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Update on the pathophysiology and therapeutics of chorea disease

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ABSTRACT

Chorea is a primary category of involuntary movement disorders arising from aberrant neural circuitry connecting the frontal cortical motor regions and the basal ganglia. Clinically, the syndrome manifests as a high frequency of brief, erratic, and involuntary muscle contractions. Although chorea may result from various aetiologies, the most common contributors include dysregulation of glucose metabolism, thyroid dysfunction, and renal impairment. Neurochemical abnormalities have been implicated in its pathophysiology, notably dysfunction of the presynaptic nigrostriatal dopaminergic pathway, which may lead to increased dopamine turnover. The authors emphasize that the current pharmaceutical armamentarium for chorea remains limited, offering few therapeutic options to clinicians. Tetrabenazine and its derivative, deutetrabenazine, are the principal agents approved by the US Food and Drug Administration specifically for the treatment of chorea associated with Huntington's disease. This case underscores the persistent and substantial challenges faced by healthcare professionals in managing this complex neurological condition. Further research is urgently warranted in order to expand the therapeutic landscape and to elucidate the pharmacodynamics and pharmacokinetics of existing and emerging agents across diverse patient populations affected by chorea. The objective of this article was to provide a concise overview of the biochemical alterations and pharmacological interventions relevant to chorea.

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1. Introduction

Chorea is a primary category of involuntary movement disorders resulting from aberrant neural networks linking the frontal cortical motor regions and the basal ganglia. The condition is characterized by a frequent succession of brief, erratic, involuntary muscle contractions, which may arise from a variety of aetiologies[1]. The World Federation of Neurology Committee on Classification defines chorea as *"a state of excessive, spontaneous movements, irregularly timed, non-repetitive, randomly distributed, and abrupt in character"*. The severity of these movements ranges from subtle, intermittent exaggerations in gesture and facial expression to restlessness involving hand twitching, an unstable dance-like gait, or a continuous stream of violent, incapacitating motions. The term "chorea", akin to choreography, reflects the dance-like quality of these movements. Chorea is classified as primary when idiopathic or genetic in origin, and secondary when associated with infectious, immunological, or other systemic causes[2].

2. Biochemical alterations in patients with chorea disease

Glutamate, the principal excitatory neurotransmitter in the brain, has been found to be significantly reduced in the striatum of individuals with chorea compared to controls. This reduction is hypothesized to reflect decreased neuronal volume in the affected region. Notably, elevated levels of spermidine were observed in the striatum. Spermidine, along with putrescine, spermine, and agmatine, belongs to the class of polyamines (PAs), whose biosynthesis is tightly regulated. Dysregulated PA metabolism has been implicated in Alzheimer's disease and other neurodegenerative conditions[3]. PAs play essential roles in the central nervous system, where they initiate the polyamine stress response in reaction to various transient stressors, including heat, ultraviolet radiation, reactive oxygen species, and ageing. As such, PAs are considered primordial stress inducers[4].

3. Pharmacological targets in chorea disease

Investigating pharmacological targets in chorea requires a comprehensive understanding of the underlying neurobiological mechanisms and potential therapeutic pathways. The literature provides valuable insights into the pathophysiology of chorea, particularly through the lens of motor control and the intricate interplay among striatal neuronal populations. Liu[5] emphasizes the role of striatal circuitry – specifically of large aspiny cholinergic interneurons – in maintaining dopaminergic transmission balance and regulating movement, thereby underscoring the importance of the cholinergic system in Parkinson's disease. This perspective suggests that analogous pathways may be leveraged in the treatment of chorea, where motor control is similarly disrupted.

Research addressing both inherited and acquired forms of chorea has broadened the therapeutic scope. Detailed analyses underscore the importance of timely and accurate diagnosis, particularly in identifying treatable causes of acquired chorea, which may stem from autoimmune, metabolic, or other systemic disorders. The integration of advanced next-generation sequencing technologies has significantly enhanced the ability of researchers and clinicians to detect genetic underpinnings associated with these heterogeneous conditions. In parallel with discoveries concerning the striatal cholinergic system's role in chorea pathogenesis, the expanding genetic landscape and growing recognition of reversible causes underscore the potential for targeted pharmacological interventions. These developments hold promise for improving patient outcomes and refining therapeutic strategies[6].

The recognition of the striatum's central role in both Parkinson's disease and chorea provides a compelling framework for future research aimed at identifying and precisely targeting pharmacological interventions to alleviate motor symptoms in these complex disorders. Elucidating the connections between neurophysiological processes and clinical manifestations enhances our understanding of chorea's pathophysiology and paves the way for innovative treatment modalities. Ultimately, as novel

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therapies are developed and implemented, this integrative approach may significantly improve patients' quality of life[7].

4. Current pharmaceutical interventions for chorea disease

Current data on pharmaceutical interventions for chorea reveal a nuanced interplay between underlying aetiologies and symptomatic treatment strategies. This evolving field includes a focused analysis of levodopa's role in chorea management, highlighting both its therapeutic potential and limitations. Although levodopa has occasionally yielded symptomatic improvement – particularly in patients with brain-thyroid-lung syndrome – the overall evidence base remains limited and insufficiently documented. Only 18 cases have been reported demonstrating a response to levodopa across diverse aetiologies, raising critical questions about its generalizability and efficacy in broader chorea populations. In fact, levodopa's effectiveness may be closely tied to the specific underlying disorder being treated, reinforcing the need for rigorous research in order to delineate its role in chorea associated with various movement-impairing conditions[8].

Importantly, the pharmaceutical landscape for chorea remains narrow, with few therapeutic options available to clinicians. Tetrabenazine and its derivative, deutetrabenazine, continue to be the primary medications approved by the US Food and Drug Administration for the treatment of chorea associated with Huntington's disease. This case exemplifies the persistent and formidable challenges faced by healthcare providers in managing this complex neurological disorder. As the field advances, further research is urgently needed in order to explore additional treatment modalities and to deepen our understanding of the pharmacodynamics and the pharmacokinetics of these agents across diverse chorea patient populations[9].

In contrast, Ortigoza-Escobar[10] addresses the diagnostic and therapeutic challenges of chorea as a manifestation of inherited metabolic disorders. In this regard, the importance of prompt genetic testing and disease-specific interventions is emphasized, particularly in acute presentations where chorea is prominent. A holistic treatment approach is advocated, encompassing not only motor symptoms, but also comorbidities such as mental health conditions. The discussion of dietary therapies (including zinc supplementation for Wilson disease and low-lysine diets for glutaric aciduria) highlights the relevance of metabolic considerations in chorea management.

4. Conclusion

While current models attribute choreic disorders to neural imbalances, emerging evidence suggests that biochemical alterations in brain activity may also contribute to symptomatology. This review has examined the biochemical factors implicated in chorea pathogenesis and has emphasized the importance of understanding neurobiological mechanisms and therapeutic pathways. Continued investigation is essential in order to unravel these complexities and to advance the clinical management of chorea.

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Conflicts of interest

None exist.

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