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
  – 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

  – 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% *(Lamml 2000, Laursen 2003, Mickiene 2002)*
  – significant improvement over the first year
TBE: neurological sequelae (2)

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

- **Movement coordination disorders** 39% (*Karelis 2012*)

- **Sensory disorders** (*Lamml 2000*)
  - Photophobia 18%
  - Hearing loss 11%

- **Muscle wasting and weakness** 16 to 20% (*Lamml 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 reasoning

• 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 Bangladesh
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 Bangladesh

- **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

  - 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