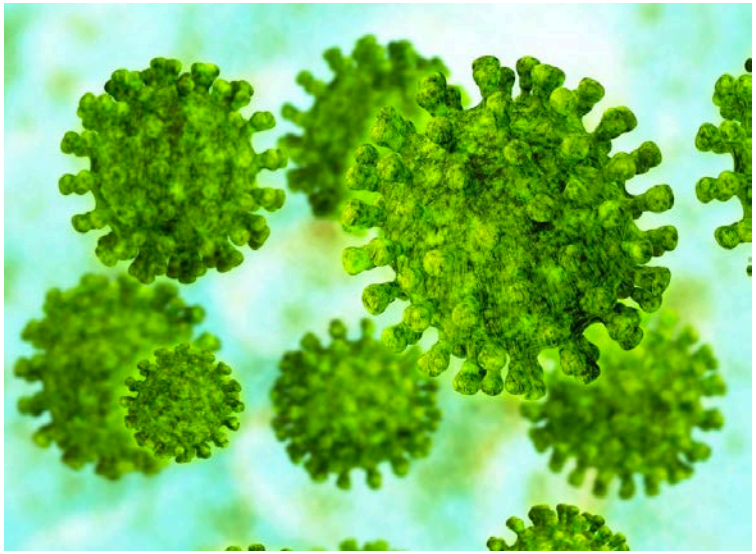
HOT TOPICS AND BREAKING NEWS IN ENCEPHALITIS

Alexandra Mailles
Santé publique France
JNI Lille, juin 2016

- Conflict of interest: none.

New viruses and encephalitis



VSBV-1

FRIEDRICH-LOEFFLER-INSTITUT
FLI
Bundesforschungsinstitut für Tiergesundheit
Federal Research Institute for Animal Health

Variegated squirrel 1 bornavirus
(VSBV-1)

https://openagrar.bmel-forschung.de/servlets/MCRFileNodeServlet/Document_derivate_00014101/Steckbrief_VSBV-1_20160301_engl2.pdf

VSBV-1

- 2011/2013, Germany : 3 patients with encephalitis admitted in the same hospital
  - Male, aged 62 to 72 y.o.
  - Sub acute onset
  - Bilateral crural veinous thrombosis in 3, pulmonary embolism in 2
- Evolution to coma, death after 2-4 months
- CSF results : variable
- Necropsy : oedema, perivascular lymphocyte infiltration, necrosis, microglial activation
- No etiology identified
- All 3 patients knew each others, breeded variegated squirrels imported from South America and had exchanged squirrels

Hoffmann B. et al, NEJM 2015

VSBV-1 : investigations and findings

- Identification of Variegated Squirrel Bornavirus 1
  → In brain samples for the 3 patients, and CSF and serum for one
  → In several organs of a squirrel

- Positive serology in squirrels of other species within *Callosciurinae* from zoo and private breeders in 5 German Lander
  https://www.fli.de/en/news/short-messages/short-message/?tx_news_pi1%5Bnews%5D=171&cHash=eea6fb9dcde2e5b85097e04c921cc123

- Investigations in humans
  – No other symptomatic cases
  – All family members negative in serology
  – Positive serology in another squirrel breeder, no symptoms : meaning ?

  Source : Denis Tappe, ECCMID 2016

→ Real emergence ? Medical and public health relevance ?

LGSV-1//KM114265/1993
PaBV-2/EU781967/2006
PaBV-2/FJ620690/2008
PaBV-1/JX065207/2001
PaBV-1/GU249595/2008
PaBV-4/JN035148/2009
PaBV-4/JN014948/2009
PaBV-4/JX065209/2008
PaBV-4/JN035149/2009
PaBV-4/JN014950/2009
PaBV-4/GU249596/2008
PaBV-4/JN014949/2009
ABBV-1/KF578398/2011
ABBV-1/KJ756399/2014
CnBV-1/KC464471/2011
CnBV-2/KC464478/2010
CnBV-3/KC595273/2012
VSBV-1/LN713681/2014
VSBV-1/LN713680/2014
BoDV-2/AJ311524/1998
BoDV-1/AJ311522/1980
BoDV-1/BDU04608/1929
BoDV-1/AJ311523/1994
BoDV-1/AB032031/1999
BoDV-1/AB258389/1997
BoDV-1/AB246670/2004

Elapid 1 bornavirus
Psittaciform 1 bornavirus
Waterbird 1 bornavirus
Passeriform 1 bornavirus
Variegated squirrel 1 bornavirus
Mammalian 1 bornavirus

Sciurus variagetoides

Hoffmann B et al, NEJM 2015

VSBV- 1
Unanswered questions

- Can VSBV-1 be responsible for less severe clinical presentations in humans ?

- Is VSBV-1 pathogenic in squirrels ? In which squirrels ?
- Are variegated squirrels the *real* reservoir ?

- Zoonotic transmission only ? Human to human transmission ?

- Transmission : Bite ? Air-borne ? Animal feces ?

- Specific risk factors in hosts ?

Other new discoveries in encephalitis patients

Zhou et al. Virology Journal (2015) 12:197
DOI 10.1186/s12985-015-0431-0

Virology Journal

SHORT REPORT Open Access

A novel gemycircularvirus in an unexplained case of child encephalitis

Next-Generation Sequencing for Diagnosis and Tailored Therapy: A Case Report of Astrovirus-Associated Progressive Encephalitis

M.-L. Frémond,[1,2] P. Pérot,[3] E. Muth,[4] G. Cros,[1,2] M. Dumarest,[3] N. Mahlaoui,[1,2,5,6] D. Seilhean,[7] I. Desguerre,[8] C. Hébert,[4] N. Corre-Catelin,[9] B. Neven,[1,2] M. Lecuit,[1,10,11] S. Blanche,[1,2] C. Picard,[1,6] and M. Eloit[3,4]

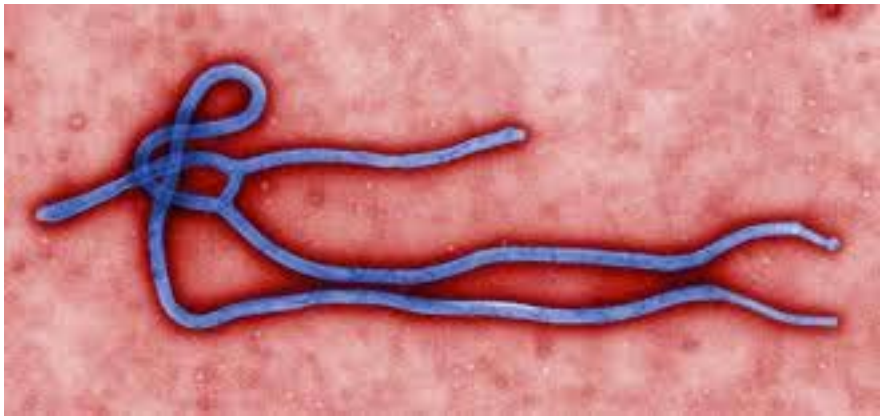
Molecular, serological and *in vitro* culture-based characterization of Bourbon virus, a newly described human pathogen of the genus *Thogotovirus*

Amy J. Lambert, Jason O. Velez, Aaron C. Brault, Amanda E. Calvert, Lesley Bell-Sakyi, Angela M. Bosco-Lauth, J. Erin Staples, Olga I. Kosoy

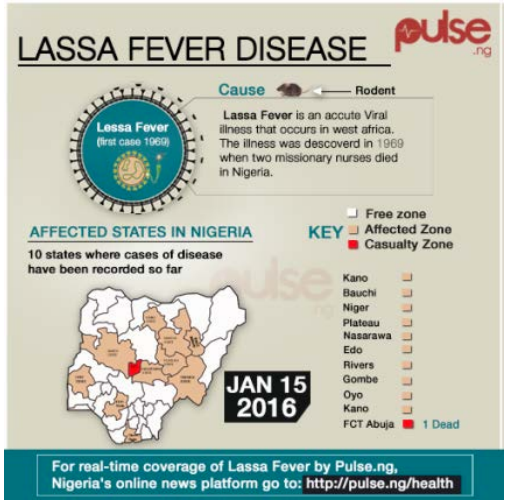
→ Obviously much more to discover

→ Uneasy interpretation of new viruses with regards to public health

« Old » viruses with recent neurological issues



Lassa fever virus



- Arenavirus, BSL4
  - Asymptomatic in 80%
  - Severe disease in 1/5 patient
  - Rare encephalitis cases reported (*Ikerionwu, J.Trop.Med.Hyg. 1978*)
  - Hearing loss frequent in survivors (25% - 30%)

- Endemic in West Africa, seasonal
- 2016 : major outbreak Nigeria, Benin, Togo
  - 657 cases in Nigeria
  - Imported cases in Germany with secondary cases, and in the USA *http://ecdc.europa.eu/en/publications/Publications/RRA-Lassa-fever-Germany-march-2016.pdf*

Lassa fever encephalitis in Sweden, April 2016

- Female patient, 73 y.o., 6-week stay in Liberia, exposed to rodents
- 6 days after return : fever, headaches, pain, diarrhea
- Admitted on D9 of symptoms: diagnosed with encephalitis of unknown cause
- PCR + for Lassa virus on D26 (PCR) → Isolated in reference hospital
- Recovered with hearing loss
- 74 contacts followed-up for 21 days : no secondary cases

→ Only standard protections during the acute episode

→ Lassa not always presenting as a viral hemorrhagic fever

→ Lassa not the first-line hypothesis for encephalitis in travelers but to be considered for endemic/epidemic countries

→ Exposure can go unnoticed

http://www.who.int/csr/don/8-april-2016-lassa-fever-sweden/en/

Ebola and the brain

- Unpreceded outbreak in West Africa 2014-16

- Neuro-Ebola ?
  - Neurological symptoms in case-series and case reports from previous outbreaks : limited number of cases, limited data, limited investigation
  - Recent papers suggest 30% have neurological complications

- Neurotropism is difficult to assess
  - Limited resources in affected countries
  - High number of patients in West Africa
  - Imaging/ EEG rarely available in Ebola treatment centers, or isolation facilities in the USA or Europe
  - LP and CSF analysis rarely performed in Ebola patients
  - Very severe disease, frequent multi-organ failure, devastating inflammation (“cytokine storm”) : Encephalopathy ? Viral encephalitis ? Vasculitis ?

Ebola and the brain : recent case reports

- Neurological symptoms occur in the second week of the disease (*Sagui E., CID 2015*)
- Metabolic disorders/sepsis associated in some patients, but ruled out in others (*Kreuels B., NEJM 2014 ; Chertow D., Annals Intern Med 2016)*
- Imaging carried out during the convalescent stage but still visible lesions *(Howlett P., EID 2016; Chertow D., Annals Intern Med 2016)*
- RT-PCR not systematically concordant in CSF and blood/plasma *(Howlett P, EID 2016)*
- Possible effect of compational therapy ? *(Uyeki TM, NEJM 2016)*

Ebola and the brain : neurological sequelae in survivors

- Prevail III, Liberia (preliminary results : *Bowen et al, AAN 2016)*
  - 82 patients, 6 months after onset
  - Neurological manifestations in all patients (mRankin)
    - Memory loss, headaches, weakness, depressed mood
    - Tremors and abnormal reflexes in 1/3 patients
    - Abnormal sen in1/3
    - Frontal release signs in 1/6

- Donka treatment center, Guinea (Qureshi CID 2015)
  - 105 patients
  - Memory loss 27%
  - Mood disorders 32%
  - Diziness 10%

Ebola and the brain: relapse with meningo-encephalitis

- Female patient, 38 yo, HCW with severe but « standard » Ebola disease in Jan. 2015, recovery, discharge

- Relapsed 9 months later : meningitis
  - meningitis signs, GCS 15/15, no uveitis
  - RT-PCR + in CSF and plasma, CT value CSF >>> plasma

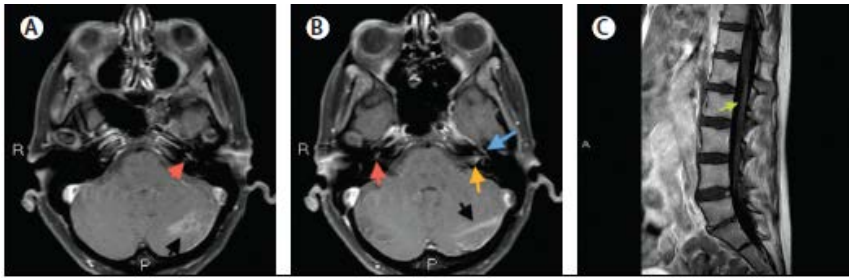
- Evolution : meningo-encephalitis
  - Seizures,
  - Double vision, speech disorders, cranial nerves palsies,
  - Decreased consciousness
  - Hypoventilation
  - Cerebellar signs

Jacobs M. et al, Lancet 2016

Ebola and the brain: relapse with meningo-encephalitis

- Late evolution
  - Improvement of consciousness but
  - Hearing loss, dizziness, tinnitus, fatigue
  - Bladder voiding disorders, leg weakness
  - Discharge at D52 with persisting neurological signs

- Imaging : MRI on D31
  - Brainstem, left cerebellum, cauda equina



- Virology
  - CT values always higher in CSF
  - Infectious virus in CSF but never in blood

→ Real meningo-encephalitis as the presentation of Ebola disease relapse
→ CNS as the main site of replication ?

Jacobs M. et al, Lancet 2016

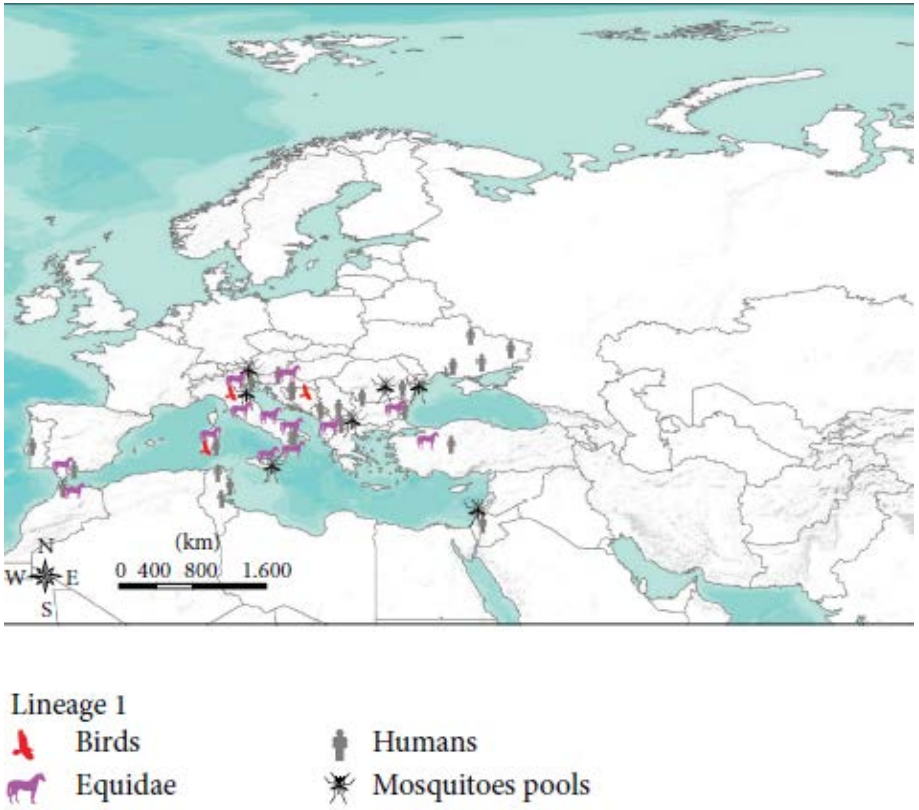
Ebola and the brain

- Ebola encephalitis does exist but might not be responsible for all neurological presentations observed
- More clinical research needed to distinguish between encephalitis / encephalopathy and neurological sequelae/PTSD
- Neurological management in the field needs to be anticipated for future outbreaks
- How to make cerebral imaging feasible and available in Ebola patients ?
- Not a major cause of encephalitis in travelers, HSV, malaria and many others are more probable

Ongoing and possible future threats

West Nile virus in Europe

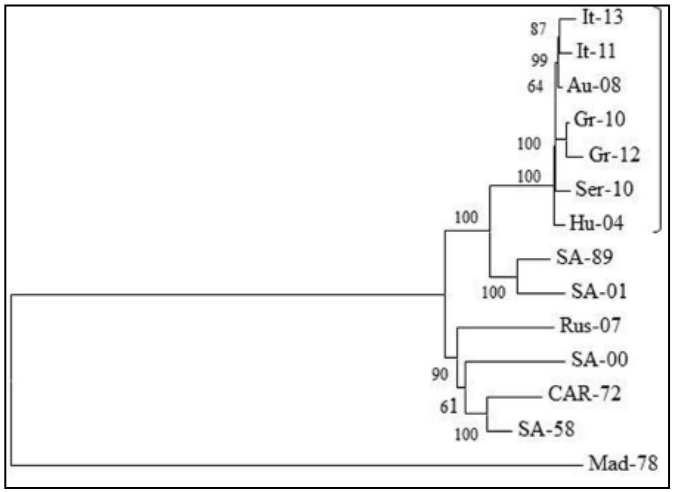
- Co-circulation of lineages 1 and 2
- Historically lineage 1
- Major outbreak in Romania in 1996
- Recurrent clusters in Balkans, Russia, Italy
- Viral circulation in birds, horses, humans
- In the EU, surveillance under the ECDC

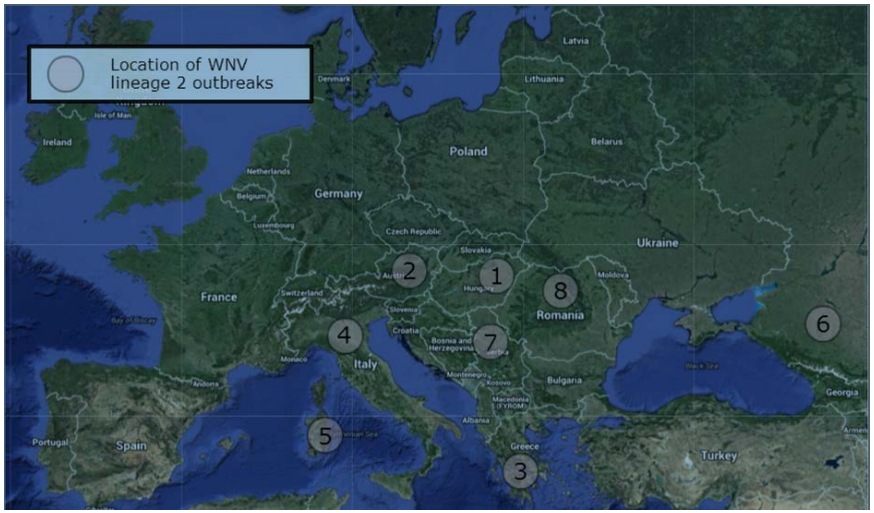


Di Sabatino D. et al, BioMed Research International 2014

West Nile virus in Europe

- Identification of lineage 2 in 2004 in Hungary in birds
- First outbreak related to WNV lineage 2 in humans in Greece in 2010
  - 262 cases: 197 WNND, 33 deaths
- Later identification in Austria, Italy, Sardinia, Romania, Serbia
  - Human cases, WNND
  - Limited impact on horses
- Phylogeny suggests over-wintering and spread of the 2004 Hungarian strain
- High potential for future outbreaks in Europe





Hernandez-Triana et al, Frontiers in Public Health 2014

Chikungunya encephalitis

- Before 2005 :
  - Mild febrile disease, considered self limited,
  - Under-estimation of arthritis burden
  - Rare neurological cases

- Outbreak in La Reunion island in 2005/6
  - Estimated 300 000 cases
  - 57 neurological cases
    - → incidence 8.6/100 000 hbs (95IC 6.9 – 10.4)
    - → 24 encephalitis/33 encephalopathies
    - → CFR 10%

Gerardin et al. Neurology 2016

Chikungunya encephalitis (2)

- Early features
  - No specificity of clinical features
  - Infants < 1 y.o. and adults
  - More severe neurological disease in adults

- 3-year follow-up (10 adults/13 infants)
  - 1 adult died with ADEM 3 months after discharge
  - 4/10 adults with apparent full recovery
  - 1/13 infants developed cerebral palsy *Gérardin P. et al. Neurology 2016*
  - 4/13 infants with poor development quotient

- Neurological presentations also reported in French West Indies
  - 3 encephalitis cases / 160 000 estimated total cases *(Crosby L. et al, Int J Inf Dis 2016)*
  - No report from other epidemic countries ...
  - Under-diagnosis ?
  - More virulent strain ?

Last but not least…

www.nature.com/scientificreports

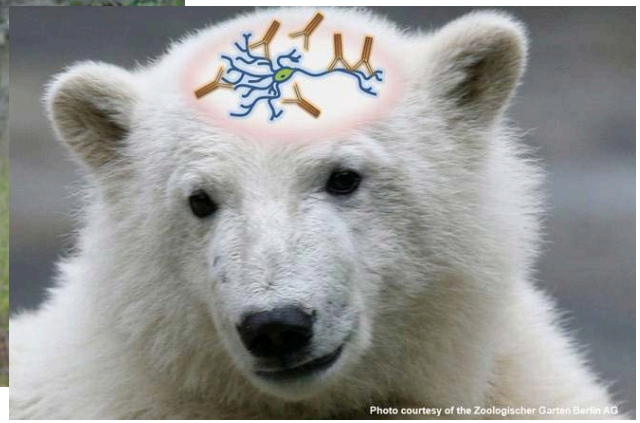
SCIENTIFIC REPORTS

OPEN

Anti-NMDA Receptor Encephalitis in the Polar Bear (*Ursus maritimus*) Knut

Received: 10 December 2014
Accepted: 06 July 2015

H. Prüss[1,2,*], J. Leubner[1,*], N. K. Wenke[1], G. Á. Czirják[3], C. A. Szentiks[3] & A. D. Greenwood[3]



Take-home points

- Encephalitis is a sentinel of emerging/spreading infections
- Most emerging/ re-emerging threats are vector-borne diseases: prevention first !
- Exotic pets will ever bring new threats
- New insights in viral hemorrhagic fevers
- All new causes are rare compared to HSV and do not have specific treatment
- Expect the unexpected !

Thank you for your attention