

Villars-sur-Ollon, Switzerland
 ESCMID Postgraduate Technical Workshop
 Intracellular Bacteria: From Biology to Clinic
 27 August 2013

Whipple's disease and *Tropheryma whippelii*

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***Tropheryma whippelii* and Whipple's disease**

- 1907 First description of Whipple's disease (Metabolic trouble)
- 1952 First treatment with antibiotics
- 1961 Bacteria-like structures observed using Electron Microscopy
- 1991 Identification of the agent of Whipple's disease using 16S rRNA PCR followed by sequencing A rare bacterium causing a rare chronic infection
- 2000 First establishment of a strain of *T. whippelii*
- 2013 *T. whippelii*: A common bacterium
 Whipple's disease: Top of the iceberg of the manifestations caused by *T. whippelii*

-Lagler JC, Fenollar F, Raoult D. From Whipple's disease to *T. whippelii* infections. Med Mal Infect. 2010;39:11-22.
 -Schneider T, Moos V, J, Raoult D. Whipple's disease: New aspects on pathogenesis and treatment. Lancet Infectious Diseases 2008; 8:179-90.
 -Fenollar F, Puechal X, Raoult D. Whipple's Disease. N Eng J Med 2007; 356:55-66.

From 2001 to July 2010, in our center

- Lagler JC, Lepidi H, Raoult D, Fenollar F. Systemic *T. whippelii*: Clinical presentation of 142 patients with infections diagnosed or confirmed in a Reference Center. Medicine (Baltimore) 2010;89:337-45.

215 diagnoses or confirmations of chronic *T. whippelii* infections

Among them 142 patients with enough information

- 113 classic Whipple's disease (80%)
- 29 localized chronic infections (20%):
 - 16 endocarditis (11%)
 - 5 neurologic infections
 - 2 uveitis
 - 2 adenopathies
 - 2 joint infections
 - 2 pulmonary infections

Classic Whipple's disease

Systemic disease characterized by the presence of typical histologic lesions observed in small-bowel biopsies using PAS-staining

- Typical patient: 50 year-old Caucasian man
- Clinical manifestations: protean and non specific:
 As nearly all organs could be involved

Most often: arthralgia, weight-loss and/or chronic diarrhea
 Cardio-vascular manifestations
 Neurologic manifestations
 Ophthalmologic manifestations
 Mediastinal and/or mesenteric adenopathy
 Skin involvement and other...

Classic Whipple's Disease

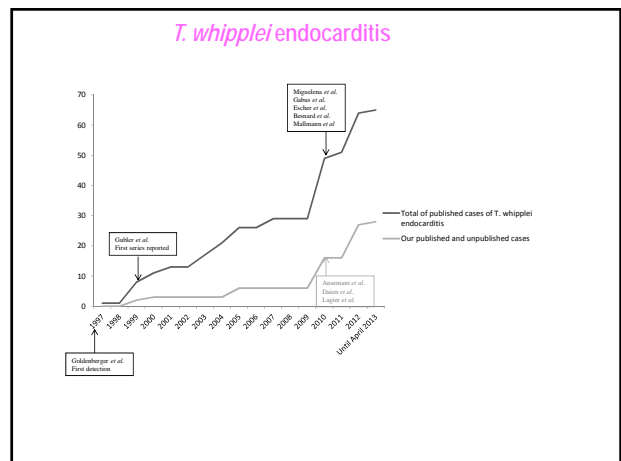
-Fenollar F, Puechal X, Raoult D. Whipple's disease. New Engl J Med 2007;356:55-66
 -Lagler JC, Lepidi H, Raoult D, Fenollar F. Systemic *T. whippelii*: Clinical presentation of 142 patients with infections diagnosed or confirmed in a Reference Center. Medicine (Baltimore) 2010;89:337-45.
 -Lagler JC, Fenollar F, Halle O, Lepidi H, Raoult D. Efficacy of antibiotic therapy in polyarthritides: a clue suggesting WD. Int J Antimicrob Agents 2009;34:389-90.

Review of the literature 2007:

Feature	Patients with Whipple's Disease no./total no. (%)
Male sex	770/886 (87)
Arthralgia or arthritis	244/335 (73)
Diarrhea	272/335 (81)
Weight loss	223/240 (93)
Fever	128/335 (38)
Adenopathy	174/335 (52)
Melanoderma	99/240 (41)
Neurologic signs†	33/99 (33)
Ocular signs‡	6/99 (6)
Pleural effusion	26/190 (14)

Data 2010:
 Main symptom: Arthralgia (88/113, 78%)
 Misdiagnosis:
 Inflammatory rheumatoid disease (56/113, 50%)
 Improvement with a short course of antibiotics

Prodromal stage
 Average time = 6 years
 Steady-state stage
 More rapid clinical progression with immunosuppressive therapy



T. whipplei endocarditis

-Geissdorfer W, Moos V, Moter A, Loddenkemper C, Jansen A, Tandler R, Morgust AJ, Fenollar F, Raoult D, Bogdan C, Schneider T. High frequency of *T. whipplei* in culture negative endocarditis. J Clin Microbiol. 2012;50:216-22.
 -Fenollar F, Olsard M, Lager JC, Lepidi H, Fournier PE, Raoult D. *Tropheryma whipplei* endocarditis: a 28 patient series and review. Em Inf Dis. November 2013.

- Typical patient: 60 year-old Caucasian man
- Apyrexia (fever observed for 32%)
- « Cardiac » presentation :
 - Cardiac insufficiency (71%)
 - Acute ischemic stroke (27%)
 - Peripheral arterial emboli (14%)
- Aortic valve involvement (62%)
- Cardiac vegetation (82%)
- Discrepancies between French/International and German series :
 - Presence of arthralgia (75% / 61% and 7.2%)
 - Previous valvular disease not systematically observed (32% / 36% and 87%)

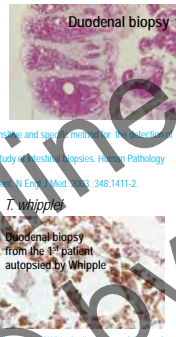
T. whipplei encephalitis

-Fenollar F, Nicoli F, Paquet C, Lepidi H, Cozzone P, Antoine JC, Pouglet J, Raoult D. Progressive dementia associated with ataxia or obesity in patients with *Tropheryma whipplei* encephalitis. BMC Infect Dis 2011;11:171.

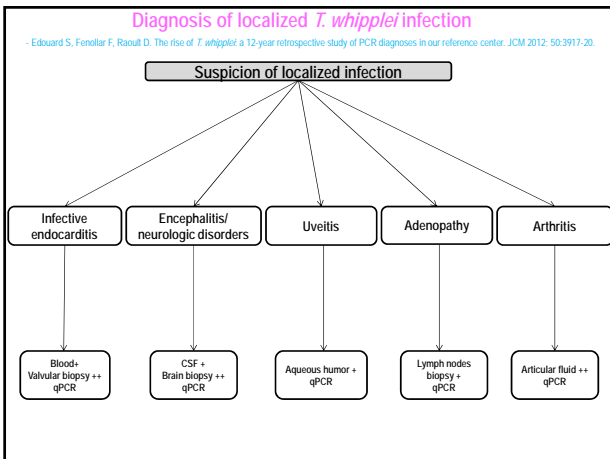
- 25 cases reported in the literature (10 these last 3 years)
- Can mimic symptoms of almost any other neurologic condition:
 - Cognitive changes may even extend to dementia
 - Psychiatric symptoms such as depression and personality changes
 - Supranuclear ophthalmoplegia
 - Myoclonus
 - Hypothalamic involvement
 - Movement abnormalities of the eye muscles: Oculomasticatory or oculofaciocervical myorhythmia
- New clinical manifestation:
 - 3 patients
 - Association of dementia, cerebellar ataxia, and weight gain (25 kg, 12 kg, 15 kg)
 - All the manifestations are sensitive to doxycycline (-17 kg, -7 kg, -4 kg)

Diagnostic tools

- Periodic acid-Schiff (PAS) staining
 - Fenollar F, Raoult D. Whipple's disease. Clin Diagn Lab Immunol 2001;8:1-8.
 - Lack of sensitivity and specificity
- Immunohistochemistry
 - Balsden BL, Lepidi H, Dumler JS. Diagnosis of Whipple disease by immunohistochemical analysis: a sensitive and specific method for the detection of *T. whipplei* in paraffin-embedded tissue. Am J Clin Pathol. 2002;118:742-8.
 - Lepidi H, Fenollar F, Raoult D. Whipple's disease: immunospecific and quantitative immunohistochemical study of tissue biopsies. Hepatol Pathology 2003;24:588-94.
 - Dumler JS, Balsden BL, Yardley JH, Raoult D. Immunodetection of *T. whipplei* from Dr Whipple's 1907 patient. N Engl J Med 2003;348:1411-2.
 - Production of rabbit polyclonal antibodies specifically directed against *T. whipplei*
 - Excellent specificity and sensitivity
- Molecular diagnosis
 - Fenollar F, Laouira S, Lepidi H, Robinson M, Raoult D, Valadier J. *T. whipplei* quantitative PCR assay for the diagnosis of Whipple disease: usefulness of saliva and stool specimens for first-line screening. Clin Infect Dis. 2008;47:659-67.
 - Edouard S, Fenollar F, Raoult D. The rise of *T. whipplei*: a 12-year retrospective study of PCR diagnoses in our reference center. JCM 2012; 50:3917-20.
 - Specific real-time qPCR
 - 16S rRNA PCR followed by sequencing (lack of sensitivity)



Immunohistochemistry

Treatment of Whipple's disease

Without treatment, the natural evolution is the death.

- Empirical treatment of classic Whipple's disease:
 - Induction treatment (15 days) using penicillin and streptomycin or ceftriaxone or imipenem followed by 1-year of oral trimethoprim/sulfamethoxazole (STX)
 - Spectacular efficacy: Disappearance of arthralgia and diarrhea in 1 week but a lot of relapses and failures
 - This treatment is still supported by the German team.
- In vitro susceptibilities against T. whipplei:
 - Penicillin and streptomycin are effective both intracellularly and in axenic medium.
 - Ceftriaxone is effective in axenic medium, but not intracellularly.
 - Imipenem is effective in axenic medium but heterogeneity in susceptibility has been reported intracellularly.
 - Trimethoprim is not effective in vitro, trimethoprim/sulfamethoxazole is a monotherapy.

-Faurie GE, Moos V, Bisker H, Loddenkemper C, Moter A, Stroux A, Marth T, Schneider T. Intravenous ceftriaxone, followed by 12 or 3 months of oral treatment with trimethoprim-sulfamethoxazole. J Infect. 2013;66:263-70.
 -Faurie GE, Junga NS, Marth T. Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. Gastroenterology. 2010;138:478-86.
 -Kolta AK, Raoult D, Fenollar F. T. whipplei as a commensal bacterium. Future Microbiol. 2013;8:57-71.

Acquired resistance to sulfamethoxazole

Bakkali N, Fenollar F, Biswas S, Rolain JM, Raoult D. Acquired resistance to trimethoprim/sulfamethoxazole during Whipple's disease and expression of the causative target gene. *J Infect Dis* 2008;196:101-8.
 Fenollar F, Rolain JM, Alric L, Pajo T, Chauveheid MP, van de Beek D, Raoult D. Resistance to trimethoprim/sulfamethoxazole and *T. whipplei* Int. *J Antimicrob Agents*. 2009;34:255-9.

- From our database and samples collection :
 4 patients with clinically acquired resistance to STX
 1 patient with biological failure to STX

-*folP* gene encodes for the dihydropteroate synthase (DHPS), the target of sulfonamides

Overall, 62 complete sequences of *folP* gene from 59 patients were obtained

↓
 2 mutations (N4S and S234F) were detected that significantly predicted failure

New therapeutic propositions

- Lagier JC, Fenollar F, Lepidi H, Giorgi R, Million M, Raoult D. Treatment of classic Whipple's disease: from *in vitro* results to clinical outcome. *J Antimicrob Chemother*. 2013. Epub ahead of print.

- Vacuole acidification has been shown to be critical to the survival of *T. whipplei* in phagosomes.
- Agents that increase the intravacuolar pH decrease bacterial viability.
- Usefulness of an alkalinizing agent, hydroxychloroquine for the treatment?
- Efficacy of hydroxychloroquine and doxycycline:
 Only bactericidal treatment against *T. whipplei in vitro*

New therapeutic propositions

Bakkali N, Fenollar F, Rolain JM, Raoult D. Comment on therapy with Whipple's disease. *J Antimicrob Chemother* 2008;61:968-9.
 Fenollar F, Raoult D. How should classic Whipple disease be managed? *Nat Rev Gastroenterol Hepatol* 2010;7:246-8.
 Fourlis GE, Moos V, Schneider T, Fenollar F, Raoult D. *J Antimicrob Chemother*. 2012;67:1295-6.
 - Lagier JC, Fenollar F, Lepidi H, Giorgi R, Million M, Raoult D. Treatment of classic Whipple's disease: from *in vitro* results to clinical outcome. *J Antimicrob Chemother*. 2013. Epub ahead of print.

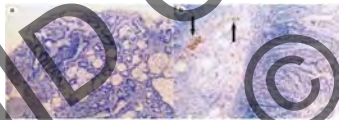
-Treatment of classic Whipple's disease:

Doxycycline (100 mg X 2 per day) and Hydroxychloroquine (200 mg X 3 per day) for at least 12 months

Spectacular efficacy, until now no clinically acquired resistance observed, but...

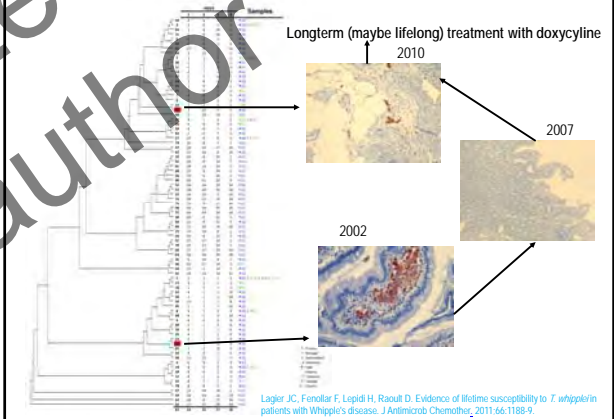
End of the treatment
 in February 2007

Relapse in October 2009



Duodenal biopsies

Lifetime susceptibility to *T. whipplei* in patients with Whipple's disease



Lagier JC, Fenollar F, Lepidi H, Raoult D. Evidence of lifetime susceptibility to *T. whipplei* in patients with Whipple's disease. *J Antimicrob Chemother*. 2011;66:1188-9.