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A Case Report: A 15 Year-Old-Female with Elevated C - Reactive Protein, Major Depression and Maltreatment in Early Childhood

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Brielle A. Marks*, Kyle Humphrey, Nim Chan and Melanie V. Rowson
Trinity School of Medicine, USA
Address for Correspondence:
Brielle A. Marks, Trinity School of Medicine, 5755 North Point Parkway, Suite 230, Alpharetta, GA 30022, USA, Tel: (215) 815-9090; E-mail: briellealanamarks@gmail.com

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Abstract

Ms. S is a 15 year old female with refractory major depressive disorder. She has a history of early childhood maltreatment and currently has an elevated C - reactive protein (CRP) concentration. Many studies have found CRP to be elevated in patients with major depressive disorder. A recent study found that having a CRP>3 mg has a strong connection with symptoms of major depressive disorder [1]. Another study of patients with a prior history of maltreatment before eight years of age, showed elevated CRP levels once they have reached adolescence [2]. Drugs targeting inflammation, such as Infliximab and Acetylsalicylic Acid (ASA), have shown early promise in the treatment of depression. Infliximab outperformed placebo in patients with treatment resistant depression and an elevated CRP [3]. ASA in combination with an SSRI showed a 52.4% response rate in non-responding patients [4]. Therefore, further studies of anti-inflammatory drugs in the treatment of depression are needed, especially in combination with standard treatments.

Objective

To consider treatment of antidepressant resistant patients to combine or substitute antidepressant medications with anti-inflammatory medications.

Clinical Case

Ms. S is a 15 year old Caucasian female with a past medical history of Ehler Danlos, obsessive thoughts, anxiety attacks, PTSD, and depressed mood and sadness. At the age of 5, the patient had experienced her first encounter of child molestation from her grandfather and the abuse continued for several years until she was about 10 years old. She first began to experience a depressed mood in fourth grade, and this lasted for about two years until she was well into the sixth grade. During this time the patient developed self-injurious behavior that involved cutting her thighs, abdomen and arms with razor blades. After the news of the molestation came to light during a therapy session, CPS was contacted, and an investigation was opened against the grandfather. During this time, the patient started exhibiting symptoms of anxiety as well as multiple, obsessive thoughts that she found to be disturbing in nature. She was followed by outpatient care in 2013-2014 and was later recommended for a six-eight week intensive outpatient program (IOP) on April 24, 2015 for her self-injurious behavior, anxiety and depression.

Four days after admission to IOP, on April 28, 2015, Ms. S was hospitalized for suicidal ideation with intent to harm by cutting her wrists. She was later discharged from the hospital on May 5, 2015 and shortly after, was re-admitted to IOP about a week later. During this time, the IOP provided medication management, high intensity counseling and support which included group therapy, art therapy, individual and family therapy. Through therapy she continued to have thoughts of self-harm with depressed mood.

After a week in the IOP program, the patient had her first appointment with the Psychiatrist. At this time, she was taking Duloxetine 30 mg, but was reporting experiencing gory visions. Ms. S had previously taken SSRIs in the past, but those were quickly discontinued after the patient reported having visions of "dead people", "bloody images", and hearing "screaming". During this appointment, the Psychiatrist continued the Duloxetine, but added Aripiprazole 5 mg to the patient's regimen.

5 weeks after starting Aripiprazole 5 mg and Duloxetine 30 mg daily, the patient reports to the Psychiatrist that her mood had improved from "depressed to neutral". However, she continued to have thoughts of harming herself, passive suicidal ideation, uncomfortable flashbacks to her childhood abuse, as well as flashes of gory images in her head of "knives and murder" of people she has never seen before. At this point, her Psychiatrist increased her Duloxetine level from 30 mg to 60 mg. Shorty after this appointment, Ms. S reported to her mother that due to the stress of a close friend moving away, she had started self-harming again by cutting "up and down her arms", as well as on her chest, stomach and shoulder with razor blades. At this point, her mother and the IOP team developed a crisis plan. With the support of the IOP program and her outpatient therapist, Ms. S's mother actively sought outpatient DBT treatment.

After 21 days in IOP treatment, Ms. S was discharged and referred to Dialectical Behavioral Therapy and follow-up appointments with the Psychiatrist. The patient's DBT was oriented around her self-injurious behavior and her previous abuse. During another appointment with the Psychiatrist, a Center for Epidemiological Studies Depression Scale for Children (CES-DC) was done. The patient's total assessment score was 43, which correlates with a diagnosis of moderate depression. She describes having neutral

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moods that would quickly switch to depressed mood with self-injurious thoughts and behavior. By this time, Ms. S reported feeling this way 1-2 times per week despite compliant attendances to DBT and family therapy.

Then, approximately a month later, the patient had her next appointment with the Psychiatrist to whom she reported having multiple panic attacks during the first week at school, as well as self-injuring three days prior. A CES-DC was redone at the appointment, and her scale from a 43, a month prior, increasing to 46. The patient's Duloxetine was increased from 60 mg to 80 mg and Aripiprazole 5 mg was kept the same. For months following this appointment, the patient continued to have self-injurious behavior and depressed mood, and the Duloxetine was increased to 90 mg.

By winter of the following year, the patient reported self-injurious behavior 24 hours prior, which resulted in 10 to 12 cuts with a thumbtack on her ankles. Over the last few weeks, the patient also reported feeling "dissociated" and "dazed". Her mother was advised to monitor the patient closely at home and take the patient to the emergency room or call 911 if she was unsafe. Soon after, the patient was readmitted to the IOP program that winter for self-injurious behavior, anxiety, and depression.

Due to lack of a positive response to her current treatment regimen, the Psychiatrist recommended a genetic study to determine the appropriate treatment plan for the patient based on her biology. This genetic study is a psychogenetic combinatorial approach that allows physicians and patients to understand their body and the ability of their body to metabolize medication appropriately. Ms. S' results showed that she is a poor metabolizer of the CYP2D6*4 allele enzyme with reduction in both allelic enzymes, CYP2C9*2 and CYP2D6*9, making it difficult for her metabolize specific medications. In addition to these allelic reductions, Ms. S also showed that she carries the T allele C677T polymorphism in the MTHFR gene. Patients carrying this gene experience difficulty in metabolizing folic acid. As a result, the patient has a decreased amount of homocysteine and folate levels in the body. These metabolites are essential building blocks for the formation of mood neurotransmitters.

Based off these results, her medications were changed at her following appointment with the program Psychiatrist, and L-methylfolate 15 mg, a medical food, was added to the patient's treatment regimen for depression with a plan to taper off Duloxetine and add Desvenlafaxine. Her Aripiprazole was discontinued and Lurasidone 20 mg was started. The patient reported another self-harming episode that resulted in cuts on her inner thighs, and complained of having frequent, violent, suicidal thoughts. Her medication regimen was then changed to Duloxetine 50 mg, Lurasidone 20 mg, Desvenlafaxine 25 mg, and L-methylfolate 15 mg. All of these medication adjustments were made due to the recommendation of the genetic results and the patient's physiologic response to the medications.

By the spring, Ms. S complained of experiencing frequently fluctuating high and low moods. During her elevated moods, Ms. S describes herself as being uncharacteristically talkative and impulsive with continuous racing thoughts, as well as experiencing insomnia during this period. Ms. S's Lurasidone 20 mg was increased to 40 mg and her Duloxetine 50 mg was decreased to 30 mg with a plan to taper to 20 mg. Later, her Lurasidone was increased to 60 mg and her Duloxetine was tapered to discontinue. The patient then reported in June 2016 of having another hyper-elevated mood episode, upon which her Lurasidone was then increased from 60 mg to 80 mg.

Given Ms. S' refractory depressive symptoms, the treating psychiatrist ordered a typical metabolic panel which included tests for C-reactive protein. The C-reactive protein was added to the panel in order to seek alternative treatment options based off of current literature. Her results were received and indicated some metabolic abnormalities, including an elevated CRP of 5.8 (normal limit of 0.4-4.9). This result correlates with recent studies which have suggested that elevated inflammatory cytokines is correlated to an increase in risk of depression. The lab results, in respect to the elevated CRP, were addressed by the psychiatrist and discussed with Ms. S and her treating pediatrician.

Ms. S claims that she is doing well and able to cope with life stresses. Her treatment regimen hasn't changed. She is soon graduating from DBT and seeking an outpatient therapist. She denies any recent self-harm or suicidal ideation, to date.

Discussion

Studies are currently showing the relationship between C-reactive protein (CRP) and depression as well as the effects of CRP on neurotransmitter pathway and the basal ganglia. Our goal for this paper is to (1) discuss the pathway of C-reactive proteins effects on neurotransmitter synthesis and metabolism; (2) explore the relationship between C-reactive protein and depression in a case setting; (3) consider the connection between child maltreatment and elevated C-reactive protein; (4) treatment options for elevated C-reactive protein in refractory depression.

C-reactive protein (CRP) is an inflammatory cytokine that is stimulated in response to illness or trauma. This inflammatory cytokine is under the control of Interleukin-6 that stimulates the hepatocytes in the liver to release CRP during an acute phase reaction [5]. Current research being conducted is showing major support for the relationship between the immune system, increasing CRP, and the association with depression [5]. Inflammatory cytokines impact the tryptophan pathway causing an increase in glutamate and manipulation of pertinent mood neurotransmitters like dopamine, norepinephrine and serotonin [1,6].

Inflammatory cytokines interrupt indoleamine 2,3 dioxygenase; this enzyme is required for the breakdown of tryptophan, the primary building block for serotonin, and conversion into kynurenine. In the brain, kynurenine is then converted by microglia and macrophages to quinolinic acid. Quinolinic acid then affects glutamate in the astrocytes by binding to the N-methyl-D-aspartate receptors. By binding the product to the receptors, it no longer allows astrocyte reuptake of glutamate. Research has found that decreased levels of quinolinic acid to be associated with depression-like symptoms: specifically anhedonia [7]. Cytokines have also been associated with the re-uptake pathway of monoamines. The mediated effects of the cytokines under the mitogen-activated protein kinase pathways can influence the increase in activity of the serotonin, norepinephrine and

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dopamine membrane transporters [6].

Not only do inflammatory cytokines interfere with important neurotransmitters, but they also cause damage to neural tissue as well. Inflammatory cytokines stimulate microglia and astrocytes to release reactive oxygen species and nitrogen species. In combination with quinolinic acid, these free radicals can cause significant oxidative damage leading to disruption of the lipid membranes resulting damage of neuronal cells and serotonin transmission [6,7]. Having a decrease in these neurotransmitters causes the chemical imbalance that is associated with depression and mood disorders.

Inflammation and the inflammatory response can also be caused by maltreatment-associated trauma increasing risk for depression. This activation of the inflammatory pathway occurs both peripherally and in the brain. These stressors, like early life childhood maltreatment, can cause an increase in peripheral CRP levels [6]. Examples of maltreatment used in studies are as follows: taken into foster care, physically hurt by someone, sexually abused, separated by mother, and/or separated by father [2].

A retrospective analysis was conducted by Slopen and her research team, who analyzed children ranging 1.5-8 years of age, and have experienced maltreatment. Simultaneously, their mothers were asked if their child had experienced any of the above-named maltreatments, and to what severity on a four-point scale. The scale was rated by (0=no experience; 4=very upset by the event). The sum was totaled across the seven encounters for each of the five events listed. The information was then placed in a z-score. The results were as follows, taken into foster care: 3-5; physically hurt: 122-181; sexually abused: 1-8; separated from mother: 125-383; separated from father: 286-876 [2]. "At age 10, CRP and IL6 were significantly correlated with each other ($r=0.46$, $p<0.0001$); and each was also significantly correlated with CRP at age 15" [2]. The C-reactive protein serum levels were then recorded from these patients once they reached the ages of 10 and 15 years old.

In patients ranging from ages 1.5 through 6 years of age showed no correlation between IL6 and CRP. When examining patients in the 7 and 8 year old age group, they showed elevated IL6 and CRP; IL6 (B=0.07, p=0.002) and ($B=0.05$, $p= <0.001$) respectively; and CRP ($B=0.06$, $p=0.002$) and ($B=0.04$, $p=0.03$). Ages 2.5, 3.5, 4.5, 6, and 7 years, were not strongly associated with elevated CRP at age 15. However, at 8 years old, CRP was significantly elevated at age 15 (B=0.05, p= 0.02) with cumulative event scores of ($B=0.05$, $p=0.04$) [2]. In this model explored by Slopen and her team, it was concluded that there was an association between depression and elevated CRP in patients 15 years of age. There was a marked increase in inflammatory cytokines by the age of 10 in patients who were exposed to maltreatment before the age of 8. This inflammatory process continued from childhood into adolescence [2].

In another study, patient's plasma and CSF CRP were used to determine whether the elevation of CRP was connected to major depression. The experiment examined the relationship between plasma CRP and CSF CRP on basal ganglia concentrations of glutamate. Patients were divided into three groups - Low CRP (<1 mg), medium CRP (1-3 mg), and high CRP (> 3 mg). Patients who fell into the "high CRP" category resulted in increased basal ganglia glutamate concentrations when compared to the low CRP group [1]. This study further showed that increased concentrations of glutamate is connected to elevated CRP and the symptom of anhedonia.

A meta-analysis was conducted by extrapolating data from multiple papers regarding inflammatory markers and major depression. The material was then analyzed according to each inflammatory marker and its impact on major depression in that patient profile. Articles that analyzed patients with a diagnosis not based on the DSM criteria, minor depression, bipolar disorder, or co-morbidities were excluded from the material [8]. After proper exclusion was made, there were 58 articles left that were analyzed and 20 of those papers included C-reactive protein. In these papers, "there was a medium association with CRP and major depressive disorder (MDD) (N=20, combined d=0.47; 95% CI =0.28-0.65; total MDD=746). Statistical significance ($p<0.00001$) was achieved after 14 studies, and the association did not change after six more studies were conducted" [8]. Patients were asked to stop the use of antidepressants before their blood samplings. These samples revealed a strong association between major depression and elevated inflammatory markers.

It has been shown that CRP and other cytokines present in the peripheral blood are associated with inflammation and depression. Targeting inflammation could open new doors in the treatment of those with depression and increased inflammatory markers especially in patients who are refractory to traditional antidepressant treatments. There are several anti-inflammatory approaches that can be made to assist in the treatment of depression. One method is to inhibit TNF- α by using a cyclooxygenase 2 inhibitor. This method has been shown to decrease depression in patients in this trial [3].

In a study done by Miller et al. that used infliximab (a TNF inhibitor) on treatment-resistant depressed individuals, it was found that infliximab outperformed placebo and had similar effect size as standard antidepressants in patients with a CRP concentration ≥ 5 mg [3]. There was also "separation from placebo" in the group with a CRP concentration>3 [3].

Another study used acetylsalicylic acid (ASA) in combination with a selective serotonin reuptake inhibitor (SSRI) in non-responder depressed patients. 160 mg/day of ASA was added to the patients' current antidepressant regimen and resulted in a 52.4% response rate. "Remission was achieved in 43% of the total sample and 82% of the responder sample. In the responder group, a significant improvement was observed within week 1 (mean Hamilton Depression Rating Scale-21 items at day 0=29.3±4.5, at day 7= 4.0±4.1; P<0.0001) and remained sustained until day 28" [4]. Therefore, the ASA in combination with the SSRI had an "accelerating effect" on the treatment [4]. This could clinically be useful since the effects of SSRIs often aren't seen until three weeks after the initiation of treatment. It would also be useful to study the ASA-SSRI combination in patients with elevated CRP. A pitfall to the use ASA and SSRI is that both medications cause an increased risk for bleeding. More research should be explored in the use of ASA and SSRIs in the pediatric community and the risks of bleeding.

Conclusion

There are currently many theories being studied in the clinical

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psychiatric community, some having to do with neurotransmitters and inflammatory cytokines. Studies show that there is correlation between elevated CRP levels and depression. It has also been shown that maltreatment in early childhood relates to elevated CRP in adolescence. Ms. S, a 15 year old female with a CRP of 5.8 and a history of sexual abuse, falls into both of these categories. Ms. S, also experienced multiple changes to treatment options and therapy, while consistently remaining refractory to changes in regimens. Further studies can be conducted to analyze the potential benefits of targeting refractory depression with the combination of anti-inflammatory medications and typical antidepressant regimen. Additionally, given our patient's episode hyper-elevated mood, avenues should also be explored with the connection of inflammatory cytokines and bipolar or unipolar disorders.

Informed Consent

The patient and legal guardian have been made aware of this research paper and the use of personal medical information. All terms and agreements have been discussed with the patient and guardian and both agree to these terms.

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