More than meets the eye:

Herpes virus retinitis

Joanna von Hofsten
Dept. of Clinical Neuroscience
Institute of Neuroscience and Physiology
Sahlgrenska Academy
University of Gothenburg

On May 17, 2023, Joanna von Hofsten defended her thesis, "Herpes virus retinitis—Clinical and virological characteristics," at the Dept. of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg. Her main supervisor was Prof. Madeleine Zetterberg, Dept. of Clinical Neuroscience, University of Gothenburg, Dept. of Ophthalmology, Sahlgrenska University Hospital, Mölndal. Her co-supervisor was Prof. Tomas Bergström, Dept. of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg.

Herpesviruses have been infecting us for millions of years. In most cases, infection does not result in disease. In this thesis, we wanted to focus on two rare but serious diseases caused by these ubiquitous viruses: acute retinal necrosis (ARN) and cytomegalovirus retinitis (CMVr). Because herpesviruses can remain latent in the body and reactivate, we wanted to investigate whether traces of virus existed in the aqueous humor of asymptomatic patients planned for cataract surgery. We found that none of the patients were positive for Epstein–Barr virus, herpes simplex virus (HSV) 1 or 2, varicella zoster virus (VZV), or cytomegalovirus. Shedding of virus in the aqueous humor of asymptomatic patients is thus unlikely.

Patients with ARN have high levels of herpes virus in the intraocular fluid at diagnosis, however. We investigated all intraocular samples positive for any herpes virus in southwestern Sweden over 10 years. Only those with HSV1, HSV2, or VZV fulfilled the clinical criteria for ARN. The amount of virus found intraocularly was not correlated with visual prognosis; however, the time from the first symptom to sampling may influence viral load.

Samples from two patients with ARN caused by VZV were analyzed with deep sequencing of the viral genome. These sequences are among the first published on viruses found in aqueous humor. These viruses were phylogenetically similar and exhibited no increased variation (suggesting that recombination was unlikely), compared to viruses found previously in other body parts.

Another herpes virus that has infected 50–80% of the world population is cytomegalovirus. This virus can also cause serious retinitis, although only if the patient is immunocompromised, in contrast to ARN, which mostly affects immunocompetent individuals. We investigated all patients with a diagnosis of CMVr in Sweden over 11 years. The cause of their underlying immunosuppression was hematopoietic stem cell transplant (27%), hematologic cancer (24%), HIV (16%), autoimmune disease (16%), solid organ transplant (14%), and diabetes mellitus (3.2%). CMVr in patients with diabetes mellitus as the sole risk factor was a surprising finding and may be explained by the disruption of the blood–retina barrier from diabetic retinopathy combined with immunosuppression secondary to hyperglycemia. We also found that older patients with an increased intraocular inflammatory reaction were more likely to have a delayed diagnosis.

Key points:

- Herpesviruses are not present in the aqueous humor of asymptomatic individuals.
- ARN is only caused by HSV or VZV, belonging to the alpha herpesvirus group.
- Viral load in intraocular fluids is not a prognostic factor for visual prognosis in ARN patients.
- The varicella virus genome from the aqueous humor of ARN patients is similar to what has been found previously in skin blisters. Therefore, the characteristics of the viral genome do not explain why immunocompetent individuals develop ARN.
- Diabetes mellitus may increase the risk of CMVr.

Future directions:

- Ongoing collaboration projects should investigate whether host genetics can explain why immunocompetent individuals develop ARN. Two recent publications have reported minor defects in autophagy and innate immunity in the host genome, found with deep sequencing.
- Deep sequencing and PCR on intraocular fluids may find viral causes of inflammatory diseases that have previously been idiopathic.
- Future larger international investigations are needed to optimize the treatment of CMVr and ARN because both diseases are rare and data is limited.

References

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