ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

COPPER DEFICIENCY- A REVIEW

M. Trinadha Rao*, P. Sravani, P. Sandya Rani, Ch. Lalitha Kumari, G. Nagamani

Adarsa college of Pharmacy, G.Kothapalli, Gokavaram, Andhra Pradesh, India

*Corresponding Author E-mail: **thrinadh_81@rediffmail.com.**

ARTICLE INFO

Key words:
Copper deficiency, Copper metabolism, Menke's disease, Menkes kinky hair disease, Wilson disease.

Access this article online
Website:
https://www.jgtps.com/
Quick Response Code:

ABSTRACT

In1993, the candidate gene for menke's disease and wilson's disease were cloned and remarkable progress has been made in the study of copper metabolism during the past 10years. The proteins induced by the ATP7A and transporter membrane proteins and control cellular copper transport recently three chaperones supplying copper to the intracellular copper metabolism is becoming more and clearer. Numerous copper requiring enzymes are present in the body; therefore copper deficiency may lead to various disorders. Menke's disease is well known as an inherited disorder of the copper transport from the intestine resulting in copper deficiency. In regarding to acquired copper deficiency nutritional deficiency is probably the most common cause, and may be seen in malnourished low birthweight infants, newborns, and small infants. Copper deficiency is also been reported to develop after gastrointestinal surgery Intractable diarrhea, and prolonged parenteral or enteral nutrition. in this article present a review of copper deficiency and its treatment.

INTRODUCTION:

Copper is one of the essential trace elements in humans and disorders associated with its deficiency and excess have been reported Menke's (kinky hair) disease is well known to be associated with copper deficiency due to an inherited disorder of copper transport from the intestine metabolism and Wilson disease inherited disorder of cellular copper transport resulting in copper accumulation acquired copper deficiency is mainly attributable to nutritional deficiency and may be seen in malnourished low birth weight infants, newborns, and small infants copper deficiency has also been reported to develop after gastrointestinal surgery Intractable diarrhea, and prolonged parenteral or essential nutrition.. However since copper supplementation of intravenous and enteral nutritional formulas was made mandatory,the incidence of copper deficiency has decreased dramatically an acquired copper excess state has been described in cases of Indian childhood cirrhosis, non-Indian children cirrhosis, excessive copper intake and parenteral bolus administration of copper for the treatment of copper deficiency. Many aspects regarding the physiological roles of copper in the body remain unknown. However remarkable progress in the understanding of copper metabolism has been made since the cloning of the candidate genes for Menke's disease (ATP7A) and Wilson disease (ATP7B). It has been revealed that the proteins induced by these genes(ATP7A)and(ATP7B)arehighlyhomologous,andareP-typeATP-related copper transporter membrane proteins that control cellular copper transport. Furthermore, the mechanism by which copper is transported into cells and the chaperones(three kinds)supplying copper to the

copper requiring enzymes have been discovered, and the physiologyofcellularcoppermetabolismisbeingg raduallyelucidated.Forlackofspacethephysiologi cal role of copper in humans are not discussed here. And Fig.1shows a chart of the various steps in copper metabolism in hepatocytes. See sited references for further details. The discussion in this article is mainly focused on copper deficiency in humans. General symptoms of copper deficiency: The clinical symptoms associated with copper deficiency are extremely diverse. The most common features include anemia, leucopenia, bone lesions (scorbutic-like bone changes and occipital horn) and vesicle diverticulitis. In children, some commonly noted findings arehypotonia,psychomotor retardation, and hypothermia Fig. 1 to 3 shows the images of the symptoms of copper deficiency[1] Clinical symptoms associated with copper deficiency are extremely diverse. The most common features include anemia, leucopenia, bone lesions (scorbutic-like bone changes and occipital horn) and vesicle diverticulitis. In children, some commonly noted findings arehypotonia, psychomotor retardation, and hypothermia.[1].

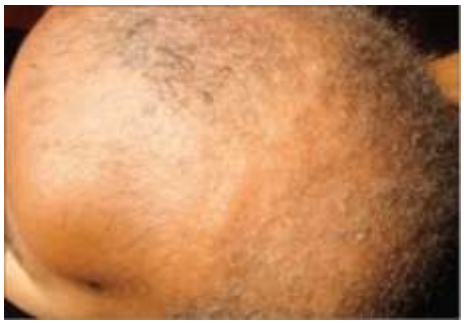


Fig.no1: Copper deficiency in infants

Fig.no2: Menke's disease

Fig.no 3: Kayser-Fleischerring

Hematological abnormalities

Microcytic hypochromic anemia: This is attributable to a decrease in the ferroxidase activity of Ceruloplasmin (Cp) and reduced iron oxidation. When anemia is noted in low-birth weight infants, patients with chronic diarrhea and patients received prolonged enteral or parenteral nutrition, copper deficiency must be suspected in addition to iron deficiency.

Neutropenia: Granulocyte maturation disorder in the bone marrow and vacuolation in neutrophils are observed.

Bone lesions in copper deficiency states:

Rachitic-like or scorbutic-like changes(enlargement of the epiphysealarea and the margin)are observed in the bones of extremities. They may be accompanied by osteoporosis and occipitalhorn formation after adolescence.These are attributable to functional impairment of copper requiring enzymes, such as ascorbic oxidase and lysyloxidase, associated with copper deficiency.

Vascular lesions:

Menke's disease is characterized by tortuosity and winding of arteries and increased capillary fragility. Caution must be exercised to avoid prolonged copper deficiency in humans, since this may lead to abnormal vascular tortuosity and increased capillary fragility.

Central nervous system disorder and convulsion:

Reports of central nervous system disorder and convulsion associated with copper deficiency are rare,but they are characteristic features of menke's disease. Progressive Menke's disease is fatal. Prolonged copper deficiency may cause degeneration of the

cerebrum and cerebellum (numerous copper requiring enzymes are present in the brain, such as dopamine B-hydroxylase and cytochromec oxidase).Associated with slowing of mentation and muscular rigidity, as well as hemorrhagic changes due to increased capillary fragility. In children, hypotoniais often observed.

Hair abnormalities: Change of hair texture, namely, kinky hair, may be observed in children with menke's disease.Hairchanges are,however, considered rare incases with secondary copper deficiency. On the other hand, the possibility of changes in the hair should be borne vin mindin cases of prolonged copper content of the hair and nail is decreased in Cases of copper deficiency.

Others: Attention should be paid to the development of hypothermia, achromoderma, splenohepatomegaly, and susceptibility to infections in copper deficiency states.

Diagnosis and evaluation of copper deficiency states and indicators:

The above described clinical findings are important pointers for the diagnosis of copper deficiency. In addition, when copper deficiency is suspected, the following test must be conducted. The most important indicators of the status of copper deficiency of the serum Ceruloplasmin(Cp)level and the serumcopper level.[2].Caution must be exercised in interpreting their values, because new borns and low-birth weight infants of ten have physiological hypercerulo-plasminemia and hypocupremia, which make the diagnosis and assessment of copper deficiency difficult in these cases.[3].

Serum Cp level: Except in newborns, low birth weight infants, and small infants, serum cp levels may be interpreted as follows: 10 to 20 mg /dl, mild decrease; 5 to 10 mg/dl, moderate decrease;5mg/dl or less, marked decrease.

.Serum copper level: Except in newborns, low birth weight infants, and small infants, serum copper levels may be interpreted as follows: 60 to 80 mg/dl mild decrease; 40 to 60 mg/dl , moderate decrease; 40mg/dlor less, marked decrease. In addition, information regarding the copper content of the hair and nails and as tudy of the urinary copper excretion and copper balance would be use. [4].

Treatment of copper deficiency: Treatment of copper deficiency in low-birth-weight infants and newborns. When copper is administered intravenously, the amount of copper accumulating is proportional to the amount administered, and a large amount of non-Cp copper in the blood may induce toxicity. Therefore, oral administration is recommended, were possible. Intravenous administration may become necessary if no improvement in the clinical condition is observed after oral administration for about a week. However, this should be avoided as far as possible during the first 3 weeks after birth when copper supplementation should be conducted gradually. Treatment of copper deficiency in infants and children. As a general rule, oral administration should be employed. When oral administration isimpossible, treatment should be provided by either intravenous or subcutaneous injurious

COPPER DEFICIENCY MAINLY CAUSED TWO TYPESOF DISEASES:

A. Menke's Disease

B. Wilson Disease

MENKE'SDISEASE

Menke's disease is a genetic disorder of copper transport in the body. And disorder of copper absorption and excretion is noted in the intestinal tract and uriniferous tubules. Menke's disease gene is located on the long arm of the X chromosome (xq 13.3). The protein induced by this gene is an intracellular copper transport, membrane protein calledATP7A.TheMenke's disease gene is predominantly express in the duodenum, upper part of the small intestine and renal proximal tubules, while no expression is noted in hepatocytes (the Wilson disease gene is strongly expressed in the hepatocytes). Therefore, this disease is transmitted by X-linked recessive inheritance and develops in boys, at an estimated incidence of about 1in100,000-200,000.In this disease[6],copper absorption from the intestine is impaired, resulting in a copper deficiency state. Central nervous system disorder, collagen metabolism disorder, bone lesions, hair abnormalities, abnormality of pigmentation, vesicle diverticula ,and decreased skin elasticity may

be noted. However, hematological abnormalities, which are commonly seen in cases of nutritional copper deficiency, are rare. Hypothermia and weakbreast-feeding may be noted during the neonatal period in some cases but many of the infants grow normally until 3 or 4 months of age, when the disease often manifests by features such as convulsion, etc[7]. The central nervous symptoms are progressive, may become serious even during the early stages, and then regress. Typically, kinky hair (nodules, trichorrhexis, andkinky) is noted and the hair is rough, brittle and breaks easily. However, this may not be evident in some cases. Hypercerulo-plasmenia and hypercupremia are seen on blood biochemical tests. Copper absorption is noted to be poor in the oral copper sulfate tolerance test, with no increase in the serum CPlevel or copper serum level.

The typical form of this disease is called classic Menke's disease, which is a serious condition. In addition, mild Menke's disease and extremely mild Menke's disease (occipital horn syndrome and Ehlers-Danlos syndrome, type 1X) may also be seen, and abnormality of the Menke's disease gene has been confirmed in both cases. Themildtype disease develops between 6 and 24 months after birth, and the extremely mildtype is often discovered from the age of 5or 6years through adolescence.[8].

There is no radical cure for this disease. Parenteral administration (intravenous or subcutaneous injection)may be administered, but it is ineffective against advanced cerebral disorder. Parenteral copper administration is believed to resolve the systemic condition, bone and hair change and the susceptibility to injection, and to prolong patient lives. It is considered effective against mild and extremely mildcases.[9]

Figure 4:Menke's kinky hair disease.

MENKE'S KINKY HAIR DISEASE:

Menke's kinky hair disease is a rare X-linked recessive disorder of copper metabolism. In1962, Menke's first described the syndrome and Drank *et al*. noted the association with copper metabolism. In Menke's kinky hair disease, intestinal copper uptake is normal, but copper transport too thert issues is affected [10]. The defective protein is a copper-binding ATP ase, ATP7A, [11]. Responsible for distribution and metabolism of copper in tissues.A defect in intestinal copper transport with associated low serum copper and ceruloplasmin levels results in defective functioning of copper-dependent enzymes like lysyloxidase,cytochromec oxidase, dopamine β-hydroxylase, tyrosinase, and superoxide dismutase with subsequent clinical manifestations. Depigmentation of hair and skinfall or are due to tyrosinase deficiency, hypothermia is due to cytochromec oxidase deficiency, and lysyloxidase deficiency causes tortuous arteries in brain, and progressive vascular changes predispose to thrombosis and deficient blood supply to the developing brain.[12].

Individuals with Menke'skinky hair disease typically have hypotonia and seizures when they are infants. Although development initially appears normal, marked developmental delays are noted within the patient's first year of life. Hair abnormalities are the most striking signs in this syndrome. Scalp hair become hypopigmented, sparse, short, and brittle.Skin may become hypopigmented, pale, mottled, and doughy. [13]. Examination under microscope reveals a variety of abnormalities, most of tenpilitorti (twistedhair),monilethrix (varying diameter of hair shafts),and trichorrhexisnodosa (fractures of the hair shaft at regular intervals). A6-month-old male infant born of no consanguineous marriage, admitted in the hospital with the complaint of recurrent respiratory difficulty. The mother informed that the child's social smile was absent and he was not able to recognize her. History of convulsions was not present. He was born at term with normal birth weight. The pregnancy was uneventful. He was the first child of the parents.The head circumference and

bodyweight were 40cm and 4.7 kg, respectively.[14].

Eye contact was absent; the child was not responding to any stimuli. There was no fixation. Ophthalmic examination findings were suggestive of cortical blindness. Fundus examination was within normal limits. He had poor head control and no roll over response, no social smile suggesting developmental delay. The child was referred to skin OPD for hair and cutaneous examination [15].

On clinical examination, the child was irritable with fair complexion, chubby cheeks and depressed nasal bridge. The most striking finding was the appearance of te scalp hair. Hair were hypo pigmented, short, sparse, thin, brittle and kinky. The scalp hair was fragile and fractured easily, resulting in apparent generalized alopecia.MRI of brain showed delayed myelination of white matter corresponding to myelination at birth. Demyelization involving optic radiation and occipital lobe was noted. Serum copper and ceruloplasmin levels were lower than normal values; with 54 µg/dl (ref.70-155) and 8.3 mg/dl (ref. 187-320 mg/l) respectively. Light microscopic examination of the scalp hair showed pili torti (twisted hair shafts) [16].

There were no metaphyseal changes of long bones on X-rays. Routine blood investigations and abdominal ultrasonography were with in normal limits. The child was treated symptomatically

For acute lower respiratory tract infection and was put on B-complex and mineral supplements. The child was advised to come for monthly follow-ups. Menke's disease almost exclusively affects males and females are the carrier. There is norace predilection. The disease becomes evident at the age of 2-3 months; patients die by the time they are 3-4years old usually because of pneumonia, although some patients with Menke's disease may die suddenly. The clinical spectrum of Menke's disease encompasses [17].

several distinct variants. Individuals with the mild variant are developmentally delayed with cerebellarataxia,dysarthria and pilitorti, and no seizures. The characteristic facial appearance with fair complexion, chubby cheeks, and depressed nasal bridge was similar to the reported

Low levels of serum copper and ceruloplasmin will usually confirm the diagnosis. The early neuroimaging record shows extensive lesions in white matter that seem secondary to a progressive brain destruction and collapse of the myelination process.

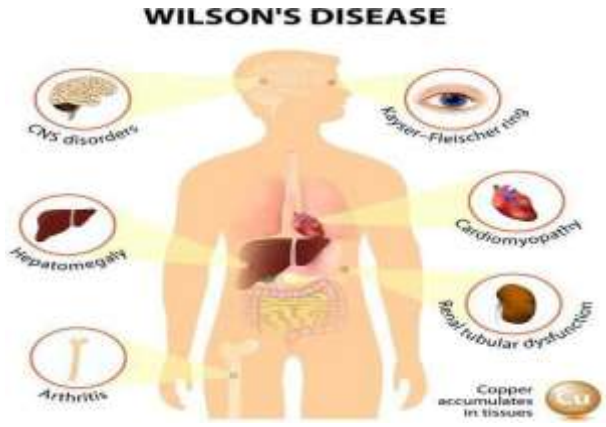
The diagnosis was confirmed by low serum copper and ceruloplasmin levels and neuroimaging finding of defective myelination of the brain whitematter. [18].

B. WILSON'SDISEASE:

Wilson's disease, also known as hepatolenticular degeneration and progressive lenticular degeneration, is a rare genetic disorder that causes copper poisoning in the body. It affects about1 in 30,000 people worldwide.

In a healthy body, the liver filters out excess copper and releases it through urine. With Wilson's disease, the liver cannot remove the extra copper properly. The extra copper then builds up in organs such as the brain, liver, and eyes.[19]

Early diagnosis is crucial for stopping the progression of Wilson's disease. Treatment may involve taking medication or getting a liver transplant.[20] Delaying or not receiving treatment can cause liver failure, brain damage, or other life-threatening conditions



Talk to your doctor if your family has a history of Wilson's disease. Many people with this condition live normal, healthy lives.

THE SIGNS AND SYMPTOMS OF WILSON'S DISEASE

Fig.no.5:Wilson's disease

EASE:

The signs and symptoms of Wilson's disease vary widely, depending on which organ is affected. They can be mistaken for other

diseases or conditions.[21] Wilson's disease can only be detected by a doctor and through diagnostic testing.

The signs and symptoms of Wilson's disease vary widely, depending on which organ is affected. They can be mistaken for other diseases or conditions. Wilson's disease can only be detected by a doctor and through diagnostic testing[.23]

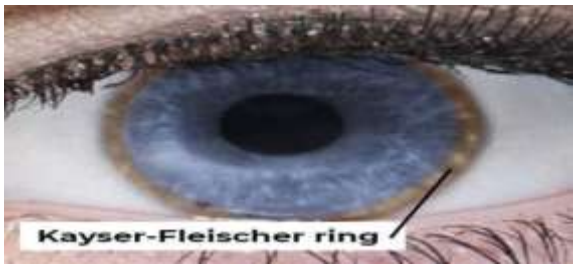
- Neurological:
- Copper accumulation in the brain can cause symptoms such as:
- Memory, speech,or vision impairment
- Abnormal walking
- Migraines
- Drooling
- Insomnia
- Clumsiness with hand
- Personality changes
- Changes in mood
- Depression
- Problems in school

In the advanced stages, these symptoms may include muscle spasms, seizures, and muscle pain during movement.[24]

KAYSER-FLEISCHERRINGS AND SUNFLOWER CATARACT:

Your doctor will also check for Kayser-Fleischer (K-F) rings and sunflower cataract in the eyes. K-F rings are abnormal golden-brown discolorations in the eyes that are caused by deposits of excess copper. K-F rings show up in about 97 percent of people with Wilson's disease. Sunflower cataracts show up in 1 out of 5 people with Wilson's disease. This is a distinctive multicolored center with spokes that radiate outward.[25]

Fig.no7:Kayser-Fleischerring.



OTHER SYMPTOMS

The buildup of copper in other organs can cause:

- Bluish discoloration in the nails
- Kidney stones
- Premature osteoporosis, or lack of bone density
- arthritis
- menstrual irregularities
- low blood pressure

WHAT'STHECAUSEAND who'satriskforwilson'sdisease

A mutation in the *ATP7B* gene, which codes for copper transportation, causes Wilson's disease. You must inherit the gene from both parents in order to have Wilson's disease. This can mean that one of your parents has the conditioner carries the gene.

The gene can skip a generation, so you may want to look further than your parents or take a genetic test.

HOW IS WILSON'S DISEASE DIAGNOSED

Wilson's disease may be difficult for doctors to initially diagnose. The symptoms are similar to other health issues like heavy metal poisoning, hepatitis C and cerebral spasy.

Sometimes your doctor will be able to rule out Wilson's disease once neurological symptoms occur and there's no K-F ring visible. But this isn't always the case for people with liver-specific symptoms or no other symptoms.[26]

A doctor will ask about your symptoms and ask for your family's medical history. They'll also use a variety of tests to look for damage caused by copper accumulations.

PHYSICAL EXAM

- During your physical, your doctor will:
- Examine your body
- Listen for sounds in the abdomen
- Check your eye sundera bright light for K-Frings or sunflower cataracts
- Tests your motor and memory skills

LAB TESTS

For blood tests, your doctor will draw samples and have them analyze data lab to check for:

- Abnormalities in your liver enzymes
- Copper levels in the blood
- Lower levels of ceruloplasmin, aprotein that carries copper through the blood
- A mutated gene, also called genetic testing

- Low blood sugar
- Your doctor may also ask you to collect your urine for 24 hours to look for copper accumulation.

IMAGING TESTS

Magnetic resonance imaging (MRI) and computerized tomography (CT)scans may help show any brain abnormalities, especially if you have neurological symptoms. These findings can't diagnose the condition, but they can help determine a diagnosis or how advanced the condition is. Your doctor will look for weak brain stem signals and damage to the brain and liver.

LIVER BIOPSY

Your doctor may suggest a liver biopsy to look for signs of damage and high levels of copper .If you agree to this procedure, you may need to stop taking certain medications and fast for eight hours beforehand. Your doctor will apply a local anesthetic before inserting a needle to take a tissue sample. You may ask for sedatives and pain medication, if needed. Before going home, you'll need to lie on your side for two hours and wait an additional two to four hours. If your doctor finds the presence of Wilson's disease, they may recommend your siblings take a genetic test too. It can help identify whether you or your other family members are at risk for passing on Wilson's disease. You may also want to consider future screening for your newborn if you're pregnant and have Wilson's disease.

DISEASETREATED HOWISWILSON'S

Successful treatment of Wilson's disease depends upon timing more than medication. Treatment often happens in three stages and should last a lifetime. If a person stops taking the medications, copper can build back up again.[27].

Pathophysiology

FIRSTSTAGE

The first treatment is to remove excess copper from your body through chelating therapy. Chelating agents include drugs like d-penicillamine and trientine, or Syprine. These drugs will remove the extra copper from your organs and release it into the bloodstream. Your kidneys will then filter the copper into the urine. Trientine has fewer reported side effects thand-penicillamine. Potential side effects d-penicillamine include

- fever
- rash
- kidney issues
- bone marrow issues

Your doctor will provide lower dosages of chelating drugs if you're pregnant, as they can cause birth defects.

SECOND STAGE

The goal of second stage is to maintain normal levels of copper after removal. Your doctor will prescribe zinc or tetrathiomolybdate if you've finished the first treatment or show no symptoms but have Wilson's disease. Zinc taken orally as salts or acetate (Galzin) keeps the body from absorbing copper from foods. You may have slight stomach upset from taking zinc. Children with Wilson's disease but no symptoms may want to take zinc to prevent the condition from worsening or slow its progress.

THIRD STAGE

After the symptoms improve and your copper levels are normal, you'll want to focus on long-term maintenance therapy. This includes continuing zinc or chelating therapy and regularly monitoring your copper levels.

You can also manage your copper levels by avoiding foods with highlevels, such as: Liver, Dried fruit, Mushrooms, Nuts, Shellfish, Chocolate, Multivitamins

You might want to check your water levels at home, too. There may be extra copper in your water if your home has copper pipes. Medications can take any where from four to six months to work in a person who is experiencing symptoms. If a person doesn't respond to these treatments, they may require a liver transplant. A successful liver transplant can cure Wilson's disease. The success rate for liver transplants is 85 percent after one year.

How to prepare liver biopsy: A few medical centers have clinical trials for a new drug calledWTX101.Wilson Therapeutics developed this drug for the treatment of Wilson's disease. It carries a chemical named tetrathiomolybdate, which keeps the body from absorbing copper. It has shown trusted source to be effective for people in the early

stages of Wilson's disease, especially in people with neurological symptoms.[28]

WHAT'S THE OUTLOOK FOR WILSON'S DISEASE

The earlier you find out if you have the gene for Wilson's disease, the better your prognosis is. Wilson's disease can develop into liver failure and brain damage if left untreated. Early treatment can help reverse neurological issues and liver damage. Treatment in a later stage may prevent further progress of the disease, but it won't always rest ore the damage. People in the advanced stages may have to learn how to manage their symptoms over the course of their life.

CAN YOU PREVENT WILSON'S DISEASE

Wilson's disease is an inherited gene that's passed down from parents to their children. If parents have a child with Wilson's disease, they could potentially have other children with the condition as well.

Although you can't prevent Wilson's disease, you can delay or slow the onset of the condition. If you find out you have Wilson's disease early on, you may be able to prevent the symptoms from showing by taking medications like zinc. A genetic specialist can help parents determine their potential risk for passing Wilson's disease to their children.[29].

NEXT STEPS

Make an appointment with your doctor if you or someone you know may have Wilson'sdisease or are showing symptoms of liver failure. The biggest indicator for this condition isfamily history, but the mutated gene can skip a generation. You may want to ask for a genetic test alongside the other tests your doctor will schedule.

You'll want to start your treatment immediately if you get a diagnosis for Wilson's disease. Early treatment can help prevent or delay the condition, especially if you aren't showing symptoms yet. Medication includes chelating agents and zinc and may take up to six months to work. Even after your copper levels return to normal,you should continue taking medication, as Wilson's disease is a life[30]

Table no 1: Difference between Menke's and Wilson disease

	Menke's disease	**Wilson disease**
Inheritance	X-linked recessive	Autosomal recessive
Prevalence	1/140,000malebirth	1/35,000
Genelocation	Xq13.3	13q 14.3
Geneproduct	Cu-bindingP-typeATPase(ATP7A)	Cu-binding P-type ATPase (ATP7B;60%IdentifywithMD)
Expression in normal human	All tissues except liver	Liver, kidney and placenta
Mutations	No common mutation	R778Lis a common mutation
Pathogenesis	Defect of intestinal Cu absorption, reduced activities of Cu-dependent enzymes	Defect of biliary Cu excretion and Cu incorporation into ceruloplasmin in the liver
Clinical findings	Onset is soon after birth. Severe neurological degeneration, abnormal hairs,hypothermia,bonechanges,cutislaxa,arterialrupture/thrombosis	Onset is during childhood. Liver disease, loss of coordination,involuntary/movements, dysarthria,Kayser-Fleischerrings

Acknowledgments: Authors are thankful to Shri Dr P. Kanaka Raju Chairman, Adarsa group of institutions for providing the necessary facilities for carrying out this research work.

BIBLIOGRAPHY:

1. Shoaid M.Wazir and Ibrahim ghobrial. Copper deficiency,a new traidanemia andleucopeniaandmyeloneuropathy. Journal of community hospital internal medicine perspective ,2017,vol.7,pg no .265-268.
2. DM Williams, Semi Hematol-Copper deficiency in humans.NLM.,1983April.pg no.118-128.
3. Zin W Myint et al. Ann Hematol,TheinHOo, Kyaw Z Thein, Aung M Tun, HayderSaeed-Copper deficiencyanemia, Annals of hematology-2018 September,97(9) :pg no 1527-1534.
4. ByLarry E Johnson M.D –Copper deficiency,MSD, December 12,2021.
5. Marco Altarelli et al .Nutrclinpract-Copper deficiency causes, manifestation andtreatment, NLH, 2019 August,34(4):pg no 504-513.
6. CeliaHChang-Menke'sdisease-updated2020December18.
7. Antony Donsante A, Yi L, Zerfas PM, Brinster LR, Sullivan P,Goldstein D S, ProhaskaJ,Centeno JA, Rushing E,Kaler SG. ATP7A gene addiction to the choroid plexus results in longer –term rescue of the lethal copper transport defect in a Menkes disease mouse model. The American society of gene and cell therapy . 2011 Dec ;19[12]pg no 2114-23.
8. TumerZ,Moller LB. disease .Eur J Hum Genet .menkes disease European journal of human genetics 2010 May;18[5];5pg no 511-518
9. Kaler SG, FeereriraqCR,Yam LS. Estimated birth prevalence of Menkes disease and ATP7A-realted disorders based on the Genome Aggregation Database [gnomAD].Molecular Genetic Metabolism Reports .2020sep;24;100602.
10. VulpeC, Levison B, Whitney S, PackmanS, GitschierJ.Isolation of a candidate gene for Menkes disease ad evidences that it encodes a copper transporting ATPase. Nat Genet. 1993 Jan ;3[1]:pg no7-13
11. Choudhary SV,GadegoneRW,KoleyS.Menkes kinky hair disease . Indian J Dermatol .2012 sep;57[5];pg no407-409.
12. Rahul ojna and asuriN.prasadMenkes JH . Kinky hair disease ; What a multidisciplinary approach open acess to scientific and medical research . 2016 Aug 17;9:371- 85.
13. Danks DM, cartWright E, Stevens BJ, Townley RR. Menkes'kinky hair disease: future definition of the defect in copper transport . Science. 1973 Mar 16;179 (4078):pg no1140-2.
14. Ramani PK, Parayil Sankaran –Menke'skinkyhairdiseaseBookselfID–NBK430685, last update2021July30.
15. Sajeev V Chowdhary, Rutuja W Gadegone, SankhaKoley –Menke's kinky hairdisease-Article 684309,volume2012 September.
16. SuguruImaeda-DermatelogicmanifestationsofMenke' skinkyhairdisease.2020 Dec 18
17. Rozil Gandhi, RituKakkar ,SajeevRajan, RashmiBhangale, Srinivas Desai-Menke'skinkyhair syndrome-Ararareneurodegenerativedisease.2012 march 17 pages 4
18. Stephen G Kaler, M.D M.PH Courtney,S Holmes, MT David, Goldstein, JingrongTang-Neuonateldiagnosisandtreatmentof Menke'sdisease-2008Febuary7.
19. Kryssialsabel Rodriguez –Castro, Francisco, JarierHeria-Urrutia and Giacomo CarloSturniolo-Wilsonsdiseaseworld Journal of hepatology 7(29) pg no 2859-28702015 december 18

20. KatieMena,MD,Lydia Krause-Wilsondisease-2018September29.
21. RichardKGilroy-Wilisondisease-2019Febuary14.
22. ScheinbergIH ,Sternlieb I Wilsons disease in :smith JL ,editor.1984
23. SHAH ab chernov I zhangHT ,Ross BM Das k,Lutsenkos,ParanoE,pavoneL,EvgrafovO,Ivanova-Smolenskaya,IA,et al. Identification and analysis of mutation in the willasondiseae gene [ATP7B]S 1997 Aug 61(2) pg no 317-328
24. Scott J,GollanJL,SamourianS,Sherlock S. wilsons disease ,presenting as chronic active hepatitis .gastroenterology.1978;74pg no :645-651.
25. SaiyoT.presenting symptoms and natural history of Wilson disease .EUR pediatr 1987;146pg no:261-265.
26. .Del Rosario MA ,davisMM,chong WK wobbly handwriting .lancet.1998;351:336.
27. Walshe JM.wilson disease ;new oral therapy .lancet.1956;270:pg no 25-26.
28. Hoogenrad TU van den hamer CJ koevet R, korverEG .oral zinc in oral Wilsons disease .lancet 1978 ;2:1262-1268
29. SmolarekC,Stremmel W,[Therapy of Wilson diease]Z gastroenterol. 1999;37(4);pg no 293-300
30. Walshe JM,YeallandM.Chelation treatment of neurological Wilson‘s disease .Q Journal Medical . 1993;86(3)pg no;197-204.