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Vaccine-Induced Viral Reactivation and Autism Spectrum Disorder: A Review, Hypothesis, and Implications

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Abstract

Understanding the origins of autism spectrum disorder is imperative given its increasing prevalence and significant global impact. This review examines existing research on the role of viral infections in the etiology of autism and scrutinizes emerging data on post-vaccination viral reactivation. It introduces a novel hypothesis that vaccines may inadvertently reactivate latent viral infections, triggering the onset or exacerbation of autism. Through a comprehensive literature review across multiple medical databases, this review analyzed studies, case reports, and observational research focusing on viral infections, post-vaccination viral reactivation, and autism. This search yielded 13 studies implicating viral infections and viral encephalitis as potential causal factors in the development of autism spectrum disorder. Moreover, 17 studies were identified, suggesting an association of viral reactivation following vaccination. This connection raises important questions about the role of vaccines in the onset of autism. The findings advocate for continued vigilance in vaccine safety research, particularly concerning neurodevelopmental disorders.

Keywords: Autism spectrum disorder, viral reactivation, viral encephalitis, vaccination, herpes simplex, rubella

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by challenges in social interaction, communication, and the presence of restricted and repetitive behaviors. (1) Commonly developing during early childhood, the etiology of ASD is believed to be multifactorial, involving a complex interplay of genetic, environmental, and neurobiological factors. (2) The relationship between vaccinations and ASD has been at the center of public and scientific controversy for more than two decades. Following a now-retracted 1998 study by Wakefield et al. (3) that suggested a link between the measles, mumps, and rubella (MMR) vaccine and autism, a systematic review and meta-analysis of observational studies were conducted and concluded that vaccines were not associated with the development of ASD. (4) However, these studies failed to account for potential underlying biological variables that may be affecting a subset of the population.

There is a growing body of research on the etiology of ASD suggesting that viral infections and subsequent viral encephalitis play a significant role in its onset. (5) Furthermore, there is a substantial body of evidence that supports an association between the reactivation of latent viral infections and recent immunization events. (6–8) This evidence invites a cautious examination of the potential connections,

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underscoring the need for further rigorous research to understand the implications of these findings.

This investigation posits a novel hypothesis: that vaccinations may facilitate the reactivation and replication of latent viral infections. Such reactivation, particularly when it manifests as viral encephalitis, could be a precipitating factor in the development of ASD. By examining the links between viral infections and ASD, and post-vaccination viral reactivation, this review aims to contribute to the understanding of potential biological mechanisms underlying ASD and to open avenues for further research into vaccine safety.

Materials and Methods

A comprehensive electronic search was conducted across various databases, including PubMed and Google Scholar, to gather pertinent articles for this narrative review. The focus was placed on viral infections due to the potential links in ASD and vaccination, acting as a catalyst for viral reactivation.

The search encompassed several key terms: "viral infections and autism", "rubella and autism", "cytomegalovirus and autism", "herpes simplex and autism", "herpes encephalitis and autism", "vaccination and viral reactivation", "herpes and vaccination", "zoster and vaccination", "vaccination and encephalitis", "neurological inflammation and autism", "natural killer cells and autism", "vaccination and autism". Utilizing these terms resulted in the acquisition of 54 articles pertinent to this review. The selected literature includes a variety of study types, such as case-control studies, case reports, and epidemiological research. While there was no restriction on publication date, preference was given to studies published in English that directly tackled the relationship between viral infections, viral encephalitis, vaccinations, and viral reactivation, and the associated risks of ASD.

Results

Viral Infections, Viral Encephalitis, and Autism Spectrum Disorder

The intricate interplay between viral infections and neurodevelopmental disorders, particularly Autism Spectrum Disorder (ASD), has emerged as a pivotal area of research in recent years. (5) It has been shown that acute illness during pregnancy and maternal immune activation are risk factors for having a child with ASD, (9) and numerous studies have suggested a connection between prenatal viral infections, including rubella, herpes simplex, cytomegalovirus, and a heightened risk of ASD in children. (10–13) These case studies highlight the possibility that congenital infections can disrupt the development of the central nervous system and subsequent neurodevelopmental outcomes in affected children.

Viral encephalitis is characterized by an inflammatory process within the cerebral parenchyma, precipitated by viral agents that infiltrate and replicate within the brain tissue. The clinical manifestations of this pathology can vary widely, encompassing symptoms such as fever, headache, altered mental status, seizures, and potentially culminating in significant neurological impairment or mortality, contingent upon the etiological virus and the immunological response of the host. (14)

A growing body of clinical evidence has suggested a connection between viral encephalitis, predominantly herpes simplex encephalitis, and subsequent ASD development. Case studies have documented instances where individuals, after experiencing viral encephalitis at various ages, exhibit symptom presentation and meet clinical diagnostic criteria of ASD thereafter. (15–19) This pattern suggests that the relationship between virus-induced encephalitis and ASD may extend beyond early developmental stages, and that viral encephalitis could trigger or exacerbate autistic behaviors across different life stages. Furthermore, a significant portion of individuals with viral encephalitis display pathological involvement of the temporal lobes. (20,21) The temporal lobes, known for their roles in social cognition, emotional processing, and language comprehension, have long been implicated in the neuropathology of autism. (22,23)

Research has demonstrated that viruses such as herpes simplex virus type 1 (HSV-1) can establish latency in the central nervous system, which is particularly concerning in the context of ASD. (24) Given the evidence that viral encephalitis may play a causal role in the onset of ASD, understanding the mechanisms of HSV-1's latency and reactivation in the CNS is crucial, as it may shed light on the complex etiology of ASD and related neurodevelopmental conditions. (25)

A particularly noteworthy study provided support for the role of viral infections in the etiology and pathology of ASD. (26) By analyzing serum samples from forty autistic children and forty healthy controls, researchers found that a significantly higher proportion of autistic children had antibodies against nerve tissue, particularly in regions such as the amygdala, caudate nucleus, and hippocampus,

compared to the controls. Notably, 65% of the autistic children had elevated HSV IgM antibodies, indicating acute or active infection, with 96% of these children also possessing anti-encephalon antibodies, suggesting a strong correlation between HSV infection and autoimmune mechanisms in autism.

The neuroinflammatory hypothesis of ASD posits that chronic brain inflammation and immune dysregulation are central to the pathogenesis of the condition. This hypothesis is supported by multiple studies that have identified persistent neuroinflammatory states in individuals with ASD, characterized by elevated levels of pro-inflammatory cytokines in the cerebrospinal fluid. (27,28) Additionally, research has documented abnormalities in natural killer (NK) cell function in children with ASD, suggesting potential deficiencies in viral infection control and immune regulation. (29,30) In one study, the researchers hypothesized that these abnormalities in NK cell function could be a consequence of unresolved early infectious events.

Research has identified elevated levels of interleukin-6 (IL-6) in the cerebrospinal fluid and brain of individuals with ASD. (31) This cytokine, known for its role in immune responses to infections and tissue damage, has also been implicated in altering behavior and neuroendocrine function. Interestingly, studies have shown that IL-6 may be linked to the reactivation and latency of HSV-1 in the brain. (32) Chronic IL-6 expression during latent HSV-1 infection may lead to persistent inflammatory processes within the nervous system. The elevation of IL-6 in the brains of those with ASD and HSV-1 encephalitis suggests a shared inflammatory pathway, where chronic viral infections or reactivations may contribute to neuroinflammatory conditions like ASD.

A pivotal study on genetic expression in the brains of individuals with autism has provided further support for the viral hypothesis of ASD. Utilizing gene correlation network analysis, researchers compared gene expression profiles between autism and control brains, revealing significant overlaps in gene modules, indicative of similar transcript co-expression patterns in both groups. Notably, one specific module, mod5, exhibited distinct differential expression in autism, characterized by an enrichment of M2-microglial cell states and the Type I Interferon pathway, which are typically associated with viral infections. (33)

There is substantial evidence suggesting that ongoing microglial activation in the brain plays a critical role in the pathology of ASD and impacts the inhibitory-excitatory balance in the CNS. (34) Moreover, viral infections of the CNS have been shown to induce widespread microglial activation. (35) A study by Marques et al. demonstrated that microglia remained persistently activated in the brains of mice infected with HSV-1, even 30 days after infection, despite the absence of detectable viral replication. (36) The authors proposed that this prolonged microglial activation could play a significant role in the neuronal damage and long-term neurological consequences observed in patients with herpes simplex encephalitis.

The existing body of research on post-mortem tissue analysis for viral infections in the brains of individuals with ASD is notably limited. In fact, only one study has addressed this topic, revealing elevated levels of JC virus, BK virus, and simian virus 40 in the brains of those with ASD compared to a control group. (37) However, it's important to note that this study was constrained by a small sample size, examining just 15 autistic individuals, which limits the generalizability of its findings. Despite these limitations, the results hint at a potential viral involvement in ASD, underscoring the need for further research in this area.

This investigation returned 29 articles pertinent to this review. This review focuses exclusively on the body of research that highlights the association between viral infections and ASD. However, it is crucial to acknowledge the inherent limitations of this narrow focus, as the etiology of ASD is widely considered to be multifaceted, involving a complex interplay of numerous environmental and genetic factors.

Vaccine-Induced Viral Reactivation

Vaccine-induced viral reactivation is an immunological event where vaccination triggers the reactivation of pre-existing latent viral infections, resuming replication and pathogenic activity. (8) Although a causal link has not been established, multiple case reports and observational studies have suggested an association. Previous studies have identified various factors that can lead to viral reactivation, including aging, physical or emotional stress, immunosuppression, and some medications. (38)

Prior to the initiation of the COVID-19 vaccination campaign, the body of research on vaccine-induced viral reactivation was notably limited. Nonetheless, multiple instances of such reactivations have been documented within medical research databases:

- An early investigation titled "Reactivation of herpesvirus infections after vaccinations?" by Walter et al. reported three cases of viral reactivation following vaccinations to the Swiss Drug Monitoring Centre SANZ; (7)
- In a subsequent study, an additional 10 cases of herpes virus reactivation following vaccination were reported. The authors noted that the clustering of reports after the original publication pointed to a previous underreporting of similar cases; (8)
- A study examining the association between influenza vaccination and herpes zoster (HZ) reactivation observed a slight increase in herpes zoster risk in the first 1-15 days following immunization; (39)
- A case report documented herpes simplex type 2 reactivation following influenza vaccination in a 57-year-old woman; (40)
- In a case study titled "Immunologic factors may play a role in herpes simplex virus 1 reactivation in the brain and retina after influenza vaccination", a 47-year-old male experienced herpes simplex encephalitis, post-HSE complications, and acute retinal necrosis, each incident following consecutive annual influenza vaccinations; (41)
- A cohort study noted a significant increase in herpes zoster ophthalmicus recurrence in those vaccinated with recombinant zoster vaccine compared to an unvaccinated control group. (42)

The accelerated deployment of the COVID-19 vaccines heightened the focus on vaccine-related adverse events, particularly post-vaccination viral reactivations. Recent studies have suggested an association between the administration of COVID-19 vaccines and the reactivation of viruses like varicella zoster and herpes simplex:

- A comprehensive systematic review and meta-analysis revealed that VZV reactivation occurred at a rate of 14 instances per 1,000 vaccinations. Similarly, for HSV reactivation, the observed rate was 16 per 1,000 vaccinations. Analysis of 149 cases revealed reactivations of various human herpesviruses following different COVID-19 vaccines; (43)
- In a cohort study examining the incidence of herpes zoster, also known as shingles, following COVID-19 vaccination, a significant increase in HZ cases was observed in vaccinated individuals compared to a control group. While the exact molecular mechanisms behind VZV reactivation remain unclear, the authors hypothesized that a temporary weakening of VZV-specific T-cell-mediated immunity could be a contributing factor in the post-vaccination emergence of HZ; (44)
- A literature review concluded that herpetic eye diseases may develop shortly after COVID-19 vaccination; (45)
- Within the scope of this review, it is noteworthy that multiple cases of herpesvirus-induced neurological diseases have been observed subsequent to COVID-19 vaccinations, including herpes simplex encephalitis. (46–53)

The result of this search returned 17 articles relevant to vaccine-induced viral reactivation. These findings, although limited in scope, collectively suggest an association between vaccinations and the reactivation of latent viral infections, particularly involving herpesviruses. While the evidence is primarily observational, the consistency of reports across different populations and vaccine types warrants further investigation into the underlying mechanisms and potential implications of this phenomenon. Understanding these dynamics is essential not only for enhancing vaccine safety and efficacy but also for informing clinical practices and public health policies, especially in the rapidly evolving landscape of vaccine development and deployment.

In conclusion, the evidence amassed from numerous studies suggests a complex relationship between viral infections and the risk of ASD. Furthermore, this review has highlighted a significant body of evidence suggesting viral reactivation following vaccination, which may potentially play a causal role in triggering viral encephalitis and the onset or exacerbation of ASD. The current body of research highlights the importance of further exploration into the viral hypothesis of ASD, underscoring the need for a multifaceted approach to understand the interplay between viral infections, vaccine-induced viral reactivation, neuroinflammation, immune dysregulation, and their cumulative impact on neurodevelopmental outcomes.

Discussion

This analysis suggests a notable connection of viral infections in the etiology of ASD. More significantly, it highlights the potential role of vaccinations in reactivating latent viruses and triggering viral encephalitis, which may contribute to neurodevelopmental changes associated with ASD.

If substantiated, this hypothesis would carry significant implications for patient safety and clinical vigilance. In practice, clinicians should take a precau-

tionary stance by investigating and evaluating histories of congenitally acquired viral infection, neurotropic herpesvirus infection, or prior encephalitic illness, maintaining a low threshold for post-immunization assessment of new focal neurologic symptoms, and considering targeted virologic testing when presentations are suggestive.

From a research standpoint, a priority is to move beyond case reports toward preregistered, prospective studies that collect baseline and post-immunization biospecimens to objectively detect viral reactivation and neuroinflammatory signals and link this data to clinical outcomes in registry-based, nested case–control designs, and probe mechanisms in animal and human neural–glial models. Standardized case definitions for "post-vaccination viral reactivation," transparent adverse-event reporting, and exploration of host susceptibility factors (including genetics, immune phenotypes, and toxicology reports) are essential.

This stepwise, evidence-first program would be intended to rigorously test and, if unsupported, falsify this safety signal while keeping the emphasis on cautious clinical observation and patient protection amid ongoing uncertainty. This hypothesis, while still requiring further empirical validation, underscores the complexity of vaccine interactions within the human body, particularly concerning neurodevelopmental health.

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