

Case report

## Wilson's disease with myoclonus and white matter lesions

Egberto Reis Barbosa<sup>a</sup>, Laura Silveira-Moriyama<sup>a</sup>, Alexandre Costa Machado<sup>a,\*</sup>,  
Luiz Alberto Bacheschi<sup>a</sup>, Sérgio Rosemberg<sup>b</sup>, Milberto Scaff<sup>a</sup>

<sup>a</sup>Department of Neurology, São Paulo University Medical School, R. Sergipe, 401-conj.311 R. 01234-001 Sao Paulo, SP, Brazil

<sup>b</sup>Department of Pathology, São Paulo University Medical School, R. Sergipe, 401-conj.311 R. 01234-001 Sao Paulo, SP, Brazil

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### Abstract

White matter lesions (WML) and epilepsy have been occasionally seen in Wilson's disease. No cases of generalized myoclonus have been reported so far. We present a patient with psychiatric symptoms starting at age 16, followed by tremor, generalized dystonia and severe generalized myoclonus. In addition to classical findings, the MRI showed also extensive WML in temporal, parietal and frontal regions, preserving interhemispheric fibers. Necropsy revealed marked alterations of white matter, cortex and basal ganglia. We subsequently review the literature concerning WML and myoclonus in Wilson's disease.

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### 1. Introduction

Wilson's disease (WD) is a hereditary disease of the copper metabolism. Clinical presentation includes hepatic, psychiatric (particularly behavioral disorders) and neurologic manifestations such as dystonia, tremor and parkinsonism. Focal epilepsy has been occasionally described but no cases of generalized myoclonus. Brain magnetic resonance imaging (MRI) characteristically shows cortical–subcortical atrophy and focal lesions, especially in basal ganglia, thalamus, and brain stem. We present a clinico-pathological report of a patient with psychiatric symptoms starting at age 16, followed by tremor, generalized dystonia, dementia and severe generalized myoclonus. The MRI showed classical findings and extensive WML. We subsequently review relevant literature.

### 2. Case report

A 16-year-old boy, with no significant family history or past medical history, presented with progressive decline of the academic performance, irritability and aggressive behavior leading to abandonment of school. During the next year his handwriting deteriorated and he developed slurred speech. At the age 17, during an acute episode of fever, he presented jerks of the four limbs, sometimes also affecting the head, with no loss of conscience reported. Worsening of psychiatric features (without hallucinations or delusions) lead to a hospitalization in a psychiatric institution for 45 days with a prescription at discharge that included chlorpromazine and haloperidol.

At age 18, he presented unsteady gait, impaired coordination with action tremor of upper limbs, difficulty in swallowing solid foods and frequent nasal bleedings. He required assistance for all daily living activities and further became bedridden. At 19 years he again presented jerks affecting the four limbs and was referred to our Department of Neurology.

\*Corresponding author. Tel./fax: +55 11 32141457.

E-mail address: alexandreamachado@hotmail.com.br (A.C. Machado).

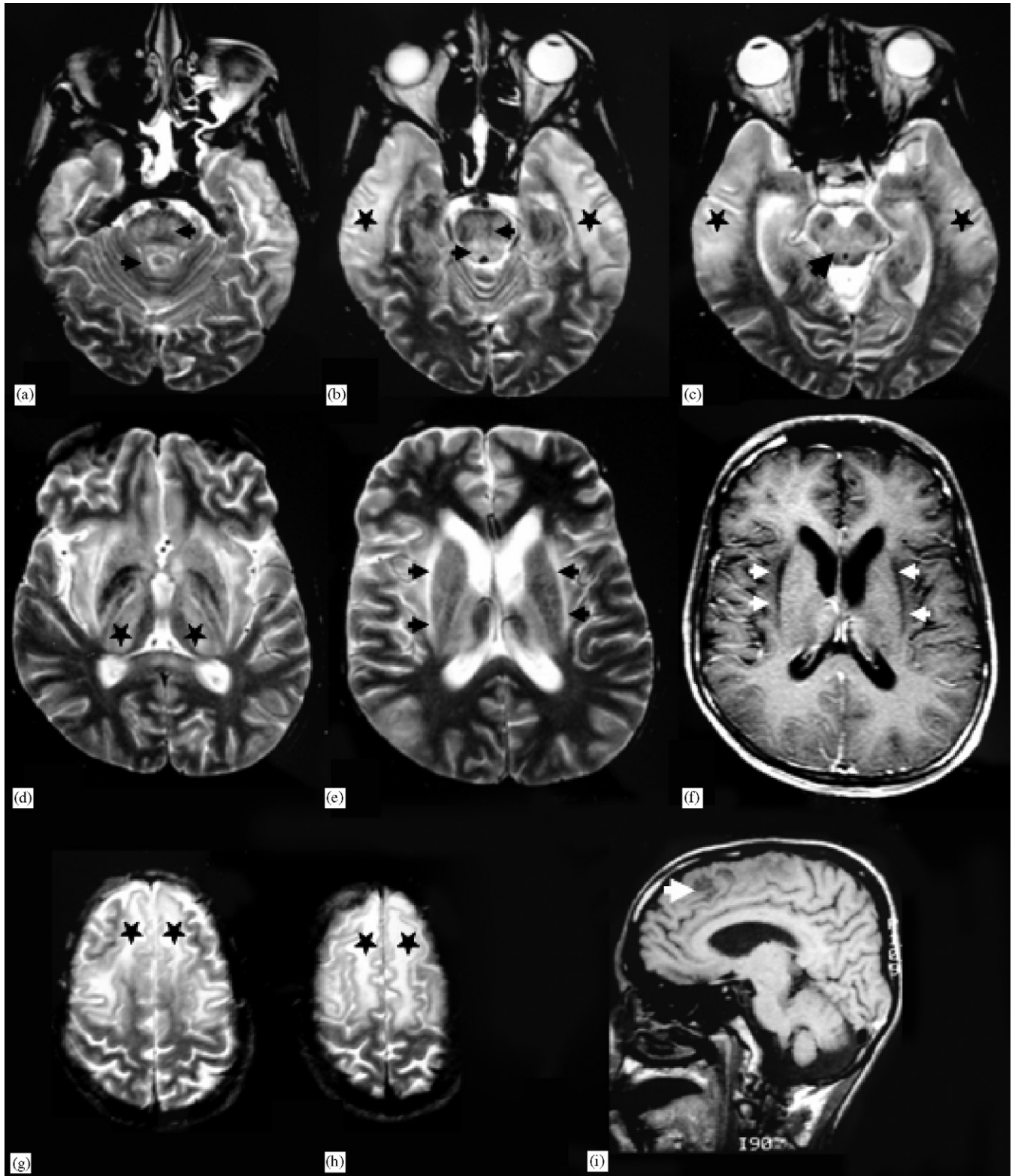


Fig. 1. MRI: (a) Axial T2-weighted image shows increased signal intensity in basilar and tegmental pons (arrows); (b) Axial T2-weighted image shows increased signal intensity in basilar and tegmental pons (arrows) and increased signal intensity is seen in bilateral temporal white matter (stars), suggesting demyelination; (c) Axial T2-weighted image shows increased signal intensity in periaqueductal gray matter (arrow) and loss of characteristic low signal in the red nuclei. Increased signal intensity is seen in bilateral temporal white matter (stars); (d) Axial T2-weighted image shows abnormal increased signal intensity in both thalami (stars); (e) Axial T2-weighted image shows bilateral high signal in putamen lateral border, external capsule and claustrum boundaries (arrows); (f) Axial T1-weighted image shows the same lesions of (e) with low signal intensity (arrows); (g) and (h) Axial T2-weighted images show high signal intensity of bilateral frontal white matter demyelination compatible (stars); (i) Sagittal T1-weighted image show low signal intensity in frontal white matter (arrow).

Neurological examination showed extensive motor impairment; cognition seemed severely altered, although evaluation was precluded by the motor impairment; snouting and grasping responses were present. He presented dystonic flexion postures affecting the four limbs, mainly on left side, dysmetria and intention tremor in upper limbs; gait and stance were impossible. He also presented anarthria and severe dysphagia requiring feeding tube. He presented generalized hyperreflexia, plantar reflex responses were flexor and superficial abdominal reflexes were normal. There were episodic synchronous myoclonus affecting the four limbs and trunk. The slit-lamp examination of the cornea disclosed Kayser-Fleischer rings bilaterally. The plasma ceruloplasmin level was 2 mg/dl (25–60 was 9 µg/2mg/dl), the serum copper was 15 µg/dl (70–160 µg/dl) and the urinary copper excretion rate was 9 mg/24 h (3–35 µg/24 h). Cerebrospinal fluid analysis revealed mild pleocytosis (9 cells: 75% lymphocytes, 17% reticulocytes, 7% neutrophils) with protein levels of 44 md/dL and normal protein electrophoresis.

Electroencephalogram revealed disorganized background activity without epileptiform discharges; during the exam the patient did not present myoclonus. At admission, cranial tomography (CT) showed cortical atrophy, ventricular enlargement and bilateral hypodense lesions in putamen and frontal white matter. A cranial MRI, performed 2 weeks later, revealed general-

ized brain atrophy, low signal changes on T1 weighted images in putamen, globus pallidus and frontal white matter. Furthermore there was also high signal changes on T2 weighted images in thalami, striatum, midbrain and brainstem associated with extensive frontal and temporal WML with the same characteristics (Fig. 1).

Based on the clinical, laboratorial and neuroimage findings the diagnosis of WD was made without liver biopsy. Treatment was started with penicillamine (1 g/day) for 4 weeks but due to leucopenia was replaced by zinc sulfate (660 mg/day). No response was obtained and the patient died of infectious complications after 2 months of treatment.

General autopsy (9 h after death) showed extensive broncho-pneumonia and a macro and micronodular liver cirrhosis. Brain weighted 1600 g and was edematous and soft to palpation mainly in both frontal lobes and left parietal lobe. Coronal slicing showed cavitations and an almost liquefied aspect of the white axes of the circumvolutions of frontal, parietal and temporal with sparing of the occipital lobes. Basal ganglia were softened with brownish discoloration. Microscopically, there were profound alterations of the white matter (demyelinated on its superficial aspect and cavitated on its cores; U fibers not spared) and of the underlying cortex with areas of loosening of the neuropil, microcavitations, some capillary proliferation, severe neuronal loss and gliosis; there were some ball and ring

Table 1  
Cases of Wilson's disease and extensive white matter lesions in brain imaging

Year	Author	Sex	Age	Duration of disease	Main neurological manifestations	Main psychiatric manifestations	Classification of Epilepsy	Location of WML
1989	Chu [8]	M	16	5	Tremor, dystonia, dysphagia, dysarthria, quadriplegia	Absent	Focal	Bifrontal, biparietal
1989	Chu [8]	M	23	6	Slurred speech, tremor, rigidity, dysphagia, ataxic gait	Absent	Absent	Bifrontal and right centro parietal
1989	Chu [8]	M	19	4	Dysarthria, tremor, dystonia, hyperreflexia	Altered behaviour	Focal	Right frontal
1989	Chu [8]	M	23	6	Tremor	Absent	Focal	Left frontal
1991	Jardim [9]	M	16	1	Dysarthria, bedridden, dysphagia, hyperreflexia	Absent	Focal	Right frontal
1995	Huang [6]	F	20	2	Hand tremor, drooling, left hemiparesis	Irritability, paranoid delusion	Focal	Bifrontal
1995	Huang [6]	M	26	14	Drooling, dysarthria, tremor, dystonia, rigidity, hyperreflexia	Psychosis, mental retardation	Focal	Bifrontal
1995	Huang [6]	M	23	2	Tremor, akathisia, truncal ataxia, dystonia	Irritability, paranoid delusion	Focal	Bifrontal
1996	Yoshii [5]	M	22	?	Tremor, dysarthria, dysphagia, ataxia	Personality change	Focal	Right frontal
2002	Hedera [10]	M	13	2	Dysarthria, tremor, dystonia, rigidity	Decline in academic performance	Absent	Bifrontal
2004	Our case	M	19	3	Dysarthria, dysphagia, dystonia, bedridden, hyperreflexia	Aggressive behaviour	Myoclonus	Bifrontal, biparietal, bitemporal

hemorrhages. Caudate nuclei and putamens were severely affected. Thalamic nuclei were somewhat gliotic without evident cell loss. Globus pallidus as well as mesencephalon, pons, medulla and cerebellum were microscopically unremarkable. In general, Alzheimer type II cells were present but not predominant and there were no Opalski cells. No copper deposits were found by rhodanine staining. Spinal cord was not removed. Meninges had no inflammatory alterations.

### 3. Discussion

Psychiatric presentation, mainly depression and irritability, is the first clinical manifestation in at least 20% of patients with WD. In a review of 44 literature and 14 personal cases of epilepsy related to WD Dening [1], mentions only one case of suspected myoclonus. Severe, generalized myoclonus has never been reported.

WML were present in 6 out of 30 cases reviewed by Saatci [2] (two clearly extensive), 5 out of 22 seen by Starosta-Rubinstein [3] (at least one extensive) and one (extensive) out of 25 neurologically symptomatic WD patients seen by Roh [4].

Pathophysiology of WML in WD is unknown. They may correlated with advanced [5] or early [6] phases of the illness. Two cases [5–7] had concomitant improvement of basal ganglia lesion with worsening of WML in follow-up, suggesting they might have different pathogenesis, but in our case there were no differences in anatomopathological findings between basal ganglia and white matter. The brainstem lesions observed in MRI in our case were not confirmed in necropsy, suggesting transient alterations (like edema) as the substrate for these image findings.

Image and clinical presentations in 10 cases of extensive WML that have been reported [5,6,8–10] with comprehensive description of neurological and psychiatric features are very similar (Table 1). Epilepsy and

psychiatric features were present in 80% and 60% of patients, respectively. Incidence of epilepsy was higher than in general WD population (6.2% the 200 patients Cambridge series [1]). Frontal lobe was compromised in all cases.

Although previous studies suggested that the nature of white matter and basal ganglia lesions might be different we found no significant anatomopathological differences between these two types of lesions. The characteristics of this case are quite unique on account of WD is a highly pleomorphic entity.

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