European Network for Collaboration on Encephalitis Investigations & Follow-up **(ENCEIF)**

ENCEIF –Protocole – 1st July 2017

Context

- Significant number of encephalitis with presumed infectious cause have no aetiological diagnosis
- Most frequent causes are HSV, VZV and various arboviruses
- Encephalitis are valuable sentinels for infectious emerging diseases (Nipah, Hendra, EV-A71, West Nile, etc.)
- Sequelae following encephalitis are a major issue and are neglected
  - Individual level
  - Public health burden
  - Healthcare system sustainability

Protocol

- Prospective observational cohort study
- Acute episode + follow-up after 6 months, 1 year and 5 years
- No specific intervention, patients are managed as usual
- In France : no formal consent but information and search for non-opposition from the patient/family/carregiver

  → to be adapted to national situations
- In France, authorization from national ethical committee n° DR-2015-300 → includes the computation of data in an online system
- Data are computed online (anonymous data)

Case Definition *(long….)*

- Patient ≥ 18 years old
- Prospective enrollment
- Patient hospitalized
- Altered mental status : decreased consciousness, lethargy, confusion, behavioral disorders,
- Lasting at least 24 h,
- No alternative cause identified,

and ….

Case Definition *(long….)*

At least 2 of the followings:

- fever ≥ 38°C *(at neurological onset or in the 72 h before)*
- Generalized or partial seizures in patient with no preexisting epilepsy
- Focal neurological signs of recent onset
- CSF WBC count ≥ 5 WBC/mL
- Brain imaging evocative of encephalitis
- EEG anomaly evocative of encephalitis with no other explanation.

Exclusion criteria *(long too…)*

- Hospitalization length < 5 days without death
- Previously known HIV infection
- CNS primary or autoimmune vasculitis
- Brain thrombophlebitis when primary
- Bacterial meningitis
- Brain abcess when primary
- Neuromalaria
- Brain tumor, brain disorders during blood cancer
- Toxic and metabolic encephalopathy
- Creutzfeldt Jakob and other prionic diseases
- ADEM
- Primary auto-immune encephalitis without infectious encephalitis as a trigger (ex. NMDAr, LGi1, etc.)

Investigating the infectious cause of encephalitis

- According to the usual practice and protocol of the hospital
- Taking into account specific clinical or epidemiological features (travels, ongoing outbreak of arboviral infections or measles for ex.)

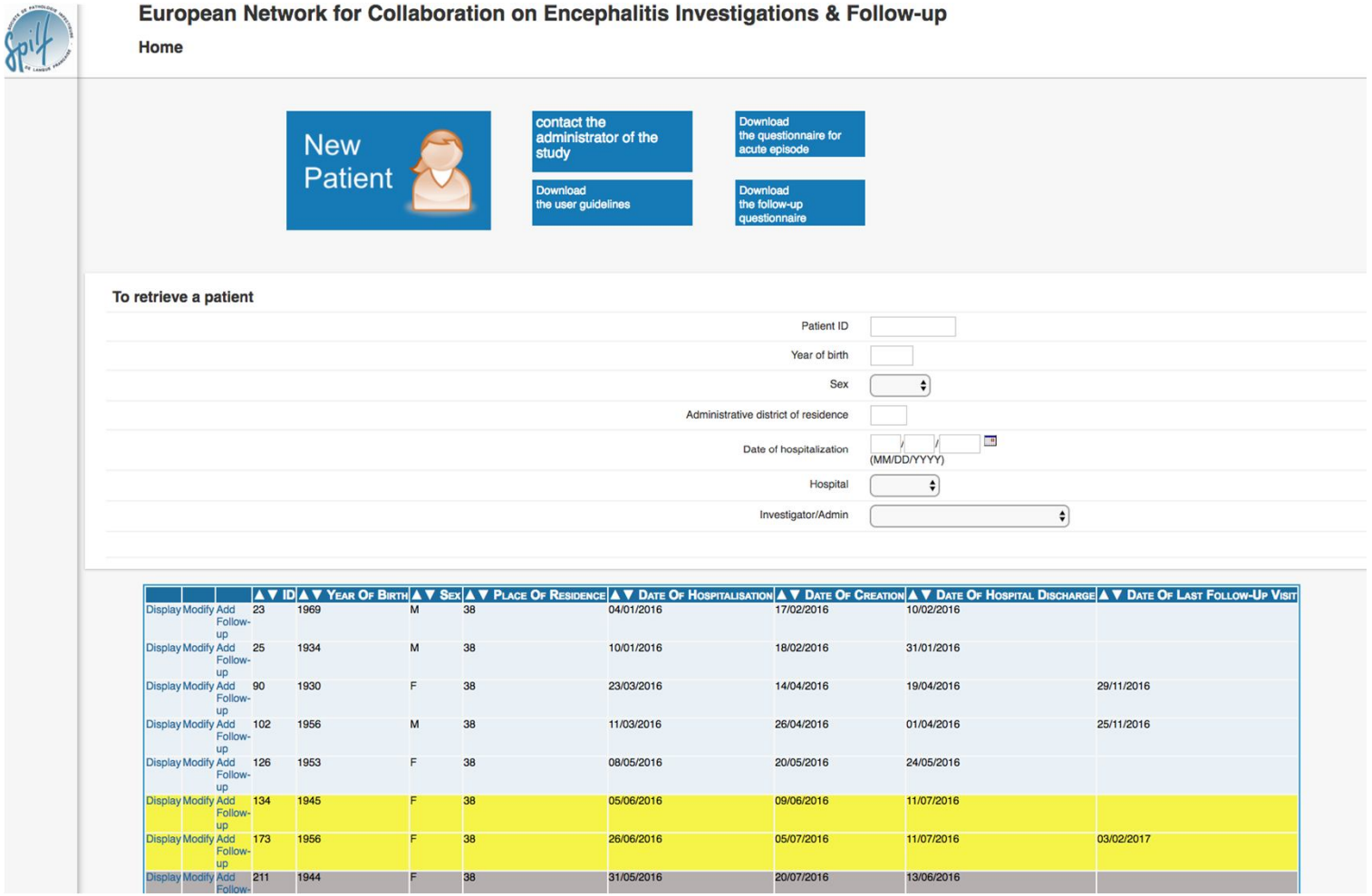
- Guidelines were recent published in France about management of encephalitis, including aetiological investigation (2017)

http://www.infectiologie.com/fr/recommandations.html (in French, free download)

and *Stahl et al. Médecine et maladies infectieuses 2017; 47(3):179-194. doi: 10.1016/j.medmal.2017.01.005* (in English)

Online data computing

- « user friendly »



			ID	Year Of Birth	Sex	Place Of Residence	Date Of Hospitalisation	Date Of Creation	Date Of Hospital Discharge	Date Of Last Follow-Up Visit
Display	Modify	Add Follow-up	23	1969	M	38	04/01/2016	17/02/2016	10/02/2016	
Display	Modify	Add Follow-up	25	1934	M	38	10/01/2016	18/02/2016	31/01/2016	
Display	Modify	Add Follow-up	90	1930	F	38	23/03/2016	14/04/2016	19/04/2016	29/11/2016
Display	Modify	Add Follow-up	102	1956	M	38	11/03/2016	26/04/2016	01/04/2016	25/11/2016
Display	Modify	Add Follow-up	126	1953	F	38	08/05/2016	20/05/2016	24/05/2016	
Display	Modify	Add Follow-up	134	1945	F	38	05/06/2016	09/06/2016	11/07/2016	
Display	Modify	Add Follow-up	173	1956	F	38	26/06/2016	05/07/2016	11/07/2016	03/02/2017
Display	Modify	Add Follow-	211	1944	F	38	31/05/2016	20/07/2016	13/06/2016	

Future publications

- All investigators co-author the publications
- Investigators can participate in the analysis and preparation of a publication, or come with new ideas to use the data
- Every participating country is the owner of the data from its patients

- Up to date
  - ESCMID 2017
  - Journées nationales d’infectiologie (juin 2017)

For any question or clarification or support

enceif@hotmail.com

The follow-up protocol for patients enrolled in the ENCEIF cohort

it's easy !

When to do it ?

- Date of reference = date of discharge from acute healthcare hospitalization

- Follow-up scheme
  - 1st follow-up examination : during the 6th month after discharge
  - 2nd : during the 12th month after discharge
  - 3rd : during the 60th month after discharge (meaning 5 years after discharge from hospital)

- Exception : if the patient appears to have fully recovered at the time of the 6th-month follow-up visit, then no further follow-up

- BUT : full recovery means cognitive abilities and behavioral disorders, not only infection-related symptoms

Who can do it ?

- Ideally: the attending (ID specialist, neurologists, internist, rehabilitation specialist) + a neuropsychologist

- In the absence of the neuropsychologist : the attending alone can do it

→ tests were chosen so that everybody with a medical background can use them

What do to and how ?

- A standard clinical examination (including neurological examination)

- Standardized questionnaire: https://drive.google.com/open?id=0B0PhiSGOcKLMWC0tV3VYZlV5c3c
  - Persisting or newly appeared symptoms
  - Major changes in everyday life
  - Autonomy
  - Tests (next slides)

- MOCA and SWLS tests for all patients *TRY THEM !!!!!*
  - MOCA : MOntreal Cognitive Assessment
    - 9 questions for **cognitive** assessment
  - SWLS : Satisfaction With Life Scale
    - 5-questions for **quality of life** assessment

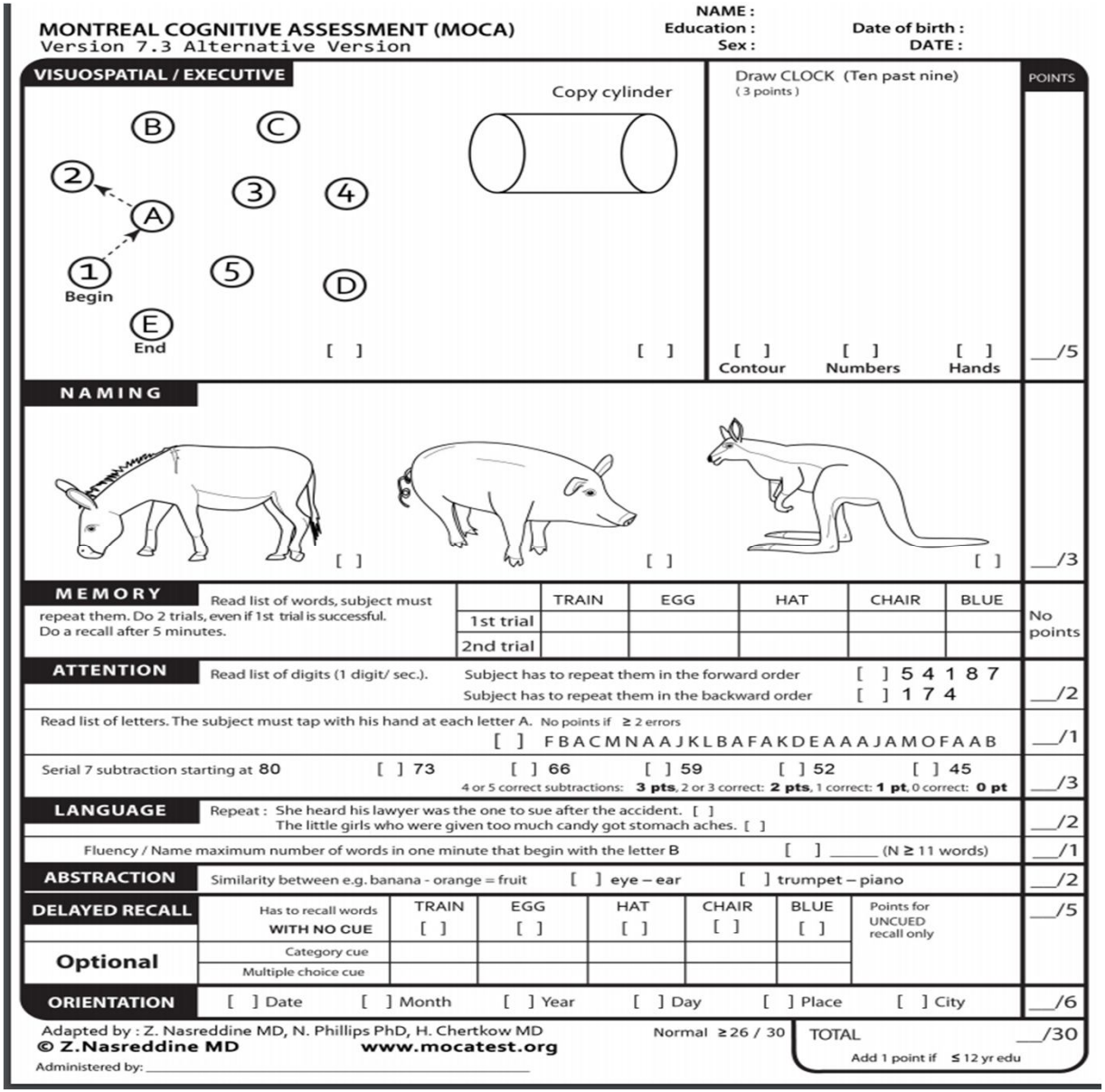
- For patients who were unable to return to their home
  - Idem + Barthel index

It's easy

It is usefull to screen ***invisible impairment*** *that needs to be adressed !*

MOCA

- Try it !
- Moca test is available for free at *moca.org*
- Moca is validated in more than 40 languages



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.3 Alternative Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cylinder

Draw CLOCK (Ten past nine) (3 points)

[ ] Contour [ ] Numbers [ ] Hands ___/5

NAMING ___/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	TRAIN	EGG	HAT	CHAIR	BLUE
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 5 4 1 8 7
Subject has to repeat them in the backward order [ ] 1 7 4 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/1

Serial 7 subtraction starting at 80 [ ] 73 [ ] 66 [ ] 59 [ ] 52 [ ] 45
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE Repeat : She heard his lawyer was the one to sue after the accident. [ ]
The little girls who were given too much candy got stomach aches. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter B [ ] _____ (N ≥ 11 words) ___/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] eye – ear [ ] trumpet – piano ___/2

DELAYED RECALL ___/5

	Has to recall words WITH NO CUE	TRAIN [ ]	EGG [ ]	HAT [ ]	CHAIR [ ]	BLUE [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
© Z.Nasreddine MD www.mocatest.org
Administered by: _____

Normal ≥ 26 / 30

TOTAL ___/30
Add 1 point if ≤ 12 yr edu

SWLS

SWLS

Scale:

Instructions: Below are five statements that you may agree or disagree with. Using the 1 - 7 scale below, indicate your agreement with each item by placing the appropriate number on the line preceding that item. Please be open and honest in your responding.

- 7 - Strongly agree
- 6 - Agree
- 5 - Slightly agree
- 4 - Neither agree nor disagree
- 3 - Slightly disagree
- 2 - Disagree
- 1 - Strongly disagree

_____ In most ways my life is close to my ideal.

_____ The conditions of my life are excellent.

_____ I am satisfied with my life.

_____ So far I have gotten the important things I want in life.

_____ If I could live my life over, I would change almost nothing.

Scoring:

Though scoring should be kept continuous (sum up scores on each item), here are some cut-offs to be used as benchmarks.

- 31 - 35 Extremely satisfied
- 26 - 30 Satisfied
- 21 - 25 Slightly satisfied
- 20 Neutral
- 15 - 19 Slightly dissatisfied
- 10 - 14 Dissatisfied
- 5 - 9 Extremely dissatisfied

Barthel index

THE BARTHEL INDEX

Patient Name: _____
Rater Name: _____
Date: _____

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

Provided by the Internet Stroke Center — www.strokecenter.org

Additional informations

- Record any additional assessment carried out in the hospital or as an outpatient
  - Imaging
  - Comprehensive neuro-psychological battery
  - Etc.

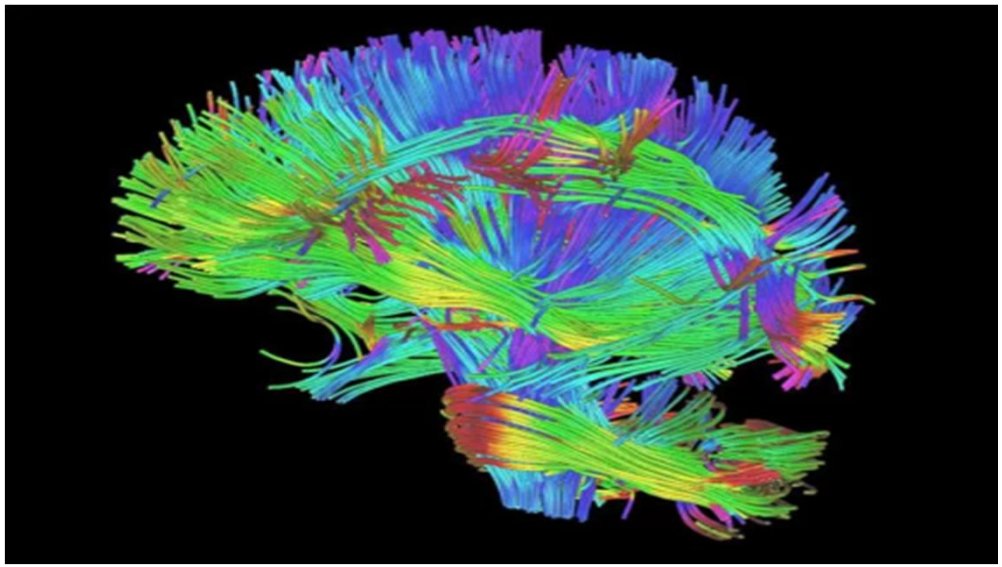
- If patient is deceased or lost to follow-up since discharge or last visit, this status has to be recorded

- Any abnormal result or finding should prompt the attending to set up a consultation with the appropriate specialist (neurologist, psychiatrist, rehabilitation physician, etc.)

Take-home points

- The follow-up as designed for the protocol can be done by any physician
- It really can be a benefit for patients in case of detection of an « invisible » impairment
- Any question or support: enceif@hotmail.com

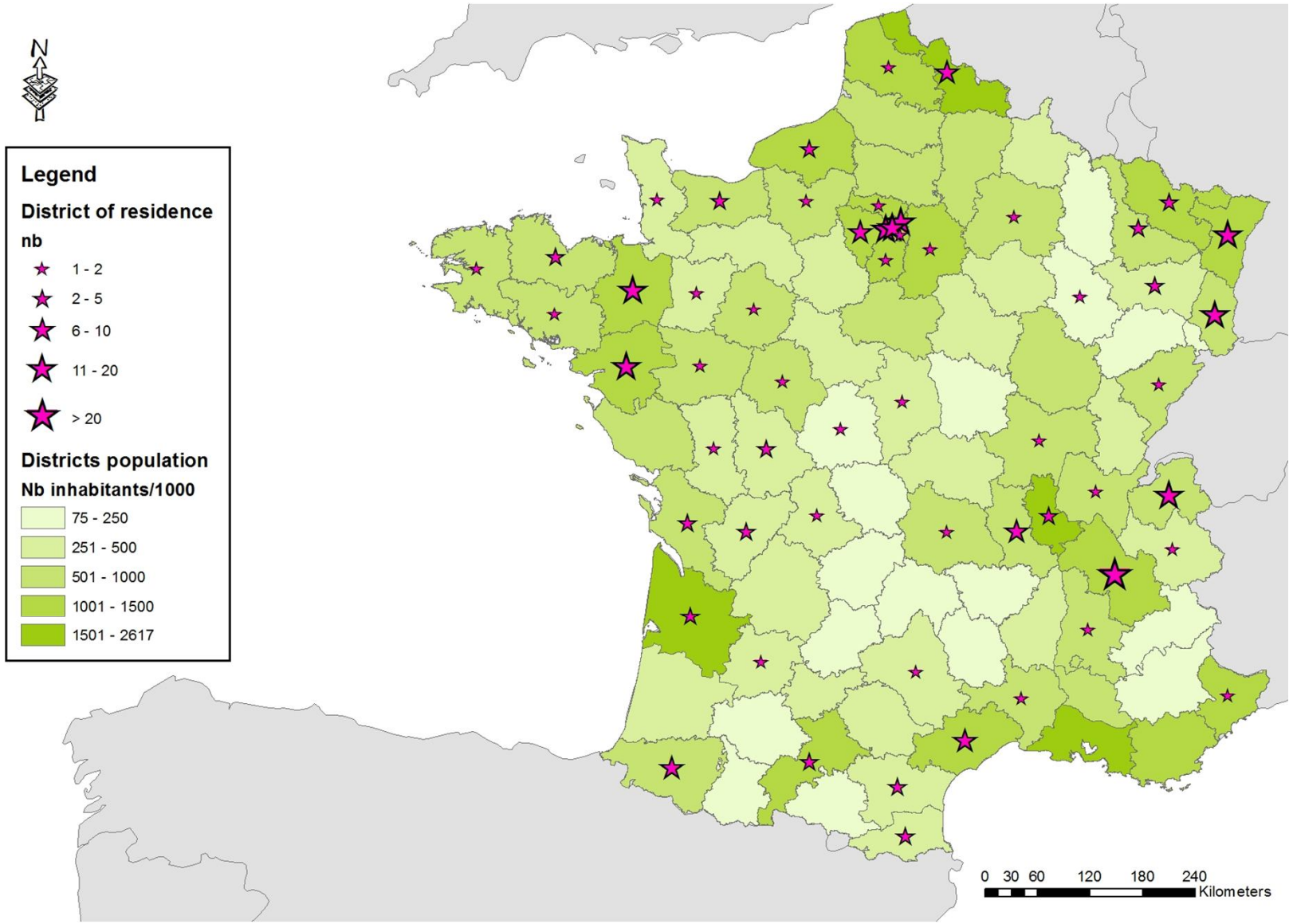
Results on Jan.1st 2018



Number of cases and demography

- 276 patients enrolled
- Sex ratio H/F = 1,8
- Median age 60 years
  - range 18 – 94
  - 25% > 74 y.o.a.
  - 51% retired, 4% students

- Most of them living in France : n= 269 (97%)


N
Legend
District of residence
nb
1 - 2
2 - 5
6 - 10
11 - 20
> 20
Districts population
Nb inhabitants/1000
75 - 250
251 - 500
501 - 1000
1001 - 1500
1501 - 2617
0 30 60 120 180 240
Kilometers

Clinical key points

- 33% with comorbidity or important history

- 257(93%) independent living before encephalitis

- ICU stay: n=117; 42%
- Mechanical ventilation n= 63; 24%
- Coma n=49; 18%
- Convulsions n= 65; 24%

- Death : n=24; 9%
  - Senior (median 75 ans)
  - Comorbidities/history 71%

- Discharge to home 65%, rehabilitation 30%

Aetiological diagnosis

- Aetiological investigation finished for 268 cases/276
  - **173 cases had a diagnosis→ 65%**

✓	HSV	n=62;	22 %
✓	VZV	n=34;	12 %
✓	TBEV	n= 15;	6 %
✓	*L. monocytogenes*	n=12;	5%
✓	Influenza	n=9;	3%

Unexpected findings

- 1 Zika encephalitis (Carteaux, NEJM 2016)
- 2 measles encephalitis (*unexpected, really ???*)

- TBE outbreak in Alsace (june 2016):
  - 25 cases, 8 encephalitis
  - A multinational outbreak, crossing borders (Switzerland, Germany)
  - Still a high number of cases (better screening ?)

Enceif vs 2007

	ENCEIF (N=276)	2007 adults (N=222)	p
Aetiological diagnosis	173/268 (65%)	117 (53%)	**0,01**
Solid cancer	23 (8%)	8 (4%)	**0,03**
Hemopathy	12 (6%)	6 (3%)	**0,06**
Transplant	12 (6%)	1 (0.5%)	**0,006**
Immunodepression	23 (12%)	6 (3%)	**$<10^{-3}$**
Mean duration of hospital stay	23,8 jours	30,8 jours	**0,004**
ICU	117 (43%)	111 (50%)	NS
Death cases	24 (9%)	26 (12%)	NS

Enceif vs 2007 (2)

	Enceif (N=276)	2007 adults (N=222)	p
HSV	62	54	NS
VZV	34	17	NS
TBEV	**15**	**3**	**0,02**
L. monocytogenes	12	13	NS
Influenza	**9**	**0**	**0,007**
M. tuberculosis	**6**	**20**	**$<10^{-3}$**
EBV	6	1	0,10
West Nile	3	1	NS
Enterovirus	3	0	NS
Japanese encephalitis	2	0	NS
JC	2	0	NS
Measles	2	0	NS
Zika	1	0	NS

Conclusions

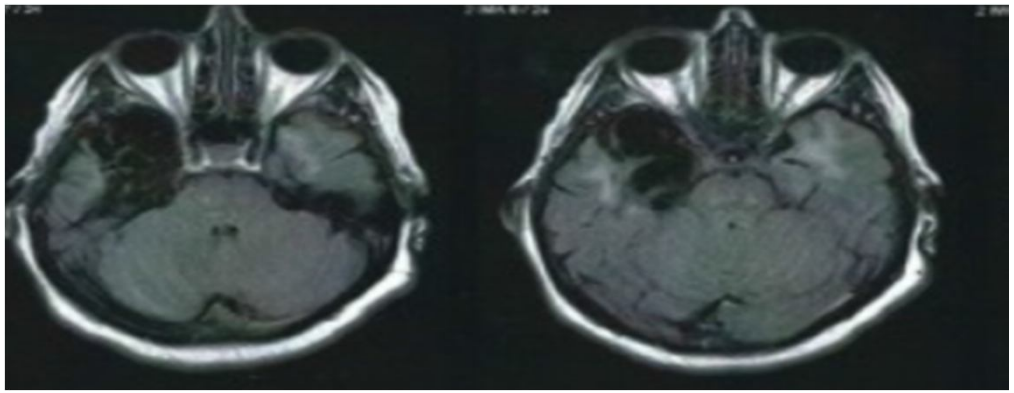
- Always keep in mind HSV, VZV → Aciclovir
- TBE : an isolated outbreak or a long lasting trend to increase? Better screening?
- Dramatic decrease of *M. tuberculosis :* why?
- More « exotic» cases
- We reached the study objective for the acute phase of the infection

Conclusions 2

- Patients are older, have more comorbidities, but less death cases and ICU stays
- Hospital length of stay is shorter: general trend in hospitals?
- What about sequels?
  - Analysis on going
  - Difficult to motivate investigators
  - It is the late objective, but not the least

Future

- Sequels



- Europe

Joining us : enceif@hotmail.com

Thank you for your attention