Epidemiology of sequelae following infectious encephalitis

And the role of the infectious diseases specialists

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Why talk about post-encephalitis sequelae in a course of the ESCMID ?

- Because sequelae are frequent and may be invisible
- Because an early assessment is important
- Because rehabilitation has to be anticipated.... during the infectious course of the disease

Sequelae and Outcome

- Individual aspects
  - Objective symptoms and subjective complaints
  - Impairment, disability and handicap
  - Different consequences according to the occupation, way of life and environment

- Public health aspect
  - Sequelae participate in the burden of encephalitis
  - Access to rehabilitation
  - Availability of specific facilities and HCW

  → Public Health policies

Data about post-encephalitis sequelae

- Few case-series, many case-reports

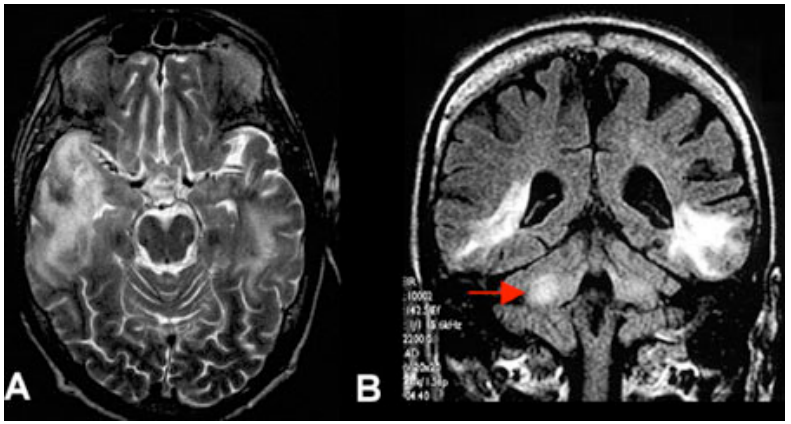
- Important limitations
  - Relevance of assessment tools
  - Neuro-invasive vs encephalitis
  - Evaluation limited to those evaluable
  - Not all domains evaluated in all case-series
  - Various delays between onset and assessment

→ Crude figures to be taken cautiously

Herpes simplex encephalitis sequelae

- Dramatic improvement thanks to Aciclovir (ACV) since the early 80's
  - Lower case-fatality rate
  - Still severe long-term persisting symptoms

- Survival and sequelae directly correlate with early ACV treatment



HSV : cognitive sequelae

- Major issue : > 70 % of patients affected *(Utley 1997)*
- Memory
  - Impaired in 30- 70 % *(Mc Grath 1997, Mailles 2012)*
  - Disorientation in space and time
  - Anterograde and retrograde memory
  - All domains : visual, verbal, delayed memory
- Attention disorders, lack of concentration 67% *(Mailles 2012)*
- Executive functions impaired in 41% *(Utley 1997)*

HSV : cognitive sequelae (2)

- Language : 30-40% patients *(Utley 1997, Mailles 2012)*
  - Aphasia
  - Dysarthria
  - Anosmia

- Intelligence
  - Full scale IQ : 23% with mild deficit *(Utley 1997)*
  - Children : mental retardation in 50% after 5 years *(Michaeli 2014)*

HSV : neuropsychiatric sequelae

- Major issue
- Behavioral changes : 45-50 % *(Mc Grath 1997, Mailles 2012)*
  - Possible denial from patients and caregivers
  - Irritability
  - Aggressiveness : violent outbursts, physical violence
  - Disinhibition, inappropriate laughs or speech
  - Emotional lability
  - Children : ADHD 66%, tic disorders 50% *(Michaeli 2014)*

HSV : neuropsychiatric sequelae (2)

- Depression, Anxiety 17% *(Mc Grath 1997)*
  - Sleeping disorders
  - Lack of motivation or commitment
  - Suicide attempt (rare)
- Most severe cases
  - Indifference
  - Kluver-Bucy syndrome
  - Spatial neglect
- Consequences on care-givers

HSV : neurological sequelae

- Unfrequent compared to other agents, and compared to cognitive and behavioral sequelae following HSE

- Motor deficit
  - Paresis 6% *(Mailles 2012)*
  - Limb paralysis
  - Weakness

- Ataxia : 2 of 4 patients (*Berlit 1988*)
- Seizures 3% to 5%

HSV : functional outcome

- Severe presentations with patients in vegetative state still reported despite ACV

- Post ACV data
  - Severe disability : 13 to 20% *(Raschilas 2002, Sili 2014, Mc Grath 1997)*
  - Return to work 75% after 3 years *(Mailles 2012)*
  - Children : learning issues *(Mc Grath 1997)*

Flaviviruses

- Tick-Borne Encephalitis virus
- West Nile virus
- Japanese Encephalitis virus
- Tropism for thalamus, basal ganglia, brainstem
- Most studies enrolled encephalitis, encephalomyelitis, meningitis, non neuroinvasive infections

Tick-Borne Encephalitis (TBE)

- Reports about sequelae in case-series patients since USSR → possible different management over time

TBE : cognitive sequelae

- Globally : cognitive impairment in up to 42% *(Czupryna 2011)*
  - some patients described as Alzheimer-like patients *(Gustav-Rothenberg 2008)*
  - no significant differences between encephalitis and other presentations on a long term in children *(Fowler 2013)*

- Intelligence in children *(Fowler 2013)*
  - global IQ significantly lower than the average
  - decreased ability to solve problems
  - problems with organization of the environment and time

TBE : cognitive sequelae (2)

- Memory impairment : 20 to 35 % *(Lämmli 2000, Gustav-Rothenberg 2008, Mickiene 2002)*
  - Specifically : working memory significantly below the average in children ($p<0.001$) *(Fowler 2013)*

- Attention and concentration disorders : 20 to 42% *(Lämmli 2000, Mickiene 2002, Laursen 2003, Karelis 2012)*

→ improvement after 1 year for concentration disorders but not for memory *(Mickiene 2002)*

TBE : neuropsychiatric sequelae

- Up to 44% patients with severe presentation require psychiatric therapy after discharge *(Czupryna 2011)*

- Depression and anxiety *(Lämmli 2000, Czupryna 2011, Karelis 2012)*
  - Depression 29%
  - Anxiety 6% to 11%
  - Sleep disorders 13% to 42%

- Behavioral disorders
  - Mood disorders in 47 % *(Karelis 2012)*
  - Irritability 16% *(Lämmli 2000)*
  - Emotional instability 19% *(Mickiene 2002)*

TBE : neurological sequelae

- Focal deficit 24%-27% *(Kaiser 1999, Lammli 2000, Mickiene 2002, Karelis 2012, Czupruna 2011)*
  - Up to 14% shoulder girdle paralysis
  - Visual accommodation deficit 19%
  - Facial palsy 5%
  - Paresis in the extremities of limbs 20%
  - Hemiparesis 3%
  - Spinal nerve paralysis 2%

- Parkinsonism, tremors 5% to 10% *(Lammli 2000, Laursen 2003, Mickiene 2002)*
  - significant improvement over the first year

TBE : neurological sequelae (2)

- Balance disorders
  - Ataxia 21 to 24% *(Lammli 2000, Czupryna 2011)*
  - Diziness up to 40% *(Lammli 2000, Karelis 2012)*

- Movement coordination disorders 39% *(Karelis 2012)*
- Sensory disorders *(Lammli 2000)*
  - photophobia 18%
  - hearing loss 11%

- Muscle wasting and weakness 16 to 20% *(Lammli 2000, Laursen 2003, Karelis 2012)*

TBE : post-encephalitis subjective complaints and functionnal outcome

- Subjective complaints
  - Fatigue 49% *(Lammli 2000, Mickiene 2002)*
  - Headache up to 58% *(Karelis 2012)*

- Functionnal outcome
  - 50 - 60% full recovery after 1 year *(Gunther 1997, Mickiene 2002)*
  - Need for everyday assistance 14% *(Karelis 2012)*
  - Walking troubles 18%, writing difficulties 14% *(Lammli 2000)*

West Nile virus

- Most papers published following North-American outbreak, and more recently Greece

WNV : cognitive sequelae

- Subjective cognitive complaints : no difference according to clinical presentation (WNM, WNE, WNF)

- Objective assessment of cognitive decline *(Sejvar 2008)*
  - encephalitis > meningitis but no significant difference after 18 months
  - 56% patients impaired in at least one cognitive domain after 1 year

- Worst cognitive disorders in patients with neurological sequelae, correlation with age

WNV : cognitive sequelae

- Memory impairment
  - 40% in unselected patients
  - 40 to 60% in WNND after 18 months *(Klee 2004, Carson 2006, Anastasiadou 2013)*
  - Persistence over time : 11% at 1 year, 9% at 8 years *(all clinical presentations, Murray 2014)*

- Attention/concentration :
  - Lower scores than controls and higher latency to response (*Sejvar 2003*)
  - 38% at 18 months (*Klee 2004, Sadek 2010*)

WNV : cognitive sequelae

- Executive functions impaired in 36%, severely impaired in 15% *(Carson 2006, Sadek 2010)*

- Cognitive slowness in 56% (*Sadek 2010)*
  - tasks processing following visual recognition
  - reasoning and planning : longer delay in solving problems tests

WNV : neuropsychiatric sequelae

- Depression, anxiety
  - 21 to 31% after 1 year, major depression for half of them *(Murray 2007)*
  - 47% at 8 years *(Nolan 2012)*
  - Sleep disorders : 47% after 18 months *(Klee 2004)*

- Personality change 45% *(Klee 2004, Murray 2007)*
  - Increased irritability, anger
  - Decreased social life
  - Increased sensitivity

WNV : neurological sequelae

- Ataxia : 43% at 18 months *(Klee 2004)*
- Tremors, « parkinsonism » 23% *(Sadek 2010)*
- Motor deficit : 48% *(Sadek 2010 ,Anastasiadou 2013, all WNND)*
  - Paraparesis, tetraparesis
  - General muscle motor weakness
  - Limb paresis or paralysis

  → irreversible when denervation or motor neuron loss

- Hearing loss 13% in Greek patients *(Anastasiadou 2013)*

WNV : neurological sequelae

- Possible improvement over time *(Murray 2014, all WNND)*
  - Ataxia — 15% at 1 year, 4% at 8 years
  - Limb paralysis — 9% at 1 year, none at 8 years
  - Tremors — 5% at 1 year, none at 8y
  - Dizziness — 5% at 1 year, none at 8y

Japanese Encephalitis sequelae

- Children +++, elderly
- More data than other agents, up to 27 years after onset
- Sequelae are more disabling in rural settings

JE : cognitive sequelae

- Short-term memory impaired in 30% of children 6 months after onset *(Ooi 2008)*
  - Still present in 5% by 5 years *(Sarkari 2012)*
- Inappropriate judgement and reasonning
- Inability to count and use currency *(Sarkari 2012)*
- Intelligence :
  - 28% subnormal, 18% with global IQ < 70 *(Ding 2007)*
  - Significant improvement in most patients by 5 years *(Sarkari 2012)*

JE : neuropsychiatric sequelae

- Behavioral disorder
  - 70% at discharge *(Sarkari 2012)*
  - 38 to 50% after a couple of months *(Maha 2009, Ooi 2008)*
  - Psychosis
  - Social withdrawal

- Depression in a third of patients, but 99% recovered by 5 years

- Emotional instability in 40%, but 98% cured by 5 years

JE : neurological sequelae

- Motor deficits
  - At discharge 21% to 38% *(Kakoti 2013, Rayamajhi)*
  - Limb paralysis in 31% → 93% recovered by 14y *(Sarkari 2012)*
  - Cortical-spinal deficits in 69% → 95% recovered by 14y

- Movements disorders *(Kalita 2009, Sarkari 2012)*
  - Hyperkinetic movements 21% → all improved but not recovered by 14 years
  - Parkinsonism, tremors, dystonia 56% → 97% improved but not recovered by 14 years

JE : neurological sequelae (2)

- Speech disorders *(Sarkari 2012)*
  - Mixed cognitive and neurological deficits in 78% at discharge
  - Constant improvement in most patients over time *but*
  - Persisting dysarthria and monotonous speech in 44% by 14 years, and

- Seizures 6%-8% *(Ding 2009, Ooi 2008)*

JE : Functional outcome

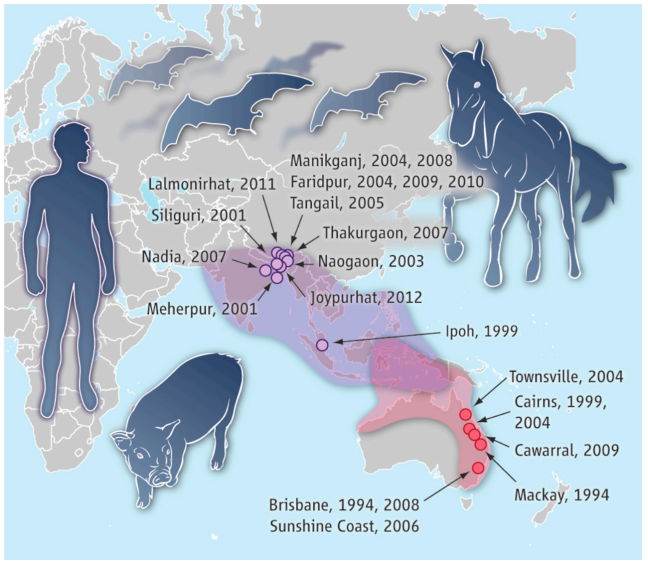
- 25% patients dependant on caregivers after 1 year *(Maha 2009)*

- 15% abnormal ADL scores,

  6% near incapacitation several years after discharge *(Ding 2007)*

Nipah

- Emergence in the late 90s
- Malaysia and Bengladesh



Nipah virus : Malaysia outbreak, 1999

- At discharge : 14/91 (15%) had cognitive impairment *(Goh 2000)*
- 2 years after discharge *(Ng 2004)*
  - Attention deficit 3/8,
  - Impaired immediate and delayed memory 5/8 ,
  - Back to premorbid intellectual function : 5/8, below expected level : 3/8
- Neuropsychiatric sequelae (after 2 y)
  - Major depression 5/9, difficulties coping with uncertainty 4/9
  - Personality change 2/9,
  - Chronic fatigue syndrome 2/9
- 5% of all patients remained vegetative (8% of survivors) *(Goh 2000)*

Nipah virus : data from Bengladesh

- Neurological sequelae *(Sejvar 2007)*
  - Cranial nerves palsies 4/22,
  - Myoclonus 3/22,
  - Ataxia or gait problems 3/22 ,
  - Delayed -onset abnormalities up to 1 year : oculomotor dysfunction in 3, cervical dystonia in 1.

- Subjective complaints *(Sejvar 2007)*
  - subjective cognitive complaint 10/22 (memory, attention)
  - mood problems 13/22,
  - fatigue 15/22

Outcome in cohorts of unselected patients

- Sweden, 2000/2004, 71 children *(Fowler 2010)*
  - Sequelae in 54% after 5 years
- England, 2005/2006, 198 patients *(Granerod 2010)*
  - Poor outcome in 35% after 6 months (*M. tuberculosis*, HSV, VZV ++)
- France 2010, 176 patients *(Mailles 2012)*
  - Poor outcome 39% after 3 years (HSV +++++++)

Perspective: rehabilitation

- Start early
- Complete assessment (challenging)
- Need for patient's participation
- Define the objective with the patient
- Take into account the caregiver
- Emphasize any improvement to maintain the patients' commitment

Conclusions and perspectives

- High burden during acute infectious phase of encephalitis
- Long-term severe sequelae are common → close monitoring and follow-up
- Need for close collaboration between ID, neurology and rehabilitation specialists since the onset of the disease