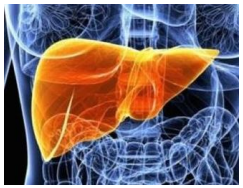



CRMR Maladie de Wilson et autres maladies rares liées au cuivre

The 12th World Congress on Controversies in Neurology (CONy)
March 22-25, 2018 | Warsaw, Poland

Acquired copper deficiency in patients with and without Wilson disease

Fabienne Ory-Magne, Aurélia Poujois, France Woimant
National Reference Centre for Wilson's disease,
Neurology Department, University Hospital Toulouse, France
Neurology Department, University Hospital Lariboisière, AP-HP, Paris, France

Hôpitaux de Toulouse

ToNIC Toulouse NeuroImaging Center UMR1214

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

The 12th World Congress
on Controversies in Neurology (CONy)
March 22-25, 2018 | Warsaw, Poland

Acquired copper deficiency in patients with and without Wilson disease

French National reference center for Wilson Disease and other rare copper diseases
Neurology Department - Hôpital Universitaire, Toulouse, France

Fabienne Ory-Magne, MD

Disclosure of Interest: Nothing to Disclose

INTRODUCTION

- **Copper**:
  - ✓ an essential trace element found in our daily diet
  - ✓ acts as cofactor for many important enzymes
  - ✓ fundamental role in normal functioning of many systems (neurological, haematological …)

- **Acquired Copper deficiency (ACD) in adults is:**
  - ✓ rare but frequently misdiagnosed
  - ✓ Important to diagnose as treatable : a cause of reversible myelodysplasia and myelopathy
  - ✓ 2 different mechanisms when related or not to Wilson Disease (WD)

- **Our objectives** were to
  - ✓ review all cases of ACD
    - ✓ with neurological symptoms, in patients without WD
    - ✓ in patients with WD
  - ✓ compare ACD in patients with and without WD

Poujois A, Djebrani-Oussedik N, Ory-Magne F, Woimant F. Intern Med J. 2017
Dzieżyc K, Litwin T, Sobańska A, Członkowska A. Neurol Neurochir Pol. Polish Neurological Society; 2014

METHODS

- Between January 2011 and January 2018,
- ACD in the Toulouse and Lariboisiere registries of copper trace element diseases

- Reports focused on:
  - Neurological examination
  - Electrophysiological data
  - Imaging data: spinal cord and brain MRI
  - Biological features: complete blood count, liver function, vitamins B12 and vitamin E.
  - CSF if available
  - Toxicological screening: copper, zinc and iron levels
  - Treatment proposed (drug, doses, formulation, duration)
  - Evolution of clinical, biological and imaging data at last follow-up

RESULTS

Ten patients with ACD were reported within the last seven years

7 patients without Wilson disease (ACD)

- 4 males/3 females
- Mean age 57.4 +/-9.7 years (44-72)
- Mean time between first neurological symptom and ACD diagnosis: 6.5 +/-4.9 months (2.5-15)

3 patients with Wilson disease (WD-ACD)

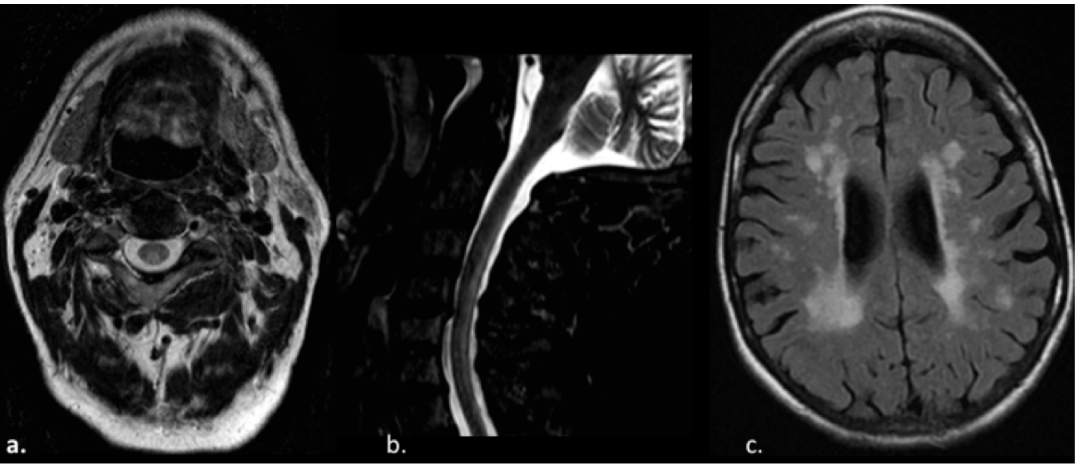
- 3 males
- Mean age 58 +/- 19.5 years (39-57)
- Mean time between first neurological symptom and ACD diagnosis: 12 +/-10.4 months (6-24)

RESULTS: ACD without Wilson disease (1)

CLINICAL PRESENTATION

- Progressive **sensory ataxic gait** disorder: 7/7
- Sub-acute ascending **paresthesias**: 5/7
- **Posterior cord syndrome** (PCS) : 7/7
- Subacute combined degeneration: 3/7

IMAGING



Spine MRI: abnormal in 4/7

- extended posterior cervical and thoracic spinal cord hyperT2 signal
- No contrast enhancement

Brain MRI: abnormal in 3/7

- widespread white matter T2 and Flairhypersignal

RESULTS: ACD without Wilson disease (2)

ELECTROPHYSIOLOGICAL STUDIES

- available in 6 patients
- lower limbs sensory neuropathy in 4/6
- demyelinating (2/4) or an axonal (2/4) pattern

BIOLOGY

- Hemogramme:
  - Normo- or macrocytic anaemia in 6/7
  - mild lymphopenia in 5/7
- Vitamin B12 : normal
- CSF : normaL

TOXICOLOGY

- Serum copper: decreased in all (1 +/-1.2 µmol/L - N > 12 µmol/L)
- Ceruloplasmine decreased in all (0.04 +/-1.2 g/l 0.2<N <0.6
- Urinary copper excretion: normal in all
- Serum and urinary zinc: high in 4 patients
- **Iron levels: normal in all**

RESULTS: ACD without Wilson disease (3)

ETIOLOGIES

2 causes of ACD were found:

- chronic use of dental cream enriched in zinc (4/7).
  - Mean duration of prolonged use of denture adhesive paste was 9 +/-1.8 years.
- malabsorption syndrome secondary to surgery (gastrectomy, oesophagectomy with jejunostomy, bariatric surgery) (4/7)
- One patient had an association of two causes.

TREATMENT

- (1) acute treatment: copper Histidine sc

mean dose 3.2 +/-0.4 mg/d during 4 +/-5.4 days,

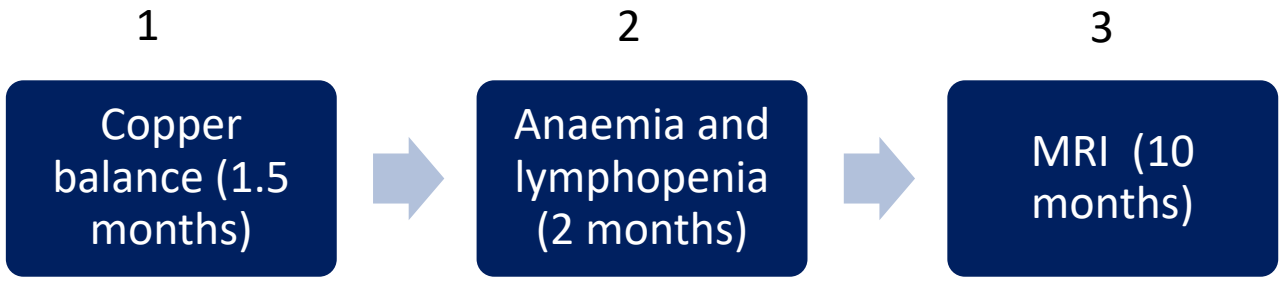
- (2) prolonged supplementation (per os or enteral) by copper oligosol.

mean dose of 1.6 +/-0.5 mg/d.

- 6/7 are still on treatment at the last follow-up. 1/7 stopped his treatment after seven months as he fully recovered.

RESULTS: ACD without Wilson disease (4)

After copper supplementation: Normalization progressively



After a **mean follow-up of 2 +/- 2.1 years**:

- all patients except one improved

2/7 : normal neurological examination but complained of transient subjective paresthesias.

4/7 : improved their gait and balance with less paresthesias
and moderate PCS at examination.

RESULTS: ACD in Wilson disease patients (1)

3 WD patients (3 males, mean age 58 +/-19.5 years) in the registry of 338: **0.9%**

Diagnosis of Wilson disease:

- mean age at diagnosis : **38.3 +/-17.9 years** (versus 18.6 +/-11 in the French registry)
- Initial presentation:
  - 1 diagnosed on familial screening
  - 1 had a compensated cirrhosis with KFR,
  - 1 had a mild cirrhosis associated with isolated writer cramp
- Normal brain MRI in all

Treatment of Wilson disease: all received zinc for more than 6 years

- 1 was on zinc acetate 150 mg/d during 6 years
- 1 was on Trolovol 900 mg/d during 6 years then zinc acetate 150 mg/d during 13 years
- 1 was on Trolovol 900 mg/d during 13 years then Trientine 600 mg/d + zinc sulphate 1200 mg/d during 17 years

RESULTS: ACD in Wilson disease patients (2)

ACD-WD:
Mean 17.4 +/-14 years [5.8-33] after initiation of WD treatment

Mean time to diagnosis : twice longer than for ACD: 12+/-10.4 months [6-24].

Presentation:

- 1 patient: isolated pancytopenia
- 2 patients developed neurological symptoms

Progressive sensory ataxic gait disorder with lower limbs paresthesias,
+ posterior cord syndrome (PCS) at examination

Normal MRI and electroneurography

RESULTS: ACD in Wilson disease patients (3)

Biology:

- pancytopenia 1/3
- **anaemia in all**

Toxicology:

- Serum copper, exchangeable copper and urinary copper excretion were low (respectively 0.36+/-0.11; 0.22+/-0.12; 0.09+/-0.01)
- Serum and urinary zinc values were high (27.6+/-3.4; 80.2+/-23.4).
- **Serum Iron levels were low (low serum iron, high transferrin, low cSt)**

WD Treatment adjustment:

- Two third decrease of zinc acetate doses in 1
- Discontinuation of zinc acetate in 1
- Two third decrease of zinc sulfate doses and stopping Trientine in 1
- **2/3 received iron supplementation**

RESULTS: ACD in Wilson disease patients (4)

Evolution after treatment adjustment:

At 6 and 15 months' follow-up,

- neurological patients subjectively better
- biological data unchanged

After 31 months' follow-up,

- objectively neurological improvement
- haematological disturbances and iron deficiency resolved in 2/3
- exchangeable copper values still low
- urinary copper excretion started to increase

DISCUSSION (1)

- **ACD is exceptional** in industrialized countries as copper is largely present in numerous foods.
- First manifestation is usually haematological (myelodysplasia)
- ACD revealed by **neurological presentation is less frequent** as demonstrated by our study. A recent retrospective national Scottish study over a same period, identified 12 ACD patients with neurological symptoms.
- Neurological presentation of ACD **mimics a vitamin B12 deficiency** : PCS leading to a sensory ataxic gait and that can extend to a sub-acute combined degeneration.
- Imaging:
  - **Spine MRI can be tricky** as it can be normal (50%) despite the neurological presentation.
  - Brain MRI may show widespread periventricular white matter lesions
  - Dysfunction of the methylation cycle, which requires copper, is suspected to cause failure of myelin maintenance and explain lesions

Gabreyes et al. 2012

DISCUSSION (2)

- **Causes of ACD**
  - digestives
  - excess of zinc intake secondary to use of dental cream enriched in zinc
  - Prolonged treatment by zinc salts in Wilson disease patients:
    = 5.8-33 years in our experience
    = 5-16 years in the Polish experience

- **In our experience, WD patients who developed ACD-WD:**
  - Had a late form of WD (mean age at diagnosis: 38.3 +/-17.9 years (versus 18.6 +/-11 in the French registry)
  - Were all treated by zinc salts (alone or associated to a chelator)
  - Differed from ACD by the presence of an **iron deficiency anaemia. Mechanism ?**

Poujois A, Djebrani-Oussedik N, Ory-Magne F, Woimant F. Intern Med J. 2017
Dzieżyc K, Litwin T, Sobańska A, Członkowska A. Neurol Neurochir Pol. Polish Neurological Society; 2014

DISCUSSION (3)

- **Treatment of ACD :**

⇒ **treatment of the cause and copper supplementation for non WD ACD**

  - based on a chronic copper supplementation but no guidelines exist on the best formulation, route, dose and duration of treatment required
  - A dose between 1.5 and 3 mg/d seems the most consensual.
  - In our experience, we associate an acute subcutaneous treatment, 2 mg/d, to a chronic one (per os or enteral) at a lower dose.

- **Treatment of ACD-WD:**

⇒ decrease or discontinuation of the zinc salt

⇒ Iron supplementation

⇒ Adaptation to the urinary copper excretion and the exchangeable copper

- **Evolution of neurological symptoms**
  - Very slow regression of PCS or SCD

CONCLUSION

- Copper deficiency in WD patients is extremely rare but has to be known
- **Regular follow-up with clinical and biological evaluation is needed to adjust treatment and prevent ACD**
- **Worsening of gait disorder should alert and PCS at examination** should evoke a copper deficiency
  - Urinary copper excretion is extremely low < 0.20 µmol/l, as well as ExCu
  - Anaemia/leucopenia is more complex to interpret due to liver anomalies
  - Iron deficiency is specific to ACD in WD
    - Due to saturation of metalothioneins by the zinc but not present in ACD secondary to zinc overload ?
    - Due to the reduced ferroxidase activity ?

The French Reference Centre:
Wilson's disease and other rare diseases linked to copper

A NETWORK

2 Reference Centres

Coordinator site: Lariboisière Hospital (Paris)

Constituent site: HFME Hospital (Lyon)

8 Competence Centres:

Paris (Paul Brousse, Necker), Lille, Besançon, Marseille, Toulouse, Bordeaux, Rennes)

1 Patient organization

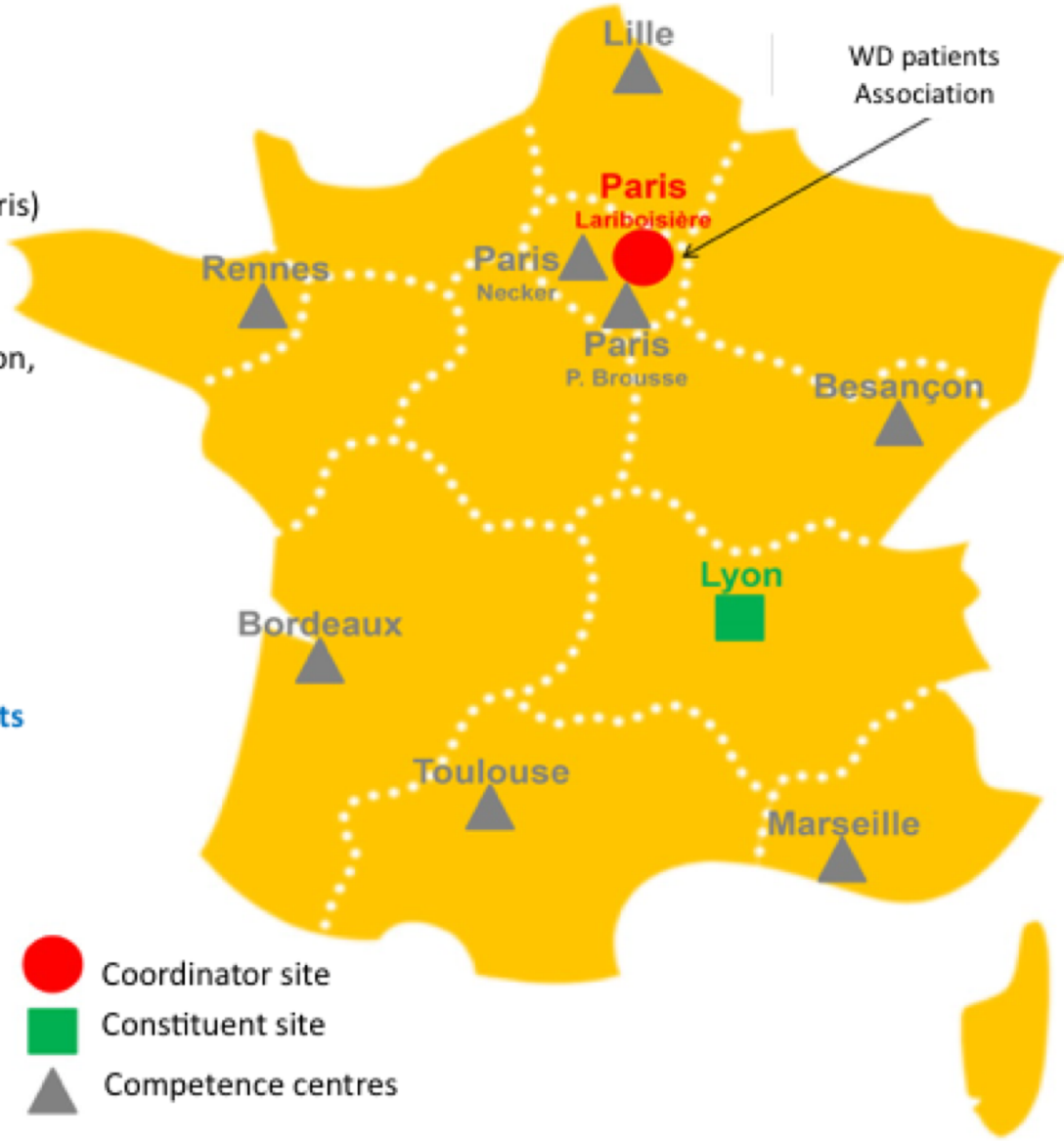
A MULTIDISCIPLINARY TEAM

Paediatry/Hepatology/Neurology

Molecular Biology Laboratory

Toxicology laboratory, metals and trace elements

A NATIONAL WD REGISTRY



www.cnrwilson.com