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REVIEW ARTICLE

Diagnostic Issues in Early-Onset Obsessive-Compulsive Disorder and their Treatment Implications

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Abstract: ***Background*:** The lifespan approach and recent shift in the conceptualization of Obsessive-Compulsive Disorder (OCD) promoted by the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM5) along with novel insights into the pathogenesis of this heterogeneous disorder are driving the development of new outcome measures and new treatments for a disease that, on the other hand, is characterized by high rates of refractoriness.

***Objective and Methods*:** The aim of this review is to provide a discussion of the translational evidence about Early Onset OCD (EO) in compliance with a neurodevelopmental and RdoC perspective.

***Results and Conclusion*:** EO might be considered the neurodevelopmental subtype of OCD. Indeed there is evidence that different clusters of symptoms and dimensions at an early stage predict different trajectories in phenotype and that distinct neurocircuit pathways underpin the progression of the disorder. Despite the development of high refractoriness in the course of the disorder, evidence suggests that EO may be particularly treatment responsive in the early stages, thus showing the need for early recognition and additional recovery oriented studies in this subgroup.

Consistent with the neurodevelopmental perspective, immunity and glutamate neurotransmission are emerging as novel pathways for parsing out the neurobiology of OCD, the EO form, in particular, supporting the implementation of new multisystemic models of the OCD phenotype. Brain connectivity patterns, immune and microbiome profiles are standing out as promising areas for biomarkers with the potential for targeted personalized therapies in EO.

Keywords: Early-onset OCD, pediatric OCD, neurodevelopmental disorders, neuroinflammation, glutamatergic agents, gut microbiome, RDoC.

1. INTRODUCTION

Obsessive-compulsive disorder (OCD) with a lifetime prevalence ranging from 1.5% to 3.5% [1] is an important cause of disability among brain disorders [2]. The burden of disease conveyed by this condition is related to its early onset [3, 4] and high degree of refractoriness [5] and call for the implementation of studies that yield biosignatures to stratify the broad-illness phenotype into a finite number of treatment relevant subgroups.

There is evidence that age-of-onset constitutes a useful variable for parsing the obsessive-compulsive (OC) phenotype [6]. According to latent class analysis, early onset OCD (EO) represents a distinct subgroup (mean onset 11 years) and the most common form of the disorder compared to a later onset subtype (LO), with 21 years as empirically defined cutoff [7]. Multiple meta-analysis indicate that EO and LO could be reliably distinguished in terms of gender distribution, clinical features and genetic load [7], with EO presenting higher prevalence in males, higher level of comorbidity with tics and other OC spectrum disorders, higher genetic heritability [8] and higher global OCD severity [9], not only justified by the longer duration of illness [10]. On the other hand, the two putative subtypes seem not to differ significantly in terms of the factor structure of symptoms, which tend to co-occur together [11, 12].

Mega-analysis of neuroimaging data indicates different patterns of subcortical abnormalities in pediatric versus adult OCD patients [13], with thalamus implicated in pediatric

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OCD and pallidum and hippocampus in adult OCD. Stratified analyses showed that adult OCD patients with an early disease-onset exhibit larger pallidum volumes than controls, hypothesizing that it could be related to the progression of EO. On the other hand, the clear distinction in thalamic volume across pediatric and adult OCD patients suggests that an increased thalamic volume may be an early marker of altered neurodevelopment in EO. The same morphological characteristic has been found in patients diagnosed with other neurodevelopmental disorders, such as ADHD [14] and Tourette's syndrome [15] and notably, an early pharmacological treatment has been suggested to have a normalizing effect on thalamus volume in pediatric OCD [16].

Although research is still needed to determine the optimal criteria for establishing age of onset and whether EO and LO differ in their biology, the fact that OCD tends to present its onset in pre-adult age support the appropriateness of a research and clinical approach towards OCD and specifically EO that take into account the neurodevelopmental perspective [17].

2. EO: A NEURODEVELOPMENTAL DISORDER. DIMENSIONS AND TRAJECTORIES.

The high heterogeneity and degree of comorbidity reported by OCD patients support the need for dimensionally dissecting the OCD phenotype. From a neurodevelopmental perspective, EO constitutes the subtype of choice for using this quantitative approach, thus driving the identification of more robust endophenotypes [18].

Although OCD affects approximately 0.5 to 2.0% of children, subclinical OC symptoms are present in around 10%-15% of the pediatric population [19, 20] and they have been found to predict the development of full OCD and other psychiatric comorbidities later in life [21]. Due to the fact that in the early stage symptoms are often hard to be attributed exclusively to a specific category of disorder, there is often a delay in diagnosis of EO [22] and OCD in these cases is associated with a long duration of untreated illness and long standing developmental impairment, including cognitive features [23]. On the contrary, earlier diagnosis and treatment are positively related to outcome in EO and some studies found that pediatric OCD remission rates are considerably higher and most durable than in adult samples [24-26].

Distinguishing prodromal OCD from physiological developmental behavior may be a critical issue for the clinician. A family history and genetic load seem to be predictors of subsequent progression towards the full disorder [8]. However, given the evidence that OC symptoms are dimensional rather than categorical in their frequency/severity distributions [27], it may be beneficial to study non-clinical populations to understand the course of the OC symptoms–OCD continuum and when and how best to intervene. A population-based study [28] found that three profiles were distinguishable in a sample of school-aged children scoring high on OC symptoms: a subgroup with only OC symptoms, a subgroup with both additional externalizing and internalizing symptoms, and a subgroup with primarily autistic symptoms. Longitudinal follow up of these profiles would help translation towards establishing profiling and staging of the disorder.

On the other hand, prospective categorical studies on clinical samples have shown how OCD does not behave as a unitary disorder, but rather different subgroups can be identified by distinctive lifetime trajectories in comorbidities. A large multicenter study [29] demonstrated specific associations between first and later comorbid diagnosis in OCD patients, with separation anxiety disorder, ADHD and tic disorders as first comorbid diagnosis predicting respectively additional anxiety and somatoform disorder, higher frequencies of substance abuse and higher lifetime frequencies of OC spectrum disorders in the course of the disorder. Notably, most comorbid disorders in OCD are related to the age of onset of the disorder rather than to the current age: while adolescent-onset OCD patients show higher rates of anxiety and depressive disorders, childhood-onset OCD patients show higher rates of other neurodevelopmental disorders [30, 31] and this corroborates the importance of a transdiagnostic and multidimensional perspective.

It has been reported that attention-deficit/hyperactivity disorder (ADHD) presents a prevalence estimate of 19% in youth with a primary diagnosis of OCD [32]. Previous research has also found that comorbid ADHD may interfere with success in OCD treatment, with poorer treatment outcomes in cognitive behavioral therapy (CBT) [33]. However, a recent study [34] has found that when treating a child or adolescent with co-occurring OCD and clinically significant attention problems when OCD-onset clearly precedes ADHD-like inattention, clinicians may wish to target obsessive-compulsive symptoms first to have also inattention improved.

A high prevalence of autistic traits has been found in OCD samples both in adults and in children [35] and comorbidity between autism spectrum disorder (ASD) and OCD may significantly affect treatment outcome [36]. One study [37] associated the poorer response to CBT in OCD to abnormalities in the left dorsolateral prefrontal cortex (DLPFC) that may be also associated with autistic traits.

As concern comorbidity between OCD and tic disorders (TD), it is so frequent in a specific subgroup of patients that many experts believe that the two disorders represent a specific subtype of the illness, which might be referred to as Obsessive-Compulsive Tic Disorder (OCTD), the further elaboration of the DSM-5 OCD tic-related specifier [38-40]. Available literature [41] suggests that OCTD is characterized by early onset, male gender, sensory phenomena and obsessions of symmetry, aggressiveness, hoarding, exactness and sounds, impulsive behaviors and ADHD comorbidity.

It has been argumented that this putative subtype could be particularly resistant to pharmacological treatment [41], requiring combination/augmentation treatment with serotonin reuptake inhibitors (SRIs) plus antipsychotics at the highest tolerated dosage. However, although tic disorders have shown to adversely impact the outcome of serotonin reuptake inhibitors use in pediatric OCD, CBT outcomes seem to be not impacted by comorbid tic disorders [42, 43].

Increasing evidence found that the phenotypical heterogeneity observed across the EO subgroup and in the same

Table 1. Clinical moderators and predictors of response to SSRIs and CBT in pediatric OCD.

First Line Treatments for Pediatric OCD	Clinical Moderators of Response	Clinical Predictors of Response
CBT	family history [45]	Severity; anxiety and depressive symptoms; ADHD; ASD [33, 45]
SSRI	Tics [45]; Early improvements (2weeks) [48]	Severity; anxiety and depressive symptoms [45, 48]

patient in the course of the disorder is associated with likewise neurobiological complexity.

Moreover, recent studies found that the co-occurrence of OC symptoms, tics and attention-deficit/hyperactivity symptoms can be only partly explained by shared pathogenetic pathways and there is still need for longitudinal dimensional studies that examine subdimensions and identify more genetically homogenous symptom subtypes [44]. The need for further dissecting the EO phenotype is confirmed by the significant variability in how well children and adolescents with OCD respond to CBT and SSRI [45].

Current practice guidelines for pediatric OCD, recommend using CBT monotherapy in patients with mild to moderate symptom severities and combined SSRI e CBT treatment for more severe cases [46] or when the patient has not shown adequate response to CBT alone [47]. But the severity of OCD symptoms seems not be the only factors that should be considered in guiding treatment recommendations. Beyond the unmet need for reliable endophenotypes, the available evidence concerning clinical predictors of response in EO, found that the presence of comorbid tics and a family OCD history may moderate CBT outcomes in this population [45], and early improvement to SSRIs may predict response [48] (Table **1**).

3. EO: THE IMMUNOLOGICAL ASPECT AND THE ROLE OF GLUTAMATE

From a pathophysiologic perspective, approaching EO as a neurodevelopmental disorder implicates the involvement of microglia and more broadly the immune system as a whole [49].

The link between OCD and immunity has been brought into light since the 1980s with case series reporting abrupt pre-pubertal onset of OC and tic symptoms occurring in patients with Sydenham's chorea (SC) [50]. These observations led to the definition of PANDAS [51] -pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections- and then to the umbrella category of PANS [52] pediatric acute-onset neuropsychiatric syndrome- where infection seems to be implicated as the primary inciting factor in more than half patients [53]. Despite the discussion about its existence as a separate entity, PANDAS has constituted a model for autoimmune OCD, developing an immune-driven pathogenetic hypothesis, putative immune biomarkers and specific immunomodulant therapy still waiting support for validation [54]. Growing evidence is now supporting the fact that immune dysregulation may contribute not only to PANDAS but to the pathophysiology of OCD as a whole [55, 56]. After all, the neuroinflammatory theory of OCD is in line with the change of paradigm that all psychiatry is coming across and which is based upon the increasing evidence that the crosstalk between the immune system and neurocircuits is pivotal in the pathogenesis of many psychiatric disorders [57]. Peripheral cytokine alterations profiles have been detected in the majority of psychiatric disorders as well as accumulating evidence indicate that M1-like microglia (proinflammatory) are significantly increased in comparison to ramified microglia (resting) and elongated M2-like microglia (anti-inflammatory) phenotypes in many psychiatric diseases [58]. A recent study [56] investigating inflammation in the brain of OCD, has demonstrated the presence of a microglial activation throughout all the cortico-striato-thalamo-cortical (CSTS) circuit, so beyond the basal ganglia which have been implicated in the pathogenesis of PANDAS and beyond the childhood onset. This outstanding study suggests the potential for neuromodulatory drugs that can shift the monocyte/microglia phenotypes, such as azithromycin and minocycline [59]. The potential usefulness of antibiotic therapy in OCD is as well emerged in the clinical practice, where azhitromycin and beta-lactams – the drugs of choice to treat group A streptococcus (GAS) infections – have been extensively used to treat PANDAS patients. A recent review analyzing the evidence supporting this practice-based use [60], concluded that even if conclusive studies that assess superiority of antibiotics vs placebo in the PANDAS/PANS population are still missing, the available evidence suggests the existence of a pediatric OCD subgroup that goes beyond the boundaries of PANDAS and PANS and that is sensitive to antibiotic therapy, independently of antiinfective activities. Studies have demonstrated that both azhitromycin and beta-lactams molecules confer neuroprotective effects, the first related to its ability to induce M2 polarization in microglia and peripheral macrophages [61], the second increasing genic expression of glutamate transporter GLT1 and consequently minimizing glutamate neurotoxicity [62]. This latter effect is particularly relevant considering that converging evidence coming from preclinical [63, 64] and genetic studies [65, 66] indicates the importance of glutamate transmission in the pathophysiology of OCD. Although the efficacy of any glutamatergic agents either in combination with selective serotonin reuptake inhibitors or as monotherapy in the treatment of OCD has not yet been established [67] some data suggest that there might be a subgroup in OCD more sensitive to these agents [68]. Interestingly, a recent study found that brain glutamate might moderate treatment response to CBT in pediatric OCD [69].

There is still need for studies concerning glutamatergic agents, especially for pediatric OCD, where just riluzole

[70], D-cycloserine [71] and NAC [72] have been investigated in RCTs, with inconclusive results concerning the first two and promising results for the latter.

Independently of the diagnosis, there are preliminary data suggesting the potential use of memantine and N-acetylcysteine (NAC) in the treatment of compulsivity/impulsivity in pediatric patients [73].

Although we couldn't find specific studies comparing the effectiveness of memantine in OCD across age groups, it's been reported that in two cases of refractory OCD treated with an augmentation of memantine [74], only the case with early onset showed immediate and substantial improvement.

An open label study [75] conducted in treatment-resistant OCD patients who had failed at least one adequate trial of an antipsychotic in augmentation with an SRI, showed that minocycline augmentation of SRI pharmacotherapy may not improve OCD in all adult OCD patients, but may improve symptoms in those with early-onset OCD and those with primary hoarding. Minocycline, a tetracycline derivative used for chronic acne, next to the anti-inflammatory actions on microglia/macrophages seems to also modulate NMDA-R transmission [76].

It's been hypothesized that one putative mechanism of action of glutamatergic agents in OCD could be related to their property to reverse the downstream effects of pro-inflammatory cytokines [77]. Despite the inconsistent results of previous research about cytokines abnormalities in OCD probably related to confounding effects of medication and comorbid depression, one study conducted in drug naïve comorbidity free OCD patients [78] found elevated levels of cytokines that - through the kynurenine pathway- may be responsible for alterations in glutamate transmission [77, 78]. A recent study conducted specifically in pediatric medication-free OCD patients and notably excluding clinically suspected cases with PANDAS/PANS detected an increase in serum TNF-alpha levels compared to unaffected controls [79].

Another study conducted in pediatric OCD patients found that while there was no difference in basal cytokines production compared to controls, they present a higher percentage of proinflammatory monocytes and enhanced proinflammatory innate response [80].

If increasing evidence is suggesting that OCD pathogenesis involve immune response, on the other hand effectiveness of SSRIs, the first line of treatment for OCD, may also be mediated by some of the immunomodulatory and anti-apoptotic effects that they have been shown to exert [81-83] and that however could be modulated by the quality of the living environment [84].

One study analyzing drug-similarity based on side effect profiles indicates indeed that some antidepressants and some immune-related drugs may affect common molecular pathways, such as cytokines levels and glucocorticoid signaling [85].

Two randomized clinical trials [86, 87] showed the efficacy of anti-inflammatory COX-2 inhibitor celecoxib as an adjunct in the treatment of OCD; it's been hypothesized that this effect may be mediated by the anti-inflammatory propriety but also by the effect on glutamatergic neurotransmission, seeing that COX-2 inhibitors have been proven to be beneficial in prevention of glutamate-mediated neuronal death [88].

The complex interplay between brain and immunity leads to consider another actor that may probably play an important role in the pathogenesis of OCD, namely the gut microbiome. There is an extensive literature about the relationship between gut microbiome and brain development and function [89] and how the immune pathway –through cytokines balance and microglial activation- constitutes an important mechanism of mediation between the two systems. The gut microbiome acts upon the brain through direct and indirect actions, producing neurotransmitters (GABA, serotonin, catecholamines and acetylcholine), and short chain fatty acids that act as neuroimmuneactive substances modulating the Hypothalamic-pituatary-adrenal (HPA) axis, the gut and blood-brain barrier permeability, the production of brain-derived neurotrophic factor (BDNF), and histone deacetylases (HDACs) and microglial activities [90]. Increasing preclinical evidence corroborates the fact that microbiota plays an important role in neurodevelopment leading to alterations in gene expression and resulting in perturbation to the programming of social and cognitive behaviors [91]. Evidences have shown how phases of more instability in the composition of gut microbiome –namely perinatal, adolescent and old ages- overlap with the windows of greater vulnerability in brain development [90]. On the other hand, clinical studies that have characterized the gut microbiome in neuropsychiatric conditions, especially neurodevelopmental, neurodegenerative and mood disorders, found an association with gut microbial dysbiosis [90].

Although studies specifically concerning microbiome and OCD are still missing [92], the evidence linking microbiome and neurodevelopmental disorders - particularly autism spectrum disorders and ADHD - and stress-related disorders - as well as the promising results concerning the efficacy of the so called "psychobiotics" in these conditions [90], suggest that the gut microbiome may convey potential biomarkers and constitute a modifiable factor in the development of OCD. Consistently, probiotic treatment appeared comparable to fluoxetine in attenuating mouse OCD-like behaviors [93].

Growing evidences are elucidating the interplay of the inflammatory and glutamate pathways in OCD opening the way to identify immune and connectivity biomarkers and subtype this heterogeneous disorder into biologically meaningful component conditions. Although further studies are needed to examine the relationship between cytokines and individual symptom dimensions and to verify if cytokine levels could be predictor of response, evidence support the existence of a subtype of OCD - which probably overlap with EO and supersede the boundaries of PANDAS- that is particularly associated with immune pathophysiology and that would particularly beneficiate of augmentation with immunomodulating and glutamatergic therapies. In the meantime, the complex interplay between brain-immunity and gut in the pathogenesis of OCD drives the implementation of studies aiming to assess the multimodal activities of drugs in the treatment of this population.

4. TOWARDS A NEUROBIOLOGICALLY BASED APPROACH

The intersystemic pathogenesis and neuro-developmental progression of EO calls for the implementation of targeted and real-time approaches that take into account the clinical staging of the disorder in the single patient.

The challenge of parsing out the heterogeneity of OCD and EO is finally in the hands of the Research Domain Criteria (RDoC) project [94], that following an individual-centric approach constitutes the framework to inform Big Data coming from genomics, physiology, psychopharmacology, system biology and behavioral science, then constituting the roadmap for the realization of the claims of Precision Psychiatry.

Based upon the paradigm of mental disorders as disorders of brain circuitries, the circuit level becomes the pivotal level of analysis and the most promising field in order to individuate biomarkers.

Several preclinical and clinical studies have uncovered substantial evidence that dysfunction in cortico-striatal-thalamo-cortical (CSTC) loops may underlie compulsive behavior [95]. Over the past 5 years, optogenetic studies have led to great progress in further dissecting these neural circuits and argue that multiple paths may subtend perseverative behavior – *i.e.* through dysfunction of either habit system or goal-directed/limbic system [96].

However, an individual-specific approach is critical in identifying biomarker and there is still need for implementing studies that detect functional brain circuit connections that track changes in global and dimension-specific symptom severity longitudinally, in the same patient. Recently, one study conducted in OCD patients [97] found that changes in connectivity pre-post treatment in the individual patient can predict YBOCS improvement, while connectivity was less predictive in template-based comparisons.

The individuation of connectivity biomarkers and the anatomical characterization of individuals may promote identification of new outcome measures and true integration between psychopharmacology, psychotherapy and neuromodulation in order to magnify therapeutic efficacy in the single patient. The RDoC framework with its multilevel approach constitutes the more comprehensive basis for the development of outcomes-based assessment in clinical settings that, next to the symptom assessment based on self-report measures and observed behaviors, include genetic, microbiome and neuroimaging data. The subjective dimension should become the starting point for the translation clinician, from which, thanks to the RDoC framework, delving into the neurobiological aspects of the patient.

CONCLUSION

The available evidence supports understanding EO as a neurodevelopmental disorder and this implies complexities in assessment as well as opportunities in treatment.

In over 50% of all OCD cases, symptoms emerge during childhood or adolescence and although there is evidence that in late stages EO is a higher resistent subgroup in OCD, data suggest that an early diagnosis and treatment in EO may confer better outcomes than treatment in the general adult OCD population. Indeed, approximately one half of children with OCD experience remission of OCD symptoms with first line therapies. Despite some available clinical predictors of treatment outcome to CBT or SSRI, further studies are needed in order to identify moderators of response and further treatments once firstlines prove not to be helpful.

Increasing evidence suggests that the immune and glutamatergic pathways may be particularly involved in this subtype of OCD, highlighting the need for multisystemic models of the disorder and longitudinal RDoC-oriented studies, in order to detect reliable biomarkers that might go beyond the boundaries of the nervous central system. Next to studies aiming to dissect the heterogeneous OCD phenotype and identifying endophenotypes, it would be also beneficial to implement studies assessing the multimodal activities of drugs in this population, going beyond the fictitious boundaries of the old nomenclature of drugs and driving the development of a multimodal neuroscience-based therapy.

The existing literature supports EO as a useful diagnostic specifier of OCD and suggests the need for the fine tuning of a multimodal assessment in the individual patient that takes into account the type of onset, the immunological profile, the specific dimensions involved with particular attention towards the cognitive and motor aspect, the genetic load and the course and staging of the disorder.

The neurodevelopmental progression of EO indeed suggests the need for studies investigating recovery rather than resistence, and consequently implement an early, high intensity treatment approach that could multimodally combine psychotherapy, neuromodulation, psychodrugs, and immunomodulant-neuroprotective interventions.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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