Clinical Features of West Nile Fever

Tomas Jelinek
MD PhD DTM&H FFTM FRCP(Glas)

- Medical Director, Berlin Center for Travel & Tropical Medicine
- Scientific Director, Center of Travel Medicine, Düsseldorf
- Ass. Professor, Institute for Social Medicine, Epidemiology and Health Economics, Charité, Berlin
- Consultant, Armed Forces Hospital Berlin
- Expert Consultant to WHO

West Nile Virus (WNV)

- Flavivirus (JE antigen complex)
  - Single strand RNA Virus (10-11 KB)
- Transmission by various mosquitoes
  (Culex spp.)
  - rarely also diaplacentar, transfusion, Tx
- Birds (> 110 species) are reservoir
- Mammals can become infected, mostly without symptoms
- Severe disease in horse an man
West Nile Fever

- Manifestation index approx. 1:5
- Incubation period 2-14 days
- Mostly self limited, febrile, flu-like disease (3-6 days)
- Ca. 1 case of encephalitis/meningitis per 150 infections (?)
- Severe neurological disease more frequent >50y
WNV: Manifestation

- Encephalitis (1:5000-1:150?)
- Neurological symptoms
- Unspecific symptoms
- Unspecific symptoms
- Infected persons

West Nile Virus Transmission Cycle

- Mosquito vector
- West Nile virus
- Incidental infection
- Bird reservoir hosts
- West Nile virus
- Incidental infection
- West Nile virus
**WNV: Alternative Transmission**

- Mother-Child-Transmission
- Lactation
- Transfusion
- Transplantation
- Trans ovaries (Mosquito)

**West Nile Fever - Epidemiology**

- WNV first isolated in Uganda (1937)
- Endemic in Africa, West Asia (i.e. Israel), Central Asia
- Epidemics, e.g. in Rumania (1996), Czechia (1997), Russia (1999)
- Outbreaks in horses, e.g. in Italy (1998) and France (2000)
West Nile Fever
Relevance in Endemic Areas (Egypt 1956)

- Sero prevalence up to 74%
- Predominantly asymptomatic
- Manifestation in early childhood with unspecific symptoms
- Occurs during summer months
- Humans and horses are dead-end hosts (short viremia)
- Birds are most important amplification hosts
- Sero prevalence in humans correlates with that in crows
- Main ecological factors
  - Population density of birds and mosquitos
  - Population density of humans
  - Intensity of agriculture

1937 – Isolation & Identification of WNV in West-Nile-District, Uganda

Until Mid-1990s – occasional outbreaks of mild febrile disease in groups of soldiers, children or healthy adults in Israel and Africa
Since Mid-1990s:
increase of frequency and severity of disease

          with several hundred severe cases each

Since 1999 regularly outbreaks in the USA
West Nile Virus Spread in USA

- August 1999: First cases in New York
- Import probably with infected birds
- Local transmission by Culex mosquitos
- Spread by birds (>110 species)

Cumulative Cases:

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Deaths</th>
<th>States</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999/2000</td>
<td>83</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>2001</td>
<td>149</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>1/11/2002</td>
<td>3399</td>
<td>193</td>
<td>33</td>
</tr>
</tbody>
</table>
West Nile Virus in USA 2003

Total 9585 Cases
252 Deaths

West Nile Virus in USA 2004

Total 2237 Cases
73 Deaths
Most WNV-infections are asymptomatic (approx. 80%)!
Approx. 1/5 of infections (20%) are mild
Approx. 1/150 severe neurological disease
Incubation period: 3-14 days
Duration of disease in mild cases 3-6 days

Febrile disease with sudden onset, accompanied by:
• Malaise
• Headache, retroorbital pain
• Nausea, vomiting
• Arthralgia, myalgia
• Exanthema
• Lymphadenopathy
Clinical Presentation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>NYC (n=59)</th>
<th>Romania (n=393)</th>
<th>Israel (n=233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>90%</td>
<td>91%</td>
<td>98%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>51%</td>
<td>53%</td>
<td>31%</td>
</tr>
<tr>
<td>Kephalgia</td>
<td>47%</td>
<td>77%</td>
<td>58%</td>
</tr>
<tr>
<td>Disorientations</td>
<td>46%</td>
<td>34%</td>
<td>40%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>27%</td>
<td></td>
<td>19%</td>
</tr>
<tr>
<td>Exanthema</td>
<td>19%</td>
<td></td>
<td>21%</td>
</tr>
<tr>
<td>Meningism</td>
<td>19%</td>
<td>57%</td>
<td>29%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>17%</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>Coma</td>
<td></td>
<td>13%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Death rates in hospitalised patients:

- Romania 1996 = 4% 
- Israel 2000 = 15%

Patients above 70y:

- Romania 1996 = 15% 
- Israel 2000 = 29% 
- Michigan 2002 = 35% (Emig & Apple CID 2004)
Possible reasons for increase of cases numbers and disease severity:

- Virus variation → different virulence?
- Demographic changes (older patients)?
- Waning immunity?
- Underlying chronic diseases?

Clinical signs of WNV-infection are determined by amount of CNS invasion

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**Signs & Symptoms**

- Fever
- Fatigue
- GI symptoms
- Maculo-papular or morbilliform Rash (rare)
- **Altered mental state**
- **Encephalitis > aseptic meningitis**
Signs & Symptoms

- **severe muscle weakness** and „acute flaccid paralysis“ (not in Europe!)

→ During 1999-outbreak in NYC: 27% muscle weakness and & 10% flaccid paralysis
  

DDx.: Guillain-Barré-Syndrome
  
  Ahmed et al.: *Neurology* 2000

BUT: axonal lesions plus CSF-pleocytosis = uncommon in GBS!

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Signs & Symptoms

- Acute flaccid paralysis = **polio-like**!
- Asymmetric weakness
- Areflexia, no pain
- NO sensoric effects
  
  → Damage of spinal cord cells
  
  → Occurs during acute stage of disease in combination with fever, leucoctosis and encephalitis (unlie GBS)
„Polio-like“ Flaccid Paralysis

Michigan 2002 (Emig & Apple CID 2004):

- Adults < 65 years → rather monoparesis
- Adults > 65 years → rather para- or tetraparesis

Limited viral spread in the spinal cord of younger patients?

Patients with encephalopathy (altered consciousness) show increased death rate ↔ aseptic meningitis (stiff neck + CSF-pleocytosis)
• Respiratoric paralysis
  ➔ Neuro muscular weakness (“iron lung”)
  ➔ Diaphragmal-elevation, CO2-retention
  ➔ Dysphagia and Dsyarthria are early warning sings
    (OR=60)
  ➔ Inflammation of brain stem and cervical spinal cord ➔ MRT!
  ➔ Case series in USA (n=12): median intubation time 66d
• Bladder incontinence

• Further neurological symptoms
  – N. opticus neuritis (Anninger & Lubow CID 2004)
  – Abnormalities of further cranial nerves
  – Ataxia and extrapyramidal signs
  – Polyradikulitis
  – Myelitis
  – Seizures
MRT: increased signal in striatum & post. thalamus

Case reports with:

- Myocarditis
- Pancreatitis
- Fulminant Hepatitis
Different manifestations in children??

5 children during the Houston-Outbreak:
• Seizures
• Maculo-papular exanthema
• Acute flaccid paralysis
• Diarrhoea

KM Lillibridge, 4th internat. conference on
Emerging Infectious Diseases, Altanta, März 2004

Significant risk factors for severe neurological
disease:
• Old Age (>50 years)

NYC:
Increased risks compared to 0-19 years:
Persons 50-59 years → 10-fold
Persons > 80 years → 43-fold

Patients with chronic diseases: viraemia and severity of disease:

- **Haematological disease > solid cancer**
  

- **Immunosuppression (HIV?)**
  
  Szilak & Minamoto *N Eng J Med* 2000

- **Diabetes mellitus:**
  
  NY-1999: RR= 5,1 (95%CI 1,5-17,3)
  
• Hypertension & hypertension inducing drugs (cocaine):
  → increased permeability of blood brain barrier
  → increased viral neuro-invasion

2002-outbrak in Houston (n=90):
  → 52% art. hypertension = significantly (p<0.005) associated with encephalitis
  → 17% cocaine-users

KM Lillibridge, 4th internat. conference on Emerging Infectious Diseases, Altanta, März 2004

<table>
<thead>
<tr>
<th>Risk Factors for death, meningo-encephalitis(^1), or muscular weakness(^2):</th>
<th>NY-State (n=59)</th>
<th>Romania (n=393)</th>
<th>Israel (n=233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 J.</td>
<td>8.8 (1.1-68)</td>
<td></td>
<td>13.5 (4.5-39)</td>
</tr>
<tr>
<td>D. mellitus</td>
<td>5.1 (1.5-17.3)</td>
<td>2.9 (0.58-16)(^1)</td>
<td>2.0 (0.9-4.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.1 (0.3-12)</td>
<td>1.4 (0.49-4)(^1)</td>
<td></td>
</tr>
<tr>
<td>Immunosupp.</td>
<td>1.6 (1.0-2.6)(^2)</td>
<td></td>
<td>3.1 (1.0-9.5)</td>
</tr>
<tr>
<td>Ribavirin-Thx</td>
<td></td>
<td></td>
<td>6.7 (3.0-15)</td>
</tr>
<tr>
<td>Stayed outdoors &gt;6h</td>
<td></td>
<td>5.6 (1.9-16)(^1)</td>
<td></td>
</tr>
</tbody>
</table>
When to suspect WNV

- Encephalitis / aseptic meningitis in persons > 50y in summer or autumn (USA)
- Local activity of WNV (death birds), local human cases (outbreak), history of travel to endemic areas
- BUT: all-year transmission in some areas!
- Cases in all age groups!

DDx

- HSV-1 Encephalitis Therapy!
  (Herpes labialis? Abnormalities in temporal lobes: EEG, CT/MRT)
- Enterovirus aseptic meningitis
  (Freshwater exposure? Diarrhoea? No confusion)
- Other arboviral encephalitis:
  Japanese Encephalitis, St. Louis Encephalitis, Western Equine, …
Lab Results

- Blood Count:
  - Leucocytes: normal or slightly increased
  - Lymphocytopenia,
  - Occasional anaemia
  - SGOT, SGPT ↑
- Hyponatriaemia (esp. with encephalitis)
- CSF: lymphozytic pleocytosis with Leucocyte count between 0 and 1782 cells/mm³
  Total serum protein ↑↑(51-899 mg/dL), glucose normal

Therapy / Management

Supportive
- Hospitalisation
- i.v.-fluids
- Ventilation
- Prevention of secondary infections (antibiotics)
**Therapy / Management**

**Ribavirin and α2b-Interferon**
- In Israel: higher mortality in patients with ribavirin than without! Patient selection?
  - Chowers et al. *Emerg Infect Dis* 2001

**Intravenous Immunoglobulin (IVIG)**
- Best results 4-6 days post infection! Few case reports
  - Haley et al. *CID* 2003

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**Clinical Outcome**

1 year after the 1999-outbreak in NYC:
- Fatigue 67%
- Memory impaired 50%
- Difficulties walking 49%
- Muscular weakness 44%
- Depression 38%

New York Dep. of Health, 2001
Summary

• Since mid-90s WNV outbreaks with high proportion of severe disease
• Risk factors: age, diabetes mellitus, immunosuppression, hypertension
• Clinical signs are dominated by falccid paralysis and/or encephalitis, meningitis
• WNV is most certainly underdiagnosed
• No specific therapy

Questions?