Journal of Current Medical Research and Opinion
Received 15-09-2022| Revised 28-09-2022| Accepted 30-09-2022| Published Online 05-09-2022

DOI: https://doi.org/10.52845/CMRO/2022/5-9-2

ISSN (O) 2589-8779 | (P) 2589-8760

CMRO 05 (09), 1372–1379 (2022)

Original Research:

Essential Case Report Study on Wilson Disease

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Abstract:

Impaired copper metabolism is the hallmark of Wilson's disease (WD), which is caused by a faulty ATP7B protein product. Its clinical effects range from asymptomatic states to fulminant hepatic failure, chronic liver disease with or without cirrhosis, and neurological and mental symptoms. To avoid missing cases of WD, particularly less florid patients with only mild transaminase elevations or limited neuropsychiatric involvement, a high degree of suspicion is warranted. It is required to screen the first and second-degree relatives of index cases, and treatment must start as soon as a diagnosis is made. Chelators like D-penicillamine and trientine are used as treatment options, and zinc salts act as methallothionein inducers, which promote a negative copper balance and a decrease in free plasmatic copper. Research is sparse in this area because it is an orphan disease; particularly in relation to therapeutic approaches that improve patient compliance and may eventually also undo existing damage. About 50% of WD patients have liver illness upon presentation. Acute liver failure, cirrhosis, asymptomatic abnormal liver tests, and chronic hepatitis all have different liver presentations. Similar to the histology, there are various patterns in acute hepatitis with submassive or massive necrosis, steatosis or steatohepatitis, chronic hepatitis, and mild nonspecific alterations. These are all general and not just for WD. Special stains for copper and copper-associated proteins, as well as copper content in liver tissue, are aids to the histologic diagnosis.

KEYWORDS: WILSON DISEASE (WD), TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS), GAMMA-AMINOBUTYRIC ACID (GABA), TOTAL LEUCOCYTES COUNT (TLC)

Introduction:

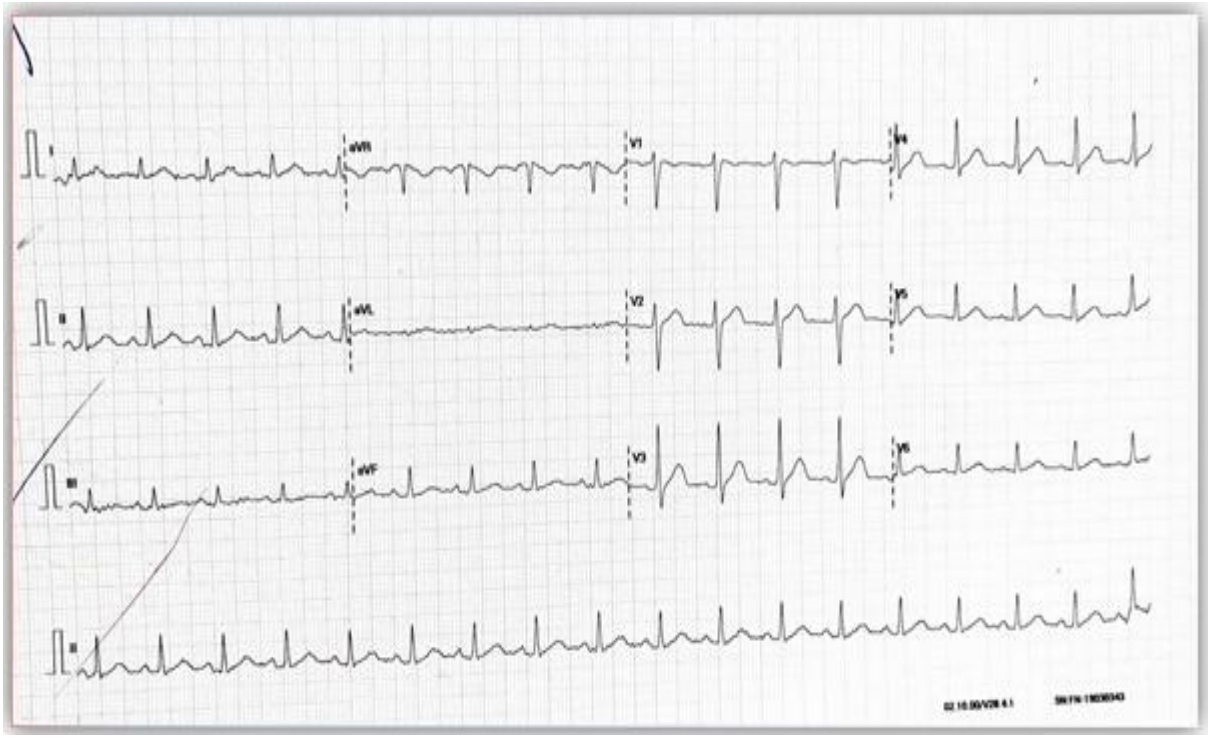
Wilson's disease (WD), was first identified by Kinnear Wilson in 1912 and is an autosomal recessive disease that is sporadic in onset and is caused by mutations in the area of chromosome 13q14 that codes for the protein ATP7B.[1] Moreover, homozygous or more frequently compound heterozygous mutations impair copper's normal integration into apo-ceruloplasmin and result in the development of holoceruloplasmin, which interferes with copper's normal excretion into bile.[2] This deficiency has

the effect of impairing copper metabolism, which leads to copper toxicity. Despite the extremely low levels of circulating apoceruloplasmin (ceruloplasmin), which has a shorter half-life than holoceruloplasmin and plays one of the most crucial roles in the body being present the gene for this protein is located on chromosome 3 preserving one of the most crucial clinical diagnostic resources for WD.[3,4] Two main mechanisms—direct oxidative stress, which results in lipid peroxidation of membranes, DNA, and mitochondria; as well as uncontrolled apoptosis—lead to cell death when copper induces changes in the anti-apoptotic protein, X-linked inhibitor of apoptosis, and its loss of inhibitory control over caspase-3. Copper overload, and actually free copper as the main acting element, exerts its toxicity through these two main mechanisms.[5,6] It is now understood that copper intoxication, as opposed to ceruloplasmin-bound copper, is caused by free copper in the bloodstream, not copper buildup, which is harmful to the organism.[7] Thus, the notion of normalising free copper concentrations in the bloodstream has replaced the outdated paradigm of removing copper stores as the therapeutic objective.[8] The copper-carrying ATP gene in the liver is altered by the genetic abnormality, which is located on the long arm of chromosome 13 (13q).[9] The majority of Wilson disease patients experience liver impairment within the first ten years of life.[10] The third or fourth decade of life is when the neuropsychiatric symptoms first appear. Wilson illness is uncommon, yet it can be fatal if it is not identified and treated.[11] The liver and brain's trans-Golgi networks are home to the protein transporter.[12] The liver accounts for 95% of the body's excretion of copper. The liver is where the extra copper first gathers before spilling into the blood and other organ systems.[13,14] The extra copper results in the production of free radicals, which oxidise essential lipids and proteins. The mitochondria, nuclei, and peroxisomes frequently undergo the earliest alterations.[15] Wilson disease is characterised by a malfunctioning copper excretory system that causes copper to build up in the liver and leak into the blood, where it starts to accumulate in various organs and tissues, including the subthalamus, putamen, cortex, kidneys, and cornea.[16] A hazardous hydroxyl group is formed when copper levels are too high, causing oxidative stress in the cells.[17] Copper is a transition metal. The cells are damaged by this oxidative stress, which results in clinical manifestations such as liver failure, behavioural issues, mobility difficulties, and corneal Kayser-Fleischer rings.[18] The body needs copper, mostly as a cofactor for enzymes including tyrosinase, ceruloplasmin, cytochrome-c oxidase, dopamine beta-hydroxylase, and superoxide dismutase.[19] Using the copper membrane transporter 1 protein found in the cells of the small bowel, copper enters the body through the digestive tract (SLC31A1 {protein coding gene}).[20] This transporter aids in the movement of copper within cells, where some of the copper is transported by ATOX1 gene to an organelle known as the trans-Golgi network, and some of the copper is bound to metallothionein. An enzyme known as ATP7A releases copper into the portal vein to the liver in response to growing copper levels. CMT1 (Charcot-Marie-Tooth disease type 1) and metallothionein are carried by liver cells, where they are then bound inside of the cell by ATOX1. At this point, ATP7B joins the copper to ceruloplasmin and releases it into the bloodstream while secreting any extra copper into bile.[21] Wilson's illness compromises both of ATP7B's functions. In contrast to ceruloplasmin, that is released in a copper-free state and breaks down quickly in the bloodstream and hence copper builds up in the liver. Through a process known as oxidative damage, this is caused when the copper level in the liver outweighs the proteins that normally bind it. Chronic active hepatitis, fibrosis, and cirrhosis are the results of this damage.[22] Unbound copper that is not ceruloplasmin-bound is released into the bloodstream by the liver. In the kidneys, eyes, and brain in particular, this free copper precipitates throughout the body. The basal ganglia, putamen, and globus pallidus (i.e., lenticular nucleus) of the brain all contain copper deposits that are involved in neurocognitive processes like enhancing mood regulation. The neuropsychiatric symptoms of Wilson's disease are caused by damage to these regions. Wilson's

illness is mostly treated with copper chelation therapy using penicillamine and trientine. Since trientine has fewer adverse effects, it is preferable. Additionally, oral zinc may be administered since it competes with copper for absorption at metallic ion transporters.[23] The patient must be informed of the negative effects of persistent chelation therapy, which can exacerbate symptoms. The foetus is not at risk when using d-penicillamine during pregnancy. Transjugular intrahepatic portosystemic shunt (TIPS) can be recommended if the patient develops liver cirrhosis and its accompanying morbidity in addition to recurrent variceal bleeding. Transplanting a liver is therapeutically treatment hence, LEVODOPA, BACLOFEN, anticholinergics (TRIHEXYPHENIDYL), GABA antagonists, and LEVODOPA may be used to treat parkinsonian symptoms such as muscle rigidity, spasticity, and tremor. When medical treatment fails to sufficiently address neurological impairment in a patient, liver transplantation appears to have been helpful.[24] It is advised to eat a diet low in foods containing copper and to stay away from foods like mushrooms, chocolate, almonds, dried fruit, liver, and shellfish. The neurologic form of the condition benefits from physical and occupational treatment. These therapies can help with ataxia, dystonia, and tremors as well as avoid contractures that can come from dystonia and movement problems. The copper-chelating treatment can take up to six months to start functioning. The patient needs to be informed about the benefits of eating low-copper foods.[25] The patient should not be taking any medications that can impair the liver, according to the clinical pharmacologist. Alcohol usage needs to be prohibited. The neuropsychiatric symptoms should be periodically evaluated by the mental health nurse because they might need to be treated with additional medications. Although liver transplantation is a curative procedure, patients must be watched closely for any negative consequences of the immunosuppressant medications. Chelation therapy needs to be closely monitored by the clinical pharmacologist because it can have a number of unfavorable effects that can make the symptoms worse. Chelation therapy must occasionally be stopped. Results will be improved by a team approach comprising nurses, pharmacists, and clinicians.[26]

Case History:

A 17 years old patient who was diagnosed with Wilson's disease (WD) has a history of irregular behavior, movement of hands since from the date of joining 14/07/2022; followed by dwindling in talk. Generally, as the patient was bedridden, hence bed sores were marked forcibly. No history of seizures was seen. On the other hand, patient was tested with ICPMS (Inductively Coupled Plasma Mass spectrometry) is used to detect the level of heavy traced copper materials in biological tissues. Secondly, he was tested with Urine essay results was **1200 ml/day** and was resulted with Wilson Disease. Test Ceruloplasmin serum* was done to detect the copper containing in body result came out with **25.83 mg/dl**. Total Leucocytes Count (TLC) was **15.3H** which normally counts as **4.0-10.0.** Patient was started with prophylaxis treatment with specific 3rd generation of antibiotic followed by parkinsonism treatments and few general medicines for proper rhythmic heart-rate and also to maintain GI tract. Medicines are INJ PANTOPRAZOLE 40 MG, Tab ZINCOVA 50MG, INJ ZOFER 4 ML, TAB SYNODOPA 125 MG, TAB BACLOF 10 MG, INJ LEVIPRIL 5 ML, TAB PACITANE 2 MG, TAB LEVOCON 25 MG, INJ CEFTRIAZONE 1GM, TAB D PENICILLAMINE 125 MG, INJ CLINDAMYCIN 600 MG, INJ ACTACREZ 2.25 MG , TAB ACLOFEN 10 MG TAB STAMLO 5MG, INJ LEVERA 15 GM and INJ PHENORGAN 25 MG was given. His tests of every report is attached below with appropriate ECG details and also with other CT-scan, X-Ray was done. Patient is still under strict monitoring by physicians and clinical pharmacologist to get some positive outcome. Moreover, patient has been instructed for physiotherapy under prioritize routine schedule. Although Wilson Disease are not curable but can be treated with efficient intake of zinc, magnesium supplements and foods.

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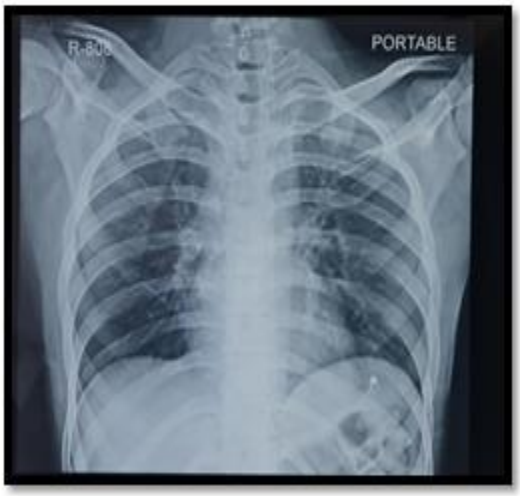
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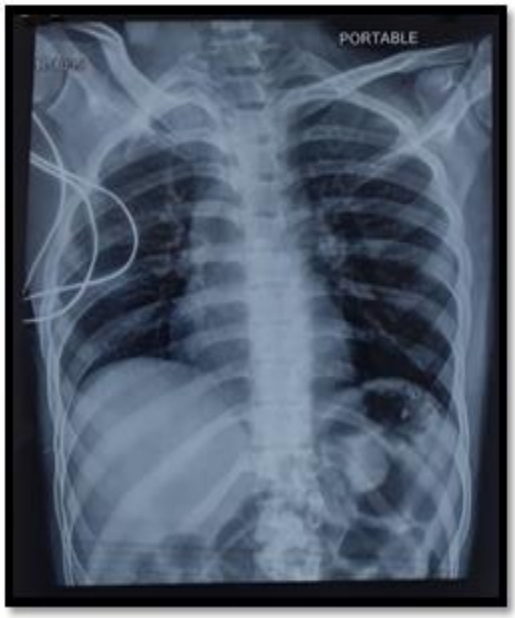
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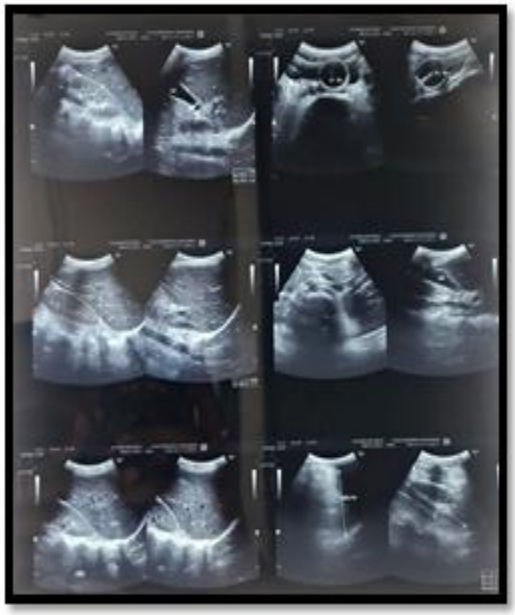

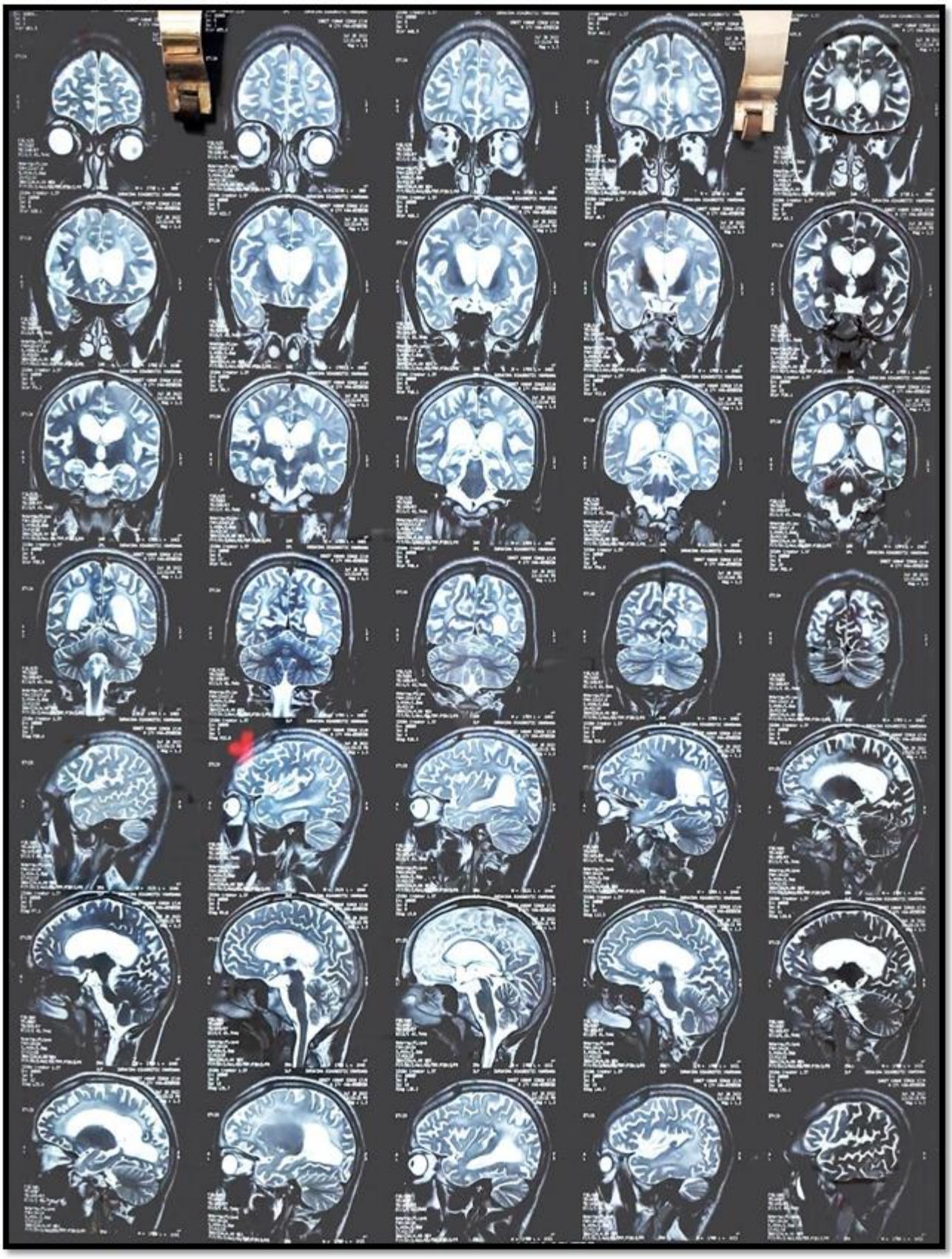

Discussions and Conclusions:

Overabundant copper is retained in several human tissues, including the liver, brain, and corneas of the eyes, in Wilson disease, a rare genetic illness. The illness progresses and, if untreated, may result in mortality, central nervous system dysfunction, and liver (hepatic) disease. Preventing major long-term impairment and potentially fatal complications may be possible with early diagnosis and treatment. The goal of treatment is to lower the level of stored copper in the body and then maintain normal copper levels. The following conditions can have symptoms that resemble

Wilson's illness: a differential diagnosis may benefit from comparisons. The most frequent incorrect diagnosis in cases of mild liver illness is viral hepatitis. Studies on copper and viral antigens should be distinct. Alcoholic cirrhosis is frequently misdiagnosed in patients with well-established cirrhosis who also consume alcohol.[27] Studies on copper should be differentiated. If the patient exhibits tremors, an inaccurate diagnosis of early Parkinson's disease or essential tremor may be made. Studies on copper should again be differentiated. If psychiatric symptoms are severe, it could be mistakenly assumed that the patient is abusing drugs. Studies on copper should again make distinctions. The following conditions are occasionally mistaken for Wilson's: about 5 to 10 percent of cases of rheumatic fever are followed by the acute, typically self-limiting illness known as Sydenham's chorea. On one or both sides of the body, the condition often starts with jerky, uncontrolled, non-repetitive muscular movements. Rapid, unconscious movements that might impact speech, arm movements, and walking are developed in patients even face grimacing and clumsiness are frequent in many cases. Primary biliary cholangitis is a chronic, progressive liver disease that is suspected to be linked to immune system disorders. Initial signs of this condition typically include generalised, persistent itching, black urine, light stools, and jaundice. Eventually, too much copper builds up in the liver, and the soft tissue of the liver hardens into fibrous or granular structures. Moreover, a neurologic movement disease called Tourette syndrome is also characterised by recurrent verbal and motor tics and also associated with Wilson's disease. Rapid blinking of the eyes or grimacing of the face are typically the first signs to appear in children. Additionally, involuntary movements of the shoulders, face, and voluntary muscles as well as the extremities are possible symptoms. Some individuals with Tourette syndrome may vocalise involuntarily; these sounds or words may be imprecise. The symptoms of Tourette syndrome tend to vary and have a long-term waxing and waning pattern. However, it is not a progressive or degenerative illness. Beginnings typically happen before the age of 16. A brain injury that occurs during infancy or at birth can cause cerebral palsy, a neuromuscular condition. Lack of muscular control and coordination is the main sign of this condition. There is no progression to cerebral palsy. In general, developmental delays in babies might occur during the first or second year, along with muscle weakness and aberrant muscle tone. Wilson's disease symptoms such as poor speech and coordination can mirror cerebral palsy signs. WD outrages the conclusion that the disease is a Hepatobiliary copper excretion disorder which is characterised primarily by hepatic and neurologic copper toxicosis and an inherited autosomal recessive pattern.

Rferences:

1. Hedera P, Wilson's disease: A master of disguise. Parkinsonism & related disorders. 2019 Feb [PubMed PMID: 30797706]

2. Nagral A,Sarma MS,Matthai J,Kukkle PL,Devarbhavi H,Sinha S,Alam S,Bavdekar A,Dhiman RK,Eapen CE,Goyal V,Mohan N,Kandadai RM,Sathiyasekaran M,Poddar U,Sibal A,Sankaranarayanan S,Srivastava A,Thapa BR,Wadia PM,Yachha SK,Dhawan A, Wilson's Disease: Clinical Practice Guidelines of the Indian National Association for Study of the Liver, the Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition, and the Movement Disorders Society of India. Journal of clinical and experimental hepatology. 2019 Jan-Feb [PubMed PMID: 30765941]

3. Pfeiffenberger J,Lohse CM,Gotthardt D,Rupp C,Weiler M,Teufel U,Weiss KH,Gauss A, Long-term evaluation of urinary copper excretion and non-caeruloplasmin associated copper in Wilson disease patients under medical treatment. Journal of inherited metabolic disease. 2019 Mar [PubMed PMID: 30746719]

4. Gerosa C,Fanni D,Congiu T,Piras M,Cau F,Moi M,Faa G, Liver pathology in Wilson's disease: From copper overload to cirrhosis. Journal of inorganic biochemistry. 2019 Apr; [PubMed PMID: 30703747]

5. Takkar B,Temkar S,Venkatesh P, Wilson disease: Copper in the eye. The National medical journal of India. 2018 Mar-Apr; [PubMed PMID: 30829235]

6. Zou L,Song Y,Zhou X,Chu J,Tang X, Regional morphometric abnormalities and clinical relevance in Wilson's disease. Movement disorders : official journal of the Movement Disorder Society. 2019 Feb 28; [PubMed PMID: 30817852]

7. Capone K,Azzam RK, Wilson's Disease: A Review for the General Pediatrician. Pediatric annals. 2018 Nov 1; [PubMed PMID: 30423186]

8. Horn N,Møller LB,Nurchi VM,Aaseth J, Chelating principles in Menkes and Wilson diseases: Choosing the right compounds in the right combinations at the right time. Journal of inorganic biochemistry. 2019 Jan; [PubMed PMID: 30384011]

9. Duncan A,Yacoubian C,Beetham R,Catchpole A,Bullock D, The role of calculated non-caeruloplasmin-bound copper in Wilson's disease. Annals of clinical biochemistry. 2017 Nov [PubMed PMID: 27742851]

10. Stezin A,Kamble N,Jhunjhunwala K,Prasad S,Pal PK, Clinical Utility of Longitudinal Measurement of Motor Threshold in Wilson's Disease. The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques. 2019 Mar [PubMed PMID: 30665472]

11. Poujois A,Sobesky R,Meissner WG,Brunet AS,Broussolle E,Laurencin C,Lion-François L,Guillaud O,Lachaux A,Maillot F,Belin J,Salamé E,Vanlemmens C,Heyd B,Bellesme C,Habes D,Bureau C,Ory-Magne F,Chaine P,Trocello JM,Cherqui D,Samuel D,de Ledinghen V,Duclos-Vallée JC,Woimant F, Liver transplantation as a rescue therapy for severe neurologic forms of Wilson disease. Neurology. 2020 May 26; [PubMed PMID: 32398357]

12. Nazer H,Ede RJ,Mowat AP,Williams R, Wilson's disease: clinical presentation and use of prognostic index. Gut. 1986 Nov; [PubMed PMID: 3792921]

13. Guillaud O,Dumortier J,Sobesky R,Debray D,Wolf P,Vanlemmens C,Durand F,Calmus Y,Duvoux C,Dharancy S,Kamar N,Boudjema K,Bernard PH,Pageaux GP,Salamé E,Gugenheim J,Lachaux A,Habes D,Radenne S,Hardwigsen J,Chazouillères O,Trocello JM,Woimant F,Ichai P,Branchereau S,Soubrane O,Castaing D,Jacquemin E,Samuel D,Duclos-Vallée JC, Long term results of liver transplantation for Wilson's disease: experience in France. Journal of hepatology. 2014 Mar; [PubMed PMID: 24211743]

14. Qu W,Wei L,Zhu ZJ,Sun LY,Liu Y,Zeng ZG, Considerations for Use of Domino Cross-auxiliary Liver Transplantation in Metabolic Liver Diseases: A Review of Case Studies. Transplantation. 2019 Sep [PubMed PMID: 30801517]

15. Choudhary NS,Saigal S,Saraf N,Rastogi A,Goja S,Bhangui P,Thiagrajan S,Gautam D,Govil D,Vohra V,Soin AS, Outcome of Living Donor Liver Transplantation for Wilson's Disease in Adults: A Single Center Experience. Journal of clinical and experimental hepatology. 2018 Jun; [PubMed PMID: 29892175]

16. Belkhribchia MR,Belabbes S,Loukili M,El Hasni I,El Makkaoui M, An unusual and devastating presentation of neurologic Wilson's disease with extensive brain MRI lesions. Presse medicale (Paris, France : 1983). 2018 Jun; [PubMed PMID: 29776795]

17. Nicastro E, Loudianos G, Zancan L, D'Antiga L, Maggiore G, Marcellini M, Barbera C, Marazzi MG, Francavilla R, Pastore M, et al. Genotype-phenotype correlation in Italian children with Wilson's disease. *J Hepatol*. 2009;50:555–561. [PubMed] [Google Scholar]

18. Lee BH, Kim JH, Lee SY, Jin HY, Kim KJ, Lee JJ, Park JY, Kim GH, Choi JH, Kim KM, et al. Distinct clinical courses according to presenting phenotypes and their correlations to ATP7B mutations in a large Wilson's disease cohort. *Liver Int*. 2011;31:831–839. [PubMed] [Google Scholar]

19. Ferenci P, Caca K, Loudianos G, Mieli-Vergani G, Tanner S, Sternlieb I, Schilsky M, Cox D, Berr F. Diagnosis and phenotypic classification of Wilson disease. *Liver Int*. 2003;23:139–142. [PubMed] [Google Scholar]

20. Schilsky ML, Scheinberg IH, Sternlieb I. Liver transplantation for Wilson's disease: indications and outcome. *Hepatology*. 1994;19:583–587. [PubMed] [Google Scholar]

21. Walshe JM. Wilson's disease presenting with features of hepatic dysfunction: a clinical analysis

of eighty-seven patients. *Q J Med*. 1989;70:253–263. [PubMed] [Google Scholar]

22. Scott J, Gollan JL, Samourian S, Sherlock S. Wilson's disease, presenting as chronic active hepatitis. *Gastroenterology*. 1978;74:645–651. [PubMed] [Google Scholar]

23. Stremmel W, Meyerrose KW, Niederau C, Hefter H, Kreuzpaintner G, Strohmeyer G. Wilson disease: clinical presentation, treatment, and survival. *Ann Intern Med*. 1991;115:720–726. [PubMed] [Google Scholar]

24. Saito T. Presenting symptoms and natural history of Wilson disease. *Eur J Pediatr*. 1987;146:261–265. [PubMed] [Google Scholar]

25. Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update. *Hepatology*. 2008;47:2089–2111. [PubMed] [Google Scholar]

26. Svetel M, Potrebić A, Pekmezović T, Tomić A, Kresojević N, Jesić R, Dragasević N, Kostić VS. Neuropsychiatric aspects of treated Wilson's disease. *Parkinsonism Relat Disord*. 2009;15:772–775. [PubMed] [Google Scholar]

27. Svetel M, Kozić D, Stefanova E, Semnic R, Dragasevic N, Kostic VS. Dystonia in Wilson's disease. *Mov Disord*. 2001;16:719–723. [PubMed] [Google Scholar]