



HAL
open science

Infectious encephalitis in elderly patients: a prospective multicentre observational study in France 2016-2019

Paul Petitgas, Pierre Tattevin, Alexandra Mailles, Pierre Fillâtre, Jean-Paul Stahl

► **To cite this version:**

Paul Petitgas, Pierre Tattevin, Alexandra Mailles, Pierre Fillâtre, Jean-Paul Stahl. Infectious encephalitis in elderly patients: a prospective multicentre observational study in France 2016-2019. *Infection*, 2023, 10.1007/s15010-022-01927-3 . hal-03798463

HAL Id: hal-03798463

<https://hal.science/hal-03798463>

Submitted on 15 Feb 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 ORIGINAL PAPER

2 **Infectious encephalitis in the elderly: a prospective multicentre observational**
3 **study in France 2016-19**

4 Paul Petitgas¹⁻², Pierre Tattevin¹, Alexandra Mailles³, Pierre Fillâtre⁴, Jean-Paul Stahl⁵, on behalf
5 of the ENCEIF scientific committee and investigators group*

6
7 ¹Université Rennes 1, Service des Maladies Infectieuses et Réanimation Médicale, CHU Rennes,
8 France

9 ²Service des Maladies Infectieuses et de Médecine Interne, CHU de Saint-Pierre, La Réunion,
10 France

11 ³Santé Publique France, direction des maladies infectieuses, Saint-Maurice, France

12 ⁴Service de Réanimation Polyvalente, CH Saint-Brieuc, France

13 ⁵Université Grenoble Alpes, CHU, Maladies Infectieuses, France

14
15 Corresponding author:

16 Pierre Tattevin, Service des Maladies Infectieuses et Réanimation Médicale, Hôpital Pontchaillou,
17 Centre Hospitalo-Universitaire (CHU), 35000 Rennes, France

18 E-mail address: pierre.tattevin@chu-rennes.fr

19

20 **Abstract**

21 **Purpose.** Data on encephalitis in the elderly remain scarce. We aimed to describe the
22 characteristics, aetiologies, management, and outcome of encephalitis in patients older than 65
23 years.

24 **Methods.** We performed an ancillary study of ENCEIF, a prospective cohort that enrolled all cases
25 of encephalitis managed in 46 clinical sites in France during years 2016-2019. Cases were
26 categorized in 3 age groups: i) 18-64; ii) 65-79; iii) ≥ 80 years.

27 **Results.** Of the 494 adults with encephalitis enrolled, 258 (52%) were ≥ 65 years, including 74
28 (15%) ≥ 80 years. Patients ≥ 65 years were more likely to present with coma, impaired
29 consciousness, confusion, aphasia, and rash, but less likely to present with fever, and headache
30 ($P < 0.05$ for each). Median cerebrospinal fluid (CSF) white cells count was $61/\text{mm}^3$ [13-220] in 65-
31 79 years, 62 [17-180] in ≥ 80 years, vs. 114 [34-302] in < 65 years ($P = 0.01$). The proportion of cases
32 due to *Listeria monocytogenes* and VZV increased after 65 years ($P < 0.001$), while the proportion
33 of tick-borne encephalitis and *Mycobacterium tuberculosis* decreased with age ($P < 0.05$ for each).
34 In-hospital mortality was 6/234 (3%) in < 65 years, 18/183 (10%) in 65-79 years, and 13/73 (18%)
35 in ≥ 80 years ($P < 0.001$). Age ≥ 80 years, coma on admission, CSF protein ≥ 0.8 g/L and viral
36 encephalitis were independently predictive of 6-month mortality.

37 **Conclusion.** The elderly represent $> 50\%$ of adult patients with encephalitis in France, with higher
38 proportion of *L. monocytogenes* and VZV encephalitis, increased risk of death, and sequels. The
39 empirical treatment currently recommended, aciclovir and amoxicillin, is appropriate for this age
40 group.

41 **Keywords:** Infectious encephalitis; elderly; observational cohort; herpes simplex virus; varicella-
42 zoster virus; *Listeria monocytogenes*; empirical treatment.

43

44 **Introduction**

45 The diagnosis of encephalitis usually relies on the combination of suggestive clinical presentation
46 and indirect markers of brain inflammation, including meningitis and characteristic brain imaging
47 features [1]. The International Encephalitis Consortium elaborated a case definition [2] to ensure
48 that clinical studies will use similar inclusion criteria, which allows comparability of
49 epidemiological studies throughout the world, and contributes to a better awareness of this puzzling
50 disease.

51 Aetiologies of acute encephalitis may be infectious or non-infectious, including
52 autoimmune, neoplastic and paraneoplastic causes [3][4][5]. In most recent prospective studies,
53 the cause of acute infectious encephalitis was found in about 50% of cases [3][6][7][8].
54 Encephalitis is a rare disease, with an incidence estimated between 0.07 and 12.6
55 cases/year/100,000 inhabitants [9]. The prognosis of infectious encephalitis varies according to the
56 pathogen, with in-hospital mortality rates close to 10% in contemporary studies [5][7][8][10][11].
57 Other prognostic factors include age, comorbidities, and the extent of brain lesions by the time
58 appropriate treatment is initiated for herpes meningoencephalitis, the most common cause of
59 encephalitis in developed countries. Long-term consequences of encephalitis are common: A large
60 prospective multicentre study performed in France showed that 24% of patients previously active
61 had not returned to work at 3 year-follow up, and 5% had died [12].

62 French [1], and American [13] guidelines for the management of encephalitis insisted on
63 the challenges associated with aetiological diagnosis of encephalitis, which often requires expert
64 laboratories, and infectious diseases expertise. Indeed, encephalitis may mimic psychiatric [14] or
65 non-infectious neurological diseases [15], particularly in the elderly [16][17].

66 Infectious diseases in the elderly have become an increasingly important issue with
67 population ageing. According to the world health organization (WHO), one in six people

68 worldwide will be aged 65 or more in 2050 and the number of people aged 80 or more is expected
69 to triple between 2019 and 2050, to reach 426 million. A better knowledge of the particularities of
70 encephalitis in the elderly could lead to better management, particularly in the choice of diagnostic
71 investigations, and empirical treatments. To date, only one large study focused on encephalitis in
72 the elderly, but it was retrospective [18]. We report a prospective multicentre cohort of encephalitis
73 in the elderly, to decipher the characteristics of encephalitis in patients older than 65 years.

74 **Methods**

75 Patients were enrolled in the National Cohort of Infectious Encephalitis in France (the “ENCEIF”
76 cohort), a multi-centre prospective cohort study, that enrolled all consecutive patients diagnosed
77 with infectious encephalitis in the participating sites from January 1st 2016 to December 31st 2019
78 [19]. Briefly, the objective of the ENCEIF study was to describe the epidemiology, the
79 characteristics (clinical, biological, imaging), the management, and the outcome of acute infectious
80 encephalitis in metropolitan France.

81 The study presented herein is an ancillary study which aims to compare the characteristics,
82 the management and the outcome of infectious encephalitis in three different age groups: i) 18 to
83 64 year-old (comparator group); ii) 65 to 79 year-old; iii) more than 80 year-old. Inclusion and
84 exclusion criteria as well as data collected are described in detail elsewhere [19]. Briefly, all adult
85 patients hospitalised with suspected infectious encephalitis according to the case definition of the
86 International Encephalitis Consortium [2] with no alternative diagnosis, were invited to participate.
87 Acute encephalitis was defined as neurologic symptoms of acute onset, for more than 24 h, without
88 any differential diagnosis, with at least two of the following signs: fever $\geq 38^{\circ}\text{C}$, seizure, recent
89 focal neurologic symptoms, cerebrospinal fluid (CSF) white cells count $\geq 5/\text{mm}^3$, inflammatory

90 brain lesion on magnetic resonance imaging (MRI), or computed tomography (CT)-scan, and
91 suggestive abnormalities in electroencephalogram (EEG).

92 Patients or their close relatives received oral and written information about the study, and
93 could refuse to be enrolled, but no written consent was required according to the French regulations
94 for observational studies. Data were collected on a standardized questionnaire and computerized
95 using a secure, web-based application Voozadoo (Epiconcept©, Paris). This study was authorized
96 by French Commission for Data Protection, the "Commission Nationale Informatique et Liberté"
97 (CNIL, DR-2015-300) and was approved by the Advisory Committee on Research Information
98 Processing, the "Comité Consultatif sur le Traitement de l'Information en matière de Recherche
99 dans le domaine de la Santé" (CCTIRS).

100 Outcomes were categorized using the Glasgow outcome scale (GOS) and the modified
101 Rankin scale (mRS). The GOS scores range from 1 (death) to 5 (minor neuro-psychological deficits
102 with no impact on daily life) [20]. The modified Rankin scale is defined by 7 grades, grade 0
103 corresponding to a patient without symptoms, and grade 6 to death [21]. Statistical analyses were
104 performed using the R 4.0.5 software with the "survival" package. Categorical variables were
105 described as frequencies and percentages, and quantitative variables as median and interquartile
106 range. Categorical variables were compared by chi-square or Fisher's exact test, and continuous
107 variables were compared by Mann Whitney test or Kruskal-Wallis test as appropriate.

108 Kaplan-Meier overall survival curves until day 180 were computed and were compared
109 using a log-rank test. Baseline risk factors of death at day 180 were assessed within the whole
110 cohort using univariate and multivariate cox regression. Baseline variables (i.e available during the
111 first hours of hospital admission) included in the multivariate model were those with $P < 0.20$ in
112 univariate analysis with respect of proportional hazard assumption. If this assumption was not
113 respected, the model was stratified on this prespecified variable. The alpha risk was set at 5%.

114 **Results**

115 **Demographics and comorbidities**

116 During the study period (2016-2019), 494 patients with complete dataset have been enrolled in the
117 ENCEIF prospective cohort study. Of them, 258 (52%) were older than 65 years, including 184
118 (37%) in the 65-79 year-old group, and 74 (15%) older than 80 years. Demographics and
119 comorbidities are detailed in Table 1. There was a slight male predominance in all age categories
120 that tended to decrease with age (65% in patients younger than 65 years, 59% in the 65-79 year-
121 old, and 56% in patients older than 80 years). As expected, older patients had more comorbidities,
122 including diabetes, cancer, haematological malignancy, autoimmune diseases, and
123 immunodeficiency ($P<0.01$ for each category). The proportion of patients who travelled abroad
124 within the last 6 months decreased with age, from 24% in patients younger than 65 years, to 7% in
125 patients older than 80 years ($P<0.001$).

126 **Clinical features on admission**

127 Table 1 details clinical features on admission. Older patients were more likely to present with coma,
128 impaired consciousness, confusion, aphasia, and skin rash, but less likely to present with fever, and
129 headache ($P<0.05$ for each).

130 **Investigations**

131 On admission, most findings were similar in the elderlies and in the rest of the population with
132 encephalitis, except for CSF white cells count, almost twice lower in patients older than 65 years
133 ($P=0.01$). Other CSF characteristics were similar, as well as the proportion of patients who
134 underwent brain imaging (>95% in all age groups), the proportion of patients who underwent EEG
135 (>75% in all age groups), and the proportion of these investigations that revealed abnormalities
136 (Table 2).

137 **Aetiologies of infectious encephalitis**

138 Investigations identified the cause of encephalitis in 324/494 patients (66%) overall, and this
139 proportion was similar throughout age groups (Table 3). The proportion of encephalitis due to
140 *Listeria monocytogenes*, and varicella-zona virus (VZV) increased with age ($P<0.001$), the latter
141 becoming the primary cause of infectious encephalitis after 80 years. Conversely, the proportion
142 of cases due to tick-borne encephalitis (TBE) virus, and *M. tuberculosis* decreased with age
143 ($P<0.05$).

144 **Management and outcome**

145 The proportion of patients treated with intravenous aciclovir increased with age ($P=0.045$), but
146 time from symptoms onset to aciclovir treatment was similar (Table 4). Older patients had longer
147 hospital stay, and worse prognosis, whatever the criteria: GOS, mRS, in-hospital as well as 6-
148 month case fatality rate (CFR). During the initial hospital stay, 37/494 patients died (8%).

149 **Univariate and multivariate analysis of risk factors for six-month mortality**

150 On univariate analysis, age ≥ 65 years, immunodeficiency, coma on admission, CSF protein ≥ 0.8
151 g/L, and CSF white cells count $< 80/\text{mm}^3$ were associated with increased 6-month CFR (Table 5),
152 while headache on admission was associated with decreased 6-month CFR. On multivariate
153 analysis, age ≥ 80 years (Figure 1), coma on admission, CSF protein ≥ 0.8 g/L and viral encephalitis
154 were independently predictive of 6-month CFR.

155 **Discussion**

156 The major findings of this multicentre prospective cohort study of acute encephalitis are as follows:
157 i) the elderly represent a large proportion of cases, as 258/494 adults with encephalitis were older
158 than 65 years (52%), and 74/494 (15%) older than 80 years; ii) the elderly were more likely to
159 present with coma, impaired consciousness, confusion, aphasia, and skin rash, but less likely to

160 present with fever, and headache ($P<0.05$ for each); iii) CSF white cells count was lower in the
161 elderlies, with a median of $61/\text{mm}^3$ [13-220] in 65-79 years, and 62 [17-180] in ≥ 80 years, vs. 114
162 [34-302] in patients younger than 65 years ($P=0.01$); iv) the proportion of encephalitis due to *L.*
163 *monocytogenes*, and VZV increased with age ($P<0.001$), the latter becoming the primary cause of
164 infectious encephalitis after 80 years. The proportion of TBE and *M. tuberculosis* encephalitis
165 decreased with age ($P<0.05$). Overall, about one third of cases remained undocumented whatever
166 the age group; v) In-hospital mortality was 6/234 (3%) in patients younger than 65 years, 18/183
167 (10%) in 65-79 year-old, and 13/73 (18%) in patients older than 80 years ($P<0.001$). Not
168 surprisingly, age was also associated with increased 6-month CFR, and higher risk of sequelae, for
169 GOS as well as mRS ($P<0.001$ for all criteria); vi) age ≥ 80 years, coma on admission, CSF protein
170 ≥ 0.8 g/L and viral encephalitis were independently predictive of 6-month CFR.

171 To the best of our knowledge, this is the first prospective study focusing on encephalitis in
172 the elderlies. Our findings are in line with previous retrospective cohorts, in terms of clinical
173 presentation, more often incomplete in the elderlies [16][22]. Indeed, fever is absent in 44-77% of
174 cases in recent studies [3][6][7], particularly in the elderly [16][17]. Of note, we observed striking
175 differences regarding the prevalence of fever on admission: 146/236 (62%) of encephalitis cases
176 in patients younger than 65 years, vs. 73/184 (40%) in 65-79 years, and 14/74 (19%) in patients
177 older than 80 years ($P<0.001$). Lower CSF white cells count in encephalitis in the elderlies has
178 been documented by others [22][23][24]. Age has repeatedly been identified as an independent risk
179 factor for fatal outcome in encephalitis [4][5][8][22][25][26][27][28]. This may be largely driven
180 by immuno-senescence [29], and comorbidities. Interestingly, only age ≥ 80 years remained
181 associated with mortality in our multivariate analysis, while the age group 65-79 years was not
182 independently predictive of death. This confirms that age by itself should not be considered as a
183 criteria for limitation of care in most cases: Indeed, this tricky decision must be individualized,

184 taking into account comorbidities, frailty, neurological status on admission, and quality of life
185 before the onset of encephalitis. Whenever possible, the patient, the closest relatives, and the
186 general practitioner must be involved in this complex decision process.

187 The third most common pathogen responsible for encephalitis in patients older than 65
188 years, after HSV and VZV, was *L. monocytogenes*. Although rarely reported in encephalitis cohorts
189 from other countries [3][6][7], listeriosis was the fourth pathogen of all ages in the previous large
190 cohort study in France, in 2007 [8], and the third in the population aged over 65 years. This outlines
191 the importance of local epidemiological studies to monitor the epidemiology of encephalitis, as it
192 informs the selection of empirical treatment: Indeed, French guidelines are unique in their
193 recommendation to add amoxicillin to aciclovir as the first-line empirical treatment for acute
194 encephalitis [1]. This combination seems appropriate in the elderly, as it covers 94% (44/47) of
195 the pathogens identified in the subgroup of encephalitis in patients ≥ 80 years. The ENCEIF study
196 also allowed to detect the emergence of TBE [30], as in neighbouring countries [31] but as it is
197 mostly associated with outdoor activities [32], the elderly are not the primary target, with no case
198 diagnosed in patients older than 80 years in our study.

199 Our findings outline the difficulties to diagnose encephalitis in elderly patients, as i)
200 cardinal signs, such as fever, are usually absent; ii) confusion or delirium in the elderly may be
201 triggered by many other mechanisms, including metabolic, neoplastic, vascular, septic, or toxic
202 pathways. Central nervous system infections, including encephalitis, may be mistaken for many
203 other diseases, and this is especially true in the elderly, for whom the diagnosis of encephalitis is
204 particularly challenging [33][34]. Nevertheless, in our study, time from symptoms onset to
205 aciclovir treatment start was similar across all age groups.

206 Our study has limitations. First, as this was performed in one single country, with
207 epidemiological particularities, our findings not necessarily apply to other countries. Second, given

208 the rapid evolution of infectious diseases in the XXIst century, the repartition of pathogens may
209 change rapidly, which would require iterative surveillance studies to remain informed on the
210 primary pathogens encountered in each age groups. Third, we used the threshold of 65 years to
211 define the elderlies, in line with most other scientific publications, and the WHO, although this
212 represents a very heterogeneous group. Although we dichotomized the elderlies in two groups (65-
213 79, and ≥ 80 years), we did not use a comorbidity or frailty score, which may have allowed a better
214 stratification of patients. However, our study also has strengths, including the prospective and
215 standardized collection of data, the multicentre design, and the involvement of a collaborative
216 network of experts in the field, which allowed the enrolment of the largest sample size of
217 encephalitis in the elderlies to date.

218 In conclusion, we found that $>50\%$ of adult patients with encephalitis are ≥ 65 years, with
219 higher proportion of *L. monocytogenes* and VZV, and lower proportion of TBE virus and *M.*
220 *tuberculosis* encephalitis. Current recommendations for empirical treatment with aciclovir and
221 amoxicillin seem appropriate given the current epidemiology in France. In-hospital CFR increases
222 from 3% in patients <65 years to 18% in patients ≥ 80 years, with higher risk of sequelae in the
223 elderlies. Age ≥ 80 years, coma on admission, CSF protein ≥ 0.8 g/L and viral encephalitis are
224 independently predictive of 6-month CFR.

225

226 **References**

- 227 1. Stahl JP, Azouvi P, Bruneel F, et al. Guidelines on the management of infectious
228 encephalitis in adults. *Médecine Mal Infect* **2017**; 47:179–194.
- 229 2. Venkatesan A, Tunkel AR, Bloch KC, et al. Case Definitions, Diagnostic Algorithms, and
230 Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium. *Clin*
231 *Infect Dis* **2013**; 57:1114–1128.
- 232 3. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their
233 clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect*
234 *Dis* **2010**; 10:835–844.
- 235 4. George BP, Schneider EB, Venkatesan A. Encephalitis Hospitalization Rates and Inpatient
236 Mortality in the United States, 2000-2010. *PLoS ONE* **2014**; 9:e104169.
- 237 5. Singh TD, Fugate JE, Rabinstein AA. The spectrum of acute encephalitis: Causes,
238 management, and predictors of outcome. *Neurology* **2015**; 84:359–366.
- 239 6. Glaser CA, Honarmand S, Anderson LJ, et al. Beyond Viruses: Clinical Profiles and
240 Etiologies Associated with Encephalitis. *Clin Infect Dis* **2006**; 43:1565–1577.
- 241 7. Bodilsen J, Storgaard M, Larsen L, et al. Infectious meningitis and encephalitis in adults in
242 Denmark: a prospective nationwide observational cohort study (DASGIB). *Clin Microbiol Infect*
243 **2018**; 24:1102.e1-1102.e5.
- 244 8. Mailles A, Stahl J. Infectious Encephalitis in France in 2007: A National Prospective Study.
245 *Clin Infect Dis*. **2009**;49(12):1838-47.
- 246 9. Granerod J, Tam CC, Crowcroft NS, Davies NWS, Borchert M, Thomas SL. Challenge of
247 the unknown: A systematic review of acute encephalitis in non-outbreak situations. *Neurology*
248 **2010**; 75:924–932.
- 249 10. Davison KL, Crowcroft NS, Ramsay ME, Brown DWG, Andrews NJ. Viral Encephalitis

- 250 in England, 1989–1998: What Did We Miss? *Emerg Infect Dis* **2003**; 9:234–240.
- 251 11. Quist-Paulsen E, Kran A-MB, Dunlop O, Wilson J, Ormaasen V. Infectious encephalitis:
252 A description of a Norwegian cohort. *Scand J Infect Dis* **2013**; 45:179–185.
- 253 12. Mailles A, De Broucker T, Costanzo P, et al. Long-term Outcome of Patients Presenting
254 With Acute Infectious Encephalitis of Various Causes in France. *Clin Infect Dis* **2012**; 54:1455–
255 1464.
- 256 13. Tunkel AR, Glaser CA, Bloch KC, et al. The Management of Encephalitis: Clinical Practice
257 Guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* **2008**; 47:303–327.
- 258 14. Schlitt M, Lakeman FD, Whitley RJ. Psychosis and herpes simplex encephalitis. *South Med*
259 *J.* **1985**;78(11):1347–1350.
- 260 15. Solomon T, Hart IJ, Beeching NJ. Viral encephalitis: a clinician’s guide. *Pract Neurol* **2007**;
261 7:288–305.
- 262 16. Gavazzi G, Krause K-H. Ageing and infection. *Lancet Infect Dis* **2002**; 2:659–666.
- 263 17. Yoshikawa TT, Norman DC. Geriatric Infectious Diseases: Current Concepts on Diagnosis
264 and Management. *J Am Geriatr Soc* **2017**; 65:631–641.
- 265 18. Hansen MA, Samannodi MS, Castelblanco RL, Hasbun R. Clinical Epidemiology, Risk
266 Factors, and Outcomes of Encephalitis in Older Adults. *Clin Infect Dis* **2020**; 70:2377–2385.
- 267 19. Mailles A, Argemi X, Biron C, et al. Changing profile of encephalitis: Results of a 4-year
268 study in France. *Infect Dis Now.* **2022** Feb;52(1):1-6.
- 269 20. Jennett B. Assessment of outcome after severe brain damage. *The Lancet.*
270 **1975**;305(7905):480-4.
- 271 21. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J. Interobserver
272 agreement for the assessment of handicap in stroke patients. *Stroke.* **1988**; 19:604–607.
- 273 22. Logar M, Bogovič P, Cerar D, Avšič-Županc T, Strle F. Tick-borne encephalitis in Slovenia

274 from 2000 to 2004: Comparison of the course in adult and elderly patients. *Wien Klin Wochenschr*
275 **2006**; 118:702–707.

276 23. Hebant B, Miret N, Bouwyn JP, Delafosse E, Lefaucheur R. Absence of Pleocytosis in
277 Cerebrospinal Fluid does not Exclude Herpes Simplex Virus Encephalitis in Elderly Adults. *J Am*
278 *Geriatr Soc* **2015**; 63:1278–1279.

279 24. Schoonman GG, Rath JJG, Buren M, Melief PHGJ, Wirtz PW. Herpes Simplex Virus
280 Encephalitis Without Cerebrospinal Fluid Pleocytosis Is Not Unusual. *J Am Geriatr Soc* **2012**;
281 60:377–378.

282 25. Raschilas F, Wolff M, Delatour F, et al. Outcome of and Prognostic Factors for Herpes
283 Simplex Encephalitis in Adult Patients: Results of a Multicenter Study. *Clin Infect Dis* **2002**;
284 35:254–260.

285 26. Vora NM, Holman RC, Mehal JM, Steiner CA, Blanton J, et al. Burden of encephalitis-
286 associated hospitalizations in the United States, 1998-2010. *Neurology* vol. 82,5 (2014): 443-51.
287 **2014**; :10.

288 27. Campbell GL, Marfin AA, Lanciotti RS, Gubler DJ. West Nile virus. *Lancet Infect Dis*.
289 **2002** Sep;2(9):519-29.

290 28. Hjalmarsson A, Blomqvist P, Skoldenberg B. Herpes Simplex Encephalitis in Sweden,
291 1990-2001: Incidence, Morbidity, and Mortality. *Clin Infect Dis* **2007**; 45:875–880.

292 29. Miller RA. The aging immune system: primer and prospectus. *Science*.
293 **1996**;273(5271):70–74.

294 30. Velay A, Solis M, Kack-Kack W, et al. A new hot spot for tick-borne encephalitis (TBE):
295 A marked increase of TBE cases in France in 2016. *Ticks Tick-Borne Dis* **2018**; 9:120–125.

296 31. Office fédéral de la santé publique. Encéphalite à tique: extension des zones à risque où la
297 vaccination est recommandée. Available at: <https://www.bag.admin.ch/bag/fr/home/das->

298 bag/aktuell/news/news-04-02-2019.html. [Accessed 24 apr 2021].

299 32. Haut Comité de Santé Publique. Avis relatif à l'inscription de l'encéphalite à tiques sur la
300 liste des maladies à déclaration obligatoire Available
301 at: <https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=856>. [Accessed 24 apr 2021].

302 33. Sili U, Tavsanlı ME, Tufan A. Herpes Simplex Virus Encephalitis in Geriatric Patients.
303 *Curr Geriatr Rep* **2017**; 6:34–41.

304 34. Sheybani F, Naderi H, Sajjadi S. The Optimal Management of Acute Febrile
305 Encephalopathy in the Aged Patient: A Systematic Review. *Interdiscip Perspect Infect Dis* **2016**;
306 2016:1–13.

307

308 **Acknowledgments**

309 The authors would like to thank the investigators' group and the scientific committee of ENCEIF.

310

311 ***The investigators' group are:** Sophie Abgrall (Paris), Laurent Argaud (Lyon), Xavier Argemi
312 (Strasbourg), Nathalie Asseray (Nantes), Guillaume Baille (Lille), Aurélie Baldolli (Caen), Julien
313 Biberon (Tours), Charlotte Biron (Nantes), Geneviève Blanchet-Fourcade (Narbonne), Mathieu
314 Blot (Dijon), Anne Bonnetain (Paris), Elisabeth Botelho-Nevers (Saint-Etienne), Frédéric
315 Bourdain (Paris), David Boutoille (Nantes), Hélène Brasme (Paris), Cédric Bruel (Paris), Fabrice
316 Bruneel (Versailles), Rodolphe Buzele (Saint-brieuc), Etienne Canoui (Paris), Philippe Casenave
317 (Libourne), Bernard Castan (Périgueux), Charles Cazanave (Bordeaux), Céline Cazorla (Saint-
318 Etienne), Thibault Challan-Belval (Annemasse), Pascal Chavanet (Dijon), Catherine Chirouze
319 (Besançon), Tomasz Chroboczek (Villefranche), Johan Courjon (Nice), Thomas De Broucker
320 (Saint-Denis), Arnaud De La Blanchardière (Caen), Etienne de Montmollin (Saint-Denis), Thècle
321 Degroote (Paris), Marine Delaroche (Paris), Eric Denes (Limoges), Colin Deschanvres (Nantes),
322 Capucine Diard-Detoeuf (Paris), Aurélien Dinh (Boulogne-Billancourt), Olivier Epaulard
323 (Grenoble), Pierre Fillatre (Saint-Brieuc), Emmanuel Forestier (Chambéry), Thibault Fraisse
324 (Alès), Marie Froidure (Annemasse), Benjamin Gaborit (Nantes), Amandine Gagneux-Brunon
325 (Saint-Etienne), Nicolas Gaillard (Montpellier), Arnaud Galbois (Quincy sous Sénart), Mathieu
326 Godement (Paris), François Goehringer (Nancy), Simon Gravier (Colmar), Valentin Greigert
327 (Colmar), Isabelle Gueit (Rouen), Thomas Guimard (La Roche sur Yon), Carole Henry (Saint-
328 Denis), Maxime Hentzien (Reims), Jean-Etienne Herbrecht (Strasbourg), Pierre Jaquet (Paris),
329 Fanny Jommier (Paris), Lydie Katchatourian (Nantes), Solene Kerneis (Paris), Jessica Krause
330 (Paris), Manuela Le Cam (Paris), Marion Le Maréchal (Grenoble), Gwenael Le Moal (Poitiers),
331 Paul Le Turnier (Nantes), Raphael Lecomte (Nantes), Anne-Sophie Lecompte (Nantes), Romain
332 Lefaucheur (Rouen), Stéphanie Lejeune (Annecy), Xavier Lescure (Paris), Olivier Lesieur (La
333 Rochelle), Philippe Lesprit (Suresnes), Guillaume Louis (Metz), Christelle Lucas (Paris), Rafael
334 Mahieu (Angers), Alain Makinson (Montpellier), Guillaume Marc (Saint-Nazaire), Alexandre
335 Maria (Montpellier), Nathalie Marin (Paris), Aurélie Martin (Strasbourg), Guillaume Martin-
336 Blondel (Toulouse), Martin Martinot (Colmar), Alexandre Mas (Montpellier), Philippe Mateu
337 (Charleville-Mézière), Morgan Matt (Paris), Laurence Maulin (Aix-en-Provence), Frédéric Mechai
338 (Paris), Jean-Paul Mira (Paris), Eugénie Mutez (Lille), Jérémie Orain (Nantes), Anne Schieber-

339 Pachart (Colmar), Nathalie Pansu (Montpellier), Solene Patrat-Delon (Rennes), Patricia Pavese
340 (Grenoble), H el ene Pelerin (La Roch sur Yon), V eronique Pelonde-Erim ee (Fort de France),
341 Isabelle Pierre (Grenoble), Diane Ponscarne (Paris), Dimitri Psimaras (Paris), Mathilde Puges
342 (Bordeaux), Mathilde Reveillon-Istin (Le Havre), Sylvain Rheims (Lyon), Aur elie Richard-
343 Mornas (Lyon), Agn es Rich e (Angoul eme), Vincent Roubeau (Paris), Yvon Ruch (Strasbourg),
344 Isabelle Runge (Orl eans), H el ene Savini (Marseille), Romain Sonnevillle (Paris), Jean-Paul Stahl
345 (Grenoble), Pierre Tattevin (Rennes), Kelly Tiercelet (Paris), Saber Touati (Grenoble), Jean-Marie
346 Turmel (Fort-de-France), Isabelle Tyvaert (Nancy), Marc-Olivier Vareil (Bayonne), Magalie
347 Vidal-Roux (Clermont-Ferrand), Virginie Vitrat (Annecy), Heidi Wille (Bayonne), Mathieu Zuber
348 (Paris).

349 **The scientific committee are:** Laurent Almoyna-Martinez (Aix-en-Provence), Olivier Bouchaud
350 (Bobigny), Thomas de Broucker (Saint Denis), Fabrice Bruneel (Versailles), Bernard Castan
351 (P erig eux), Eric Denes (Limoges), Olivier Epaulard (Grenoble), Nadine Girard (Marseille), Jean-
352 Louis Herrmann (Garches), J erome Honnorat (Lyon), Alexandra Mailles (Saint Maurice), Patrice
353 Morand, (Grenoble), Fran ois Raffi (Nantes), France Roblot (Poitiers), Jean-Paul Stahl (Grenoble),
354 Romain Sonnevillle (Paris), Pierre Tattevin (Rennes).

355

356 **Funding**

357 French Infectious Diseases Society (Soci et  de pathologie infectieuse de langue fran aise, SPILF)

358

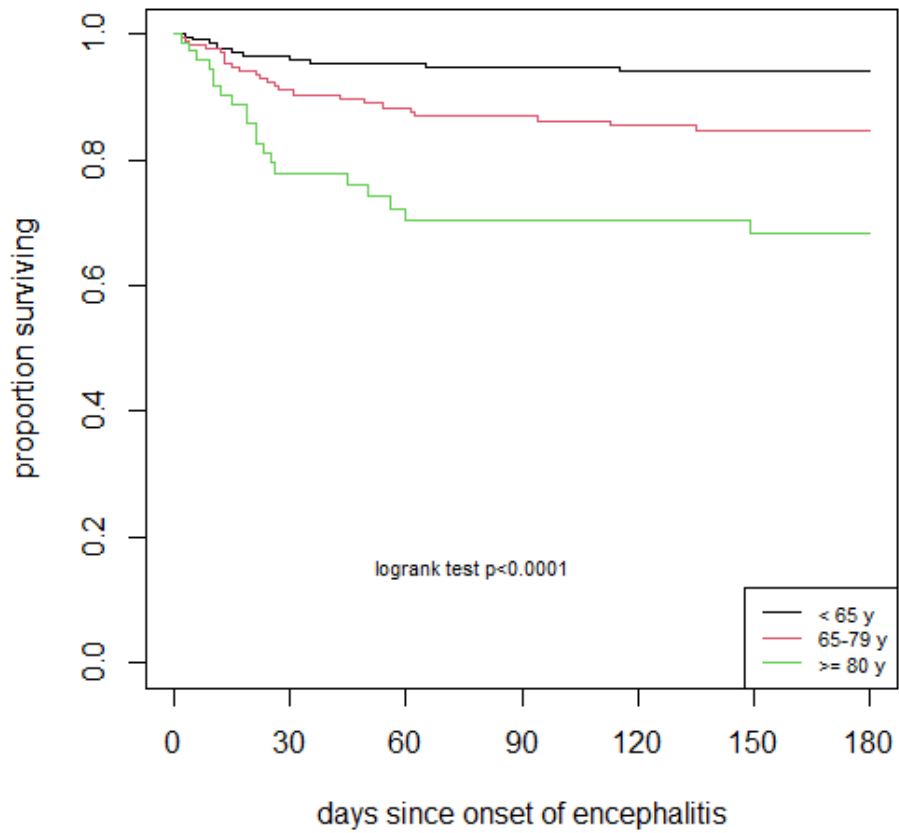
359 **Conflict of interest**

360 None to declare

361

362

1 **Figure 1.** Survival of patients with encephalitis according to age (<65, 65-69, ≥80 years)



		number at risk					
< 65 y	234	162	151	145	142	138	128
65-79 y	183	138	127	121	117	114	104
≥ 80 y	73	44	39	38	37	35	33

2

3

4

1 **Table 1.** Patients characteristics

	<65 years (n= 236)	65-79 years (n=184)	≥80 years (n=74)	<i>P</i>
Male gender	153/236 (65)	109/184 (59)	41/73 (56)	0.304
Diabetes	19/233 (8)	33/184 (18)	15/74 (20)	0.003
Cancer	3/236 (1)	21/183 (11)	15/73 (21)	<0.001
Haematological malignancies	3/235 (1)	19/183 (10)	5/73 (7)	<0.001
Immunodeficiency	9/236 (4)	39/184 (21)	11/74 (15)	<0.001
Autoimmune diseases	3/233 (1)	14/183 (8)	6/71 (8)	<0.001
Neurological diseases	8/236 (3)	14/184 (8)	7/74 (9)	0.054
International travel within the last 6 months	54/225 (24)	22/173 (13)	5/69 (7)	<0.001
Coma	18 (8)	9 (5)	11 (15)	0.025
Impaired consciousness	84 (36)	74 (41)	39 (53)	0.032
Confusion	127 (54)	126 (69)	53 (72)	0.002
Seizure	33 (14)	30 (16)	11 (15)	0.803
Headache	146 (62)	73 (40)	14 (19)	<0.0001
Infratentorial neurological signs	46 (20)	37 (20)	9 (12)	0.298
- Cerebellar syndrome	19 (8)	22 (12)	3 (4)	0.107
- Cranial nerve palsy(ies)	29 (12)	20 (11)	6 (8)	0.602
Supratentorial neurological signs	84 (36)	90 (49)	32 (43)	0.022
- Deficit (motor/sensitive)	32 (14)	18 (10)	9 (12)	0.495
- Aphasia	63 (27)	79 (43)	28 (38)	0.002
Fever	146 (62)	73 (40)	14 (19)	<0.001
Skin rash	16 (7)	18 (10)	17 (23)	<0.001
Respiratory symptoms	29 (12)	20 (11)	6 (8)	0.602
Digestive symptoms	50 (21)	33 (18)	11 (15)	0.430
Rheumatological symptoms	11 (5)	7 (4)	0 (0)	0.173

2 Data are presented as numbers (%)

3 **Table 2.** Investigations

	<65 years (n= 236)	65-79 years (n=184)	≥80 years (n=74)	<i>P</i>
CSF white blood cells count, /mm³	114 [34-302]	61 [13-220]	62 [17-180]	0.010
CSF glucose, mmol/L	3.2 [1.8-4.1]	3.2 [0.8-4.3]	3.4 [2.5-4.6]	0.197
CSF protein, g/L	0.9 [0.6-1.4]	0.9 [0.6-1.4]	0.9 [0.6-1.6]	0.666
CSF lactates, mmol/L	2.8 [2.2-3.4]	2.6 [2.2-3.3]	3.3 [2.2-4.5]	0.211
Electroencephalogram				
- performed	181/232 (78)	135/183 (74)	59/73 (81)	0.407
- abnormal	125/173 (72)	106/134 (79)	44/59 (75)	0.385
Brain imaging (CT scan or MRI)				
- performed	231/236 (98)	182/184 (99)	73/74 (98)	0.796
- abnormal	132/230 (57)	115/180 (64)	35/73 (48)	0.060

4 Quantitative data are presented as median [interquartile range], qualitative data are presented as numbers (%)

5 CSF, cerebrospinal fluid

6

7 **Table 3.** Aetiologies of infectious encephalitis

	<65 years (n=236)	65-79 years (n=184)	≥80 years (n=74)	<i>P</i>
Causative agent identified	152 (64)	125 (68)	47 (64)	0.692
Herpes simplex virus	64 (27)	53 (29)	15 (20)	0.368
Varicella-zona virus	16 (7)	27 (15)	22 (30)	<0.001
<i>Mycobacterium tuberculosis</i>	10 (4)	1 (0.5)	0 (0.0)	0.023
<i>Listeria monocytogenes</i>	3 (1)	13 (7)	7 (9)	<0.001
Arboviruses ¹	20 (8)	14 (8)	1 (1)	0.107
- Tick-borne encephalitis	17 (7)	9 (5)	0 (0)	0.032
Enterovirus	5 (2)	1 (0.5)	0 (0)	0.317
<i>Cryptococcus neoformans</i>	1 (0.4)	3 (2)	0 (0)	0.373
Influenza virus	8 (3)	3 (2)	0 (0)	0.210
Epstein-Barr virus	4 (2)	1 (0.5)	1 (1)	0.534
JC virus	1 (0.4)	2 (1)	0 (0)	0.744
<i>Borrelia burgdorferi</i>	1 (0.4)	2 (1)	0 (0)	0.744
Measles virus	3 (1)	0 (0)	0 (0)	0.385
<i>Mycoplasma pneumoniae</i>	4 (1.7)	0 (0.0)	0 (0.0)	0.210
Miscellaneous ²	12 (5)	5 (3)	1 (1)	0.276
Unknown	84 (36)	59 (32)	27 (36)	0.692

8 Data are presented as numbers (%)

9 ¹**Other arboviruses:** Chikungunya (n=1), Japanese Encephalitis (n=2), Toscana virus (n=1), West-Nile virus (n=4),
10 Zika (n=1).

11 ²**Miscellaneous:** CMV (n=1), HHV6 (n=2), Parvovirus B19 (n=1), VIH (n=1), *Anaplasma spp.* (n=1), *Bartonella spp.*
12 (n=1), *Capnocytophaga spp.* (n=2), *Coxiella spp.* (n=1), *Francisella tularensis* (n=1), *Legionella spp.* (n=1),
13 *Leptospira spp.* (n=2), *Rickettsia spp.* (n=1), *Treponema pallidum* (n=1), *Tropheryma whipplei.* (n=2).

14 **Table 4.** Management and outcome

	<65 years (n=236)	65-79 years (n=184)	≥80 years (n=74)	<i>P</i>
Management				
Intravenous aciclovir	200/229 (87)	156/179 (87)	71/73 (97)	0.045
Time from symptoms onset to aciclovir start, days	3 [1-6]	2 [1-6]	2 [1-4]	0.848
Corticosteroids	54/221 (24)	30/173 (17)	9/70 (13)	0.058
Antibacterial treatment	163/229 (71)	119/181 (66)	47/73 (64)	0.382
Outcome				
Shock	10/235 (4)	9/183 (5)	5/74 (7)	0.633
Intensive Care Unit (ICU) admission	109/235 (46)	69/184 (38)	27/74 (36)	0.117
ICU length of stay, days	6 [2-13]	5 [4-12]	4 [2-10]	0.648
Hospital length of stay, days	15 [9 - 25]	19 [12 - 31]	20 [12 - 26]	0.005
Glasgow outcome scale on discharge				<0.001
- 1	6/230 (3)	18/180 (10)	13/72 (18)	
- 2	0/230 (0)	2/180 (1)	0/72 (0)	
- 3	19/230 (8)	20/180 (11)	12/72 (17)	
- 4	58/230 (25)	45/180 (25)	17/72 (24)	
- 5	147/230 (64)	95/180 (53)	30/72 (42)	
Modified Rankin scale on discharge				<0.001
- 0	56/212 (26)	26/165 (16)	11/66 (17)	
- 1	62/212 (29)	39/165 (24)	7/66 (11)	
- 2	40/212 (19)	24/165 (15)	10/66 (15)	
- 3	27/212 (13)	32/165 (20)	6/66 (9)	
- 4	15/212 (7)	20/165 (12)	17/66 (26)	
- 5	6/212 (3)	6/165 (4)	2/66 (3)	
- 6	6/212 (3)	18/165 (11)	13/66 (20)	
In-hospital mortality	6/234 (3)	18/183 (10)	13/73 (18)	<0.001

15

16 Quantitative data are presented as median [interquartile range], qualitative data are presented as numbers (%)

17

18

19 **Table 5.** Univariate and multivariate analysis of risk factors for six-month mortality (Cox model)

	Univariate analysis			Multivariate analysis ¹		
	HR	CI 95%	<i>P</i>	HR	CI 95%	<i>P</i>
Age (ref < 65 years)						
- 65-79 years	2.6	[1.3 – 5.3]	0.0084	1.9	[0.9-4.1]	0.1124
- ≥80 years	6.1	[2.9 – 12.7]	<0.0001	5.2	[2.3-11.7]	<0.0001
Male gender	0.8	[0.5 – 1.4]	0.4160	-	-	-
Diabetes	1.1	[0.5 – 2.2]	0.8814	-	-	-
Immunodeficiency	3.1	[1.7 – 5.5]	<0.0001	-	-	-
Coma on admission	3.8	[1.9 – 7.3]	<0.0001	3.4	[1.6-6.9]	0.0011
Confusion on admission	1.1	[0.6 – 2.0]	0.6313	-	-	-
Seizure on admission	1.2	[0.6 – 2.5]	0.5967	-	-	-
Fever on admission	0.7	[0.4 – 1.2]	0.1873	0.8	[0.4-1.6]	0.5931
Headache on admission	0.3	[0.2 – 0.6]	0.0006	0.8	[0.4-1.7]	0.5827
Skin rash on admission	1.2	[0.6 – 2.7]	0.6230	-	-	-
Infratentorial neurological signs on admission	0.4	[0.2 – 1.0]	0.051	0.7	[0.3-1.8]	0.4377
Supratentorial neurological signs on admission	0.9	[0.5 – 1.5]	0.696	-	-	-
Abnormal EEG	1.6	[0.7 - 3.6]	0.2470	-	-	-
Abnormal brain imaging	1.6	[0.9 – 3.0]	0.1060	-	-	-
CSF Protein ≥0.8 g/L	1.9	[1.1 – 3.4]	0.0313	2.6	[1.4-5.0]	0.0028
CSF white cells ≥80/mm³	0.6	[0.3 – 0.9]	0.0467	0.6	[0.3-1.1]	0.0926
Viral encephalitis	1.7	[0.9 – 3.0]	0.0690	1.9	[1.0-3.7]	0.0418
Bacterial encephalitis	1.1	[0.4 – 2.8]	0.8090	-	-	-
Parasitic encephalitis	3.1	[0.4 – 22.8]	0.2580			

20 ¹ Stratified on immunodeficiency, and brain imaging

21 CSF, cerebrospinal fluid; EEG, electroencephalogram; CI 95%, confidence interval 95%