Oral health conditions in Wilson's disease patients: A clinical diagnostic study

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Abstract

Aim The aims of this study were: To evaluate oral health conditions, oral health behaviours and eating habits in Wilson's disease (WD) patients; to assess the possible relationship between oral health status and long-term pharmacological therapies undertaken.

Methods Sixty WD patients were selected and their data were compared to those of an age-matched control group of 62 subjects. Clinical examinations were carried out and a questionnaire on oral health behaviours and eating habits was submitted to both groups. WD patients were interviewed on long-term pharmacological therapies undertaken. Statistical analysis was performed.

Results The mean DMFT value was 3.75±4.65 in the WD group and 2.81±4.65 in the control group. The difference in the mean DMFT value between the two groups was not statistically significant. Modified Dental Enamel Defects (DDE) Index showed significantly higher values in WD group than in control group. No statistical differences in Visible Plaque Index (VPI), Gingival Bleeding Index (GBI) and malocclusions were observed between groups. In relation to the questionnaire, the differences between groups were statistically significant for: dental visits in a year; brushing teeth after a snack; drinking soft beverages; using mouthwash. For WD patients no statistical correlation between oral health status and long-term pharmacological therapies undertaken was observed.

Conclusion WD patients did not show worse oral health conditions than the control group, despite worse oral health behaviours and eating habits. Nerveless, WD patients showed higher presence of dental enamel defects. Finally, for WD group oral health status was not correlated to the long-term pharmacological therapies.

KEYWORDS Wilson's disease, Oral health status, Modified Dental Enamel Defects (DDE).

Introduction

Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism. It is caused by mutations in the ATP7B gene encoding a copper transporting P-type ATPase, required for copper excretion into the bile [Bandmann et al., 2015]. This defect induces the accumulation of the copper primarily in the liver and then in other organs, especially nervous system and corneas. The world incidence of WD is approximately 1:55,000 [Saba et al., 2019].

Wilson's disease is characterised by a clinical heterogeneity that often causes a delay or even a failure to diagnose. Usually, the average age of onset for disease manifestations is 12 years. The main clinical manifestations are hepatic signs and symptoms, like abdominal distention and pain, hepatomegaly, transaminase elevation [Iorio et al., 2003]. Wilson's disease, if not recognised or not properly treated, can determine hepatic steatosis, acute liver failure with haemolysis, acute hepatitis, possible evolution of the latter in liver cirrhosis, with the need for liver transplant [Ahmad et al., 2017]. Other manifestations include: neurological and psychiatric symptoms; mild cognitive impairment; presence of the Kayser-Fleischer ring, due to copper deposition on Descemet's membrane of the cornea; sleep disorders; change of mood and behaviour; changes of renal function and cardiac, endocrine, pancreatic and skeletal alterations [Cochen De Cock et al., 2018; Favre et al., 2017; Litwin et al., 2018; Lukas et al., 2019]. Other neurological manifestations may be disorders of movement (dysgraphia, dysphagia, dysarthria), postural tremors and ataxia, up to parkinsonian-type manifestations with hypokinesia, rigidity and tremors at rest [Raveh et al., 2018].

There is not a single laboratory test for a certain diagnosis of WD [Woimand et al., 2019]. An early diagnosis is obtained through the evaluation of: presence of Keyser-Fleischer ring, typical neurological symptoms, concentration of ceruloplasmin < 20 mg/dl [Mak et al., 2008]. In the absence of the Keiser-Fleischer ring and with normal levels of ceruloplasmin, the diagnosis is based on the evaluation of laboratory indices related to copper metabolism: cupremia <60 µg/dl, high copper excretion > 70 µg/24 hours, and liver copper content > 250 µg/g dry tissue in the absence of cholestasis. The confirmatory test for the positive diagnosis of Wilson's disease is represented by the quantitative determination of liver copper with values

> 250 µg/g dry tissue. Histological analysis of the liver alone cannot be used for diagnosis [Yang et al., 2015]. In addition, in patients where diagnosis is difficult to establish on the basis of conventional clinical and biochemical parameters, and in family members of Wilson's disease patients, it is possible to perform molecular analysis to search for known mutations of the ATP7B gene [Li et al., 2019]. Finally, in the diagnostic process, brain magnetic resonance imaging (MRI) can play an important role, showing SNC abnormalities, due to copper deposition [Alkhalik Basha et al., 2019].

Specific treatment should begin upon diagnosis in asymptomatic children, identified by family screening as soon as 2 to 3 years of age, and in symptomatic children to avoid progression of liver and/or neurological manifestations [Socha et al., 2018]. The therapy consists of a long-term treatment with copper chelators, like D-penicillamine and trientine, or with zinc salts, like zinc sulfate and zinc acetate, which inhibit intestinal copper absorption. Elimination from the diet of copper-rich foods is advised until remission of symptoms and biochemical abnormalities [Roberts and Schilsky, 2008]. D-penicillamine, which remains standard therapy, is a copper chelator and permits its excretion via the urinary tract; it has been demonstrated to avoid the disease progression in asymptomatic children [Kalita et al., 2014]. Significant adverse effects are reported with the use of D-penicillamine. Early adverse effects include: sensitivity reactions, characterised by fever and cutaneous eruptions, neutropenia or thrombocytopenia, lymphadenopathy, and proteinuria. Other medium and long-term adverse effects include: development of immune mediated disease, a lupus-like syndrome, characterised by haematuria, proteinuria, arthralgia, bone marrow toxicity with severe thrombocytopenia or aplasia; skin changes, related to D-penicillamine's anticollagen effects, such as elastosis perforans serpiginosa, cutis laxa, pemphigus, lichen planus, and aphthous stomatitis [Chang et al., 2013; Ranucci et al., 2017]. Trientina (triethylenetetramine), the other chelating agent, was used as an alternative therapy in patients who presented adverse events after taking D-penicillamine [Taylor et al., 2009]. Finally, zinc salts are being increasingly used as first-line therapy for the treatment of pre-symptomatic patients and for maintenance therapy after initial de-coppering with a chelator in symptomatic patients [Chang et al., 2013]. Zinc salts are better tolerated than D-penicillamine and result in a faster normalisation of transaminases than D-penicillamine. There are different formulations of zinc salts: zinc sulphate, less tolerated, and the most used, zinc acetate. Combination therapy, in which zinc is administered together with the chelating agent, allows to block the absorption of copper and to promote the excretion of excess copper [Appenzeller-Herzog et al., 2019].

Unfortunately, scientific literature on oral health conditions in patient affected by WD is poor. Two studies have investigated the dento-maxillofacial structures both in children and in adults with WD [Kılıç et al. 2013; Zang et al., 2019]. Two case reports described dental treatments performed on a total of 4 WD patients [Ozturk et al. 2015; Pandyan et al., 2019]. One review summarised the clinical aspects of Wilson's disease and their impact on dental management [Lohe et al., 2011].

Therefore, in order to compensate the lack of knowledge, the aims of this study were: to evaluate oral health conditions, oral health behaviours and eating habits in Wilson's disease patients; to assess the possible relationship between oral health status and long-term pharmacological therapies undertaken.

Materials and Methods

This clinical diagnostic study was conducted by the Department of Neuroscience, Reproductive and Oral Sciences, Section of Pediatric Dentistry, in association with the Department of Translational Medical Sciences, Section of Paediatrics and Section of Internal Medicine, University of Naples Federico II, Italy.

The study was carried out from December 2018 to June 2019. The research protocol and related documents of this study, such as questionnaires and consent forms, were reviewed and approved by the ethical committee of the University of Naples Federico II, Italy (PT n. 346/18). Sixty WD patients (Wilson's disease group) were recruited from the Department of Translational Medical Sciences, Section of Pediatrics and Section of Internal Medicine, University of Naples Federico II, Italy, and their data were compared to those of an age-matched control group of 62 volunteers, randomly selected from schools of the Regional Campanian district, if under the age of 18, or from the Federico II University, Naples, Italy, if over the age of 18. The ethical principles stated in the World Medical Association Declaration of Helsinki were followed in this study. Subjects participating in the study and/or parents and caregivers, if subjects were under the age of 18, were informed about the protocol and the aim of the study and they gave their written informed consent.

Inclusion criteria for Wilson's disease (WD) group required: patients affected by Wilson's Disease; male and female subjects; age between 14 and 30 years. Exclusion criteria for WD group required: patients not suffering from Wilson's disease; age under 14 and over 30 years; patients undergoing orthodontic treatment; patients having daily smoking habit. Inclusion criteria for the control group required: age between 14 and 30 years; male and female subjects; healthy subjects. Exclusion criteria for the control group required: subjects with a systemic disease; age under 14 and over 30 years; subjects undergoing orthodontic treatment; subjects having daily smoking habit.

Clinical examinations were carried out by two calibrated dentists at the Department of Neuroscience, Reproductive and Oral Sciences, Section of Paediatric Dentistry, University of Naples Federico II, Italy, in compliance with the standard dental examination procedures (appropriate lighting and the use of buccal mirror and explorer). Prior to the examination, a calibration exercise was conducted between the examiners on a group of 30 patients, apart from the main study. The inter- and intra-examiner concordances assessed with Cohen's kappa coefficient were all above 0.75. The presence of dental caries was assessed using the DMFT index: number of decayed, missing, and filled teeth/tooth surfaces for permanent dentition. Developmental enamel defects were recorded using the modified DDE (Defects of Dental Enamel) index, assessing the different type of defect: demarcated opacities white/cream, demarcated opacities yellow/brown, diffuse lines opacities, diffuse patchy opacities, diffuse confluent opacities, diffuse confluent/patchy opacities with hypoplasia missing enamel, hypoplasia pits, hypoplasia missing enamel, any other defects.

Visible Plaque Index (VPI), a dichotomous index indicating the presence or absence of visible plaque, and Gingival Bleeding Index (GBI), a dichotomous index indicating the presence or absence of gingival bleeding following probing of the marginal gingiva, were also recorded on permanent maxillary and mandibular first molars and central incisors. The malocclusion was assessed through Angle classes: Class I, in which the mandibular first molar occludes mesially to the maxillary first

	WD group					Control group				
	N	Minimum	Maximum	Average	Standard deviation	N	Minimum	Maximum	Average	Standard deviation
DMFT	60	0	22	3.75	4.65	62	0	14	2.81	3.65
DECAYED	60	0	8	0.98	1.62	62	0	4	0.45	1.01
MISSING	60	0	9	0.90	1.75	62	0	7	0.80	1.62
FILLED	60	0	16	1.85	3.04	62	0	14	1.65	1.68

TABLE 1 DMFT distribution in WD group and Control group.

molar, with the mesiobuccal cusp of maxillary first molar occluding in the buccal groove of mandibular first molar; Class II, in which the mesiobuccal cusp of the maxillary first molar occludes anterior to the buccal groove of the mandibular first molar; Class III, in which the mesiobuccal cusp of the maxillary first molar occludes posterior to the buccal groove of the mandibular first molar.

All subject participating in the study filled in a questionnaire about oral health behaviours and eating habits. In particular, each subject was asked: if he/she has ever gone to the dentist and why; how many times a year; how many times a day he/she eats sweet foods, washes his/her teeth; if he/she brushes his/her teeth after the main meals and after a snack; if he/she drinks soft beverages; how he/she evaluates his/her oral hygiene; if he/she uses mouthwash and dental floss in daily routine oral hygiene. WD patients were then interviewed on long-term pharmacological therapies undertaken: type of drugs (D-penicillamine, zinc sulphate and zinc acetate) were recorded and analysed in relation to DMFT index, modified DDE index, VPI, GBI.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, using one-way analysis of variance (T-student) and Chi-square. For all statistical tests, a confidence interval of 95% and significance level of 5% ($p < 0.05$) were adopted.

Results

Clinical evaluation

The analysed sample consisted of 122 subjects: 60 were affected by Wilson's disease (WD group) (34 males and 26 females) with an average age of 21.7 years, and 62 were healthy volunteers (control group) (26 males and 36 females) with an average age of 21.5 years. The results showed that the mean DMFT value was 3.75 (DS±4.65) in the WD group, and 2.81 (DS±3.65) in the control group. Table 1 also showed the distribution of the DMFT components for both groups: decayed, missing and filled teeth. The difference in the mean DMFT between the two groups was not statistically significant (Table 2).

Dental enamel defects, assessed through the modified Dental Enamel Defects (DDE) index, were present in 38.3% of the WD group and in 21% of the control group, respectively. Statistical analysis showed significantly higher values in WD group than in control group (p=0.028) (Table 2). In particular, the distribution of the different types of dental enamel defects for both groups was summarised in Figure 1.

Visible plaque, assessed through the VPI, was present in 33.3% of the WD group and in 40% of the control group. Gingival bleeding, assessed through the GBI, was presented in 63.3% of the WD group and in 60 % of the control group. There were no statistically significant differences between the two groups in relation to VPI and GBI, respectively (Table 2). Regarding the type of malocclusion, in the WD group, 67.8% presented Class I, 31.7% presented Class II, and 1.7% presented Class III; in the control group, 68.5% showed Class I, 29.5% showed Class II and 2% showed Class III. There was no statistically significant difference between the two groups in relation to the type of malocclusion (Table 2).

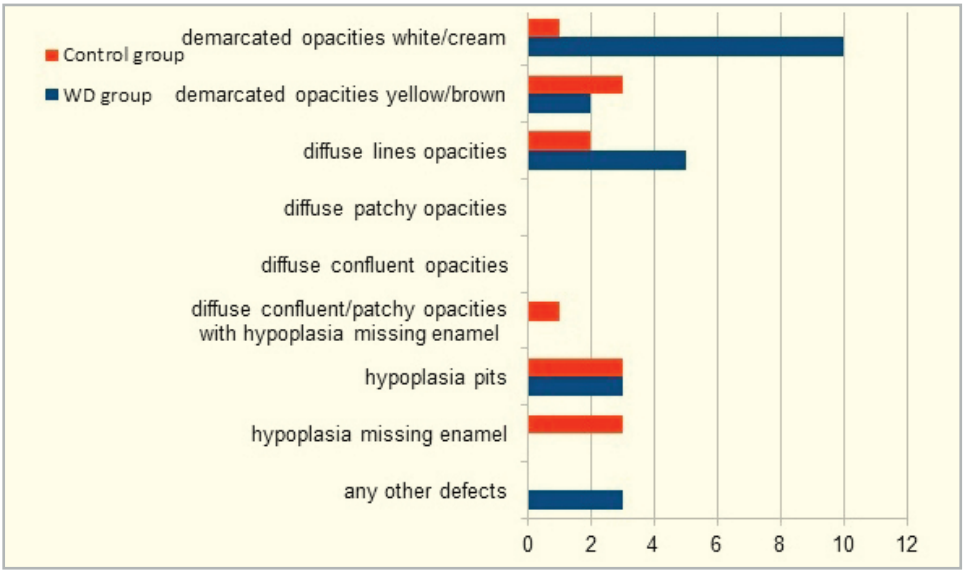

FIG. 1 Distribution of different types of DDE in WD group and Control group.

Variables	WD group	Control group	P-value
DMFT	3.75 with DS±4.65	2.81 with DS±3.65	ns
Modified DDE index	23	13	0.028*
VPI Yes No	 20 40	 25 37	ns
GBI Yes No	 38 22	 37 25	ns
Malocclusion I class II class III class	 40 19 1	 42 19 1	 ns ns ns

*** p<0.01 Strong statistical significance *p<0.05 Statistical significance ns: not significant*

TABLE 2 Statistical significance of DMFT between groups, evaluated by T-student test, and statistical significance of modified DDE index, VPI, GBI and malocclusion between groups, evaluated by $\chi 2$ test, respectively.

Questionnaire

In relation to the following answers on oral health behaviours and eating habits the differences between the two groups were statistically significant for: dental visits in a year (p=0.003); brushing teeth after a snack (p=0.04); drinking soft beverages (p=0.008); using mouthwash in daily routine oral hygiene (p=0.04) (Table 3).

In relation to the following answers on oral health behaviours and eating habits the differences between the two groups were not statistically significant for: ever going to the dentist and why; eating sweet foods; daily tooth-brushing frequency; washing teeth after the main meals; rating individual oral hygiene; using dental floss in daily routine oral hygiene (Table 3).

Long-term pharmacological therapies

In relation to long-term pharmacological therapies undertaken by WD group, results showed that D-penicillamine was administered to 56.7% of patients, zinc sulphate to 30%, zinc acetate to 91.7% during their life. The 65% of patients changed drug during the course of therapy; in particular, 79.2% interrupted D-penicillamine to start a zinc-based therapy (in most cases Zinc acetate); instead 20.8% of patients switched zinc therapy with D-penicillamine. Of the whole group, 35% never changed pharmacological therapy.

There was no statistical correlation between DMFT index and D-penicillamine, zinc sulphate and zinc acetate assumption, respectively (Table 4).

There was no statistical correlation between modified DDE index and D-penicillamine, zinc sulphate and zinc acetate assumption, respectively (Table 5).

There was no statistical correlation between VPI and D-penicillamine, zinc sulphate and zinc acetate assumption, respectively (Table 6).

There was no statistical correlation between GBI and D-penicillamine, zinc sulphate and zinc acetate assumption, respectively (Table 7).

Questionnaire	WD group	Control group	P-value
Have you ever been to the dentist? - for a check-up dental visit - for dental extraction - for dental restorative treatment - for orthodontic treatment	55 36 23 26 12	58 47 13 28 10	ns
How many times a year do you go to the dentist? - none - once - twice or more	 20 24 16	 5 34 23	0.003**
How many times a day do you eat sweet food? - none - once - twice - three times or more	 8 30 15 7	 7 28 21 6	ns
How many times a day do you brush your teeth? - none - once - twice - three times or more	 1 9 36 14	 1 7 30 24	ns
Do you brush your teeth after the main meals? - yes - no	 22 38	 32 30	ns
Do you brush your teeth after a snack? - never - sometimes - always	 25 31 4	 13 45 4	0.04*
Do you drink soft beverages during the day? - never - once - twice - three times or more	 11 36 10 3	 27 19 11 5	0.008**
How do you rate your oral hygiene? - good - bad - sufficient	 11 44 5	 21 33 8	ns
Do you use dental floss in daily routine oral hygiene? - yes - no	 8 52	 13 49	ns
Do you use mouthwash in daily routine oral hygiene? - yes - no	 21 39	 33 29	0.04*

*** p<0.01 Strong statistical significance*
**p<0.05 Statistical significance*
ns: not significant

TABLE 3 Statistical significance in relation to the questionnaire on oral health behaviours and eating habits between the two groups ($\chi 2$ test).

Discussion

Wilson's disease is a very rare and inherited autosomal recessive disease of copper metabolism [Pandyan et al., 2019].

The present study analysed oral conditions in a group of WD patients, their oral health behaviour and oral hygiene habit, compared to a control group, and investigated the possible relationship between long term pharmacological therapies undertaken and oral health status.

In relation to the DMFT index, the difference between the

Pharmacological therapy	WD patients	DMFT	P-value
D-penicillamine - Yes - No	 34 26	 4.03 (DS±4.7) 3.38 (DS±4.65)	 ns
Zinc sulphate - Yes - No	 18 42	 4.11 (DS±5.48) 3.60 (DS±4.31)	 ns
Zinc acetate - Yes - No	 55 5	 3.49 (DS±4.52) 6.60 (DS±5.68)	 ns

*** p<0.01 Strong statistical significance *p<0.05 Statistical significance ns: not significant*

TABLE 4 Statistical correlation between DMFT and D-penicillamine, zinc sulphate and zinc acetate assumption, respectively in WD group (T-student).

Pharmacological therapy	Presence of DDE	Absence of DDE	P-value
D-penicillamine - Yes - No	 11 12	 23 14	 ns
Zinc sulphate - Yes - No	 7 16	 11 26	 ns
Zinc acetate - Yes - No	 22 1	 33 4	 ns

*** p<0.01 Strong statistical significance *p<0.05 Statistical significance ns: not significant*

TABLE 5 Statistical correlation between the modified DDE index and D-penicillamine, zinc sulphate and zinc acetate assumption, respectively in WD group ($\chi 2$ test).

Pharmacological therapy	Presence of VP	Absence of VP	P-value
D-penicillamine - Yes - No	 12 8	 22 18	 ns
Zinc sulphate - Yes - No	 9 11	 9 31	 ns
Zinc acetate - Yes - No	 19 1	 36 4	 ns

*** p<0.01 Strong statistical significance *p<0.05 Statistical significance ns: not significant*

TABLE 6 Statistical correlation between VPI and D-penicillamine, zinc sulphate and zinc acetate assumption, respectively in WD group ($\chi 2$ test).

Pharmacological therapy	Presence of GB	Absence of GB	P-value
D-penicillamine - Yes - No	 21 17	 13 9	 ns
Zinc sulphate - Yes - No	 12 26	 6 16	 ns
Zinc acetate - Yes - No	 34 4	 21 1	 ns

*** p<0.01 Strong statistical significance *p<0.05 Statistical significance ns: not significant*

TABLE 7 Statistical correlation between GBI and D-penicillamine, zinc sulphate and zinc acetate assumption, respectively in WD group ($\chi 2$ test).

two groups was not significant. This result was in contrast with the consideration obtained from the review of Pandyan et al. [2019], according to whom the risk of caries might be increased in WD patients due to the use of anti-parkinsonism drugs, reducing salivary flow.

In relation to dental enamel defects, assessed through the modified Dental Enamel Defects (DDE) index, statistical analysis showed significantly higher values in WD group than in controls.

These data were in line with another study, which showed a correlation between liver disease and dental enamel defects, sustaining the hypothesis that the presence of systemic diseases in early childhood may interfere with the correct development of hard tissues such as teeth [Ferrazzano et al., 2013]. In fact, a variety of medical conditions such as coeliac disease, cystic fibrosis, and renal disease have been studied in relation to enamel defects. Overall, it appears that the prevalence of dental enamel defects is significantly higher in medically compromised populations [Crombie et al., 2009; Ferrazzano et al., 2009]. To explain this correlation it should be remembered that dental enamel often acts as a biological marker of systemic insults received during the growth period, because the developing tooth germ is sensitive to a wide range of systemic disturbances and is unable to recover once damaged [Ferrazzano et al., 2012b]. Ameloblasts are highly susceptible to relatively minor changes in their environment: increases in temperature, variations in ion concentrations, and pH levels can disturb the normal process of amelogenesis, and that the susceptibility to environmental conditions can be influenced by genetics [Crombie et al., 2009]. Also, DDE may have a significant clinical impact on aesthetics, tooth sensitivity, tooth wear and dentofacial anomalies. Therefore, dentists should be trained to treat DDE in WD patients. Treatment options may depend on the severity of dental enamel defects and could comprise: dental restoration for anterior aesthetically compromised teeth, management of dental sensitivity through the use of desensitising agents [Ferrazzano et al., 2012b].

Periodontal health, assessed through the use of VPI and GBI index, showed no statistically significant differences between the two groups. On this matter, instead, an interesting case report evaluated copper accumulation in oral tissues in three patients with WD. After a tooth extraction, samples were taken from the tooth and surrounding gingiva. Excessive copper accumulation in gingiva and tooth of all three patients with WD was detected. According to the authors, accumulation in oral tissues can cause tendency to periodontal diseases [Ozturk et al., 2015].

In relation to the type of malocclusion, there was no statistically significant difference between the two groups. The present study was in accordance with the first study investigating craniofacial features of children with WD: it was found that patients with WD and healthy children had approximately same dento-maxillofacial structures. Increased

palatal plane inclination was different, that might be a specific finding of WD [Kılıç et al., 2013]. By contrast, another study present in the literature, analysing dento-maxillofacial structures in WD patients, found that both male and female had more craniofacial features such as maxillary protrusion and vertical mandibular growth pattern compared with controls. Protrusion of maxilla was a relatively rare deformity in a normal population. It is related to genetic component, mouth breathing, oral habits and skeletal factors. Furthermore, female patients with early onset age of neurological symptoms were more inclined to have vertical mandible growth and mandibular retrusion compared with controls [Zang et al., 2019].

To understand if distinct craniofacial features can be associated to WD, further investigations with a large sample size should be performed. In relation to the questionnaire on oral health behaviours and eating habits, WD group showed worse oral health behaviours and eating habits than the control group. In fact, WD patients tended to go to the dentist once a year, to wash their teeth after a snack and to use mouthwash less frequently than control subject. Instead, they tend to drink soft beverages more frequently during the day with respect to control subjects. In this context, improving oral health behaviour and eating habits can help to prevent oral disease development; above all, soft drinks consumption should be avoided, because it was strongly associated with erosive tooth wear [Ferrazzano et al., 2012a]. Furthermore, in WD patients the life- long pharmacological therapies seemed to not influence oral health status, assessed through DMFT index, modified DDE index, VPI and GBI.

The medical and dental literature shows extensive scientific evidence that a range of drugs have the potential to induce changes in teeth, leading to tooth discolouration (intrinsic and extrinsic), physical damage to tooth structure (enamel, dentin, and cementum), and alteration in tooth sensitivity [Tredwin et al., 2005]. Regarding D-penicillamine, zinc sulphate and zinc acetate, this is the first study in literature aimed to analyse this correlation.

Conclusion

WD patients did not show a worse oral health condition than controls, despite worse oral health behaviours and eating habits. Nerveless, WD patients showed higher presence of dental enamel defects. Finally, for WD group oral health status was not correlated to the long-term pharmacological therapies. Dentists can establish prevention-based care from a young age, as soon as diagnosis is made, to avoid any oral disease development. Also, it is important that dentists be aware of the physiopathology of WD in order to plan a dental treatment that suits the patient's conditions.

References

- Ahmad A, Torrazza-Perez E, Schilsky ML. Liver transplantation for Wilson disease. Handb Clin Neurol 2017;142:193-204.
- Alkhalik Basha MA, Refaat R, Ahmed AF, Yousef HY, Alsowey AM, Metwally MI, Aly SA, Hussien HM, El-Saadany HF, AlGhobashy AA, Talat MA, Amer MM, Eid AM. Brain magnetic resonance spectroscopy (MRS) as a diagnostic tool for detecting early neurological changes in children with Wilson's disease. Eur J Radiol 2019;111:41-46.
- Appenzeller-Herzog C, Mathes T, Heeres MLS, Weiss KH, Houwen RHJ, Ewald H. Comparative effectiveness of common therapies for Wilson disease: A Systematic review and meta-analysis of controlled studies. Liver Int 2019;39:2136-2152.
- Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. Lancet Neurol 2015;14:103–13.
- Chang H, Xu A, Chen Z, Zhang Y, Tian F, Li T. Long-term effects of a combination of D-penicillamine and zinc salts in the treatment of Wilson's disease in children. Exp Ther Med 2013;5:1129-1132.
- Cochen De Cock V, Girardot-Tinant N, Woimant F, Poujois A. Sleep Abnormalities in Wilson's Disease. Curr Treat Options Neurol 2018;20:46.
- Crombie F, Manton D, Kilpatrick N. Aetiology of molar-incisor hypomineralization: a critical review. Int J Paediatr Dent 2009;19:73-83.
- Favre E, Lion-Francois L, Canton M, Vanlemmens C, Bonneton M, Bouillet L, Brunet AS, Lachaux A. Cognitive abilities of children with neurological and liver forms of Wilson's disease. J Pediatr Gastroenterol Nutr 2017;64:436-9.
- Ferrazzano GF, Orlando S, Sangianantoni G, Cantile T, Ingenito A. Dental and periodontal health status in children affected by cystic fibrosis in a southern Italian region. Eur J Paediatr Dent 2009;10:65-8.
- Ferrazzano GF, Coda M, Cantile T, Sangianantoni G, Ingenito A. SEM investigation on casein phosphopeptides capability in contrasting cola drinks enamel erosion: an in vitro preliminary study.
- Eur J Paediatr Dent 2012a;13:285-8.
- Ferrazzano GF, Sangianantoni G, Cantile T, Amato I, Orlando S, Ingenito A. Dental enamel defects in Italian children with cystic fibrosis: an observational study. Community Dent Health 2012b;29:106-9.
- Ferrazzano GF, Sangianantoni G, Cantile T, Iorio R, Ingenito A. Oral health status in liver transplant Italian children. Eur J Paediatr Dent 2013;14:323-7.
- Iorio R, D'ambrosi M, Mazzarella G, Varrella F, Vecchione R, Vegnente A. Early occurance of hypertransaminasemia in a 13-month-old child with Wilson disease. J Pediatr Gastroenterol Nutr 2003;36:637-8.
- Kalita J, Kumar V, Chandra S, Kumar B, Misra UK. Worsening of Wilson disease following penicillamine therapy. Eur Neurol 2014;71:126-31.
- Kilic N, Sumbullu MA, Ertekin V, Catal G, Cakur B, Oktay H, Selimoglu MA. Do children with Wilson's disease have distinct craniofacial morphology? A cephalometric study. Int J Pediatr Otorhinolaryngol 2013;77:1276-9.
- Li H, Tao R, Liu L, Shang S. Population screening and diagnostic strategies in screening family members of Wilson's disease patients. Ann Transl Med 2019;7(Suppl 2):S59.
- Litwin T, Dusek P, Szafrański T, Dzieżyc K, Członkowska A, Rybakowski JK. Psychiatric manifestations in Wilson's disease: possibilities and difficulties for treatment. Ther Adv Psychopharmacol 2018;8:199-211.
- Lohe VK, Kadu RP, Degwekar SS, Bhowate RR, Wanjari AK, Dangore SB. Dental considerations in the patient with Wilson's disease. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:20-3.
- Lukas J, Pospech J, Oppermann C, Hund C, Iwanov K, Pantoom S, Petters J, Frech M, Seemann S, Thiel FG, Modenbach JM, Bolsmann R, de Freitas Chama L, Kraatz F, El-Hage F, Gronbach M, Klein A, Müller R, Salloch S, Weiss FU, Simon P, Wagh P, Klemenz A, Krüger E, Mayerle J, Delcea M, Kragl U, Beller M, Rolfs A, Lerch MM, Sendler M. Role of endoplasmic reticulum stress and protein misfolding in disorders of the liver and pancreas. Adv Med Sci 2019;64:315-323.
- Mak CM, Lam CW, Tam S. Diagnostic accuracy of serum cerulo- plasmin in Wilson disease: determination of sensitivity and specificity by ROC curve analysis among ATP7B-genotyped subjects. Clin Chem 2008;54:1356-62.
- Ozturk M, Karacelebi E, Gungor K, Coskun S, Boysan E. Evaluation of oxidative events and copper accumulation in oral tissues of patients with Wilson's disease: three case report. Int J Clin Exp Pathol 2015;8:3943-5.
- Pandyan DA, Giri GVV, Shanthi K, Suthanraj AK, Kumar S. Copper extraction: Dental consideration for Wilson's disease - An uncommon case report. Natl J Maxillofac Surg 2019;10:235-237.
- Raveh Y, Khoury T, Lachish M, Safadi R, Kohn Y. Acute Psychosis and Movement Disorders as First Presentations of Wilson's Disease. Isr Med Assoc J 2018;20:788-789.
- Ranucci G, Di Dato F, Leone F, Vajro P, Spagnuolo MI, Iorio R. Penicillamine-induced elastosis perforans serpiginosa in Wilson's disease: is useful switching to zinc? J Pediatr Gastroenterol Nutr 2017;64:e72-3.
- Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update. Hepatology 2008;47:2089–111.
- Saba L, Tiwari A, Biswas M, Gupta SK, Godia-Cuadrado E, Chaturvedi A, Turk M, Suri HS, Orru S, Sanches JM, Carcassi C, Marinho RT, Asare CK, Khanna NN, B K M, Suri JS. Wilson's disease: A new perspective review on its genetics, diagnosis and treatment. Front Biosci (Elite Ed) 2019;11:166-185.
- Socha P, Janczyk W, Dhawan A, Baumann U, D'Antiga L, Tanner S, Iorio R, Vajro P, Houwen R, Fischler B, Dezsofi A, Hadzic N, Hierro L, Jahnel J, McLin V, Nobili V, Smets F, Verkade HJ, Debray D. Wilson's Disease in Children: A Position Paper by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2018;66:334-344.
- Taylor RM, Chen Y, Dhawan A. Triethylene tetramine dihydrochloride (trientine) in children with Wilson disease: experience at King's College Hospital and review of the literature. Eur J Pediatr 2009;168:1061-8.
- Tredwin CJ, Scully C, Bagan-Sebastian JV. Drug-induced disorders of teeth. J Dent Res 2005;84:596-602.
- Woimant F, Djebrani-Oussedik N, Poujois A. New tools for Wilson's disease diagnosis: exchangeable copper fraction. Ann Transl Med 2019;7(Suppl 2):S70.
- Yang X, Tang XP, Zhang YH, Luo KZ, Jiang YF, Luo HY, Lei JH, Wang WL, Li MM, Chen HC, Deng SL, Lai LY, Liang J, Zhang M, Tian Y, Xu Y. Prospective evaluation of the diagnostic accuracy of hepatic copper content, as determined using the entire core of a liver biopsy sample. Hepatology 2015;62:1731-41.
- Zhang Y, Yu H, Bao W, Ni W, Dong Y, Wu Z. A cephalometric study in patients with Wilson's disease. J Clin Neurosci 2019;67:105-108.