



OPEN Clinical and neuroimaging features in neurological Wilson's disease with caudatum lesions

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According to early research, the incidence of caudatum lesions in patients with neurological Wilson's disease (WD) was inconsistent, ranging from 1.8 to 75% on magnetic resonance imaging (MRI). Our study aims to explore the incidence, clinical presentation features, iconography features, and possible pathological mechanisms in WD patients with caudatum lesions on magnetic resonance imaging (MRI), to characterize the clinical, and brain imaging findings and possible pathological mechanisms in the patients with WD. Retrospective cases meeting the inclusion criteria were studied for analyzing MRI characteristics and associated physicochemical examination data in neurological WD patients with caudatum lesions. 443 (66.3%) with brain MRI abnormalities were screened from 668 WD patients. The three (0.7%) patients with the caudatum lesions characteristics on MRI images were: (a) "bright caudatum" in T2-weighted and FLAIR sequences, (b) bilateral symmetrical, (c) non-isolated lesions, (d) occurred only in severe neurological manifestations. The caudatum lesions are not common in neurological WD and mainly appear in cases with severe neurological symptoms. On MRI, the "bright caudatum" signs may be a radiographic marker of neuroinflammation, the features of the lesions showed bilateral symmetry, and hyperintensity signals on T2-weighted, FLAIR, and DWI.

Keywords Wilson's disease, Caudatum, Brain MRI, Copper, Neuroinflammation

Wilson's disease (WD) is a rare, autosomal recessive disorder of copper metabolism caused by an ATP7B gene mutation, resulting in the unregulated accumulation of copper in various tissues such as the liver and the brain¹. Most particularly in the brain, and its clinical manifestations are progressive neuropsychiatric symptoms, the most common neurological presentations being extrapyramidal manifestations, including chorea, tremor, and dystonia², which significantly affect the quality of life and prognosis. Neurological WD occurs in 22–55%, with the first neuropsychiatric symptoms most often occurring between the ages of 20–30 years, and increasing as age advances, early diagnosis and correct treatment are the key to successful rehabilitation of WD³. Magnetic resonance imaging (MRI) is the most frequently used imaging method to evaluate the degree and extent of brain lesions in neurological WD. Typical imaging manifestations include cerebral atrophy, cerebellum, the white matter of the cerebral hemispheres, and symmetrical hyperintensity or mixed intensity on T2-weighted image changes in the basal ganglia, thalamus, and brainstem^{4,5}.

In recent years, potential brain MRI pathognomonic signs, such as "face of the giant panda", "miniature panda", "split thalamus", and "whorl", have been found and proposed to be pathognomonic for WD^{6,7}. However, these signs have also been described in Leigh syndrome, glutaric aciduria type 1, isoniazid-included ataxia, as well as in other disorders, including methanol poisoning or Japanese B encephalitis^{8–10}, indicating that the frequency and pathological significance of these signs still needs to be further established. The "bright caudatum" sign was described as the caudatum hyper signal in T2 weighted. Proton density sequences in 3/4 (75%) of neurological WD patients, appear to be a new pathology sign and are subsequently considered a potential MRI finding^{11,12}. Recently, a new study came to a new and different conclusion, finding the "bright caudatum" sign occurred in only 1.8% (1/55) of neurological cases¹³. Therefore, the MRI imaging features and pathological mechanisms of the "bright caudatum" sign need to be further elucidated.

The caudatum was thought to play a key role in sensory integration and consciousness; it may very well be a regional "skeleton key" that is at the root of, and also links and contributes to, a variety of brain disorders¹⁴. The "bright caudatum" sign on brain MRI was also found in other neurological diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD), Lewy body dementia (LBD), schizophrenia, autism, and especially

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in neuroinflammatory diseases such as rapidly increasing reported COVID-19 infection and autoimmune epilepsy^{15–18}. Significant changes in the structure and volume of the caudate nucleus were seen in several neurological conditions; similar lesions are described as affecting either the caudate nucleus, the external capsule, or both, so it may not be truly pathognomonic of WD. The latest research methods, such as neuroimaging, proteomics, and tractography, have helped to obtain new information about caudate nucleus lesions. It is required to further explore and study whether the role of neuroinflammation is involved in its pathological mechanism and represents an imaging marker of neuroinflammation in the brain.

Neurological manifestations in neurological WD patients have been frequently described in recent years. There is still debate about the significance of these proposed pathognomonic brain MRI signs, particularly concerning the “bright caudate nucleus” sign, and few large studies have explored the clinical features and possible lesion mechanisms. The caudate nucleus is a brain region that has been investigated for over 200 years, yet its precise function remains unknown. We must maintain curiosity by recognizing the key symptoms and characteristics, manifested with the caudate nucleus lesions signs onset, progression, and pathomechanism, to make a prompt diagnosis and initiate early treatment modalities, drastically improving the disease course, prognosis, and decreasing the risk of complications of neurological WD patients. Our study aimed to evaluate the frequency and significance of caudate nucleus lesions signs on MRI, consolidate the pathognomonic neuroradiological knowledge about the neurological manifestations, and present the pathophysiology of neurological manifestation of the caudate nucleus lesions in WD.

Patients and methods

Participants retrospective

A retrospective study of WD patients (2020.3–2023.12), hospitalized in the department of neurology from our hospital, were undertaken with the following inclusion criteria: (a) patients meeting WD diagnostic criteria, with the WD diagnosis based on the Leipzig score and genetics analysis as described previously¹⁹; (b) abnormal brain MRI scan that accords with the main imaging characteristics of WD patients; (c) patients who underwent brain MRI scans at 1.5T or 3.0T before the chelation therapy or follow-up in the treated phase of the illness; (d) no history of previous or concomitant neurologic disorders.

Information including demographic data, clinical features, diagnostic findings, therapeutic interventions, and clinical outcomes of patients were acquired. The pathological brain regions on MRI were recorded. The scanning sequences included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). The severity of brain imaging injury was assessed by the semiquantitative brain MRI score of WD (bMRIsc-WD)²⁰. The typological severity and profile were quantified using the Global Assessment Scale for WD (GAS for WD), composed of two parts: global disability (GAS-Tier 1) and neurological impairment (GAS-Tier 2)²¹. All the retrospections were completed by a separate team, guided by the assigned researcher.

Literature review of the caudate nucleus lesions

Searches for identification of studies were run from 1990 to the present day in MEDLINE and PubMed. The search keywords were as follows: “caudate nucleus”; “caudate nucleus lesions”; “caudate nucleus sign” “bright caudate nucleus”; “caudate nucleus damage” and “caudate nucleus hyperintensity”. The bibliography of each of the retrieved articles was examined to identify relevant references that may have been missed by the electronic search. For each available citation considered, the abstract was read and then screened for cases in which reported lesions included the caudate nucleus according to neuroimaging.

Results

Clinical and neuroimaging features in patients with neurological WD

443 (66%) patients, 378 underwent MRI scans at 1.5 T, and 65 at 3.0 T, showed brain MRI abnormalities from 668 WD patients. Among them, 89% (395/443) were neurological WD, showing neuropsychiatric symptoms, and 11% (48/443) were hepatic WD, showing hepatic symptoms. The lenticular nucleus was the most commonly affected site, being involved in 80.9% (356/443) of patients, the frequency followed by brain atrophy (234/443, 52.8%), thalamus (148/443, 33.4%), brain stem (115/443, 30%), and caudate nucleus (126/443, 28.4%). Unfrequent signal abnormalities were noted: encephalomalacia (12/443, 2.7%), cerebellum (12/443, 2.7%), white matter lesion (8/443, 1.8%), corpus callosum (8/443, 1.8%), and caudate nucleus (3/443, 0.7%), (Fig. 1). In the three patients, showing “bright caudate nucleus” signs, the most common signs and symptoms were motor disorders (3/3), speech problems (3/3), nonspecific cognitive impairment (3/3), sleep disturbances (3/3), delusions (1/3), hallucinations (1/3), non-seizure electroencephalography (EEG) abnormalities (1/3), GAS-WD Tier1(12–18), GAS-WD Tier2 (25–35), bMRIsc-WD (11–16) (Table 1).

Neuroimaging features on MRI in WD with caudate nucleus lesions

All three patients with caudate nucleus lesions underwent a brain MRI 1.5T scan before chelation therapy, symmetrical and obscure hypointensity was seen in the caudate nucleus, and the extended lentiform nucleus presented high, low, or mixed signals on axial T1-weighted images. Axial T2-weighted and FLAIR images demonstrated bilateral high signals in the caudate nucleus, with the exact location and alteration extent of the signal across varying the four cases. The caudate nucleus lesions showed a high signal on both DWI images, without restricted diffusion. All bilateral involvement was present in the patients, and the “bright caudate nucleus” sign was easily recognizable in each case, (Fig. 1).

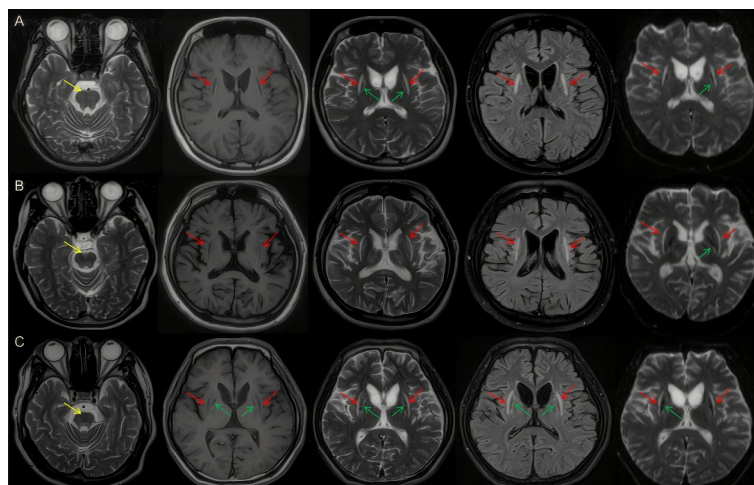


Fig. 1. The brain lesions on MRI axial scanning T1-weighted, T2-weighted, FLAIR, DWI sequence in three WD patients. In caudate, symmetrical bilateral hypointensity on T1-weighted and hyperintensity on T2-weighted, FLAIR, and DWI images (red arrow). In putamen, incomplete symmetrical bilateral mixed intensity on T1-weighted, T2-weighted, FLAIR, and DWI images (green arrow). In brainstem, incomplete symmetrical hyperintensity on T2-weighted images (yellow arrow).

Clinical data	Case #1	Case #2	Case #3
General information	22-year-old man	19-year-old man	21-year-old female
Disease duration (years)	15	4	3
Age of onset (years)	7	15	18
Initial indication	Blood ALT elevated	Cirrhosis	Movement clumsy
Motor symptoms	Slurred speech, limb torsion, swallowing difficulty	Slurred speech, clumsy movements, hands trembled, walking difficulty	Unsteady walking, unclear speech, swallowing difficulty
Non-motor symptoms	Cognitive impairment, Insomnia, delusion	Cognitive impairment, depression, insomnia,	Cognitive impairment, Drowsiness, hallucinations
Serum ceruloplasmin (mg/L)	48.7	34.0	34.5
Copper oxidase (OD)	0.035	0.025	0.018
Serum copper ($\mu\text{mol/L}$)	1.12	2.03	1.10
Blood ammonia ($\mu\text{g/L}$)	4	10	15
Serum iron ($\mu\text{mol/L}$)	8.70	11.26	16.39
Serum zinc ($\mu\text{mol/L}$)	21.97	23.46	16.45
Serum uric acid (UA) (mol/L)	167	142	251
C-reactive protein (CRP) (mg/L)	0.70	2.95	3.51
D-dimer (mg/L)	0.48	0.63	0.81
Superoxide dismutase (SOD) (u/ml)	241.30	137	225.90
24-h urinary copper (mg/24 h)	144.61	107.69	187.91
Kayser-Fleischer ring (grade)	++++	++++	+++
Modified Leipzig score	8	7	7
GAS-Tier1 (points)	18	16	18
GAS-Tier2 (points)	35	32	32
BMRIsc-WD (points)	16	14	13

Table 1. Clinical features of the three WD patients with caudate lesions.

Literature review of the caudate lesions on MRI

A total of 72 studies were initially identified. After excluding duplicates, 48 studies were screened by title and abstract, and 22 studies were excluded because the cases or MRI images were incomplete and did not meet the eligibility criteria. Finally, 27 papers, including 22 individual cases and 5 cohort studies, with a total of 56 patients and 16 disease species, were included in this literature review (Fig. 2). Among them, the distribution was as follows: 35 (62%) in epilepsy-related diseases; 13 (23%) in encephalitis-related diseases; 7 (13%) in WD; and 1 (1%) in ischaemic stroke. In terms of spatial distribution, 55 (98%) were bilateral, except for 1 (2%) ischaemic stroke which was unilateral. Isolated the caudate lesions on MRI were present in 20 (35.7%) (Table 2).

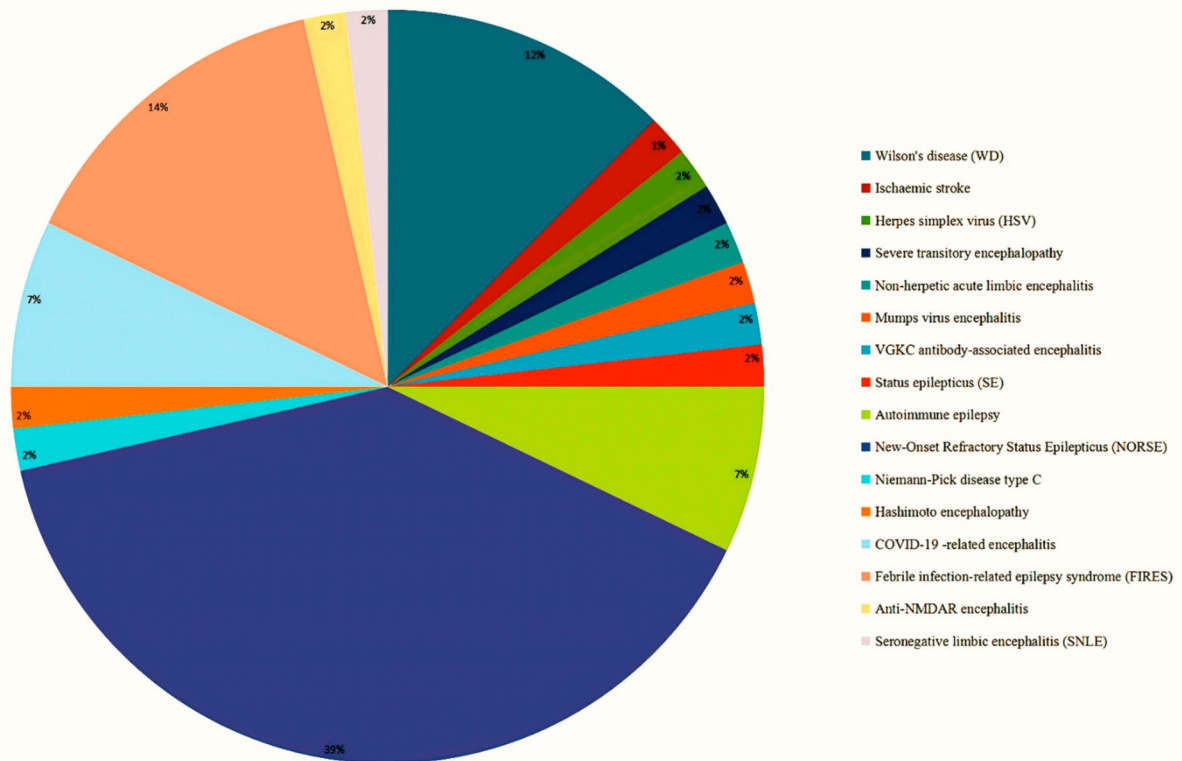


Fig. 2. Disease species distribution of the claustrum lesions on MRI from reported literature cases (%).

Discussion

The T2-weighted/FLAIR hyperintensity of the claustrum, the so-called claustrum sign or “bright claustrum” in neurological WD, has been described^{11,13}, however, whether it is a new potential sign of MRI in patients with WD is controversial. In our study, the sign on MRI was found in 3/443 (0.7%) of neurological WD, and the incidence rate is lower than that reported in the literature. As shown in our study results, MR imaging examinations of the four patients with a variety of claustral disorders, our study shows that the claustrum lesions on MRI imaging in WD patients have the following features: (a) “bright claustrum” on T2-weighted and FLAIR sequences, (b) bilateral symmetrical, (c) non-isolated lesions, (d) occurred only in severe neurological manifestations. Thus, the sign can be seen as a potential brain MRI pathognomonic sign that occurs relatively rarely across all patients, most commonly in patients with severe neurological symptoms, and this knowledge may advance the pathophysiology of WD.

Our study in the literature revealed that the claustrum sign is more associated with neuroimmune diseases, it may not be as pathognomonic as the majority of these indications, including potential brain MRI pathognomonic signs “face of the giant panda” and “miniature panda”. Therefore, it did not attract sufficient attention from the clinicians. A minority of WD patients with neurological involvement may not have brain MRI abnormalities or the Kayser-Fleischer ring, while patients with liver illness or presymptomatic subjects may have these abnormalities due to the wide variability of the WD phenotype⁴⁵. Since the WD phenotype varies widely, it is still unknown what factors contribute to it. Although the absence of these imaging signs does not exclude a WD, clinicians should be aware that their presence may be useful to diagnose it. Patients suffering from WD experience a large build-up of copper in their brains, which leads to long-term damage to the brain parenchyma and morphological abnormalities as well as different degrees of brain shrinkage⁴⁶. The most prevalent kind of neurologic WD is putaminal involvement; sensitivity of T2-weighted and FLAIR sequences is comparable; the number of MRI lesions is linked with disease severity but not with prognosis⁴⁷. The basal ganglia exhibit characteristic brain MRI alterations associated with WD that are typically characterized as symmetric, hyperintense, or with mixed intensity in T2-weighted imaging, showing gliosis, edema, and demyelination. When the disease reaches its severe stages, they are located in the same area as hypointense alterations in T1-weighted sequences, which indicate necrosis^{13,20}.

In our study, T1-weighted sequences on MRI located in the claustrum in cases showed varying degrees of hypointense changes, which may be reflecting necrosis. In the T2-weighted, FLAIR, DWI sequence located in the claustrum, all patients showed varying degrees of hyperintensity changes, reflecting existing necrosis and edema. Despite the presence of excess copper within the brain in WD, pathological findings are limited primarily to the basal ganglia, thalamus, midbrain, and pons. The excess copper accumulation and deposition are toxic to

Authors	Year	Cases (n)	Clastrum lesions	Extend lesion sites	Disease species
Sener RN. ¹¹	1993	3	Bilaterally thickened and bright castrum long-TR MR images	The bilateral basal ganglionic and subcortical white matter involvement	WD
Kimura S, et al. ²²	1994	1	Bilateral the castrum high signals on T2-weighted, mild low signal on T1-weighted	Bilateral lesions of the external capsule	HSV
Sperner J, et al. ²³	1996	1	Reversible bilateral castrum hyperintense on T2-weighted, hypointense on T1-weighted	Bilateral lesions of the external capsule	Severe transitory encephalopathy
Ishida H, et al. ²⁴	2006	1	Bilateral castrum on T2-weighted	Right hippocampus	NHALE
Ishii K, et al. ²⁵	2011	1	High-intensity lesions of the bilateral castrum on T2-weighted	No	Mumps virus encephalitis
Panda AK. ¹²	2013	1	Hyperintensity in the bilateral castrum on T2-weighted	Putamen, caudate nucleus, and thalamus	WD
Hiraga A, et al. ²⁶	2014	1	Hyperintensity in the bilateral castrum on T1-weighted	Bilateral medialtemporal lobes	VGKC antibody-associated encephalitis
Hwang KJ, et al. ²⁷	2014	1	Hyperintensities in the right castrum on T2-weighted/FLAIR	Bilateral external capsule	SE
Goyal S, et al. ²⁸	2015	1	Bilateral hyperintense in castrum on T2-weighted/FLAIR	Bilateral thalami, basal ganglia, and dorsal mesencephalon, red nucleus.	WD
Steriade C, et al. ²⁹	2017	4	Castrum hyperintensities on T2-weighted/FLAIR	Hippocampal tail/fornix	Autoimmune epilepsy
Meletti S, et al. ³⁰	2017	12	Hyperintense foci in bilateral castrum on T2-weighted/FLAIR	No	NORSE
Georgi K, et al. ³¹	2018	1	Isolated left castrum lesion	No	Ischaemic stroke
Choi JY, et al. ³²	2019	10	Bilateral castrum on T2-weighted/FLAIR	Neocortex, bilateral mesial tempora and pulvinar	NORSE-LE
Kulak-Bejda A, et al. ³³	2020	1	Bilateral symmetrical hyperintensities in castrum on T2-weighted	The putamen, globus pallidus, heads of caudate nucleus, and thalamus	WD
Mukherjee D, et al. ³⁴	2021	1	Bilateral symmetrical hyperintensities in castrum on axial T2-weighted/FLAIR	Medial temporal lobe, uncus, basifrontal region and insularregion	Niemann-Pick disease type C
Ayatollahi P, et al. ³⁵	2021	1	Bilateral castrum hyperintensities on axial T2-weighted/FLAIR	Extreme capsules, insular cortices	Acute SARS-CoV-2 Infection
Jegatheeswaran V, et al. ³⁶	2021	1	Bilateral castrum hyperintensities on axial T2-weighted/FLAIR	Right mesial temporal lobe	HE
Zuhorn F, et al. ³⁷	2021	1	Bilateral castrum signal alterations on FLAIR, DWI, and ADC map	External capsule regions	Parainfectious encephalitis in COVID-19
Laura Susani E, et al. ³⁸	2021	1	Hyperintensities bilaterally but especially on the left side of the castrum on FLAIR	Bilaterally but especially on the left side of the putamen, the insula cortex, and the frontotemporal cortex	Parainfectious COVID-19 encephalitis
Yang F, et al. ³⁹	2021	5	Symmetrical low signal lesions incastrum on T1, high signal lesions on T2-weighted, and FLAIR.	No	FIRES
Acampora R, et al. ⁴⁰	2022	1	Hyperintense incastrum on FLAIR	Insular	FIRES
Muccioli L, et al. ⁴¹	2022	1	Right-predominant hyperintensity and Swelling of the Castrumon FLAIR and T2-weighted	The pulvinar, and hippocampus	FIRES
Datta AK, et al. ⁴²	2022	1	Bilateral castrum hyperintensities on FLAIR and T2-weighted	Hippocampal tail/fornix	Anti-NMDAR encephalitis
Humayun MB, et al. ⁴³	2023	1	Bilateral hyperintense castrum on T2-weighted	No	Post-COVID-19 Encephalitis
Safan AS, et al. ⁴⁴	2023	1	Sparing of the intervening castrum bilaterally on FLAIR and T2-weighted	Left thalamus, symmetric external and extreme capsules	SNLE
Di Dier K, et al. ⁴⁵	2023	1	Bilateral castrumT2-hyperintense	The mesiotemporal structures	FIRES
Guo K, et al. ⁴⁶	2023	1	Symmetric or asymmetric T2/FLAIR hyperintensity in the bilateral castrum		FIRES
Rędzia-Ogrodnik B, et al. ¹³	2023	1	Bilateral hyperintense in castrum on T2-weighted/ FLAIR	Bilateral putamen, globus pallidus, heads of caudate nucleus and thalamus	WD

Table 2. The castrum lesions on MRI reported and clinical data of literature review cases. *MRI* magnetic resonance imaging, *DWI* diffusion-weighted imaging, *FLAIR* fluid-attenuated inversion recovery, *WD* Wilson's disease, *SNLE* seronegative limbic encephalitis, *HE* Hashimoto encephalopathy, *FIRES* febrile infection-related epilepsy syndrome, *HSV* herpes simplex virus, *VGKC* voltage-gated potassium channel, *NORSE* new-onset refractory status epilepticus, *LE* limbic encephalitis, *NHALE* non-herpetic acute limbic encephalitis, *SE* status epilepticus.

the central nervous tissue and can further lead to the generation of oxygen-free radicals, cell membrane damage, and reactive astrocytes⁴⁸. Histopathology studies showed atrophy, spongy softening, cavitations, neuronal loss, increased cellularity, and the presence of opalski cells⁴⁹. Currently, the pathophysiological mechanisms of patients can be partially revealed by MRI imaging techniques, such as cytotoxic edema-like, and vasogenic edema-like two patterns on diffusion MRI, which were observed by quantitative evaluations of the ADC maps in WD⁵⁰. Our study found that the claustrum lesions showed high signals on both DWI, indicating that there may be cytotoxic edema in the claustrum lesions local tissue.

The claustrum is a thin sheet of grey matter lying underneath the surface of the insular cortex having widespread connections with neocortical and subcortical structures, and it forms part of the brain circuitry that plans and executes motor behaviors^{51,52}. While the claustrum's anatomy renders lesion studies challenging, isolated claustrum lesions are rare and predominantly occur in the spectrum of autoimmune encephalitis. The most common clinical manifestations of claustrum lesions are that patients experience different levels of cognitive, perceptual, and motor dysfunction, as well as seizures, mental states, and sleep disorders⁵³. Literature studies of claustrum lesions reveal that the disease species distribution was as follows: 35 (62%) in epilepsy-related diseases; 13 (23%) in encephalitis-related diseases; 7 in WD (13%); and 1 (2%) in ischaemic stroke. In space distribution, 55 (98%) were bilateral, except for 1 (2%) ischaemic stroke unilateral. Limitation to the claustrum lesions site as the sole region of involvement on MRI was seen in 20 (35.7%) of our literature review studies. Our studies showed that only a few clinical studies have described neurological lesions or conditions where the claustrum was the sole region of involvement. This may support the idea that dysfunction in the claustrum results primarily in disruption of higher behavioral and cognitive functions associated with the functional networks, rather than a specific, unitary deficit⁵⁴. In our study, 3 patients with claustrum lesions were unable to stand and walk, 3 patients were accompanied by sleep disorder, and 2 patients were accompanied by psychiatric symptoms; these may be related to the participation of claustrum lesions.

Understanding how the claustrum operates is difficult because it is located deep within the brain and injury to it is extremely rare. Earlier reported findings of lesions involving the claustrum comprised cases with asphyxia, WD, ischemic white matter disease, thalamic arteriovenous malformation, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, viral encephalitis, and PD⁵⁵. Current evidence shows that the bilateral claustrum hyperintensity as a unique radiological marker on T2-weighted/FLAIR sequences of MRI brain, described typically in association with immune-inflammatory-mediated encephalopathy, the sign has been specifically identified in the background of autoimmune epilepsy, anti-VGKC, anti-glutamic acid decarboxylase (GAD), anti-Ma-2 antibodies and post-COVID^{26,56–58}. In WD, mixed intensity in the basal ganglia and hyperintense linear rim at the peripheral putamen were similar to those seen in Japanese encephalitis⁵⁹. These immune effector cell-associated neurotoxicity syndromes may represent a specific marker of cytokine-mediated neuroinflammation⁶⁰. Therefore, the claustrum may have a potential role and constitute a therapeutic target in neurological WD patients associated with disturbances of cognition, behavior, and cortical excitability. Accumulating evidence reveals that inflammation is not confined to archetypal inflammatory diseases like multiple sclerosis, but rather is an intrinsic characteristic of many psychiatric and neurological conditions that are not traditionally classed as neuroinflammatory⁶¹.

Excessive copper deposition can lead to neuroinflammation in the brain of WD patients, excessive free copper leads to its participation in the redox reactions that produce reactive oxygen species (ROS), leading to catastrophic damage to lipids, proteins, and DNA^{62,63}. Growing evidence suggests that extracellular copper accumulation triggers pathological microglial activation and subsequent neurotoxicity, copper overload-mediated activation of NLRP3 inflammasome leads to progressive neuropathology, and levels of inflammatory cytokines are elevated in the brain of murine WD models^{64,65}. Besides WD, there was robust evidence that copper has been linked to AD, PD, amyotrophic lateral sclerosis, Huntington's disease, and prion-mediated encephalopathies⁶⁶. From here, we see that neuroinflammation occurs as one of the most common pathological outcomes in various neurological disorders, making it a promising therapeutic target⁶⁷. These studies can be used to evaluate therapeutic strategies to alleviate behavioral disturbances and cerebral pathology observed in WD when the claustrum is damaged. The effects are severe and better therapies are urgently needed. Therefore, starting from neuroinflammation, it may be a potential therapeutic strategy for neurological WD. At present, the pathological mechanism of neuroinflammation caused by copper deposition in WD has not been fully clarified. Specific markers of neuroinflammation are lacking clinically, so serum levels of uric acid (UA), c-reactive protein (CRP), superoxide dismutase (SOD), and d-dimers have been used as biomarkers of inflammatory or oxidative stress, but they are nonspecific to neuroinflammation^{68,69}. Due to the little-understood area of the claustrum, it may be the next frontier in improving outcomes for brain-damaged patients. Based on recommendations for neurological follow-up in these patients, brain MRI should also be considered as part of long-term treatment monitoring during neurological examinations⁷⁰. In conclusion, so-called "bright claustrum" imaging signs on MRI may be an imaging marker of neuroinflammation.

Through this research, our findings regarding the incidence, imaging characteristics, distribution population, and possible pathomechanism of claustrum lesions in WD patients were preliminarily discussed. However, this study has some limitations. This study was a retrospective analysis of the data, and MRI neuroimaging changes in WD only provide us with clues to thinking. It is already known that there are also links between the claustrum and perception, salience, and the sleep-wake cycle, in addition to movement disorders. We did not observe a significant relationship between relevant clinical-specific signs and the claustrum lesions of WD, which could be due to a small sample size and insufficient recognition of the lesion. It follows that the lack of clinical focus on the claustrum lesions may mean there are many more cases yet to be uncovered. Moreover, as a neurology department, we did not receive and treat patients with extremely severe hepatic type WD, such as acute and chronic liver failure. Therefore, our sample may not be fully representative of all WD patients.

Conclusions

Here, our study has summarized the suggestive, but not conclusive, body of evidence that implicates the claustrum in the underlying pathology of neuroinflammation. The claustrum lesions are not common in neurological WD and mainly appear in cases with severe neurological symptoms. Clinically, it can manifest as severe motor function limitations and a specific sleep disorder, depression, or mental excitement. On MRI, the “bright claustrum” signs may be an imaging marker of neuroinflammation, the features of the lesions showed bilateral symmetry, and hyperintensity signals on T2-weighted, FLAIR, and DWI. Cytotoxicity and neuroinflammation induced by copper deposition may be involved in the pathological mechanism of the claustrum lesions, but it needs to be further clarified.

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Author contributions

CRedit authorship contribution statement M.X.F., and F.L.Y. evaluated the specimens. L.K. collected the data; J.P. and T.G.A. analyzed the data; W.G.Q. conceived the study, drafted and wrote the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics statement

This study was performed in line with the principles of the Declaration of Helsinki, approval was granted by the ethical committee of the Affiliated Hospital, Anhui University of Chinese Traditional Medicine (NO: AHSYS-2023LC-015). The data were anonymous, no patient privacy information was exposed, and The ethics exemption certificate was issued by the ethics committee.

Additional information

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