



Radiological Imaging Features of Wilson's Disease in an Early Adolescent Male: Case Report

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Inborn defect in the copper metabolism leads to Wilson's disease (WD) with an autosomal recessive pattern of inheritance. Abnormal accumulation of copper in various tissues is caused by ATP7B mutation. In individuals affected by WD, however, impaired copper metabolism and excretion leads to the deposition of redundant free copper in the brain, liver, cornea, kidney and other organs, resulting in organ damage. Diagnosis of WD is made based on various neurologic and hepatic clinical symptoms, Kayser-Fleischer (K-F) rings in the cornea and biochemical tests for copper. Neurological manifestations of WD include pyramidal and extrapyramidal features, as well as cognitive and psychiatric symptoms. Earlier diagnosis and intervention are necessary for patients with WD. Both clinical symptoms and neuroimaging abnormalities are partially reversible with anti-copper treatment. Radiological imaging features were evaluated in a 13 years old preadolescent male with WD, who presented with involuntary movements of extremities, drooling of saliva, dysarthria, vomiting, itching and behaviour disorders for the past 45 days.

Keywords: Hepatolenticular Degeneration; Kayser-Fleischer Rings; Wilson's Disease**Introduction**

Wilson's disease (WD) also known as Hepatolenticular degeneration (HLD), is due to a defective function of the enzyme ATPase 7B in hepatocytes which causes reduced excretion of copper into bile [1,2].

WD is known to be more prevalent amongst the Chinese and other Asian populations with incidence varying from 1/30,000-1/10,000 and carrier frequency roughly about 1/90 [3].

WD is traditionally considered a disease of children and young adults. Abnormal accumulation of copper causes damage to various organs resulting in broad-ranging clinical symptoms, especially dominated by signs of brain damage (mainly basal ganglia and cerebellum) and liver.

Of the WD, neurologic presentation accounts for 40-60% [4,5]. WD is diagnosed based on a combination of clinical and diagnostic tests including presence of corneal Kayser-Fleischer (K-F) rings, decreased serum ceruloplasmin, and 24 hours increased urinary copper excretion [6,7]. If WD is diagnosed early, prior to the development of more severe damage, especially to the liver and brain, it is treatable.

The purpose of the study was to describe the range of abnormalities seen on radiological imaging of early adolescent male patient with WD and correlate with clinical findings.

Case Report

An early adolescent male aged 13 years presented with involuntary movements of extremities, drooling of saliva, dysarthria, vomiting, itching and behaviour disorders for the past 45 days duration.

He was diagnosed to be suffering from WD at the age of 7 years and was on irregular treatment. History of 2nd degree consanguineous marriage of the parents noted.

Clinical examination showed generalised dystonia involving limbs, tremor in the hands, yellowish discolouration of skin and sclera, KF ring in the eye (Figure 1). Other Vitals were unremarkable. Laboratory examination revealed reduced haemoglobin of 10.9g/dl, elevated total bilirubin (1.68), direct bilirubin (0.79) and SGOT (84). Gamma Glutamyl transferase (13 u/l) was reduced with increased urine excretion of 24hour copper of 980 ug. Peripheral smear showed macrocytic anaemia with mild thrombocytopenia. Prothrombin time (14.4 sec) and Activated Partial Thromboplastin Clotting Time (APTT) was prolonged.

WD is diagnosed based on hypocupraemia, hypo-aceruloplasminemia, 24-hour increased urinary copper, confirmed by molecular analysis, and clinically by Kayser-Fleischer rings in the cornea.

Magnetic resonance imaging (MRI) of brain, showed small focal hypo intensities in bilateral basal ganglia on T1W sequences (Figure 2), small focal hypo intensities with minimal surrounding hyperintensities in bilateral basal ganglia on T2W and FLAIR (Figure 3), small focal areas of blooming in bilateral basal ganglia on T2W gradient echo (GRE) images (Figure 4), small focal hypointensities with minimal surrounding area of restricted diffusion in bilateral basal ganglia in diffusion weighted imaging (DWI) and No contrast enhancement in these regions (Figure 5).

Computed Tomography (CT) of brain revealed small focal hypodensities in bilateral basal ganglia with tiny calcifications in bilateral lentiform nucleus (Figure 6).

Ultrasonogram (USG) examination of abdomen revealed Chronic liver parenchymal disease (Figure 7) and Splenomegaly (13.6 centimetre).

Diagnosis of WD was confirmed, based on the clinical, laboratory and imaging findings.

Discussion

Historically, in 1912 Wilson first noted the neurologic symptoms of WD and provided detailed accounts of the clinical presentation, including descriptions of various movement disorders, drooling, dysarthria and psychiatric symptoms in 12 patients [8].

WD is characterized by abnormal accumulation of copper in various tissues, particularly in the liver and the brain caused by



Figure 1: (A, B): 13 years old early adolescent male with WD, eyes showing thin rim of brown coloured Kayser-Fleischer (KF) rings in the cornea.

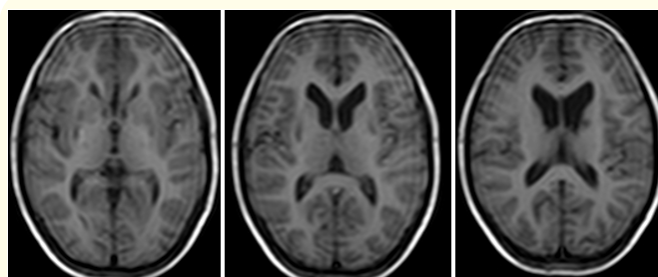


Figure 2: (A-C): Axial T1W MRI images reveal small focal hypo intensities in bilateral basal ganglia of a 13 years old male with WD.

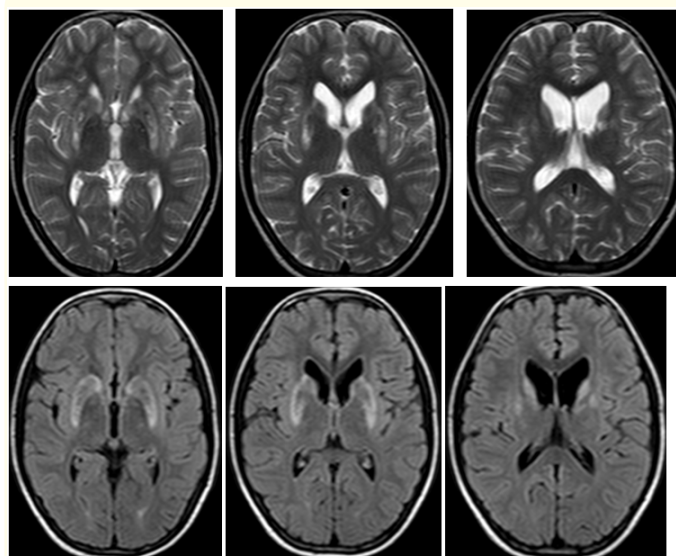


Figure 3: (A-F): T2W Axial (A-C): and FLAIR. (D-F): MR images show small focal hypo intensities with minimal surrounding hyperintensities in bilateral basal ganglia of a 13 old male patient with WD.

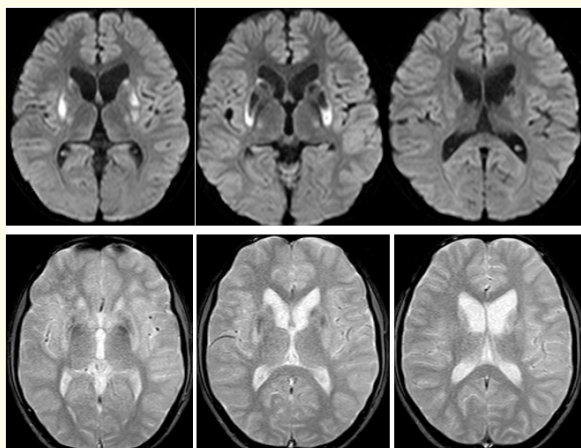


Figure 4: (A-F): DWI (A-C): Show small focal hypointensities with minimal surrounding area of restricted diffusion in bilateral basal ganglia and T2W gradient echo images. (D-F): Reveal small focal areas of blooming in bilateral basal ganglia of a 13 years old male patient with WD.

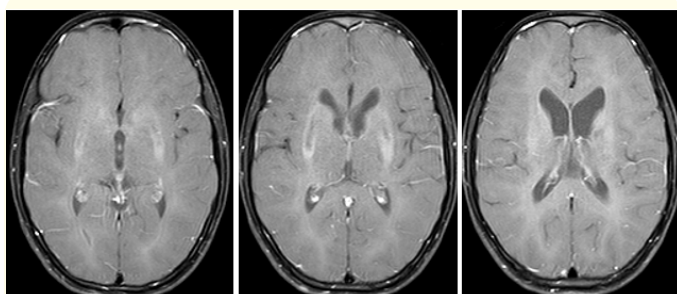


Figure 5: (A-C) Contrast enhanced MR axial images did not show any enhancing lesions of Basal ganglia in a 13 year old patient with WD.



Figure 6: (A-C): Axial Computed tomography (CT) images of Brain of 13 years old male patient with WD shows small focal hypodensities in bilateral basal ganglia with tiny calcifications in bilateral lentiform nucleus.

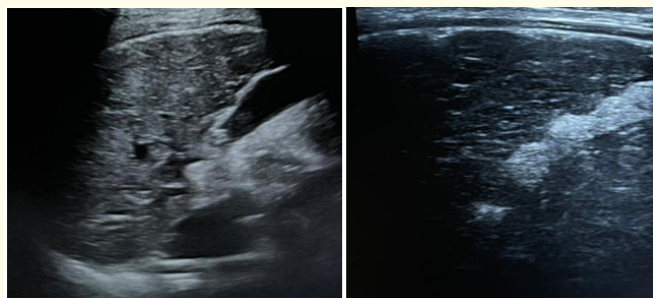


Figure 7: (A,B)Ultrasound image of 13 years old male patient with WD, showing coarse altered heterogenous echotexture of liver with nodular surface contours.

uncommon, autosomal recessive, inborn defect in copper metabolism.

ATP7B is the pathogenic gene, situated at chromosome 13q14.3 which, encodes for a copper-transporting ATPase that facilitates the combination of copper and Alpha 2-globulin into ceruloplasmin in liver; a process that is responsible for the elimination of 90% of the copper found in the circulation in normal individuals [9].

In individualities affected by WD, still impaired copper metabolism and excretion leads to the deposition of redundant free copper in the brain, liver, cornea, kidney and other organs, resulting in organ damage [10].

WD is less commonly seen in women than in men. The most common age of onset WD is between 5 - 35 years, reflecting the potential copper storage capacity of the liver [11]. Multiple studies showed that the youngest age of onset of WD was 3 and the oldest age was 80 years [12,13]. Our patient age at onset was 7 years and presented to us at 13 years which correlates with the former study [11].

WD Clinically, presents with neurologic, hepatic, or psychiatric manifestations or their combinations. WD neurologically may manifest with pyramidal and extrapyramidal features, as well as cognitive and psychiatric symptoms. WD is one of the few hereditary conditions that shows significant improvement of symptoms and responds well to treatment, with a regular regimen of de-coppering agents [14].

The foremost symptoms of WD are dysarthria and difficulty with the hands [15], but personality and psychiatric problems de-

velop latterly, together with neurologic abnormalities that can be grouped into four common clinical types: Parkinsonian, pseudo sclerotic (tremor, dysarthria, and ataxia), dystonic, and chorea. The extrapyramidal system is complex but in a simplified form can be thought of as having a major circuit through the cortex, lentiform nuclei, caudate, and thalamic nuclei and minor circuits involving the lentiform nuclei, subthalamic nuclei, substantia nigra, pons, cerebellum, middle cerebellar peduncles, and red nuclei [4]. The symptom of torsion spasm in WD seems to indicate abnormalities in the midbrain and cortex and, the symptom of choreoathetosis generally suggests damage in the caudate nucleus.

Histopathologic studies of the cerebral system in WD have shown abnormalities throughout with atrophy, spongy softening, cavitation, general reduction of neurons, increased cellularity, and the presence of Opal ski cells [16].

In our study, early adolescent male of 13 years was suffering from WD with extrapyramidal pseudo sclerotic symptoms (dysarthria and ataxia), hepatic dysfunction and behaviour disorders for a duration of 6 years with irregular treatment and intermittent symptoms when treatment was stopped.

In WD, accumulation copper in brain causes neurologic symptoms associated with neuroimaging abnormalities best visualized by cerebral MRI. In former reports, the most constantly linked MR imaging abnormality was bilateral symmetric hyperintensity in the putamen on T2W images [17,19,36].

In a study by Kim., *et al.* [18] high-signal-intensity lesions on T2W images were most constantly located in the putamen (83%), followed by the caudate nucleus (67%), globus pallidus (58%), thalamus (50%), midbrain (42%), pons (8%) and 42% showed T2W dark signal intensity in the globus pallidus, putamen, or caudate nucleus, surrounded by peripheral high signal intensity. In WD, it has been noticed that the phagocytes containing iron pigment were seen in the globus pallidus and substantia nigra [19], which explains T2W dark signal intensity.

Our study showed dark signal intensity in the globus pallidus, putamen, and caudate nucleus, surrounded by peripheral high signal intensity on T2W and FLAIR images (Figure 3), analogous to the study by Kim., *et al.* [18] and Dosek P., *et al.* [20].

T2W hyperintensities in the deep gray matter (DGM), brainstem, and cerebral white matter (WM) and T2W hypo intensities in the DGM and global atrophy are the abnormal findings at MRI [20]. T2W hypo intensities and atrophy are largely irreversible and may even progress after treatment initiation, whereas T2W hyperintensities are reversible with treatment, [21,22]. Generalized susceptibility and longstanding effect of the copper intoxication on central nervous system leads to diffuse brain atrophy.

At brain MRI, a semiquantitative scale for visual assessment of WD severity was developed and validated lately [21]. Accordingly, it is made of 2 scores 1) the acute toxicity score-representing the extent of T2W hyperintensities and 2) chronic damage score-representing the extent of atrophy and T2W hypo intensities. The extent of neurologic symptoms correlated substantially with the chronic damage score [21].

Other 3 established MRI signs that could help us to prove the diagnosis include 1) "face of giant panda sign" (T2W hyperintensity in the tegmentum of midbrain, hypo intensity of the superior colliculus and normal signal intensity of red nuclei and lateral portion of the pars reticulata of the substantia nigra), 2) "face of the miniature panda sign" or "trident sign," or "panda cub sign" seen in the pontine tegmentum (eyes of the panda -T2W relative hypo intensity of the medial longitudinal fasciculi and central tegmental tract, nose and mouth of the panda-T2W hyperintensity of the aqueduct opening into the fourth ventricle, bounded inferiorly by the superior medullary velum) and 3) "bright claustrum sign" (T2W hyperintense thin rim in lateral part of claustrum) [23-25].

Brain lesions may be present in multiple spots in WD, exhibiting symmetrical abnormal signal in bilateral hemisphere [26]. The white matter was constantly also involved in the frontal, parietal, temporal, and occipital lobes regardless of whether cortex lesions were observed, with the former presenting as a diffuse abnormal signal extending from the frontal to the occipital lobe [28]. In addition, WD lesions could also involve corpus callosum [29] and the conduction tracts, including the cerebellopontine, corticospinal, red nucleus thalamic tracts [30].

In the present study, we found that the basal ganglia were the most commonly affected site, a finding that was consistent with a former report [27].

Several imaging, electrophysiologic, and pathologic studies indicate widespread myelin damage in WD. Methodical analysis of T2-weighted MRI scans verified WM involvement, including the corticospinal, dentate-rubro-thalamic, and pontocerebellar tracts, in more than 40% of patients with WD [30], whereas conduction time extension suggestive of demyelination was detected with somatosensory and brainstem auditory evoked potentials [31].

Abnormal T1W hyperintensity in the pons, midbrain, globus pallidus, and putamen is characteristic of chronic hepatocellular dysfunction [32,33], attributed to manganese deposits [34].

Quantitative analyses of diffusion tensor imaging (DTI) parameters have demonstrated altered tissue microstructure in normal-appearing lobar WM and the thalamus [35-37].

The Unified WD Rating Scale (UWDRS) assessed the neurologic severity associated with the regularized brain volume, brain parenchymal fraction, and total volumes of Gray and white matter [38].

In recent studies, modified Young scale, assessed the disability associated with the degree of volume loss in the putamen and globus pallidus [39], whereas eye movement abnormalities in treated neurologic WD was associated with brainstem atrophy [40]. Also, T2W hypo intensities in the DGM on post mortem MRI and histopathologic study confirmed iron deposits, which correlate with neuropathologic severity [41].

Proton MR spectroscopy (MRS) can be affected by accumulation of paramagnetic copper. Leandro, *et al.* [42], noticed decreased NAA/Cr ratio, particularly in frontal white matter and parieto-occipital cortex, despite normal MRI. They also found increased Myo-inositol (mI)/Cr ratio suggestive of gliosis.

A study by W. Zhong, *et al.* [43] revealed that patients with disease durations of over a year, all had abnormal MRI manifestations, and that the disease duration of MRI-abnormal patients was significantly longer than that of patients with normal MRI results, which correlated with our study.

In young patient with acute hepatitis, Basal ganglia calcification may be result of WD [44]. Hypoparathyroidism due to copper deposition in parathyroid glands has been reported in WD, which may cause secondary brain calcification [45] (Figure 6).

In comparison to other types of cirrhosis, WD involving the liver has several unique CT features which include hyperdense nodules and a honeycomb pattern in the pre-contrast scan and also in portal and parenchymal phases [46].

Ultrasonography of WD cases shows hyperechoic liver representing hepatic steato-fibrosis and irregular liver surface, thickened gall bladder walls, dilated portal vein with decreased inflow rate, portosystemic shunts, and splenomegaly are found in the case of hepatic cirrhosis. Right lobe to Caudate lobe of liver ratio equal to or >0.65 and perihepatic hyperechogenic zone suggests WD as a possible cause of cirrhosis [47] (Figure 7).

Early diagnosis and intervention for patients with WD are essential, and MRI, which retain a level of specificity and sensitivity far superior to that of CT [48], can be a particularly important tool in this regard, especially for patients presenting with initial neurological symptoms.

Chelating agents, used to 'de-copper' patients, such as penicillamine and Trientine, facilitate the urinary excretion of copper. Patients with neurological presentations, still have unpredictable outcomes and the majority have ongoing neurological symptoms or disability [49]. Combination of genetic new born screening and gene therapy may be the ultimate solution for WD.

Conclusion

Early diagnosis and intervention for patients with WD are essential, and MRI, which retain a level of specificity and sensitivity far superior to that of CT can be a particularly important tool in this regard, especially for patients presenting with initial neurological symptoms.

Follow-up MR imaging in WD patients, revealed interval changes which has a close correlation with clinical features and can be useful in assessing the clinical response to treatment. Patients with neurological presentations, still have unpredictable outcomes and the majority have ongoing neurological symptoms or disability. Combination of genetic new born screening and gene therapy may be the ultimate solution for WD.

Bibliography

1. Bull PC., *et al.* "The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene". *Nature Genetics* 5 (1993): 327-337.
2. Tanzi RE., *et al.* "The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene". *Nature Genetics* 5 (1993): 344-350.
3. Ala A., *et al.* "Wilson's disease". *Lancet* 369.9559 (2007): 397-408.
4. Walshe JM and Yealland M. "Wilson's disease: The problem of delayed diagnosis". *Journal of Neurology, Neurosurgery and Psychiatry* 55 (1992): 692-696.
5. Brewer GJ and Yuzbasiyan-Gurkan V. "Wilson disease". *Medicine (Baltimore)* 71 (1992): 139-164.
6. Pfeiffer RF. "Wilson's disease". In: Watts RL, Koller WC, editors. *Movement Disorders. Neurologic Principles and Practice*. New York: McGraw-Hill Medical Publishers (2004): 779-797.
7. Sternlieb I. "Perspective on Wilson's disease". *Hepatology* 12 (1990): 1234-1239.
8. Wilson SAK. "Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver". *Brain* 34 (1912): 295-507.
9. Arruda WO., *et al.* "Pathogenic compound heterozygous ATP7B mutations with hypoceruloplasminaemia without clinical features of Wilson's disease". *Journal of Clinical Neuroscience* 21.2 (2014): 335-336.
10. Patil M., *et al.* "A review and current perspective on Wilson disease". *Journal of Clinical and Experimental Hepatology* 3.4 (2013): 321-336.
11. Czlonkowska A., *et al.* "Late onset Wilson's disease: therapeutic implications". *Movement Disorders* 23.6 (2008): 896-898.
12. Wilson DC., *et al.* "Severe hepatic Wilson's disease in pre-school-aged children". *The Journal of Pediatrics* 137.5 (2000): 719-722.
13. Ala A., *et al.* "Wilson disease in septuagenarian siblings: raising the bar for diagnosis". *Hepatology* 41.3 (2005): 668-670.
14. Wagner S., *et al.* "Diagnosis and care of Wilson disease with neurological revelation". *Archives de Pédiatrie* 19.3 (2012): 271-276.
15. Rutledge JN., *et al.* "Study of movement disorders and brain iron by MR". *Air* 149 (1987): 365-379.
16. Greenfield JG., *et al.* "Nutritional deficiencies and metabolic disorders". In: Greeizfield's iu'urojut/zology, 5th edition, London: Edward Arnold (1992): 838-840.
17. Nazer H., *et al.* "Magnetic resonance imaging of the brain in Wilson disease". *Neuroradiology* 35 (1993): 130-133.
18. TJ Kim., *et al.* "MR Imaging of the Brain in Wilson Disease of Childhood: Findings Before and After Treatment with Clinical Correlation". *American Journal of Neuroradiology* 27 (2006): 1373-1378.
19. King AD., *et al.* "Cranial MR imaging in Wilson disease". *American Journal of Roentgenology* 167 (1996): 1579-1584.
20. Dusek P., *et al.* "Neurologic impairment in Wilson disease". *Annals of Translational Medicine* 7.2 (2019): S64.
21. Dusek P., *et al.* "Semiquantitative Scale for Assessing Brain MRI Abnormalities in Wilson Disease: A Validation Study". *Movement Disorders* 35.6 (2020): 994-1001.
22. Dusek P., *et al.* "Brain iron accumulation in Wilson's disease: A longitudinal imaging case study during anticopper treatment using 7.0T MRI and transcranial sonography". *Journal of Magnetic Resonance Imaging* 47.1 (2018): 282-285.
23. Hitoshi S., *et al.* "Mid-brain pathology of Wilson's disease: MRI analysis of three cases". *Journal of Neurology, Neurosurgery and Psychiatry* 54 (1991): 624-626.
24. Sener RN. "The claustrum on MRI: the bright claustrum as a new sign in Wilson's disease". *Pediatric Radiology* 23 (1993): 594-596.
25. Jacobs DA., *et al.* "The double panda sign in Wilson disease". *Neurology* 61 (2003): 969.
26. Ranjan A., *et al.* "MRI and oxidative stress markers in neurological worsening of Wilson disease following penicillamine". *Neurotoxicology* 49 (2015): 45-49.

27. Litwin T., *et al.* "The effect of gender on brain MRI pathology in Wilson's disease". *Metabolic Brain Disease* 28.1 (2013): 69-75.
28. Trocello JM., *et al.* "Extensive striatal, cortical, and white matter brain MRI abnormalities in Wilson disease". *Neurology* 81.17 (2013): 1557.
29. Trocello JM., *et al.* "Corpus callosum abnormalities in Wilson's disease". *Journal of Neurology, Neurosurgery and Psychiatry* 82.10 (2011): 1119-1121.
30. Van Wassenae-van Hall HN., *et al.* "Cranial MR in Wilson disease: abnormal white matter in extrapyramidal and pyramidal tracts". *American Journal of Neuroradiology* 16.10 (1995): 2021-2027.
31. Grimm G., *et al.* "Evoked potentials in assessment and follow-up of patients with Wilson's disease". *Lancet* 336.8721 (1990): 963-964.
32. Pujol A., *et al.* "Hyperintense globus pallidus on T1-weighted MRI in cirrhotic patients is associated with severity of liver failure". *Neurology* 43 (1993): 65-69.
33. Genovese E., *et al.* "MR imaging of CNS involvement in children affected by chronic liver disease". *American Journal of Neuroradiology* 21 (2000): 845-851.
34. Kim TJ., *et al.* "MR imaging of the brain in Wilson disease of childhood: findings before and after treatment with clinical correlation". *AJNR. American Journal of Neuroradiology* 27.6 (2006): 1373-1378.
35. Wang A., *et al.* "Study on Lesion Assessment of Cerebello-Thalamo-Cortical Network in Wilson's Disease with Diffusion Tensor Imaging". *Neural Plasticity* (2017): 7323121.
36. Favrole P., *et al.* "Clinical correlates of cerebral water diffusion in Wilson disease". *Neurology* 66.3 (2006): 384-389.
37. Jadav R., *et al.* "Diffusion tensor imaging (DTI) and its clinical correlates in drug naïve Wilson's disease". *Metabolic Brain Disease* 28.3 (2013): 455-462.
38. Smolinski L., *et al.* "Brain volume is related to neurological impairment and to copper overload in Wilson's disease". *Neurological Sciences* 40.10 (2019): 2089-2095.
39. Zou L., *et al.* "Regional morphometric abnormalities and clinical relevance in Wilson's disease". *Movement Disorders* 34.4 (2019): 545-554.
40. Hanuška J., *et al.* "Eye movement abnormalities are associated with brainstem atrophy in Wilson disease". *Neurological Sciences* 41.5 (2020): 1097-1103.
41. Dusek P., *et al.* "Brain iron accumulation in Wilson disease: a post mortem 7 Tesla MRI - histopathological study". *Neuropathology and Applied Neurobiology* 43.6 (2017): 514-532.
42. Lucato LT., *et al.* "Proton MR spectroscopy in Wilson's disease: Analysis of 36 cases". *American Journal of Neuroradiology* 26 (2005): 1066-1071.
43. Wei Zhong., *et al.* "A study of brain MRI characteristics and clinical features in 76 cases of Wilson's disease". *Journal of Clinical Neuroscience* 59 (2019): 167-174.
44. Fatima J., *et al.* "Hypoparathyroidism in a case of Wilson's disease: rare association of a rare disorder". *Indian Journal of Endocrinology and Metabolism* 17.2 (2013): 361-362.
45. Li W., *et al.* "Unique CT imaging findings of liver in Wilson's disease". *Abdominal Imaging* 36.1 (2011): 69-73.
46. Akhan O., *et al.* "Unusual imaging findings in Wilson's disease". *European Radiology* 12 (2002): 66-69.
47. Van Wassenae-van HH., *et al.* "Wilson disease: findings at MR imaging and CT of the brain with clinical association". *Radiology* 198.2 (1996): 531-536.
48. Walshe JM. "The conquest of Wilson's disease". *Brain* 132.Pt 8 (2009): 2289-2295.