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BRIEF ARTICLE

Liver transplantation in Wilson's disease: Single center experience from Saudi Arabia

Musthafa Chalikandy Peedikayil, Hamad Ibrahim Al Ashgar, Abdullah Al Mousa, Mohammed Al Sebayel, Khalid Al Kahtani, Faisal Aba Alkhail

Musthafa Chalikandy Peedikayil, Hamad Ibrahim Al Ashgar, Abdullah Al Mousa, Khalid Al Kahtani, Department of Medicine, King Faisal Specialist, Hospital and Research Center, Pin 11211, Riyadh, Saudi Arabia
Mohammed Al Sebayel, Faisal Aba Alkhail, Liver Transplantation and Hepatobiliary Surgery, King Faisal Specialist Hospital and Research Center, Pin 11211, Riyadh, Saudi Arabia
Author contributions: Peedikayil MC designed the study, collected data and wrote the paper; Al Ashgar HI, Al Mousa A, Al Sebayel M, Al Kahtani K and Alkhail FA contributed in writing the project and preparation of manuscript.
Correspondence to: Hamad Ibrahim Al Ashgar, MD, Department of Medicine, King Faisal Specialist, Hospital and Research Center, PO Box 3354, Pin 11211, Riyadh, Saudi Arabia. alashgar@kfshrc.edu.sa
Telephone: +966-1-4424729 Fax: +966-1-4427499
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Abstract

AIM: To determine liver transplantation outcomes in Wilson's disease (WD) patients, focusing on neurological manifestations.

METHODS: This retrospective study assessed data from 16 WD patients (nine males, 56%) who had liver transplants between 1991 and 2007. Survival, graft function, and neurological complications were assessed during a follow-up period of up to 15 years. In addition, each patient's medical record was reviewed in detail to find the type of Wilson's disease (hepatic or hepatic plus neurological WD), indication for liver transplantation, use of chelating agents prior to transplantation, immediate and long term complications following transplantation, the donor details, and the pathology of explanted liver.

RESULTS: End-stage liver disease was the indication for transplantation in all 16 WD patients. Four patients displayed WD-related neurological symptoms in addition to liver disease. Living-related liver transplantation was done in three cases. One patient died on postoperative day 6 due to primary graft non-function. One-year post liver transplant survival was 94%. Neurological manifestations of all four patients disappeared during their follow-up. Four patients developed acute cellular rejection, but all responded to treatment. One patient developed chronic ductopenic rejection after 15 years post-transplantation and their graft failed; this patient is currently waiting for re-transplantation. Fourteen patients (88%) are still living. The long-term average survival is currently 10.5 years, with a current median survival of 8 years. Long-term graft survival is currently 81%.

CONCLUSION: Short- and long-term survival in WD patient liver transplantation was excellent, and neurological and psychological WD manifestations disappeared during long-term follow-up.

Key words: Wilson's disease; Liver transplantation; Neurological; Psychiatric; Penicillamine; Saudi Arabia; Transplantation

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INTRODUCTION

Wilson's disease (WD) is a rare autosomal recessive inborn

error of copper metabolism resulting from mutations of the *ATP7b* gene on chromosome 13[1]. The *ATP7b* gene product, a P-type ATPase transporter, is responsible for copper excretion into bile. In Wilson's disease, impaired biliary copper excretion leads to accumulation of this metal in the liver. When liver storage capacity is exceeded, hepatocyte death ensues with copper release into the plasma. Elevated circulating copper results in hemolysis and copper deposition in extra-hepatic tissues[2]. With treatment, hepatic, neurological and psychiatric manifestations gradually improve. Prognosis is generally poor without treatment, with advanced liver disease, acute liver failure, and haemolysis. Patients presenting with neurological symptoms fare better with life expectancy. But the neurological symptoms only partially reverse with medications and may worsen initially with treatment[3].

The recommended initial treatment of symptomatic WD patients or those with active disease is with chelating agents. Symptomatic liver disease generally shows signs of recovery within 2-6 mo of treatment, but further recovery can occur during the first year of treatment. Maintenance medical therapy is required for an indefinite period. Failure to comply with therapy may lead to significant progression of liver disease and liver failure within 1-12 mo following discontinuation of treatment, resulting in death or necessitating liver transplantation[2,4].

Liver transplantation is an effective option for WD patients with acute liver failure and for patients presenting with advance decompensated liver disease that is unresponsive to medical therapy or caused by interrupted medical therapy. However, the efficacy of transplantation in managing patients with neurological WD, in the absence of hepatic insufficiency, remains uncertain[5].

The worldwide prevalence of WD ranges from 10 to 30 cases per million persons[6]. The literature describing liver transplantation experience in WD is limited; the number of cases in each series ranges from 6 to 55[5,7]. None of the studies published from Saudi Arabia discuss the results of liver transplantation in WD[8-11]. A large cohort of WD patients are being treated at our center, and we identified 16 patients who had undergone liver transplantation. The objectives of our study were to assess the outcomes of WD patients after liver transplantation and study the role of liver transplantation in WD patients with neurological and psychiatric manifestations.

MATERIALS AND METHODS

The study was conducted in a tertiary care hospital in Riyadh. We included WD patients who had undergone liver transplantation either in our institute or other centers but with follow-up at our center. Between 1991 and 2007, 16 WD patients from a cohort of 71 WD patients treated in our center underwent liver transplantation. The Research Promotion Group of the Department of Medicine and the Research and Ethics Committee of our Institute approved the research protocol. A retrospective study was conducted and the data were statistically analyzed using SPSS version 16 software (IBM, Amonk, NY).

Patients were diagnosed with WD if they had evidence of liver and/or neuropsychiatric illness along with one or more of the following criteria: (1) Presence of Kayser-Fleischer (KF) rings by slit lamp examination; (2) Low serum ceruloplasmin level < 200 mg/L; and (3) Elevated pre-treatment 24-h urinary copper excretion > 0.6 μmol/d. A 24-h urine excretion after challenge with D-penicillamine was performed when required[2].

Wilson's patients were classified as having hepatic WD if they had asymptomatic hepatomegaly, isolated splenomegaly, persistently elevated serum aminotransferase activity (alanine transaminase/aspartate transaminase), fatty liver, acute hepatitis, apparent autoimmune hepatitis, cirrhosis (compensated or decompensated), or acute liver failure[2]. Patients were diagnosed with neurological WD if they had one or more of the following symptoms: movement disorders (tremor, involuntary movements), drooling, dysarthria, rigid dystonia, pseudobulbar palsy, dysautonomia, migraine headaches, insomnia, or seizures[2].

Liver disease presentation was classified as chronic (*i.e.*, slow deterioration of liver function in a patient with known WD and disease-related cirrhosis); fulminant hepatic failure (*i.e.*, occurrence of hepatic decompensation within six months from the diagnosis of liver disease in patients without known WD); acute-on-chronic presentation (*i.e.*, acute decompensation in the context of diagnosed WD)[12].

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables are given as mean and medians. The data were analyzed by Microsoft Office Excel 2007 and SPSS version 16 software (IBM, Amonk, NY).

RESULTS

Sixteen patients underwent liver transplantation for WD. Nine of these patients were males (56%). The mean age at the time of liver transplantation was 19.3 ± 9.6 years (range 8 to 40 years). The time interval from the diagnosis of WD to liver transplantation varied from 1 to 204 mo, with a mean of 67.6 ± 0.7 mo.

Ten patients underwent liver transplantation at our center in Riyadh, five in the United States and one in the United Kingdom. Three patients' donors were living-related and rest of the transplants were done with cadaveric livers. The indication for transplantation was chronic liver disease not responding to chelating agents (chronic). Four patients had neurological symptoms in addition to liver disease. Prior to transplantation, eight patients' Child-Turcotte-Pugh (CTP) scores were B, five patients' CTP scores were C, and three had a CTP Score of A. The median Model for End-Stage Liver Disease (MELD) score was 14 with mean MELD scores of 17.4 ± 7.7. Table 1 gives baseline characteristics of all 16 patients who had liver transplants.

Table 1 Baseline characteristics of 16 Wilson's disease patients' pre-transplant details

Case	Age (yr)	Gender	Nationality	Ascites	Jaundice	HE	Neuro	24-h Copper	Ceruloplasmin	Penicillamine	KF ring	CTP	MELD
1	14	F	Saudi Arabia	Yes	Yes	No	Yes	-	100	Yes	Yes	C	19
2	14	F	Saudi Arabia	Yes	Yes	Yes	No	-	155	-	No	C	31
3	3	M	Saudi Arabia	No	Yes	No	No	-	325	Yes	No	B	12
4	12	M	Saudi Arabia	No	Yes	No	No	14.1	395	Yes	No	B	11
5	8	M	Saudi Arabia	Yes	Yes	No	No	-	250	-	No	B	11
6	4	M	Saudi Arabia	Yes	Yes	Yes	No	4.5	< 71	Yes	No	C	18
7	12	F	Saudi Arabia	No	Yes	No	No	10.02	54	Yes	No	B	10
8	38	M	Saudi Arabia	Yes	Yes	No	No	14	71	-	No	B	19
9	13	M	Saudi Arabia	Yes	Yes	No	No	10.2	227	Yes	No	B	13
10	6	M	Syrian Arab	Yes	Yes	No	No	-	< 72	-	No	B	13
11	25	F	Saudi Arabia	Yes	Yes	Yes	Yes	6.84	< 71	Yes	Yes	A	12
12	23	F	Saudi Arabia	Yes	Yes	Yes	Yes	0.89	128	-	Yes	C	34
13	18	M	Saudi Arabia	Yes	Yes	No	No	37	346	Yes	No	C	27
14	7	F	Saudi Arabia	No	Yes	No	No	17.06	360	Yes	No	A	-
15	22	F	Saudi Arabia	Yes	Yes	Yes	Yes	1.86	< 71	Yes	Yes	A	14
16	5	M	Yemeni	No	Yes	No	No	0.88	373	-	No	B	-

Age: Age at the time of diagnosis of Wilson's disease; M: Male; F: Female; HE: Hepatic encephalopathy; KF ring: Kayser-Fleischer ring; CTP: Child-Turcotte-Pugh score; MELD: Model for end-stage liver disease; Penicillamine: These patients had received treatment with D-penicillamine prior to liver transplantation.

One patient died on postoperative day 6 following liver transplantation. The patient developed portal vein thrombosis and decreased flow in the right hepatic artery on postoperative day 1. The same day patient underwent portal vein thrombectomy, but developed primary graft non-function, acute liver failure, severe brain edema, and status-epilepticus, and died.

Three patients underwent living-related liver transplantation. All donors had uneventful postoperative courses. Case number 10, who died on postoperative day 6 following liver transplantation, had received the liver from his brother. All three cases of living-related transplantation were done in Riyadh. The other two patients who received living donors were case numbers 14 and 16; the recipients are healthy after liver transplantation (> 4 years).

Only one patient was lost from follow-up after 6 years post-transplantation. The patient had developed complications such as Castleman's disease, cardiomyopathy, and Kaposi's sarcoma and was not traceable for verification of survival.

Four patients developed acute cellular rejection, but all of them responded to treatment. One patient developed chronic ductopenic graft rejection after 15 years post-transplantation. This patient also developed chronic kidney disease and recovered from rapamycin-induced pancytopenia. The patient is being listed for liver re-transplantation. Thirteen patients are still being followed in our center; one patient's care was transferred to another center after 8 years post-transplantation. Table 2 describes post-transplantation details of the 16 patients.

Two of our patients were found to have small hepatocellular carcinoma (HCC) in the explanted liver; both of them are healthy and surviving after transplantation. Both cases were within Milan criteria; one had surgery in United States and the other in United Kingdom.

One-year post-liver transplant, graft survival, and patient survival were 94%. The long-term graft survival was 13/16 (81%) and patient survival 14/16 (88%). The long-term average survival was 10.5 years with a median survival of 8 years.

Four of our patients had neurological symptoms prior to transplantation, in addition to the liver disease. The neurological symptoms prior to transplantation in these patients are described in Table 3. The indication for transplantation for these four patients was decompensated end-stage liver disease. Their magnetic resonance imaging (MRI) brain findings, KF ring status, and improvement of neurological and psychological symptoms after liver transplantation is given in Table 3.

Case numbers 1, 11, 12 and 15 had neurological and or psychological symptoms and signs before liver transplantation. Case number 1 underwent liver transplantation in 1991 in the United States. The patient is 20 years post-transplantation now and free from neurological symptoms and signs.

Case number 11 had transplantation in our center. The patient's post-operative period was problematic, and included many complications including methicillin-resistant Staphylococcus aureus pneumonia, acute respiratory distress syndrome, central pontine myelinolysis, and major depression during the immediate postoperative period following transplantation, and required a prolonged hospital stay. After three months hospital stay, the patient went home and is currently doing fine. During post-transplant follow-up, the patient's neurological symptoms and depression disappeared.

Case number 12 was our third patient in the series with neurological symptoms. The neurological symptoms and psychiatric features disappeared during follow-up. Brain MRI 3 years post-transplantation was impressive; all of the findings (Table 3) that were there before transplantation had disappeared.

Case number 15 was our fourth patient with neurological symptoms. The patient is currently 5 years post-transplant, and not on any medication for bipolar depression. The KF ring that was there before transplantation

Table 2 Post-liver transplant details of 16 Wilson's disease patients

Case	Gender	Age	Year of TX	Indication for TX	Neurological WD	TX center	Donor	Rejection	Graft survival	Pt survival	Death or lost FU	HCC
1	F	14	1991	Chronic	Yes	United States	Cad	No	20 yr	20 yr	-	No
2	F	14	1994	Chronic	No	KFSHRC	Cad	Chronic	15 yr	17 yr	-	No
3	M	11	1995	Chronic	No	United States	Cad	No	6 yr	6 yr	Lost FU	No
4	M	12	1995	Chronic	No	KFSHRC	Cad	No	16 yr	16 yr	-	No
5	M	13	1995	Chronic	No	United States	Cad	Acute	16 yr	16 yr	-	Yes
6	M	13	1995	Chronic	No	KFSHRC	Cad	No	16 yr	16 yr	-	No
7	F	12	1996	Chronic	No	United Kingdom	Cad	No	15 yr	15 yr	-	Yes
8	M	40	1999	Chronic	No	United States	Cad	No	12 yr	12 yr	-	No
9	M	22	2003	Chronic	No	United States	Cad	No	8 yr	8 yr	-	No
10	M	23	2004	Chronic	No	KFSHRC	LR	No	6 d	6 d	Died	No
11	F	40	2004	Chronic	Yes	KFSHRC	Cad	No	7 yr	7 yr	-	No
12	F	23	2004	Chronic	Yes	KFSHRC	Cad	Acute	7 yr	7 yr	-	No
13	M	18	2006	Chronic	No	KFSHRC	Cad	Acute	5 yr	5 yr	-	No
14	F	9	2006	Chronic	No	KFSHRC	LR	No	5 yr	5 yr	-	No
15	F	25	2006	Chronic	Yes	KFSHRC	Cad	Acute	5 yr	5 yr	-	No
16	M	8	2007	Chronic	No	KFSHRC	LR	No	4 yr	4 yr	-	No

Age: Age at the time of transplantation; M: Male; F: Female; WD: Wilson's disease; HCC: Hepatocellular carcinoma; TX: Transplantation; FU: Follow-up; KFSHRC: King Faisal Specialist Hospital and Research Center.

Table 3 Neurological and psychiatric manifestations of Wilson's disease before and after liver transplantation

Characteristics	Case 1	Case 11	Case 12	Case 15
Neurological symptoms before transplantation	Akinesia dysarthria abnormal movement	Tremor dysarthria abnormal movement	Tremor nystagmus	Abnormal movement
Psychiatric abnormalities before transplantation	Negative	Negative	Depression restlessness	Delusion of persecution depression restlessness hallucination
MRI brain before transplantation	No available data	High signal intensities involving the thalami, mid brain, and pons	Bilateral and symmetrical abnormal hyper-intensity at level of basal ganglia	High signal intensity in the basal ganglia and substantia nigra with mild cerebral atrophy
KF ring before transplantation	Positive	Positive	Positive	Positive
Neurological symptoms after transplantation	Negative	Negative	Negative	Negative
Psychiatric abnormalities after transplantation	Negative	Negative	Negative	Negative
MRI brain after transplantation	No available data	Normal MRI of the brain	No available data	No available data
KF ring after transplantation	Negative	Negative	Negative	Negative

KF ring: Kayser-Fleischer ring; MRI: Magnetic resonance imaging.

has also disappeared.

DISCUSSION

The current study explored the results of liver transplantation in WD patients and the effect on neurological manifestations of WD. Our study proves excellent short- and long-term survival, and total recovery from the neurological manifestations of WD following liver transplantation.

In our series, 16 patients' data were analyzed. Almost equal number of males and females underwent liver transplantation. Many of them had surgery in the second or third decade of life. Transplantation was done after a mean of 5.5 years from the WD diagnosis. Many of our patients underwent liver transplantation for end-stage liver disease and few others for acute-on-chronic liver failure. Five of the transplanted patients had one or more affected siblings in the family. Ten patients were treated with chelating agents such as D penicillamine before transplantation. Ten patients underwent liver transplantation in our center, and fourteen patients were Saudi nationals.

The outcome of liver transplantation in our series was excellent; only one patient died and another lost from follow-up. One patient lost their liver graft after 15 years post-transplantation and developed decompensated liver disease.

In 1971, DuBois *et al*[13] demonstrated that liver transplantation is an effective treatment modality to reverse the metabolic effects of WD. In 1984, Sternlieb *et al*[14] described the indications for liver transplantation in WD as cirrhosis with severe hepatic decompensation not responding to medical therapy, fulminant hepatic failure, and hepatic decompensation after discontinuation of previously effective treatment. The role of liver transplantation in neurological WD is questioned by some experts in this field[15].

The various centers that perform liver transplantation have done transplants in only a small number of WD patients. The long-term survival after transplantation varies in different centers, from 74% to 100%. Our center's long-

term patient survival following transplantation is 14/16 (87%) (including one patient who was lost to follow-up). The long-term graft survival was 81% and median survival was 8 years. Our short- and long-term survival results are comparable to the results of other centers.

The improvement of neurological symptoms after transplantation was remarkable in our series. Four of our patients who had neurological symptoms related to WD are still alive and have no residual neurological symptoms or signs. One patient had bipolar mood disorder, which also disappeared after transplantation, and was able to discontinue all psychiatric medications.

The experiences of a few other transplant centers agree with our findings. In a series from Turkey that described 24 patients who had liver transplantation for WD, nine had neurological symptoms and seven patients improved symptomatically after transplant. A study by Eghtesad *et al*[16] from United States had 14 patients with neurological symptoms in addition to liver disease in a 45 WD patient series that had liver transplants. Ten of fourteen patients improved from neurological manifestations of WD after the liver transplantation. From our experience and other center's experiences, we believe that transplantation should not be denied to WD patients with neurological or psychiatric manifestations. However, the current study did not include patients with severe neurological/psychiatric WD. Hence we are not sure about the role of liver transplantation in disabling neurological/psychiatric WD.

Twelve patients' pathologies of explanted liver showed features of micro- or macronodular cirrhosis and some had varying cholestasis. Two patients' explanted livers had features of HCC, which is generally considered rare in WD[17]. One patient in the Turkey series who had transplantation for WD reported HCC in the hepatectomy specimen. This information suggests that HCC in WD is probably missed rather than rare.

The current study describes the largest number of WD patients who had liver transplantation from Middle East. The limitation of the current study is that it was a retrospective study. We did not face major hurdles in retrieving crucial information due to availability of excellent medical records, which we had for many years. Moreover, to study a rare genetic disease and procedure such as liver transplantation, we believe the retrospective study is still the best study design.

Liver transplantation for WD with end-stage liver disease is an effective treatment. Short- and long-term survival in our series was excellent; 94% of our patients survived at 1 year, with a median long-term survival of 8 years. Neurological and psychological manifestations of WD in our series disappeared during long-term follow-up.

COMMENTS

Background

The worldwide prevalence of Wilson's disease (WD) ranges from 10 to 30 cases per million persons. These patients generally present with acute or acute-on-chronic or chronic liver disease, and or neurological and psychiatric symptoms and signs. The disease is treated by chelating agents such as D Penicillamine or trientine. Liver transplantation is a treatment option for patients who are not responding to medical therapy, with acute liver failure or with advanced decompensated liver disease. Liver transplantation for severe neurological WD is controversial.

Research frontiers

The experience of liver transplantation for WD is limited. Over a period of 15 years, the authors gathered 16 WD patients who underwent liver transplantation and followed up in one single center. The authors studied short and long term survival following transplantation and the effect of liver transplantation on neurological and psychiatric manifestations.

Innovations and breakthroughs

The current study demonstrates that short and long term prognosis of WD patients with liver transplantation is excellent. The one year survival was 94%. The long-term average survival is currently 10.5 years, with a current median survival of 8 years. Long-term graft survival is currently 81%. Liver transplantation has a positive effect on neurological and psychiatric symptoms and signs. All of the patients with neurological and psychiatric symptoms and signs improved with liver transplantation.

Applications

The application of this study is that liver transplantation is an excellent method of treatment when it is really indicated for WD. Patients with mild to moderate degree of neuro-psychiatric symptoms and signs should not be denied chance for liver transplantation.

Terminology

WD is a rare autosomal recessive inborn error of copper metabolism resulting from mutations of the *ATP7b* gene on chromosome 13. The *ATP7b* gene product, a P-type ATPase transporter, is responsible for copper excretion into bile. In WD, impaired biliary copper excretion leads to accumulation of this metal in the liver. When liver storage capacity is exceeded, hepatocyte death ensues with copper release into the plasma. Elevated circulating copper results in hemolysis and copper deposition in extra-hepatic tissues such as brain, red blood cells, renal, *etc*.

Peer review

The current study provides valuable information of a rare inborn error of metabolism, and the short and long term results of liver transplantation. The drawback of the study is that the numbers represented in the study is small and it is a retrospective study. Only few centers have published papers relating this subject and the numbers from each center is similar to this one. Moreover, the knowledge of such rare metabolic disorders often comes from retrospective studies.

REFERENCES

1 **Thomas GR**, Forbes JR, Roberts EA, Walshe JM, Cox DW. The Wilson disease gene: spectrum of mutations and their consequences. *Nat Genet* 1995; **9**: 210-217 [PMID: 7626145]

2 **Roberts EA**, Schilsky ML. Diagnosis and treatment of Wilson disease: an update. *Hepatology* 2008; **47**: 2089-2111 [PMID: 18506894]

3 **European Association for Study of Liver**. EASL Clinical Practice Guidelines: Wilson's disease. *J Hepatol* 2012; **56**: 671-685 [PMID: 22340672]

4 **Schilsky ML**, Scheinberg IH, Sternlieb I. Prognosis of Wilsonian chronic active hepatitis. *Gastroenterology* 1991; **100**: 762-767 [PMID: 1993498]

5 **Schilsky ML**, Scheinberg IH, Sternlieb I. Liver transplantation for Wilson's disease: indications and outcome. *Hepatology* 1994; **19**: 583-587 [PMID: 8119682]

6 **Medici V**, Trevisan CP, D'Incà R, Barollo M, Zancan L, Fagiuoli S, Martines D, Irato P, Sturniolo GC. Diagnosis and management of Wilson's disease: results of a single center experience. *J Clin Gastroenterol* 2006; **40**: 936-941 [PMID: 17063115]

7 **Geissler I**, Heinemann K, Rohm S, Hauss J, Lamesch P. Liver transplantation for hepatic and neurological Wilson's disease. *Transplant Proc* 2003; **35**: 1445-1446 [PMID: 12826186 DOI: 10.1016/S0041-1345(03)00464-0]

8 **Al Jumah M**, Majumdar R, Al Rajeh S, Awada A, Al Zaben A, Al Traif I, Al Jumah AR, Rehana Z. A clinical and genetic study of 56 Saudi Wilson disease patients: identification

of Saudi-specific mutations. *Eur J Neurol* 2004; **11**: 121-124 [PMID: 14748773]
9 **al Mofleh IA**, al Rashed RS, Ayoola EA, Sabah DM, Hafeez MA. Hepatic manifestations of Wilson's disease: frequency and pattern in Saudi patients. *Trop Gastroenterol* 1993; **14**: 91-98 [PMID: 8109051]
10 **Bahemuka M**, Karrar ZA, Mofleh IA, Bahakim H, Hafeez MA. Protean manifestations of Wilson's disease: a review of seven Saudi patients. *Trop Geogr Med* 1988; **40**: 131-138 [PMID: 3407002]
11 **Fashir B**, Sivasubramaniam V, Al Momen S, Assaf H. Pattern of liver disease in a Saudi patient population: a decade of experience at security forces hospital, Riyadh, KSA. *Saudi J Gastroenterol* 1996; **2**: 50-52 [PMID: 19864842]
12 **Martin AP**, Bartels M, Redlich J, Hauss J, Fangmann J. A single-center experience with liver transplantation for Wilson's disease. *Clin Transplant* 2008; **22**: 216-221 [PMID: 18339142]
13 **DuBois RS**, Giles G, Rodgerson DO, Lilly J, Martineau G, Halgrimson CG, Schroter G, Starzl TE, Sternlieb I, Scheinberg IH. Orthotopic liver transplantation for Wilson's disease. *Lancet* 1971; **1**: 505-508 [DOI: 10.1016/S0140-6736(71)91121-4]
14 **Sternlieb I**. Wilson's disease: indications for liver transplants. *Hepatology* 1984; **4**: 15S-17S [PMID: 6363255]
15 **Brewer GJ**, Askari F. Transplant livers in Wilson's disease for hepatic, not neurologic, indications. *Liver Transpl* 2000; **6**: 662-664 [PMID: 11041671]
16 **Eghtesad B**, Nezakatgoo N, Geraci LC, Jabbour N, Irish WD, Marsh W, Fung JJ, Rakela J. Liver transplantation for Wilson's disease: a single-center experience. *Liver Transpl Surg* 1999; **5**: 467-474 [PMID: 10545532]
17 **Savas N**, Canan O, Ozcay F, Bilezikci B, Karakayali H, Yilmaz U, Haberal M. Hepatocellular carcinoma in Wilson's disease: a rare association in childhood. *Pediatr Transplant* 2006; **10**: 639-643 [PMID: 16857005]

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