Eye Involvement in Wilson’s Disease

Subjects: Ophthalmology

Contributor: Kevin Chevalier , Martine Mauget-Faÿsse , Vivien Vasseur , Georges Azar , Michaël Alexandre Obadia , Aurélia Poujois

Wilson’s disease (WD) is an autosomal recessive genetic disorder due to a mutation of the ATP7B gene, resulting in impaired hepatic copper excretion and accumulation in various tissues. Ocular findings are one of the hallmarks of the disease. Many ophthalmological manifestations have been described and new techniques are currently available to improve their diagnosis and to follow their evolution. The most common ocular findings seen in WD patients are Kayser–Fleischer ring (KFR) and sunflower cataracts. Other ocular manifestations may involve retinal tissue, visual systems and eye mobility. Diagnosis and follow-up under decoppering treatment of these ocular findings are generally easily performed with slit-lamp examination (SLE). However, new techniques are available for the precocious detection of ocular findings due to WD and may be of great value for non-experimented ophthalmologists and non-ophthalmologists practitioners.

Wilson’s disease | Kayser–Fleischer ring | eye involvement | sunflower cataract | copper

1. Introduction

Wilson’s disease (WD), also known as hepatolenticular degeneration, is a rare genetic condition due to a recessive mutation of the ATP7B gene. The disease consists of a continuous copper accumulation in many tissues and requires life-long treatment. With fewer than 1000 cases in France [1], this condition is mainly characterized by hepatic, ophthalmological and neurological features due to copper accumulation in those organs. Treatments available for this disease rely mainly on copper chelators (D-Penicillamine and trientine salts) and zinc salts.

The ophthalmological manifestations are one of the hallmarks of the disease. Corneal deposition of copper, called Kayser–Fleischer ring (KFR), is typical in WD and constitutes one of the diagnostic criteria for this disease [2]. A sign of extra-hepatic copper accumulation, KFR is a useful biomarker that allows the evolution under chelator treatments. It is a reversible sign and may disappear under treatment. Apart from KFR, many other ophthalmological manifestations have been described. In addition, new techniques have made it possible to improve the diagnosis of these manifestations and to follow their evolution [1].

2. Eye Involvement in Wilson’s Disease

2.1. Cornea Involvement

KFR was first described in 1902 and 1903, respectively, by two German ophthalmologists, Benhard Kayser and Bruno Fleischer. It consists of a ring-shaped copper deposit in the anterior chamber angle within the internal corneal layer of the Descemet's membrane, at the Schwalbe's line (**Figure 1**) [3][4]. In fact, copper is deposited throughout the cornea, and sulfur-copper complexes producing the visible copper deposits are formed only in Descemet's membrane [5]. On SLE, KFR appears like a golden-brown, golden-green, green-yellow, golden-yellow, bronze or reddish-brown coloring ring in the limbic area of the cornea [6]. It first develops in the superior part of the cornea (at the 12-o'clock position), then inferiorly, and finally in the horizontal meridian forming a closed ring. [3][7][8][9] Thus a closed KFR is evidence of a long-term disease [3]. This pattern of formation and resolution of the KFR could be explained by the vertical flow of aqueous fluid in the anterior chamber of the eye [10]. It is usually bilateral [3] but a unilateral case was reported in 1986 [11].

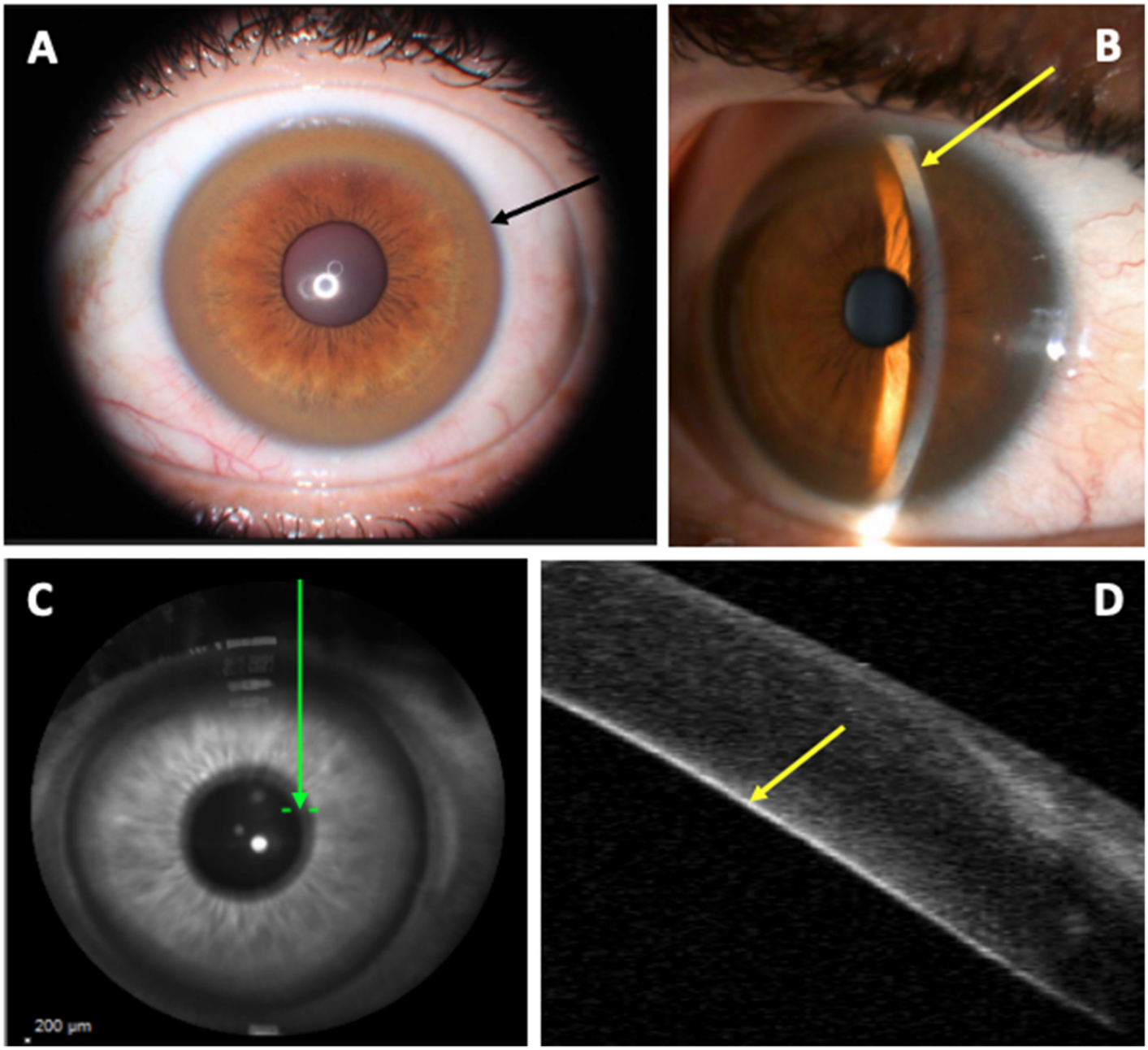

Figure 1. Kayser–Fleischer Ring. (**A**): Slip-lamp examination showing a diffuse circumferential Kayser–Fleischer ring in the left eye (black arrow); (**B**): Slit-lamp examination: visualization of the copper deposit at the posterior part of the cornea in fine slit (yellow arrow); (**C**): Corneal B-scan localization (Spectralis; Heildelberg Engineering) (green arrow); (**D**): marked hyperreflectivity of the posterior part of the cornea corresponding to the copper deposit (yellow arrow).

KFR confirms the presence of excess free copper in the bloodstream but is not pathognomonic for WD, as it may occur in any disorder with impaired biliary copper excretion [7][12][13][14][15][16]. KFR is not constantly detected by the classical SLE in WD; its prevalence is estimated between 36–62% in patients with hepatic manifestation, between 77.8–85.2% in patients with neurological manifestation [3][5][17] and between 10–30% in asymptomatic WD patients [3][4][5][9][17][18][19][20][21][22][23]. The incidence of KFR also varies according to the age of the diagnosis. Indeed, the largest pediatric cohort in WD has been recently published by Couchonnal et al. describing 182 children with WD. In this cohort, at diagnosis, 149 (81.8%) children had an ophthalmologic evaluation [24]. Among them, 58 (38.9%) had a detectable KFR: 40/129 (31.0%) were hepatic patients and 18/19 (94.7%) were neurological patients. The youngest patient with a detectable KFR was a seven-year-old, and a total of eight patients (13.7%) with detectable KFR were younger than 10 years, all were hepatic patients. The incidence of KFR in children is much lower than in adults. Nevertheless, it is puzzling that KFR is more frequent in neurological patients (like in adults) but more early in hepatic patients.

In vivo confocal microscopy (IVCM) shows that KFR consists of granular, bright particles that increase in density toward Descemet's membrane and is associated with a decreased number of keratocytes and peculiar dark, and round areas in all stromal layers. When the ring is not visible in subjects with WD, changes to the corneal microstructure are insignificant [25].

The presence of KFR, identified with SLE by a skilled examiner or rarely with the naked eye, is included in the current diagnosis criteria of WD [2][26][27]. KFR usually disappears progressively with effective treatment of WD, fading initially from lateral and medial aspects of the cornea, then finally from its superior part. As its recurrence suggests a non-adherence to treatment, close monitoring of the ocular status during the follow-up is highly recommended [3][6][9][23][25][26][28][29][30][31][32]. Nevertheless, its disappearance is not correlated with the resolution of the other signs or symptoms of the disease [3][6][8][14].

The sensitivity (Se) of SLE to detect a KFR is known to be low (KFR was missed in more than 50% of hepatic WD patients) [2][33]. That could be explained by the predominance of copper deposits in the anterior chamber angle that cannot be detected with a standard SLE. Therefore, a thorough ophthalmological exam with gonioscopy, which permits a detailed examination of the iridocorneal angle structures, remains crucial [3]. SLE and gonioscopy both required experiment operators, as non-trained ophthalmologists could miss the KFR [3]. These findings lead to the proposal of other methods that could be used to assess the presence and progression of copper deposits in the cornea.

Anterior segment optical coherence tomography (AS-OCT) could be used for the detection of KFR. The KFR appears on a grey scale as a hyper-reflective layer at the level of Descemet's membrane in the peripheral cornea (**Figure 2**). On a color scale, it appears as a green/green-yellow/yellow/yellow-orange band. KFR can be easily measured using the gray scale of AS-OCT [3][28][29]. In a study of 29 patients with WD, 15 had normal slit-lamp evaluation but abnormal AS-OCT ($p < 0.001$) hypothesizing that AS-OCT is a more accurate diagnostic tool that could detect significantly more cases of KFR as compared to the slit-lamp evaluation in participants with hepatic and neurological WD manifestations [3]. This technique could permit more easy recognition of KFR for non-experimented ophthalmologists, as well as non-ophthalmologists practitioners [28][30]. Moreover, it is also useful in children and non-cooperative patients because the imaging process involves fixation for only a few seconds without exposure to bright light [34]. AS-OCT could possibly determine the density of copper deposit in KFR and help the clinician determine the severity of the disease. Further studies are needed to know if AS-OCT can distinguish KFR from pigmented corneal rings in non-Wilsonian liver disease or arcus senilis and if repetitive AS-OCT could help assess the good response of chelator treatments in WD [28].

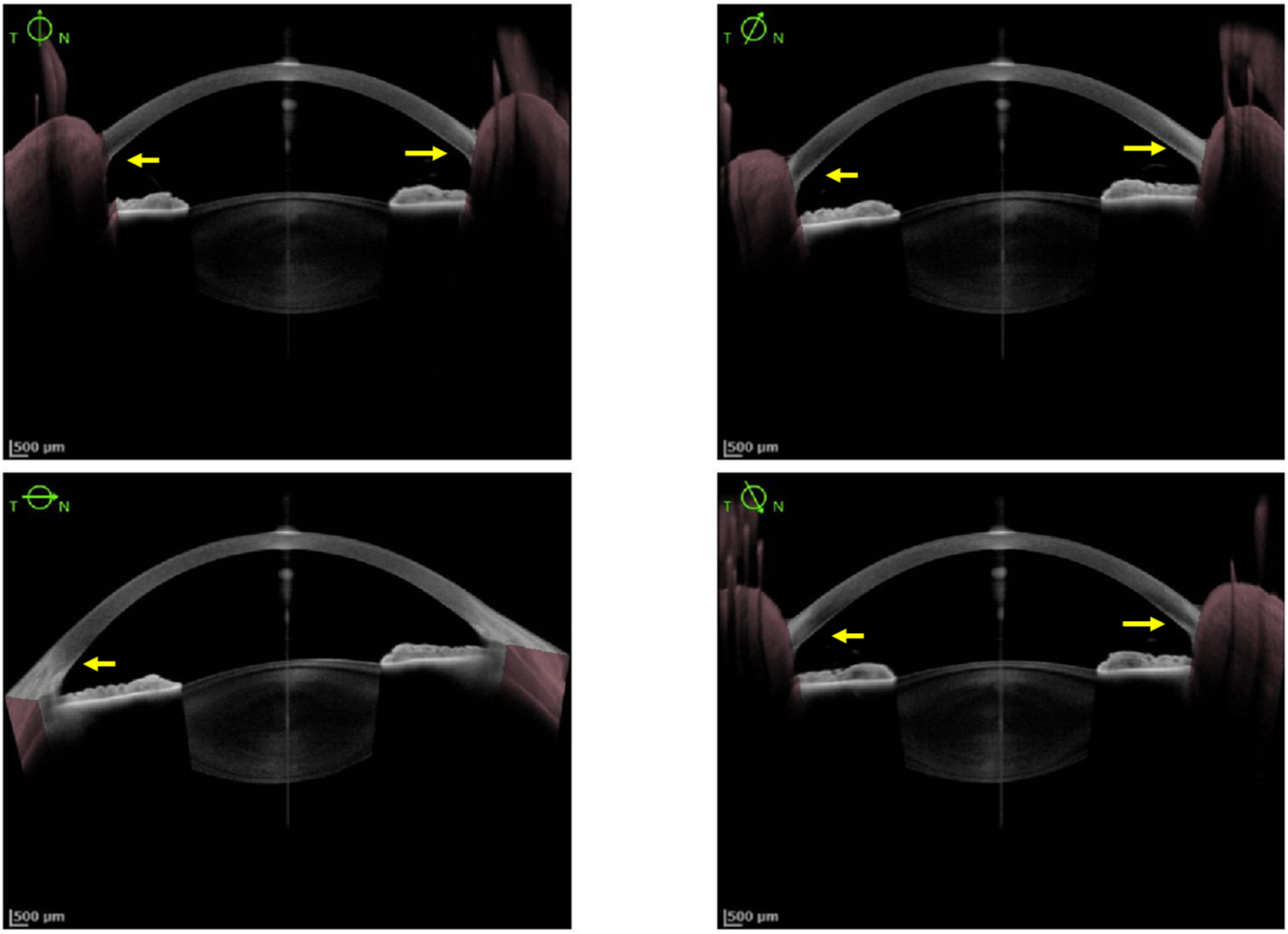

Figure 3. High-resolution Swept Source technology (Anterion®, Heidelberg Engineering, Heidelberg, Germany) provides images of very high quality allowing the detection of a faint Kayser–Fleischer ring (KFR) hardly visible on slit-lamp examination (yellow arrow).

Pentacam HR Scheimpflug imaging is a device that can provide three-dimensional image representations of the anterior segment, which may be useful for screening narrow angles.

Aside from KFR, corneal nerve fibers are also impacted by copper deposits.

2.2. Lens Involvement

Sunflower cataract is another classical ocular manifestation of WD, the frequency of which varies widely in the literature (between 2 and 20%) [10]. A recent study performed by Langwinska-Wosko et al. on 81 consecutive newly diagnosed WD patients reported that such cataract was detected in only one (1.2%) of all patients, suggesting that sunflower cataract is a very rare ocular sign of WD in de novo and untreated patients. After a year of treatment, the cataract fully disappeared [17]. This manifestation was first described by Siemerling and Oloff in 1922 as "cataracts like rays of the sun" [35]. The scholars already noted the similarities between the cataract seen in their patients with WD to the one produced by an intraocular foreign body containing copper [9]. Sunflower cataract consists of copper deposition in the lens capsule and not within the lens cortex or nucleus itself, and has an aspect of a central disk with radiating petal-like spokes that give its name [7].

Sunflower cataracts usually do not impair vision, cannot be seen with the unaided eye or with an ophthalmoscope, and require slit-lamp evaluation for detection [23]. Like KFR, sunflower cataracts usually regress with copper-chelating treatment [17][36].

2.3. Macula, Retinal Nerve Fiber Layer and Visual Pathways Involvement

Correlation between brain MRI lesions and impairment of visual pathways, macula and retinal nerve fiber layer (RNFL) was found by Langwinska-Wosko et al. [37]. They compared 58 WD patients mean age 38.7 years, with or without brain lesions on MRI (39 MRI+ and 19 MRI−, respectively) and 30 healthy controls (mean age 39.6 years). Total RNFL measured spectral-domain optical coherence tomography (SD-OCT) was thinner in WD patients MRI+ than WD patients MRI− ($p = 0.001$). Central macular thickness (CMT) was also significantly thinner in WD patients MRI+ than WD patients MRI− ($p < 0.001$). No significant difference was found in RNFL or CMT between WD patients MRI− and controls. Latency of visual evoked potentials (PEV) and electroretinography (ERG) were prolonged in WD patients MRI+ compared to WD patients MRI− ($p < 0.001$ and $p < 0.001$, respectively). Interestingly, some WD patients MRI− had electrophysiological abnormalities. These results confirmed what had been already demonstrated by a German team in 2012 [38]. An Indian team has also shown prolonged latencies in PEV and ERG in WD patients with neurological manifestations compared to controls and the improvement of PEV and ERG latencies after treatment of WD [39].

2.4. Eye Mobility

WD is responsible for eye movement abnormalities such as slow horizontal and vertical saccades [23][40][41], abnormal vertical smooth pursuit [42], increased antisaccadic latency and error rate [43]. Ingster-Moati et al. found that 91% of 34 WD patients (mean age 29 years, 24 neurological forms, 9 hepatic forms and 1 asymptomatic

patient) had abnormalities of ocular motility detected by electro-oculography. Here, 29 patients (85%) had an abnormal vertical smooth pursuit, 41% a vertical optokinetic nystagmus and 41% an impaired horizontal smooth pursuit. Among the 27 who underwent MRI, seven patients had normal brainstem and lenticular nuclei images despite the detection of ocular motility abnormalities [42]. Brain MRI of WD patients showed a strong association between prolonged latencies of prosaccades and the brainstem atrophy ($r = -0.53$ and $p = 0,02$ for horizontal latencies and $r = 0.47$ and $p = 0.004$ for vertical maximum speed in prosaccades, respectively). Impairment in eye movement is probably secondary to the lesions induced by the copper deposit in the brainstem as the nerve centers responsible for vertical and horizontal eye tracking are located in the midbrain and the pons, respectively.

3. Conclusions

Ocular manifestations may be the first presenting symptoms of WD, which must be recognized to prevent fatal outcomes.

As KFR is an essential criterion for the diagnosis of WD, multiple methods have been studied to improve its diagnosis. So far, SLE is the gold standard for detection of KFR, but its Se is low and it requires experimented ophthalmologists. Since 2016, AS-OCT studies demonstrated a better Se and Sp to diagnose KFR compared to SLE. Its interpretation appears easier and more accessible for non-experimented ophthalmologists and non-ophthalmologist practitioners [28][30]. The density of copper deposit in the cornea at the diagnosis and during the follow-up of WD could determine the severity of the disease and the response under chelator treatment [28]. Pentacam HR Scheimpflug imaging using ImageJ software and calculation of the ratio between anterior and posterior peak signal presents also a good Se (96%) and specificity (Sp, 95%) to detect KFR. Nevertheless, the utilization of those methods to assess therapeutic efficacy needs further evaluation.

It appears that ophthalmological involvement is frequent in WD patients, in particular for the KFR and, to a lesser extent, sunflower cataracts. Other manifestations involving retinal and visual systems, eye mobility or other structures of the eye have been described with various frequencies. AV is nearly often preserved despite corneal or neurological involvement. The evolution of ophthalmologic manifestations seems to be correlated with decoppering treatment, especially for KFR and sunflower cataracts. New methods like AS-OCT and Scheimpflug imaging are alternatives to traditional SLE. These methods allow non-ophthalmologists to look for and quantify KFR more easily and are useful tools to follow the evolution of these abnormalities under chelating treatment. In the near future, the recent development of AI in the analysis of ophthalmic imaging will probably be helpful for the screening of WD anomalies.

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