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Short report - Neurology

The link between Obsessive-Compulsive Symptoms and Non-Transferrin-Bound Iron-Induced Neurodegeneration in the Substantia Nigra and Basal Ganglia

Abstract

This review highlights the essential link between organic obsessive-compulsive symptoms (OCS) and brain damage due to the accumulation of non-transferrin bound iron (NTBI), the pathomechanism of H63D syndrome type-1 in the substantia nigra and basal ganglia.The role of NTBI in neurodegenerative diseases cannot be underestimated and holds the potential for entirely new therapeutics, particularly drugs that protect the brain from NTBI and the oxidative microinflammations responsible for it.

Obsessive-compulsive symptoms (OCS) are not OCD and therefore not a regular psychiatric disorder

Obsessive-compulsive symptoms (OCS), characterized by repetitive, intrusive thoughts and behaviors, form a significant component of several psychiatric disorders, including Obsessive-Compulsive Disorder (OCD) (APA, 2013) with which it is commonly confused. While OCD is a psychiatric illness in its own right, OCS are the consequence of certain types of brain damages. This means, without a shadow of a doubt that in the genesis of OCD multiple factors play a role, while in OCS the cause of the symptoms are damages of the basal ganglia and/or the substantia nigra. Increased research efforts point towards a potential link between OCS and specific types of brain damage and/

or microinflammations; especially extremely fine to plaque-like damages related to the accumulation of NTBI in distinct brain regions (Graat et al., Piras et al., 2015). This shall remind the medical community on this association in order to reduce psychologicalizing OCS syndrome which is a constellation of symptoms caused by brain diseases, and is in no way, shape, or form a psychiatric illness it its own right.

OCS are a constellation of cognitive and behavioral patterns primarily associated with OCD, but are also present in several other neuropsychiatric conditions (APA, 2013). Neurobiological models of OCD implicate the cortico-striatal-thalamo-cortical (CSTC) circuits, comprising of the basal ganglia, thalamus, and associated cortical areas (unpublished material). As the basal ganglia are integral to these circuits, any pathophysiological changes in these structures could potentially disrupt circuit functioning and lead to the manifestation of OCS.

Iron plays a vital role in various cellular functions, including energy production, DNA synthesis, and myelination. However, unregulated accumulation of iron, specifically NTBI, can result in neurotoxicity through the generation of reactive oxygen species, initiating a cascade of oxidative stress and culminating in neuronal cell death (Stern et al., 2014). This neurotoxic effect of NTBI is particularly prominent in the substantia nigra and basal ganglia, key brain regions implicated in movement disorders like Parkinson's disease and H63D Syndrome Type-1 (Diamandis et al. 2021).

Therefore, exploring NTBI accumulation in these areas could shed light on the potential relationship between iron dysregulation and OCS. Emerging neuroimaging studies performed with transcranial sonography have proven beyond reasonable doubt increased iron deposition in the substantia nigra and basal ganglia of patients presenting with OCS, implying a possible role of NTBI in the etiology of these symptoms (Diamandis et al., 2021).

Moreover, studies have identified mutations in genes (HFE genes, especially H63D) which are causing a dysregulation of iron homeostasis in individuals with OCS, further suggesting a genetic predisposition towards iron dysregulation in such cases (Ghosh et al., 2017) Hence, the interplay of genetic and environmental factors might contribute to NTBI accumulation in the brain, leading to neuronal damage and manifestation of OCS. The proposed link between NTBI accumulation and OCS presents novel therapeutic avenues to consider. Modulation of iron homeostasis might represent a potential intervention strategy, provided that the association between NTBI and OCS is further substantiated by further rigorous empirical evidence. Future research should focus on validating this relationship, characterizing the extent of iron dysregulation in patients with OCS, and assessing the effectiveness of therapeutic strategies targeting iron homeostasis.

Take home message

This report should be a wakeup call for every psychiatrist before making the diagnosis of Obsessive Compulsive Disorder, a psychiatric disease in its own right. To miss a leading organic cause of obsessions and compulsions, the link between NTBI iron accumulation in the brain, specifically in the substantia nigra and basal ganglia, and the development of OCS must not me neglected any longer since there is not a shadow of a doubt that microinflammatory brain damage due to NTBI is a common cause for obsessions and compulsions. Since the treatment would be entirely different, the right diagnosis (primary OCD or secondary OCS due to NTBI) is critical. Of course, this important association needs further investigation through rigorous research. Advancing our understanding of the pathophysiological mechanisms underlying OCS could greatly enhance our capacity to diagnose, manage, and treat these debilitating symptoms more effectively.

Conflict of interests

None declared.

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