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Review Article

Obsessive–compulsive disorder in chronic epilepsy

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ABSTRACT

There is a long-recognized association between obsessive–compulsive disorder (OCD) and chronic epilepsy, most notably refractory temporal lobe epilepsy (TLE). The literature documents this association with case reports, patient series, and some larger controlled studies that reveal that almost a quarter of patients with TLE exhibit OCD features, which may go unrecognized. Obsession features with ordering, symmetry, exactness, handwashing, and religiosity occur more often in persons with right- or left-sided epileptic foci than in those with idiopathic generalized epilepsies or controls. Neurobiological and social factors suggest abnormalities of the frontal–thalamic–pallidal–striatal–anterior cingulate–frontal circuits stemming from the observation that certain diseases, damage, or surgery along these circuits may produce or, conversely, reduce OCD in TLE. This review explores the literature on case reports, case series, and larger retrospective controlled studies and looks at the associations of epilepsy with OCD. Contemporary speculation on the theoretical neurobiological underpinnings provides some basis on how and where to direct treatment. Invasive deep brain stimulation has triggered recent controversy on newer treatment modalities.

1. Introduction

There has been a long association between epilepsy, behavioral disturbance, and psychiatric conditions. Many authors have noted more specific associations, particularly between psychiatric morbidity and chronic focal epilepsy rather than idiopathic generalized epilepsy [1–3]. Mesial temporal lobe epilepsy (MTLE), often associated with a poor response to antiepileptic drugs and mesial temporal sclerosis, illustrates the system dysfunction in epilepsy that shares comorbidity with impairment of the limbic circuits involved in controlling mood, behavior, and emotions. In summary, patients with temporal lobe epilepsy (TLE) have higher lifetime frequencies of psychiatric disorders (70%), mood disorders (49.3%), anxiety (42.5%), depression (27.4%), and obsessive–compulsive disorder (OCD) (11.0%) [4]. In other surveys, up to 40% of patients with chronic focal epilepsy have been found to have comorbid psychiatric dysfunction, moreso with refractory epilepsy, with almost one-fourth having OCD [5].

Attention has centered on which types of epilepsy, the lateralization, and which circuits involved in the epileptic process relate to well-characterized OCD features. Findings using investigative tools, including magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon-emission computed tomography (SPECT), have been correlated with neuropsychiatric and psychological testing to suggest specific sites of brain dysfunction along orbitofrontal–frontal–thalamic–pallidal–striatal–anterior cingulate–frontal circuits. Recent work has also indicated clinical variables that are crucial in the appearance of this specific psychopathology, such as brain injury, and how it might affect the clinical course of disease [6], and has addressed controversial treatments such as deep brain stimulation.

2. Epilepsy, behavioral disturbance, psychiatric morbidity, and obsessive–compulsive disorder

Epilepsy is one of the more frequent neurological disorders in adults [7,8] and can affect about 1 to 1.5% of the population. Seizures in more than 25% of patients are refractory to medical treatments, who are subject to a greater prevalence of psychiatric problems including behavioral abnormalities—such as personality, emotional, and memory disturbances that confer professional and social disabilities [3,9,10]. With refractory TLE, almost 4 in 10 are or become impaired [9], whereas axis I psychiatric disorders are seen in up to 80% [11]. Use of the Symptom Checklist-90—Revised (SCL-90-R) showed a prevalence of 88% for psychological problems by symptom scoring in the index [12]. Although depression, mood disorders, and anxiety (25%) [2] are more frequent [13], many patients have OCD.

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3. Behavioral and thought disturbances in epilepsy

The nature of behavioral problems in TLE may arise from the condition itself as well the triggering by seizures. Some speculate that the problems occur or are released in the postictal period, or represent a psychiatric comorbidity of the epilepsy. The picture is further obscured by the possibly complicating effects of epilepsy treatments ranging from medications with neuroleptic and antiepileptic effects, to vagus nerve and deep brain stimulation, to seizure surgery. There is thus the possibility that the etiology and anatomy of the epilepsy play at least a part in the induction or release of obsessive-compulsive (OC) behaviors. Although temporal lobe seizures (80%) are often associated with OCD, generalized tonic–clonic seizures, particularly in the setting of juvenile myoclonic epilepsy (JME), a genetic nonfocal epilepsy [14], rarely occur in OCD.

4. Obsessive–compulsive spectrum

Obsessive–compulsive disorder subsumes a spectrum of clinical features with two prominent aspects. Foremost are the intrusion of compulsions, persistent thoughts, and ideas and the consequent release of ritualistic and aberrant behaviors. The induced or released behaviors often relieve the compulsive pent-up need of these mental imperatives. Behavioral patterns consisting of a sequence of or repetitive manual activities are usually performed in certain sequences that dominate much of the person's attention, consuming potentially "useful" waking time with unproductive, but overwhelming rituals.

Obsessive–compulsive disorder has a lifetime prevalence of about 3% [15]. Despite treatments that include behavioral therapy and medications, about 10–20% remain markedly affected in professional and social functioning [15,16]. Many psychiatric conditions may include OC symptoms, but a stand-alone disorder (OCD) has been delineated. Both OC symptoms and OCD appear in focal epilepsy, particularly in refractory cases of TLE [3], leading to the suggestion that the two conditions are linked. Several theories based on lesion and anatomical location led to the elaboration of a circuit theory underlying the coexistence of the conditions.

5. Links between temporal lobe epilepsy and obsessive–compulsive disorder

It has long been observed that patients with epilepsy may display OC traits [17–19]. It was speculated that patients manifested obsessional personality characteristics that were linked to particular types of epilepsy [20]. Behaviors noted between seizures have been delineated in an *interictal behavior syndrome,* with religious, circumstantiality, and hypergraphic features that substantially impair the patient's life [21,22]. A *TLE syndrome* would typically include hypergraphia, religiosity, and obsessional features [21] and was described in patients with either a left- or right-sided focus [18,23,24]. Bear and Fedio went further to describe particular elements typical of OCD [25], the appearance of which coincided with the occurrence of seizures or their suppression. They noted a higher percentage of OCD in TLE than the 2.5% prevalence of OCD seen in the general population [25,26].

An aggregate of case reports and case series initially suggested that a right hemisphere focus in TLE predisposed to OCD, particularly when supported by the delineation of structural lesions on the same side. Imaging studies including MRI and EEG lateralization further supported these associations [27,28]. Nonetheless, others have found no correlation between TLE laterality, personality characteristics, and obsessionality [29].

These few subjects suggested an association between TLE and OCD that was later explored with larger retrospective and prospective group studies. The investigations into forced thinking in TLE were designed to determine whether there was a chance of comorbidity or a clear association using structured neuropsychological instruments and specifically trained personnel. Bias was addressed by including comparisons with a control population.

To systematize the association of OCD with epilepsy, investigators examined a profile of TLE features to determine if OCD and TLE might share common neural mechanisms [3]. The prevalence of OC features was assessed using an Obsessive–Compulsive Inventory and compared with that of normative controls, revealing that patients with OCD had impaired processing in nonverbal memory and visuospatial tasks. This was supported by imaging studies in patients with OCD without epilepsy, although others showed bilateral involvement [3,27,30,31]. It was therefore unclear if indeed there was a right hemisphere TLE predominance with OCD. In the TLE group, features included checking, neutralizing, washing, ordering, and hoarding, showing that the more obsessive qualities predominated [3]. Revealing this skew toward obsessive elements suggested that the anatomy of the neurobiological pathways subserving compulsive thought was different from that subserving obsessive thinking. Doubting, checking, and hoarding might therefore be impairments related to memory in patients with TLE, in contrast to hoarding, which might arise from organizational problems localized to frontal lobe function [3].

Monaco and colleagues [2] distinguished *traits* (features) of the individual from a *state*, which represented the role that the disease played in life [1]. Concern for selection bias, dependence on self-rating scales, and lack of some commoner psychometric tools [1] prompted efforts to address these limitations. Reviewing consecutive patients with TLE and patients with idiopathic generalized (presumed genetic) epilepsy (IGE), Monaco and colleagues had trained clinical psychometricians use the Structured Clinical Interview for DSM Disorders-IV Patient Version for OCD Diagnosis and the Yale–Brown Obsessive Compulsive Scale (Y-BOCS). Obsessionality as a trait was assessed with a version of the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) that included a Pt clinical scale and OBS content scales for evaluations of fear, compulsions, obsessions, excessive doubts, perfectionist personality traits, and fear. OC features included checking, neutralizing, ordering, doubting, washing, and hoarding. OC symptoms and behaviors, "maladaptive ruminations," and obsessive thoughts were tallied on an OBS scale supplemented by the Beck Depression Inventory and State–Trait Anxiety Inventory Y1 and Y2. For the 164 enrolled subjects and 82 controls, features including seizure control, age, gender, epilepsy duration, antiepileptic drug (AED) use, and EEG and MRI findings were evaluated. Compared with patients with IGE and normal controls, patients with TLE had higher Pt and OBS scale scores that were not correlated with epilepsy severity, seizure control, medication, or etiology. Hence in patients with a biological predisposition and a psychiatric history, obsessionality appeared as a trait of TLE, with almost 15% of patients with TLE having OCD. The difference from Isaacs and colleagues' study, in which 22% of patients with TLE had OCD features [3], was explained by the fact that their population included patients with refractory TLE. The Monaco et al. study indicated an association between mesolimbic regions and personality characteristics in which involvement of particular brain areas in various epilepsy syndromes suggested a specific psychopathological expression in psychiatric conditions [1]. Profiles of healthy controls resembled those of patients with IGE, separating both groups from patients with TLE. Parenthetically, it was striking that only one of the nine patients had been previously diagnosed with OCD, highlighting the low recognition of OCD in an outpatient epilepsy setting, possibly because of the lack of psychiatrically trained investigators in an outpatient epilepsy clinic.

As a mechanism, the authors suggest amygdalar involvement with connections to the striatum in OCD. This might enhance the automatic and ritualistic behavior in reaction to danger. Circuits including the amygdala, ventral striatum, and stria terminalis may underlie the effects of rituals and repetitive behaviors in allaying anxiety [32]. A recent Brazilian study of 73 patients noted that patients with TLE, usually with childhood onset, long duration (mean >30 years), and a mean of 4.8 seizures per month (95.9% complex partial), displayed a

wide array of psychiatric conditions, most frequently mood, depressive, and anxiety disorders, but also OCD [4]. Most patients on monotherapy were treated with carbamazepine (64.4%), with seizures in most being refractory (80.8%). Lifetime frequency of psychiatric problems was 69.9%, with a clear underrecognition of depression and anxiety in the clinic population with TLE.

In a Swiss study that included 85 patients with chronic epilepsy with psychiatric problems, six had OCD, with all but one having a temporal or posterior focus and with four of six having a focus on the right; average age at onset was 17.7 years and epilepsy duration was 21 years [5].

Several studies have indicated that the epileptogenic zone in patients with OCD is usually on the right [33–35]; another study of patients with refractory TLE found OCD in 22%, but without predominance on one side [3], although patients with right-sided TLE had more severe OCD features as indicated by OCD inventory subscale scores.

Ertekin and colleagues evaluated associations of TLE with unilateral mesial temporal sclerosis (MTS) versus IGE in patients with psychiatric comorbidities including OCD [2]. These investigators—experienced in psychiatry and epilepsy—then compared 29 patients with TLE with 27 patients with IGE from an epilepsy clinic and 30 control subjects. Investigating these three groups along with their results from MRI and EEG studies, a structured clinical interview (Structured Clinical Interview for DSM Disorders I [SCID-I]) and the Y-BOCS Symptom Checklist with ~50 types of obsessive and compulsive characteristics, they rated severity and symptoms. Some 10% of patients with TLE had OCD and 24% had subsyndromal OCD, higher proportions than in the matched IGE group (3.7 and 7.4%, respectively; not statistically significant). Depression was the commonest comorbidity with OCD [2]. This time, there was a predominance of left-sided epileptic foci.

6. Possible anatomical relationships and mechanisms underlying obsessive–compulsive disorder and epilepsy

There is much speculation on the interplay between psychiatric comorbidity and epilepsy, along with the social and neurobiological interplay. Swinkels and colleagues noted that predisposition and chronicity of brain dysfunction are important [11]. It seemed that anatomical factors were of greater significance. Ertekin and colleagues found that OCD was also highly associated with depression, as had Monaco and colleagues [1,2]. The findings of Ertekin and colleagues revealed that patients with TLE have a greater obsession with contamination and a compulsion to wash than do patients with IGE, as well as greater symmetry/exactness obsessions and ordering compulsion. In contrast, Isaacs and colleagues revealed more checking, doubting, washing, ordering, hoarding, and neutralizing. Some of the patients with TLE had religious preoccupations [2,3,36].

Studies have shown an association between frontal lobe epilepsy (FLE) and OCD. Involvement of the frontal–cingulate–thalamic–limbic circuit might underlie the neurobiological functional dysregulation and result in OC symptoms and OCD [19,28,37].

In limbic epilepsy there are automatisms that resemble some aspects of ritualistic behavior of OC symptoms and some patients have repetitive movements and automatic behavior, but little work has been done.

Rare conditions with both epilepsy and clinical manifestations of repetitive behaviors include the hand wringing of Rett syndrome, some aspects of Angelman syndrome and autism spectrum disorder, and certain presentations of limbic encephalitis.

With the striking cases of patients with particular anatomical brain lesions and the new onset of OCD, more attention has been paid to formulating a neurobiological basis to the disorder. OCD rarely occurs after the age of 50, but a number of etiologies, including encephalitis, Parkinson's disease, Huntington's disease, Sydenham's chorea, Tourette syndrome, brain tumors, trauma, strokes, gliomatosis cerebri, and seizures, may precipitate late-onset OCD [38–40].

To explain the circuitry underlying OCD expression, Modell and colleagues postulate the presence of anatomical loops that can be disturbed in the triggering of OCD behaviors [36]; these include basal ganglia/limbic, striatal, and thalamocortical circuits. A glutamate-mediated loop circles through the thalamo-orbitofrontal regions, and a striatal–orbitofrontal–thalamic serotonin/dopamine/GABA connection controls the thalamo-orbitofrontal loop. A loop that includes the orbitofrontal cortex stimulates the caudate and pallidum to inhibit the medial thalamic nucleus. This then returns to frontal cortex, regulating hyperactivity in orbitofrontal–thalamic circuits. When these circuits are disrupted along some point in the pathway, OC symptoms are induced, resulting in OC features [36]. Neurobiochemical findings have been variable. Metabolites of serotonin in the cerebrospinal fluid have been found to be increased, decreased, or unchanged in OCD; nonetheless, serotonin is believed to play a role.

A link between basal ganglia and epileptic disorders is more tenuous. Although related largely to motor control, the basal ganglia may modulate generalization of epileptic spike–wave discharges in idiopathic generalized epilepsies via feedback circuits in the cerebral cortex and thalamus, with substantia nigra being essential in the propagation of seizures [41]. There may therefore be increased functional connectivity and greater integration within the basal ganglia in IGE.

Using MRI, fMRI, and PET, Huey and colleagues differentiated idiopathic forms from acquired OCD [42] and suggested that initiation of appropriate behavioral patterns by the orbitofrontal cortex is gated by the basal ganglia, which link behaviors and reward, and further filtered by the anterior cingulate, enabling perception of which behavior triggers reward. Patients with secondary OCD were less anxious even while compelled to perform ritualistic behaviors than were patients with idiopathic OCD, suggesting that control of anxiety and impelled behaviors are quelled once the ritual is completed [42].

In other cases, there is a paradoxical improvement in OCD when tumors or strokes intervene or with the use of deep brain stimulation [43–45]. It is speculated that malfunction along these cerebral loops connecting orbitofrontal cortex with the anterior cingulate gyrus, basal ganglia, and thalamus can trigger OCD [45,46].

7. Timing of obsessive–compulsive disorder onset relative to epilepsy onset

In TLE, OCD onset has been characterized as occurring early after the onset of seizures [47,48]. Late-onset OCD was particularly characterized by frontobasal ganglia circuits, with most patients showing lesions localized in these regions [6,39,49]. Idiopathic forms manifesting in the second and third decades of life have been favored by morphometric and functional imaging studies suggesting corticostriatal–pallidal–thalamic circuits. To link OCD with epilepsy, it has been postulated that the two conditions may share mechanisms and, alternately, OCD may be incidental [46]. A shared pathological organization might explain why focal neurosurgical interventions can improve seizures, but trigger OCD [44]. When seizures regress, there is a “forced normalization” [50,51]. Surgical interruption of excitation, with an increase in inhibition, destabilizes psychiatric equipoise to explain the concepts of “forced normalization” and “latent disease theory” [50,51] that affect a minority of patients.

Seizures might trigger impulsive thinking. From observations in patients with simple or complex partial seizures, obsessive thoughts were observed in the preictal period, during seizures, or postictally [1].

Ertekin and colleagues speculated that particular AEDs, such as carbamazepine, might make patients more susceptible to OCD than if they were taking valproate [2]. In support of limbic involvement is the

comorbid presence of depression in both OCD and epilepsy, prompting the need to identify and treat it [2].

8. Surgery and obsessive–compulsive disorder

Although temporal lobe surgery can increase OCD, paradoxically, some patients improve. This paradox has also been observed with extratemporal foci and with Lennox–Gastaut syndrome. Some premorbid psychopathologies may worsen with surgery, even if seizures regress [46,52,53]. Other psychiatric conditions can emerge after surgery including depression and psychosis, suicide [53–56], de novo psychosis [56], depression in 8% [54,57], and new-onset schizophrenia [54], most occurring in the first 8 weeks or so [35]. In the first 4 weeks after temporal lobectomy, 6 of 74 patients had new-onset psychosis and six suicide attempts [58,59]. At 6 weeks postsurgery, about half of the patients who previously had not manifested psychiatric symptoms/disorders developed anxiety, depression, and emotional lability [60]. Surgery on the nondominant hemisphere seemed to favor greater psychiatric morbidity [61,62], despite findings indicating that in patients without epilepsy, lesions on either side could trigger OCD.

9. Controversial implementation of deep brain stimulation as treatment in obsessive–compulsive disorder

Building on previous results from the use of deep brain stimulation (DBS) in psychiatric disease (e.g., refractory depression), several investigators have used DBS, a novel surgical procedure, as a treatment of last resort for patients with severe OCD [43,44,63,64]. Publishing several small case series, several authors found encouraging results in selected populations of carefully screened patients with OCD [43,44,63,64]. On the basis of these findings, the device manufacturers applied for a human device exemption (HDE) to enable better access to the procedure. This maneuver removes the requirement for a clinical trial that would normally provide the needed statistical power and sample size to demonstrate effectiveness and safety. Several authors have expressed strong reservations, as this procedure bypasses "the rigors of such trials, puts patients at risk, limits opportunities for scientific discovery and gives device manufacturers unique marketing opportunities." Fins and colleagues argued for more oversight of such an application of HDE that might pose ethical and policy issues and place patients at risk before adequate data on DBS and OCD have been collected for a fuller analysis [65].

10. Research on obsessive–compulsive disorder with epilepsy

The nature of the association between epilepsy and OCD still warrants much work. Multicenter studies might look at patients without epilepsy or, conversely, patients with primary or idiopathic OCD [3]. Special tools might be developed to examine the clinical features of writing compulsion and religiosity in patients with epilepsy and the increased depressive comorbidity in both patients with OCD and those with epilepsy [2].

Optimally, larger prospective studies with carefully selected OCD profile tools and personnel trained in both OCD and epilepsy might better define the neurobiological circuits that favor one or other main clinical features of OCD and, further, lead to a better understanding of the types of epilepsy that place patients at special risk for OCD. Management can then be tailored to the different types of OCD and epilepsy. Newer techniques that point to specific anatomical loci, for example, nonmotor neurons in the subthalamic nucleus [66], may help guide the use of newer interventions, including DBS, for OCD. Well-designed trials with sufficient subjects are needed to better establish the value of these invasive techniques in OCD before widespread adoption of such treatments.

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