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Comparative evaluation of anterior segment optical coherence tomography and in vivo confocal microscopy for Kayser-Fleischer rings assessment in Wilson disease

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Abstract

Objective To compare the diagnostic accuracy of anterior segment optical coherence tomography (AS-OCT) and in vivo confocal microscopy (IVCM) in evaluating Kayser–Fleischer (KF) rings in patients with Wilson disease (WD).

Methods and analysis A prospective observational study enrolled 36 subjects (16 women) and 36 controls (16 women). All participants underwent both AS-OCT and IVCM, and the results were analyzed using McNemar's test to assess diagnostic concordancet.

Results KF rings were not detected either with AS-OCT or with IVCM in any of the controls. Among the WD patients, seven subjects who did not show KF rings on AS-OCT were found to have them on IVCM ($p < 0.05$), six of whom were identified diagnosed with hepatic WD.

Conclusion Both AS-OCT and IVCM can provide objective assessment of KF rings. IVCM offers better accuracy compared to AS-OCT, particularly for hepatic WD.

Keywords Kayser–Fleischer rings, Anterior segment optical coherence tomography, In vivo confocal microscopy, Ophthalmic imaging

Introduction

Wilson disease(WD) is a hepatolenticular degeneration caused by a recessive mutation of the ATP7B gene [1]. This disorder impairs hepatic copper excretion, resulting in copper accumulation in various organs such as the liver, nervous system, kidney, and eyes. If left untreated, WD can lead to severe disability and even death, but early diagnosis and effective treatments can prevent or reverse many of its symptoms.

The Kayser-Fleischer (KF) ring, a hallmark of WD, is due to copper deposition in Descemet membrane of the cornea. It has been extensively documented and is included in diagnostic algorithms such as the Leipzig diagnostic criteria. According to these guidelines, the presence of KF rings in patients with hepatic, neurological, or psychiatric symptoms warrants further diagnostic evaluation for WD [2, 3]. Thus, the KF ring serves as a key diagnostic feature of WD. Subjective slit-lamp examination (SLE) remains the most common evaluation method for its detection. However, early-stage KF

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rings are often difficult to detect and their identification heavily relies on the ophthalmologist's expertise. Recent advancements in objective evaluations, such as the anterior segment optical coherence tomography (AS-OCT) [4] and in vivo confocal microscopy (IVCM) [5], offer promising alternatives for KF rings assessment but lack of comprehensive comparative studies. This study aimed to compare AS-OCT and IVCM efficacy in accessing KF rings in WD patients.

Patients and methods

We conducted a prospective observational study involving 36 consecutive patients diagnosed with WD in the liver disease division based on international criteria [3] between March 2022 and June 2023. The inclusion criteria were: newly diagnosed WD, sufficient visual acuity and general health status that allowed participation. Neurologic and hepatic manifestations were classified based on the clinical signs and symptoms at diagnosis. Thirty-six healthy controls, who were matched for age and gender with the patient group, were recruited from the outpatient department of our institution after confirming the absence of systemic or ocular diseases through medical history and clinical examination. The study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University, China, and in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after the study protocol was explained. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Each patient underwent a complete ophthalmic evaluation, including visual acuity, SLE, anterior segment photography, AS-OCT (Visante OCT 1000, Carl Zeiss Inc, Dublin, California, USA), IVCM (Heidelberg Engineering GmbH, Heidelberg, Germany) and dilated fundus examination to assess the lens and retina. IVCM was conducted in accordance with the protocol outlined in our previous study [5]. As KF rings are bilateral, only the right eye of each patient was included in the analysis. Both AS-OCT and IVCM were performed on the Descemet membrane of the peripheral superior cornea. All assessments were conducted by a single researcher, and the results were reviewed by two experienced ophthalmologists who were blinded to WD status until all data were complete. The hyper-reflective area on Descemet membrane indicated a positive result on AS-OCT, while IVCM findings were judged basing on our published article [5].

The differences in diagnostic outcomes using AS-OCT and IVCM were assessed using McNemar's test for the entire sample and subsets (patients with hepatic and mixed manifestations). A p-value of <0.05 was considered statistically significant. All analyses were performed using the SPSS v.24 (IBM, USA) bundle.

Table 1 Demographic and clinical data

Subjects *N* = 36 (F = 16)	**Mean (SD)**
Controls *N* = 36 (F = 16)	
Age– all subjects	25.1 (10.8)
Age– hepatic manifestation *N* = 18	22.8 (10.8)
Age– neurologic manifestation *N* = 9	25.8 (8.8)
Age– mixed manifestation *N* = 9	28.9 (12.4)
Age– controls	25.8 (11.2)
	No. of cases (%)
IVCM-confirmed KFr– controls	0
IVCM-confirmed KFr– all subjects	30(83.3)
IVCM-confirmed KFr– hepatic manifestation	13 (72.2)
IVCM-confirmed KFr– neurologic manifestation	9 (100)
IVCM-confirmed KFr– mixed manifestation	8(88.9)
AS-OCT-confirmed KFr– controls	0
AS-OCT-confirmed KFr– all subjects	23(63.9)
AS-OCT-confirmed KFr– hepatic manifestation	7(38.9)
AS-OCT-confirmed KFr– neurologic manifestation	9(100)
AS-OCT-confirmed KFr– mixed manifestation	7(77.8)

N: Number; SD: Standard deviation; IVCM: In vivo confocal microscopy; KFr: Kayser–Fleischer ring

Results

Both WD patients and control groups included 20 males and 16 females each, with a mean age of 25.1(± 10.8) years for the WD group and 25.8(± 11.2) years for the control group. The WD group was further divided into three subgroups: 18 patients with hepatic WD, nine patients with neurologic WD and nine patients with mixed manifestations. Demographic and clinical data of the WD patients involved in the study are presented in Table 1. No significant age differences were observed between the WD and control groups ($P>0.05$). Normality of distribution and variance homogeneity were confirmed for all analyzed variables (Table 1). All data generated or analyzed during this study are included in Supplementary 1.

None of the participants exhibited the sunflower cataract. Based on the results from IVCM and AS-OCT, three distinct outcome categories were identified (Fig. 1). Using McNemar's test, a significant trend was observed across the entire cohort, where subjects initially presenting without Kayser-Fleischer (KF) rings on AS-OCT were found to have KF rings when examined with IVCM. IVCM revealed copper deposits too subtle to be detected by AS-OCT, adding seven subjects ($p=0.02$) to the cohort, including six patients in the hepatic manifestation group ($p=0.04$) and one patient in the mixed manifestation group ($p>0.05$). This finding confirms the superior accuracy of IVCM compared to AS-OCT, particularly in patients with hepatic manifestations. Notably, no KF rings were observed in any control subjects on either IVCM or AS-OCT.

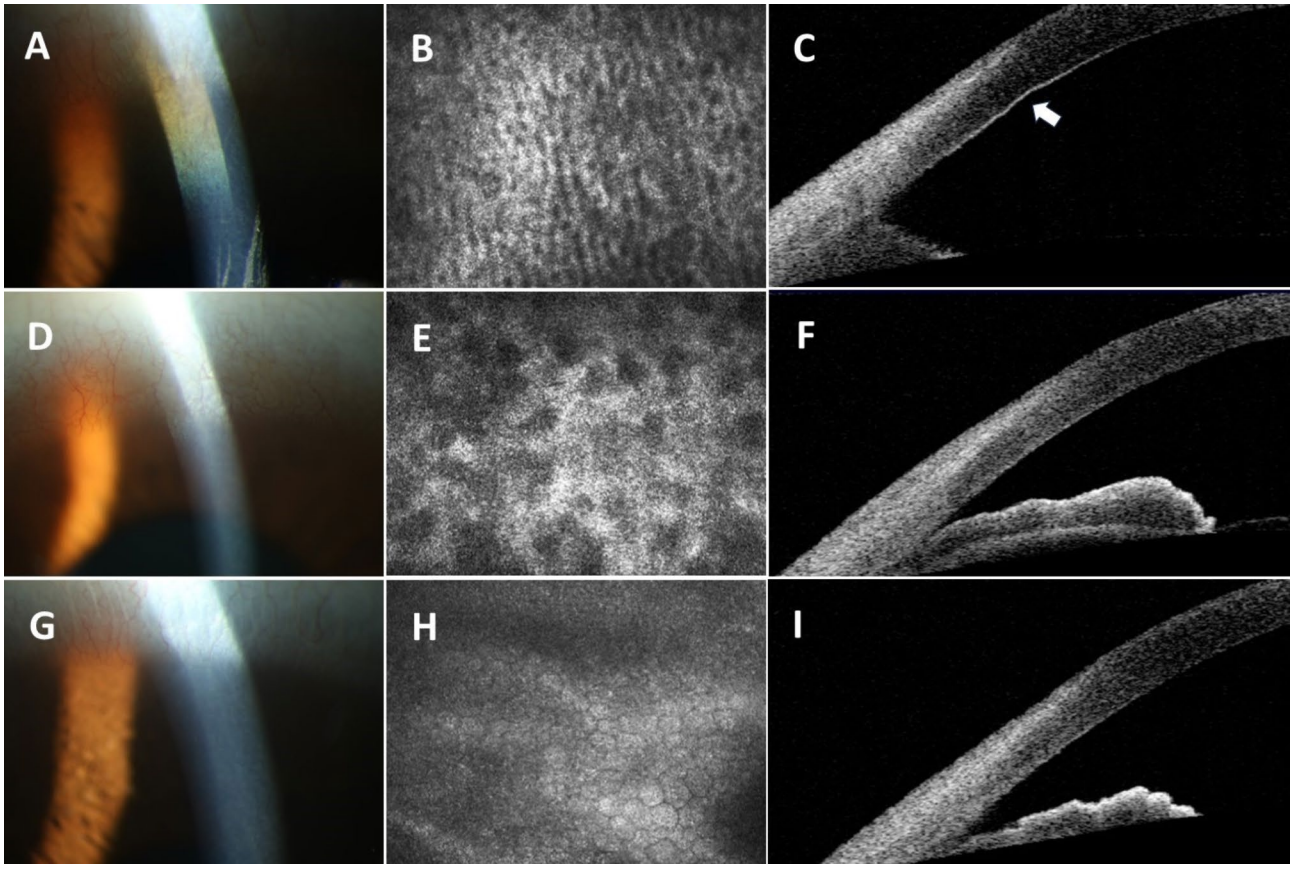

Fig. 1 Anterior segment photography, IVCM, and AS-OCT images in Wilson disease and healthy controls. (**A**–**C**) Positive KF ring: (**B**) Stripy pattern of the KF ring observed with IVCM (×800); (**C**) Arrow indicates hyper-reflective deposits on the Descemet membrane, as seen with AS-OCT. (**D**–**F**) Weakly positive KF ring: (E) Patchy pattern of the KF ring observed with IVCM(×800). (**G**–**I**) Negative KF rings

Discussion

The KF ring, first described in 1902 by Bernhard Kayser and Bruno Fleischer, remains an important sign of WD. It is observed in 90.4–100% of WD patients with neurologic and psychological symptoms, and in over half of those without neurologic symptoms [6, 7]. Early diagnosis and treatment with copper-chelating agents can lead to regression or even disappearance of the KF ring in more than 80% of patients after successful therapy [8]. Consequently, detecting the KF ring is essential not only for diagnosing WD but also for screening first-degree relatives and monitoring treatment response.

The KF ring appears as a golden-green, green-yellow, golden-yellow, bronze or reddish discoloration at corneal periphery. Copper is initially deposited in the superior cornea [2, 9], due to the vertical flow of aqueous fluid [10]. Thus, the Descemet membrane of the peripheral superior cornea is the most prominent location for copper deposits, making it the key area to be examined for KF rings.

The traditional method to detect KF rings, SLE, is highly dependent on the examiner's experience and can lead to misinterpretations, particularly when distinguishing between true KF rings and pseudo-KF rings [11]. The Pseudo-KF rings commonly observed in patients with hepatic diseases due to bilirubin deposition in the posterior corneal stroma [12], may resemble the appearance of KF rings but is typically located adjacent to the Descemet membrane. However, AS-OCT can effectively differentiate between these two conditions [11]. With its high resolution, AS-OCT provides a non-contact, easily applicable method to assess copper deposits, clearly visualizing the layer where they reside. On AS-OCT, KF rings appear as intense hyperreflectivity at the Descemet membrane in the peripheral cornea (Fig. 1C, F) [13]. In the Broniek-Kowalik study, provided greater objectivity and accuracy than SLE in detecting copper deposition and KF rings, with a detection rate of 86.2% [4]. In our study, the detection rate was 63.9%, likely due to the use of a lower-resolution OCT system and differences in patient characteristics. For example, the percentage of patients with neurological manifestations was 55% in their study, compared to 25% in ours, and neurological involvement is associated with a higher detection rate of KF rings.

In addition to slit-lamp examination, gonioscopy has been proposed as an alternative method for detecting early KF rings. Unlike AS-OCT and IVCM, gonioscopy does not provide objective, high-resolution, layer-specific imaging. While gonioscopy may help in some cases, it relies on the examiner's subjective assessment and lacks the detailed imaging capabilities of AS-OCT and IVCM.

Although the SS-OCT offers good resolution (4–7 microns), IVCM, with its Ultra-high-resolution technology (1 microns), even greater clarity, enabling the detection of minimal copper deposits [5, 14]. This makes IVCM possible to detect weakly positive KF rings, which are more commonly observed in hepatic WD (Fig. 1E). Although the hepatic WD can detect the KF ring earlier, the positivity rate for KF rings is lower than in other forms of WD, and more than 50% of patients with hepatic WD may be misdiagnosed [14]. Additionally, 9.7% of hepatic WD patients had KF rings detectable by AS-OCT that were not visible on SLE [11]. IVCM can help reduce both misdiagnoses and missed diagnoses. However, IVCM is more complex, time-consuming, operator-dependent than AS-OCT, which limits its widespread use compared to AS-OCT. This study has some limitations including a relatively small sample size, which may affect the reliability of the results. Furthermore, the AS-OCT system used in this study was not the latest version, which has higher resolution. Future advancements in OCT technology may narrow the gap in detection sensitivity between AS-OCT and IVCM.

Currently, numerous studies focus on grading systems ranging from Scheimpflug imaging [15] to deep leaning [16]. However, we believe that such a system may not be necessary, as no established correlation exists between the degree of KF ring visibility and the severity of WD Brain MRI pathognomonic signs may be more likely to predict the severity of WD [17]. Additionally, a thorough medical history remains critical, as KF rings can also be found in conditions like chalcosis bulbi, where copper deposits occur within the eye. Chalcosis bulbi typically presents with both KF rings and sunflower cataracts, and these cases can be differentiated based on the patient's medical history [18]. Another diagnostic challenge arises in cases where the KF ring occurs unilaterally. Although the KF ring in Wilson's disease typically appears bilaterally due to its systemic nature, unilateral KF rings have been reported in patients with a phthisical eye [19].

In conclusion, both AS-OCT and IVCM can provide objective imaging of KF rings. While AS-OCT offers greater accessibility and ease of use, IVCM provides superior sensitivity, particularly in detecting minimal copper deposits in hepatic WD. Therefore, AS-OCT can serve as an initial screening tool and for monitoring treatment efficacy, whereas IVCM may be recommended for equivocal cases or when hepatic WD is suspected. In hepatic WD patients, IVCM may offer more accurate KF ring detection. Regardless of the examination method, the Descemet membrane in the superior cornea remains the key area for detecting KF rings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12886-025-04032-9.

Supplementary Material 1

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Author contributions
Jiao Tian, Xiuqin Yin and Yangyan Xiao conceived and designed the experiments. Jiao Tian and Xiuqin Yin performed the experiments. Jiao Tian and Yangyan Xiao analysed the data and wrote the paper.

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Data availability
Sequence data that support the findings of this study have been deposited in supplement 1.

Declarations

Ethics approval and consent to participate
All patients signed informed consent forms before undergoing IVCM imaging. The study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University, China(2020No.91).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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