Wilson's Disease; Clinical Presentations among Patients Attending Gastroenterology Clinic/ Baghdad Teaching Hospital

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Abstract

Background: Wilson's disease (WD) is an inherited disorder of copper metabolism that is characterized by tremendous variation in the clinical presentation.

Objective: To assess demographic distribution, clinical presentations, diagnostic evaluation, and any association between clinical presentations and other studied variables of a sample of Iraqi patients with WD.

Methods: A descriptive cross sectional study with analytic elements was conducted during 2011, from the 1st of February till the 10th of June. The sampling method was a convenient non-random one, carried out through consecutive pooling of registered WD patients. A questionnaire-form paper had been developed for the process of data collection.

Results: The study had enrolled 29 patients, with a male to female ratio of (1.07:1), their mean age was 27.12±12.18 years. 82.8% of them lived in urban area. 48.3% were singles. Only 20.7% of patients had a positive family history of WD. 69% of patients had consanguineous parents. The main initial clinical presentations were; hepato-neurologic (31%), pure hepatic (27.6%), neuro-psychiatric (13.8%) and other presentations (27.6%). Hepatic manifestations were seen in (82.8%) of patients; jaundice was the most frequent (89.7%). Ophthalmologic manifestations in (55.1%) of patients including; Kayser-Fleischer rings (51.7%), diplopia (6.9%) and cataracts (3.4%). Neurologic manifestations existed in 44.8% of patients; tremors were the most frequent (41.4%). Psychiatric manifestations existed in 31% of patients; depression was the commonest (27.6%). Joints manifestations existed in 20.7% of patients. The diagnosis delay was 11.26±8.2 months.

Conclusion: The higher percentage of patients were of hepato-neurologic and pure hepatic presentations. Patients with hepato-neurologic type are diagnosed in older age, while those with neuro-psychiatric type are diagnosed in younger age and with longer diagnosis delay.

Keywords;wilson, copper, kayser, Presentation, Iraq.

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Introduction

Wilson's disease (WD) is a rare autosomal-recessive disorder of copper metabolism. It is a hepatolenticular degeneration that characterized by the accumulation of copper in various body organs. It is fatal unless treated, is a potentially treatable condition with the availability of effective pharmacologic therapy, while if not treated; it can cause severe brain damage, liver failure and death[1,2,3,4].

The prevalence of WD is about 1:30,000 and a frequency of heterozygotic carriers is about 1:90. WD resembles 6.9% of chronic liver diseases in Iraq[1,2,3,5,6,7,8].

The gene for WD is located on chromosome 13[6,9].Although this biochemical defect is already present at birth, but symptoms are rarely observed before the age of 5 years, the age at onset of symptoms is usually from 6 to 40 years; mainly between 10 and 24 years, at that time WD is predominantly hepatic, while neurologic symptoms typically appear later in life, and liver failure is four times more common in females than males[1,7,10,11] .

The variation in the clinical presentation is tremendous, ranging from asymptomatic to those with crippling neurologic symptoms. The five main categories of clinical presentation include hepatic, neurologic, psychiatric, hematologic, and ophthalmologic[10].

Symptoms may be vague and nonspecific, occasionally as a self-limited illness resembling acute hepatitis or resembling chronic liver disease[3,7].

Neurologic Presentation often resembles that of Parkinson's disease, seizures and pseudobulbar palsy. It tends to occur in the second and third decades or later[1,2,4,7].

In hematologic presentation; patients present with hemolysis; so the constellation of young age, liver dysfunction and hemolysis should be assumed as WD until proved otherwise[10].

Pure psychiatric presentation;wasseen in as many as 20% of patients with WD. Symptoms are highly variable; depression, phobias or compulsive (aggressive or antisocial) behaviors may occur[7].

Kayser-Fleischer ring (K-F ring) is seen in 40% of pre-symptomatic cases, 65-70% of cases with only hepatic manifestations and in almost every patient with neurological manifestations[12,13].

In Iraq WD resembles 6.9% of chronic liver diseases[8], but; with no available descriptive study to assess WD's clinical presentations; thus the objective of this study is to assess demographic distribution, clinical presentations, diagnostic evaluation, and any association between clinical presentations and other studied variables of a sample of Iraqi patients with WD.

Methods

This is a descriptive cross sectional study with some analytic elements. The data was collected at the Department of Gastroenterology, Baghdad Teaching Hospital of Medical City, Baghdad, Iraq. Data collection was extended from the 1st of February to the 10th of June 2011.The target population wasall registered and newly diagnosed WD patients[14]. The sampling method was a convenient non-random one, carried out through consecutive pooling of all WD patients. A data of 29 patients was collected by direct interviews, full clinical assessment and medical records analysis. Patients who accepted to participate in study, completed the required parameters and fit the inclusion criteria during the study period were included in study.The inclusion criteria were; history and clinical examination findings suggestive of WD as: hepatic manifestations, neuropsychiatric manifestations, family history of WD, serum ceruloplasmin level below 200 mg/L[1,2], presence of K-F ring, liver biopsy: if the liver copper concentration more than 250µg/g dry weight[1,2], serum copper level below 70 µg/dl "below 11µmol/L"[1,2], 24-hr. urinary copper excretion more than 100µg/24-hr.[1,2], and/or positive Penicillamine challenge test (if 24-hr. urinary Copper more than1600µg/24-hr., more than 25mmol/ L)[1,2]. The patient age should be fulfilling at least three of the above criteria andthe last criterion is a definite diagnosis. These diagnostic standards had been proposed basing on***Sternlieb's criteria*** [10,14].

The exclusion criteria were; pregnant, age above 60 years, evidence of coexisting liver diseases including; viral hepatitis A, B C or E, chronic liver disease with cholestatic component, Alpha one antitrypsin deficiency, Coomb's positive hemolysis, history of Alcohol intake, history of use of copper containing intrauterine devices (IUCD) or oral contraceptive[5], history of intake of medications that may cause extrapyramidal side effect such as antipsychotic drugs and Metoclopramide and/or history of chorea.

The Statistical Package for the Social Science (**SPSS**) version **17.0** software had been used for all computerized statistical analysis. Numerical; normally distributed variables was expressed as mean ± standard deviation; while categorical variables were expressed as frequency, range and percentage. Continuous variables were compared by ANOVA test for the variance analysis and categorical variables were compared by using Chi-square tests. P-value equal or less than 0.05 was considered as a statistically significant.

Results

The patients' total number was 29, males were 15 (51.7%) and females were 14 (48.3%), giving a male to female ratio of (1.07: 1). Their mean age at interview was 27.12±12.18 years (yr.) (14-56 yr.), at diagnosis was 24.88±12.21 yr. (12.67-56 yr.), and at onset of symptoms 23.72±12.50 yr. (10-56 yr.). The majority of patients 24 (82.8%) lived in an urban area.14 (48.3%) were singles, 12 (41.4%) were married and having siblings, 3 (10.3%) were married but had no siblings and no one was divorced or widowed. Most of patients 20 (69%) had consanguineous

parents, 23 (79.3%) had no family history of WD.(Table 1).

The four main initial clinical presentations were; mixed hepato-neurologic presentation in 9 (31%) of patients, only hepatic in 8 (27.6%), neuro-psychiatric (pure or mixed neurologic) in 4 (13.8%), and other presentations in 8 (27.6%).

The major proportion 24 (82.8%) of patients were presented with hepatic manifestations, 16 (55.1%) had ophthalmologic manifestations, neurologic manifestations in 13 (44.8%), psychiatric manifestations in 9 (31%), hematologic manifestations in 8 (27.6%), and only two patients (6.9%) showed articular manifestations [Figure (1)].

K-F rings were positive bilaterally at time of diagnosis in 15 (51.7%) of patients; (8 females and 7 males), but with no significant association between gender and frequency of K-F rings (P=0.746). Diplopia were seen in 2 (6.9%) of patients, both were females, cataracts in one (3.4%) male patient. Statistically; no significant association between gender and diplopia (P=0.573) and cataracts (P=0.327). Joints manifestations were seen in 6 (20.7%) of patients; all had joints pain, 2 (6.9%) of them had joint swelling, tenderness and crepitus.Jaundice was seen in 26 (89.7%) of patients. Abdominal distention, hepatomegaly and hepato-splenomegaly in 9 (31%) of patients, for each, spleenomegaly in 4 (13.8%) of patients, hematoemesis or melena in 4(13.8%), ascites in 10 (34.5%), and evidence of cholecystitis, gall stone or cirrhosis on abdominal ultrasound in 3 (10.3%) of patients.On OGD; which was done to 24 patients, esophageal varieces were seen in 5 (20.83%) of them.Neurologic manifestations were seen in 13 (44.8%) of patients and psychiatric manifestations in 9 (31%) of patients; tremors were the most frequent symptom, 12 (41.4%), while 10 (34.5%) of patients had at least a mental function abnormality; [depression in 8 (27.6%), change in intellectual performance in 6 (20.7%), emotional liability and memory problems in 5 (17.2%) patients, for each, confusion or delirium and phobiain 4 (13.8%) patients, for each, and behavioral changes in 3 (10.3%) of patients]. A 6 (20.7%) had developed at least a dystonic feature[stiffness in 6 (20.7%), ataxiaandslowness of movements in 5 (17.2%) of patients, for each, abnormal posture in 4 (13.8%), decreased face expressions in 3 (10.3%) and cervical dystonia in one (3.4%) of patients].Choreoathetosisin 8 (27.6%), speech difficulties in 5 (17.2%), abnormal movements' coordination in 4 (13.8%), weakness in 3 (10.3%) and seizures in 2 (6.9%) of patients. The diagnosis delay was 11.26±8.2 (ranging between 0.5 and 30) months.

Regarding gender distribution among patients with different clinical presentations; the largest proportion of males compared to females [7/8 (87.5%)] were seen in other types, while neuro-psychiatric presentation included no males, pure hepatic presentation was equally subdivided into males and females, in hepato-neurologic type 5 (55.6%) of patients were females, and this was significantly different (P=0.035) [Figure (2)].

The mean age of patients at time of diagnosis was the highest (34.11±15.90yr.) among those with hepato-neurologic presentation and the lowest (13.75±3.86) in those with neuro-psychiatric presentation, and this was significant P= 0.011(<0.05)]. The age at onset of symptoms was the highest (34.82±15.53 yr.) among those with hepato-neurologic presentation, and the lowest (15.11±4.21) among those with neuro-psychiatric presentation, and this was significant [P=0.011(<0.05)] [Table (2)].

The majority of participants from all presentations were from an urban area, which included; all those with pure hepatic, 7 (78%) of those with hepato-neurologic, 3 (75%) of those with neuro-psychiatric and 6 (75%) of those with other presentations. Concerning consanguinity of patient's parents, it was positive in all (4 (100%)) patients with neuro-psychiatric presentation, 6 (75%) of those with other presentation, 6 (66.7%) of those with hepato-neurologic presentation and 4 (50%) of those with pure hepatic presentation. Positive family history of WD was the highest

(4/9 (44.4%) patients) in patients with hepato-neurologic presentation and negative in all those with other presentations, it was also positive in one (25%) of those with neuro-psychiatric presentation, and only one (12.5%) of patients with pure hepatic presentation [Table (3)].

Evidence K-F rings at initial presentation was the highest 3/4 (75%) among patients with neuro-psychiatric presentation, 6/9 (66.7%) of patients with hepato-neurologic presentation, 5/8 (37.5%) of those with pure hepatic presentation and 5/8 (37.5%) of those with other presentation. The longest diagnosis delay (18.5± 9.4 months) was in those with neuro-psychiatric presentation, while shortest delay (8.59±8.14 months) was in pure hepatic presentation, the delay was (9.78±7.01 months) in hepato-neurologic presentation, and it was (12.09±8.13 months) in other presentation [Table (4)].

Discussion:

In this study sample; males were slightly outnumber female patients, giving a male:female (m:f)ratio 1.07:1. Similar findings were obtained by*(Soni et al,2009)*; males were 56.7%[16]; by *(Sinha, et al,2006)*; the, m:f was (1.32:1)[17]; by *(Samiullah et al, 2008*); male preponderance was 62.5%; m:f was 1.17:1[18], and by *(Medici et al,2006)*; males were 68.6%[19].

In the current study the mean age which was assessed at interview, diagnosis and onset of symptoms. Similar results were reported by;*Lowette et al,* study (Belgium 2009); the age at onset was (8 to 40 yr.) with a mean age (20.79 (±7.91) yr.)[20], *Soni et al*, study (India, 2009); was 19±7.2 (11–47) yr.[16],*Huoet al*, study (China 2008); was 20±1 (4-53) yr.[21].In many of these studies, the cause of this difference remains largely unexplained; may be due to unrecognized environmental factors (soil, water, food or others), habit of cooking in copper utensils (in 40% of cases of these Indian and Pakistan studies) or due to misdiagnosis of psychiatric WD as a teenage changes[22,23].

Concerning residence; patients were mainly from urban areas, thiscan be attributed to; the location of the study and geographic accessibilityand alsoto;urbanization (industrialization) which leads to environmental hazards, in air, water and food chainand increasing exposure to toxic substances[24].

The highest percentage of current study's patients were singles, and this may be attributed to the effect of WD on pattern of patient's life, and because of the fact that the main age of presentation of WD is between 10 and 24 yr.[1,7,24].

Sixty nine percent of the patients had consanguineous parents. Comparing this result with other studyby (*Talyet al,*); consanguinity was 54%[25]. This is expected because WD is an inherited autosomal recessive disease, and it is agreed that; the incidence of congenital malformation controlled by recessive genes are higher among offspring of consanguineous marriages[1,2,6]. Only 20.7% of patients had a positive family history, this is in agreement with (*Huoet al*, study,2008)[21], and with(*Panagariya et al*, study,2006)[23].

Regarding clinical presentations of patients in current study; similar results were found by (*Samiullah, et al,2005–2008)*; thehepato-neurologic presentation was in 33.3%, pure hepatic involvement: 25%, neurologic presentation: 16.7% and 25% of patients were presymptomatics[18]; by (*Lowette et al,1969-2009)*; 50% of patients were with mixed hepatic-neurologic presentation, 33.3% with hepatic presentation, 4.16% with neurologic presentation, and 12.5% were presymptomatic[20], and by*(Medici et al,2006)*; 34.3% of patients had both neurologic and hepatic involvement[19].

Regarding clinical manifestations;majority of current study's patients were presented with hepatic manifestations, compared with other previouscase series study by (*Walshe et al,2010)*; hepatic manifestations in 52% of patients, neurological symptoms in 44%[26]. This can be explained by the fact that, patients included in this study were enrolled form the Department of Gastroenterology, in addition

to that, WD has a tremendous variation in its clinical presentation[1,10,27].K-F rings were positive bilaterally at time of diagnosis in 51.7% of patients (57.1% were females). This is in agreement with (*Rodrigo Agudoet al,Spain, 2008)*[28], (*Merle et al, 2000-2005)*[29], *(Karim et al, 2007)*[30], and*(Samiullah et al, 2005–2008)*[19]. This result can occur, because; the percentage of K-F rings is variable in different clinical presentations; they are seen in 65-70% of cases with only hepatic manifestations and almost every patient with neurological manifestations[3,12].

Hepatic manifestations were relatively highin current study compared with other studies and jaundice was the most frequent (89.7%) symptom. Comparing these results with former studies showed variable results according to the ages of patients and place of data collection; in the University of Cambridge/Great Britain (2010) (*Walshe et al,*); hepaticmanifestations were seen in 52% of cases and the commonest symptom was jaundice or hepatosplenomegaly[26], while Leuven/Belgium (1969-2009) (*Lowette et al,*)which conducted on 24 patients; hepatic manifestations were seen in 67% of patients[20].

Neurologic and psychiatric manifestations were seen in 44.8% and 31% of patients, respectively. Tremor was the most frequent symptom (41.4%). Similar findings were observed in a *(Samiullah et al, 2005–2008)*[23]. These results are expected as; in WD; movement disorder as tremors tend to occur earlier and spastic dystonia generally develop later and reflect a lenticular degeneration[4], while psychiatric symptoms are highly variable and depression is common [7,31].

The mean diagnosis delay was 11.26±8.2 months and the longest delay was in patients with neuro-psychiatric presentation.Comparing this with other previous studies; *(Merle et al, 2000-2005, Heidelberg, Germany)*; it showed that the neurological symptoms were associated with a significantly longer time from onset to diagnosis than hepatic symptoms (44.4 v 14.4 months, p=0.05)[29].This delay can be attributed to the absence of jaundice and past family history. In addition, rare diseases like WD, itremain commonly misdiagnosed especially in absence of effective screening programs or diagnostic tests. In addition to that, in WD; diagnosis delay depends on type of clinical presentation, so it is shorter in hepatic presentation than in neurologic presentation[1,2,6,7,22,24].

Regarding the presence of K–F rings in patients with different presentations, it was the highest among those withneuro-psychiatric presentation. This wasn't significant in this study, but it was significant in other studies which reported similar results as; *Merle et al* study, Germany (2000-2005);(p= 0.001)[29], by *Medici et al*, Italy (1980-2006)[19] and by *Lowette et al,*Belgium (2009); K-F rings were detectable in all patients with neurologic symptoms, but in 68.75% of those with liver disease[20].This is supported by the fact that the presence of K-F rings is variable according to the initial clinical presentation; so they are seen in 65-70% of cases with only hepatic presentation and almost every patient with neurological presentation[3,12].

Conclusions:

Most of WD patients in current study are males, singles from urban area, having consanguineous parents and with a negative family history of WD.The highest percentage of the WD patients are presenting with hepato-neurologic and pure hepatic presentations, some with neuro-psychiatric presentation and only few with hematologic, articular, or a mixed form of the mentioned presentations.Jaundice was the most frequent manifestation, ophthalmologic manifestations (mainly K-F rings) are seen in more than a half of WD patients, while tremors are the most frequent neurologic symptom and depression is the most frequent psychiatric manifestation

Tables and Figures

Table (1): Socio-demographic characteristics and family history of Wilson's disease for the study group (n=29).

The character		No=29	%
Gender	Male	15	51.7
	Female	14	48.3
Residence	Urban	24	82.8
	Rural	5	17.2
Marital status	Single	14	48.3
	Married & having siblings	12	41.4
	Married not having siblings	3	10.3
Consanguinity of patient's parents	Positive	20	69.0
	Negative	9	31.0
Family history of Wilson disease	Positive	6	20.7
	Negative	23	79.3
The character		**Mean±SD**	**Range**
Age of patient at onset of symptoms (years)		23.72±12.5	10-56
Age of patient at diagnosis (years)		24.88±12.21	10-56
Age of patient at interview (years)		27.12±12.18	14-56
No; number, %; percent, SD; standard deviation.			

Table (2): Distribution of the study group by the clinical presentation and the age variables(n=29).

The age (in years) at	The main initial presentation				*P value*
	Hepatic	Hepato-neurologic	Neuro-psychiatric	Other	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Onset of symptoms	20.50±7.69	34.11±15.90	13.75±3.86	20.25±7.03	0.011
At diagnosis	21.17±7.16	35.05±15.72	16.72±5.88	21.26±6.80	0.015
SD; standard deviation.					

Table (3): Socio-demographic characteristics of the study group (n=29).

The character		*The main initial presentation*								*Total*		*P value*
		Hepatic		*Hepato-neurologic*		*Neuro-psychiatric*		*Other*				
		No	%	No	%	No	%	No	%	No	%	
Residence	Urban	8	100	7	78	3	75	6	75	24	82.75	0.507
	Rural	0	0	2	22	1	25	2	25	5	17.25	
Parents' consanguinity	Positive	4	50	6	66.7	4	100	6	75	20	68.96	0.347
	Negative	4	50	3	33.3	0	0	2	25	9	31.04	
Family history of WD	Positive	1	12.5	4	44.4	1	25	0	0	6	20.68	0.135
	Negative	7	87.5	5	55.6	3	75.0	8	100	23	79.32	
Total		8	100	9	100	4	100	8	100	29	100	

No; number, %; percent, DF; degree of freedom, P; P value, Wilson disease; WD.

Table (4): Distribution of the study group by the clinical presentation and the evidence of K-F rings variables and diagnosis delay(n=29).

Evidence of Kayser Fleischer rings	*The main initial presentation*								*Total*		*Comparison of Significance*
	Hepatic		Hepato-neurologic		Neuro-psychiatric		Other				
	No	%	No	%	No	%	No	%	No	%	*P value*
Positive	3	37.5	6	66.7	3	75.0	3	37.5	15	51.73	0.396
Negative	5	62.5	3	33.3	1	25.0	5	62.5	14	48.27	
Total	8	100	9	100	4	100	8	100	29	100	
Diagnosis delay (month)	Mean±SD (month)		Mean±SD (month)		Mean±SD(month)		Mean±SD (month)		Mean±SD (month)		*P value*
	8.59±8.14		9.78±7.01		18.5±9.4		12.09±8.13		0.233		8.59±8.14

No; number, %; percent, DF; degree of freedom, P; P value, SD; Standard Deviation.

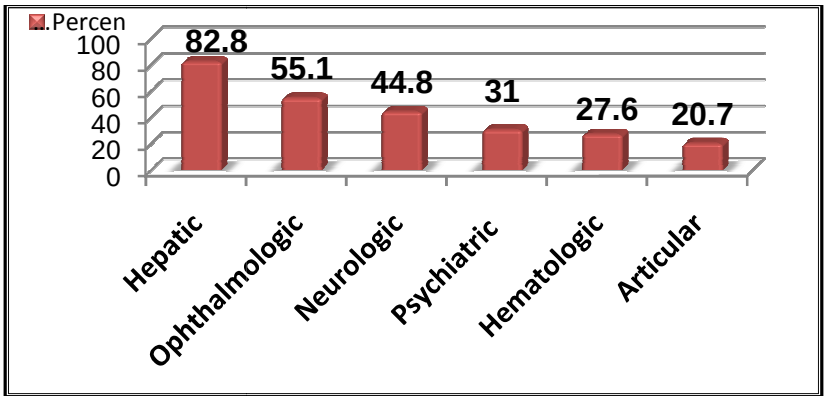

Figure (1): Clinical manifestations of the study group (n=29).

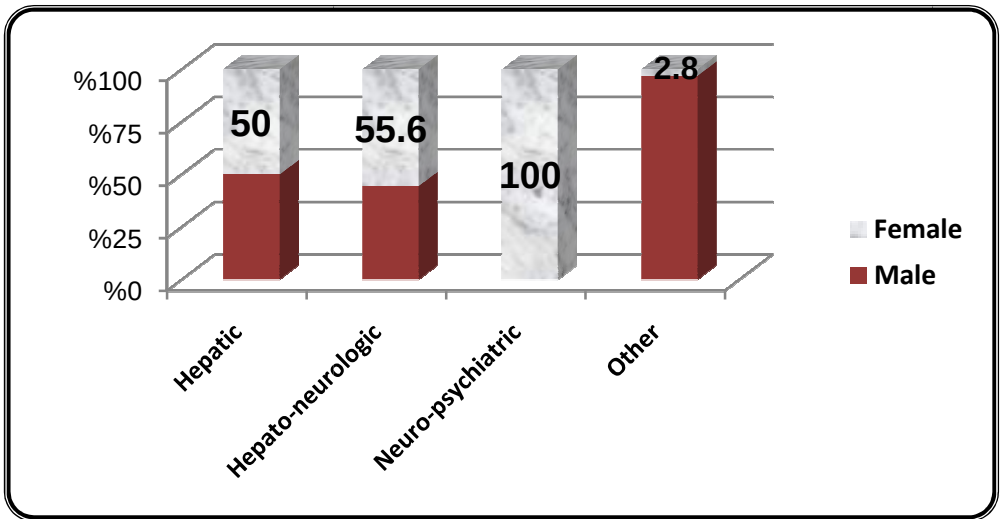

Figure (2): Distribution of the study group by the clinical presentation a nd the gender variables(n=29).

References:

1.Merle U, Stremmel W: Wilson's Disease. In: Friedman SL, eds. HenrykDancygier Clinical Hepatology Textbook Vol (2). 1st ed. New York: Springer, 2010;1035-1043.

2.Niederau C: Wilson's Disease. In: Mauss S, Berg T, Rockstroh J, eds. Hepatology-A Clinical Textbook 2nd ed. Germany: FlyingPublisher, 2010;405-415.

3.Olivarez M, Caggana M, Pass KA, Ferguson P. Estimate of the frequency of Wilson's disease in the US Caucasian population: a mutation analysis approach. Annals of Human Genetics. 2001;65:459–463.

4.Hoffmann GF, Engelmann G: Liver Disease. In: Hoffmann G, Zschocke J,Nyhan W, eds. Inherited metabolic diseases-Clinical Approach. 1st ed. New York: Springer, 2010;100-101.

5. Nakayama K, Kubota M, Katoh A. [2008] Early and presymptomatic detection of Wilson's disease at the mandatory 3-year-old medical health care examination in Hokkaido Prefecture with the use of a novel automated urinary ceruloplasmin assay.J Molecular Genetics and Metabolism94; 363–367.

6.Moseley RH: Approach to the patient with abnormal liver chemistries. In: Yamada T, Alpers D, Kalloo A, eds. Principles of clinical gastroenterology. 1st ed. Oxford: Blackwell Publishing, 2008;409.

7. Diane W, Roberts C: Wilson Disease. In Feldman M, Friedman L,Bradnt L, eds.Sleienger&Fordtran`s gastrointestinal and liver disease. 8th ed. California: Elsevier, 2006;1601-1610.

8.Al-Rawi F, Kassir Z. [1996] Chronic liver disease in Iraq, evaluation of clinical and diagnostic parameters. Phd Thesis. Iraqi Comission For Medical Specialization, Internal Medicine Department;16.

9. Ferenci P. Wilson's disease.J Clinical Gastroenterology Hepatology 2005 Aug;3(8): 726-33.

10. Poterucha J: Metabolic Liver Disease. In: Hauser C, Pardi D, Poterucha, eds. Mayo clinic gastroenterology and hepatology board review 3rd ed. 2010; 369-374.

11. Ferenci P, Czlonkowska A, Merle U. Late onset Wilson's disease: A cohort study, Austria:JGastroenterology 2007;132:1294–8.

12.Suvarna J.Kayser-Fleischer ring. J Postgrad Med 2008;54:238-40.

13.Rodman R, Burnstine M, Esmaeli B, et al. Wilson's disease. Pre-symptomatic patients and Kayser Fleischer rings: a retrospective analytic study done in Dep. of Ophthalmology, University of Michigan Medical School, USA: J Ophthalmic Genet. 1998 Dec;19(4):215-8.

14. Roberts EA, Schilsky ML. American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease; an update.J Hepatology 2008 Jun;47(6):2089-111.

15.Soloman B: Medical problems during pregnancy. In: Paulman P, Paulman A, Harrison J, eds. Taylor's Manual OfFamily Medicinee3rd ed. Lippincott Williams and Wilkins, 2008; (14.6): 525-531.

16. **So**ni D, Shukla G, Singh S, et al. Cardiovascular and sudomotor autonomic dysfunction in Wilson's disease—Limited correlation with clinical severity.J Autonomic Neuroscience: Basic and Clinical 151,2009;154–158.

17. Sinha S, Taly A, Ravishankar S. Wilson's disease: Cranial MRI observations and clinical correlation: An Indian series study: J Neuroradiology 2006;48:613–621.

18.Samiullah S, Salma S, Faheemullah S. Wilsons' Disease: Various shapes of one disease: A descriptive case series study. Pak J Med Sci2010 ; January - March 2010 Vol. 26 No. 1;158-162.

19. Medici V, Trevisan C, D'Inca` R. Diagnosis and Management of Wilson's Disease: Results of a Single Center Experience: A cohort study, Italy. J ClinGastroenterol _ Volume 40, Number 10, November/December 2006;40:936-941.

20.Lowette K, Desmet K, Witters P. Wilson's disease: Long-term follow-up of a cohort of 24 patients treated with D-penicillamine, Leuven, Belgium. European Journal of Gastroenterology &Hepatology 2010;22:564–571.

21.Huo L, Liao R, Chen X. Ophthalmic manifestations of Wilson's disease.Zhonghua Yan KeZaZhi. J 2008 Feb;44(2):128-30.

22. Lorincz M. Neurologic Wilson's disease. Ann. N.Y. Acad. Sci. 1184 2010; 173–187.

23. Panagariya A, Sureka R, Sharma A. Wilson's disease: A prospective study of 21 cases from north-west India. Ann Indian AcadNeurol 2007;10:255-8.

24.Park K: Principles of Epidemiology and Epidemiologic Methods. In:Park K, eds. Park's textbook of preventive and social medicine. 16th ed. BanarisidasBhanot Publishers: India. 2001;27:56-8.

25.Taly A,Meenakshi-Sundaram S, Sinha S. Wilson disease: Description of 282 patients evaluated over 3 decades, India. Medicine (Baltimore) J 2007 Mar;86(2):112-21.

26.**W**alshe J. Wilson's disease the presenting symptoms: A case series study included 25 patients (University of Cambridge). BMJ 2010;253-256.

27. Schilsky M,Shneider B. Population screening for Wilson's disease. The Journal Of Pediatrics Volume 140,Number 5 2002;614.

28. Rodrigo A, Valds M, Vargas A, et al. Clinical presentation, diagnosis, and long-term outcome of 29 patients with Wilson's disease, Spain. J Rev EspEnferm Dig. 2008 Aug;100(8):456-61.

29.Merle U, Schaefer M, Ferenci P. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: A cohort study in Heidelberg, Germany. J Gut 2007;56:115–120.

30. Karim M, Rahman M, Islam M. Wilson's disease with hepatic presentation in childhood.Mymensingh Med J. 2007 Jan;16(1):29-32.

31. Semba R: Inborn Errors of Metabolism. In: Semba R, eds. Handbook of Nutrition and Ophthalmology. 1st ed. HUMANA Press: New Jersey. 2007;464-7.

Al – Kindy Col Med J 2013; Vol. 9 No. 1 P: 125

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