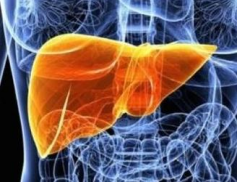

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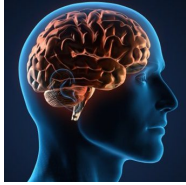

Liver transplantation for neurological Wilson disease: selecting the right candidate

Aurélia Poujois, MD, PhD

on belhalf on the French neuroLT group

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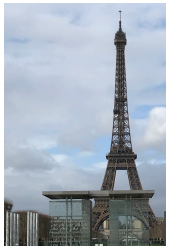
French National Reference Centre for Wilson disease, Neurology Department

Wilson India – Webinar 17th October 2020

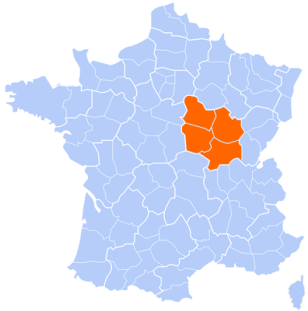


centre de référence maladies rares

CRMR Maladie de Wilson et autres maladies rares liées au cuivre

ROTHSCHILD FOUNDATION HOSPITAL
HEAD AND NECK EXPERTISE

Good afternoon from Burgundy, countryside in France !



Thank you to the organizers to have maintain these 3 days about Wilson !

Aurélia POUJOIS, MD, PhD

Disclosure of Interest: Nothing to Disclose

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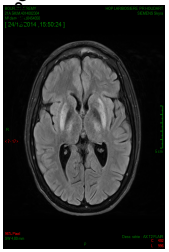
Case 1: primary neurological worsening despite medical treatment

Poujois, Wilson National reference center - France



Day 1

UWDRS 15
mRankin:1

J.B. 18y, one month of slight parkinsonism, can run => WD Diagnosis => slow introduction of DP

2 months

UWDRS 42
mRankin:2

Continuous worsening of symptoms (park, dystonia, swallowing) => DP switched to Trientine 2HCL

5 months

UWDRS 85
mRankin:3

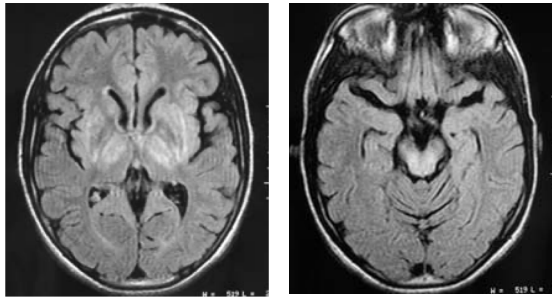
Continuous worsening of parkinsonism, dystonia, severe dysarthria and dysphagia (gastrotomy)

6.5 months

UWDRS 110
mRankin:5

Bedridden due to severe parkinsonism and dystonia,
can not swallow,
can not speak

Case 2: secondary neurological worsening



February 2000

M.B. , aged 13

<u>January 2000</u>: Diagnosis of WD

- Mild dystonic features in lower limbs
- Abnormal MRI, presence of bilateral KF rings
- Mild cirrhosis

=> Trientine 2HCL 900 mg/d (acute side effect with DP)

<u>February 2002</u>:

Clinical recovery. No more neurological symptoms.

MRI improved; bilateral KF rings decreased

Stable cirrhosis

<u>June 2002</u>: went to holidays in Morocco and stopped his treatment during three months …

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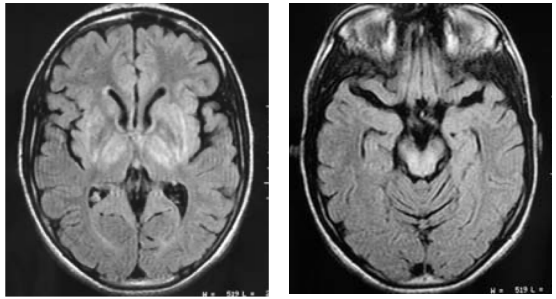
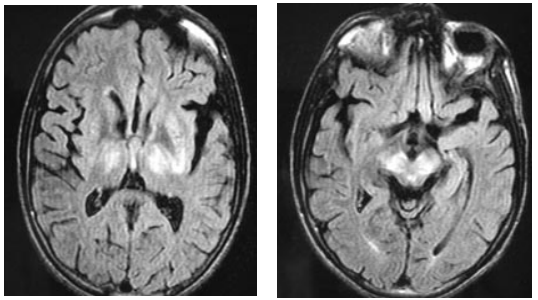
Case 2: secondary neurological worsening



February 2000

June 2002: interruption of treatment



September 2002

2,5 years after WD diagnosis

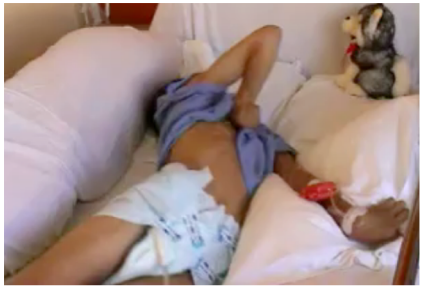
« Fulminant » neurologic deterioration two months after stopping treatment

(generalized dystonia with “status dystonica”)

⇒ re-introduction of Trientine 2HCL

⇒ Adjunction of zinc acetate

⇒ **NO EFFECT after 2.5 months of combination therapy**



UWDRS 129
mRankin:5

NEUROLOGICAL WORSENING

- **Not so rare**
  - **11 - 24%** of neurological patients
  - With all three drugs: DP: 13.8 % >Trientine: 8 % > ZS: 4.3 %

- **Dramatic condition**
  - Irreversible in 44% of patients, resulting in severe disability or death despite optimal therapy
  - outcome depends on the severity of the neurological involvement as assessed by UWDRS. In a cohort of 15 patients with early neurological worsening despite medical treatment, the Polish team (Litwin et al.) showed that patients with a:
    - ✓ UWDRS score >75 did not recover
    - ✓ **UWDRS score >97 died** in less than two years

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Merle, 2007; Prashanth, 2005; Svetel, 2009; Litwin, 2015

NEUROLOGICAL WORSENING

- **Mechanisms of deterioration are unknown: many hypotheses**
    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 : a « *start low—go slow* » regimen

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NEUROLOGICAL WORSENING

How to deal with these dramatic situations ?

⇒ Since there is currently no other more effective medical treatment, what could be the **place of liver transplantation** in these catastrophic situations ?

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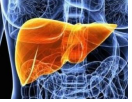

LIVER TRANSPLANTATION and WILSON'S DISEASE

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)

Pure Neurologic forms with worsening of symptoms despite medical treatment

- remains controversial

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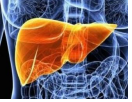
Guillaud, 2014; Laurencin, 2017; Modi, 2015; Mocchegiani, 2014;Cheng, 2009; Duarte-Rojo, 2009; Marin, 2007; Suess, 2007; Suzuki, 2003; Schumacher, 2001; Robles, 1999; Bax, 1998; Kassam, 1998; Schilsky, 1994; Mason, 1993



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- 15 cases-reports on LT for strict neurological indication published :

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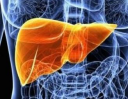
Authors, Journal, year	Country	Number of patients and age at LT	Evaluation	Duration of Follow-up	Neurological outcome	Death
Laurencin C et al. Eur Neurol. 2017	France	2 (17y, 19y)	Rankin, UWDRS, MRI	3 and 4 years	Clinico-radiological improvement in both patients (could walk unaided, no more gastrostomy feeding, dysarthria and dystonia improved). Patient 1: Rankin improved from 4 to 3, UWDRS from 79 to 45 Patient 2: Rankin improved from 4 to 2, UWDRS from 74 to 28	0
Modi P et al. Saudi J Kidney Dis Transpl., 2015	India	1 (14y)	Medici score, KFR, MRI	1 year	Major improvement (pre-LT score:14/30; post-LT: 27/30). Walked and went back to school six months after LT. No need for tracheostomy after LT. MRI improvement. KFR disappeared 9 months after LT	1 (12 months after LT after stopping medications for two months)
Mocchegiani F et al. Transplant Proc., 2014	Italy	1 (19y)*	Medici score, KFR, MRI	4 years	Major improvement (pre-LT score: 8/30; post-LT score: 28/30) with full recovery of neuropsychiatric symptoms. MRI: significant improvement KFR disappearance	0
Guillaud O et al. J Hepatol 2014	France	6 (range 14·5-42y)	Clinical examination, MRI	Up to 79 months	3 had major clinical and MRI improvement	3 (sepsis 2, 4 and 36 months after LT)
Cheng F, et al. Transplantation, 2009	China	2	Medici score	6 months	1 complete improvement 1 partial improvement	0
Duarte-Rojo A et al. Rev Gastroenterol Mex. 2009	Mexico	2*	Clinical evaluation, MRI	80 months	Complete clinical remission and MRI improvement	0

Authors, Journal, year	Country	Number of patients and age at LT	Evaluation	Duration of Follow-up	Neurological outcome	Death
Marin C et al. Transplant Proc. 2007	Spain	4	Clinical examination, MMSE, MRI	1-17 years	1 had an incomplete neurological improvement and is alive 17y after LT 3 became normal at 6 months MRI improvement in all	0
Suess T et al. Mov Disord 2007	Germany	1 (31y)	Clinical examination, MRI	2 years	Major improvement. Slight dysarthria and mild tremor MRI improvement	0
Suzuki S et al. Transplant Proc. 2003	Japan	1 (17y)	Clinical examination, MRI	12 months	Major neurological improvement - residual symptoms (dysarthria, tremor). MRI improvement	0
Schumacher G et al. Transplant Proc. 2001	Germany	4 (range 15-34y)	Clinical examination	Range 5-10 years	4 major improvement (more rapid in young patients, mild residual symptoms in 2)	0
Robles R et al. Transplant Proc. 1999	Spain	4	Clinical and neuropsychiatric examination, MRI	Range 1-9 years	2 fully recovered and went back to work 1 improved incompletely	1 (sepsis 4 months after LT)
Bax RT et al. Neurology 1998	Germany	1 (14y)	Neurologic score, MRI	1 year	Major improvement with almost normal neurologic status Stable MRI	0
Kassam N et al. Can J Gastroenterol. 1998	USA	1 (22y)*	Clinical and neuropsychiatric examination, CT	43 months	Progressive neurological improvement Psychiatric disturbances persisted with behavioural disinhibition	1 (suicide)
Schilsky ML et al. Hepatology 1994	USA	1 (25y)	Neurological examination	ND		1 (ruptured splenic artery aneurysm)
Mason AL et al. Dig Dis Sci. 1993	USA	1 (27y)	Neurological examination	6 weeks	Early onset of improvement	1 (ruptured splenic artery aneurysm)



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- 15 cases-reports on LT for strict neurological indication published :
  - 32 patients, heterogeneous evaluation and follow-up
  - A majority of good outcome
  - No survival rates available

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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

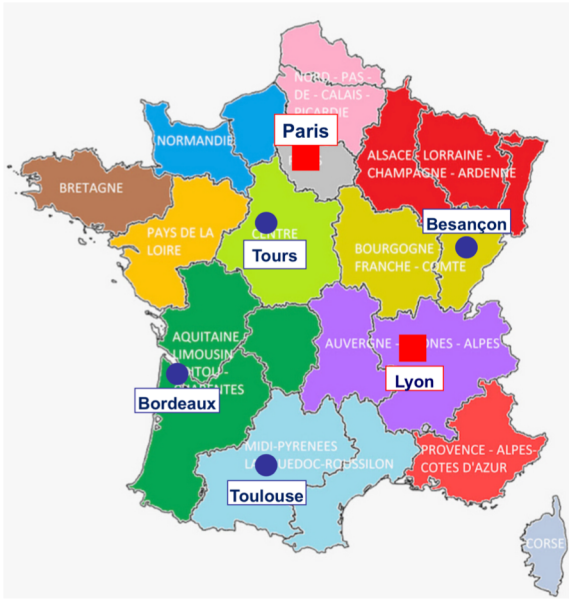
FRENCH EXPERIENCE ON LT FOR PURE NEUROLOGICAL INDICATION

In France, thanks to rare 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



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ARTICLE CLASS OF EVIDENCE

Liver transplantation as a rescue therapy for severe neurologic forms of Wilson disease

Aurélia Poujois, MD, PhD, Rodolphe Sobesky, MD, PhD, Wassilios G. Meissner, MD, PhD, Anne-Sophie Brunet, MD, Emmanuel Broussolle, MD, PhD, Chloé Laurencin, MD, Laurence Lion-François, MD, Olivier Guillaud, MD, Alain Lachaux, MD, PhD, François Maillot, MD, PhD, Jérémie Belin, MD, Ephrem Salamé, MD, Claire Vanlemmens, MD, Bruno Heyd, MD, Céline Bellesme, MD, Dalila Habes, MD, Christophe Bureau, MD, PhD, Fabienne Ory-Magne, MD, Pascal Chaine, MD, Jean-Marc Trocello, MD, PhD, Daniel Cherqui, MD, PhD, Didier Samuel, MD, PhD, Victor de Ledinghen, MD, PhD, Jean-Charles Duclos-Vallée, MD, PhD, and France Woimant, MD

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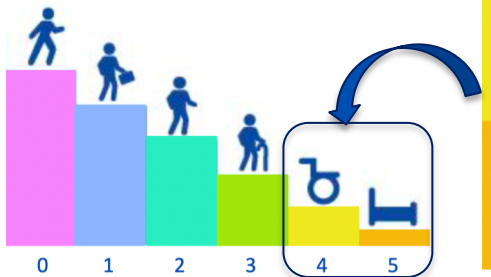
Neurology® 2020;94:e2189-e2202. doi:10.1212/WNL.0000000000009474

LT IN NEUROLOGICAL WD PATIENTS: METHODS-1

- Ambispective 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

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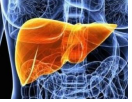

LT IN NEUROLOGICAL WD PATIENTS: METHODS-2

- 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

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LT IN NEUROLOGICAL WD PATIENTS: METHODS

BASELINE DATA BEFORE LT

- ✓ **Demographic** data: age at diagnosis, time between worsening and LT, age at LT,
- ✓ **Clinical** evaluation:
  - modified Rankin score (mRs)
  - UWDRS score with main neurological symptoms (dystonia, parkinsonism, tremor, behavioural disturbances)
  - ophthalmological score
  - severity of liver disease (MELD and Child scores)
- ✓ **Biological, copper balance and imaging** data (brain MRI)
- ✓ Type and number of **drugs** prescribed

- ✓ Occurrence of severe sepsis
- ✓ Admission to an intensive care unit (ICU)
- ✓ Need for tracheostomy, gastrostomy or jejunostomy

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LT IN NEUROLOGICAL WD PATIENTS: METHODS

LIVER TRANSPLANTATION

- All patients received grafts from cadaveric donors
- Standard immunosuppression
- Histo-pathological analysis of the native liver

OUTCOMES FOLLOWING LIVER TRANSPLANTATION

For each patient,

- Duration of follow-up
- mRs
- UWDRS, KFR and brain MRI scores
- liver function tests
- copper metabolism
- Late complications after LT
- number and cause of death

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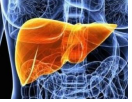

LT IN NEUROLOGICAL WD PATIENTS: OUTCOMES

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.

Neurological improvement was arbitrarily considered :

- **major** : if UWDRS score decreases above 66%,
- **moderate:** if UWDRS score decreases between 33% and 65%
- **mild or absent** : if UWDRS score decreases below 33%

SECONDARY OUTCOMES

Evolution at the last follow-up of:

- ophthalmological score (KFR)
- brain MRI score

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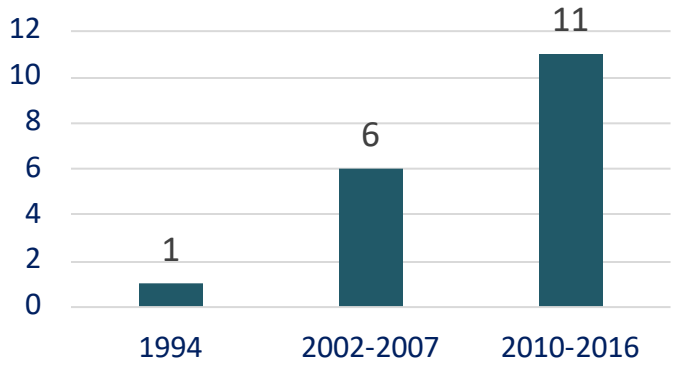
LT IN NEUROLOGICAL WD PATIENTS: RESULTS-1

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**

LT for neurological indication in WD patients during the 1994-2016 period of time



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

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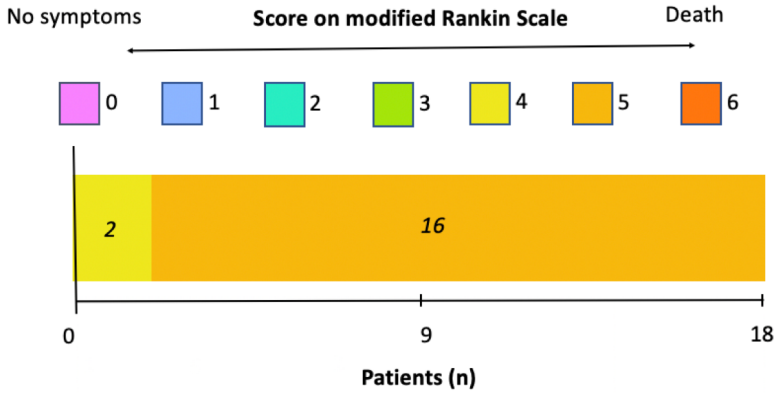
LT IN NEUROLOGICAL WD PATIENTS: RESULTS-2

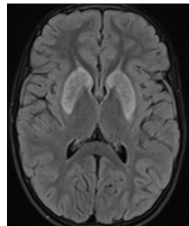
PATIENT CHARACTERISTICS AT INCLUSION BEFORE LT

- **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



- **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.



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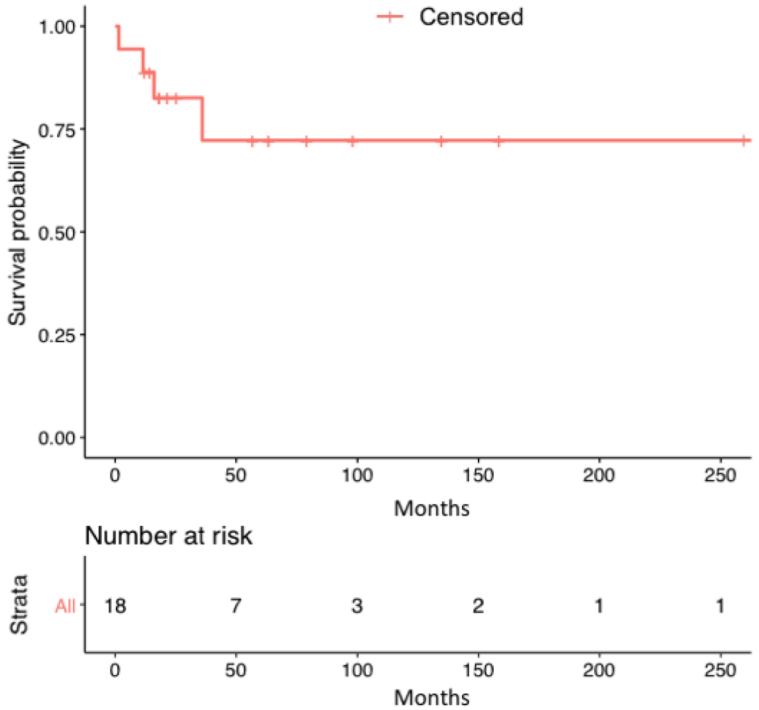
LT IN NEUROLOGICAL WD PATIENTS: RESULTS-3

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**



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

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LT IN NEUROLOGICAL WD PATIENTS: RESULTS-5

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

- After a mean follow-up of 71+/-74 months (5.8 y)

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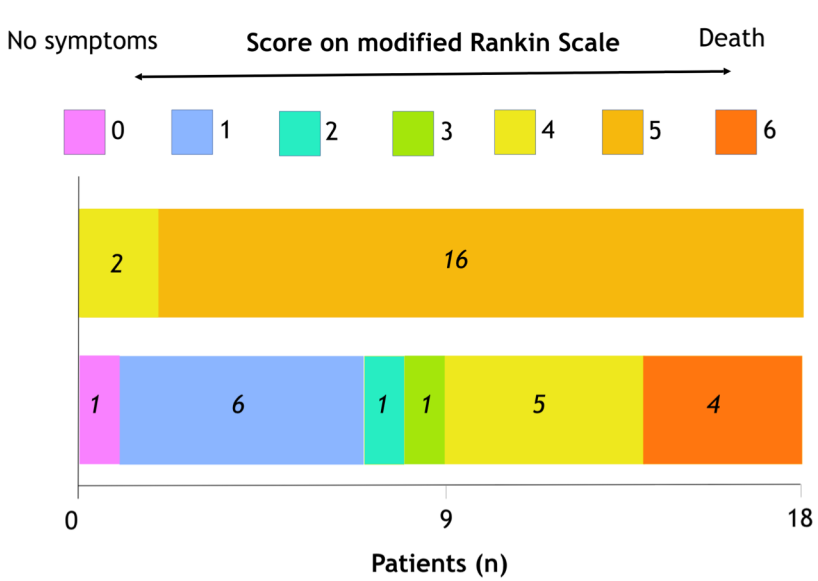

Pre-LT

Post-LT

- ✓ 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

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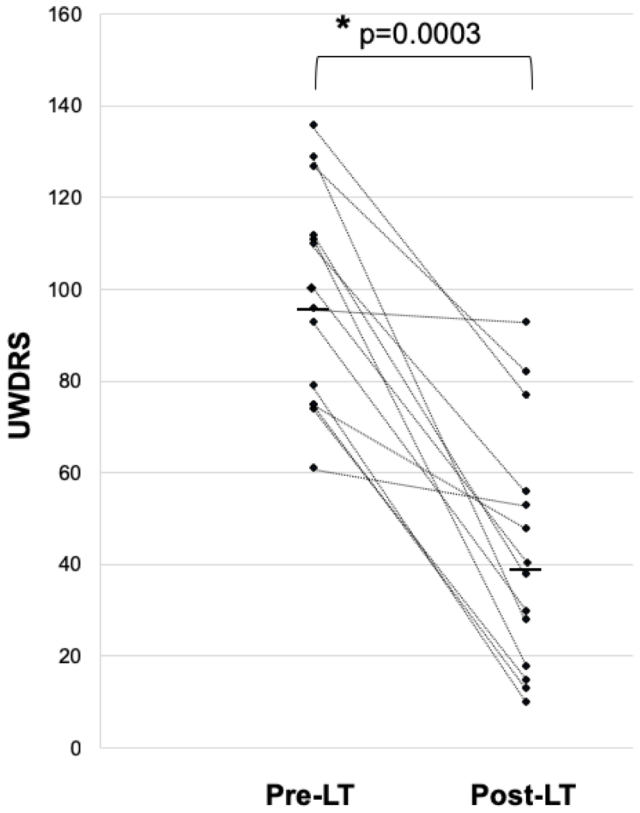
LT IN NEUROLOGICAL WD PATIENTS: RESULTS-6

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

- mean follow-up 71+/-74 months (5.8 years)
- **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



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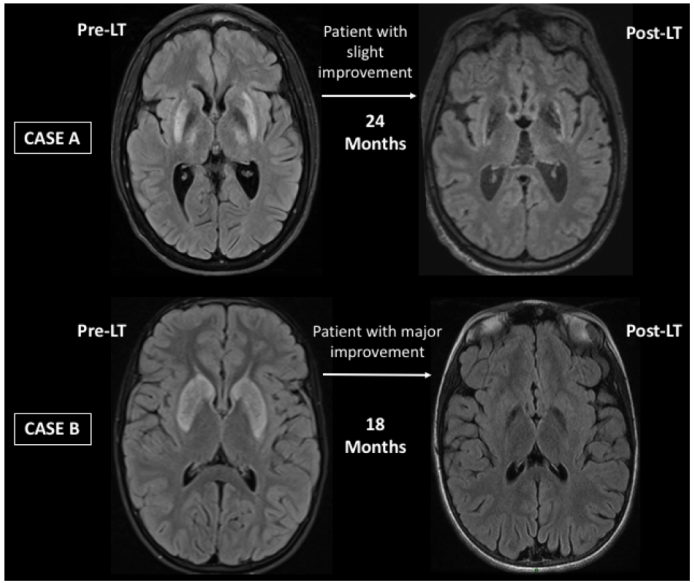
LT IN NEUROLOGICAL WD PATIENTS: RESULTS-7

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.



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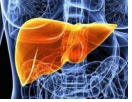

LT IN NEUROLOGICAL WD PATIENTS: RESULTS-7

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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

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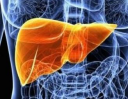

LT IN NEUROLOGICAL WILSON: DISCUSSION

- Currently the **largest cohort** with a **prolonged follow-up** in this specific indication of pure neurological presentation. But has a major limit : is not a controlled study

- **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 LT was proposed as a **rescue treatment** : before LT, patients
    - ✓ were all bedridden and required constant nursing care
    - ✓ had a constant deterioration despite chelation

- **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)

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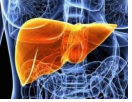

LT IN NEUROLOGICAL WD PATIENTS: CONCLUSION

- LT could be 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 ? Not too early not to late either
  - 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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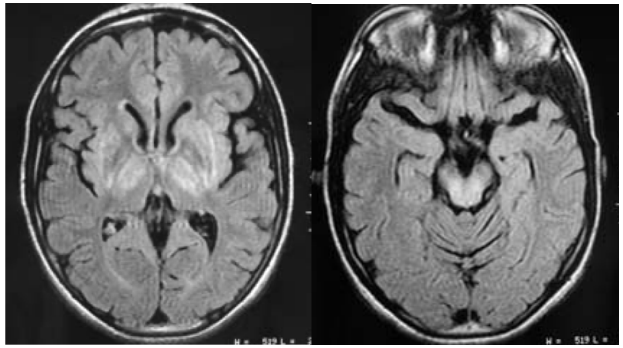
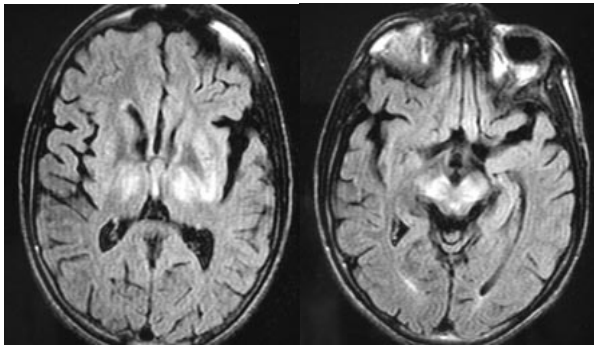


February 2002

June 2002: interruption of treatment



September 2002

Mehdi B

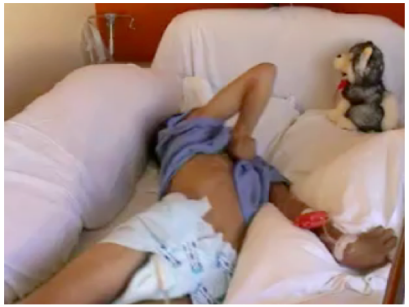
2,5 years after WD diagnosis

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

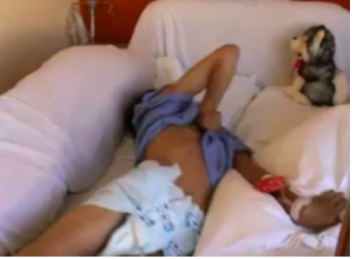
⇒ re-introduction of Trientine

⇒ Adjunction of zinc acetate

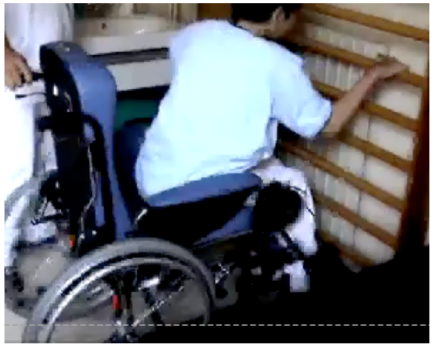
⇒ **NO EFFECT after 2.5 months of combination therapy**



Mid-November 2002: Liver transplantation

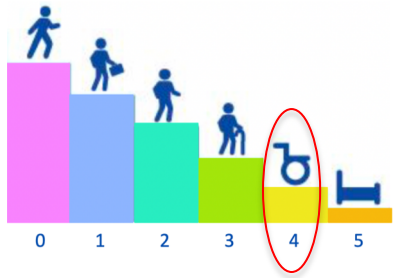


May 2003 - 6 months

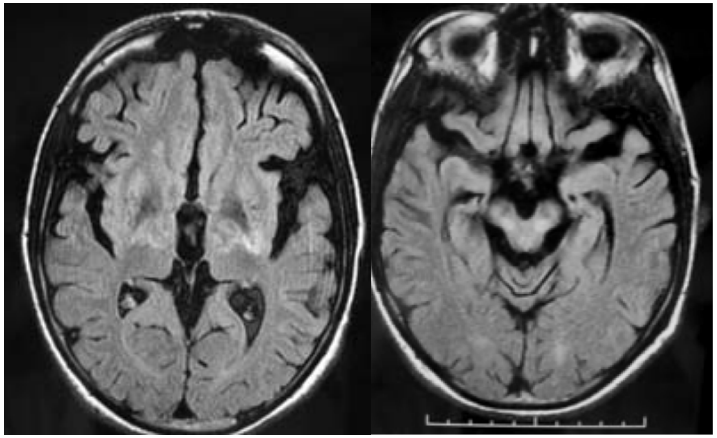


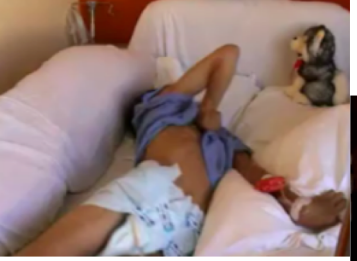
Stands-up alone, takes a few steps

…



Improvement of brain MRI:
decrease of high T2 signals in basal ganglia and brainstem
But major atrophy

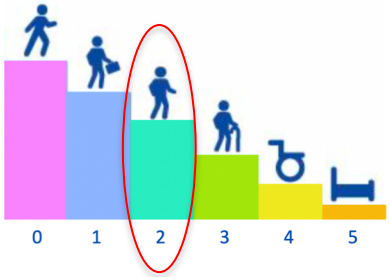


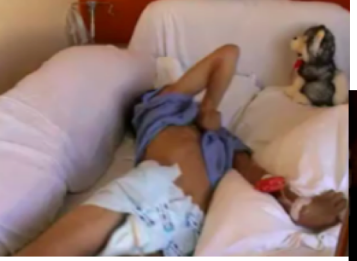


6 months

November 2004 -2 years

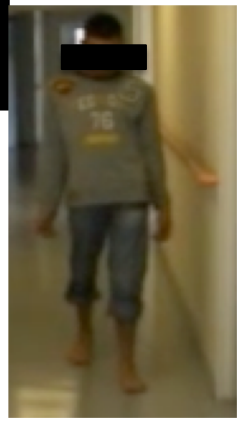
Walks alone,
Autonomous in activities
of daily living

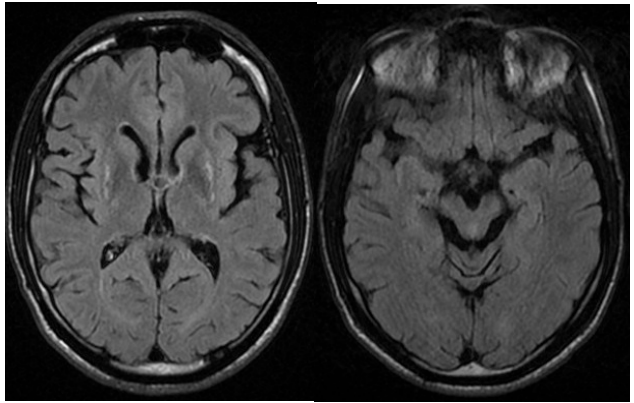




6 months

2 years

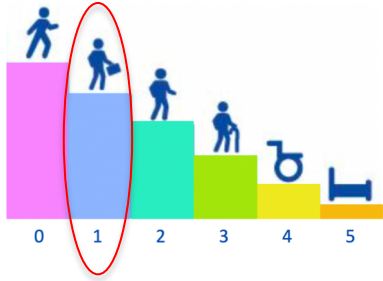




Sub-normal MRI

January 2015 - 12 years

Totally independent
Got married
Has children …



UWDRS 28
mRankin:1

Dr A Poujois, Wilson National reference center - France

French National Reference Centre for Wilson disease

Coordinator-site

Hôpital Fondation Adolphe de Rothschild, Paris

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CRMR Maladie de Wilson et autres maladies rares liées au cuivre

centre de référence maladies rares

HÔPITAL FONDATION Adolphe de ROTHSCHILD
LA RÉFÉRENCE TÊTE ET COU

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Dr Erwan Morvan
Dr Alexandre Obadia



Psychiatrics : Dr Diane Samama
Liver specialist : Dr Carole Frey


psychologist: Sabine Lassalle
Neuropsychologist : Gwennaëlle Perez
Speech therapist : Michaela Pernon
Diététicien: Vincent Petit




Clinical Research Associate
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Caregiver Hypnotherapist
Nathalie Combet

Nurse
Hélène de Saint Vaurly

Social worker
Stéphanie Morel

Secretary
Edith de Boisvilliers

Communication
Mélanie Roulleau

Toxicologists:
Dr Nouzah Djebrani-Oussedik
Dr Joël Poupon
Molecular biologist : Dr Corinne Collet



Hôpital Lariboisière Fernand-Widal AP-HP

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

A NETWORK

2 Reference Centres

Coordinator site: Hospital Foundation A de Rothschild, Paris (former Lariboisière hospital, Paris)

Constituent site: HFME Hospital (Lyon)

8 Competence Centres:

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

1 WD Patient organization

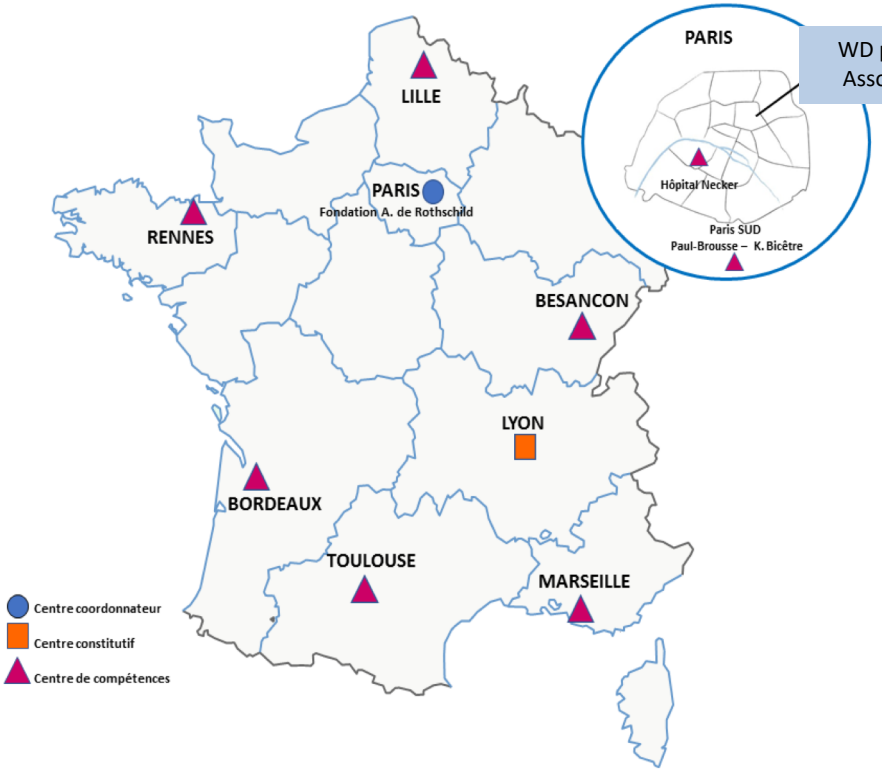
A MULTIDISCIPLINARY TEAM

Paediatry/Hepatology/Neurology

Molecular Biology Laboratory

Toxicology laboratory, metals and trace elements

A NATIONAL WD REGISTRY



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Thank you for
your attention !

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