Parkinsonism and Related Disorders 24 (2016) 15–19

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Subclinical neurological involvement does not develop if Wilson's disease is treated early

Raffaele Dubbioso [a, 1], Giusy Ranucci [b, 1], Marcello Esposito [a, 1], Fabiola Di Dato [b], Antonietta Topa [a], Mario Quarantelli [c], Margherita Matarazzo [d], Lucio Santoro [a], Fiore Manganelli [a, 2], Raffaele Iorio [b, *, 2]

[a] Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples Federico II, Italy
[b] Department of Translational Medical Sciences, Section of Pediatrics, University of Naples Federico II, Italy
[c] Institute of Biostructure and Bioimaging, National Research Council (CNR), Naples, Italy
[d] Department of Translational Medical Sciences, Section of Internal Medicine, University of Naples Federico II, Italy

ARTICLE INFO

Article history:
Received 23 September 2015
Received in revised form
13 January 2016
Accepted 26 January 2016

Keywords:
Wilson's disease
Therapy
Neurological diagnostic techniques
Outcome

ABSTRACT

Background & aims: Wilson's disease (WD) is a genetic disorder of copper metabolism causing dysfunctions of various organs, mostly the liver and brain. If untreated, WD is fatal, but early treatment results in a good prognosis, although the long-term neurological outcome has not yet been clarified. To address this issue, we evaluated the neurological status of early-treated WD patients without overt nervous system impairment using neurophysiological, neuropsychological and neuroimaging procedures at least 10 years after treatment onset.

Methods: Thirty-eight WD patients (18 females, aged 24.47 ± 7.50 years), who received an early diagnosis (in presymptomatic or mild/moderate liver disease stages without neurological involvement) and prompt treatment, were clinically evaluated with the Global Assessment Scale. Presentation was hepatic in 36 subjects (95%), while 2 patients (5%) were presymptomatic. A neurophysiological study was performed to explore the central motor conduction time of the upper and lower limbs, and motor cortex excitability using single pulses and paired-pulse transcranial magnetic stimulation. Neuroimages were obtained with brain magnetic resonance scans. Cognitive abilities, and psychiatric and behavioral disturbances were evaluated with neuropsychological tests.

Results: Patients were undergoing treatment with penicillamine (7 patients) or zinc salts (31 patients) with good adherence. They did not present any neurological signs at clinical evaluation or at specific scale of impairment, the mean Global Assessment Scale score was 0.3 ± 0.7. Magnetic resonance imaging, transcranial magnetic stimulation studies and neuropsychological/neuropsychiatric assessment ruled out subclinical involvement.

Conclusions: This study suggests that early diagnosis and treatment of WD may prevent the onset of neurologic damage, even at subclinical level.

1. Introduction

Wilson's disease (WD) is a widely known condition in many medical fields as it can present with different clinical features depending on the site of excessive copper accumulation and subsequent copper toxicity [1]. It was first described in detail in 1912 and defined as “progressive lenticular degeneration causing a familial nervous disease associated with cirrhosis of the liver” [2]. At that time, neurological dysfunctions and advanced liver impairment were considered an inevitable part of the disease. With the advent of effective drugs, prolonged survival has become the norm

Abbreviations in order of appearance: Wilson's Disease, WD; Central Nervous System, CNS; Global Assessment Scale, GAS; D-Penicillamine, DPA; Magnetic Resonance Imaging, MRI; Resting Motor Threshold, RMT; Active Motor Threshold, AMT; Short Interval Intracortical Inhibition, SICI; Intracortical Facilitation, ICF; Cortical Silent Period, CSP; Mini-Mental State Examination, MMSE; Frontal Assessment Battery, FAB; Raven's 47 Colored Progressive Matrices, RCPM; Beck Depression Inventory Scale, BDI; Neuropsychiatric Inventory, NPI; Barrott Impulsiveness Scale Vision 11, BIS 11.

* Corresponding author. Department of Translational Medical Science, Section of Pediatrics, University of Naples Federico II, Via Pansini 5, Naples 80131, Italy.
E-mail address: riorio@unina.it (R. Iorio).

[1] These authors contributed equally to this work as first authors.
[2] These authors contributed equally to this work as senior authors.

http://dx.doi.org/10.1016/j.parkreldis.2016.01.024
1353-8020/

for WD patients.

In general, prognosis depends on the severity of liver and neurological disease and adherence to treatment. Early treatment with chelators or zinc salts can control symptoms related to liver or brain damage [3,4], therefore the prognosis of WD is strictly related to the time of diagnosis. Unfortunately, because of the wide clinical spectrum of WD and its variable onset time, the condition is usually diagnosed, and hence appropriately treated, almost one year after the onset of clinical manifestations. Although the efficacy of therapy with chelators or zinc is well documented, there is a subset of WD patients in whom the liver disease persists despite treatment [4–8]. Accordingly although the central nervous system (CNS) seems to be protected from copper accumulation in appropriately treated patients [7,8], it remains to be established whether minimal copper deposition can cause subclinical neurologic impairment. In an attempt to shed light on this issue, we used clinical, radiological, neurophysiological and neuropsychological tools to evaluate the CNS of a large group of WD patients who were diagnosed and treated in the early stage of the disease.

2. Patients and methods

We recruited 38 patients (18 females and 20 males) with clinical, biochemical and genetic or histological evidence of WD. Their mean age was 24.47 ± 7.50 years with a mean disease duration (time from clinical onset) of 19.24 ± 6.50 years, a mean treatment duration of 17.54 ± 6.46 years and 13.5 ± 3.9 years of schooling. Patients were selected from among those observed at Pediatric Liver Unit of University of Naples Federico II in the period 1984–2013, if the following inclusion criteria were met: (1) diagnosis of WD confirmed by molecular analysis of the ATP7B gene (standard methods, Regional Hospital for Microcytemia, Cagliari, Italy) or by liver copper content of dry tissue higher than 250 μg/g or both; (2) available data of clinical-laboratory features, copper metabolism and treatment (dosage and compliance) at the time of diagnosis and throughout the observation period; (3) diagnosis of WD made during the presymptomatic or mild or moderate liver disease stages followed by prompt treatment, i.e., “early treated” patients; and (4) absence of overt neurological involvement. Presentation was hepatic in 36 subjects (95%), while 2 patients (5%) referred for family screening were diagnosed in a presymptomatic stage. Mutation analysis of the ATP7B coding region was performed in 36/38 patients. Disease-causing mutations were detected in 30 (83%) patients on both chromosomes (12 homozygotes and 18 compound heterozygotes) and in 4 (11%) subjects only on one chromosome. No mutations were detected in 2 (6%) patients (a couple of siblings) in whom WD diagnosis was confirmed by other parameters such as ceruloplasmin serum levels, urinary copper and liver copper content (Ferenci score [9] 4 and 5, respectively). Overall, 34 patients of 29 unrelated families carried 25 different mutations. The enrolled patients were prospectively examined at the Department of Neurosciences between 2011 and 2013.

Clinical features of nervous system impairment were evaluated in each patient by a neurologist using a standard neurological examination and the neurological assessment section (tier 2) of the Global Assessment Scale (GAS) for WD [10]. To assess subclinical CNS involvement, patients underwent brain magnetic resonance imaging (MRI), transcranial magnetic stimulation (TMS) studies and neuropsychological/neuropsychiatric evaluation. TMS studies were also performed in a separate group of 15 WD patients with neurologic signs and Kayser–Fleischer rings (8 males and seven females; mean age 28.2 ± 12.1 years, mean treatment duration 15.8 ± 9.14 years). Fifteen age-, education-, and sex-matched healthy subjects, not affected by any neurological, psychiatric or other relevant clinical conditions (10 females and five males; mean age 26.7 ± 9.1 years; years of schooling 13.2 ± 2.4) served as the control group for clinical, neurophysiological, neuropsychological and neuropsychiatric evaluation.

Written consent to participate in the study was obtained from all subjects. The protocol was approved by the local ethics committee, and the research was conducted in accordance with the 1964 Declaration of Helsinki.

2.1. Treatment

As recommended by EASL and AASLD [11,12], D-penicillamine (DPA) was used as initial and maintenance therapy for symptomatic patients, zinc salts were used as initial and maintenance therapy for presymptomatic patients, and as maintenance therapy after a first phase with DPA for symptomatic patients. Starting from 1995, zinc was also used as first-line therapy in WD patients with a mild liver disease. Adherence to treatment was assessed based on treatment schedule data (prescribed dose, number of daily doses, and adequate interval between medicine and meals), and on levels of urinary copper excretion (<75 μg/24 h), urinary zinc levels (>2000 μg/24 h) and serum zinc levels (>150 mg/dl) for patients treated with zinc, and urinary copper levels (values between 200 and 500 μg/24 h after a year of treatment) for patients treated with DPA [11,12]. Treatment efficacy was evaluated based on the absence of manifestations of WD other than liver disease, on the maintenance of liver enzymes (aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase) within normal range and on a basal urine copper level lower than 75 μg/24 h for patients treated with zinc, and between 200 and 500 μg/24 h for patients on DPA. A standard ultrasonography of liver was performed in all patients.

2.2. Neuroradiological evaluation

All Magnetic Resonance Imaging (MRI) studies were carried out with three Tesla on the same MRI scanner (Trio, Siemens Medical Systems, Erlangen, Germany). The brain MRI studies included T2-weighted turbo spinecho (TR/TE 4400/100 ms) and FLAIR (TR/TE/TI 8000/100/2200 ms) sequences, T1-weighted conventional SE (TR/TE 580/15 ms). During the MRI study, subjects laid supine with the head lightly fixed by straps and foam pads to minimize head movement, and were asked to relax with eyes closed.

2.3. Neurophysiological assessment

Neurophysiological study was performed to explore the central motor conduction time of the upper and lower limbs, and motor cortex excitability using single pulses and paired-pulse TMS. We evaluated the following TMS parameters of the stimulated motor cortex: (1) resting motor threshold (RMT) and active motor threshold (AMT); (2) short interval intracortical inhibition (SICI) and intracortical facilitation (ICF); (3) cortical silent period (CSP) [13]. Details regarding the transcranial stimulation procedures we used are reported in Supplementary Material.

2.4. Neuropsychological and neuropsychiatric assessment

The Mini-Mental State Examination (MMSE) was used to assess general cognitive abilities, and the Frontal Assessment Battery (FAB) to screen frontal functions [14]. In addition, we used the following neuropsychological tests to evaluate selected cognitive domains: (1) Corsi's block-tapping test and verbal span for words to assess short-term memory; (2) Rey's immediate and delayed recall of 15 words and of a short passage to evaluate long-term memory and learning; (3) attentional matrices and the shortened form of