REVIEW ARTICLE

A Systematic Review Article Determining the Prevalence and Causal Association of Chronic Lupus Patients Developing Obsessive Compulsive Disorder

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Abstract

Introduction: The incidence of neuropsychiatric lupus ranges from 25% to 75% with obsessive–compulsive disorder (OCD) being a common manifestation. The cardinal correlation and pathophysiological mechanism of OCD in chronic lupus patients is still under research. The objective of this article is to determine the prevalence and causal association of a chronic lupus patient developing OCD in its course of disease.

Materials and methods: Human studies, randomized control trials, non-randomized control trials, cohort series, and cohort studies were included. This search resulted in 940 published, peer reviewed scientific articles as of March 2018. There was a repetition of the articles but yet the total was above 800 articles which were individually reviewed, thoroughly analyzed, and exquisitely interpreted.

Results: The brain regions and cortico-striatal-thalamic-cortical (CSTC) circuits dysfunction with abnormalities of serotonin (5-HT), glutamate, and dopamine neurotransmitters in OCD were determined. The proposed pathophysiological hypotheses of activation of autoimmunity and inflammatory mechanism with predominant role of antibodies like anti-RP antibody, *N*-methyl-d-aspartate receptor antibodies, anti-phospholipid antibodies etc. and also increased proinflammatory cytokines like interleukin (IL)-6, IL-8 etc., were shown with probable heterogeneous neurological origin. This hypothesis was further strengthened by evidentiary support of neuroimaging modalities like brain magnetic resonance imaging (MRI), resting functional MRI, voxel-based morphometry, diffusion-tensor imaging, quantitative susceptibility mapping etc., which even though has provided mixed inferential data, there is consistent and repeated demonstration of structural abnormalities in basal ganglia and CSTC circuits.

Conclusion: The evaluation and treatment approach would be different for the patients with only OCD and the one harboring OCD with underlying lupus. In the future, more studies involving neuroimaging and pathophysiology are recommended with similar prospects for better advancement.

Keyword: Neuroimaging, Neuropsychiatric, Obsessive compulsive disorder, Systemic lupus erythematous.

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Introduction

'Some days I can't balance it all. I just have to lay in bed'.

—Toni Braxton

A physical sensation crawls up my arm as I avoid compulsions and the world resets itself for a moment after I complete the act. She complained of constant urges to check her handbag. She required constant reassurance, a self-consolation of the count of the items in her handbag after walking every turn of the staircase, for she had entered a different dimension and if she had forgotten something she would not be able to bring back which was indeed itself distressing. This was the mental condition of hypothetical patient Susan Mayer, who was already a known case of systemic lupus erythematous (SLE), a debilitating multisystem chronic disorder[1] and now started showing signs of obsessive–compulsive disorder (OCD).

Obsessive–compulsive disorder is a frequent and persistent mental illness in which a person experiences uncontrollable, recurrent thoughts (obsessions) and behaviors (compulsions)[2] that they feel the need to repeat. It is one of the highly incapacitating global psychiatric disorders with prominent negative impacts on the quality of life.[3–5] Its etiology is less understood but there is impaired excitatory–inhibitory control.[6]

Lupus is a chronic incurable autoimmune connective tissue disorder.[1,4,5] It is multisystemic in nature with autoantibody production and their deposition in various organs leading to tissue injury. It shows female preponderance with higher incidence in Asians, Africans, and Hispanics in comparison to Caucasians. It has a remitting and relapsing course with pathophysiology only partially understood. Lupus is frequently presented with psychological comorbidities and when this neurological involvement is presented it is termed as neuropsychiatric lupus (NP lupus).[1]

This article is an attempt to explore the recent literature to broaden our understanding pertaining to OCD occurring in patients with lupus which may indeed help clinicians, scientists, and patients.

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Studying the association in depth would also aid in diagnosing and treatment modalities. The 19 Neuropsychiatric syndromes in patients with SLE have been described by the American College of Rheumatology (Table 1), which can be broken down into central and peripheral nervous system symptoms.[1]

Obsessive–compulsive disorder falls into the category of anxiety disorder. It is among the widespread manifestations of neuropsychiatric systemic lupus erythematosus (NPSLE).[1] Neuropsychiatric systemic lupus erythematosus incidence ranges from 25% to 75%.[1,7,8] Despite high prevalence depicted in past studies, the precise etiology is not known and its pathophysiology is controversial. Multiple factors like lacking of social support, chronic treatment regimen or stress of a chronic disease itself support the secondary nature but several possible mechanisms like autoantibody-mediated neurotoxicity, direct action of inflammatory cytokines, complement activation, intrathecal production of immune complexes, blood–brain barrier (BBB) disruption, may hint at it as a direct consequence of autoimmunity.[9–11] There is suggestive dysfunction of basal ganglia in lupus.[12] Obsessive–compulsive disorder is diagnosed using DSM-5 criteria and explained to an extent by orbitofronto-striato-thalamic circuit model.[13]

In this article, we would discuss pathophysiology of OCD, highlight the importance of the excitatory and inhibitory circuits (Flowchart 1), neurotransmitter imbalance, neuroimaging, and topographical changes in the brain regions involved in the disease and the currently applied interventions (Flowchart 2). We would also discuss the heterogenicity of the disease and focus on the implied pathophysiological causal association of OCD in lupus patients who developed the symptoms of OCD during their course of the disease. Various proposed mechanisms of autoimmunity and inflammatory origin would be discussed and their association would be established. Implied correlation of neuroimaging studies will also be included in this article.

Table 1: Types of neuropsychiatric syndromes identified by the American College of Rheumatolog[1]

Headache	Psychosis
Seizure disorders	Acute confusional state
Cerebrovascular disease	Peripheral nervous system
Demyelinating disease	Mononeuropathy
Myelopathy	Polyneuropathy
Movement disorder	Cranial neuropathy
Aseptic meningitis	Acute inflammatory demyelinating polyradiculopathy
Cognitive dysfunction	Plexopathy
Mood disorders	Myasthenia gravis
Anxiety disorder	Autonomic disorder

Methods

To understand the precise association between OCD and lupus and its relevant significance, a comprehensive review of published literature was done.

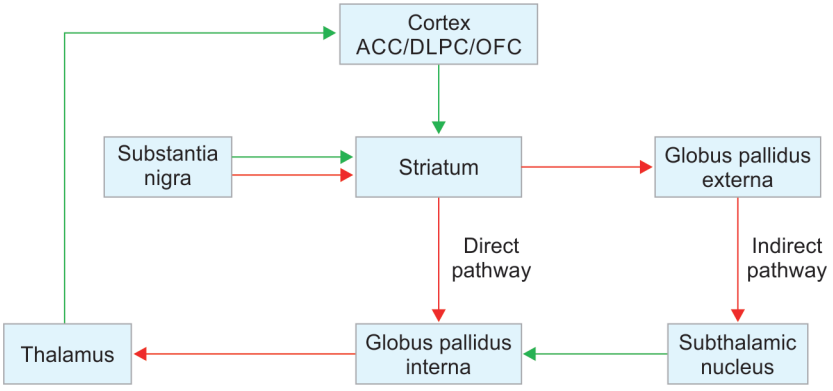
Materials and Methods

The data were collected from databases including PubMed, Google Scholar, MEDLINE, JAMA Neurourology Journal of Clinical Neuroscience. A thorough research was conducted on the relevant articles dedicated to the subjects of OCD, lupus, and basal ganglia. The database of PubMed was searched using "lupus anxiety" as the keyword, the search result showed 90 papers, "neuropsychiatric lupus" returned 338 papers, 168 papers for "obsessive compulsive disorder basal ganglia," "obsessive compulsive disorder circuits" provided 83 articles, "MRI obsessive compulsive disorder" showed 248 papers, and only 13 papers for "lupus basal ganglia." This search resulted in 940 published, peer reviewed scientific articles as of March 2018. There was a repetition of the articles but yet the total was above 800 articles.

Inclusion Criteria

- To conduct this review, articles relevant to the topic which contained keywords in their title or abstract were chosen.
- Studies included were both randomized and non-randomized control trials, cohort series, and cohort studies.
- Only articles with human-based studies were taken.
- A strict selection criterion was appointed to select articles dated between 2013 and 2017.
- Studies conducted all over the world were included.

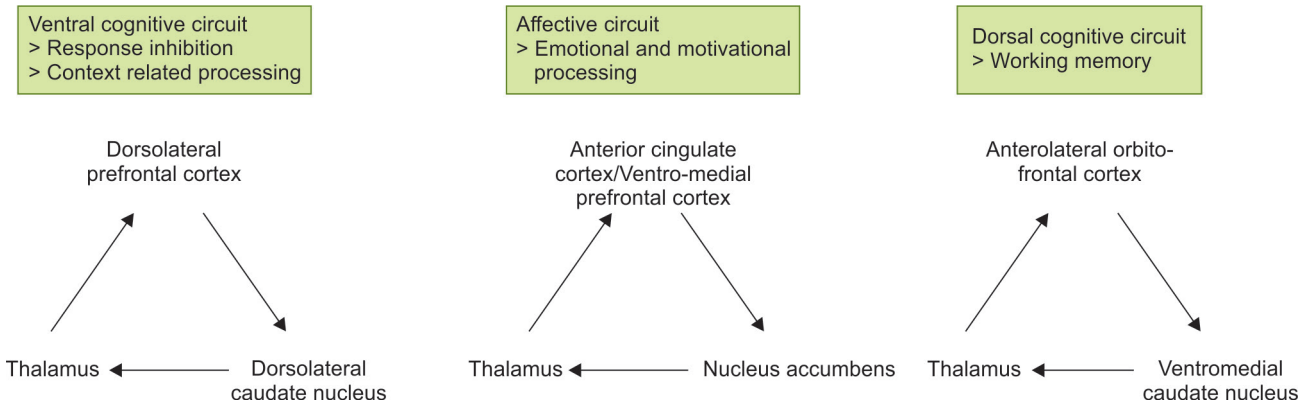
Flowchart 1: Excitatory and inhibitory pathways involved in obsessive–compulsive disorder



*Direct pathway activation increases inhibitory signals to the globus pallidus interna. This case decreased inhibitory signals to the thalamus which leads to increased excitatory action of cortical areas.

**Indirect pathway predominates in OCD. Its activation results in stratum inhibiting globus pallidus externa inhibition of subthalamic nucleus. Subthalamic nucleus then excites globus pallidus externa finally resulting in thalamic inhibition.

Flowchart 2: Brain regions involved in obsessive–compulsive disorder



Exclusion Criteria

- Studies that had no direct relation to the topic or keywords were excluded.
- Articles dated prior to 2013 were excluded.
- Animal-based studies were excluded.
- Most selected articles had English transcript available or came with the English translation.
- Studies that depicted confusion and vague findings with no clear pathophysiological associations pertaining to the topic and its keywords were excluded.

Ethical Issues

The entire information was acquired lawfully and reported accurately. Confidentiality of the people and organizations was maintained.

Discussion

Obsessive–Compulsive Disorder

Obsessive–compulsive disorder is a chronic psychiatric disorder, characterized by repetitive impulses, images, and thoughts (obsessions) and repetitive behaviors (compulsions) which negatively affect multiple domains of life.[2,3] Despite the recently changed diagnostic criteria in DSM-5, OCD was reclassified into a novel group of "obsessive–compulsive and related disorders" (previously "anxiety") mainly focusing on repetitive behaviors, but its core clinical features remain the same.[14,15]

Brain Circuits

Owing to clinical heterogeneity, medication confounds, insufficient power, and mixed statistical analytic method, our knowledge regarding pathological changes is still restricted due to inconsistent and ambiguous earlier findings.[16–18] A dysfunctional cortical–basal ganglia circuit may play a role in OCD as demonstrated through recent functional magnetic resonance imaging (fMRI) studies of resting state connectivity which have further expanded this also to include abnormal connectivity of the orbitofrontal cortex, ventral as well as dorsal striatum, anterior thalamus, putamen, and lastly anterior cingulate. There is a demonstration of further sections comprising subthalamic nucleus, cerebellum, and temporal cortex. However, there are differences in the results of these studies, which may be related to the type of symptom, the peculiar area being studied, or the use of medicine.[19–22]

Neurotransmitters

According to previously conducted studies, the pathophysiology of OCD may involve imbalance in inhibitory and/or excitatory brain function. Khedr et al.[6] in their study on patients with OCD, bolstered the case for inhibitory deficits or increased facilitation in their cortical circuits.

Serotonin

According to the study conducted, there was positive correlation between 5-HT1B receptor availability in the basal ganglia with prepulse inhibition (PPI) in controls; however, in OCD groups these correlations were either lost or even reversed. Moreover, presence of widespread positive correlations with PPI in cortical regions in OCD patients was witnessed in comparison to the controls. This positive association was observed only in the orbitofrontal cortex as well as the amygdale thus suggesting functionally relevant alterations in OCD in the serotonergic regulation of cortical/subcortical balance.[23] Nevertheless, 40–60% of patients with OCD remain treatment-resistant despite the effectiveness of serotonergic compound.[24]

Glutamate

The deregulation in fronto-striatal glutamatergic signaling is crux of understanding OCD. It is believed that there was a plausible increment in Glx (Glu, glutamine, and GABA combination) in the striatum across patients with OCD.[24] Thus, agents targeting glutamate neurotransmission like memantine and riluzole may be presented as promising candidates and benefits have been reported.[24,25] But no glutamate modulator has been demonstrated to be an effective means of treating OCD.[25]

Dopamine

There is a proposed role of mesolimbic dopaminergic pathway in OCD. Investigating the plausible abnormality of dopaminergic neuronal brain circuits of patients with OCD in vivo utilizes L-3,4-dihydroxy-6-[F-18] fluorophenylalanine positron emission tomography. The brain of patients with OCD brain showed trends toward increased dopaminergic metabolism in regions of left frontal premotor cortex ($p < 0.001$), posterior cingulate gyrus, cuneus, lingual gyrus, and right side of cuneus and praecuneus, lingual gyrus, middle temporal gyrus, and both sides of the cerebellum ($p < 0.01$). These findings contrasted with the healthy individuals. Therefore, indicating possibility of these brain regions with increased dopaminergic neuronal activity contributing to the development of OCD.[26]

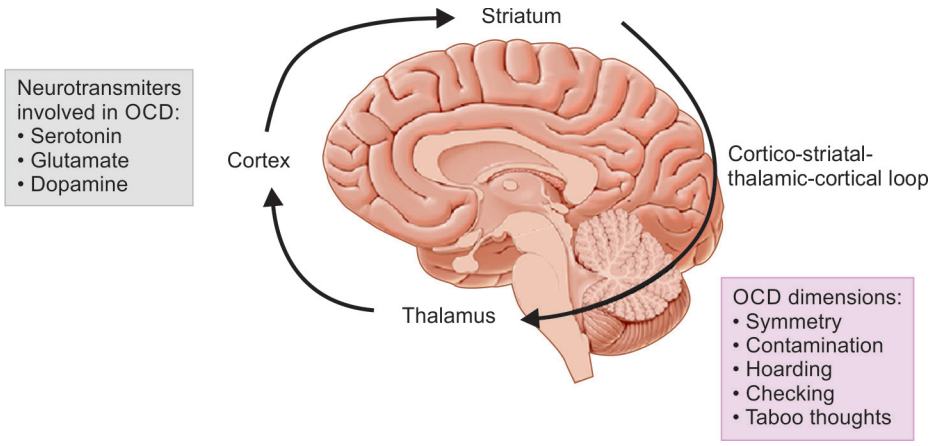


Fig. 1: Cortico-striatal-thalamic-cortical loop and the neurotransmitters involved in obsessive–compulsive disorder (OCD) with OCD dimensions

Gene Studies

Recently, studies on genome-wide linkage and association have provided some candidates. Even though OCD genome-wide association studies have been underpowered. Serotonin and glutamate along with dopamine-related genes have been focusing on candidate gene investigations due to the postulated functions of these neurotransmitters in OCD (Fig. 1). Thus, definitive genome-wide candidates have yet to be fully elucidated.[27–29]

Neuroimaging and Interventions

Eng et al.[30] believed and depicted decreased activation of anterior cingulated cortex, dorsolateral prefrontal cortex, medial frontal cortex, inferior frontal gyrus, and caudate while changing of tasks along with decreased activation in areas of putamen and caudate while execution of inhibition and interference tasks in patients with OCD. Banca et al.'s[31] recent imaging study, however, showed that OCD patients had hyperactivation of STN and putamen along with caudate–prefrontal circuits deactivation when exposed to symptom-provoking stimuli that were interpreted through dissociation between areas participating in habitual behaviors and goal-directed behaviors, respectively. Putamen hyperactivity and its subsequent deactivation demonstrated during symptom provocation followed by avoidance of the inciting stimuli and relief, respectively, this study further revealed a crucial role for putamen in habit formation in OCD.

In another study conducted by Tang, all subjects went through brain MRI and resting fMRI, and also voxel-based morphometry (VBM) method. Detailed investigation exhibited higher cortical structures and cerebellum with increased gray matter volume and activation, whereas subcortical structures exhibited decreased gray matter volume and activation. Also, after receiving selective serotonin reuptake inhibitors (SSRIs) medication, patients with OCD showed improvements in their symptoms and brain structure.[32] Fouche et al.[33] showed in their study, decreased cortical thickness in the OCD group in comparison to the controls involving precentral, posterior cingulate, superior and inferior frontal, inferior parietal and precuneus gyri, and middle temporal. This not only partially supported OCD fronto-striatal model but also indicated its extension into the limbic, temporal as well as parietal regions in understanding its pathophysiology. Whereas the study conducted by Fan et al. on patients showed prominent increase in the right inferior parietal cortical thickness. The regions of left lateral occipital, left middle frontal, insula, right supramarginal and precuneus gyrus had significant increased gyrification with no relevant regional difference was observed in patients and controls on areal contraction/expansion maps. The severity prediction done using Yale-Brown Obsessive-Compulsive Scale (YBOCS) of the symptoms correlated with the gyrification of the insula.[34] Ling et al. detected increased regional grey matter (GM) in OCD patients relative to control with no demonstration of decreased GM volume and further suggested that structural changes in the GM may also extend to temporo-parietal cortex in pathogenesis of OCD.[35] However, Jingming Hou demonstrated significant increased gray matter volume in the left thalamus, left caudate, and posterior cingulate cortex in addition to decrease in gray matter volume in the left inferior frontal gyrus, bilateral medial orbitofrontal cortex, and left anterior cingulate cortex. Additionally, malfunction in the cortico-striatal-thalamic-cortical (CSTC) circuits and default mode network was shown using the morphologic deficiencies areas mentioned above as seed regions. The overall YBOCS score was then linked with morphological abnormalities within left thalamus and CSTC circuits which were showing increased functional connectivity.[36] Koch et al.[37] in their comparison studies between OCD patients and healthy control group demonstrated abnormalities in fronto-striatal-thalamo-cortical loop along with white matter on diffusion tensor imaging (DTI) in the former group.

The underlying neurobiological mechanisms, nevertheless, remain a mystery. In past years, morphometric study findings have been at odds with the models that have been traditionally suggested. Although there are discrepancies shown in interpretation of various studies in their result, there is consistent and repeated demonstration of structural abnormalities in CSTC circuits involving orbitofrontal cortex, anterior cingulate cortex, and striatum.[38–40] Deep brain stimulation (DBS) has now become investigative treatment for OCD and other NP disorder when it is successful, efficacious, adjustable, reversible, and relatively safe for various movement disorder including Parkinson disease.[41]

Heterogeneity of the Disease

Therefore, we can conclude that pathophysiology of OCD is heterogeneous in nature. Various functional studies suggested strong evidence indicating pathophysiology of OCD to be conceptualized as distributed neuronal brain network and highly unlikely to be the result of a dysfunctional neurotransmitter

system or single abnormal brain region. Also, Alexander Glahn in his hypothesis highlighted the underlying heterogeneity of this disorder by demonstrating widespread cerebral changes.[42,43]

OCD in Lupus Patient

Prevalence of the Association of OCD and Lupus

Systemic lupus erythematous is a chronic, incurable, multisystemic autoimmune disorder with production and deposition of the autoantibodies, consequently leading to tissue injury. The etiology of SLE is partly understood[1] as well as occurrence of OCD, which itself has heterogeneous pathophysiology[43] in a patient who is a diagnosed case of lupus further complicates the understanding and knowledge with respect to both the diseases and thus limiting treatment modalities and overall well-being of an individual. The NP symptoms in a lupus patient range from 25% to 75% primarily involving depression, anxiety, cognitive impairment to seizures, and rarely psychosis.[1,7,8] Maciel et al.[12] and Uguz et al.[44] in their studies showed that 15 of 54 (27.8%) patients and 20% of 45 patients had OCD, respectively.

Mechanism

Antibodies

Anti-RP antibody was considered one of the most relevant antibodies in NPSLE and a specific antibody of SLE, primarily targeting C-terminal region of ribosomal P protein, specifically ribosomal phosphoprotein P0, P1, and P2.[45,46] Nonetheless, several studies indicated that the relationship between NP symptoms and anti-RP antibodies was insignificant.[47] In the studies conducted, there was a demonstration of elevated levels of antibodies to *N*-methyl-D-aspartate (NMDA) receptor antibodies or anti-phospholipid antibodies along with anti-ribosomal-P antibodies during acute phase and also increased interleukin (IL)-6 in cerebrospinal fluid in patients presenting with NP symptoms.[7,48] However, interferons-driven (IFN-driven) microglia-dependent synapse loss and microglia transcriptome data have been identified in the study conducted by providing clarification on the neurological symptoms observed in some patients with lupus thus connecting central nervous system (CNS) lupus to other CNS diseases.[7] Earlier studies have demonstrated that anti-NMDA receptor subunits NR2A/B (anti-NR2A/B) antibodies have been linked with collective or specific NP syndromes, although inconsistently. However, owing to inconsequential sample size of patients, the interpretation of the literature has been rendered difficult. As a result, Tay et al.[49] concluded in his meta-analysis, regarding the diagnostic implication of circulating anti-NR2A/B antibody in NPSLE but evidence till date is unable to distinguish between specific NP syndromes based on anti-NR2A/B antibody positivity.

Van der Meulen et al.[50] in their study compared and differentiated non-NPSLE and NPSLE and based on the combination of IgG autoAbs against histone H2B, heparan sulfate and vimentin suggested of four IgG and seven IgM autoAbs significantly associated with inflammatory NPSLE. Iseme et al.[51] believed that underlying mechanism of NP symptoms was the upregulation of proinflammatory cytokines like interferon caused by anti-RP antibody leading to neuronal death via apoptosis. Furthermore, recent studies demonstrated that anti-NR2 binds on the surface of endothelial cells and enhances their production of proinflammatory cytokines, IL-6 and IL-8, through subsequent activation of NFkB.[52]

Table 2: Antibodies involved in pathogenesis of obsessive–compulsive disorder in chronic lupus patient

1. Anti-ribosomal P antibodies
2. *N*-methyl-D-aspartate receptor antibodies
3. Anti-phospholipid antibodies

Inflammation and Autoimmunity

Attwells et al. believed that their recent study was the first to demonstrated the inflammation in the neurocircuitry of OCD. The translocator protein distribution volume (TSPO VT) in the orbitofrontal cortex significantly correlated with the YBOCS measure of distress related to preventing compulsive behaviors, and this elevated TSPO VT and its regional distribution supported the idea that autoimmune/neuroinflammatory theories of OCD should not only extend to the CSTC but also involve the basal ganglia. This shifts the focus to immunomodulatory therapies.[53] Sato et al.[48] also concluded that the basal ganglia had high-intensity lesions in patients of complete resolution owing to immunosuppressive therapy thus indicating that NP symptoms in SLE may result from inflammation and the activation of the autoimmune system. Tumor necrosis factor-alpha levels in the serum have also been observed to be higher, indicating that inflammation plays a part in depression in SLE patients who experience mood and anxiety.[54]

Role of Blood–Brain Barrier

Recent studies have shown that there was elevation of CSF IgG, CSF anti-NR2, Q albumin and CSF anti-NR2 index, CSF anti-NR2, CSF anti-Sm,[55–57] CSF IL-6, CSF C3,[58] and other antibodies in comparing to non-NPSLE control implicating their transduction through damaged BBB from the systemic circulation into the CSF. Moreover, BBB damage severity plays a role development of diffuse acute coronory syndrome (ACS). Thus, disruption of BBB has pivotal role in NPSLE pathogenesis and its integrity can be investigated by Q α2MG and Q albumin. However, intrathecal production of the aforementioned antibodies is a possibility too. Therefore, two mechanisms can be intimated in the pathogenesis of OCD in lupus patients involving either transudation of the antibodies through the damaged BBB and/or intrathecal synthesis of the same (Table 2).[55–58]

Neuroimaging

Ogasawara et al. in their study investigated the visually normal basal ganglia of NPSLE patients on conventional MRI further evaluated the same with quantitative susceptibility mapping (QSM). He concluded that there is a substantial correlation between putamen QSM values and duration of disease duration, with QSM being highly sensitive to small alterations. He also found that putamen QSM values are much higher in NPSLE.[59] In NPSLE and non-NPSLE patients, Shastri et al. showed decreased white matter integrity in the anterior corona radiate and corpus callosum, as well as changes in the uncinate fasciculus on diffusion tensor tractography which subsequently correlated with the clinical changes (SLEDAI scores), but were independent of conventional T2 lesion burden.[8] In his research, Sarbu explored the potential of neuroimaging as biomarkers for NP lupus diagnosis and prognosis. He used visual scales to assess atrophy and white matter hyperintensities, VBM, and Freesurfer to measure brain volume, and DTI to assess white matter and gray matter damage in 28 NPSLE patients and 20 healthy controls. He concluded that NPSLE

patients had less gray matter and white matter than controls in the fronto-temporal regions and corpus callosum. Additionally, the right frontal lobe white matter's fractional anisotropy was decreased while the temporal lobe white matter's diffusivities were raised.[60]

Conclusions

In this article, despite any prior specific elaborate research, development of OCD symptoms in a chronic lupus patient can be attributed to the underlying pathophysiology of lupus intrinsically, which itself is under extensive research. Obsessive–compulsive disorder and lupus have been hypothesized to be allied through inflammatory autoimmune mechanisms, and this study supports that hypothesis. In my studies we found a well-established prevalence of the association of OCD and lupus and thus highlighted the role of anti-RP antibody, NMDA receptor antibodies, anti-phospholipid antibodies, increased IL-6 along with various other antibodies which were either intrathecally synthesized and/or result of transudation through the damaged BBB leading to activation of autoimmune mechanisms of lupus in the brain and causing destruction and inflammation to various brain regions including the basal ganglia and also CSTC circuit which indeed is the main pathway for the voluntary movements and making postural adjustments and therefore contributing to the developing symptoms of OCD in a chronic lupus patient. The autoantibodies and cytokines cause abnormal connectivity in negative feedback mechanism of CSTC circuit precipitating imbalance in predominant neurotransmitters serotonin (5-HT), glutamate, and dopamine. Serotonin, glutamate, and dopamine-related genes have been the focus of candidate gene investigations due to the postulated functions of these neurotransmitters in OCD. In addition, this hypothesis was further strengthened by the theory of heterogenicity of OCD and advanced approach of neuroimaging including MRI, fMRI, VBM, DTI, and QSM which even though have provided mixed inferential data, there is consistent and repeated demonstration of structural abnormalities in basal ganglia and CSTC circuits. Moreover, DBS has recently emerged as an investigative treatment for OCD. As of now, I believe that OCD develops in a lupus patient by a pathophysiological phenomenon which demands more understanding in the near future probably for competent and efficacious treatment modalities. The author for now strongly feel and know that when patient approaching with only OCD symptoms and the one with OCD also battling lupus seem indistinguishable and yet are very contradistinctive. They will enumerate similar symptoms but with distinctive sub-stratal pathophysiology. As such, controlling inflammatory autoimmune mechanisms with already prescribed pharmaceuticals for lupus with suitable modifications could be a crucial part in treating OCD in the same.

This study is a sincere attempt to explore the recent literature and provide a framework for further studies undertaken with similar prospects. It would help clinicians, scientists, diagnosticians, professional, and even a patient to unearth these aspects and have a holistic approach to the disorder. In future an elaborate clinical history with intensive investigations would be executed determine the course and prognosis of OCD in lupus patients. This detailed exploration for lupus would help in outlining the outcome of the disease and manipulating treatment modalities in favor of the patient. However, the author believe that the above evidence is still inconclusive as there may be missing evidence due to non-documentation, exclusion of animal-based studies, and inclusion of only recent advancements and literature. She believes, for finer perspectives, future studies involving neuroimaging of OCD and on concealed micro details of pathophysiological associations between OCD and lupus are recommended.

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