The ENCEIF cohort: a valuable tool to monitor encephalitis trends and emerging neurotropic pathogens in France

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Introduction

- Infectious encephalitis are severe diseases caused by an unlimited number of infectious agents
- In an average of 50% of cases, no causative diagnosis is obtained with significant consequences: no specific treatment, no prognosis, no possible public health intervention
- Previous study in France in 2007 : 222 enrolled adult cases, 53% adult patients with an etiological diagnosis, Top 4 causative agents : HSV, VZV, *M. tuberculosis*, *L. monocytogenes* [1]

Methods

- Prospective cohort study
- Patients enrolled by voluntary centers
- Case definition [adapted from 2] and study protocol available at https://drive.google.com/open?id=0B0PhiSGOcKLMRDMxaVZsYjN6X2c

Table 1: Enceif patients vs national 2007 study

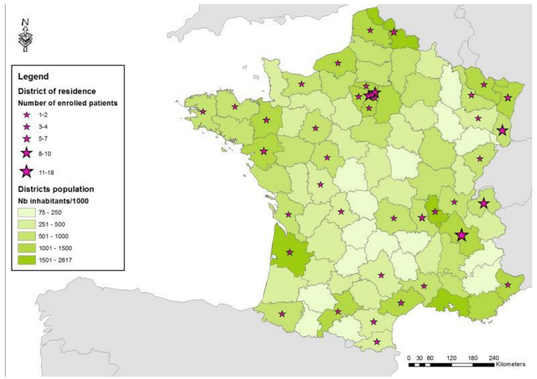
	2007 (N=222)	Enceif (N =162)	p
Mean Age (range)	56 (18 – 89)	59 (18 – 90)	NS
M/F ratio	1.6	1.8	NS
Comorbidities	72 (32%)	34/162 (21%)	**0.01**
Nb cases with aetiological diagnosis	117/222 (53%)	92/152* (61%)	NS
Mean lenght of hospital stay (range)	31 (2 – 284)	23 (1 – 147)	**0.007**
Nb cases deceased during hospitalization	26 (12%)	12 (7%)	NS

References
1-Mailles A, et al. Clin Infect Dis.2009;49(12):1838-47.
2 - Venkatesan A, et al. Clin Infect Dis. 2013;57(8):1114-28
3 - Carteaux G, et al.N Engl J Med. 2016;374(16):1595-6.

Results

- 162 patients enrolled from 1/1/16 to 28/2/17
  - Ratio M/F =1,7
  - Median age = 63 y.o. (range 18 – 90)
  - 50% retired
  - Main regions: French Alps, Paris and surroundings, Brittany (**Figure 1**)

Figure 1: District of residence of Enceif patients



- Medical history: 55 (34%) had a relevant medical history:
  - 14 had solid cancer
  - 11 were transplant receivers
  - 17 had diabetes
  - 11 had hemopathy
- Severity and outcome (N=157, 5 still hospitalized)
  44 (28%) had seizures
  31 (20%) experienced coma
  11 (9%) died during hospitalization

- Cause of encephalitis (N=152, causative diagnosis still pending for 10)
  - Determined in 92 (61%) **(Table 1)**
  - 60 of unknown cause (39%)
  - 5 imported cases: West Nile (n=3), Japanese encephalitis (n=1), Zika virus (n=1)

- Unexpected findings
  - TBE virus : Usually less than 10 cases/ year in France. 8 patients enrolled in the cohort were part of a local outbreak occurring during spring in Alsace. Total number of cases in the outbreak was 25.
  - Zika : a case of encephalitis with a proven diagnosis of Zika virus infection was reported in a traveler returning from South Pacific [3]

- Enceif vs adult patients enrolled in the national 2007 study **(Table 2),**
  - Enceif patients had more frequently comorbities: cancer, hemopathy and transplant-related suppressive treatment (data not shown)
  - Some causative agents usually associated with immunodepression were more frequently diagnosed in Enceif (EBV, JC virus) (**Table 1)**
  - The lenght of hospitalization was shorter by a mean 7-days when compared with 2007

Discussion – Conclusions

- The Enceif cohort is likely to be representative of encephalitis patients hospitalized in mainland France
- Enceif is a usefull tool to follow-up on trends: HSV and VZV still most frequent pathogens, increase of immunocompromized patients presenting with encephalitis
- The decrease of the number of encephalitis patients due to tuberculosis may reflect the global trend of this disease as seen in general population
- Enceif is sensitive to local outbreaks as seen with the cases of TBE during Spring 2016 and to emerging diseases such as WNV or Zika virus infections

Table 2: Aetiological diagnosis of encephalitis

Causative infectious agents (Nb cases, %)	2007 (N =222)	Enceif (N =152)	p
Herpes Simplex virus	54 (24%)	36 (24%)	NS
Varicella Zoster virus	17 (8%)	16 (11%)	NS
Tick-borne encephalitis	3 (2%)	8 (5%)	**0.02**
Epstein Barr virus	1 (0.5%)	6 (4%)	**0.01**
Listeria monocytogenes	13 (6%)	5 (3%)	NS
Influenza virus	0	4 (3%)	**0.01**
Mycobacterium tuberculosis	19 (9%)	3 (2%)	**0.005**
West Nile virus	1 (0.5%)	3 (2%)	NS
Enterovirus	0	2 (1%)	NS
JC virus	0	2 (1%)	NS
Borrelia burgdorferri	1 (0.5%)	2 (1%)	NS
HHV-6	0	1 (1%)	NS
Japanese encephalitis virus	0	1 (1%)	NS
Cryptococcus neoformans	1 (0.5%)	1 (1%)	NS
Legionella pneumophila	1 (0.5%)	1 (1%)	NS
Zika Virus	0	1 (1%)	NS

- The shorter lenght of hospitalisation may reflect changes in the global management of patients and optimisation of hospital ressources. Enceif would therefore also be a usefull tool to assess any public health intervention or professional recommandation on patients' management. Further studied are needed to confirm this hypothesis.

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