White matter hyperintensities – from medical comorbidities to bipolar disorders and back

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Abstract

White matter hyperintensities (WMHs) are among the most replicated neuroimaging findings in studies of patients with bipolar disorders (BD). Despite the high rates of WMHs, their role and etiology in BD are not well understood. WMHs occur in multiple other conditions frequently co-morbid with BD. From the available studies it seems that WMHs are not a primary risk factor/endophenotype for BD. More likely, these lesions indicate the presence of medical co-morbidities with specific links to BD. Furthermore, the etiology of the WMHs in BD may represent different processes depending on age. In certain forms of BD, such as pediatric BD, WMHs may represent co-morbidity with developmental disorders. High frequency of migraine in BD and high prevalence of WMHs in migraine may suggest that a substantial proportion of WMHs in early adulthood to midlife BD subjects may be related to co-morbidity with migraine. Among elderly subjects with BD, or those with late-onset BD, WMHs are likely related to the presence of cardiovascular/metabolic disorders. With further research WMHs may enhance our knowledge about various pathological pathways involved in BD, help in decreasing the etiological heterogeneity of BD, and become useful as markers of severity or subtype of BD.

Keywords

Bipolar disorder; cardiovascular disorders; heterogeneity; migraine; multiple sclerosis; white matter hyperintensity

Introduction

Bipolar disorder is a severe and often chronic mental illness that imposes a high burden on patients, their families, and society in terms of increased mortality, human suffering, impaired quality of life, and costs related to hospitalizations and loss of productivity (1,2). The diagnosis of BD is phenomenological, based on description of behavioral

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manifestations, rather than on etiology, pathology, genetic or biological markers of the disorder. These issues contribute to the fact that in a third of the patient population the correct diagnosis is made more than 10 years after the onset of first symptoms, and between 40% and 70% of patients with BD are misdiagnosed (3,4). There is thus a great need for more research into biological underpinnings of BD. Neuroimaging techniques provide ideal tools for the study of processes underlying psychiatric disorders. The neuroimaging findings in BD are, however, inconsistent, often with contradicting results and a few replications (5). Among the most replicated neuroimaging findings in BD are white matter hyperintensities (WMHs) (6).

White matter hyperintensities are localized changes in the water content of the cerebral white matter. They appear as foci of high signal intensity on T2-weighted magnetic resonance images (MRI). White matter hyperintensities may be found in the deep white matter (DWMH) or in periventricular regions (PVH). The histopathological substrate of WMHs is ischemia (predominantly in DWMH), ependymal loss (predominantly in PVHs), demyelination (predominantly in PVHs), or dilated perivascular spaces (7,8). Importantly, WMHs with the same appearance on MRI can be due to different pathological causes (7,8).

Bipolar patients have up to six times greater odds of showing WMHs than controls (6). Despite their frequent nature, the role and etiology of WMHs in BD is not well understood. WMHs in BD are predominantly found in the deep white matter and to a lower extent also in periventricular regions. The histopathology of WMHs appears to be the same in mood disorders as in other diseases (7,8).

White matter hyperintensities are not specific to BD and have been described in multiple other conditions, such as cardiovascular and metabolic (9), genetic (10,11), demyelinating (12), and neurodevelopmental disorders (13,14), as well as migraine (15,16) - all of which are co-morbidities of BD. The fact that the above-mentioned disorders co-occur with BD at greater than chance rates and share a common biological marker, (WMHs), suggests etiological links between these disorders. Learning about WMHs in these conditions might, therefore, advance our knowledge about the etiopathological heterogeneity of BD. Furthermore, a better understanding of WMHs may aid in the diagnosis and treatment of BD. In this paper we thus discuss the etiopathogenesis of WMHs in conditions co-morbid with BD, in order to gain a better insight into the biology of BD.

Vascular and metabolic disorders

A number of studies have reported high rates of WMHs in subjects with cardiovascular or metabolic disorders, including atherosclerosis (9), hypertension (9), diabetes (17), dyslipidemia, and elevated fasting glucose (18). Lesions found in these conditions typically appear in deep white matter, similarly to lesions associated with natural ageing (19).

A proposed etiology of WMHs in cardiovascular and metabolic disorders is a disruption of vascular endothelium and blood-brain barrier, leading to leakage of plasma into surrounding brain tissues and vascular walls, which exposes neurons to altered levels of electrolytes, proteases, and infectious and toxic agents (20). Other potential causes of WMHs in

cardiovascular and metabolic disorders include oxidative stress, chronic inflammation leading to vasodilation and stasis, as well as impaired fibrinolysis (21).

Cardiovascular and metabolic disorders are frequent medical complications of BD (22) and are responsible for the largest number of excess deaths in patients with BD (23). Iatrogenic factors such as the use of weight gain-promoting medications play a role, but they are not the only contributor to this co-morbidity. There is likely an intrinsic association between BD and cardiovascular/metabolic disorders that goes beyond the effects of medications (24). Other factors underlying this association include: lifestyle; socio-economic status; the presence of atypical depressive symptoms (e.g. hypersomnia and hyperphagia with carbohydrate craving); endocrine dysregulation (e.g. hypercortisolemia); immunological effects (e.g. over-expression of inflammatory markers); hemostasis-related factors (e.g. activation of thrombocytes); autonomic nervous system abnormalities (25); or dysregulation of specific biochemical pathways involving the Wnt protein family, the glycogen synthase kinase, or brain-derived neurotrophic factor (26,27).

Considering the high prevalence of WMHs reported in patients with cardiovascular and metabolic disorders, and the high prevalence of cardiovascular and metabolic disorders in BD, it is possible that WMHs in BD are related to co-morbidity with cardiovascular and metabolic disorders (28). A number of studies have provided support for this vascular hypothesis of WMHs in BD. First, WMHs are more frequent in older compared to younger bipolar patients (29,30), whereas the prevalence of WMHs in younger or middle-aged subjects is typically comparable to age-matched controls (31–33). Secondly, patients with mood disorders often exhibit DWMHs, indicative of vascular etiology, whereas lesions in periventricular white matter, indicative of demyelination, are rare (6,34,35). In line with this finding, cardiovascular and cerebrovascular disorders are more prevalent in BD patients with DWMHs compared to those without DWMHs (35). Lastly, WMHs are most consistently found in patients with late onset of BD, which is often secondary to cardiovascular and metabolic disorders (34,36), and patients with late onset show increased rates of WMHs relative to early-onset BD patients or elderly controls (37). It is thus possible that in a subgroup of BD patients that includes elderly or late-onset subjects, WMHs are likely associated with the presence of cardiovascular and metabolic disorders.

The nature and direction of this association, however, is not clear. Cardiovascular and metabolic disorders may predispose individuals to ischemic injury that may then facilitate the development of BD, specifically in late-onset BD (37,38). Although this scenario may provide an explanation for those with late-onset BD, the majority of BD patients manifest their first episode during early and late adolescence when the prevalence of cardiovascular and metabolic disorders is low. A more likely explanation, therefore, is that the onset of BD increases the risk of cardiovascular and metabolic disorders that, in turn, increase the risk for developing WMHs.

In any case, the vascular hypothesis does not appear to provide a sufficient explanation for the presence of WMHs among young BD subjects (6,14,39,40) or in studies using cardiovascular/metabolic disorders as exclusion criteria (41,42). Furthermore, studies have shown a lack of association between cardiovascular risk factors and WMHs in subjects with

BD (43) and a greater proportion of WMH-positive subjects in BD relative to control subjects, despite comparable prevalence of cardiovascular risk factors between groups (41,43). Alternative explanations, therefore, need to be considered to gain insight into the presence of WMHs in these populations of BD subjects. The presence of WMHs in young BD patients, together with the increased genetic burden associated with early onset of BD (44), raises the question of whether WMHs may also be genetically determined in a subset of BD patients.

Genetic risk factors for WMHs

WMHs have some level of genetic underpinnings with heritability of 0.55 (45). Certain genetic factors, such as apolipoprotein E4 (apoE4) allele and Notch3 gene mutations on chromosome 19, found in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), have been associated with WMHs (10,11). In CADASIL, decreased cerebral perfusion secondary to changes in the wall of cerebral arteries leads to early damage of the periventricular and deep supratentorial white matter. The presence of WMHs in apoE4 carriers is thought to result from deficient neuronal repair processes involving lipid metabolism (46).

CADASIL frequently presents with mood disorders, including BD (47), while the apoE4 allele has been associated with early-onset BD with psychotic symptoms (48). Although WMHs and BD are both heritable, the high prevalence of white matter lesions in BD is likely not explained by the above-mentioned genetic factors. The rare nature of CADASIL and the relatively high prevalence of WMHs in BD patients make it unlikely that the Notch3 mutation can account for the presence of WMHs in the majority of BD patients. On the other hand, the ApoE4 allele is relatively prevalent (5.2%–40.7%) (49). It is thus unfortunate that no studies have examined associations between WMHs, BD, and the apoE4 polymorphisms.

In any case, if genetic factors were to provide an explanation for the increased rates of WMHs in BD, then the prevalence of WMHs should be higher in both unaffected and affected relatives of BD patients than among controls. This is not supported by the current literature. A single study reported the presence of WMHs among both affected and unaffected family members within a single family with strong loading for BD (50). The absence of a control group, however, makes the interpretation of this finding difficult. Furthermore, a follow-up study of the same family indicated that the Notch3 gene did not meet criteria for a candidate gene of BD (10). Another study examining siblings of bipolar patients found a higher prevalence of WMHs only in patients, but not in the unaffected siblings (42). Finally, a recent large study showed comparable prevalence of WMHs between affected and unaffected offspring of bipolar probands and controls (32).

The absence of WMHs among relatives of BD probands does not support genetic underpinnings. Other conditions characterized by early onset and presence of WMHs, such as multiple sclerosis (MS), neurodevelopmental disorders, or migraine, might better elucidate the presence of WMHs in young BD patients.

Multiple sclerosis

WMHs are found in 90% of patients with MS and are distinct in their shape and location. Typical demyelinating lesions are oval or linear in shape and found in periventricular areas, the corpus callosum, cerebral and cerebellar peduncles, and the spinal cord (12). Viewed in the sagittal plane, WMHs in MS extend outward from the corpus callosum in a fimbriated pattern known as 'Dawson fingers', and in advanced cases WMHs become confluent, with sharply demarcated foci at the poles of the ventricles (51). Lesions in MS may develop due to edema, inflammation, demyelination, gliosis, and ultimately axonal degeneration (51).

Although depression is the most frequently reported psychiatric manifestation in MS patients (52), BD is up to 13 times more frequent in MS patients than in the general population (53–55). Mood disorders may be the first manifestations of MS (56,57).

Potential explanations for this association go beyond simply the psychological adaptation to having a chronic illness. Mood disorders are more prevalent in MS than in patients with other chronic and disabling neurological conditions, such as amyotrophic lateral sclerosis (58). Additionally, depression is more frequent in MS patients with brain lesions relative to those with only spinal cord involvement, and affective symptoms seem to be related to neurological impairment, but not functional disability (59).

The co-occurrence of MS with mood disorders may be the result of structural damage caused by demyelination in mood-regulating circuits, or an effect of medications used for MS treatment such as corticosteroids or interferons (60). It may also reflect shared autoimmune, infectious mechanisms, or genetic factors, such as the presence of the human leukocyte antigen (HLA-DR₂) (53).

Although the majority of patients with MS have WMHs, only a minority suffer from BD. It is, therefore, a question of whether the development of mood disorders depends on lesion location. To our knowledge, there are no controlled studies comparing lesion location in MS patients with versus without BD. Previous studies, mostly in unipolar depression, have reported that MS patients with co-morbid affective disorder relative to patients with only MS have larger lesions, mostly affecting the temporal lobe (61–63). Additionally, there is evidence that suggests an association between depressive symptoms and temporal (62), frontal (64,65), and periventricular lesions (64), along with lesions in the suprainular white matter (66). These findings are inconsistent, however, as several studies have failed to find different WMH locations between MS patients with depression versus without depression (67,68).

The hypothesis that demyelination within mood-regulating circuits may underlie the co-morbidity between MS and BD has face validity. There is, however, little supporting evidence, as controlled studies testing this hypothesis are missing. Importantly, if the etiology of WMHs in BD is demyelination, then WMHs in BD should resemble those seen in MS, which is not the case. The most typically seen pattern and location of WMHs are markedly different between the two disorders. Whereas patients with MS exhibit well delineated WMHs in locations where ischemic changes are rare, lesions in BD are not well characterized and occupy areas vulnerable to ischemic attacks, such as deep white matter.

Last but not least, considering the base rate of MS (0.9 per 1,000 subjects) (69), only a very small proportion of BD patients in fact suffer from MS.

Overall, the presence of WMHs in the majority of MS patients without BD, as well as in the majority of BD patients without MS, combined with the differences in lesion characteristics between the two conditions may indicate that, in the majority of cases, WMHs in BD are not due to demyelination or co-morbidity with MS.

Neurodevelopmental disorders

Neurodevelopmental disorders such as autism spectrum or attention-deficit/hyperactivity disorders (ADHD) have been associated with WMHs (13,14).

Contrary to schizophrenia, BD is typically not considered to be a neurodevelopmental disorder. Certain forms of BD, such as the pediatric BD may, however, carry a greater burden of co-morbidity with developmental disorders, including pervasive developmental disorders (70,71), and ADHD (72,73).

It is conceivable that WMHs, as an indicator of neurodevelopmental pathology, would be present only in some forms of BD, such as the pediatric BD, but absent in young patients with onset of the illness in adolescence or early adulthood. There is some support for this hypothesis. The majority of reports examining young/middle-aged bipolar patients with age of onset in adolescence or early adulthood did not show an increased prevalence of WMHs (29,32,33,74–76). On the other hand, of the three studies that have investigated subjects with very early age of onset in childhood and early adolescence (40,77,78), only a single study reported increased rates of WMHs in patients versus controls (40). No study directly compared rates of WMHs in BD patients with versus without co-morbid neurodevelopmental conditions.

Migraine

Meta-analytical data have shown that WMHs are four times more prevalent in patients with migraines, relative to the general population, and occur in one-quarter to one-third of migraineurs (15,16). Migraineurs typically present with multiple small foci of WMHs in deep white matter, but also in periventricular and infratentorial (mostly pontine) areas (79,80). The etiology of WMHs in migraine is unclear but may share a subset of mechanisms with those found in ageing or vascular disorders. Reduced perfusion pressure and blood flow, oligemia combined with activation of the clotting system, or vasoconstriction, could lead to arterial or venous micro-embolism, thrombosis, or ischemia. Aside from these hemodynamic/vascular factors, local changes during migraine attacks, such as excessive neuronal activation, neurogenic inflammation, neuropeptide and cytokine release, or excitotoxicity, may cause direct tissue damage (81,82).

Many symptoms of mood disorders are commonly experienced by migraineurs during the prodrome, and occasionally during migraine attacks (82–84). Even more importantly, migraine is frequently associated with BD, with a wide range of prevalence rates (13%–77%) (73,85–87), typically in excess of the prevalence of migraine reported in the general

population (0.7%–21.9%) (88). Migraine is especially frequent in BD-II, early-onset BD, or BD with anxiety disorders (82,85,89). It is also found disproportionately often in unipolar subjects; however, the presence of migraine in unipolar depression may indicate a forme fruste of bipolarity, as patients with unipolar depression suffering from co-morbid migraine clinically resemble BD-II patients (84).

The presence of shared genetic or environmental factors in migraine and bipolar disorders, as well as a specific association between migraine and bipolar disorders, is suggested by the fact that a family history of BD increases the odds of suffering from migraine by four, an effect that is not seen in subjects with family history of unipolar depression (90). In keeping with this, a recent genome-wide linkage study of co-morbid BD and migraine reported an overlapping genetic susceptibility for both disorders (91).

A number of mechanisms centered on metabolic abnormalities have been put forward in search of the overlapping etiology between BD and migraine. These mechanisms are rather distinct from those proposed in the previously discussed conditions. Both BD and migraine share alterations in sodium and calcium ion-channel signaling (channelopathy) (91–93), and disturbances in serotonergic (94), dopaminergic (95), and/or glutamatergic systems (96).

With up to 77% of BD patients suffering from migraine and over one-third of migraine patients presenting with WMHs, migraine co-morbidity may potentially explain a substantial proportion of the WMHs in young bipolar patients. Unfortunately, to our knowledge, there are no available studies comparing the prevalence of WMHs in BD patients with or without migraine as well as in migraineurs with or without BD.

Discussion

In the past, gray matter abnormalities were the focus of brain imaging research in BD. Recently, however, this focus has shifted to changes in WM tracts (97–99). Yet the etiopathogenesis and even the interpretation for the presence of WMHs, the most frequently reported WM abnormality found in BD, continue to be unknown. From the available studies it seems that WMHs are not a primary risk factor/endophenotype for BD (32,42). More likely, these lesions indicate the presence of medical co-morbidities in BD (28).

This does not mean that the particular WMH-causing medical condition is simply superimposed on BD. The greater than chance presence of the above-mentioned medical conditions in BD may indicate a specific etiopathogenetic association between these disorders and BD and may delineate a more homogeneous subtype within BD (100). The co-morbid conditions may be causally related, may have inter-correlated risk factors, or may even represent alternate manifestations of the same underlying liability (100).

To further complicate things, the etiology of the WMHs in BD may be age-specific. In certain forms of BD, including the pediatric BD, WMHs may represent co-morbidity with developmental disorders, predominantly ADHD (40). The epidemiological evidence showing high frequency of migraine in BD (73,85–87) and high prevalence of WMHs in migraine (15,16) with phenotype similar to that seen in BD, together with the early onset of migraine, may suggest that a substantial proportion of WMHs in early adulthood to midlife

may in fact be related to the presence of migraine. Solid evidence shows that among elderly subjects, or those with late-onset of BD, WMHs are likely secondary to the presence of cardiovascular/metabolic disorders (28).

In addition, different types of WMHs may have different pathoplastic effects on the clinical phenotype or severity of BD. Bipolar patients with poor outcome have a higher prevalence of DWMHs but not PVHs compared to patients with good outcome (101). A recent meta-analysis reported that BD-I suicide attempters are significantly more likely to have PVHs than BD-I suicide non-attempters (102), while another study found increased prevalence of PVHs in BD-I than in BD-II or control subjects (103). It is thus possible that the presence of PVHs may be a useful tool for clinicians. Furthermore, these documented pathoplastic effects further support the hypothesis that BD with WMHs is a distinct subtype of BD.

Due to the above-mentioned heterogeneity of WMHs, simply using the presence of WMHs would not be sufficient to decrease the etiopathogenetic heterogeneity of BD. In order to achieve this goal, the particular WMH-causing condition would need to be considered. In other words, BD with WMHs and migraine likely differs from BD with WMHs and cardiovascular disorders. Bipolar disorders and cardiovascular disorders are an example of a sequential co-morbidity, where the presence of cardiovascular/metabolic disorders increases the risk of WMHs and BD (28), as well as vice versa (37,38). On the other hand, BD and migraine may be an example of a multiformity, where the same underlying liability may have two different phenotypic expressions (i.e. bipolar II disorders and migraine), which also share the presence of WMHs (85). It is, therefore, a question as to what extent the co-morbidity between BD and a particular medical condition differs contingent on the presence or absence of WMHs.

Another question is whether the treatment of the co-morbid medical condition would have a positive effect on BD, and whether the treatment of BD would have a positive effect on the medical co-morbidity. There is already limited support for this. Insulin sensitizing treatment has a moderate effect on mood in insulin-resistant depressed patients (104) and may alleviate cognitive deficits in psychiatric disorders (105). Interestingly Li is an inhibitor of glycogen synthase kinase 3 β (GSK3 β) which is critically involved in glucose metabolism, and consequently GSK3 β inhibitors are being tested for treatment of diabetes mellitus type 2 (106).

Certain common causes of WMHs do not seem to play a major role in BD. Considering the phenotype, location of WMHs, as well as the absolute prevalence of MS in BD, it is unlikely that the pathological substrate of these lesions in the majority of BD subjects is demyelination or co-morbidity with MS. Also the genetic underpinning of WMHs in BD is questionable, since WMHs are not present in greater frequency in unaffected or affected offspring of bipolar parents relative to controls (32,42). It is thus of interest that microarray studies have found alterations in expression of myelination-related genes in bipolar patients relative to healthy controls (107). Myelination-related genes are among candidates for biomarkers of BD (108). Perhaps the assessment of macroscopic changes, such as WMHs, is not sensitive enough to investigate the effects of these genes on myelination in BD.

More sensitive methods such as diffusion tensor imaging (DTI) may provide information beyond the resolution of WMHs. Diffusion tensor imaging measures minute changes in the directionality (fractional anisotropy) and rate of water diffusion (apparent diffusion coefficient), thus providing indirect information about microscopic organization of the white matter (109). DTI changes, mostly increases in diffusivity and decreases in directionality of water diffusion, have been frequently replicated in DTI studies of BD (97–99). Furthermore, unlike WMHs, DTI changes have been associated with particular genes (110). No studies, to our knowledge, have directly measured DTI parameters from WMHs. Considering the sensitivity of DTI to subtle changes in the rate and directionality of water diffusion, it may be a useful technique for investigating microscopic changes in white matter before macroscopic changes, such as WMHs, manifest. Furthermore, combining DTI with functional MRI or resting-state connectivity analyses would allow us to study the interplay between structure and function and to investigate the neuronal correlates of emotional processing in BD (111).

To conclude, the WMHs provide a testament to the etiopathogenetic heterogeneity of BD. The phenomenological, symptom-based diagnosis of BD has such broad diagnostic boundaries and includes such a heterogeneous group of conditions that the clinical and predictive validity of this nosological entity is questionable. It is clear that multiple pathological pathways may lead to the same behavioral phenotypes (28), and that the same pathological pathway may have different behavioral manifestations (85). Relying only on the clustering of behavioral symptoms is thus unlikely to allow us to ‘cut nature at its joints’ and to distinguish subgroups of psychiatric conditions with shared etiology. Without the use of validated biological markers our diagnostic options will thus continue to be limited. Considering their frequent nature in BD and their known etiology in other conditions frequently co-morbid with BD, WMHs prove to be interesting heuristically, but also clinically. Perhaps with further research WMHs may enhance our knowledge about various pathological pathways involved in BD as well as become useful as markers of severity or subtype of BD.

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Abbreviations

ADHD	attention-deficit/hyperactivity disorder
BD	bipolar disorders
DWMHs	deep white matter hyperintensities
GSK3β	glycogen synthase kinase 3 β
MRI	magnetic resonance imaging
MS	multiple sclerosis

PVHs	periventricular hyperintensities
WMHs	white matter hyperintensities
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

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Key messages

- White matter hyperintensities (WMHs), one of the most frequently replicated neuroimaging findings in bipolar disorders (BD), are also found in conditions frequently co-occurring with BD.
- Considering their frequent nature in BD and their known etiology in other conditions co-morbid with BD, WMHs may provide new insights into the neurobiology of BD.
- WMHs in BD do not seem to represent primary changes/endophenotypes, but rather may indicate the presence of age-specific co-morbid conditions, with etiological links to BD, including ADHD in pediatric bipolar patients, migraine in early adulthood to midlife subjects with BD, and cardiovascular/metabolic disorders in late-onset or elderly bipolar subjects.