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# Varicella zoster virus central nervous system infections: characteristics, outcome, and tolerability of high-dose intravenous acyclovir

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**Background:** Varicella-zoster virus (VZV) is the second pathogen in encephalitis, after herpes simplex virus (HSV), and is associated with higher mortality. Early recognition of VZV central nervous system (CNS) infections is of importance, given that high doses of intravenous acyclovir are recommended due to lower susceptibility of VZV as compared to HSV. Limited data are available on the characteristics and outcome of VZV CNS infections, and the tolerability of acyclovir high doses.

**Material/methods:** We performed an observational study of all adult patients admitted for VZV CNS infections at Rennes University Hospital during years 2000-2015. Patients were enrolled if they presented with i) VZV infection documented by PCR on cerebrospinal fluid (CSF), or zoster rash, and ii) encephalitis fulfilling international encephalitis consortium criteria, and/or CSF cells count $\geq$5/mm$^3$. Acute renal failure was defined using AKIN criteria. Continuous variables were expressed as median [quartiles], and compared by Mann–Whitney U-test. Proportions were compared by $\chi$2 tests. A logistic regression analysis was performed to determine variables associated with renal failure, and outcome.

**Results:** Thirty-six patients fulfilled inclusion criteria (15 encephalitis, 21 meningitis). Median age was 51 years [35-76], older for encephalitis (72 [61-77]), than meningitis (38 [31-52]), p=0.003. Six patients

(17%) were immunocompromised, and 28 (78%) had zoster rash. CSF, obtained with a median delay of 5 days [3-9] after symptoms onset, was PCR VZV positive in 27/32 (84%). Three patients with negative PCR VZV on first CSF were retested on a second CSF obtained >5 days after symptoms onset and remained negative. Twelve patients underwent brain MRI, of whom 5 (42%) had findings suggestive of encephalitis. None had vasculitis. Intravenous acyclovir was administered in 33 patients (92%), a median of 4 days [3-9] after symptoms onset, for a median duration of 5 days [3-7] for meningitis, and 14 days [10-20] for encephalitis ($p<0.001$), at a median dose of 33 mg/kg/day [30-45]. Acyclovir-related renal failure occurred in 7 patients (19%), with a median delay of 5 days [3-7] after initiation, and a median creatinine increase of 118 µmol/L [50-219]. None required haemodialysis. No risk factor for renal failure was identified. No patient died, but 14 (39%) were discharged with significant sequels: 6/21 (29%) for meningitis, and 8/15 (53%) for encephalitis. Age was the only variable associated with adverse clinical outcomes (OR 1.79 [1.17-2.64] per 10 year-increment, $p=0.006$).

**Conclusions:** This case series of VZV CNS infections in adults suggests that mortality may be lower than previously reported, with early administration of high doses acyclovir, at the cost of high incidence of renal failure, and neurological sequels in up to half of patients with VZV encephalitis. Repeat testing for PCR VZV in CSF may be of limited value, as compared to HSV encephalitis.