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Original Article

Quality of Life in Children with Wilson Disease: A Single Center Study

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Abstract:
Background: Wilson disease (WD) is associated with compromised health-related quality of life (HRQoL) in both adults and children, even in the early stages of the liver disease.
Aim of the work: to assess HRQoL children and adolescents suffering from WD and to investigate factors that may affect the HRQoL among them.
Subjects and Methods: This was a case-control study including 30 WD patients and 30 age- and sex-matched normal healthy controls. The HRQoL was evaluated by the World Health Organization Quality of Life BREF questionnaire (WHOQoL-BREF) and chronic liver disease questionnaire (CLDQ) for both patients and controls.
Results: The mean ± SD age of the patients was 14.07 ± 3.36 years compared to 14.58± 3.391 years of the control group (p=0.96). At the initial presentation to our unit, 18 patients (60%) were symptomatic and 12 patients (40%) were asymptomatic. At the study enrollment, liver function tests were within normal ranges in 15 patients (50%), while the other 15 (50%) patients had deranged liver functions. Children with WD had significantly poorer HRQoL scores than normal controls regarding physical (54.3 ±14.2 vs 97.2 ±3.7) (p=0.000), psychological (33.4 ±9.9 vs 57.5 ± 7.6) (p=0.000), social (58 ±17 vs 83.5 ±9) (p=0.000), and environmental domains (40.3±11.2 vs 52.3 ±5.8) (p=0.000) of WHOQoL. Females exhibited significant declined scores in the worry domain of the CLDQ compared to males (p=0.017). Patients with longer disease duration had worse scores CLDQ in emotional (26.2 ± 2.9) and worry (13.2 ± 2.8) domains (p=0.050) and (p=0.044) respectively, but not the WHOQoL (physical p=0.2, psychological p=0.17, social P=0.85, environmental p=0.11).
Conclusion: Children with WD have significantly compromised HRQoL, compared to their healthy peers. The HRQoL in children with chronic liver disease complications were more affected in the physical aspects. Worry represents a significant morbidity among females with WD.

Keywords: children; health-related quality of life; Wilson Disease; chronic liver disease; health-related quality of life (HRQoL); chronic liver disease questionnaire
Abbreviations: ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; CLD: Chronic liver disease; CLDQ: chronic liver disease questionnaire; GGT: gamma glutamyl transpeptidase; HRQoL: health-related quality of life; INR: international normalized ratio; PT: prothrombin time; SD: Standard deviation; WD: Wilson disease; WHOQoL-BREF: World Health Organization Quality of Life BREF questionnaire

Introduction

Wilson disease (WD) is an inherited disorder affecting copper metabolism. WD results from homozygous or compound heterozygous mutations in ATP7B, which encodes the transmembrane copper-transporting ATPase 2, that governs copper excretion into bile and copper delivery for the functional ceruloplasmin synthesis (*1*). The majority of WD patients exhibit affection of liver and basal ganglia of the central nervous system (*2*). Other affected systems include renal, hematological, endocrinological as well as skeletal manifestations. Health-related quality of life (HRQoL) denotes the functional impact of a disease and its treatment on a patient, as perceived by the patient. It helps to prioritize health issues for better communication and monitoring (*3*). Few studies investigated HRQoL in patients with WD (*4*). Hence, we aimed to assess HRQoL in children and adolescents suffering from WD and to investigate factors that may affect the HRQoL among them.

Subjects and Methods

This cross-sectional case-control analytical study was conducted at Cairo University Children's Hospital. Verbal consent was obtained from the parents of all recruited patients. The Cairo University Higher Research Committee reviewed and approved the study protocol.

Participants

The study included 30 cases with an established diagnosis of WD and 30 age and sex matched healthy children as a control group who did not suffer from any chronic condition that can affect quality of life (QoL). Cases were recruited over a 6-month duration. The WD patients of both sexes were on chelation therapy as well as zinc treatment for at least 6 months before enrollment in the study. They were recruited from the Pediatric Hepatology Unit, Faculty of Medicine, Cairo University Hospitals. Those who were uncooperative, or could not comprehend the questions and those with any associated chronic condition that may compromise QoL were excluded from the study. The control group were selected from the outpatient clinic. They presented with acute simple conditions such as common cold or tonsillitis that do not influence the QOL questionnaire.

Methods

All patients underwent detailed history taking and meticulous clinical examination. The detailed history-taking was done to detect complications that may compromise QoL among WD patients; frequency of hospital visits and school absence days, complications resulting from liver cirrhosis if present (as bleeding, ascites or encephalopathy), neurological symptoms (difficulty speaking, abnormal movements, bulbar manifestations, seizures), need for hospitalization, detailed medication history and complications of treatment. They underwent the following laboratory investigations at enrollment to detect metabolic control: complete blood count (CBC), total and direct serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), serum albumin, prothrombin time (PT), international normalized ratio (INR), and 24-h urinary copper estimation. Their Leipzig scores (*5*) at the time of presentation was calculated. All patients had Leipzig score ≥ 4; the diagnostic cut off level for WD.

Both groups answered the validated Arabic translation (*6*) of the World Health Organization Quality of Life- BREF (WHOQOL BREF) questionnaire (*7*)**.** The WHOQOL-BREF Questionnaire was downloaded and permission to use it was received online through The World Health Organization Quality of Life (*8*). The questionnaire comprised 26 questions evaluating four primary domains relevant to judge HRQoL. However, one item about the appreciation of sexual life was excluded owing to the young age of the patients in the study group. The assessed domains covered: 1) Physical health: assessed the capacity to conduct daily living activity with enough energy, ability to learn, sleep satisfaction, interference of physical pain, and medical treatment with daily life. 2) Psychological health: assessed the ability to accept body appearance, to concentrate and to enjoy life, how much the patient was satisfied with him/herself, and how often the patient had negative feelings, anxiety, or depression. 3) Social relationships: assessed the satisfaction with interpersonal relationships and the support derived from them. 4) Environmental domain: assessed the satisfaction with the safety of the physical environment and the patient's residence, satisfaction with transportation and accessibility to healthcare services, opportunity of leisure activities, and the accessibility of essential information in the patient's daily-to-day life.

Each score of the four domains represented an individual's perception of HRQoL within that specific domain. Scores were scaled positively. Higher scores indicated better QoL. Scores were calculated using the standard procedure outlined in the WHOQOL Brief manual (*9*)**.** Items were related on a 5-point Likert scale and the raw scores obtained were transformed twice. The first converts raw scores to range between 4-20, and the second converts domain scores to a 0-100 scale for ease of interpretation and comparison with the WHOQoL-100 according to instructions given in the user's manual.

The studied group with WD answered the chronic liver disease questionnaire CLDQ (Annex 4) that was prepared in slang Arabic language. It included 29 items covering 6 domains: abdominal symptoms, fatigue, systemic symptoms, activity, emotional functioning, and worry (*10*)**.** Items of each domain were modified to be measured on a Likert scale of 5-points instead of 7-points involved in the original questionnaire, with the purpose of adapting to the young age of the studied patients. The CLDQ scores ranged from the 1 (worst) to the 5 (best). Patients and controls were socially classified according to the family income and parental education.
Socioeconomic status of the patients was classified according to the Socioeconomic Status Composite Scale (SES-CS), for low and middle-income countries as Egypt (*11*). This scale

integrates multiple dimensions of the socioeconomic status including parental income, education, and occupation. Socioeconomic status was classified into three levels: i) low social level are families whose per capita daily income is below 22 Egyptian pounds, and the parents have less than secondary education, ii) moderate social level are families whose per capita daily income is between 22 and 42LE and the parents have completed secondary education, and iii) high social level are families whose per capita daily income is above 42 LE with parents possessing higher education degrees.

Patients with WD were categorized into 2 groups; a group with completely normal liver function tests and a group with deranged liver functions of any of the following: ALT > 40 IU/dl, AST > 50 IU/dl, ALP > 640 IU/dl, GGT >75 IU/dl, albumin level <3.5 mg/dl, INR >1.5.

Statistical Analysis

All gathered questionnaires were examined for completeness, and the data were coded and tabulated for analysis. A Microsoft Excel database (Microsoft corporation, United States) was created for data entry. The data was then transferred to SPSS version 21 (IBM SPSS Statistics, IBM company, United States) for analysis. Simple frequencies were used for data verification. Data normality was evaluated using the Kolmogorov-Simonov; descriptive statistics, including the arithmetic mean and standard deviation (SD) to summarize quantitative normally distributed data, while the median and interquartile range (IQR) were used for non-normally distributed data. Frequency and percentage were used for analyzing the qualitative data. The Chi-square test was employed to compare qualitative data. The independent T-test was utilized to compare means across groups. A p value below 0.05 was deemed significant.

Results

Of the enrolled 30 WD patients; 16 were males (53.3%). Their age range was between 8 to 18 years with a mean ± SD of 14.07 ± 3.36 years. At the time of the initial presentation to The Pediatric Hepatology Unit, 18 (60%) patients were symptomatic (among them 3 patients had neurological symptoms as well) and 12 (40%) were asymptomatic. Healthy controls were age, sex matched and with no difference as regards socioeconomic level (p=0.96), (p= 1.0) and (p=0.6) respectively. The mean age ± SD of WD presentation was 8.3 ± 3.1 years; the median (IQR) duration of disease (from presentation to time of enrollment to the study) was 5.5 years (range= 1 and 10 years). Figure 1 illustrates the presenting symptoms of WD cases; the 12 (40%) asymptomatic cases were diagnosed either during family screening of an affected sibling or diagnosed due to accidentally discovered elevated liver enzymes. Neurological involvement was present in 3 (10%) patients in the form of speech difficulty, abnormal movements, bulbar manifestations, and seizures (they were able to comprehend the questionnaire by the assistance of their parents). Seven (23.3%) patients had a history of previous hospital admission because of hematemesis. The median (IQR) of school absence days per month was 1.5 (3) days ranging from 1-5 days. Seventeen (57%) patients had complications of CLD in the form of bleeding tendency in 13 (43%) and ascites 8 (27%).

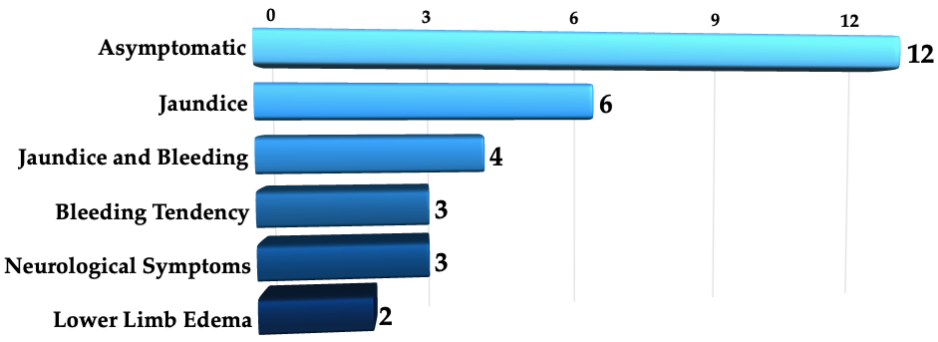

Figure 1. Presenting symptoms of children with WD.
The pre-symptomatic cases were accidently discovered or during family screening, 3(10%) had bleeding whether hematemesis and melena or from puncture sites, 3(10%) had neurological manifestations in the form of speech difficulty, abnormal movements, bulbar manifestations, and seizures.

Clinical examinations of cases revealed that two (6.7%) of the patients had short stature with height <3rd percentile and one obese patient had body weight >97th percentile. Two (6.6%) cases were jaundiced, 27 (90%) patients had hepatomegaly (only 3 (10%) patients from the asymptomatic group did not have any organomegaly) and 9 (30%) had splenomegaly. Two patients had lower limb oedema and none of the patients had ascites. Their Leipzig scores (5, 12) at the time of presentation ranged from 4–6 with a mean of 4.8 ± 1.1. All patients had Leipzig score ≥ 4; the diagnostic cut off level for WD. At enrollment, all patients abstained from diet containing high copper, all were on D-penicillamine (20 mg/kg/day) and zinc salts 75 mg/day. Twenty-one (70%) patients were compliant to therapy. At the time of study enrollment, liver function tests were within normal ranges in 15 (50%) patients, while the other 15 (50%) patients had deranged liver functions (all 15 patients had elevated transaminases, and 6 patients had synthetic dysfunction in addition). Nine (60%) patients out of the 15 with deranged liver functions were not compliant to chelation therapy.

The children with WD had lower scores in all domains of the WHO QoL questionnaire compared to normal controls, yet only the perception of compromised QoL physical domain was significant (p=0.029). (Table 1). Although males with WD had lower social and environmental domains scores and females with WD had lower scores in the physical domain, the differences were not statistically significant (Table 1). Disease duration did not have an effect on the different WHOQoL domains (physical P=0.2, psychological P=0.17, social P=0.85, environmental P=0.11). Furthermore, patients with a history of CLD complications as bleeding tendency and ascites had lower physical scores than those without complications (p=0.029). WHOQoL score of patients with normal liver functions was comparable to those with deranged liver functions (Table 2).

Table 1. WHO QoL domains of cases and controls

Domain	Control (n=30)	Cases (n = 30)	P value	Cases Mean± SD		P value
	Mean ± SD	Mean ± SD		Males	Females	
Physical	97.2 ± 3.7	54.3 ± 14.2	0.029	54.8 ±16.8	53.7 ±11.3	0.838
Psychological	57.5 ± 7.6	33.4 ± 9.9	0.129	33.2 ±10.7	33.6 ±9.4	0.917
Social	83.5 ± 9	58 ± 17	0.382	57 ±18.5	59.2 ±16.4	0.725
Environmental	52.3 ± 5.8	40.3± 11.2	0.382	37.1±10.3	43.8 ±11.4	0.105

Maximum WHO QOL score is 100.

Table 2. Comparison between patients with normal and deranged liver functions in relation to different WHO QoL domains

Domains	Patients with normal LFT (n = 15) Mean ± SD	Patients with deranged LFT (n = 15) Mean ± SD	P value
Physical	50 ±15	58.5 ± 11.4	0.105
Psychological	30 ± 9.8	36.8 ± 9.1	0.058
Social	57.8 ± 19.4	58.2 ± 15.6	0.951
Environmental	39.7 ± 11.1	40.8 ± 11.6	0.787

LFT: liver function tests; bilirubin (N< 1.3 mg/dl), ALT (N< 40 IU/dl), AST (N< 50 IU/dl), ALP (N< 640 IU/dl), GGT (N<75 IU/dl), albumin level (N >3.5 mg/dl), INR (N=1).

Table 3. Comparison between low and moderate social levels of cases in relation to WHOQoL domains

Domain	Low social level (n=18) Mean ± SD	Moderate social level (n=12) Mean ± SD	P value
Physical	53.3 ±16.3	55.7 ±10.9	0.658
Psychological	34.5 ±11.5	31.8 ±7.3	0.484
Social	53.7 ±14.5	64.5 ±19.6	0.093
Environmental	34.4 ±8.9	49 ±8.1	0.000*

WHO QOL score is 100. i) low social level are families whose per capita daily income is below 22 Egyptian pounds, and the parents have less than secondary education, ii) moderate social level are families whose per capita daily income is between 22 and 42LE and the parents have completed secondary education.

Based on the educational status of the parents as well as the family income (*11*), patients with low social level had significantly lower scores in the environmental domain of WHOQoL compared to patients with moderate social level (p =0.0001) (Table 3).

The CLDQ among patients showed mild reduction in scores of abdominal symptoms, fatigue, systemic symptoms domains, and moderate reduction in activity, emotional, and worry domains (Table 4). Female patients had significantly lower scores in worry domains rather male patients with mean ± SD 2.7 ± 3.1 versus 16.6 ± 48 for males (p= 0.017). Furthermore, patients who experienced complications of CLD including bleeding and ascites had statistically worse abdominal symptoms domain with mean ± SD 11.4 ± 2.8 when compared to those patients with no complications; 13.4 ± 1.1 (p= 0.028). There was no statistical difference regarding CLDQ domains in patients with normal and abnormal liver functions.

Table 4. Scores of children with Wilson Disease in different domains of CLDQ

Domain	Score mean ± SD	Range of score	Patients with deranged LFT (n = 15) Mean ± SD	Patient with normal LFT (n = 15) Mean ± SD	P value
Abdominal symptoms	12.2 ± 2.4	3-15	11.9±2.6	12.5±2.2	0.518
Fatigue	19.6 ± 3.5	5-25	19.1±3.3	20.2±3.7	0.418
Systemic symptoms	21.5 ± 2.6	5-25	21.3±2.9	21.8±2.3	0.633
Activity	10.8 ± 2.8	3-15	10.8±3.2	10.8±2.4	0.950
Emotional function	27.7 ± 4.3	8-40	26.5±3.9	28.9±4.4	0.131
Worry	14.8 ± 4.5	5-25	14.9±4.3	14.7±4.8	0.906

CLDQ scores are done only for cases.

Those with a disease duration of less than 5 years and those with 5 years or more had comparable results as regards the different WHOQoL domains. Yet, those with longer than 5 years disease duration had worse scores in emotional and worry domains when compared in relation to CLDQ domains (Table 4). Those with lower social level had lower scores in environmental domain compared to patients with moderate social level (P value= 0.000) (Table 5). Female patients had significantly lower scores in the worry domain of CLDQ rather male patients (p= 0.017) (Table 5). Furthermore, patients who experienced complications of CLD including bleeding and ascites had statistically worse abdominal symptoms domain when compared to patients with no complications; 13.4 ± 1.1 (p= 0.028). Patients with longer disease duration had worse scores in the emotional and worry domains of CLDQ (Table 5).

Table 5. Relation of disease duration and CLDQ domains

Domain	Sex		P value	Complications of CLD		P value	Disease duration		P value
	Males N=16	Females N=14		Yes N=17	No N=13		<5 years N=15	≥5 years N=15	
Abdominal	12.8± 1.7	11.5±2.9	0.16	11.4 ±2.8	13.4±1.1	0.028	12.2±2.6	12.2±2.3	0.95
Fatigue	20 ± 3.6	19.2 ± 3.4	0.59	18.9 ±3.8	20.6±2.9	0.20	19.7 ± 4	19.6 ± 3	0.92
Systemic	21.2± 2.5	21.2± 2.5	0.44	21 ±2.9	22.3 ±1.9	0.17	22.3±2.6	20.8±2.4	0.10
Activity	10.8± 2.6	10.8 ± 3.1	0.96	10.4 ±3.1	11.3 ±2.4	0.36	11.1±2.8	10.5±2.9	0.57
Emotional	28.8 ± 5	26.4 ± 2.9	0.12	27.5 ±5	27.9 ±3.2	0.83	29.2 ± 5	26.2±2.9	0.05
Worry	16.6 ± 48	12.7 ± 3.1	0.017	15 ±4.7	14.6 ±4.3	0.821	16.4±5.3	13.2±2.8	0.044

Abdominal symptoms domain scores ranged from 3-15, Fatigue domain score ranged from 5-25, Systemic symptoms domain score ranged from 5-25, Activity scores ranged from 3-15, Emotional functioning domain score ranged from 8-40, Worry domain score ranged from 5-25**.**

Discussion

The present study evaluated the subjective perception of HRQoL of patients with WD. It is alarming, that our study revealed a significant lower HRQoL (assessed by WHO QoL Brief Questionnaire) in children with WD as compared to healthy children in physical (54.3 ±14.2 vs 97.2 ±3.7) (p=0.000), psychological (33.4 ±9.9 vs 57.5 ± 7.6) (p=0.000), social (58 ±17 vs 83.5 ±9) (p=0.000), and environmental domains (40.3±11.2 vs 52.3 ±5.8) (p=0.000). However, our study did not find an association between duration of illness and different domains of HRQoL, in contrast to others who reported a significant correlation with the duration of treatment in relation to the physical domain (p < 0.01**)** (*13*)**.** Moreover, these attributes may be genetically predisposed as there are 1275 reported different mutations of ATP7B (*14*). Hence, the spectrum

of clinical expression of each mutation needs exploration and there might be a genetic susceptibility to perceiving quality of life as low. We did not study the effect of dietary restriction among these children, yet the strict need for dietary restriction in Wilson disease maybe another contributing factor to this dis-satisfaction among the children with Wilson disease, especially among those with disadvantaged lower socio-economic standard. This lower quality of life needs to be addressed by future enabling of these children by more environment friendly interventions, support groups, tailored competitive sports, copper free attractive foods etc. Few studies have been performed, which aimed to verify the 36-item Short Form Health Survey (SF-36) and the WHO QoL Brief Questionnaire (WHOQoL-BREF) in patients with WD. The main conclusion from these studies is that patients who experience a long delay before receiving WD treatment have poor QoL, which highlights the importance of early WD diagnosis (*12*, *15*).

There is emerging evidence that support a role of copper elevation in pathogenesis of depression (*16*). We did not assess depression among our studied cohort as it was beyond the scope of our study, yet it seems to be a venue for future research. Moreover, others have reported that up to 30% of patients with WD have deteriorated emotional status with anxiety and depression, which is greater in the neurological and mixed involvement subgroup. WD impacts patients' HRQoL, especially in the emotional domain (*17*).

The perceived dissatisfaction in our studied cohort even among those with absent CLD maybe related to the copper in WD, or related to the clinical phenotype according to genotype of WD. The pressure of life long therapy compliance are other factors that may contribute to the dissatisfaction among children with WD. Once a diagnosis of WD is established, treatment would be lifelong. Failure to adhere to lifelong therapy can lead to substantial progression of WD-associated liver disease and/or liver failure. Studies suggest that up to 45% of patients who are treated with current pharmacological therapies have poor or problematic long-term adherence; therefore, adherence should be carefully monitored in patients with WD with all forms of disease presentation (*18*). In our study, about one third of the patients were not compliant on therapy and had elevated transaminases. One of our study limitations is the relation of HRQoL to the compliance of children with Wilson disease to copper chelating drugs and management. We did not have an objective method to assess compliance and it was out of scope of this study.

The poor psychologic domain among children with WD, needs to studied prospectively. There is a gap of knowledge especially that almost all patients are expected to exhibit psychiatric manifestations during the course of illness (*19*). We did not study the burden of this poor HRQoL on the family and care givers for the patient with WD.

It is not clear why the females worried significantly more, it may be related to other confounders and small sample size as this was not reported in another bigger sample sized study.

One of our study limitations is the relatively small sample size that may affect the ability to detect more statistically significant differences either between WD patients and healthy controls or within cases themselves. We did not validate objectively the impaired quality of life as this was not part of the scope of this study. Future studies are needed to assess the implication of neuropsychiatric disease, growth parameters, adherence to treatment, presence of complications of liver disease on HRQOL and CLDQ and interventions to improve the HRQOL. Despite these limitations, this study provides important information regarding HRQoL in children with WD and its findings highlight areas for providers to focus clinical attention, assessment, and intervention when dealing with this specific group of patients. It also highlights the need of WD patients for supportive family members and age-mated colleagues' interaction. Further studies are needed to investigate the effect of family support on adherence to therapy as well as improving their social life quality (*20*).

Conclusion

Children with WD complicated by CLD have significantly compromised HRQoL, compared to their healthy peers. Females with WD have worry concerns that need to be addressed. The emotional domain of HRQoL was more affected with longer duration of WD disease. Targeted efforts to improve the perception of quality of life should be part of the lifelong intervention in WD.

Author Contributions

All authors shared in the study and drafting. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study.

References

1. A. Członkowska, T. Litwin, P. Dusek, P. Ferenci, S. Lutsenko, V. Medici, J. K. Rybakowski, K. H. Weiss, M. L. Schilsky, Wilson disease. *Nat Rev Dis Primers* **4**, 21 (2018).
2. A. Nagral, M. S. Sarma, J. Matthai, P. L. Kukkle, H. Devarbhavi, S. Sinha, S. Alam, A. Bavdekar, R. K. Dhiman, C. E. Eapen, V. Goyal, N. Mohan, R. M. Kandadai, M. Sathiyasekaran, U. Poddar, A. Sibal, S. Sankaranarayanan, A. Srivastava, B. R. Thapa, P. M. Wadia, S. K. Yachha, A. Dhawan, Corrigendum to "Wilson's Disease: Clinical Practice Guidelines of the Indian National Association for the Study of Liver (INASL), The Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition (ISPGHAN) and the Movement Disorders Society of India (MDSI)" [J Clin Exp Hepatol 9 (2019) 74–98]. *Journal of Clinical and Experimental Hepatology* **10**, 99 (2020).
3. M. Van Der Have, K. S. Van Der Aalst, A. A. Kaptein, M. Leenders, P. D. Siersema, B. Oldenburg, H. H. Fidder, Determinants of health-related quality of life in Crohn's disease: A systematic review and meta-analysis. *Journal of Crohn's and Colitis* **8**, 93–106 (2014).
4. M. Schaefer, D. N. Gotthardt, N. Ganion, S. Wohnsland, J. Seessle, W. Stremmel, J. Pfeiffenberger, K. H. Weiss, Wilson disease: Health-related quality of life and risk for depression. *Clinics and Research in Hepatology and Gastroenterology* **40**, 349–356 (2016).
5. N. Basan, M. Sheikh Hassan, Z. Gökhan, S. Nur Alper, S. Yaşar, T. Gür, A. Köksal, Usefulness of the Leipzig Score in the Diagnosis of Wilson's Disease - A Diagnostically Challenging Case Report. *IMCRJ* **Volume 17**, 819–822 (2024).
6. Abu Hashima F, Seoud IA, El Lawindi MI, and Abdelhai RA., "Quality of life and health needs for children with some chronic diseases. M.D. thesis of public health," thesis, Faculty of Medicine, Cairo University, Egypt (2004).
7. A. E. Bonomi, D. L. Patrick, D. M. Bushnell, M. Martin, Validation of the United States' version of the World Health Organization Quality of Life (WHOQOL) instrument. *Journal of Clinical Epidemiology* **53**, 1–12 (2000).
8. World Health Organization, WHOQOL: Measuring Quality of Life: Arabic_WHOQOL-BREF (2020). https://www.who.int/tools/whoqol/whoqol-bref.
9. WHOQOL: Measuring Quality of Life. Introducing the instruments (2012). https://www.who.int/tools/whoqol.
10. Z. M. Younossi, G. Guyatt, M. Kiwi, N. Boparai, D. King, Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut* **45**, 295–300 (1999).
11. H. Sacre, C. Haddad, A. Hajj, R. M. Zeenny, M. Akel, P. Salameh, Development and validation of the Socioeconomic Status Composite Scale (SES-C). *BMC Public Health* **23**, 1619 (2023).
12. P. Ferenci, K. Caca, G. Loudianos, G. Mieli-Vergani, S. Tanner, I. Sternlieb, M. Schilsky, D. Cox, F. Berr, Diagnosis and phenotypic classification of Wilson disease[1]. *Liver International* **23**, 139–142 (2003).
13. R. Komal Kumar, A. Taly, K. P. S. Nair, S. Sinha, L. Prashanth, N. Vidya, G. Arunodaya, S. Rao, Quality of life in Wilson′s disease. *Ann Indian Acad Neurol* **11**, 37 (2008).
14. Z. Beyzaei, A. Mehrzadeh, N. Hashemi, B. Geramizadeh, The mutation spectrum and ethnic distribution of Wilson disease, a review. *Molecular Genetics and Metabolism Reports* **38**, 101034 (2024).
15. World Health Organisation, WHO Quality of Life-BREF (WHOQOL-BREF), *World Health Organisation* (2016). https://doi.org/120-900-750.
16. J. Chen, W. Song, W. Zhang, The emerging role of copper in depression. *Front. Neurosci.* **17**, 1230404 (2023).
17. Z. Mariño, M. Berenguer, L. Peña-Quintana, A. Olveira, A. Miralpeix, I. Sastre, A. Reyes-Domínguez, P. Castillo, C. García-Solà, A. Bono, M. Romero, F. J. Pérez-Sádaba, S. Aceituno, A. Anguera, Health-Related Quality of Life in Patients Living with Wilson Disease in Spain: A Cross-Sectional Observational Study. *JCM* **12**, 4823 (2023).
18. K. Dzieżyc, T. Litwin, G. Chabik, K. Gramza, A. Członkowska, Families with Wilson's disease in subsequent generations: Clinical and genetic analysis. *Movement Disorders* **29**, 1828–1832 (2014).

19. T. Litwin, P. Dusek, T. Szafrański, K. Dzieżyc, A. Członkowska, J. K. Rybakowski, Psychiatric manifestations in Wilson's disease: possibilities and difficulties for treatment. *Therapeutic Advances in Psychopharmacology* **8**, 199–211 (2018).
20. O. Unavane, K. Tiwari, A. Nagral, R. Aggarwal, N. Garg, N. Nagral, B. Verma, A. Jhaveri, M. S. Setia, Quality of Life of Patients with Wilson's Disease and Their Families. *Journal of Clinical and Experimental Hepatology* **12**, 461–466 (2022).