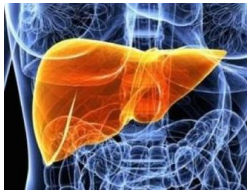
The 12th World Congress on Controversies in Neurology (CONy)
March 22-25, 2018 | Warsaw, Poland



Is liver transplantation a reasonable alternative in neurologic Wilson disease patients resistant to chelators? Lessons from the French experience in 18 cases

Aurélia Poujois*, MD, PhD and France Woimant, MD
on behalf of the French WD neuroLT group

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CRMR Maladie de Wilson et autres maladies rares liées au cuivre

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Is liver transplantation a reasonable alternative in neurologic Wilson disease patients resistant to chelators?
Lessons from the french experience in 18 cases

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

Aurélia POUJOIS, MD, PhD

Disclosure of Interest: Nothing to Disclose

INTRODUCTION

- **Wilson Disease**:
  - ✓ an inherited disorder leading to toxic copper overload mainly in the liver and the brain.
  - ✓ for 30% of patients, WD diagnosis can be made from the neurological symptoms. Can vary from 18–68% (depending of studies)*

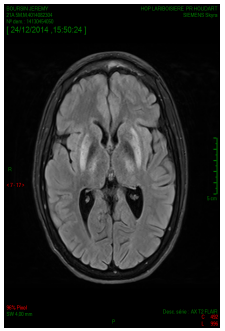
- In the French registry (619 patients):
  - ✓ **33.5 %** of patients present neurological symptoms at diagnosis
  - ✓ main initial symptoms: tremor (52,6%), dysarthria (52%), writing difficulties (31%), dystonia (27%), gait disorder (27%), drooling (23%) and dysphagia (14%).

- **Copper chelators or zinc therapy** are effective treatments in most patients: neurological symptoms decrease or completely regress, although some may persist

- However, **neurological deterioration** may happen

* EASL, 2012; Dalvi, 2014

Neurological worsening despite treatment

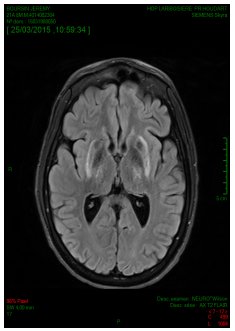


Day 1

WD Diagnosis
=> slow introduction of DP

2 months

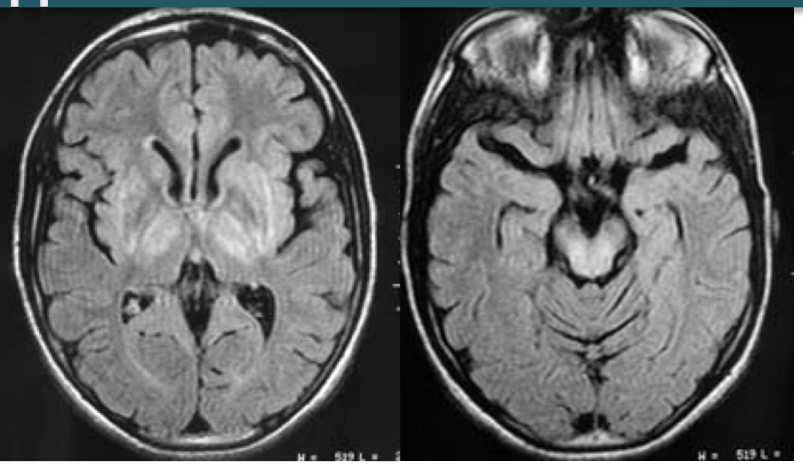
Continuous worsening of symptoms => DP changed to Trientine



5 months

Continuous worsening of parkinsonism, dystonia, severe dysarthria and dysphagia

Neurological worsening after treatment discontinuation



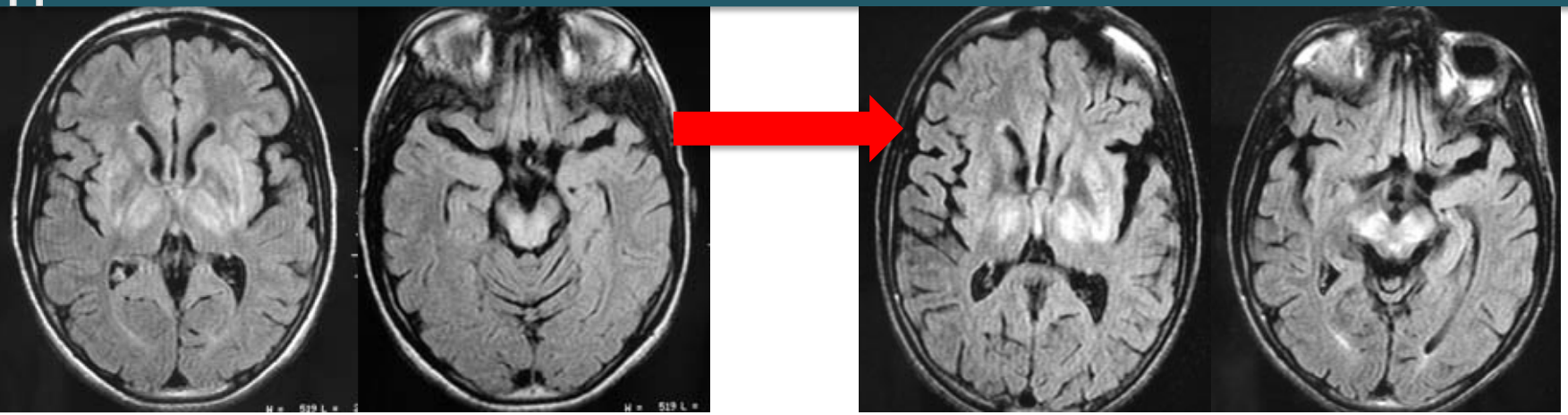
February 2002

MB, age 13
January 2000 ; WD Diagnosed
Mild dystonic features in LL
Abnormal MRI, KF rings

Treated by Trientine (acute side effect with DP)
=> Clinical neurological recovery in 1 year; MRI improved

June 2002: Holidays … where treatment was interrupted ….

Neurological worsening after treatment discontinuation



February 2002

September 2002: 2 months after interruption of treatment

MB

2,5 years after diagnosis

« Fulminant » neurologic deterioration, two months after stopping treatment (generalized dystonia with “status dystonica”)

⇒ re-introduction of Trientine

⇒ Adjunction of zinc acetate

⇒ NO EFFECT,

INTRODUCTION

- **Paradoxical worsening of neurological symptoms:**
  - **11 - 24%** of neurological patients
  - With all three drugs: DP: 13.8 % >Trientine: 8 % > ZS: 4.3 % (Merle, 2007)
  - Irreversible in 44% of patients, resulting in severe disability or death despite optimal therapy (Prashanth, 2005; Svetel, 2009)

- **Mechanisms of deterioration are unknown: many hypothesis**
  1. Treatment too slow to act in very acute forms ?
  2. Inefficacy of intracerebral chelation ?
  3. Irreversible tissue damages already present ?
  4. Direct effect of the treatment with rapid mobilization and redistribution of copper, resulting in high levels of copper in blood and brain leading to oxidative stress and accentuation of brain tissue damages ?

⇒ slow increase of chelators doses recommended : « start low—go slow » regimen

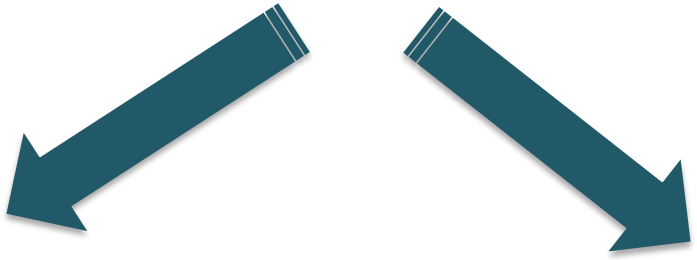
Litwin et al. J Neurol Sci 2015
Merle et al. Gut 2007
Prashanth, 2005; Svetel, 2009

INTRODUCTION

How to deal with this dramatic situation ?

⇒ As no other medical treatment exists, **what could be the place of liver transplantation ?**

LIVER TRANSPLANTATION and WD



Hepatic forms

- the recommended therapeutic option in WD with:
  - ✓ Fulminant hepatic failure
  - ✓ Severe hepatic insufficiency

- Validated indications
- Good results with 87% survival rate at 15 years in a cohort of 121 French patients (Guillaud, 2014)

Neurologic forms

- remains controversial in WD with worsening of neurological features despite treatment

- 15 cases-reports on LT for strict neurological indication published :
  - 32 patients, heterogeneous evaluation and follow-up
  - various outcome

Guillaud, 2014; Laurencin, 2017; Modi, 2015; Mocchegiani, 2014;Cheng, 2009; Duarte-Rojo, 2009; Marin, 2007; Suess, 2007; Suzuki, 2003; Schumacher, 2001; Robles, 1999; Bax, 1998; Kassam, 1998; Schilsky, 1994; Mason, 1993

FRENCH EXPERIENCE ON LT FOR PURE NEUROLOGICAL INDICATION

In France, thanks to rare diseases funding plans since 2005,

- **National reference network** for the care of Wilsonian patients
- National WD registry

CRMR Maladie de Wilson et autres maladies rares liées au cuivre

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

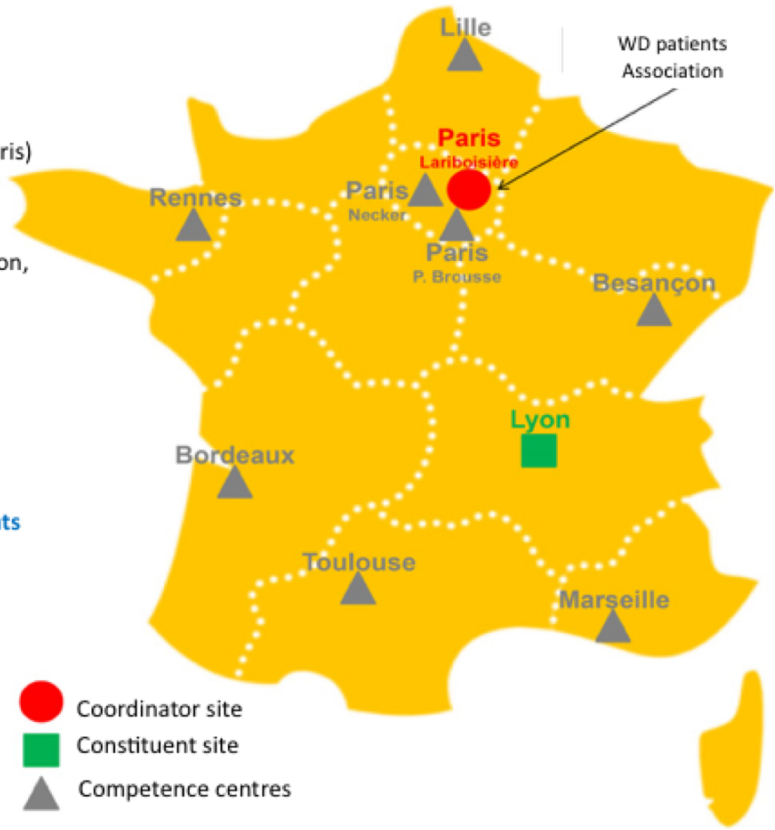
A MULTIDISCIPLINARY TEAM

Paediatry/Hepatology/Neurology

Molecular Biology Laboratory

Toxicology laboratory, metals and trace elements

A NATIONAL WD REGISTRY



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FRENCH EXPERIENCE ON LT FOR PURE NEUROLOGICAL INDICATION

In France, thanks to rare disease funding plans since 2005,

- National reference network for the care of Wilsonian patients
- National WD registry

Collaborative study to report the French experience on

- LT in patients with pure neurological aggravation despite accurate medical treatment,
- With a special attention to:
  - the survival rate
  - the long term disability
  - the possible prognostic factors

LT IN NEUROLOGICAL WD PATIENTS: METHODS

- Retrospective study (June 1994 - June 2016)
- WD patients from the WD national registry, who underwent a LT for neurologic indication and fulfilled three conditions:

1) **Leipzig score for the diagnosis of WD > 4**
2) **Constant neurological worsening despite a minimum of two months of appropriate copper chelation. Worsening defined as a minimum of :**
   - **20% increase of the Unified WD Rating Scale (UWDRS) score**
   - **and a 2-point increase in the modified Rankin score (mRs).**
3) **Severe neurological impairment with a mRs ≥ 4 at the time of LT**

4: unable to walk without assistance and unable to attend to own bodily needs without assistance

5 : severe disability ; bedridden, incontinent and requiring constant nursing care and attention

LT IN NEUROLOGICAL WD PATIENTS: METHODS

- Retrospective study (June 1994 - June 2016)
- WD patients from the WD national registry, who underwent a LT for neurologic indication and fulfilled three conditions:
  1) Leipzig score for the diagnosis of WD > 4
  2) Constant neurological worsening despite a minimum of two months of appropriate copper chelation.
  3) Severe neurological impairment with a mRs ≥ 4 at the time of LT

- Neurologic worsening could be
  = **primary** in newly diagnosed and treated neurologic patients,
  = **secondary** to the interruption of chelators/ZS

- **Criteria of non-inclusion**:
  - hepatic indication of LT
  - severe neurological patients with stable condition or without recent worsening

LT IN NEUROLOGICAL WD PATIENTS: OUTCOMES

CO-PRIMARY OUTCOMES

1) the overall **survival rate**
2) the **disability** at the last follow-up after LT as assessed by the mRS and the UWDRS.

Was arbitrarily considered as:

- **major improvement**: a decrease of UWDRS score above 66%,
- **moderate improvement** a decrease of UWDRS score between 33% and 65%
- **mild improvement** or stable condition: a decrease below 33%

SECONDARY OUTCOMES

Evolution at the last follow-up of:

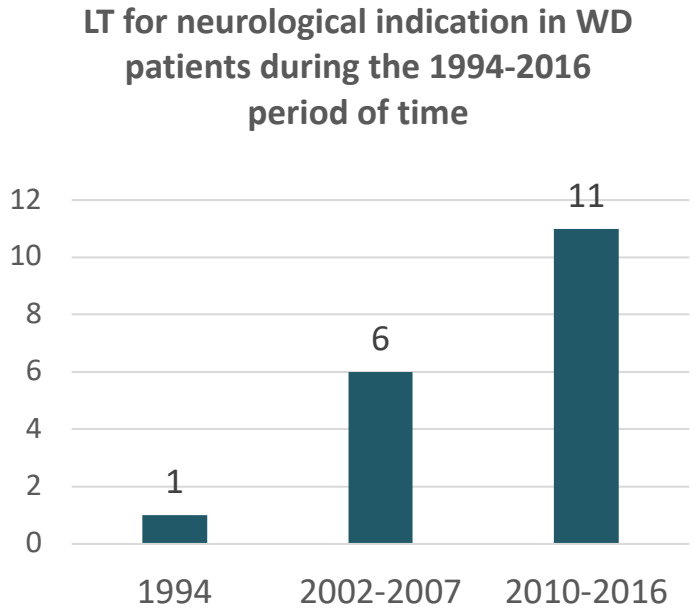
- ophthalmological score (KFR)
- brain MRI score

LT IN NEUROLOGICAL WD PATIENTS: RESULTS

STUDY POPULATION

- **18 patients** underwent LT for strict neurological indication in the 22 years period of time
  - Five liver transplant centres (8 in Paris, 4 in Bordeaux, 2 in Lyon, 2 in Besançon and 2 in Tours)
  - 60% had LT in the last six years

- Concerned **14% of the patients of the registry with neurological phenotype**



- **Characteristics of the 18 patients:**
  - 10 males/8 females
  - median **age 18.5 years** (range 16-20.8)
  - **median time between neurological worsening and LT: 6.7 months** (5.3-14.5)
  - 13/18 (72%) had a primary worsening
  - Two pathological ATP7B mutations in all

LT IN NEUROLOGICAL WD PATIENTS: RESULTS

PATIENT CHARACTERISTICS AT INCLUSION BEFORE LT

- **Mild hepatic disease**
  - CHILD A for all patients, median MELD score 8.5 (7-10.8)
  - cirrhosis in native liver (18/18)

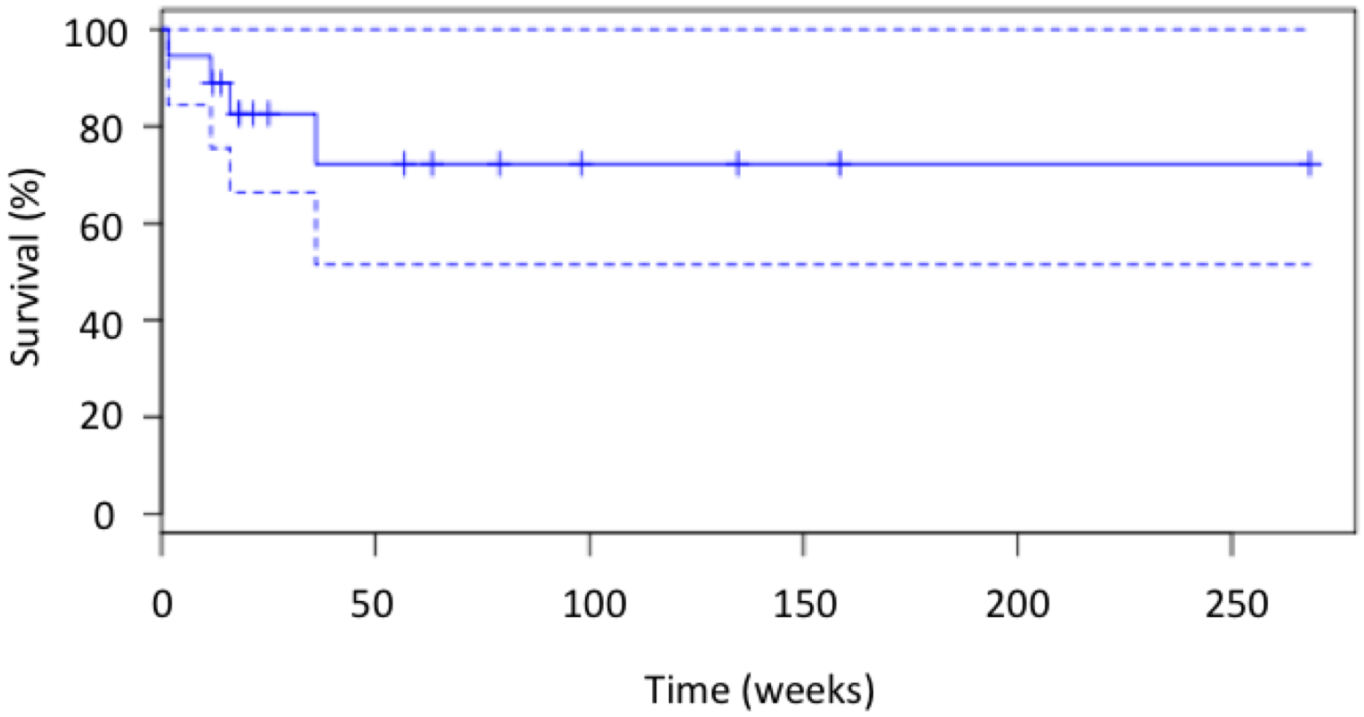
- **Severe neurological symptoms**
  - mRs = 5 in 89% patients: **heavy disability**
  - median UWDRS = 105 (79-117): **severe neurological impairment**
  - predominance of **dystonia** in 16/18 and **Parkinsonism** in 12/18
  - **jejunostomy or gastrotomy** in 78%; tracheostomy in 56%
  - brain MRI was abnormal in all patients; constant lenticular nucleus involvement

- **A fragile general condition**
  - 7/18 patients (40%): severe sepsis within 3 months before LT
  - 5/18 required an ICU admission for acute respiratory distress syndrome (ARDS) in the month prior LT.

LT IN NEUROLOGICAL WD PATIENTS: RESULTS

COPRIMARY OUTCOMES: (1) SURVIVAL RATE

- Cumulated survival rate was
  - **88.8% at 1 year**
  - 82.5% at 1.5 year
  - **72.2% at 3 years and 5 years**



LT IN NEUROLOGICAL WD PATIENTS: RESULTS

COPRIMARY OUTCOMES: (1) SURVIVAL RATE

- four patients (22%) deceased
- within a median interval of **13.8 (9-21) months** after LT
- due to sepsis of pulmonary origin

- were significantly associated with death:
  - **Severe sepsis (p=0.011**) in the month before LT
  - **ICU admission (p=0.001**) in the month before LT

- Tracheostomy and male gender tended to be associated with death

LT IN NEUROLOGICAL WD PATIENTS: RESULTS

- After a mean follow-up of 71+/-74 months (5.8 y)
- fourteen patients (78%) were alive.

LT IN NEUROLOGICAL WD PATIENTS: RESULTS

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- fourteen patients (78%) were alive.

COPRIMARY OUTCOMES: (2) DISABILITY AT THE LAST FOLLOW-UP: mRANKIN

- median mRs improved from the pre-LT state :1.5 (1-4) vs 5 (5-5); p<0.0001

= nine patients (64%) had a score below 3, and five scored 4

0 : no symptoms

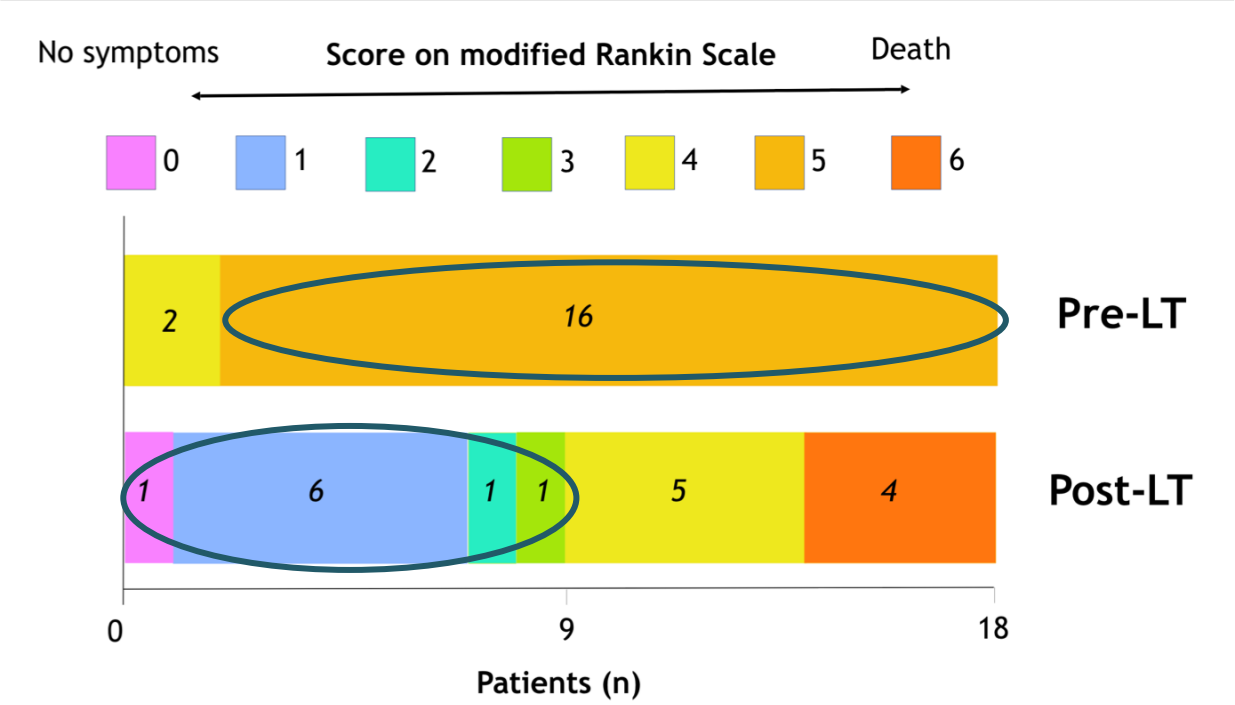
1 : no significant disability, despite symptoms ; able to carry out all usual duties and activities

2 : slight disability ; unable to carry out all previous activities but able to look after own affairs

3 : moderate disability ; requiring some help, but able to walk without assistance

4 : unable to walk without assistance and unable to attend to own bodily needs without assistance

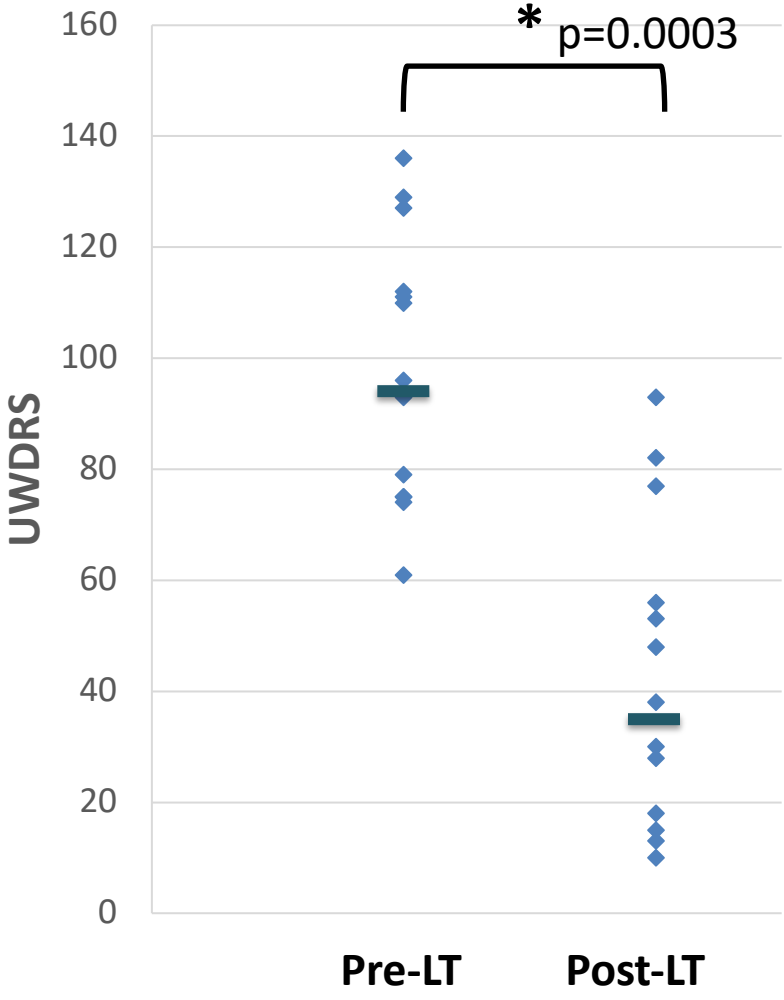
5 : severe disability ; bedridden, incontinent and requiring constant nursing care and attention



LT IN NEUROLOGICAL WD PATIENTS: RESULTS

COPRIMARY OUTCOMES: (2) DISABILITY AT THE LAST FOLLOW-UP: UWDRS

- mean follow-up 71+/-74 months (5.8 y)
- **median UWDRS score improved**: from 96 (75-112) to 38 (18-56) (p=0.0003)
  - 60% had a major improvement
  - 30% a moderate improvement
  - 10% a mild improvement/stable status



LT IN NEUROLOGICAL WD PATIENTS: RESULTS

SECONDARY OUTCOMES AT LAST FOLLOW-UP

- ophthalmological **KFR score improved** (p=0.0007)
- **brain MRI score improved** (p=0.0007)
  - ✓ Differences depending on the location: nucleus caudate (p=0.008), pons (p=0.009), thalamus (p=0.03), mesencephalon (p=0.01)
- Serum copper and Ceruloplasmin: values normalized in all
- 24h-urinary copper excretion was slightly elevated 0.60 µmol/L (N= 0,02-0,40) in seven patients at last follow-up.

LATE COMPLICATIONS

- 1 patient: re-transplantation 7 and 11 months after the first LT due to arterial complications.
- 1 patient: developed a Burkitt lymphoma three years after LT. Considered into complete remission seven years after LT.
- 1 patient: complex partial seizures due to the extension of a cortical lesion eight months after LT. Three years after LT, epilepsy is well controlled, the UWDRS score has improved

LT IN NEUROLOGICAL WD PATIENTS: DISCUSSION

- Currently the **largest cohort** with a **prolonged follow-up** in this specific indication of pure neurological presentation

- **The patient survival rate**
  - at 1 year (88.8%) was similar to those published for LT in WD because of liver failure
  - at five years (72.2%) stays reasonable since:
    - before LT,
      - ✓ patients were all bedridden and required constant nursing care
      - ✓ patients had a constant deterioration despite chelation
    - LT was proposed as a **rescue treatment**.

- **2/3 of patients had a major improvement of their neurological disability**

After almost six years of follow-up:

  - 64% gain physical independence for daily living activities (mRankin ≤ 3)
  - 60% had a major improvement at UWDRS
  - 100% had no more jejunostomy/tracheostomy

- The presence of a **sepsis before LT and an ICU admission within the month** prior to LT could be defined as predictive factors of bad outcome (associated with a higher risk of death)

LT IN NEUROLOGICAL WD PATIENTS: CONCLUSION

- LT = a therapeutic option in **selected neurologic** WD patients resistant to decoppering therapies and without severe liver disease

- LT may not be the solution for every patient but has a place as a **rescue therapy** while waiting for future therapies

- The management of transplanted patients with severe neurologic WD is complex, and should be handled by experienced multidisciplinary teams to improve long-term survival and neurological handicap

- **Many questions remain:**
  - When should we transplant these patients ?
  - What are the good prognosis factors ?
  - What are the mechanisms underlying the effect of LT on brain dysfunction ?
  - Should chelation treatment be resumed after LT ?

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THANK YOU FOR YOUR KIND ATTENTION

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