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Cranial MR in Wilson Disease: Abnormal White Matter in Extrapyramidal and Pyramidal Tracts

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PURPOSE: To describe abnormal white matter in the brain on MR in Wilson disease and to compare with anatomic location of white matter tracts. **METHODS:** Forty-six patients with Wilson disease were examined. Axial T1-weighted inversion-recovery, axial T2-weighted spin-echo, and coronal T2*-weighted gradient-echo MR images were performed. Imaging studies were compared with clinical data. **RESULTS:** Seventeen patients showed abnormalities in the region coinciding with the following white matter tracts: corticospinal tract (24%, n = 11), dentatorubrothalamic tract (24%, n = 11), and pontocerebellar tract (17%, n = 8). **CONCLUSION:** Abnormal extrapyramidal and pyramidal white matter tracts are part of the neuroimaging spectrum of Wilson disease. No significant correlation was found with neurologic groups and individual white matter tracts affected.

Index terms: Brain, magnetic resonance; White matter, abnormalities and anomalies; Wilson disease

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Wilson disease is a rare, autosomal recessive disorder of copper metabolism, which is characterized by cirrhosis of the liver, bilateral softening and degeneration of the basal ganglia, and Kayser-Fleischer rings of the cornea. Oral zinc is an effective therapy in the treatment of patients with Wilson disease (1).

In Wilson disease excess copper is found throughout the brain. The tendency for extensive damage of the basal ganglia is unexplained. If neurologic abnormalities are present, movement disorders predominate. Wilson disease is therefore considered to be an extrapyramidal disease. Well-known imaging findings include abnormalities of the gray matter nuclei and general atrophy (2–7). Abnormal white matter is frequently described in imaging studies on Wilson disease (2–7). The purpose of our study is to describe abnormalities of white matter on magnetic resonance (MR) in patients with Wilson disease and to compare these imaging abnormalities with the anatomic location of white matter tracts and clinical data.

Patients and Methods

Forty-six patients with biochemically proved Wilson disease, all of whom had received treatment, had MR examinations of the brain on a 1.5-T system. The MR imaging parameters included: axial T2-weighted spin-echo (2000/50-100/2 [repetition time/echo time/excitations]), axial T1-weighted inversion recovery (1875/30/1, inversion time 650), and coronal T2*-weighted gradient-echo (530/20/2, flip angle 20°) sequences with section thicknesses of, respectively, 8, 8, and 6 mm, intersection gaps of, respectively, 1.6, 1.6, and 0.6 mm, 225-mm field of view, and 180 × 256-mm acquisition matrix. In the first part of the study, MR examinations were independently scored for white and gray matter changes by two radiologists, who were nonblinded to the patient's disease. Agreement was reached by consensus. Secondly, these neuroimaging abnormalities and the anatomic location of white matter tracts were compared. To illustrate the course of white matter tracts in the brain, an autopsy brain of a healthy subject was used. The brain was preserved in phosphate-buffered 4% formaldehyde for 4 weeks before en block dehydration and paraffin embedding. Serial whole-brain slides, of 12-mm thickness, were cut with an

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TABLE 1: Abnormal white matter locations, specific tracts, and neurologic groups in 17 of 46 patients with Wilson disease

Case	Cerebellum	Pons	Mesencepholon	PLIC	Thalamus	Tract	Group
1	SCP, MCP	TEG	DM, CP	· · ·	· · ·	DRT, PCT, CST	P, C
2	SCP, MCP	TEG	DM	· · ·	· · ·	DRT, PCT	P
3	· · ·	rnd	CP	PLIC	· · ·	CST	P
4	SCP	· · ·	DM	?	LN	DTT	C
5	SCP	rnd, TEG	DM, CP	?	LN	DTT, CST	P, C
6	· · ·	· · ·	CP	PLIC	· · ·	CST	P
7	SCP, HEM	dif, TEG	DM	· · ·	LN	DTT, PCT	C
8	SCP, MCP	str, TEG	DM	PLIC	LN	DTT, PCT, CST	P, C
9	SCP	· · ·	DM	· · ·	LN	DTT	P
10	SCP	dif, TEG	DM, CP	· · ·	LN	DTT, PCT, CSP	P
11	HEM	TEG	· · ·	· · ·	· · ·	PCT	P, D
12	SCP	· · ·	DM	· · ·	LN	DTT	P, C
13	SCP, HEM	rnd, TEG	DM, CP	?	LN	DTT, PCT, CST	P, D, C
14	· · ·	rnd, TEG	CP	?	· · ·	CST	P, D
15	HEM	· · ·	CP	· · ·	· · ·	PCT, CST	P, D
16	SCP	· · ·	DM, CP	· · ·	· · ·	DRT, CST	A
17	· · ·	· · ·	CP	· · ·	· · ·	CST	P, D, C

Note.—A indicates asymptomatic group; C, cerebellar group; CP, cerebral peduncle; CST, corticospinal tract; D, dystonic group; dif, diffuse abnormal pons; DM, dorsal mesencephalon; DRT, dentatorubral tract; DTT, dentatothalamic tract; HEM, cerebellar hemispheres; LN, lateral thalamic nucleus; MCP, medial cerebellar peduncle; P, pseudoparkinsonian group; PCT, pontocerebellar tract; PLIC, posterior limp of internal capsule; rnd, rounded pons lesions; SCP, superior cerebellar peduncle; str, striped pons lesions; TEG, tegmentum pontis; and ?, no clear distinction between abnormal PLIC and basal ganglia.

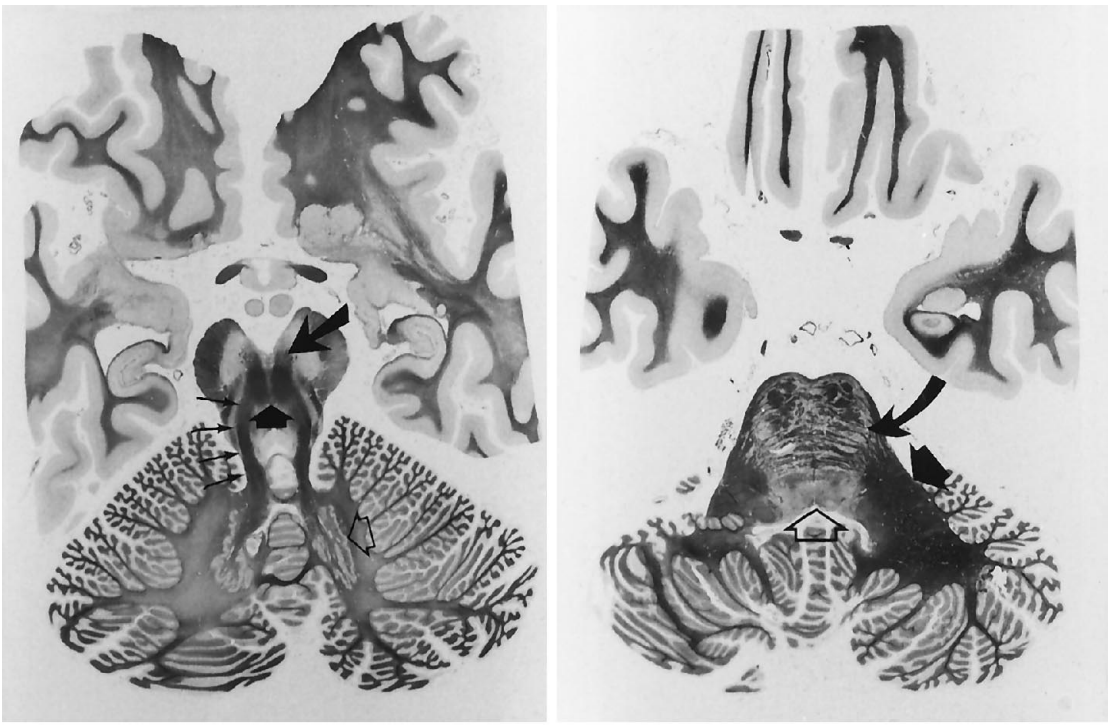


Fig 1. Whole-brain slides, stained with Klüver-Barrera for myelin, demonstrating the dentatorubral tract (A) and pontocerebellar tract (B).

A, The dentatorubral tract originating in the dentate nucleus (*open arrowhead*) contributes substantially to the superior cerebellar peduncle (*small arrows*), which decussates in the dorsal mesencephalon (*black arrowhead*) and terminates in the red nucleus (*large arrow*).

B, The pontocerebellar tract is composed mainly of fibers crossing in the base of the pons (*curved arrow*) and partially arises from the pontine tegmental reticular nucleus (*open arrowhead*). It terminates by way of the middle cerebral peduncle (*black arrowhead*) in all cerebellar lobules.

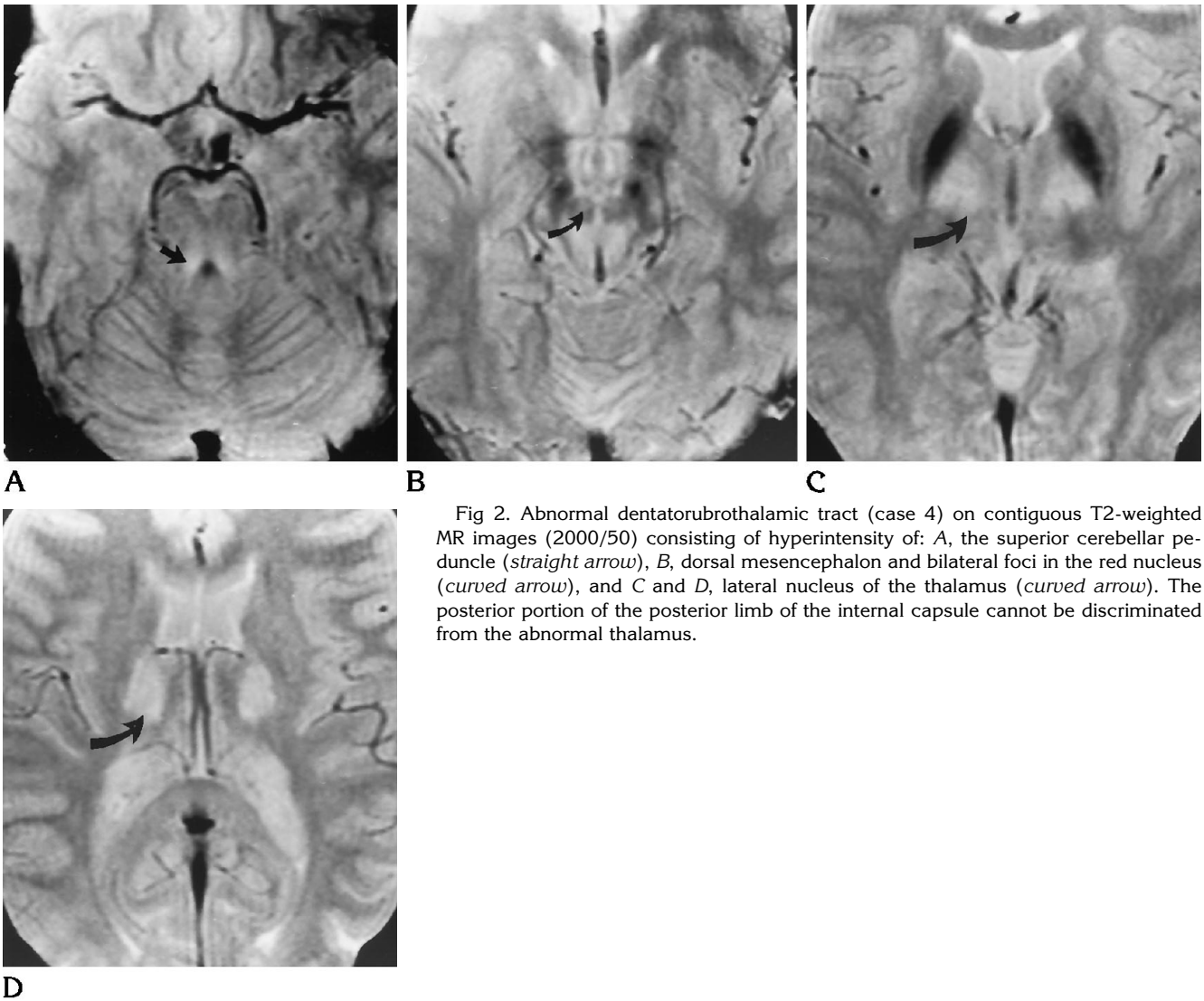


Fig 2. Abnormal dentatorubrothalamic tract (case 4) on contiguous T2-weighted MR images (2000/50) consisting of hyperintensity of: *A*, the superior cerebellar peduncle (*straight arrow*), *B*, dorsal mesencephalon and bilateral foci in the red nucleus (*curved arrow*), and *C* and *D*, lateral nucleus of the thalamus (*curved arrow*). The posterior portion of the posterior limb of the internal capsule cannot be discriminated from the abnormal thalamus.

angulation comparable to the MR images. The paraffin slides were stained according to Klüver-Barrera for myelin. The third part of the study involved comparison of imaging abnormalities with neurologic groups. Clinical examinations were performed by the same neurologist within 1 week of the imaging examinations. Neurologic signs were retrospectively put in four groups: (*a*) pseudoparkinsonian group, (*b*) dystonic group, (*c*) cerebellar group, and (*d*) asymptomatic group.

Results

Abnormal white matter changes on MR images were seen in 19 patients (41%), 16 of whom (34%) also had abnormal signal intensity of gray matter nuclei. Three patients (6%, cases 2, 11, and 16) showed only abnormal signal intensity of white matter, and 10 patients (22%) had only abnormal signal intensity of gray matter nuclei. Abnormal white matter of the brain stem, cerebellum, and posterior limb of the internal capsule was seen in 17 patients (Table 1). The signal intensity was diffusely abnormal in both cerebral hemispheres in one patient (case 18) or more localized to the frontal lobe in 3 patients (cases 11, 15, and 19). The abnormal signal intensity pattern was increased on T2*-weighted spin-echo and T2*-weighted gradient-echo images, and in 61% of patients some lesions had decreased signal intensity on T1-weighted inversion-recovery images.

In the second part of the study we noted that most abnormal white matter could be located in three tracts: the dentatorubrothalamic tract, the

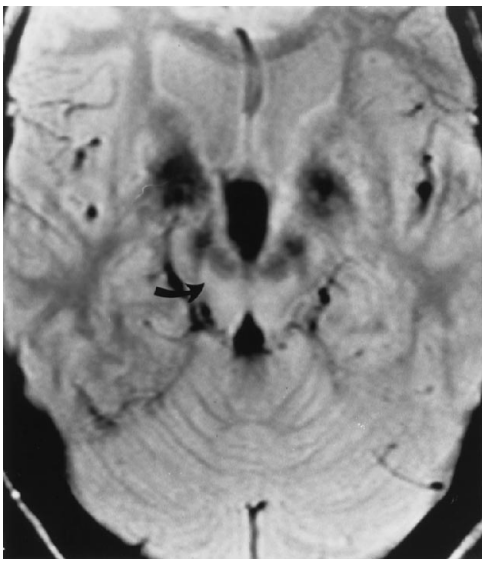


Fig 3. Abnormal dentatorubrothalamic tract (case 10) with high signal intensity around the red nucleus (*arrow*) on a T2-weighted MR image (2000/50).

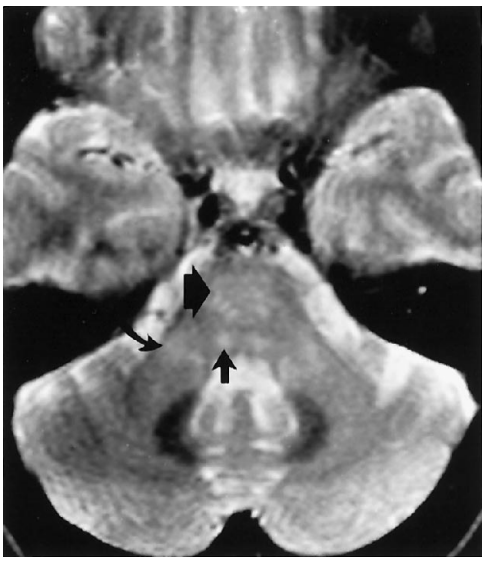


Fig 4. Abnormalities in the pontocerebellar tract (case 8) on a T2-weighted MR image (2000/100) consist of hyperintense crossing pontine fibres (*arrowhead*), pontine tegmental reticular nucleus (*straight arrow*), and middle cerebellar peduncle (*curved arrow*).

pontocerebellar tract, and the corticospinal tract (Table 1 and Fig 1). The tracts were contiguously abnormal or were involved on a patchy, noncontinuous fashion. The dentatorubral tract was concluded to be abnormal if the superior cerebellar peduncle and dorsal mesencephalon were contiguously abnormal (n = 3). The dentatothalamic tract was concluded to be abnormal if the superior cerebellar peduncle, dorsal mesencephalon, and thalamus were contiguously abnormal (n = 8, Figs 2 and 3). The pontocerebellar tract was concluded to be abnormal when abnormalities were seen in the base of the pons, cerebellar hemispheres, and/or middle cerebellar peduncle (n = 8, Fig 4). The corticospinal tract was concluded to be abnormal when abnormal signal intensity was present in the posterior portion of the posterior limb of the internal capsule and/or in the middle division of the cerebral peduncle and/or in the base of the pons (n = 11, Fig 5).

In the third part of the study we found that 19 patients (41%) were asymptomatic, and 15 of 27 symptomatic patients had neurologic signs that were scored in more than one symptom group. No significant correlation between specific white matter tract involvement and neurologic groups was found (Table 2).

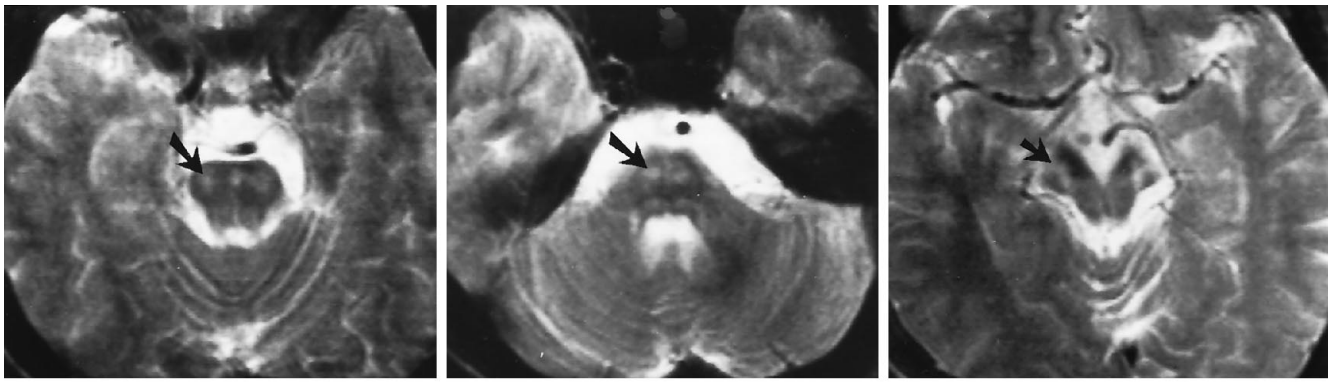
TABLE 2: Relationship between four neurologic groups and white matter tract involvement on MR in 46 patients with Wilson disease

Group	DTT/DRT	PCT	CST	NTA
Pseudoparkinsonian	8	7	10	8
Dystonic	1	3	4	4
Cerebellar	7	4	5	4
Asymptomatic	1	0	1	19

Note.—DTT indicates dentatothalamic tract; DRT, dentatorubral tract; PCT, pontocerebellar tract; CST, corticospinal tract; and NTA, no tract abnormalities seen on MR images.

Discussion

Our results showed that abnormal white matter on MR images is a common finding in Wilson disease. Light microscopic studies confirm active involvement of supratentorial and infratentorial white matter with pathologic alterations varying from capillary endothelial swelling, gliosis, and demyelination to spongy degeneration or even loss of neurons (8–13). In histologic studies central pontine myelinolysis is also found in Wilson disease (9, 12, 14). Demyelination, edema, and gliosis can explain the sig-



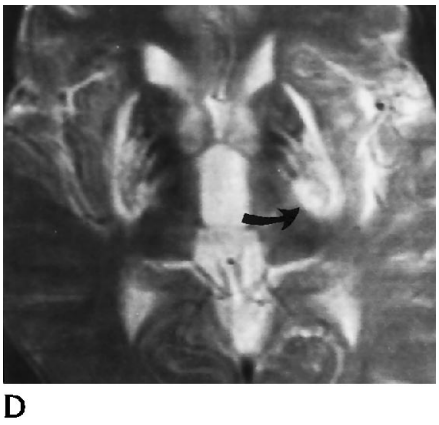


Fig 5. Abnormal corticospinal tract (case 14) on contiguous T2-weighted MR images (2000/100) consisting of *A* and *B*, rounded lesions in the base of the pons (*arrow*), and *C*, abnormal center of the cerebral peduncle (*arrow*). *D*, The posterior portion of the posterior limb of the internal capsule (*curved arrow*) cannot be discriminated from the abnormal lentiform nucleus.

nal intensity changes of white matter on the MR images. We considered that part of the white matter abnormalities could be located in both extrapyramidal and pyramidal tracts, although Wilson disease is in general considered to be an extrapyramidal disease.

The dentatorubrothalamic tract is the main efferent pathway of the cerebellum and originates in the dentate nucleus (15). The dentate nucleus mainly gives rise to the superior cerebellar peduncle, which decussates in the dorsal mesencephalon. The superior cerebellar peduncle terminates, surrounds, or traverses the red nucleus: several patients showed abnormal signal intensity around the red nucleus (Fig 3), and one patient had subtle hyperintense punctate foci within the nucleus ruber on the T2-weighted spin-echo images (Fig 2B). The dentatothalamic tract terminates in the ventrolateral nucleus of the thalamus. Abnormal signal intensity of the lateral thalamic nucleus could not be clearly subdivided in the different subgroups on MR. The pontocerebellar fibers are afferent fiber connections of the cerebellum and originate bilaterally from the pontine nuclei (15). Another contingent of pontocerebellar fibers arises from the pontine tegmental reticular nucleus, which is located in the tegmentum pontis. Pontocerebellar fibers terminate, by way of the middle cerebellar peduncle, in all cerebellar lobules. The pontocerebellar and dentatorubrothalamic tracts form the cortico-ponto-cerebello-dentato-rubro-thalamo-cortico circuit, which is part of the extrapyramidal system. Abnormality of this pathway can be secondary to the abnormal extrapyramidal gray nuclei, which are usually more severely damaged in Wilson disease. The overlap in function of the gray matter nuclei and their pathways (16, 17), the facts that one third of the patients had signs in more than one neurologic group, and that most patients with abnormal MR findings showed involvement of gray matter nuclei and white matter abnormalities in multiple tracts, may explain why we did not find significant correlations between extrapyramidal tract involvement and neurologic groups. In Wilson disease relations between abnormal lentiform nucleus and dystonic and abnormal thalamus and pseudosclerotic signs has been described (2, 3, 5, 18). Nevertheless, other studies did

not find correlations between imaging findings and clinical data (6, 7). Poor correlation between the severity of neurologic impairment just before death and the extent of the neuropathologic findings is also reported (19).

The corticospinal or pyramidal tract contains projection fibers from the cerebral cortex, which extends into the corona radiata, the posterior limb of the internal capsule (20), the center of the cerebral peduncle of the mesencephalon, rounded foci in the base of the pons, the medulla oblongata, and the spinal cord (15). Light microscopic findings in Wilson disease support active involvement of the deep pyramidal cell layers of the cerebral cortex, where the corticospinal tract originates (8–10, 12). Imaging studies in amyotrophic lateral sclerosis have described abnormal signal intensity in the posterior third quarter of the posterior limb of the internal capsule (20), coinciding with abnormalities in our patients and one case with Wilson disease reported in literature (6). Although we did not notice abnormal signal intensity in the medulla oblongata and spinal cord, neuropathologic studies on Wilson disease reported amyotrophic lateral sclerosis–like spinal lesions without gliosis and secondary degeneration of the pyramidal tracts in the spinal cord (9, 10). Abnormal muscle responses evoked by transcranial stimulation, which was not significantly correlated with clinical symptoms, in patients with Wilson disease indicated (sub)clinical involvement of the corticospinal tract (21, 22). We found patchy involvement of the corticospinal tract in 22% of our patients on MR, although none of these patients had evident clinical signs of pyramidal tract syndrome. In the literature, occurrence of subtle pyramidal signs in Wilson disease varied from "occasionally" to about 20% (21–25). In fact, the historical dichotomy of extrapyramidal and pyramidal motor systems proved inadequate: new results show extensive interconnection and cooperation of the motor systems in the control of movement (16). In addition, the clinical distinction between subtle pyramidal and extrapyramidal symptoms can be difficult in the presence of a great spectrum of neurologic abnormalities (22).

Conclusion

Dentatorubrothalamic, pontocerebellar, and corticospinal tract abnormalities are commonly noted on MR and seem part of the neuroimaging spectrum of Wilson disease. No correlation between white matter tract involvement on MR and neurologic groups was found.

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