27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

CHU Rennes

UNIVERSITÉ DE RENNES 1

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

A. Ballerie, P. Fillâtre* (Rennes, France), C. Pronier, S. Lavoué, P. Jégo, M. Revest, Y. Le Tulzo, P. Tattevin

Conflict of interest

- Travel to congress JNI 2015: Pfizer

Background

- Varicella-zoster virus (VZV) is a common viral agent of encephalitis

Glaser CA et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000. *Clin Infect Dis*. 2003.
Mailles A et al. Infectious encephalitis in France in 2007: a national prospective study. *Clin Infect Dis*. 2009.
Granerod J et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis.* 2010.

- VZV encephalitis is associated with high morbidity and mortality
  - Higher risk of unfavorable outcome if HSV or VZV compared to other agents (p=0.05)
  - Higher risk of mortality than HSV: OR 23.2 [1.9-285.5], p=0.01

Mailles A et al.Infectious encephalitis in France in 2007: a national prospective study. *Clin Infect Dis*. 2009.
Mailles A et al. Long-term outcome of patients presenting with acute infectious encephalitis of various causes in France *Clin Infect Dis*. 2012

Background

- Lower susceptibility of acyclovir on VZV than on HSV

Grahn A et al. Varicella-zoster virus infections of the central nervous system – Prognosis, diagnostics and treatment. *J Infect*. 2015.

- International guidelines advocate to use high dose acyclovir in VZV encephalitis
  - 10-12.5 mg/kg/8h in Australia and New Zealand guidelines
  - 10-15 mg/kg/8h in IDSA guidelines
  - 15 mg/kg/8h in French guidelines

Britton PN et al. Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. *Intern Med J*. 2015
Tunkel AR et al. The management of encephalitis: clinical practice guidelines by the infectious diseases society of America, *Clin Infect Dis* 2008
Stahl JP et al. Guidelines on the management of infectious encephalitis in adults.*Med Mal Infect* 2017

Background

Objectives

- Description of the characteristics and outcome of VZV CNS infections, and the tolerability of acyclovir high doses

Materials - methods

- Observational study
  - all adult admitted for VZV CNS infections at Rennes University Hospital
  - during years 2000-2015
  - Cases identified through computerized database and data collected through standardized questionnaire
- Meningitis
  - white blood cell count $\geq 5/mm^3$ on cerebrospinal fluid (CSF)
- Encephalitis
  - Fulfilling international encephalitis consortium criteria
- VZV documentation
  - PCR on CSF or zoster rash
- Acute renal failure
  - AKIN classification

Steiner I et al. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. *Eur J Neurol.* 2010
Venkatesan A et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis*. 2013.

Materials - methods

- Continuous variables were expressed as median [quartiles], and compared by Mann–Whitney U-test.
- Proportions were compared by $\chi 2$ tests or Fisher exact test
- A logistic regression analysis was performed to determine variables associated with renal failure and outcome (OR ; [IC95%], $p<0,05$).

Results

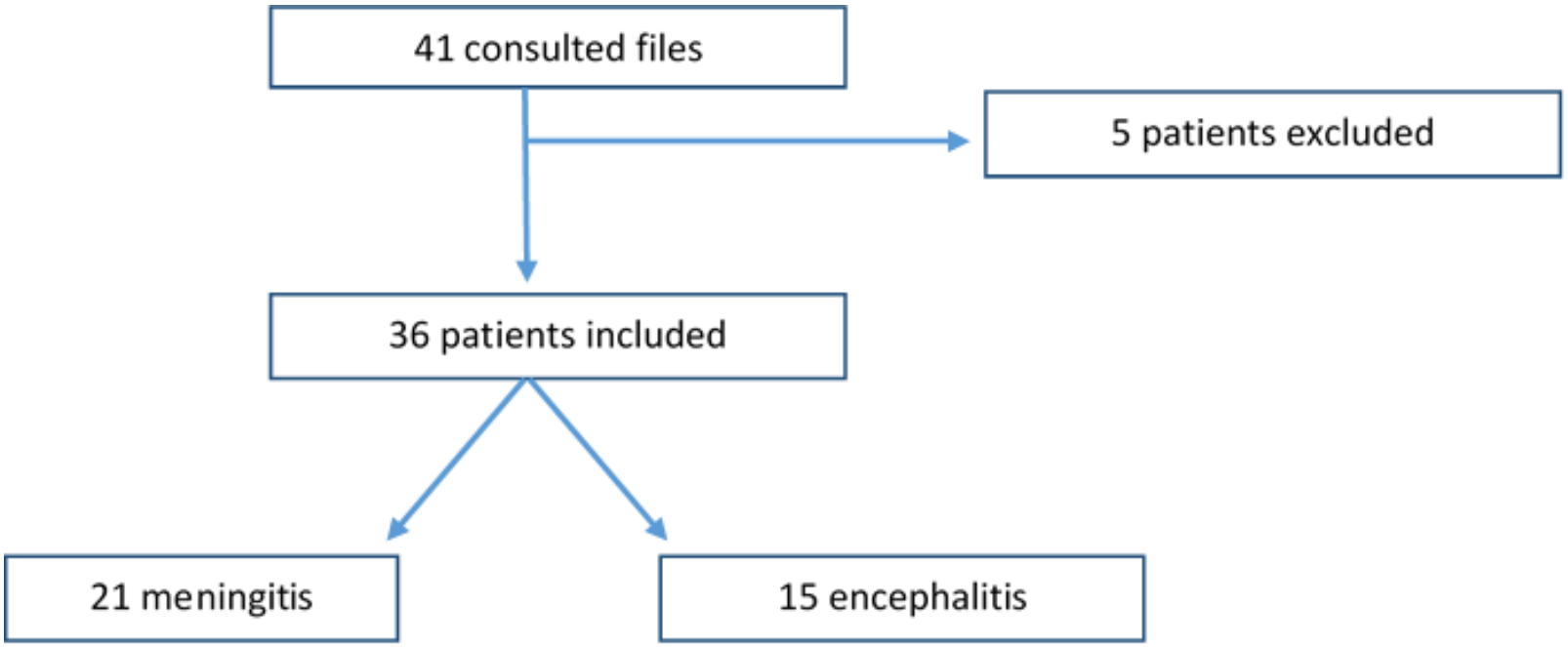


Figure 1: Flow chart

Results

	Total N=36	Meningitis N=21	Encephalitis N=15	p
Age (years)*	51 [35-76]	38 [31-52]	72 [61-77]	0.003
Immunocompromised	6 (17%)	3 (14%)	3 (20%)	0.674
Fever (°C) *	38.1 [37.8-38.6]	38.0 [37.2-38.1]	38.6 [38.2-39]	0.003
Rash	28 (78%)	16 (76%)	12 (80%)	0.845
-Herpes zoster	25 (69%)	15 (71%)	10 (67%)	1.0
-Varicella	3 (8%)	1 (4%)	2 (13%)	0.559
Headache	25 (70%)	18 (86%)	7 (47%)	0.025
Confusion	15 (42%)	3 (14%)	12 (80%)	<0.001
Glasgow coma score *	15	15 [15-15]	14 [13-15]	<0.001
Seizure	2 (6%)	0 (0%)	2 (13%)	0.167
Focal weakness	14 (39%)	6 (29%)	8 (53%)	0.175

Table 1: Clinical characteristics, * median [quartiles]

Results

CSF	Total	Meningitis	Encephalitis	p
White blood cell count (/mm3)*	165[41-429]	200 [66-466]	77 [26-240]	0,141
Neutrophils (%)*	2 [0 – 5]	1 [0-4]	5 [0-8]	0,306
Lymphocytes (%)*	92 [78-96]	95 [86-98]	80 [71-88]	0,008
Protein concentration (g/L)*	1,21[0,72-1,54]	0,87 [0,73-1,25]	1,42 [0,83-2,04]	0,108
Glucose concentration (g/L)*	0,54 [0,45-0,66]	0,52 [0,45-0,65]	0,62 [0,48-0,66]	0,453
Glucose CSF/serum ratio*	0,5 [0,4 – 0,5]	0,5 [0,4 – 0,5]	0,5 [0,4-0,5]	1,0
VZV DNA detected by PCR	84%	88%	80%	0,645

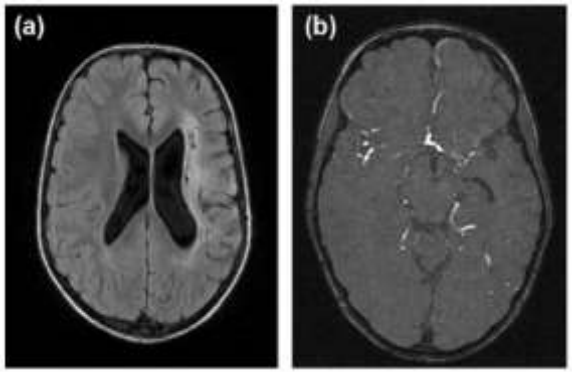
Table 2 : CSF characteristics *median [quartiles]

- Three patients with negative PCR VZV on first CSF were retested on a second CSF obtained more than 5 days after symptoms onset and remained negative.

Results

	Encephalitis
Cerebral imaging	15 (100%)
Magnetic resonance imaging	12 (80%)
Normal	3 (25%)
Specific abnormalities	5 (42%)
Vasculitis	0 (0%)
Other abnormality	4 (33%)
Computed tomography scan	11 (73%)
Normal	6 (55%)
Specific abnormalities	0 (0%)
Other abnormality	5 (45%)

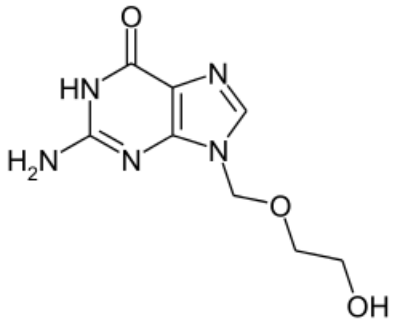
Table 3 : Imaging characteristics



Results

	Total	Meningitis	Encephalitis	p
Treated patients	33 (92%)	18 (86%)	15 (100%)	0,359
By acyclovir	32 (97%)	17 (94%)	15 (100%)	1,0
Dosage (mg/kg/8hours)*	11 [10-15]	11 [10-15]	11 [10-14]	0,876
Duration (days)*	7 [4-14]	5 [3-7]	14 [10-20]	<0,001
Switch by valacyclovir	11 (33%)	11 (61%)	0 (0%)	0,003
Duration (days)*	10 [9-10]	10 [9-10]	-	-

Table 4 : Treatment *mediane [quartiles]



Results

Acute renal injury

- Renal failure occurred in 7 patients (19%),
  - median delay of 5 days [3-7] after initiation
  - median creatinine increase of 118 µmol/L [50-219]
  - AKIN class: 4 grade I / 1 grade II / 2 grade III
  - None required haemodialysis.

- No risk factor for renal failure was identified (multivariate analysis)
  - High dose acyclovir (15 mg/kg/day) OR = 2.10 [0.34-12.8], p=0.422
  - Treatment duration (per day) OR = 1.07 [0.85-1.34], p=0.553
  - Age OR = 1.42 [0.74-2.73], p=0.389
  - GFR (per 10 mL/min) OR = 0.74 [0.46-1.20], p=0.227

Results

	Total	Meningitis	Encephalitis	p
Delay of hospitalization after symptoms onset (days)*	6 [3-9]	7 [4-9]	3 [2-8]	0,117
Delay of lumbar puncture after symptoms onset (days)*	5 [3-9]	7 [4-10]	4 [3-8]	0,146
Delay of specific treatment after symptoms onset (days)*	4 [3-9]	7 [4-11]	3 [2-8]	0,105
Length of hospital stay (days)*	9 [5-22]	6 [3-8]	23 [17-32]	<0,001
Intensive care unit hospitalization	5 (14%)	1 (5%)	4 (27%)	0,138
Deaths	0 (0%)	0 (0%)	0 (0%)	1,0
Sequelae	14 (39%)	6 (29%)	8(53%)	0,175

Table 5 : Outcome *mediane [quartiles]

- Age was the only variable associated with adverse clinical outcomes (OR 1.79 [1.17-2.64] per 10 year-increment, p=0.006).

Discussion

- Both in the meningitis and the encephalitis group, characteristics of our patients are similar to the litterature.

	Meningitis N=13	**Encephalitis N=5**	**p**
Age median	42	62	0.08
Rash	11 (84.6%)	4 (80%)	0.81
CSF lymphocyte (%)	86	86	0.48
Abnormal MRI findings	1/4 (25%)	1/2 (50%)	0.33

Baseline characteristics, CSF analysis and imaging, adapted from:

Kaewpoowat Q et al. Herpes simplex and varicella zoster CNS infections: clinical presentations, treatments and outcomes. Infection. 2016

Discussion

- But, **mortality may be lower** than previously reported:
  - 0% versus 15% (Mailles et al.) and 20% (Granerod et al.)

- Patients were discharged with **significant neurological sequelae** in up to half of patients with VZV encephalitis.

- **Age was the only variable associated with adverse clinical outcomes**
  - Immunocompromised status could be a factor associated with death (Granerod et al.)
  - No significant protective effect with
    - high dose acyclovir (OR = 1.14 [0.87-1.50, p=0.348)
    - Length of acyclovir treatment (OR = 1.06 [0.95-1.18], p=0.264)

Mailles A et al. Infectious encephalitis in france in 2007: a national prospective study. Clin Infect Dis. 2009
Granerod J et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010

Discussion

- High-dose intravenous acyclovir might be needed in VZV CNS in front of
  - A poor bioavailability of oral acyclovir
  - A less VZV sensitivity to acyclovir than HSV

Steiner I et al. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol. 2010
Chatis PA et al. Resistance of herpesviruses to antiviral drugs. Antimicrob Agents Chemother. 1992
Grahn A et al. Varicella-zoster virus infections of the central nervous system – Prognosis, diagnostics and treatment. J Infect. 2015

- With early administration of high doses acyclovir, renal failure occurred in 19% patients in our study

- But, no risk factor for renal failure was identified
  - Age, duration and dosage of the acyclovir treatment

Discussion

Limits

- Monocentric, retrospective study
- Few patients
- No data on acyclovir infusion rate

But

- Few datas on this topic

Conclusion

- In VZV CNS infections in adults
  - 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 sequelae 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