Acquired copper deficiency in patients with and without Wilson disease

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Acquired copper deficiency in patients with and without Wilson disease

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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

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
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

1. Copper balance (1.5 months)
2. Anaemia and lymphopenia (2 months)
3. MRI (10 months)

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**
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
• **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:
  o **Spine MRI can be tricky** as it can be normal (50%) despite the neurological presentation.
  o Brain MRI may show widespread periventricular white matter lesions
  o Dysfunction of the methylation cycle, which requires copper, is suspected to cause failure of myelin maintenance and explain lesions

Gabreyes et al. 2012
• **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?**

Dzieżyc K, Litwin T, Sobańska A, Członkowska A. Neurol Neurochir Pol. Polish Neurological Society; 2014
• Treatment of ACD:
  ⇒ treatment of the cause and copper supplementation for non WD ACD
    o based on a chronic copper supplementation but no guidelines exist on the best formulation, route, dose and duration of treatment required
    o A dose between 1.5 and 3 mg/d seems the most consensual.
    o 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
  o Very slow regression of PCS or SCD
• 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 metallothioneins 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