

Herpes Virus Retinitis-

Clinical and Virological Characteristics

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i R-aulan, Hus R, Sahlgrenska Universitetssjukhuset/Mölndal, Länsmansgatan 28, Mölndal, onsdagen den 17 maj 2023, klockan 9.00

av Joanna von Hofsten

Fakultetsopponent:

Prof. Sue Lightman

Institute of Ophthalmology, University College London, England

Avhandlingen baseras på följande delarbeten

- I. von Hofsten J, Johnsson Forsberg M, Zetterberg M. Cytomegalovirus Retinitis in a Patient Who Received Ruxolitinib. *N Eng J Med.* 2016 Jan 21; 374(3):296-7
- II. von Hofsten J, Bergström T, Zetterberg M. Absence of Herpesvirus DNA in Aqueous Humor from Asymptomatic Subjects. *Clin Ophthalmol.* 2022 Mar 30;16:959-962
- III. von Hofsten J, Bergström T, Zetterberg. Alpha herpes virus type and viral load in intraocular fluids in patients with acute retinal necrosis. *BMJ Open Ophthalmol.* 2019 Apr 9;4(1):e000247
- IV. von Hofsten J, Ringlander J, Norberg P, Zetterberg M, Andersson M, Lindh M, Bergström T. Deep Sequencing of Varicella-Zoster Virus in Aqueous Humor From a Patient with Acute Retinal Necrosis Presenting with Acute Glaucoma. *Open Forum Inf Dis.* 2020 May 26;7 (6)
- V. von Hofsten J, Zetterberg M. Risk factors for Cytomegalovirus Retinitis in a National Survey in Sweden. *Ocul Immunol Inflamm.* 2023 Jan 10:1-8

Herpes Virus Retinitis – Clinical and Virological Characteristics

Joanna von Hofsten

Sektionen för klinisk neurovetenskap, Institutionen för neurovetenskap och fysiologi, Sahlgrenska akademien, Göteborgs universitet, Sverige.

Abstract

In this thesis, we first aimed to determine whether there may be herpes virus deoxyribonucleic acid (DNA) in the aqueous humour of asymptomatic individuals (*paper II*). Presence of herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV) and Epstein Barr virus (EBV) in aqueous humour was measured by polymerase chain reaction (PCR) in patients eligible for cataract surgery. None of the samples were positive for herpes virus suggesting that shedding, at least frequent shedding, in aqueous humour is unlikely. Acute retinal necrosis (ARN) is a diagnosis based on criteria describing clinical signs. In *paper III*, we investigated all intraocular samples positive for HSV, VZV, CMV or EBV in south-western Sweden over almost ten years. Thirteen patients were identified with clinical signs that met the criteria for ARN. All cases were caused by alpha herpes viruses, the subgroup of herpes viruses including HSV1, HSV2 and VZV with similar tropism for neuronal tissues. Viral load in intraocular samples, measured by PCR, did not correlate with visual prognosis. However, a trend towards higher viral load in samples taken earlier, compared with later, in the disease process was observed. This thesis includes two of the first reported cases of ARN with deep sequencing of the viral genome from aqueous humour (*paper IV*). Varicella zoster virus in aqueous humour in ARN exhibited a comparatively low genetic heterogeneity similar to vesicle fluid in shingles. We performed a retrospective national study including all patients with *Cytomegalovirus* diagnosis over a period of 11 years, (*paper V*). Sixty-three patients with CMV retinitis were identified. The most common predisposing factors were haematopoietic stem cell transplantation (27%), and haematological malignancies (24%). We also found two patients with no other immunosuppression than that related to diabetes mellitus (DM) (3.2%). Clinical characteristics of patients with delayed diagnosis at >30 days from symptom onset were compared with those of patients with early diagnosis. Presence of intraocular inflammation (IOI) ($p=0.003$) and increased intraocular pressure ($p=0.023$) as well as old age ($p=0.01$) were risk factors. One reason for late diagnosis was the misconception that the patient was not immunocompromised, because of DM or as described in our case report of a patient treated with ruxolitinib for myelofibrosis (*paper I*).

Keywords: Cytomegalovirus, acute retinal necrosis, sequencing, retinitis