the elimination of pathogens and the resolution of the inflammatory challenge. In addition, it has been hypothesized that the binding of cytokines to cerebral vascular endothelium, induce the generation of secondary messengers such as prostaglandins (PGs) and nitric oxide (NO) released simultaneously in large amounts during inflammatory states. In particular, overt production of PGs and NO has been shown to occur in the damaged tissue accompanying the inflammatory processes involved in rheumatic diseases, chronic degenerative disorders, and, neurodegenerative processes associated with brain ischemia as well as in neuroinflammatory diseases (such as multiple sclerosis, demyelination, HIV-related brain disorders, or Alzheimer's disease) (26). A recent meta-analysis showed that oxidative stress markers are clearly increased in BD as shown for example by elevated levels of Nitric Oxide (NO) in bipolar patients (27). In post-mortem frontal cortex from BD patients, excitotoxicity and neuroinflammation with particular activation of Interleukin-Receptor cascade has been observed, suggesting that these changes may account for disease progression (28).

Despite the overall activation of pro-inflammatory markers, discrepancies between measures of peripheral markers of immuno-inflammation has also been observed. This might be explained by the fact that bipolar disorder is a progressive disorder characterized by a progressive brain atrophy along with cognitive decline. It has thus been suggested that BD is characterized by a progression from prodromal symptoms to a very severe and refractory presentation engendered by the cumulative exposure to acute episodes (29-31). Preliminary studies have shown that immuno-inflammatory markers, in particular TNF α , IL-6 and 10 could differentiate early and late-stage bipolar disorder, thus identifying the first bio-signatures of bipolar disorder (29, 32-33). These results led to recommendations that future research should monitor these inflammatory markers during the course of the illness.

3.2. C-reactive protein (CRP) and bipolar disorder

CRP is one of the acute phase proteins that increases during systemic inflammation. Mainly synthesized in the liver after IL-1 and IL-6 cytokine induction (5), CRP is involved in chronic inflammatory-related disorders, such as atherosclerosis and cardiovascular diseases, through a moderate increase of its serum

Table 1. Disturbances of the immune system among bipolar disorder patients

Mood states	Immunological parameters	Samples
Depression	↑IL-2, no influence of mood status	172 BD patients, 66 C ¹³⁸
	↑IL-6, IL-8, TNF-α depressed vs C, IL-10 : no differences	9 BD depressed patients, 12 BD manic patients, 21 C ²¹
	↑IL-6 depressed BD ¹ patients	23 BD manic, 24 BD depressed patients, 14 BD euthymic, 25 C ²⁴
Mania or hypomania	↑IL-2, IL-6 in mania vs C ²	14 schizophrenic patients, 10 manic patients, 21 C ¹⁰⁶
	↑IL-2, IL-6,	17 untreated BD patients, 8 treated, 9 euthymic ¹⁰⁷
	↑IL-2,	23 BD manic patients vs 23 C ²³
	↑IL-2, no influence of mood status	172 BD patients, 66 C ¹³⁸
	↑IFN-γ, IL-4, ↓TGF-β	70 BD manic patients, 96 C ¹⁴⁰
	↑IL-1RA manic vs C	29 acute manic patients, 29 remitted patients vs 20 controls ¹⁴²
	↑CD4 premedicated manic patients vs C	
	↑IFN-γ manic vs C	
	IL-2, IL-4, IL-10: no differences between patients and controls	
	↑IL-6, IL-8, TNF-α manic vs C, IL-10 : no differences	9 BD depressed patients, 12 BD manic patients, 21C ²¹
	↑IL-4, TNF-α, ↓IL-1, IL-2 among manic patients vs C	20 non medicated BD patients vs 33 C ²⁰
	↑IL-6, TNF-α, ratios IL-6/IL-4, TNF-α/IL-4, IL-2/IL-4, IFN-γ/IL-4	37 BD manic patients vs 74 C ¹³⁹
	↑IL-2, IL-4, IL-6 among BD manic patients	23 BD manic, 24 BD depressed patients, 14 BD euthymic, 25 C ²⁴
	↑IL-1RA, ↑CD8, ↑IFN-γ remitted patients vs C	29 remitted patients vs 20 controls ¹⁴²
Euthymia	IL-2, normalization after remission	23 BD manic patients vs 23 C ²³
	↑TNF receptor, willebrand factor among BD & sz vs C	125 BD, 186 schizophrenic patients, 244 C ¹⁴³
	↓IL-2, IL-6, IL-10 & IFN-γ among euthymic BD patients under Li vs C	40 euthymic BD under lithium, 10 BD never medicated, 20C ¹²⁷
After Li ³ treatment or MD ⁴	↓IL-12 among the 3 groups after 8 weeks of treatment	43 schizophrenia, 34 major depression, 25 BD, 85 C ¹⁴¹
	Normalisation TGF-β after treatment	70 BD manic patients, 96 C ¹⁴⁰
	↓IL-4, ↓IL-6 after 6 weeks of treatment (mood stabilisers)	37 BD manic patients vs 74 C ¹³⁹
	↑IL-4, TNF-α in lithium euthymic BD patients vs medicated free&C	31 BD euthymic patients (16 mediated free and 15 under Li) ¹⁴⁴
	↑IL-2, IL-6, normalization after Li treatment	17 untreated BD patients, 8 treated, 9 euthymic ¹⁰⁷

¹ BD = bipolar disorder, ²C = Controls, ³Li= lithium, ⁴MD: mood stabilizers

level (between 5 and 10 mg/l) reflecting an underlying cellular stress phenomenon (6). Many studies and a recent meta-analysis showed that depression is accompanied by an elevation of CRP, while treatment of depressive symptoms is associated with a drop of CRP (7). The magnitude of the elevation, attenuated when adjusted for Body Mass Index, is particularly overrepresented among depressive patients with cardiac disease or cancer. CRP is also considered as a risk marker for de novo major depressive disorder. Indeed, in a population-based, longitudinal study spanning the full adult range, elevated hsCRP was found to be associated with a 44% increase risk for major depressive disorder in women (8).

In bipolar disorder, to our knowledge, only five studies have investigated the relationship between CRP levels and mood states. Wadec *et al.* (9) found that acutely manic patients compared to controls had higher levels of CRP, while Huang and Lin (10) showed in a smaller sample that manic patients had higher mean hsCRP levels than patients with major depressive disorders or healthy controls. Dickerson *et al.* (11) linked CRP levels to the severity of the manic episode according to the YMRS score (11). De Berardis *et al.* (2008)(12) showed that bipolar patients, whatever the phase of the disease (manic or depressive), display higher levels of CRP while Cunha *et al.*, (13) confirmed that among bipolar disorder patients, the levels of hsCRP are increased compared to euthymic and depressed patients suggesting that the episodes of mania are particularly sensitive to inflammatory changes.

These data consistently showed that mood states among bipolar I patients are associated with elevated CRP levels. However further studies are warranted to confirm

those findings since elevated CRP levels are non specific, have not been prospectively followed, and potential bias such as medical, psychiatric comorbid disorders or motor activity, BMI, smoking etc.. have not been systematically assessed.

3.3. Autoimmunity in bipolar disorder

The antigenic stimulus that triggers immuno-inflammation in BD disorders is not known. Whether this immune response reflects a single antigen exposure or is part of a greater generalized immune activation remains also unclear. The relationship between auto-immune disorders and bipolar disorder was noticed as early as 1888 (128), especially for thyroid disorders and multiple sclerosis. Effectively, In 1888, the Committee on Myxedema of the Clinical Society of London first reported in 109 patients with myxedema and reported that “delusions and hallucinations occur in nearly half the cases, mainly where the disease is advanced” (129). Several studies have suggested that auto-immune processes may operate before the onset of bipolar disorder (34). In particular, an increased risk for auto-immune disorders in unaffected relatives of patients with BD with Multiple Sclerosis and Thyrotoxicosis has been reported, predicting the onset of bipolar disorder, but also a risk of ulcerative colitis, psoriasis and rheumatoid arthritis (34). In addition, patients with BD tend to develop organ-specific autoimmunity; such as thyroperoxidase antibodies (TPOA) associated with auto-immune thyroid failure, or antibodies to H/KATPase, associated with autoimmune atrophic gastritis and GAD65A, isoform of glutamic acid decarboxylase and an important marker of type-I diabetes (35). The link between these antibodies and the observed ? increased risk for organ-specific autoimmune disorders

remains to be tested. BD patients are known to have a three times higher prevalence of diabetes than in the general population (36) and in the case of hospitalized patients a 10% prevalence (37). The most frequently used markers of type I diabetes is GAD65A, an isoform of glutamic acid decarboxylase, which catalyses the transformation of L-Glutamate into GABA, a major inhibitory neurotransmitter in the central nervous system. Circulating thyroid antibodies, even in the absence of hormone abnormalities, are found in excess among patients suffering from mood disorders (38). In addition, it has also been recently suggested that gastro-intestinal processing of food antigens such as bovine caseins and wheat gluten is altered. Recently, a subgroup of BD patients were reported to have increased anti-casein activation, may be related to mania (39). Further studies are needed to determine if gastro-intestinal process affecting digestion, epithelial permeability, and immune over-activity are involved.

3.4. The contribution of immunogenetics in bipolar disorder

Genetic polymorphism encoding specific cytokines and their association with specific disease entities have been widely investigated. Much of the work has focused on TNF- α , although other cytokines have also been studied. For example, it has been hypothesized that genetic variations determining increased production of anti-inflammatory cytokines or decreased production of proinflammatory cytokines have been shown to be associated with successful ageing, and age related diseases such as Alzheimer's disease (40). For instance, the -308(G/A) TNF- α gene polymorphism has been studied with late-life major depression in elderly people without dementia (41). The authors suggested that the G allele of TNF- α polymorphism may affect major depression susceptibility and be involved both in Alzheimer disease and major depression development, but probably with a distinct role in the two pathologies. In the case of bipolar disorder, another study showed that the G allele of the -308 (G/A) TNF- α gene was overrepresented among bipolar type II patients (42) while the G allele of the -174 (G/C) of the interleukin IL-6 polymorphism was associated with an earlier age at onset among Bipolar type I and II patients. These data were previously observed in an independent Polish sample which found that the G allele of the TNF- α gene was associated with schizophrenia and bipolar disorder but also with a positive family history among these patients (43). Therefore, the authors concluded that TNF- α could potentially be a susceptibility gene, shared between schizophrenia and bipolar disorder.

Interleukin (IL)-1 β , a proinflammatory pleiotropic cytokine, is a member of IL-1 family that possess the ability to stimulate the expression of genes associated with inflammation and immune response, including cyclooxygenase type 2, type 2 phospholipase A, and inducible nitric oxide synthase (44). Additionally, another important proinflammatory property of IL-1 β is its capacity to increase the expression on endothelial and other cell surfaces of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1). The biallelic functional polymorphism in the promoter region of the interleukin-1

beta gene (IL1B -511C/T) has been tested among 125 elderly inpatients diagnosed with major depression compared to 282 normal elderly controls (45). The authors showed that the subjects carrying -511C allele, had a significantly earlier depression age of onset (about 7 years) (45). In the case of bipolar disorder, using a brain imaging approach, Papiol and colleagues showed that the -511C/T polymorphism (rs16944) of the IL-1B receptor gene was associated with whole-brain and left dorsolateral prefrontal cortex gray matter deficits (46).

Another way to imply evaluate the role of immunogenomics in bipolar disorder is the exploration of the proinflammatory signature. A proinflammatory signature refers to the presence of various proteins and cellular molecules involved in signaling the immune cells to take action, triggering the initiation of disease. In an attempt to explore this hypothesis, Padmos *et al*, confirmed that the monocytes of bipolar patients and their offsprings have an altered mRNA expression of genes involved in inflammation and inflammation-related processes (47). The overexpression of 19 aberrantly expressed RNAs of inflammatory, trafficking, survival and mitogen-activated protein kinase pathway seem to be stable among euthymic patients (47). However, the active disease (manic and depressed episodes) seems to be associated with a specific overexpression of some mRNAs. Additionally, lithium and antipsychotics treatment seem to down-regulate the expression of most inflammatory genes (47).

All events involving immune responses are articulated around the HLA system, which is the most studied and the most associated cluster to common diseases, especially those classified as autoimmune (130).

However, in the case of bipolar disorder such an association remains controversial. For example, a significant association has been reported with bipolar disorder for the HLA B7, B16, B21 and A29 (131-132), while three studies failed to replicate this finding (133-135). One explanation is that bipolar disorder could share HLA class I and II system with autoimmune diseases. For example, using a family approach, the authors found that the relatives of a bipolar patient with comorbid multiple sclerosis, share the same Class I and II HLA-A2, B18, CW8, DR2 and DQ1 haplotype suggesting a shared susceptibility to both disorders (136).

Another explanation can be given by epigenetic factors such as DNA methylation which controls? genetic and genomic functions, including gene transcription. In a recent study, Kaminsky and colleagues explored methylation patterns of an HLA gene (HCG9), in post-mortem brain tissues, blood samples, and germline, and found a lower methylation of HCG9 in 1409 bipolar disorder patients compared with controls with an independent effect of age (137).

There is an increasing bulk of evidence involving the immune system in bipolar disorder: biological parameters such as genetic background and immune status are clearly implicated, but environmental factors and life

style parameters, as well as infectious agents are of particular importance in this field and point to a possible viral hypothesis.

4. THE VIRAL HYPOTHESIS

The idea that microbial agents may cause psychotic disorders has a surprisingly lengthy history (3). The viral hypothesis of mental disorders has been proposed in the late-nineteenth century by French psychiatrists who considered that microbial agents might be linked to psychiatric disorders (Esquirol, 1845) followed by famous psychiatrists such as Bleuler or Kraepelin (48). However, to the best of our knowledge, little has been written regarding possible links between infectious theories and bipolar disorder, while interest was focusing mostly on schizophrenia. However several arguments might support the viral/infection hypothesis starting with the seasonality of birth in bipolar disorder suggesting an excess of birth on winter-spring period.

4.1. A winter/spring excess of birth in bipolar disorder

Epidemiological studies have revealed a modest seasonal birth predominance in the winter and spring months. In 1977, a review of literature, including more than 250 studies on the seasonality of birth in schizophrenia and bipolar disorder and carried by Torrey and colleagues, found that compared to controls, bipolar and schizophrenic patients display a consistent 5 to 8% winter/spring excess of birth (49). Torrey's protagonist study (50) in 18021 bipolar subjects, reported a 5.8% birth excess for December, January, February, and March. This association was particularly marked among manic subjects reaching up to 14%. Several interpretations have been hypothesized such as variation in sunlight, temperature, birth complications, nutrition, along with infections (3). Moreover, Magnetic Resonance Imaging (MRI) studies showed that bipolar patients who have deep subcortical white matter lesions (as well as periventricular white matter lesions) are born more frequently during the winter months (January to March) and had a worse outcome (51). Besides, winter/spring season of birth has been associated with higher levels of monoamine neurotransmitter turnover (52), which are known to be altered in bipolar disorder. The turnover of dopamine, serotonin and melatonin seems to vary with the season of birth (53); an interaction between the season of birth and the expression of dopamine and tryptophan polymorphisms has also been found among bipolar disorder subjects (54).

There is compelling evidence from epidemiological, brain imaging and genetic studies that a winter/spring seasonality of birth constitute a risk factor for bipolar disorder. The extent to which seasonality may be a proxy for environmental risk factor has encouraged researchers to explore possible explanations for this association, particularly the viral hypothesis.

4.2. Viruses and bipolar disorder

Seasonal variation of infectious agents is well established; and has been connected to psychiatric disorders e.g. influenzae virus pandemic and schizophrenia.

Indeed, prenatal exposure to viruses with affinity for the Central Nervous System, such as polio, rubella, herpes simplex type 2, cytomegalovirus (CMV) (55) or parasite such as *T. Gondii* (56) have been proposed as risk factors for psychosis. Little has been written regarding bipolar disorder and infectious risk factors although interesting data suggest that neurotropic infectious agents might be involved in bipolar disorder. In 2 studies, the Borna Disease Virus (BDV) known to affect the central nervous system via animal hosts has been associated with mood disorders (57, 58). In a Japanese study, including 33 patients, the authors found that the levels of anti-BDV antibodies were significantly higher among patients with mood disorders compared to controls ($p=0.0485$) (57). Similarly, European patients with recurrent major depression and bipolar disorder, have been shown to exhibit significantly more anti-BDV antibodies than controls (58). The authors concluded that chronic inflammation and immunopathologic reactions of the BDV could play a major role in affective disorders by changing levels of cytokines or indirectly damaging the brain tissue via an immunological pathway (57, 58). Other viruses are thought to be associated with bipolar disorder such as herpes virus type 1 or Epstein - Barr virus (EBV) and cognitive impairment (59). However, in the case of EBV, the authors were not able to confirm that infection was a necessary step in the development of bipolar depression.

It is very unlikely that viral infections can directly cause bipolar disorder; however they may initiate a cascade of events leading to dysregulation of the immune system, in the presence of other environmental factors as well as genetic background.

5. THE RETROVIRAL HYPOTHESIS: A NEW AVENUE OF RESEARCH?

HERVs are part of the human genome, composing 8% of human total DNA (60), and can be transmitted to subsequent generations through gametes. However, they evolve differently from « classical genes », as part of the (retro) transposable elements, which altogether represent 40% of the whole genome (60, 61). Interestingly, our consortium has recently demonstrated the presence of proteins associated to the type W family of HERVs (HERV-W) in the sera of 50 % of 49 patients with schizophrenia (62). These results confirm previous studies exploring HERV-W expression in schizophrenia and bipolar disorder. Indeed, repeated and independent studies suggest a role for HERV-W in psychosis, a family of HERVs initially characterized from “multiple sclerosis associated retroviral element” -MSRV- (63-68). Briefly, comparison between schizophrenic twins and non-affected monozygotic twins revealed differences in HERV-W DNA sequences (69), virion-associated RNA was detected in CSF and plasma of recent onset schizophrenic patients (Karlsson *et al.*, 2001; Karlsson *et al.*, 2004 (70-73), and HERV-W RNA over-expression was evidenced in post-mortem brains of schizophrenic, bipolar patients and in major depression (74-76). In addition, it has been shown that reactivation of this HERV-W DNA, normally silenced mostly through epigenetic control, can be induced by

infectious agents such as influenza virus (77-78). Notably, influenza infection during pregnancy is also known to be associated with an increased risk for schizophrenia or bipolar disorder in the offspring (79-81). It is interesting to note that Crow has evoked this hypothesis earlier as mentioned in the British Journal of psychiatry in 1984: «Onset of disease is due to the expression of a 'provirus', which is integrated in the genome, having been acquired either by prenatal infection or in the germ-line from an affected parent; this could explain why the season of birth effect »(82).

HERV-W family has potential to encode for three classes of HERV-W associated proteins: HERV-W GAG, HERV-W POL, and HERV-W ENV. The latest protein expression has also been shown to be increased in neurons after herpes simplex 1 infection (83).

In our pilot study, we found a correlation between elevated CRP and HERV-W ENV/ HERV-W GAG antigenaemia in sera of schizophrenic patients (62). Since chronic inflammation and pro-inflammatory molecules can also induce neuronal excitotoxicity and neurotoxicity (84), our study provides evidence for a potential link between this neuronal loss associated with cognitive deficit and inflammatory processes that might be due to the pro-inflammatory action of HERV-W ENV protein (85-88). Indeed, to date, HERV-W antigenemia has not been tested in the sera of bipolar disorder patients. However, two post-mortem studies consistently showed a dysregulation of the retroviruses expression in the brain of both schizophrenic and bipolar disorder patients (75-76). Our hypothesis is thus that HERV-W ENV antigenaemia, which expression might be dysregulated as early as in embryo – following infections during pregnancy-, might induce a chronic inflammatory state underlying acute episodes and inducing slow progressive neurodevelopmental and, later, neurobiological impairments. These HERV-W elements are (i) part of the human genome, though varying among individuals and ethnic origins, (ii) can be triggered by environmental agents such as Influenza virus and can be associated with seasonal infections “risk” during pregnancy and, (iii) can then recombine, retro-transpose, or simply transpose within host’s genome, thus creating modifications as early as in embryo’s DNA (Leboyer *et al.*, in press). Nonetheless, these elements can also be triggered later in life by Herpes viridae primary infections in young adult’s life, or with Epstein - Barr virus or Herpes Simplex viruses (78, 83, 89, 90). This reactivation provides potential secondary events boosting HERV-W pathogenicity towards clinical disease, after long-term sub-clinical phase. This potential pathogenic cascade is consistent with “gene-environment” interactions previously evoked in the aetiopathogenesis of schizophrenia and bipolar disorder. HERV-W ENV antigenaemia has been shown to be neurotoxic and to induce a chronic inflammatory state, (85) (87- 88), as revealed by elevated CRP levels. Thus, HERV-W abnormal expression might cause neuronal excitotoxicity and neurotoxicity, yielding neuronal loss associated with cognitive impairment and inflammatory phenomenon, as well as an oligodendrocytes death and subsequent demyelination (85).

This model could largely be applied to bipolar disorder as the expression of these retroviruses, inflammatory processes and infections have been found in the disease.

6. THERAPEUTIC IMPLICATIONS

Viral infections such as sinusitis, sinobronchitis, frequent colds, sore throats, cold sores and genital herpes seem to remit in patients taking lithium ((91-94). The retrospective analysis of Amsterdam *et al.*, tested the antiviral activity of various psychotropic agents in 177 subjects receiving lithium compared to 59 subjects receiving other antidepressant drugs for an affective illness. Chronic lithium administration resulted in a significant reduction in the mean rate of recurrent labial herpes infections when compared to the pre-treatment period. In contrast, the mean rate of herpes infections was unchanged in patients taking other antidepressants and the proportion of subjects reporting reduction in infection rate was greater in the lithium group (71%) compared to those receiving other antidepressants (52%) (95-96). Moreover, the authors found that among healthy women, after one year of lithium treatment, an average of 5.1% monthly reduction in the duration of each episode and a reduction in the total monthly duration of all herpes infections was observed (95). Antipsychotics and mood stabilizers have also antiprotozoal activity. Indeed, lamotrigine was developed from antimalarial drug (97- 98). However, the anti-toxoplasma activity seems to vary between mood stabilizers with a better activity for valproic acid according to one study (98). In the same way, Amantadine, an antiviral compound against BDV, has been demonstrated to attenuate depressive symptoms (99). It has been assumed that amantadine exerts an antiviral and an antidepressive action in bipolar disorder patients infected by BDV (100). An open trial, showed that amantadine appears to display comparable efficacy to standard antidepressants, in depressive bipolar type I patients (101). In this study, the majority of responders ended up with antigen-negative blood tests, whereas more than 80% of the non-responders were still positive for acute markers. The bipolar I patients, who were shown to have a high prevalence for BDV (102 - 103), showed a quick improvement without development of a (hypo-) mania (101). However, a causal relationship of BDV infection and affective disorders is controversially discussed, since amantadine is also known as having certain amphetamine-like, N-methyl- D-aspartate (NMDA)-receptor-antagonistic properties, as well as other effects on neurotransmitter systems (104).

The reciprocal association between inflammation and bipolar disorder have led to propose specific targeted therapeutics. It is well known that antipsychotics, mood stabilizers and ECT have inhibitory effects on cytokines levels of *in vivo* and *in vitro* (14, 125). However, it is often difficult to determine whether changes in the levels of cytokines are the result of the medication’s pharmacological properties or whether they are reflecting changes in the clinical status of the treated patient (13). Furthermore, it has been demonstrated that lithium is associated with a significant reduction of cytokines as

observed in healthy volunteers (127). Studies in bipolar or unipolar patients under lithium treatment (105-107); (22) (108) have shown normalization of immune parameters. Furthermore, Lithium treatment (among healthy subjects) leads to a Th1 to Th2 shift, attenuates transplant rejection (109), and alters disease parameters in Systemic Lupus Erythematosus (110-111).

One of the possible mechanisms is that mood stabilizers downregulate the brain arachidonic cascade (arachidonic acid turnover in phospholipids, expression of phospholipase A2, and cyclooxygenase (COX) enzymes) and therefore downregulate neuroinflammation and excitotoxicity (112). It has also been shown that aspirin, when added to lithium, reduces the disease progression (112). A number of therapeutic trials including anti-COX2 have been conducted. COX-2 inhibitor rofecoxib has shown clinical antidepressant effects. Comorbid depression in patients with osteoarthritis was evaluated in 2228 patients treated with rofecoxib. Before treatment, 15% of the patients had a comorbid depressive syndrome, this incidence significantly decreased to 3%, under treatment with 25 mg rofecoxib (113). Moreover the COX-2 inhibitor celecoxib was shown to have positive effects on cognition – a core-feature of depression (114).

Indeed, in a randomized placebo controlled trial of a COX-2 inhibitor with reboxetine (a noradrenergic-reuptake inhibitor antidepressant), the celecoxib group showed significantly greater improvement compared to the reboxetine-alone group (115). Cox-2 inhibitors are suspected to lower the pro-inflammatory cytokines IL-1, TNF and prostaglandins PGE2. Moreover, treatment with the COX-2 inhibitor celecoxib – but not with a COX-1 inhibitor – prevented the dysregulation of the hypothalamus-pituitary-adrenal-axis, in particular the increase of cortisol, one of the biological key features associated with depression (116). It is interesting to note that COX2-inhibitors seem to exert similar beneficial effects on schizophrenic symptoms according to three independent studies (117-119), raising the question of a common pathogenic pathway. Another interesting therapeutic approach could be the treatment of bipolar depression with omega-3 fatty acids such as eicosapentaenoic acid (EPA). In a 12-week, double-blind study, in individuals with bipolar depression randomly assigned to adjunctive treatment with placebo (n=26) or to 1 g/day (n=24) or 2 g/day (n=25) of ethyl-EPA, significant improvement of clinical symptoms among patients treated by EPA were observed (120). The author concluded that the incorporation of EPA into cell membranes could inhibit the action of phospholipase A2, an enzyme that plays a major role in the production of second messenger molecules, such as arachidonic acid (121-122). Alternatively, it may directly inhibit ‘downstream’ signalling molecules such as protein kinase C (123). However, in this study dietary intake of ethyl-EPA and the distribution among the randomised groups was not documented (124).

7. PERSPECTIVES

In the present paper, we reviewed the different hypotheses underlying the pathogenesis of bipolar disorder, and including the immuno-inflammatory dysregulation, the environmental risk factors as well as the retroviral

hypothesis. The literature has been enriched these recent years with new and promising data which tend to confirm the involvement of immune system disturbance particularly across the different phases of the disease, offering the hope to identify bio-signature as new tools to improve diagnosis and identify prognosis markers. This new approach offers great promises towards a better understanding of etio-pathological mechanisms of bipolar disorder, and for the development of innovative therapeutic strategies to better treat bipolar patients.

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