




# Neurologic Manifestations of Wilson's Disease: A 20-Year Evaluation in Iran

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## Abstract

**Background:** Wilson's disease (WD) is an autosomal recessive genetic disorder that leads to defects in copper metabolism, resulting in widespread clinical manifestations that complicate diagnosis. Recognizing the clinical and paraclinical findings in patients with WD can aid in timely diagnosis and treatment.

**Methods:** The present retrospective case series study examined all patients diagnosed with WD who were referred to Rasoul Akram Hospital, Tehran, Iran, between 2002 and 2022. Diagnosis was based on the Leipzig scoring system with confirmation by a movement specialist. Clinical, laboratory, and imaging data were recorded and analyzed.

**Results:** The study included 60 patients with neurologic WD, with a mean age of  $20.78 \pm 12$  years. The most common neurologic manifestations were dystonia (85%), tremor (79.4%), dysarthria (68.2%), gait disturbances (65%), and hypobradikinesia (52.4%). Less frequent symptoms included psychological symptoms (46.7%), rigidity (44.2%), increased deep tendon reflexes (43.8%), dysphagia (33.3%), and ataxia (33.3%). Rare symptoms included increased muscle tone (29.2%), drooling (24.2%), an upward plantar reflex (14.7%), sensory disturbances (12.5%), seizures (10%), and chorea-athetosis (9.5%). MRI, as the most precise imaging modality for detecting neurologic involvement, commonly reveals signal changes in the putamen (45%), midbrain (31%), thalamus (27%), pons (25%), caudate nucleus (19%), and tegmentum (17%). The "face of the giant panda" sign was also observed in 18% of patients.

**Conclusions:** In patients approximately 20 years of age, the presence of neurologic symptoms such as dystonia, tremor, dysarthria, gait disturbances, and hypokinesia should raise clinical suspicion for WD, prompting further paraclinical evaluations for early diagnosis. The findings of this study can aid in the early diagnosis of WD in the Iranian population, potentially reducing the morbidity and mortality associated with this condition.

**Keywords:** Copper Metabolism Disorders, Hepatolenticular Degeneration, Movement Disorders, Dystonia, Tremor

## 1. Background

Wilson's disease (WD) is an autosomal recessive genetic disorder caused by mutations in the ATP7B gene on chromosome 13, leading to defective copper metabolism. Over 700 mutations associated with this disease have been identified, and most patients are heterozygous carriers (1). Wilson's disease can present at any age, although most patients are diagnosed between the ages of 5 and 35 (2). The global prevalence of WD is estimated to be one case per 30,000 individuals, with a higher prevalence in regions where consanguineous marriages are more common (3). This disease has a wide

range of clinical manifestations, making its diagnosis challenging in a clinical setting. Wilson's disease can affect the liver, nervous system, psychiatric system, eyes, hematological system, musculoskeletal system, heart, kidneys, skin, and other organs (4). It should be considered in the differential diagnosis of any hepatic presentation (2).

The neurological manifestations of WD include a broad spectrum of movement disorders such as tremor, bradykinesia, rigidity, dystonia, chorea, dysarthria, dysphagia, and less common neurologic symptoms. These neurologic signs typically emerge in the second and third decades of life, usually approximately a

decade after the onset of hepatic involvement (5-7). Ocular manifestations, such as Kayser-Fleischer rings and sunflower cataracts, result from copper accumulation in these organs. Kayser-Fleischer rings are observed in nearly all patients with neurologic presentations and in 50% of those with hepatic presentations (2, 5, 8).

The diagnosis of WD is based on the Leipzig scoring system (6), and neurologic symptoms are assessed via the Unified Wilson's Disease Rating Scale (UWDRS) and the Global Assessment Scale (GAS) (9, 10). These systems help predict the severity of neurologic symptoms and assist in patient management (5, 10). The presence of Kayser-Fleischer rings and low serum ceruloplasmin levels are typically sufficient for diagnosis. In their absence, a comprehensive evaluation of copper metabolism is needed (2).

Treatment options for WD include D-penicillamine, trientine, zinc, tetrathiomolybdate, and dimercaprol. Once diagnosed, these medications are administered for life. Liver transplantation is reserved for patients with acute liver failure and decompensated cirrhosis (2). Early diagnosis and treatment of WD generally lead to patient improvement, whereas delayed diagnosis and disease progression can result in irreversible complications (5). Given the prevalence and broad range of neurologic symptoms in this disease, early recognition and correlation with other organ involvement and clinical tests are crucial.

## 2. Objectives

Despite advances in understanding WD, the heterogeneity and delayed recognition of its neurologic manifestations remain significant clinical challenges. The present study aims to systematically characterize the spectrum and progression of neurologic symptoms in WD in the Iranian population. We seek to improve early diagnosis, reduce morbidity and mortality, and optimize therapeutic strategies for this treatable disorder.

## 3. Methods

### 3.1. Study Design

All patients diagnosed with WD who presented at Rasoul Akram Hospital between 2002 and 2022 were included in this study. The inclusion criteria were a diagnosis of WD based on the Leipzig scoring system (6) with confirmation by a movement specialist and the absence of other diagnoses. Patients with only

gastrointestinal symptoms and incomplete records were excluded.

### 3.2. Primary Outcome

The present study primarily aimed to assess the neurological findings in patients diagnosed with WD who were referred to Rasoul Akram Hospital. This includes evaluating motor function using the UWDRS, cognitive ability using the mini-mental state examination (MMSE), and psychiatric symptoms using the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5). These examinations were performed by board-certified neurologists blinded to laboratory and imaging results. Outcomes were categorized as the presence or absence of symptoms and functional disabilities.

### 3.3. Data Collection

Clinical symptoms and laboratory data were obtained from hospital records. Imaging features included abdominopelvic sonography and brain MRI, extracted from radiologic reports generated by board-certified radiologists blinded to clinical data. Brain MRI was performed using T1-weighted, T2-weighted, and FLAIR sequences, with any unusual signal changes documented.

### 3.4. Sample Size

This study used a census sampling method to include all patients who presented to Rasoul Akram Hospital between 2002 and 2022.

### 3.5. Data Analysis

Data analysis was performed using SPSS version 26 (IBM Corp.). Descriptive statistics included frequencies and percentages for categorical variables and mean  $\pm$  standard deviation (or median and interquartile range) for continuous variables. Results were summarized in tables and figures to illustrate patterns in neurologic manifestations.

## 4. Results

### 4.1. Study Population

In the present study, the medical records of patients diagnosed with WD who were referred to Rasoul Akram Hospital, Tehran, Iran, from 2002 to 2022 were reviewed. During this period, 116 records with an initial diagnosis of WD were available. Among these patients, 25 presented with only gastrointestinal symptoms and

were excluded from the study as specialized neurological examinations were not conducted. Twelve patients were eventually diagnosed with conditions other than WD. Eleven patients had multiple hospital visits and were evaluated over several time periods. Eight patients left the hospital before completing their evaluations, resulting in incomplete records. Consequently, a total of 56 cases were excluded from the study. The analyses were conducted on 60 confirmed cases of WD with neurological manifestations. Among the 60 patients, 27 were women (45%) and 33 were men (55%), with a mean age of  $20.78 \pm 12.00$  years.

#### 4.2. Laboratory Findings

The laboratory analysis revealed that the hemoglobin (Hb) level in males averaged  $12.9 \pm 2.1$  g/dL, whereas in females, the average Hb level was  $11.5 \pm 1.9$  g/dL. Anemia appeared in 16 males (76.2%) and 8 females (34.8%). The platelet counts varied widely, averaging  $107.5 \pm 87.1 \times 10^3/\mu\text{L}$  among the 44 patients. Twenty-six patients (59.1%) had thrombocytopenia. Additionally, the white blood cell (WBC) count was noted to be  $4.9 \pm 1.72 \times 10^3/\mu\text{L}$  among 43 patients (Table 1). The liver enzyme and total bilirubin levels of the patients in this study are shown in Table 2. Among the patients, 16 (42.1%) showed elevated alanine aminotransferase (ALT), 33 (86.8%) had increased aspartate aminotransferase (AST), 27 (84.3%) exhibited elevated alkaline phosphatase (ALP), and 4 (22.2%) had elevated total bilirubin levels (Table 1).

The copper profile of patients is shown in Figure 1. We did not have any data regarding the initiation of drug therapy; therefore, the observed values may reflect both untreated disease progression and potential variability due to incomplete treatment histories (Figure 1).

#### 4.3. Gastrointestinal Findings

Gastrointestinal involvement was common, with liver cirrhosis observed in 67% of patients and splenomegaly in 36%. Further details on hepatosplenomegaly and cirrhosis, including ultrasound findings and subgroup distributions, are provided in Figure 2.

#### 4.4. Neurologic Findings

Neurologic involvement was prominent in the study population, with dystonia (85%), tremor (79.4%), and dysarthria (68.2%) as the most frequent manifestations (Table 2). Gait disturbances (65%) and hypobradycinesia (52.4%) were also common, while neuropsychological disorders (46.7%) and rigidity (44.2%) occurred less

frequently. Increased deep tendon reflexes (43.8%) and rare signs like chorea-athetosis (9.5%) were also observed, highlighting the diverse neurologic presentation of WD in this population. A detailed breakdown of neurologic findings, including subtype distributions (e.g., tremor types, dystonia patterns), is provided in Table 2.

Ophthalmologic examinations with a slit lamp were conducted on 50 patients. Among them, 36 patients tested positive for Kayser-Fleischer rings, whereas 14 patients (28%) tested negative. The negative results were predominantly from patients who were already receiving treatment for WD, which likely accounts for these outcomes.

#### 4.5. Imaging Findings

Brain MRI, a key modality for detecting neurologic involvement in WD, revealed characteristic abnormalities in our patients. Radiologic reports, utilizing standard T1-weighted, T2-weighted, and FLAIR sequences, documented signal changes in the putamen, midbrain, thalamus, and other regions, as illustrated in Figure 3. The pathognomonic "face of the giant panda" sign was identified in 18.75% of patients (Figure 3).

### 5. Discussion

We analyzed 60 confirmed cases of WD with neurological manifestations from 116 records at Rasoul Akram Hospital (2002 - 2022). Neurological symptoms were present in 64.5% of WD patients, aligning with Lankarani et al. (56%) (11) but exceeding Asadi Pooya et al.'s Shiraz cohort (12). The mean age of onset was 20.78 years, consistent with typical WD onset (2), though Soltanzadeh et al. reported an earlier onset of 16 years (13). Notably, three patients exhibited symptoms before age 6, suggesting earlier neurological involvement than previously documented (2).

#### 5.1. Neurologic Findings

Our study exclusively focused on neurological WD patients, identifying dystonia (85%), tremor (79.4%), dysarthria (68.2%), and gait disturbances (65%) as the most frequent neurologic manifestations. These findings are largely consistent with those reported in previous studies (Table 3). The differences in percentages may be due to the inclusion of a larger patient population, including WD patients with gastrointestinal symptoms. As seen in Table 3, the percentages in Asadi Pooya and Malekzadeh's studies are much lower than others, likely because they included gastrointestinal

**Table 1.** Laboratory Findings in Patients

Variables	Mean $\pm$ SD (Range)	No. (%)
WBC (n = 43)	4.9 $\pm$ 1.72 (1.9 - 9.2)	-
<b>Hb</b>		
Male (n = 21)	12.9 $\pm$ 2.1 (9.1 - 17.7)	Anemia: 16 (76.2)
Female (n = 23)	11.5 $\pm$ 1.9 (9.3 - 15)	Anemia: 8 (34.8)
Platelet (n = 44)	107.5 $\pm$ 87.1 (22 - 402)	Thrombocytopenia: 26 (59.1)
ESR (n = 18)	10.33 $\pm$ 6.4 (1 - 24)	-
ALT (n = 38)	41.73 $\pm$ 61.88 (7 - 390)	High: 16 (42.1); normal: 22 (57.9)
AST (n = 38)	34.5 $\pm$ 26.17 (17 - 150)	High: 33 (86.8); normal: 5 (13.2)
ALKP (n = 32)	244 $\pm$ 215.15 (122 - 862)	High: 27 (84.3); normal: 5 (15.7)
<b>Total bilirubin (n = 18)</b>	0.9 $\pm$ 0.911 (0.4 - 3.4)	High: 4 (22.2); normal: 14 (77.8)

Abbreviations: WBC, white blood cell; Hb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALKP, alkaline phosphatase.

**Table 2.** Neurologic Findings in Patients

Clinical Features	Total Number	Positive	Prevalence Percent
Dystonia <sup>a</sup>	40	34	85
Tremor <sup>b</sup>	34	27	79.4
Dysarthria	44	30	68.2
Gait disturbances <sup>c</sup>	40	26	65
Hypobradikinesia	42	22	52.4
Neuropsychological disorders <sup>d</sup>	30	14	46.7
Rigidity	43	19	44.2
Increased DTR	32	14	43.8
Dysphagia	36	12	33.3
Ataxia	15	5	33.3
Increased muscle tone	24	7	29.2
Drooling	33	8	24.2
Upward plantar reflex	34	5	14.7
Sensory disorder	24	3	12.5
Seizure	30	3	10
Chorea-athetosis	21	2	9.5

<sup>a</sup> Dystonia: Generalized (23.5%), dystonia in four limbs (14.7%), dystonia with tremor (14.7%), upper limb, speech, facial, and unspecified types.

<sup>b</sup> Tremor: At rest (26.5%), action (29.4%), postural (14.7%).

<sup>c</sup> Gait disturbances: Dystonic (26.9%), ataxic (15.3%), spastic (11.5%), wide-based, atonic, inability to walk, and unspecified types.

<sup>d</sup> Neuropsychological disorders: Depression (4 patients), hallucinations (2 patients), insomnia (2 patients), developmental delay (2 patients), low MMSE scores (4 patients), cognitive impairment, irritability, and delusions (1 patient).

cases in their population (11, 12). A summary of findings from prior studies can be found in Table 3.

## 5.2. Imaging Findings

In other studies, the MR images of patients have rarely been examined. In one study, the observed MRI changes included brain atrophy and increased signals in the putamen, globus pallidus, caudate nucleus, thalamus, and pons on T2-weighted images (5, 20, 21).

The midbrain, cerebellum, corticospinal tract, and other white matter regions can also be affected (2, 5, 22). The characteristic finding on MRI in WD patients is the presence of the panda sign (5, 23) (Table 3). In a study involving MRI imaging of 22 patients, 19 patients (86%) had abnormal findings. Despite differences in absolute percentage values between this study and our study, the areas affected by WD are largely the same, indicating consistency between the two studies (5, 21). According to the 2018 study by Salari et al., specific MRI abnormalities

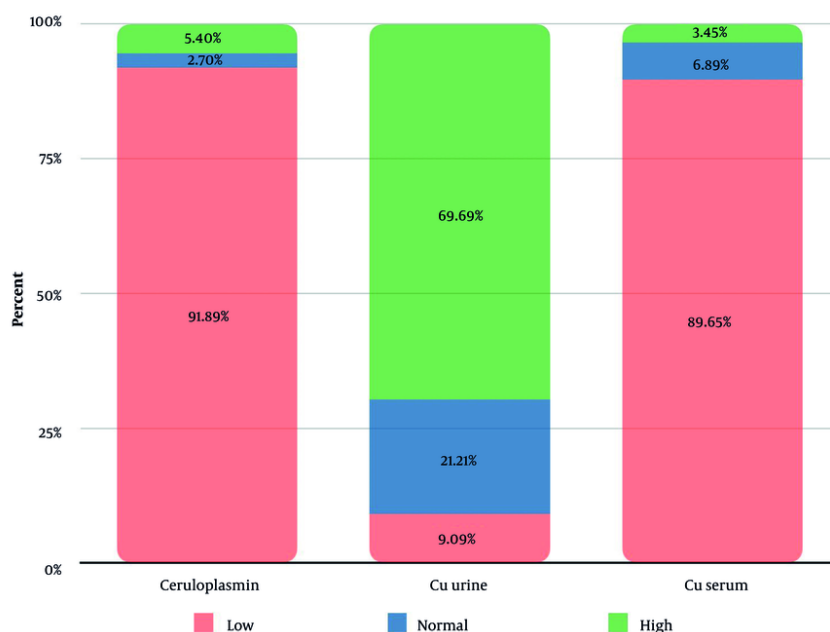


Figure 1. Copper profile of patients

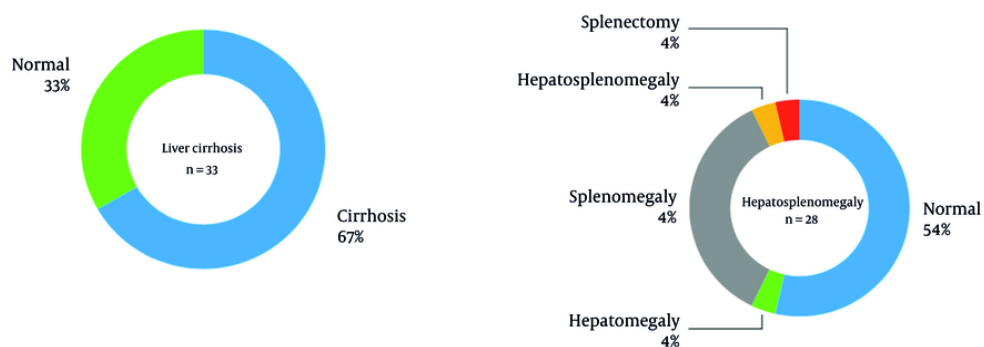


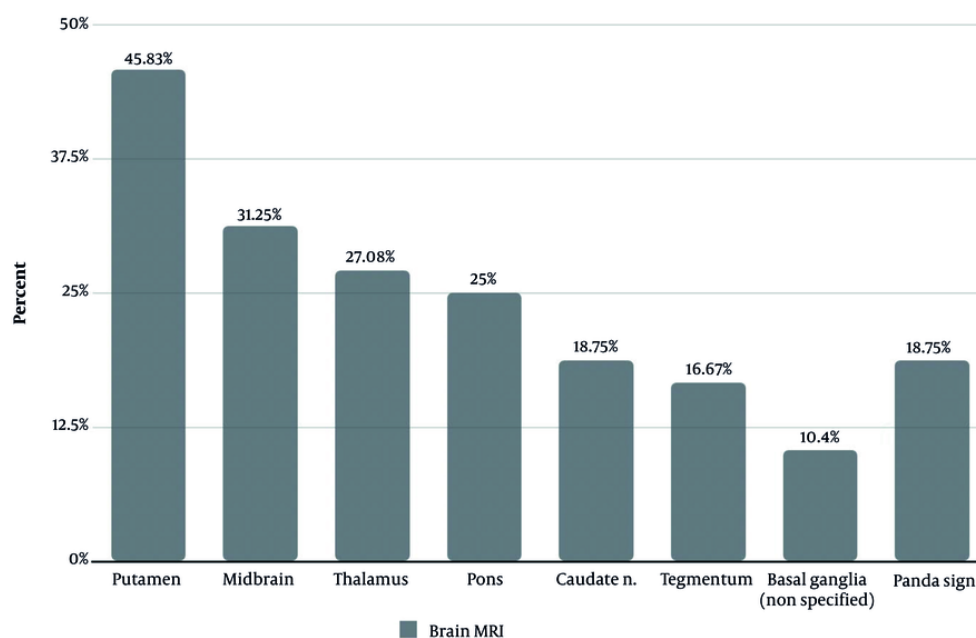
Figure 2. Liver cirrhosis and hepatosplenomegaly based on abdominopelvic sonography of patients

in WD closely correlate with clinical signs and symptoms. Dysarthria and tremor are consistently associated with lesions in the globus pallidus and thalamus; chorea correlates with caudate nucleus lesions; nystagmus is linked to abnormalities in the lentiform nucleus and thalamus; rigidity corresponds to lesions in the lentiform nucleus, white matter, and thalamus; and dystonia is associated with changes in

the globus pallidus and putamen (19). Unfortunately, further clinical research is necessary to better understand the diagnostic and prognostic implications of MRI findings in WD (5, 19).

### 5.3. Laboratory and Gastrointestinal Findings

In our study, 91% of patients exhibited low serum ceruloplasmin, aligning with WD hallmarks, though



**Figure 3.** Signal changes in the brain MR images of patients

reduced levels may also occur in heterozygotes, nephrotic syndrome, or liver disease, while elevated levels can arise during acute-phase reactions, pregnancy, or oral contraceptive use. Elevated free serum copper (89%) directly reflected systemic copper overload, yet its measurement remains limited in practice. While 70% showed increased 24-hour urinary copper, 21% had normal values, likely due to collection challenges or early-stage disease. These findings emphasize the non-specificity of isolated biomarkers and reinforce the necessity of integrating clinical, genetic, and adjunctive tests (e.g., penicillamine challenge) for definitive WD diagnosis (17).

Hepatic involvement was prominent in our cohort, with 86.6% elevated AST, 84% elevated ALKP, and 67% liver cirrhosis, aligning with the progressive hepatic spectrum of WD from transaminase elevation to cirrhosis. Splenomegaly (34%) and elevated ALT (42%) further underscored chronic liver pathology, consistent with literature highlighting ascites, hepatosplenomegaly, and jaundice as common early hepatic presentations. While acute fulminant failure was rare, the high cirrhosis prevalence mirrors WD's insidious progression, emphasizing the need for early diagnosis via biomarkers (e.g., AST/ALT ratio > 2.2) and

copper studies to mitigate morbidity. Our findings reinforce hepatic WD's heterogeneity and its critical role in timely intervention (16, 17, 24).

The observed anemia (76.2% males, 34.8% females) and thrombocytopenia (59.1%) align with the hematologic complications of WD, which are often secondary to chronic liver disease, hypersplenism, or copper-induced hemolysis (4, 24). The gender disparity in anemia prevalence may reflect iron deficiency or hormonal influences in females, though further investigation is warranted. Notably, the low platelet count ( $107.5 \pm 87.1 \times 10^3/\mu\text{L}$ ) and mild leukopenia ( $\text{WBC } 4.9 \pm 1.72 \times 10^3/\mu\text{L}$ ) are consistent with portal hypertension and splenic sequestration in advanced hepatic WD (4, 24). These hematologic abnormalities, while non-specific, reinforce the systemic nature of WD and highlight the need to integrate them with clinical and biochemical markers (e.g., ceruloplasmin, urinary copper) for comprehensive disease assessment.

#### 5.4. Study Limitations

This single-center, retrospective study at Rasoul Akram Hospital has limitations, including a small sample size, lack of follow-up data, incomplete neurological assessments (particularly in

**Table 3.** Comparison of Neurologic Manifestations and Imaging Findings in Wilson's Disease Across Studies

Study	Study Design	Location	Year Conducted	Mean Age	Most Common Neurologic Manifestations (%)	Imaging Findings (MRI) (%)
<b>Present study</b>	Case series	Rasoul Akram Hospital, Tehran, Iran	2002 - 2022	20.78	Dystonia (85); tremor (79.4); dysarthria (68.2); gait disturbances (65); hypobradikinesia (52.4); neuropsychological disorders (46.7)	Signal changes in: Putamen (45.8); midbrain (31.2); thalamus (27.1); pons (25); caudate (18.7); tegmentum (16.7); panda sign (18.7)
<b>Lankarani et al. (11)</b>	Case-control	Shiraz Organ Transplantation Center, Shiraz, Iran	2000 - 2014	16 <sup>a</sup> , 22 <sup>b</sup>	Tremor (40.5); ataxia (32.4); depression (24.3); dysarthria (21.6); drooling (21.6); fine motor task (17.6); gait disorder (17.6); anxiety (16.4); neurosis (16.2); seizure (16.2)	
<b>Asadi Pooya et al. (12)</b>	Case series	Namazee Hospital, Shiraz, Iran	1990 - 2004	11 ± 7	Dystonia (15.3); dysarthria (12.6); tremor (11.7); gait disturbances (9); impaired school performance <sup>c</sup> (7.2); psychosis <sup>c</sup> (7.2); other psychological symptoms <sup>c</sup> (9.9)	
<b>Soltanzadeh et al. (13)</b>	Case series	Shariati University Hospital, Tehran, Iran	1984 - 2004	16	Dysarthria (80); drooling (48); abnormal gait (44); psychiatric symptoms (44); tremor (44); dystonia in limbs (42); dystonia in face (36); dysphagia (30)	
<b>Machado et al. (14)</b>	Case series	University of Sao Paulo, Sao Paulo, Brazil	1963 - 2004	19.6	Dysarthria (91); gait abnormalities (75); risus sardonicus (72); dystonia (69); psychiatric symptoms (67); rigidity (66); tremor (60); bradykinesia (58); dysphagia (50); postural instability (49)	
<b>Lorincz (15)</b>	Systematic review	-	2010	Around 17	Dysarthria (85 - 97); dystonia (11 - 65); tremor (22 - 55); parkinsonism (19 - 62); ataxia (30); psychiatric features (30 - 50)	High T2 signals in: Lentiform and caudate n., thalamus, brain stem, white matter
<b>Pfeiffer (16)</b>	Systematic review	-	2016	20	Dysarthria in the vast majority; tremor (50); dystonia (69); parkinsonism (40); dysphagia (50); gait disturbances (45 - 75); cerebellar dysfunction (30); psychiatric manifestations (30 - 40)	High T2 and low T1 signal changes in: Basal, ganglia, brain stem, thalamus
<b>Mulligan and Bronstein (17)</b>	Systematic review	-	2020	10 - 20	Dysarthria (46 - 97); gait abnormality/ataxia/cerebellar (28 - 75); dystonia (38 - 69); parkinsonism (12 - 58); postural tremor (55); dysphagia (50)	Signal changes in: Basal, ganglia, thalami, pons, white matter, face of giant Panda (14)
<b>Czlonkowska et al. (5)</b>	Systematic review	-	2017	20 - 30	Tremor up to (55); dystonia (11 - 65) <sup>d</sup> , (38 - 65) <sup>e</sup> ; parkinsonism (19 - 62); ataxia (30); chorea (6 - 16); dysarthria up tp (97); dysphagia (50); drooling (46); gait and posture (44 - 75)	Hyper or mixed intensive changes in T2-weighted images localized in: Putamina, globi pallidi, caudate n., thalami, pons
<b>Dusek et al. (18)</b>	Systematic review	-	2019	20 - 40	Dysarthria (100); dysphagia (50); drooling (70); gait/posture disturbances (44 - 75); dystonia (11 - 65); parkinsonism (19 - 62); ataxia (30)	Symmetric hyperintensities in t2-w images in: Putamen (45 - 85); caudate (30 - 60); anterolateral thalamic n. (30 - 60); pons (10 - 80); mesencephalon (20 - 70)
<b>Salari et al. (19)</b>	Systematic review	-	2018	Variable	Variable in different studies	Symmetric hyperintensities in T2-W in: Pons, midbrain, basal ganglia

<sup>a</sup> Full hepatic failure patients (acute Wilson's disease).

<sup>b</sup> Chronic Wilson's disease.

<sup>c</sup> Classified as psychological sign and symptoms.

<sup>d</sup> As an initial symptom.

<sup>e</sup> During the course of disease.

gastrointestinal cases), and potential data loss over its long timeframe. Despite these constraints, the findings provide valuable insights for early diagnosis and management of WD in Iran, potentially reducing associated morbidity and mortality.

### 5.5. Conclusions

In patients approximately 20 years of age, the presence of neurologic symptoms such as dystonia, tremor, dysarthria, gait disturbances, and hypokinesia should raise clinical suspicion for WD, prompting further paraclinical evaluations for early diagnosis. The

findings of this study can aid in the early diagnosis of WD in the Iranian population, potentially reducing the morbidity and mortality associated with this condition.

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## Footnotes

**Authors' Contribution:** N. Y. contributed to the study conception and design. A. A. M., F. A. V., and F. S. performed material preparation, data collection, and analysis. A. A. M. wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

**Conflict of Interests Statement:** The authors declare no conflict of interest.

**Data Availability:** The datasets generated and/or analyzed during the study are derived from patient hospital records at Rasoul Akram Hospital, Tehran, Iran, which are confidential and not publicly available.

**Ethical Approval:** The present study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC.1401.625 ).

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**Informed Consent:** Informed consent was obtained from all participants.

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