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Microparticle-mediated VZV propagation and endothelial activation

Mechanism of VZV vasculopathy

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Study objective and summary result

This study tested the hypothesis that cerebrovascular fibroblasts infected by the varicella zoster virus (VZV) undergo phenotypic changes that promote vascular remodeling and facilitate virus transmission, and the results supported the hypothesis.

What is known and what this paper adds

Recent histologic studies have suggested that human brain vascular adventitial fibroblasts (HBVAF) act as portals for VZV entry into the cerebral circulation. This investigation shows that VZV-infected HBVAF undergo phenotypic changes that are consistent with this role, mediated by the release of apoptotic microparticles that could transmit VZV infection, in a "Trojan Horse" manner, to neighboring cells.

Participants and setting

The investigators set up an in vitro model of VZV vasculopathy to study the effects of VZV on cerebrovascular fibroblasts. They also recruited 3 children with VZV vasculopathy and 10 children with non-VZV vasculopathy through London's Great Ormond Street Hospital to examine biomarkers of VZV related vasculopathy, in comparison with non VZV vasculopathy patients and 10 age-matched healthy controls (HCs).

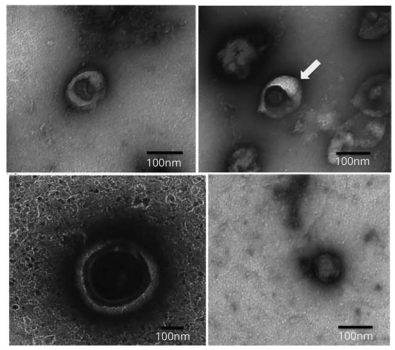
Design, size, and duration

The investigators infected HBVAF with VZV and used flow cytometry and microscopy to assess the infected cells' abilities to migrate, proliferate, transdifferentiate, and interact with endothelial cells. The investigators collected microparticles from the VZV-infected HBVAF and used mass spectrometry to analyze the microparticles' protein content. The investigators also used transmission electron microscopy to visualize VZV-positive microparticle in vitro, and assessed levels of VZV + microparticles in blood samples from the children.

Primary outcome measures

The primary outcomes were the phenotypic changes observed in the VZV-infected HBVAF, and VZV + levels of microparticles in the circulation of children with vasculopathy and stroke.

Figure Transmission electron microscopy (TEM) images of MP pellet obtained at 135000× and 95000×



Main results and the role of chance

The VZV-infected HBVAF transdifferentiated into myofibroblasts with enhanced proliferative and migratory capacities, and interactions between VZV-infected HBVAF and endothelial cells resulted in endothelial dysfunction. Microparticles from the VZV-infected HBVAF contained VZV virions that could transmit VZV to neighboring cells. The circulating levels of VZV-positive microparticles were higher in the children with VZV vasculopathy than in the children with non-VZV vasculopathy ($p = 0.01$) and the HCs ($p = 0.007$).

Bias, confounding, and other reasons for caution

The present study included relatively few patients. The inclusion of data from patients with this rare disease may nevertheless provide support for the mechanism proposed in the in vitro studies.

Generalizability to other populations

The present study's reliance on patient recruitment through a single center may limit the generalizability of the results for the biomarker data.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

