Liver transplantation in Wilson's disease: A systematic review

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Wilson's disease (WD) is a rare genetic disorder affecting the metabolism of copper that may present with neurological symptoms. In cases leading to hepatic failure, liver transplantation (LT) may be necessary. The aim of this paper is to examine the literature on LT cases related to WD in terms of disease characteristics, the neurological conditions of patients and survival rates. The keywords "Wilson and transplant*" were used to perform a title and abstract search across three databases (PubMed, Scopus, Web of Science) up until November 2018. The results from a total of 791 patients, mentioned in 28 studies, were analyzed. Thirty-nine point six percent of the patients received emergency LT and acute liver failure was more predominant in woman patients (61.7%-38.3%; $p < 0.0001$). Live donations accounted for 36.6% of the transplants with none of these patients experiencing recurrence of disease. 36.4% of the patients displayed neurological symptoms prior to the transplant; however, following the operation these symptoms decreased by 74.2%. Survival rates for 1, 2, 3, 5, 10 years were 84%, 82%, 81%, 81%, and 80%, respectively. Further research into the reasons that acute liver failure in patients suffering from WD is more common among women is needed. Moreover, while mortality rates for up to one-year post-transplant are 16%, this rate is only 4% for the following 1–10 years. As neurological symptoms experienced prior to transplantation decrease by 74.2% after the operation, further studies should be carried out into the factors that determine potential neurological improvement.

Keywords: Liver; Transplantation; Review

INTRODUCTION

Wilson's disease (WD) is a genetic disorder affecting the metabolism of copper. The disease is caused by the mutations of homozygous or conjugated heterozygote (presence of two different mutant alleles) found in the ATP7B gene. This gene encodes the transmembrane copper carrier ATPase 2 which enables copper to enter the biliary tract for the synthesis of ceruloplasmin (the major copper-carrying

protein in the blood) [1]. In a Wilson's patient, the mutated ATP7B gene causes the copper to accumulate in the hepatocytes, as it cannot be released into the biliary tract. Excess copper detached from the ceruloplasmin also causes serious neuropsychiatric symptoms in secondary tissue such as the brain. The symptoms of this illness are varied and mostly develop between the 1st and 4th decades of life [2] with a prevalence of symptomatic disease of 1 in 30,000 people [3]. While most patients can be maintained

with medical treatment, 5% develop acute liver failure (ALF) and 10% chronic liver failure (CLF) [4]. Liver transplantation (LT) can therefore be a lifesaving solution for such Wilson's patients. The first case of liver transplant on a WD patient was published in 1971 [5] and since that time substantial progress in the usage of LT has been made. In the USA, 0.5%–1.5% of all LT performed are WD related [6,7]. In addition to hepatic insufficiency, LT is also important in terms of neurological complications. Post-transplant improvements have been recorded in patients with serious neurological symptoms [8]. However, LT-related complications and inconsistencies in post-transplant neurological improvement cast doubt on the validity of recommending neurological symptoms alone as indication for LT. In this study, all cases of LT in WD patients mentioned in the literature were analyzed in terms of demographic characteristics, indications for transplantation, pre-transplantation neurological status, transplantation results, neurological improvement and post-transplant survival rates.

MATERIALS AND METHODS

Screening Strategy and Inclusion Criteria

A systematic review of all publications containing findings of LT related to WD was carried out. Using the keywords "Wilson and transplant*", three databases (PubMed,

Scopus, Web of Science) were scanned. Starting from the first recorded case, all publications until November 2018 were analyzed. Only English-language clinical trials were included in this study. Reviews, meta-analyses, case reports, poster presentations and non-human clinical studies were excluded from this review.

Data Extraction

Data extraction was completed by two authors, guided by a previously created database. The following data was recorded in the database: article name, first author name, country, center, year, type of study, number of patients, average age, patient group (pediatric or adult), gender, transplantation indication (CLF or ALF), presence of Kayser–Fleischer rings (KF), biochemical levels, neurological status pre-operative and post-operative, donor status (live, cadaver), post-transplant rejection and re-transplantation rates, causes of perioperative mortality and survival rates for 1, 2, 3, 5, and 10 years.

Statistical Method

Statistical analysis was conducted using MedCalc software (MedCalc Software, Ostend, Belgium). Both random-effect and fixed-effect models were to combine the studies and to determine the yearly mortality proportion %, and the 95% confidence interval. Statistical heterogeneity

Fig. 1. Flowchart.

of included studies was tested using I^2 statistics. Publication bias was tested by Egger's weighted regression method and a p-value <0.05 was considered indicative of statistically significant publication bias.

RESULTS

During the initial screening 558 publications were found. After excluding recurring results, 399 publications remained. The selection process can be seen in Fig. 1. Twenty-eight clinical trials performed between 1993–2018 were also included in this study [7–34]. All the studies were

retrospective and their parameters can be found in Table 1 and 2.

The average age of the 26 cases where age was mentioned was 21.4 (11–32) years. Two studies involved pediatric patients, 7 comprised adults and the remaining 19 focused on mixed groups of patients. In 18 detailed studies, a total of 216 (37.7%) pediatric and 356 (62.2%) adult patients were included. According to 25 studies that indicated gender, 393 (51.7%) patients were woman and 366 (48.2%) man. The average follow-up duration of the 20 studies that included this parameter, was 62.5 months. In total, 791 patients received a LT due to WD.

Table 1. General features of the studies and patient characteristics

First author	Year	Country	No. of patients	Child/adult	Woman/man	Mean age (yr)
Rela M	1993	UK	12	NA	8/4	19
Schilsky M	1994	USA	55	NA	32/23	23.1
Bellary S	1995	USA	39	16/23	NA	23
Chen CL	1997	Taiwan	7	0/7	4/3	21.4
Haberal M	1999	Turkey	8	NA	NA	23.3
Eghtesad B	1999	USA	45	19/26	26/19	22.3
Schumacher G	2001	Germany	21	NA	14/7	NA
Emre S	2001	USA	22	3/14	8/9	28
Wang X	2005	China	22	19/3	16/6	15.5
Tamura S	2005	Japan	5	2/3	2/3	20
Medici V	2005	Italy	37	0/37	17/20	27.5
Dhawan A	2005	UK	57	57/0	22/35	11.9
Petrasek J	2007	Czech Republic	35	0/35	26/9	24.2
Marin C	2007	Spain	14	NA	NA	NA
Sevmis S	2008	Turkey	24	NA	7/17	15.6
Martin AP	2008	Germany	11	0/11	6/5	29.7
Pabón V	2008	France	13	7/6	8/5	20
Markiewicz M	2008	Poland	13	13/0	12/1	15.5
Cheng F	2009	China	36	10/26	20/16	NA
Yoshitoshi EY	2009	Japan	32	24/8	17/15	16.6
Peedikayil MC	2013	Saudi Arabia	16	NA	7/9	19.3
Ohya Y	2013	Japan	8	NA	4/4	15.7
Weiss KH	2013	Germany	19	0/19	13/6	29.4
Guillaud O	2014	France	121	46/75	71/50	22
Yagci MA	2015	Turkey	9	NA	2/7	18.4
Lankarani KB	2016	Iran	107	NA	43/64	20.8
Choudhary NS	2018	India	18	0/18	3/15	32.4
Öcal R	2018	Turkey	19	0/19	5/14	26
Total			825	216/330	393/366	21.6
Percentage				39.5/60.5	51.7/48.2	

NA, not available.

The general characteristics of the 28 studies included in the review were summarized in the table.

Table 2. General characteristics of the transplant patients

First author	No. of transplant	Neurological complication	Kayser Fleischer	Living or cadaveric donation	Acute reject	Chronic reject	Re-transplant	Follow-up period (mon)	Mortality
Rela M	12	NA	NA	NA	NA	NA	NA	NA	NA
Schilsky M	55	8	25	NA	NA	NA	NA	32.4	12
Bellary S	39	9	20	NA	3	3	10	NA	8
Chen CL	7	7	7	NA	NA	NA	NA	62.7	NA
Haberal M	8	2	2	1/7	NA	NA	NA	NA	3
Eghtesad B	45	17	21	NA	NA	NA	11	NA	14
Schumacher G	21	9	NA	NA	NA	NA	NA	62.4	NA
Emre S	17	NA	2	NA	2	0	4	63.6	2
Wang X	22	9	19	22/0	1	1	2	18.5	1
Tamura S	5	1	4	NA	NA	NA	NA	40	1
Medici V	37	10	NA	NA	NA	NA	4	64.6	10
Dhawan A	10	51	6	NA	4	0	2	NA	2
Petrasek J	31	NA	6	NA	NA	NA	NA	NA	5
Marin C	14	4	NA	NA	NA	NA	NA	96	2
Sevmis S	24	9	18	21/3	NA	NA	1	21.7	5
Martin AP	11	5	4	NA	NA	NA	2	56.8	1
Pabón V	13	2	6	2/11	1	1	NA	120	0
Markiewicz M	11	11	NA	2/9	2	0	NA	30.8	2
Cheng F	36	15	31	NA	NA	NA	NA	45.2	9
Yoshitoshi EY	32	4	25	32/0	NA	NA	3	88	6
Peedikayil MC	16	4	4	3/13	4	1	NA	123	1
Ohya Y	6	NA	NA	2/4	0	1	1	NA	1
Weiss KH	19	4	NA	NA	1	0	2	NA	5
Guillaud O	121	29	69	4/117	51	7	17	72	15
Yagci MA	9	NA	NA	7/2	NA	NA	2	36.6	0
Lankarani KB	107	60	NA	NA	31	3	2	133.5	15
Choudhary NS	18	3	7	NA	2	0	NA	15	2
Öcal R	19	7	NA	NA	NA	NA	NA	NA	NA
Total	765/825	280/739	276/566	96/166	99/455	17/455	63/553	62.2	119/766
Percentage	92.7	37.8	48.7	36.6/63.3	21.7	3.7	11.3		15.5

NA, not available.

The characteristics of patients who underwent liver transplantation in the studies were summarized in Table 2.

Results from 10 studies show that 96 (36.6%) patients received from live donors while 166 (63.4%) patients received cadaver donor transplants. In studies where transplant indications were given, 442 (60.3%) cases were due to CLF and 290 (39.6%) due to ALF. In 284 of 604 patients, (46.6%) KF rings were present. Average biochemical levels were: bilirubin: 15.2 (3–42.2) mg/dL; standardized prothrombin time (international normalized ratio): 3.04 (1.5–10); urine copper: 1,819.2 (256–4,119) µg; serum ceruloplasmin: 12.9 (7–22.2) mg/dL. Prior to their liver

transplants, 247 out of 677 patients (36.4%) displayed neurological symptoms. There were 6 studies examining neurological status both before and after transplant [10–15]. When these studies were examined, a total of 101 patients had neurological complications before surgery. Neurological improvement was observed in 75 patients in the postoperative period. The studies highlighted a 74.2% post-transplant decrease in neurological symptoms over 101 patients. The details of these studies are summarized in Table 3. There were 19 studies that describe the periop-

erative and long-term causes of death. The most common cause was due to sepsis and the multiple organ dysfunction syndrome. These were followed by primary non-function and surgical complications. The details of the causes of mortality in these studies are shared in Table 4. It was

observed that mortality in liver transplants performed for WD was mostly due to early-stage causes. Overall survival rates for 1, 2, 3, 5 and 10 years were 84%, 82%, 81%, 81%, and 80%, respectively (Fig. 2–6). In the 10-year survival analysis, 80% of the mortalities were observed in the first

Table 3. Neurological improvement in transplant patients

First author	Number of patients	Prior	After
Wang X	22	9 (40.9)	1 (4.5)
Chen CL	7	7 (100)	1 (14.2)
Marin C	14	4 (28.5)	1 (7.1)
Peedikayil MC	16	4 (25)	0 (0)
Lankarani KB	107	60 (56)	20 (18.6)
Eghtesad B	45	17 (37.7)	3 (6.6)
Total	211	101 (47.8)	26 (12.3)

Values are presented as number only or number (%).

A 74.2% improvement in neurological complications was seen when looking at six studies examining neurological status before and after transplantation.

Table 4. Causes of post-transplant mortality

Cause of death	No. of patients	Percentage
Sepsis/MODS	44	42.7
Primer non-function	9	8.7
Surgical complications	8	7.7
Cardiac	7	6.8
B-cell lymphoma	5	4.8
Rejection	4	3.8
Haemorrhage	3	2.9
Brain abscess	3	2.9
Other reasons	20	19.4

MODS, multi-organ dysfunction syndrome.

The most common causes of mortality after liver transplantation for Wilson's disease are sepsis, MODS and other early complications.

Fig. 2. One-year survival rate. CI, confidence interval.

Fig. 3. Two-year survival rate. CI, confidence interval.

Fig. 4. Three-year survival rate. CI, confidence interval.

year, most probably within the perioperative period. No cases of recurrence were found in patients who had either cadaveric or live donor LT.

DISCUSSION

WD clearly presents as an illness pertaining to children and young adults. The mean age of the overall patient

group was 21.4 years. Studies show the mean age for LT to be 15 years (4–18) for children and 30 years for adults (19–68) [35–37]. In our study, 51.7% of the patients were woman and 48.2% man. Although the literature shows no significant difference between the genders in terms of WD diagnosis, studies indicate a significantly higher percentage of women with ALF due to WD [38,39]. In our study, we also saw that 61.7% of the patients who received LT due to

Fig. 5. Five-year survival rate. CI, confidence interval.

Fig. 6. Ten-year survival rate. CI, confidence interval.

ALF were woman compared to 38.2% man ($p<0.0001$). Further research is needed to determine the reasons why ALF is more common among women who suffer from WD.

Since the disease is caused by a defect in the body's metabolism of copper, it causes symptoms related to excess copper accumulation in various tissues, especially the liver. Initially, certain patients may be diagnosed with symptoms of ALF or decompensated cirrhosis, while in other patients serious neurological symptoms may be more evident. The type of gene mutation may be important in identifying the presenting symptoms. While missense mutation in

the gene is associated with older patients and prominent neurological symptoms, deletion mutation appears to be associated with younger patients and prominent hepatic symptoms [39,40]. However, this delineation is not absolute as most patients show a mix of both neurological and hepatic symptoms. Therefore, WD diagnosis should be made using a combination of laboratory tests and clinical findings. Twenty-four hour urine copper and liver copper concentrations, serum ceruloplasmin, ATP7B gene mutation, neurological symptoms, brain magnetic resonance imaging and hemolytic anemia are all important for the diagnosis of

WD. KF rings are seen in only 50% of cases [41] and in our study, this rate was 46%. Diagnosis of WD in patients who suffer from ALF, where clinical findings and laboratory tests are less reliable and non-specific, is also more problematic. Most tests related to copper metabolism are not available in an emergency. In addition, serum ceruloplasmin levels were found to be unhelpful in the diagnosis of WD in 5 patients with idiopathic ALF [42,43]. In a study performed on 16 ALF patients to overcome this difficulty, a serum alkaline phosphatase to total serum bilirubin ratio of less than 2, along with a serum aspartate aminotransferase to serum alanine aminotransferase ratio of greater than 2.2 were found to be 100% sensitive and specific for WD-related ALF [44].

Significantly, LT immediately corrects the defect in copper metabolism. The normalization of serum ceruloplasmin levels post-transplantation usually occurs within the first month. As excess copper leaves the body relatively more slowly, it can take up to 6–9 months for urine copper levels to return to normal. In patients with a KF ring, the ring disappears completely in 60% of transplant patients, while a gradual fading is seen among other patients [45,46].

Another important post-transplant parameter is the improvement in neurological status. In this systematic review, the rate of neurological recovery after LT was also found to be high at 74.2%. However, whether or not neurological symptoms alone should be an indication for transplantation, still remains unclear. There are very few cases in the literature of a patient undergoing LT due to neurological symptoms while displaying normal liver functions [47,48]. In the study by Wang et al. [15], 88.9% neurological recovery was recorded. Egtesad et al. [11] reported a 58.8% neurological improvement in their study, but advocated transplantation before symptoms became irreversible.

Factors affecting survival rates after LT related to WD, in the literature, are uncommon. No conclusive results were found in studies investigating the effect of factors such as age, sex, ALF or CLF. Medici et al. [8] reported the only factor affecting the survival rate to be neurological status and found that the survival rate of patients with severe neurological symptoms was significantly lower. Wang et al. [15] came to the same conclusion in their study. However, in this systematic review, long-term results were found to be very successful, independent of neurological involvement. According to this analysis, the most significant parameter affecting mortality rates is perioperative patient loss. In conclusion, although neurological status is not an indication for transplantation alone, it should be remembered that

the reversal of symptoms in patients with persistent neurological involvement is far more problematic; therefore, such patients may have a lower quality of life post-LT, indirectly leading to an increase in mortality rates over the long term.

A further concern for WD is the potential transmission of the gene mutation in the case of LT from a live family donor, causing a recurrence of the disease. No such recurrence was found in our analysis of the live-donor transplant patient data. In fact, one study showed that none of the 11 children (9 ALF, 2 CLF) who underwent live-donor liver transplants from their parents had recurrence during the average follow-up period of 31 months [49]. It seems that since WD shows autosomal recessive inheritance, live donor liver transplants can be safely performed from individuals who carry heterozygous gene and have normal urine copper and serum ceruloplasmin levels.

Examination of the average survival rates for 1, 2, 3, 5, and 10 years reveal a success rate of 82%, 81%, 81%, and 80% respectively. Arnon et al. [6] in their study reported good survival rates for 1-year and 5-year terms as well as a better survival rate for WD related LT patients compared with transplant patients related to other illnesses. Higher survival rates can be attributed to the relatively young age for transplantation, fewer co-morbidities, and no disease recurrence. Similar results were obtained in our study.

This study has some limitations. First, most of the studies in the literature on liver transplants for WD are retrospective. The number of detailed prospective studies is few. Second, the number of studies providing sufficient detail in the preoperative and postoperative follow-up of neurological symptoms is not sufficient.

CONCLUSIONS

Liver transplants for WD have a higher survival rate than those for other indications. In addition, there is an improvement in neurological symptoms at a rate of 74.2% after transplantation. Mortality was mostly perioperative and was largely due to sepsis and multiple organ dysfunction syndrome. One-year, five-year and ten-year survival rates were similar. Perioperative mortality seems to be the most important parameter in determining long-term survival rates.

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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