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Yes

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No

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Title:
Investigation into the Potential Role of Cryptic Viral Infection in Villitis of Unknown Etiology Using Pan-Viral Metagenomic Sequencing

Background:

Chronic villitis (CV) is characterized by the presence of lymphocytes, histiocytes or rarely plasma cells within villous stroma. Infectious causes of CV account for approximately 5% of cases; for the remainder (approximately 95%), pathogenesis is unclear. Chronic villitis of unknown etiology (VUE) is associated with adverse fetal outcomes, including intrauterine growth restriction and fetal demise. Aberrant maternal immune responses have been implicated as a cause of VUE, but undetected causative or precipitating infections have been difficult to exclude. Herein, we performed pan-viral sequencing of placentas with infectious villitis and VUE to potentially detect the presence of undetected viruses in cases of VUE.

Design:

CV and control cases from the period 2013-2021 were selected for evaluation, including infectious villitis due to CMV (n=4), VUE (n=31), non-CV pathology accessioned controls (n=5). All cases were re-reviewed by a single pathologist and gestational data, morphologic findings, and immunohistochemical (IHC) and special stain results were abstracted. Metagenomic sequencing using a panviral capture panel was then performed on all cases.

Results:

Of the 31 VUE cases, all were classified as high grade, while 2 of 4 CMV villitis cases showed only low grade villitis. Cytomegalovirus (and additional pathogen) staining was negative for all 31 VUE cases, while CMV was detected in the 4 infectious villitis cases. Panviral sequencing and metagenomic analysis detected CMV reads in all CMV villitis cases, ranging from 166734 to 6339077 reads (0.37% to 18.62% of total reads, respectively). By contrast, clinically significant viral reads of similar fractional abundance were not detected in any of the 31 VUE samples or 5 non-CV control cases.

Conclusion:

This work helps to exclude the possibility of cryptic viral infection as a direct cause of morphologic VUE. However, the possibility that VUE results from a transient infectious is not directly addressed and remains to be explored in future studies. In addition, the utility of panviral sequencing for detection of viruses in formalin-fixed paraffin embedded tissue is established, with implications for clinical detection of viral pathogens within the placenta (and other tissues).

Stowell-Orbison Award:
No