Epilepsy and obsessive-compulsive disorder

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Obsessive-compulsive disorder (OCD) has long been associated with epilepsy. The link with temporal lobe (usually refractory) epilepsy (TLE) is particularly prominent. Of TLE patients, 10% to 22% of patients may have OCD, often underdiagnosed in the outpatient clinic. Data on the links include case reports, case series, and controlled studies. Three larger, controlled studies in TLE patients, using comprehensive epilepsy and OCD classifications, in aggregate, have noted the obsessive qualities of washing, symmetry/exactness, and ordering, with a greater preoccupation with certain aspects of religion, compared with controls or patients with idiopathic generalized epilepsy. TLE foci may be either left- or right-sided. Social and neurobiological factors are involved in OCD in TLE. The neurobiology implicates a pathophysiological or structural impairment of the orbitofrontal-thalamic, and fronto-thalamic-pallidal-striatal-anterior cingulate-frontal circuits. Discrete anatomic lesions in these pathways, or their surgical removal, may induce (or conversely) improve OCD in TLE patients.

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Obsessive-compulsive disorder and epilepsy

Obsessive-compulsive disorder (OCD) includes a range of clinical characteristics with two major components. There is firstly the intrusion of thoughts, ideas, or compulsions; and secondly, the resulting triggering of abnormal behaviors or rituals. These actions may serve to resolve the mental imperative of the intrusive thoughts by inducing the person to perform repeated actions or movements that often appear ritualistic. The ritual is composed of sets or sequences of these behaviors, often in order, and may consume much of the patient's waking attention. OCD is not rare, and occurs with a lifetime prevalence of up to 3%.[1] Even with medication as well as behavioral modification, more than one in ten patients are significantly impaired in their activities of daily living.[2] Obsessive-compulsive symptoms (OCS) may be seen in OCD itself, or may appear in other psychiatric conditions,. However, despite a number of case reports, no unifying theory of causation has been clearly established. An increased prevalence of OCS, however, has been noted in refractory epilepsy,[3] particularly with temporal lobe epilepsy (TLE). There is therefore interest in whether these two conditions are causally linked.

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Epilepsy can affect up to 1% of the population, and is one of the commoner groups of neurological disorders in adults.[4,5] This group of disorders is defined as the clinical expression of repeated epileptic seizures occurring spontaneously (unprovoked). There may be many possible causes. These include genetic conditions with onset at various ages and stages of development, and a large spectrum of acquired insults such as conferred by trauma, strokes, neoplasia, inflammation, or infections. Most patients with frequent seizures are offered medical treatments, but even with a wide choice of antiepileptic drugs (AEDs), over one quarter of patients are refractory to medical treatment. Patients with epilepsy may also express a number of patterns of behavioral abnormality and personality characteristics, and experience memory, emotional, behavioral, and social disabilities.[6-9] Up to 40% of epilepsy patients may be so disabled, particularly in the patients with pharmacoresistant seizures.[6] Ertekin and colleagues' review[10] notes that in refractory epilepsy, some 70% had psychiatric disorders[7]; prevalence of axis I psychiatric disorders ranged up to 80%[8]; and that using the Symptom Checklist-90-Revised (SCL-90-R), adults with partial epilepsy had a prevalence of 88% mental health complaints when scoring for symptoms in the index.[9] In epilepsy, mood disorders, including depression and anxiety, are frequent.[10] In over 200 patients, anxiety was found in almost 25%.[11] As part of this behavioral disturbance, patients may present with features of OCD.

This review will examine the links between OCD and epilepsy, and review the evolution of the literature on case reports, case series, and larger retrospective controlled studies. Included will be the components of OCD seen in epilepsy, effects of medical and surgical treatments, and an overview of the theoretical neurobiological underpinnings that might link the two disorders.

Behavioral and thought disturbances in epilepsy

Teasing out the elements, types, and causes of behavioral disturbance in epilepsy presents a challenge. It is not clear whether the behavioral changes that occur following seizures or with epilepsy may, for example: (i) arise from the epilepsy itself; (ii) may appear as a form of forced change induced by the seizure; (iii) might arise from reactive or released behaviors after the seizure (as a postictal phenomenon); or (iv) may be a comorbid psychiatric condition (which often occur in epilepsy). Quite aside from the acute effects of acute seizures, is the possibility that it is the chronic progression of the epileptic disorder that might predispose to the appearance of OCS among the many possible psychiatric consequences of epilepsy. These mechanisms might also apply to the many different types of seizures that exist in the family of epilepsy syndromes, along with the various underlying and differing cerebral insults (both etiological and anatomical) that can cause epilepsy. In looking at possible seizure types that are associated with OCD, it seems that exclusively generalized tonic-clonic seizures are rarely associated with OCS. Psychiatric problems in general were greater in TLE (80%) than in juvenile myoclonic epilepsy (JME), a genetic nonfocal epilepsy.[12] Others have failed to be able to link epilepsy type with psychopathology.[13] There has been a long association between TLE and OCD, as will be explored below.

The association between OCD and TLE

There has been a long-standing observation that patients with various types of epilepsy had a higher incidence of many psychiatric conditions. More specifically, TLE patients occasionally showed clinical features of compulsive behavior. Some examples published as case reports delineate this relationship.[14-19] Many years ago Tizard suggested that epilepsy generated, or was associated with, a number of personality traits that had obsessional characteristics, suggesting that particular types of epilepsy cause certain types of psychopathology.[20] Waxman and Geschwind described an *interictal behavior syndrome* characterizing the religious, hypergraphic, and circumstantiality features in epilepsy patients, and others have noted that such qualities in an epilepsy population leads to a low quality of life.[21,22] There were suggestions that this *TLE syndrome* characterized by religiosity, hyposexuality, hypergraphia, and obsessional features[21] might correspond to a lateralized temporal lobe focus, but patients with OCD were found in some reports or studies to have left- or right-sided epileptic foci.[15,23,24] This was further underscored by the study by Bear and Fedio who isolated some of these psychological features, particularly elements of OCD.[25] Patients with the appearance or resolution of OCD features with the onset or regression of neurological disease strengthened these possible associations. Bear and Fedio suggested that the 2.5% prevalence of OCD in the general

population would be exceeded in patients with TLE (for example) if there were associative or causative factors to link the two disorders.[25,26]

Individual case reports or small series have led to the suggestion that a right hemisphere proclivity exists for manifestation of OCD in patients with TLE. Furthermore, it had been found that some patients with OCD features had right hemisphere structural abnormalities. There have also been other reports of lateralized abnormalities when TLE patients with OCD had magnetic resonance imaging (MRI) studies which revealed structural abnormalities, or had electroencephalographic (EEG) asymmetries.[27,28] Schmitz and colleagues, however, failed to find that TLE laterality correlated with varying degrees of personality characteristics, or obsessionality.[29]

Although a number of studies with a small number of subjects indicated a link between TLE and OCD, there were few group studies. It awaited the development of better retrospective and prospective studies to explore the similarity noted between the forced thinking seen in some patients with TLE and OCD, and to determine whether there was merely a chance comorbidity, or a clear association. Hence, there was a need to build upon the casual clinical impression and the several case reports of TLE and OCD, and design more systematic investigations in the form of case series or controlled studies. These studies would have to use structured neuropsychological instruments, trained personnel, and a control population to help eliminate biases inherent in many case series.

In order to systematize and lend validity to the association of OCD and epilepsy, Isaacs and colleagues looked at the profile of symptoms in TLE to see if TLE and OCD shared common neural mechanisms, and to facilitate diagnosis and symptom treatment in TLE.[3] To do this, they measured the prevalence of OC features using an Obsessive-Compulsive Inventory and compared their results with those of normative controls. They found that patients with OCD manifested abnormalities on neuropsychological tests that involved nonverbal memory and visuospatial tasks. This has been endorsed by some imaging studies in patients with OCD without epilepsy, but other reports indicate a more bilateral involvement.[3,27,30,31] Hence, from their findings, it is unclear to what degree a right hemisphere predominance of abnormalities prevails in TLE with OCD. The symptoms in the TLE group included *doubting, ordering, hoarding, checking, neutralizing and washing*, emphasizing the more compulsive components rather than the obsessive moiety of this duality.[3] This study thus indicated the possibility that the neurobiological pathways subserving compulsive thought processes may differ from those underlying obsessive traits. Hence, in TLE, compulsions may be particularly favored. Isaacs and colleagues suggest that *doubting, checking*, and *hoarding* in particular might represent the effects of behavioral impairments in patients with TLE, for example related to a problem in memory; while *hoarding* might reflect deficits in organization stemming from frontal lobe problems.[3]

The work by Monaco and colleagues has also been influential in exploring these links.[32] There has been a distinction made between the concept of *traits* (features) of a particular individual, or a state, arising from the role that a disease might play in a patient's life.[32] As Monaco and colleagues have pointed out, this analytical approach has been used with quantitative evaluation techniques that use personality psychometrics, but have been less used with neurological disorders.[32] Several factors may impair the strength of conclusion from older studies. These comprise possible selection bias, the absence of systematic data, and a reliance on self-rating scales without confirmation of validity, and finally an underuse of more prevalent psychometric tools.[32]

In their review of consecutive patients with TLE versus patients with nonfocal idiopathic generalized (genetic) epilepsy (IGE), Monaco and colleagues studied subjects employing investigators who were fully trained in clinical psychology and who used a Structured Clinical Interview for SDM-IV Patient Version for OCD diagnosis and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). They evaluated obsessionality as a trait using a Minnesota Multiphasic Personality Inventory - 2 (MMPI-2) version addressing the Pt clinical scale and OBS content scales that contain evaluations of characteristics of *compulsions, excessive doubts, obsessions, perfectionist personality traits*, and *fear*. The particular OC features investigated included *neutralizing, checking, doubting, ordering, hoarding*, and *washing*. The OBS content scale identifies OCS and behaviors, "maladaptive ruminations," and obsessive thoughts. These scales were supplemented by the Beck Depression Inventory and State-Trait Anxiety Inventory Y1 and Y2. Of the 164 enrolled subjects matched with 82 controls, AEDs, seizure control, age, gender, duration, EEG, and MRI among many items, were evaluated. TLE patients scored higher on the *Pt* and *OBS* scales than IGE and

normal controls, unrelated to seizure control, severity of epilepsy, medication, or etiology. This indicated that obsessionality is a TLE trait in patients with a biological predisposition, with a prior psychiatric history. In turn, this would suggest that there is a link between mesolimbic regions and particular personality characteristics, a link previously believed to exist in TLE patients. The study further supports the concept that involvement of particular brain areas, by the various epilepsy syndromes will be relevant to the appearance of specific psychopathological expression and psychiatric conditions. Of note was the fact that the results in the normal controls resembled those of IGE patients, differentiating these two groups from TLE. The study also revealed that almost 15% of TLE patients had OCD. Such findings contrasted with the Isaacs study which found that 22% of TLE patients had features of OCD,[3] but which had examined a refractory TLE population. An unsettling finding in the Monaco study is that only one of the nine patients had been previously diagnosed with OCD, indicating that OCD is poorly recognized in an outpatient epilepsy patient population. One reason may well be the relative lack of investigators trained in psychiatry in an outpatient epilepsy clinic setting. Regarding mechanisms, the authors note that the amygdala is involved in OCD, and has major connections with the striatum. Such affective and motivational components facilitate the conduction of automated often ritualistic behavior in response to danger. The reciprocal links to the amygdala, ventral striatum, and stria terminalis may serve the anxiety-modulating effects of rituals and repetitive behaviors.[33]

Ertekin and colleagues built on the prior investigations and constructed a study to evaluate the associations of TLE arising from unilateral mesial temporal sclerosis (MTS), and IGE with psychiatric comorbidities including OCD.[10] They compared 29 TLE patients with 27 IGE patients from an epilepsy clinic population, and with 30 control subjects, they employed investigators experienced in epilepsy and psychiatry. This team evaluated the three groups, and supplemented their evaluations with MRI imaging and EEG. Using a Structured Clinical Interview (SCID-I) and Y-BOCS Symptom Checklist that includes some 50 types of obsessive and compulsive characteristics, they were able to rate severity and type of symptom, including patients with subsyndromal characteristics of OCD. The authors found that about 10% of TLE patients had OCD, 24% had subsyndromal OCD, which was higher than in the matched IGE group (3.7% and 7.4% - not statistically significant). The commonest comorbidity with OCD was depression,[10] and there was a left-sided predominance in this association with TLE.

Overall, psychiatric comorbidity in the epilepsy population probably arises from many sources. Principal among them probably is a combination of social and neurobiological interplay. Lending support to the effect of the chronicity of an enduring condition, is the study by Swinkels and colleagues who noted that both predisposition and brain dysfunction played a part.[8] They speculated that anatomical factors, however, were more important than the chronicity of the disease. Confirming observations by Monaco and colleagues, Ertekin and colleagues found that depression was highly associated with OCD in TLE, also supporting conclusions by Isaacs and colleagues who used an Obsessive Compulsive Inventory (OCI), but not a SCID-IP or Y-BOCS to delineate an OCD diagnosis.[3,10,32] Findings by Ertekin and colleagues also endorse the Isaacs findings. They found that patients with TLE have greater obsessions with contamination and a compulsion to *wash* than do patients with IGE; similarly with *symmetry/exactness* obsessions and *ordering* compulsion; while Isaacs and colleagues found greater *washing, ordering, checking, hoarding, doubting*, and *neutralizing*. Some patients with TLE have greater preoccupation with existential aspects of religion.[3,10,34]

Other epilepsies and OCD

Frontal lobe epilepsy (FLE) is another likely candidate as a fellow traveler with OCD, possibly because of the executive and behavioral functions subserved by this part of the brain. From a neurobiological perspective, dysfunction in this region affects part of the frontal-cingulate-thalamic-limbic circuit, and hence might favor the functional dysregulation of this circuit, thus inducing elements of OCD.[16,18,28]

Another candidate is limbic epilepsy, with its unusual automatisms which may simulate the ritualistic behavior of OCS. Patients may display repetitive movements and types of automatic behavior.

Other rarer conditions may possess both epilepsy and rituals or at least repetitive behaviors as clinical expressions of a particular disease. Examples include the handwringing seen with Rett Syndrome, and other behavioral

features noted with Angelman syndrome and autism spectrum disorder.

Neurobiology of the association between epilepsy and OCD

There has been an increasing effort to formulate a neurobiological underpinning to OCD. Various theories have been advanced, and have been supported by the findings of OCD triggered by a number of neurological conditions. These include head trauma, brain tumors, cerebral infarction, and seizures. Modell and colleagues suggest that there are two principal loops or circuits underlying control of the behaviors involved in OCD.[34] They are comprised of a thalamo-orbitofrontal connection mediated by glutamate, and a collateral loop that includes striatal-orbitofrontal-thalamic interconnections mediated additionally by serotonin, dopamine, and gamma-aminobutyric acid (GABA). The latter loop controls the activity in the thalamo-orbitofrontal circuit. Normally, orbitofrontal cortex activates the caudate and then the pallidum so as to inhibit the medial thalamic nucleus that then feeds into the frontal cortex. In this manner, medial thalamic inputs would regulate hyperactivity of the orbitofrontal thalamic relays. Dysfunction of these circuits might produce OCD, with increased activity inducing obsessive characteristics and compulsive traits.[34]

However, complicating this paradigm is the paradoxical clinical resolution in some cases of established OCD by the new appearance of one of strokes, tumors, or by deep brain stimulation.[35,36] Nonetheless, such serendipitous associations have spawned a neurobiological underpinning for OCD that includes the malfunctioning of various brain circuits. Abnormally functioning circuits include the thalamus, basal ganglia, anterior cingulate gyrus, and the orbito-frontal cortex.[37,38] It has been postulated that there is an abnormality in the circuit linking frontal regions to the basal ganglia. These circuits pass through the frontal-thalamic-pallidal-striatal areas and back to the frontal regions, transiting via the anterior cingulate gyrus and the internal capsule. To support the concept of this specific circuitry underlying OCD is the finding that disruption of this pathway by surgical anterior internal capsulotomy and anterior cingulotomy enables improvements in OCD.[39] A new model for OCD has been proposed by Huey and colleagues based on studies using functional MRI, MRI, and positron emission tomography.[36] They examined patients with OCD who had other neurological disorders, and compared them to patients with idiopathic OCD. Some patients with "secondary" OCD had undergone surgery or deep brain stimulation believed to decrease hyperactivity in regions thought to provoke OCD. The group postulated that three regions are implicated in both types of OCD: orbitofrontal cortex which directs appropriate behavior, the basal ganglia that acts as a gate in connecting behaviors to subsequent reward, and the anterior cingulate region that modulates perception of which behavioral "choice" will result in reward. Patients with OCD from neurological disease had less anxiety with the compulsion than did those with the idiopathic form. Huey and colleagues postulated that the anxiety and impulse towards particular behaviors are requited only when the behavior is completed.[36]

Theories underlying the particular association between OCD and epilepsy include not only a possible shared mechanism, but an incidental OCD problem in patients with epilepsy.[39] However, a compelling explanation for the OCS-epilepsy association is the interruption of a "pathological shared organization" when certain types of focal brain neurosurgery are performed, with the effect of causing regression of seizures, but also allowing latent OCD traits to appear.[38,40] A sudden cessation of seizures after surgery might be seen as a form of "forced normalization."[41,42] Hence the surgical removal of excitation, and preponderance of inhibition, would enable the occurrence of psychiatric disorders, and have been termed the "forced normalization" concept and the "latent disease theory."[41,42] Of note however, many postoperative TLE seizure patients never develop psychiatric problems.

One of the components of OCD involving the perception of forced thoughts may occur from seizures themselves. In the classification of seizures, those seizures that involve part of the brain and which do not impair vigilance or memory, are termed simple partial seizures. It has long been noted that obsessive thoughts can occur in the preictal period, be caused by simple partial seizures as an ictal phenomenon, or occur in the postictal period.

Kroll and Drummond have suggested that the comorbidity of OCD and TLE might be due to kindling.[15] The theory of kindling is that focal chemical or electrical brain stimulation can later result in a more persistent condition (eg, epilepsy). Some speculate that this might occur in the limbic circuit, and induce OCD problems.

However, there is little evidence for this theory. Others have suggested that TLE and OCD might share a common mechanism. Problems with this theory are the absence of a single focus of neuronal deficit in OCD. In contrast, several regions have been implicated in OCD, including the basal ganglia, cingulate, and frontal areas,[23,36] with limbic areas involved in OCD and TLE.[16,18,28] The results of studies revealing a right-hemisphere TLE focus predilection, suggested an increased vulnerability to OC in this TLE population.

There may be a role of AEDs in OCD, as they might convey a neuropharmacological susceptibility to OCD. Ertekin and colleagues found in their TLE patients that most were on carbamazepine, while patients with IGE (with less OCD) were on valproate.[10] This suggests that epilepsy syndrome aside, one drug might favor, or the other drug might hinder, the development of OCD.

Because of the finding of depressive comorbidity with OCD in epilepsy, limbic dysfunction might represent an underlying neurobiological underpinning. Clinically, patients with OCD should therefore be assessed and treated for depression.[10]

The effects of surgery on OCD

In contrast to the appearance or the worsening of OCD with temporal lobe surgery as mentioned above, a subgroup of patients with particularly temporal-lobe foci may significantly benefit from resective surgery. Surgery is also sometimes effective in extratemporal foci, or with more widespread epileptic conditions with multiple seizure types (eg, Lennox-Gastaut syndrome), in which partial interruption of the corpus callosum may decrease certain types of seizures, particularly atonic seizures.

Many types of underlying premorbid psychopathology may get worse following epilepsy surgery, even when epilepsy improves.[39,43,44] There are reports of depression and psychosis, and in some cases suicide and death after temporal lobe surgery.[44-47] De novo psychosis may arise,[47] as well as de novo depression in 8%.[45,48] Leinonen and colleagues commented on new-onset schizophrenia in a group of 57 subjects[45] after surgery. Such tendencies can be evaluated before surgery and may well factor in the decision whether to advocate this treatment in affected patients.

Although Kulaksizoglu and colleagues found no particular risk factors for de novo postoperative psychiatric problems, most problems appeared to manifest within the first 2 months after surgery.[40] Six of 74 patients undergoing temporal lobectomy had new-onset psychosis with 6 suicide attempts in the first month.[49,50] In another series, by 6 weeks post-temporal lobectomy, of the previously nonsymptomatic patients for psychiatric disorders, half developed anxiety and depression, and almost half had emotional lability.[51] Other studies suggest that nondominant hemisphere surgery favors the appearance of more severe psychiatric problems,[52,53] even if lesions on either side may induce OCD in nonepileptic patients. Other neurosurgical studies support the involvement of neural loops in OCD in patients with epilepsy, and the subsequent improvement that can occur following surgery.[54] To reinforce the involvement of frontal pathways, Kulaksizoglu and colleagues review the reports on the dysfunction of frontal subcortical circuits, and the abnormalities in visual-spatial and nonverbal tasks that particularly implicate right subcortical frontal circuits in the process.[40]

Future directions in epilepsy/OCD research

There is much work to be done in establishing the causation of OCD, and possible links to epilepsy. Future studies should extend investigation to nonepilepsy neurological groups as well as a psychiatry group with OCD.[3] Multicenter studies would be valuable in looking at the entire severity spectrum of OCD in TLE. In addition, with the findings of greater religiosity and writing compulsions in patients with epilepsy, research into OCD in epilepsy would be enhanced by developing specific tools or scales that measure these parameters.[10] Greater attention might be directed at the comorbidity of depression and anxiety in OCD in patients with epilepsy, with examination of the neurobiological and structural relationships to clinical expression.[10]

As with any implied association, prospective larger studies with optimally trained personnel with experience in psychiatric testing instruments, the development of tailored characterization of OCD subtypes and feature categorization, and the application of these tools and trained personnel to carefully categorized populations of different types of epilepsy, are warranted. Multicenter trials would have a good chance of lending support to the neurobiology, causes, and optimal management in patients with the several types of epilepsies and varieties of OCD. ❑

Epilepsia y trastorno obsesivo-compulsivo

El trastorno obsesivo-compulsivo (TOC). Es muy importante la vinculación con la epilepsia del lóbulo temporal (ELT), la cual es habitualmente refractaria. De los pacientes con ELT, el 10% a 22% puede tener un TOC, el cual con frecuencia es subdiagnosticado en los pacientes ambulatorios. La información de estas vinculaciones incluye reportes de casos, series de casos y estudios controlados. Tres grandes estudios controlados en pacientes con ELT, utilizando extensas clasificaciones de epilepsia y TOC han mostrado las características obsesivas del lavado, la simetría/exactitud y el orden, como también una mayor preocupación por ciertos aspectos de la religión, en comparación con controles o con pacientes con epilepsia idiopática generalizada. Los focos de la ELT pueden estar al lado izquierdo o derecho. Los factores sociales y neurobiológicos están involucrados en el TOC y en la ELT. La neurobiología implica un deterioro estructural o fisiopatológico de los circuitos tálamo - órbitofrontal y fronto – tálamo – pálido – estriatal - cíngulo anterior - frontal. Discretas lesiones anatómicas en estas vías o su remoción quirúrgica, pueden inducir una mejoría o un empeoramiento en el TOC de los pacientes con ELT.

Épilepsie et trouble obsessionnel compulsif

Le trouble obsessionnel compulsif (TOC) a longtemps été associé à l'épilepsie. Ainsi, le lien avec l'épilepsie du lobe temporal (ELT), habituellement réfractaire, est particulièrement important. Parmi les patients ayant une ELT, 10 % à 22 % peuvent avoir un TOC, souvent sous-diagnostiqué en consultation externe. Des rapports de cas, des séries de cas et des études contrôlées permettent de faire le lien entre ces deux pathologies. Trois plus grandes études contrôlées chez des patients ayant une ELT, utilisant la classification complète de l'épilepsie et des TOC, ont permis au total, en comparaison avec des témoins ou à des patients ayant une épilepsie généralisée idiopathique, de constater des obsessions de lavage, de symétrie/précision et d'ordre, et une préoccupation particulière pour certains aspects de religiosité. Les foyers d'ELT peuvent être localisés à gauche ou à droite. Des facteurs sociaux et neurobiologiques sont impliqués dans les TOC présents au cours de l'ELT. Les études neurobiologiques ont montré une altération physiopathologique ou structurelle des circuits orbitofrontaux-thalamiques et fronto-thalamo-pallido-striatro-antérieur cingulaire-frontal. Des lésions anatomiques discrètes de ces voies, ou leur levée chirurgicale, peuvent améliorer (ou l'inverse) les TOC chez les patients atteints d'ELT.

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