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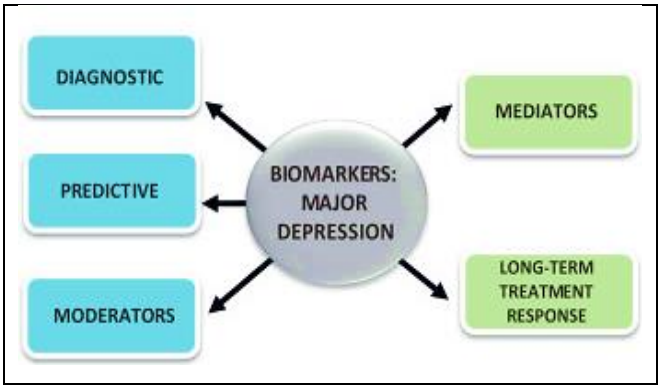
1. Identification and validation of a reproducible metabolomic biomarker signature in patient dried blood spots (DBSs) for bipolar and unipolar depression

Introduction

The two most prevalent mood disorders globally are major depressive disorder (MDD) and bipolar disorder (BD). These are clinically different mental diseases with similar etiologies. Due to similar symptoms, a delayed start of mania, and a high frequency of depressive episodes in BD patients, BD is more commonly misdiagnosed as MDD.[1] Patient self-reported symptoms are subjectively evaluated by psychiatrists, and patients are more likely to seek medical attention during depressive than manic episodes. One possible method for addressing these issues and facilitating an earlier and more objective differential diagnosis of mood disorders is biomarker profiling. However, there are a number of issues with the studies that have been conducted so far: they have used patient samples with different polarities of their symptoms and other uncontrolled factors; they have not included independent validation cohorts; and they have identified disease biomarkers in patients with established BD who have had the effects of mood-stabilizing medication confused.[2] Therefore, the purpose of this study was to determine a repeatable metabolomic biomarker signature in patient dried blood spots (DBSs) that distinguishes BD from MDD during depressive episodes and evaluate the value gained by combining it with patient self-reported data.



Methods

The Delta study's samples and data were used in this diagnostic analysis. An online survey with 635 adaptive questions, including items from the Mood Disorder Questionnaire (MDQ) and the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS), was designed specifically for 241 participants. The main goal was to identify BD in patients who had been diagnosed with MDD recently (within the last five years) and who were experiencing depressive symptoms at the time (Patient Health

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Questionnaire–9 score of 5 or higher). Participants were chosen through online voluntary response sampling.

Results

The discovery cohort consisted of 241 patients, of which 170 (70.5%) were female, 67 (27.8%) were later diagnosed with BD, and 174 (72.2%) were proven to have MDD. The mean (SD) age of the patients was 28.1 (7.1) years. The validation cohort comprised 30 individuals, of which 16 (53%) were female, 9 (30%) had a diagnosis of borderline personality disorder (BD), and 21 (70%) had major depressive disorder (MDD). The participants' mean (SD) age was 25.4 (6.3) years. DBS metabolite levels were measured in 241 patients who had recently been diagnosed with MDD and had depressive symptoms; 67 of these patients later received a diagnosis of BD by the Composite International Diagnostic Interview, while 174 patients were confirmed to have MDD. Ceramide was the strongest biomarker, with an identified 17-biomarker panel providing a mean (SD) cross-validated area under the receiver operating characteristic curve (AUROC) of 0.71 (SD, 0.12; P <0.001) (Figure 1). Models based on detailed demographic data, PHQ-9 scores, and mood disorder questionnaire results showed considerably improved diagnosis performance when biomarker data and patient-reported information were combined. During the study's one-year follow-up period, a different group of patients who were newly diagnosed with MDD or BD were able to validate the found biomarkers, which were predominantly connected with lifetime manic episodes.

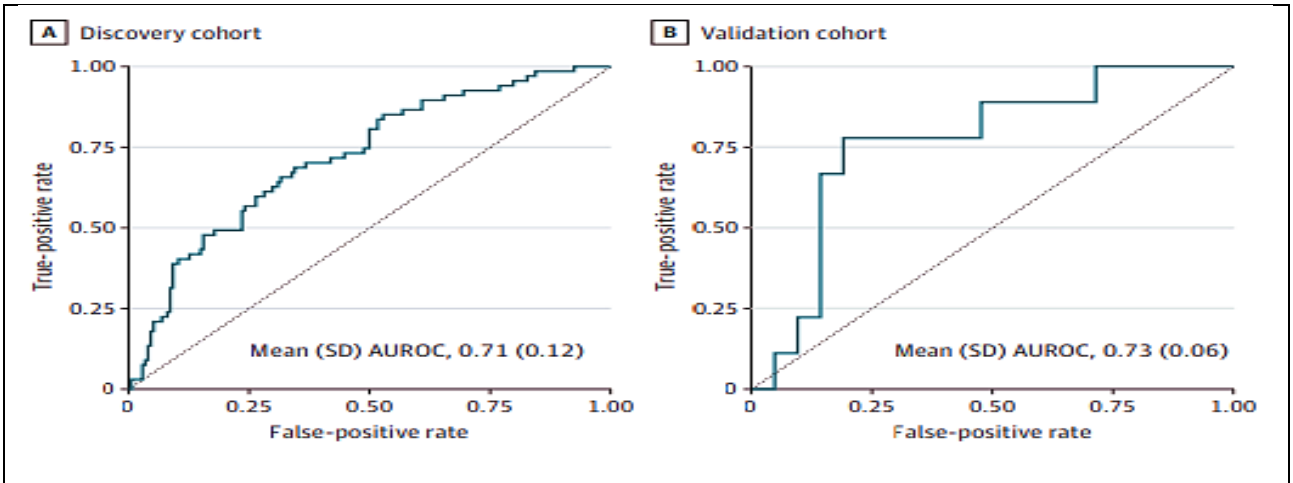

Figure 1. The dried blood spot metabolic signature, which distinguishes bipolar disorder from major depressive disorder in patients with current depressive symptoms.

Discussion

According to this study, adding biomarker measurements to diagnostic models based on patient self-reported data improves the models' capacity to differentiate between MDD and misdiagnosed BD during depressive episodes, potentially producing benefits that are clinically significant. Primarily associated with manic symptoms, the biomarkers were consistently found to be their surrogate markers.[2] According to Bernal-Vega S et al., ceramides on their own can integrate and modify brain networks, shifting focus from metabolic supplies to brain cells. This maintains brain neurochemistry and, when disturbed, increases the risk of psychiatric illnesses.[3]

Conclusion

This diagnostic investigation improved the predictive power of diagnostic models based on self-reported patient data and found a repeatable metabolomic biomarker signature in patients' DBSs that successfully distinguished misdiagnosed BD from MDD during episodes of depressive symptoms.

In clinically relevant situations, metabolomic profiling of patient DBS samples may help with mood disorder differential diagnosis.

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2. Associations between sleep issues, suicidal thoughts, and psychopathology in initial episode psychosis

Introduction

Insomnia is a prevalent symptom in schizophrenia, regardless of drug status or clinical course, and it may be caused by disordered and misaligned circadian rhythms. Sleep disruptions and anomalies in sleep architecture and spindles may be connected with the severity of symptoms, according to a new comprehensive study of individuals with early psychosis. Moreover, there is a strong correlation between suicidality and insomnia in those with mental illnesses.[1] This relationship was especially important for people with schizophrenia, who have a 27% lifetime suicide attempt rate and a 5% lifetime suicide death rate. Several studies have found an association between sleeplessness and suicidal ideation and behavior (SIB), including suicide death, in individuals with chronic schizophrenia, although only one of these investigations used a longitudinal approach. Additionally, there were some evidence that in patients with early psychosis, sleep disruption and SIB were related.[2] This study examined relationships in a cohort of individuals with first-episode psychosis between sleep issues, suicidal thoughts, and psychopathology.

Methods

Using regression models, 403 participants' data from the Recovery after an Initial Schizophrenia Episode (RAISE) study was used in this secondary analysis. Diagnoses were made by blinded, remote, centralized professionals using live, two-way video and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV. Excluded diagnoses included affective psychosis, drug-induced psychotic disorder, psychosis brought on by general medical disorders, moderate head trauma, and other serious medical conditions. Every participant had taken antipsychotics for at least six months and had only ever had one psychotic episode. Subjects were monitored for 24 months. This study's primary goal was to investigate the associations between sleep issues over the previous 2 to 4 weeks, suicidal thoughts during the previous 2 weeks, and psychopathology during the previous week for participants at baseline, 6, 12, 18, and 24 months.

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Results

At baseline, there were 57% of people with sleep issues and 15% of people with suicide thoughts. At baseline, 6 months, and 18 months, there were statistically significant variations in the incidence of suicidal thoughts between subjects with and without sleep disorders (Table 1). Baseline sleep issues were linked to a higher risk of suicidal ideation in the study, with evidence of a dose-dependent connection (OR = 2.25, 95% CI 1.15–4.41, P =0.018) after adjusting for potential covariates. Over the course of 24 months, there was a more than 3-fold increase in the odds of concurrent suicidal thoughts when sleep issues were present at any time (OR = 3.21, 95% CI 1.45–7.14, P =0.004). Chronic sleep problems were nearly 14 times more likely to advocate suicide ideation than those without sleep problems (OR = 13.8, 95% CI 6.5–53.4, P <0.001). Sleep issues were associated with higher Positive and Negative Syndrome Scale total (β = 0.13-0.22), positive (β = 0.14-0.25), and general (β = 0.16-0.27) subscale scores at baseline and follow-up visits (P <0.01 for each).

Suicidal Ideation by Visit	Total *N*	Concurrent Sleep Problem Yes *n* (%)	No *n* (%)	*P*-value
Baseline	403			.02
Yes		45 (40.0)	15 (25.1)	
No		183 (60.0)	170 (74.9)	
6 months	291			<.01
Yes		22 (17.9)	10 (6.0)	
No		101 (82.1)	158 (94.0)	
12 months	256			.06
Yes		11 (10.7)	7 (4.6)	
No		92 (89.3)	146 (95.4)	
18 months	221			.02
Yes		12 (11.4)	4 (3.4)	
No		93 (88.6)	112 (96.6)	
24 months	205			.17
Yes		7 (8.1)	4 (3.6)	
No		79 (91.9)	145 (98.4)	
Any	404			<.01
Yes		79 (25.6)	8 (8.3)	
No		229 (74.4)	88 (91.7)	

[a]*P*-values are from Chi-square test.

Table 1. Sleep issues and suicidal thoughts

Discussion

Studies on patients with early psychosis have the advantage of minimizing residual confounding from other illnesses and treatment effects. The large sample size and the examination of numerous potential confounding factors are two other strengths of the current study. This study revealed a 57% prevalence of sleep issues and a 27% prevalence of terminal insomnia.[2] According to the Batalla-Martín D et al., the prevalence of insomnia varies according to the diagnostic criteria; however, the population with schizophrenia exhibits a high prevalence of certain clinical characteristics. The quality of life is reduced for those who suffer from insomnia.[3] Suicidal thoughts, lifetime suicide attempts, and increased psychopathology were linked to insomnia in schizophrenia patients. The clinical management of patients with schizophrenia may benefit from a formal examination of insomnia as a sign of increased suicide risk and intensity of symptoms.[1]

Conclusion

The current study concluded that in first-episode psychosis, sleep disorders were very common and linked to increased psychopathology and suicidal thoughts. Formal insomnia assessment and treatment appear to be important in the therapeutic care of psychotic patients because they predict suicidal thoughts and symptom severity.

Sleep issues were a prominent symptom in a large study of first-episode psychosis patients, affecting more than half of them at baseline.

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3. Investigation of the correlation between severe or treatment-resistant depression and inflammatory joint disease

Introduction

Depression has been linked to autoimmune or immune-mediated inflammatory joint diseases (IJDs), including psoriatic arthritis (PsA), ankylosing spondylitis/spondyloarthropathies (AS), rheumatoid arthritis (RA), and juvenile idiopathic arthritis (JIA). The most studied IJD in terms of depression is RA, which has an estimated risk of serious depression of 17% in meta-analyses. Additionally, PsA, AS, and JIA have been linked to an increased incidence of depression. On the other hand, autoimmune disorders, such as IJDs, are more common in those who suffer from depression. Cohort studies using large administrative healthcare datasets conducted over the past ten years have demonstrated this elevated risk for RA. In addition, a number of case-control studies utilizing primary care data in the UK revealed depression as a risk factor for AS and PSA.[1] The immune system's involvement in inflammatory responses and other disorders that affect the central nervous system have been proposed as important contributors to the pathophysiology of depression, even though the exact details remain unclear. Apart from the aforementioned pathophysiologic factors, depression has also been linked to systemic comorbidities such as cardiovascular disease.[2] Depression severity may be estimated by treatment response and cycling. The term "treatment-resistant depression" (TRD) refers to the condition in which at least 30%, and in some studies as high as 50%, of individuals with depression do not experience remission following two or more antidepressant trials. Compared to milder and/or treatment-responsive depression, phenotypes associated with severe depression and TRD may be more strongly linked to elevated systemic inflammation. It's still unclear, though, if this means a higher risk of autoimmune diseases in general and IJD in particular. It is also unknown whether IJD patients who develop depression are more likely to experience these depressive subtypes.[1]

So, this study was conducted to determine whether depression's severity or resistance to treatment has an impact on the association between depression and inflammatory joint disease (IJD; RA, PsA, AS, and JIA).

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Methods

This parallel cohort and case-control study was carried out among 600,404 patients experiencing a depressive episode. The case-control study defined exposures as any instance recorded in the registers of any of the following: a) IJD, b) RA, c) PsA, d) AS, and e) JIA. Depression, severe depression, and treatment-resistant depression (TRD) were the three categories used to describe the outcomes. Only those who had never before appeared in the outcome registers prior to the matching date were included. Patients with depression were compared to matched population comparators in terms of their prospective and retrospective risk for IJD. Similarly, similar relationships were examined in cases of severe or treatment-resistant depression. Comorbidities and sociodemographic factors were taken into account while adjusting the analyses.

Results

Comparing patients with depression to population comparators, they showed a higher adjusted hazard ratio (aHR) for any IJD 1.34 [95% CI 1.30–1.39], for RA 1.27 [1.15–1.41], PsA 1.45 [1.29–1.63], and AS 1.32 [1.15–1.52]. According to case-control studies, patients with depression were more likely than population controls to have a history of IJD. The adjusted odds ratios, or aORs, for any IJD were 1.43 [1.37–1.50], RA 1.39 [1.29–1.49], PsA 1.59 [1.46–1.73], AS 1.49 [1.36–1.64], and JIA 1.52 [1.35–1.71] (Figure 1). There was no significant difference in these relationships between TRD and severe depression. An aOR of 1.01 was obtained when comparing the history of IJD among patients with severe depression and non-severe depression. A history of AS was significantly associated (aOR 1.23). There was an aOR of 1.02 for patients with TRD who reported having a history of IJD compared to non-TRD controls. Comparable, non-significant correlations were identified for the individual IJDs.

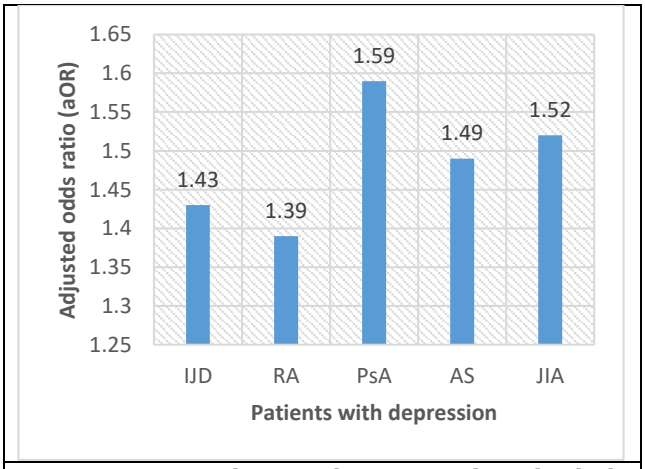

Figure 1. Compared to population controls, individuals with depression were more likely to have a history of IJD in case-control studies.

Discussion

This study's findings on the risk of IJD among individuals with depression are consistent with prior population-based studies with similar risk magnitudes. For individuals suffering from depression, this cohort study represents the first to specifically examine the risk for PsA or AS.[1] However, Lewinson RT et al. discovered that depression raised the chance of PsA development by 37%.[3] Similarly, using the same data source, the Meer E et al. demonstrated risk variables in a case-control study on RA, PsA, and AS and discovered significantly higher risks for a history of depression in all three diseases.[4]

Conclusion

The current study concluded that there was a bidirectional link between IJD and depression; however, this association does not appear to be impacted by the intensity or resistance to treatment of the depression.

Clinicians should be aware of the possibility of somatic comorbidities, such as inflammatory joint disorders (IJDs), in all patients with depression, not only those with severe or treatment-resistant depression (TRD).

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4. Case report on Postpartum Obsessive-Compulsive Disorder

Introduction

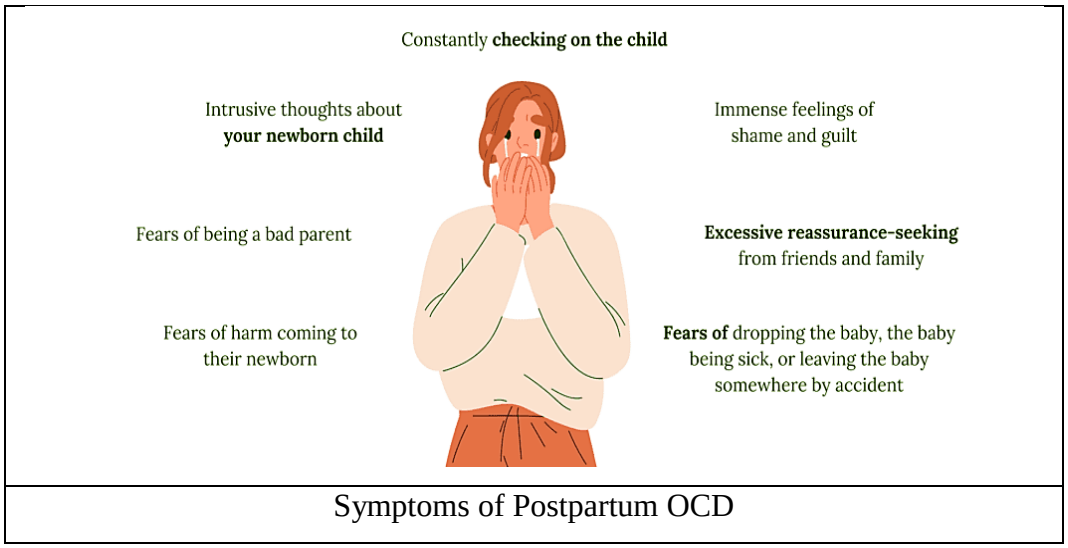
Anxiety-inducing and distressing obsessions or compulsions are the hallmark of obsessive-compulsive disorder (OCD). The great variation in people's presentations makes it challenging to differentiate between OCD cases, but it also opens up research possibilities.[1] Obsessions are defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as involuntary, recurring thoughts or desires that, in the majority of cases, generate noticeable concern or distress. Even in prenatal women without OCD, or obsessive-compulsive disorder, obsessive symptoms are often seen. Persistent thoughts about causing damage to the infant are a particularly distinctive and common characteristic of postpartum obsessions. This distinguishes postpartum psychosis, also called short psychotic disorder with postpartum onset, from postpartum onset OCD (ppOCD), which manifests as ego-syntonic wanting to harm the newborn.[2] This case report presented the distinctive appearance of postpartum-onset OCD (ppOCD) in a first-time father.

Case presentation

A 33-year-old male patient with a history of childhood depression and self-described "panic attacks" at the age of 18 came to his primary care clinic complaining of intrusive thoughts and a depressing state lasting for ten days. After the patient's first child was born eight months ago, he reported being a "very caring father" and sharing childcare duties. However, the patient had his first intrusive thought 10 days before the presentation. He was strolling with his kid in a stroller when he suddenly had the strong desire to drop her off in the middle of the road and head back home. The patient became quite depressed as a result of this thinking, as it was so upsetting. Since then, he claimed to have been sleeping most of the time, not eating or drinking enough, and being unable to carry out his usual everyday tasks. He also avoided spending alone time with the infant because he was afraid he would act on these compulsive impulses. He claims that while he is not sleeping, he frequently ruminates and conducts extensive studies about his symptoms. The patient was obviously nervous during the interview, displaying a conspicuous dysphoric mood and congruent affect. He also started crying a

lot during the conversation. He scored 22 on the nine-item Patient Health Questionnaire (PHQ-9) that he completed during the consultation.

Following the interview, the patient had a follow-up appointment with the on-site social worker, who devised a safety plan and referred the patient to a community mental health organization for the following day's examination. After the visit, the patient said he felt better and had greater hope for a speedier recovery. The patient agreed to a laboratory workup that included thyroid tests, a complete metabolic panel, and blood counts. All of the test results were normal. Escitalopram 20 mg daily was prescribed, and a 2-week follow-up appointment was set up for the patient. However, the patient was admitted to the emergency department (ED) the next day because his thoughts were becoming increasingly intrusive. He said that although at first he felt better, the thoughts kept coming back and were harder to "brush off." He denied once more having any desire to hurt his daughter or himself. He also denied having any physical symptoms, using drugs or alcohol, or having hallucinations. The patient in the emergency department was willing to go into an inpatient mental health center of their own choice. Following his relocation to a mental health facility, the patient began taking 20 mg of escitalopram and 5 mg of aripiprazole daily. After ten days in stable condition, he was allowed to go home after it was decided he could receive treatment in an outpatient facility without risk.



Symptoms of Postpartum OCD

After one month, he reported a dramatic improvement in his symptoms and denied having intrusive thoughts in the previous two weeks. The patient reported that his symptoms were under control two months after being discharged, and he had not experienced any intrusive thoughts thereafter. At this

point, his PHQ-9 score was 8. Aripiprazole dosage was lowered from 5 mg to 2 mg per day due to side effects of the medication and the patient's conditions improving significantly. He reported that his symptoms were still in remission and that the side effects had lessened two weeks later. Since his PHQ-9 stayed constant, it was decided to totally stop taking aripiprazole. Since then, the patient has visited numerous times, sometimes as long as four months after the initial presentation, and has not seen any recurrence of intrusive thoughts or well-controlled depression symptoms.

Discussion

Mothers and fathers have similar symptom profiles and intrusive thoughts connected to their babies. But the evidence that is now available indicates that women might be more distressed by intrusions than men. Additionally, evidence was provided to support the idea that dysfunctional beliefs play a part in the emergence and maintenance of post-OCD.[3] There is currently a lack of information regarding particular drug regimens for OCD patients during the perinatal stage. Clomipramine or selective serotonin reuptake inhibitors (SSRIs) are recommended first-line treatments for ppOCD.[4] Aripiprazole and an SSRI were prescribed as a dual therapy for the patient in the case study.[2]

Conclusion

A rare condition that is probably underdiagnosed, paternal postpartum onset OCD may have a significant negative impact on the quality of life for new fathers and their families. Many OCD assessment tools are available; however, they are rarely, if ever, utilized to determine whether a father has paternal ppOCD. Pharmacologic therapy options that are well-defined and efficacious are also available for treating non-pregnancy OCD, and they appear to be just as successful for patients with ppOCD.

Cognitive behavioral therapy (CBT), especially when combined with pharmacotherapy, is widely accepted as the primary first-line treatment for obsessive-compulsive disorder (OCD).

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