Chikungunya

Clinical features and complications

Prof Fabrice SIMON, MD, PhD
Department of Infectious Diseases and Tropical Medicine
LAVERAN Military Teaching Hospital - Marseille - France
Conflict of interest

• Collaboration with Valneva on a vaccine candidate
Chikungunya, two diseases in one

- **Arthropod-borne virus**
  - Transmitted by *Aedes* spp. mosquitoes

- **Alphavirus**
  - 3 lineages
  - Strong arthrotropism

- **Biphasic disease**
  - Fever & arthralgia at acute stage
  - Chronic rheumatic and general disorders

- **Long-term burden in public health**

Chikungunya ≠ dengue
The natural history of chikungunya disease: three stages

**Acute**

* D1 to D14
  * Approximately 60–80% spt

**High viremia to D5-D7**

**Intense inflammation**

Acute stage: frequently symptomatic

- > 70% of symptomatic cases in Comoros archipelago, Reunion and India, 2005-2006
- 82% asymptomatic in Philippines, 2014
- 58.3% asymptomatic children in Managua, Nicaragua; 2014
- 15.7% of asymptomatic blood donors in French West Indies

Kumar et al., 2011, Sergon et al. 2007, Sissoko et al., 2008
Yoon et al 2015, ; Kuan et al. 2016
Leparc-Goffart, personal communication
Acute stage: common features

- Fever (90-96%) : high, 2-4 days
- Multiple arthralgia +/- arthritides (95-100%) : the CHIK signature
  ➔ Brutal disability in daily life
- +/- other non severe manifestations
- Spontaneous mild to complete improvement after 10-12 days, or not…

Hochedez et al. Eurosurveillance 2007, 12: 1
Multiple joint involvement

- Bilateral, symmetrical, distal > 10 joints
- Synovitis + periarticular edema + tendonitis +/- joint effusion
- Less frequent in the elderly patients
Other common clinical manifestations

Frequent varied symptoms outpatients: 
- *cutaneous* 50%, *digestive* 40%
Common skin manifestations

**Maculo-papular exanthema**

Coll. F Simon

**Diffuse hyperemia**

Coll. F. Simon

**Facial oedema**

Coll. F Simon

**Distal subcutaneous oedema**

Coll. F Simon
Brutal multiple pain and disability

- **Outbreak in Comoros, 2005** (seroprevalence: 63%)

  ≈ 80% of CHIK-infected patients hospitalized/confined at home (mean: 6 days)

*Queyriaux et al. Lancet Infect Dis. 2008;8:2-3*
Atypical hospitalized, complicated or severe cases

- **Reunion island, Outbreak 2005-2006**
  - About one third of the population infected
  - “Rare” complications

---

**Economopoulou et al Epidemiol. Infect. 2008**
Mother-to-child transmission

• **Per-partum viremia** (7 days before - 2 days after delivery)
  - 50% vertical transmission
  - No protection by caesarian section protection

• **Neonatal infection within the first week of life**
  - Lethargy, fever, poor feeding, edema, erythrodermia followed by skin peeling

Robin et al Eur J Pediatr 2010
Fritel X et al. Emerg Infect Dis. 2010
Neonatal chikungunya

- **50% with severe infection**
  - High lethality rate
  - Hemorrhagic fever
  - Bullous skin lesions
  - Multivisceral deficiency
  - 50% encephalitis with 50% permanent disabilities and altered intellectual quotient in survivors

Gérardin et al. PLoS Negl Trop Dis 2014
Robin et al. Eur J Pediatr 2010
Fritel X et al. Emerg Infect Dis. 2010
The harmful partners of CHIKV in adults

- **Underlying diseases +++**
  - Chronic organ failure (heart, kidney, lung) → decompensation
  - Auto-immune disorders (systemic lupus)
  - And/or overwhelming CHIKV infection

- **Decubitus complications (elderly)++**
  - Thrombosis, deconditioning, ulcers

- **Iatrogenic +++**
  - Drug misuse and overuse
  - Hepatic, cutaneous or renal toxicity, diabetes under steroids

- **Co-infections +**
  - Dengue, malaria, leptospirosis, bacterial sepsis
<table>
<thead>
<tr>
<th>Complications due to CHIKV plus cofactors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEUROLOGIC</strong></td>
</tr>
<tr>
<td>Stroke, epilepsy</td>
</tr>
<tr>
<td><strong>RENAL</strong></td>
</tr>
<tr>
<td>Rhabdomyolysis, dehydration, exacerbation of preexisting chronic renal failure, NSAIDs</td>
</tr>
<tr>
<td><strong>HEPATIC</strong></td>
</tr>
<tr>
<td>Alcohol, chronic viral hepatitis, cirrhosis, acetaminophen</td>
</tr>
<tr>
<td><strong>CARDIAC</strong></td>
</tr>
<tr>
<td>Exacerbation of preexisting cardiopathy, myocardial infarction, arrhythmia</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
</tr>
<tr>
<td>Thrombosis, pulmonary embolism, cardiac failure, asthma or chronic obstructive pulmonary disorder decompensated, bacterial pneumonia</td>
</tr>
<tr>
<td><strong>CUTANEOUS</strong></td>
</tr>
<tr>
<td>Toxic epidermal necrolysis (NSAIDs)</td>
</tr>
<tr>
<td><strong>SEVERE SEPSIS, SHOCK</strong></td>
</tr>
<tr>
<td>Co-infections: dengue, malaria, leptospirosis, urinary tract infection, bacteremia</td>
</tr>
<tr>
<td><strong>HEMORRHAGIC</strong></td>
</tr>
<tr>
<td>Dengue coinfection, NSAIDs, aspirin</td>
</tr>
<tr>
<td><strong>ENDOCRIN</strong></td>
</tr>
<tr>
<td>Diabetes decompensation</td>
</tr>
<tr>
<td>Complications with a direct role of CHIKV</td>
</tr>
<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td><strong>NEUROLOGIC</strong> 1,4-3/1,000 cases</td>
</tr>
<tr>
<td>Meningoencephalitis++ Guillain Barre syndrome</td>
</tr>
<tr>
<td>Seizure, confusion</td>
</tr>
<tr>
<td><strong>HEPATIC</strong></td>
</tr>
<tr>
<td>Acute (fulminant) hepatitis</td>
</tr>
<tr>
<td><strong>CARDIAC</strong></td>
</tr>
<tr>
<td>Myocarditis</td>
</tr>
<tr>
<td><strong>SEVERE SEPSIS SHOCK</strong></td>
</tr>
<tr>
<td><strong>Aggressive clinical course</strong>, rapid haemodynamic deterioration, multisystem failure without documented coinfection or antibiotic efficacy</td>
</tr>
<tr>
<td><strong>CUTANEOUS</strong></td>
</tr>
<tr>
<td>Bullous dermatosis, epidermolysis (newborns, adults, <strong>lupus</strong>)</td>
</tr>
<tr>
<td><strong>RENAL</strong></td>
</tr>
<tr>
<td>Nephritis (interstitial)</td>
</tr>
<tr>
<td><strong>HEMORRHAGIC</strong></td>
</tr>
<tr>
<td>Newborns (vasculitis?)</td>
</tr>
<tr>
<td><strong>ENDOCRINE</strong></td>
</tr>
<tr>
<td>Inappropriate hypersecretion of antidiuretic syndrome hypoadrenalism</td>
</tr>
</tbody>
</table>

*Rare*
Chikungunya-associated mortality

• Excess deaths observed in Reunion, India (Ahmedabad)
  - Underestimation assumed in Brazil

• Case fatality rate close to that of seasonal flu
  - From 0.3-1/1,000 in Reunion Island, 2006 and Martinique, 2014
  - Sometimes higher (Brazil, Colombia) → drug misuse?

• Risk factors for chikungunya-associated severity and/or fatality
  - Age ≥ 60 years, higher if ≥ 85 years; peripartum period
  - Hypertension, underlying cardiac disorders, diabetes
  - Use of NSAIDs, alcohol abuse
  - Systemic lupus

Josseran et al EID 2006
Mavalankar et al. Emerg Infec dis 2008
INVS CIRE ARS Martinique

Tandale et al JCV 2009
Economopoulou et al Epidemiol. Infect. 2008
Gaüzère et al Réanimation 2011
Pamplona de Góes Cavalcanti 2017
The natural history of chikungunya disease: three stages

Acute
D1 to D14

Post-acute
W4 to W12

≈70% spt

Inflammation and transient immune changes
Multifocal persistence of joint inflammation → musculo-skeletal disorders

Post-acute stage (S4-S12): clinical features

• Clinical persistence or relapse after transient improvement
  - Common exacerbation at M2-M3

• Fatigue and sadness

• Osteo-tendino-articular symptoms +++
  - Polymorph and associated
  - Initial sites +/- new sites with time

The natural history of chikungunya disease: three stages

Acute

* D1 to D14

Post-acute

* W3 to W12

Chronic

* From M4 to …

- Multifocal persistence of joint inflammation ➔ musculo-skeletal disorders +++
- Rare evolution toward a chronic inflammatory rheumatism
- Psycho-social consequences

757 military policemen, Reunion Island, 2006

6 months after onset
672 answerers
M: 95%, mean age: 40 yo
→126 CHIK+

86% chronic arthralgia

Simon F, personal data
Rheumatic overmorbidity after 2 years... even after recovery!

Marimoutou C et al. Medicine 2012
Chronic stage, up to 6 years…

<table>
<thead>
<tr>
<th>Rheumatic symptoms</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>CHIK+</td>
</tr>
<tr>
<td></td>
<td>CHIK-</td>
</tr>
<tr>
<td>Stiffness</td>
<td>CHIK+</td>
</tr>
<tr>
<td></td>
<td>CHIK-</td>
</tr>
<tr>
<td>Swelling</td>
<td>CHIK+</td>
</tr>
<tr>
<td></td>
<td>CHIK-</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

French gendarmes cohort
Reunion exposure, 2006
Follow-up 2008-2012 period

Marimoutou C et al. BMC Musc Dis 2015
Chronic stage, up to 6 years…

- Long impaired quality of life
- And increased medical consumption

Marimoutou C et al. ISHEID 2014, Marseille

French gendarmes cohort
Reunion exposure, 2006
Follow-up 2008-2012 period
Prevalence of post-CHIK rheumatic disorders in adults

Fig. 4. Persistent arthralgia in chikungunya patients, retrospective studies.
Two types of post-CHIK rheumatisms

« Mechanical » musculoskeletal disorders
*No synovitis*
(tendonitis, fasciitis, arthralgia, stiffness)

Chronic inflammatory rheumatisms
*Presence of synovitis*
(rheumatoid arthritis, spondyloarthritis, RS3PE)
Mechanical musculoskeletal disorders: VERY FREQUENT

• Majority of the patients
  - Especially among those older than 30 years

• Mixed mechanisms
  - Initial articular inflammation: not treated
  - Pre-existing joint lesions
  - Prolonged overuse
  - Muscle deconditionning

• Degenerative cascade

• Multiple and evolutive

Simon F et coll. Medicine 2007 and personal data
Mainly mechanical abarticular disorders

• **NO SYNOVITIS** ← +++
  - Interest of US echography when doubt

• **Miscellaneous features**
  - Tendonitis, tenosynovitis, bursitis
  - Plantar and palmar fasciitis
  - Enthesitis
  - Distal subcutaneous oedema
  - Muscle contractures
Tenosynovitis, tendonitis
Post-CHIK neglected stiffness in many patients
Evolution of MSD with time

- Incomplete improvement, then « relapse »
- Centripetal evolution
- For years
Tunnel post-CHIK syndromes

• Higher incidence of tunnel syndromes per and post-epidemic

• Pathogenesis
  – Intense inflammatory tenosynovitis +/- direct neuropathy

Puccioni-Sohler et al. IJID 2016
Post-CHIK chronic inflammatory rheumatisms: RARE (<2%)

• PRESENCE OF SYNOVITIS, not arthralgia only
• Subsequent evolution > 3 months after acute stage
• Fitting the criteria of the classical CIR definitions

• Rheumatoid arthritis RA ↔ ↔
• Exacerbation of peripheral spondyloarthritis SA
• Rarely, other forms
  • RS3PE, unclassified polyarthritis (non RA-SA chronic polyarthritis)
Post-CHIK chronic inflammatory rheumatisms (CIR)
The post-CHIK vicious circle

- **Chikungunya**
- **Pain**
- **Stiffness**
- **Depression**
- **Handicap in daily life**
- **Stop of physical activities**
- **Self-depreciation**
- **Limitation in social life**
- **Rapid weight change Mainly gain.**
- **Deconditioning Stiffening**
The post-chikungunya clinical constellation
The high impact of a CHIK outbreak on public health

All patients having been infected

Cumulated number of cases

Months

Years

← epidemic period →  ← post-epidemic period →

End of the outbreak
The high impact of a CHIK outbreak on public health

Cumulated number of cases

- All patients having been infected
  - Suffering
    - Symptomatic patients with musculoskeletal disorders (without polyarthritis)
    - Symptomatic patients with chronic inflammatory rheumatisms
  - Money
  - Handicap
    - Asymptomatic infection, recovered patients without sequelae or active pain

Months

Years

End of the outbreak

← epidemic period →  ← post-epidemic period →
Experience-based treatment

SUFFERING

Dedicated case management

Remobilization

Patients

BETTER QUALITY OF LIFE
The high impact of a CHIK outbreak on public health

Cumulated number of cases

- All patients having been infected
- Symptomatic patients with musculoskeletal disorders (without polyarthritis)
- Asymptomatic infection, recovered patients without sequelae or active pain
- Symptomatic patients with chronic inflammatory rheumatisms

Months

Years

← epidemic period →  ← post-epidemic period →
Early adequate treatment could reduce the burden.

For « all », Optimal Treatment
For CiR, specific treatment

Cumulated number of cases

Asymptomatic infection, recovered patients without sequelae or active pain

Symptomatic patients with musculoskeletal disorders (without polyarthritis)

Symptomatic patients with chronic inflammatory rheumatisms

End of the outbreak

Early adequate treatment could reduce the burden.
TAKE HOME MESSAGES

• Mostly symptomatic for adults
• Acute stage
  • Typical features: frequent incapacitation
  • Rare complications → neonates, patients with underlying diseases
• Long-term general and rheumatic disorders for many patients
• Most patients with cumulative chronic MSD
• Some patients with CIR
• Common impact on mental health, daily life and budget
• The largest cause of the CHIKV-related burden

This lecture results from the multidisciplinary experience of the French Military Medical Services

in collaboration with:
the University Hospitals of Reunion, Martinique and Marseille,
GPs from Guadeloupe
and the expert group for the French guidelines.

fabrice2.simon@intradef.gouv.fr
chikungunya.expertise@gmail.com