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RESEARCH ARTICLE

Exploring Evidence-based Therapies for Ocular Manifestations in Bardet–Biedl Syndrome

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ABSTRACT

Background: Bardet-Biedl syndrome and Laurence-Moon syndrome are rare autosomal recessive disorders that share a similar clinical phenotype. These syndromes are characterized by progressive features including cone-rod retinal dystrophy, obesity, and hypogonadism in males. Additional clinical manifestations can include learning disabilities, renal abnormalities, and polydactyly. Despite their similarities, Bardet-Biedl syndrome and Laurence-Moon syndrome are distinguished by certain clinical features. **Ocular Manifestations in BBS:** Ocular involvement in BBS primarily manifests as rod-cone dystrophy, a form of retinal degeneration that leads to progressive blindness. The pathophysiology of retinal degeneration in BBS is linked to ciliary dysfunction, affecting the photoreceptor cells in the retina. Early diagnosis and intervention are critical in preserving vision in affected individuals. **Therapeutic Strategies:** Current evidence-based therapies for ocular manifestations in BBS focus on genetic therapies, retinal implants, and pharmacological interventions. Gene therapy approaches, including gene replacement and gene editing technologies, show promise in preclinical models, aiming to restore or replace defective proteins involved in retinal function. Additionally, retinal implants, such as the Argus II retinal prosthesis, offer partial restoration of vision in patients with advanced retinal degeneration. Pharmacological treatments, such as retinoid derivatives and anti-inflammatory agents, have shown mixed results in slowing disease progression but are not yet universally effective. **Conclusion:** While promising, therapeutic options for managing ocular manifestations in BBS are still in the experimental stages. Continued advancements in gene therapy, retinal prostheses, and pharmacological approaches may offer hope for improving the quality of life and preserving vision in individuals with BBS. Further clinical trials and research are essential to validate these therapies and develop effective treatment protocols.

Keywords: Bardet-Biedl syndrome, retinal degeneration, new therapeutic strategies

INTRODUCTION

Bardet–Biedl syndrome (BBS) and Laurence-Moon syndrome are both rare autosomal recessive conditions, often presenting with a similar phenotype. These include retinal dystrophy (cone-rod degeneration), obesity, and male hypogonadism, alongside learning disabilities and renal abnormalities. Although these syndromes share overlapping features, the presence of spasticity in Laurence-Moon syndrome and the absence of polydactyly, helps differentiate the two disorders clinically.

Laurence-Moon syndrome was first described in 1866 by John Zachariah Laurence [Figure 1a] and Robert Charles Moon [Figure 1b], who documented developmental delay and retinitis pigmentosa in four patients from the same family.

BBS was named after Georges Louis Bardet, a

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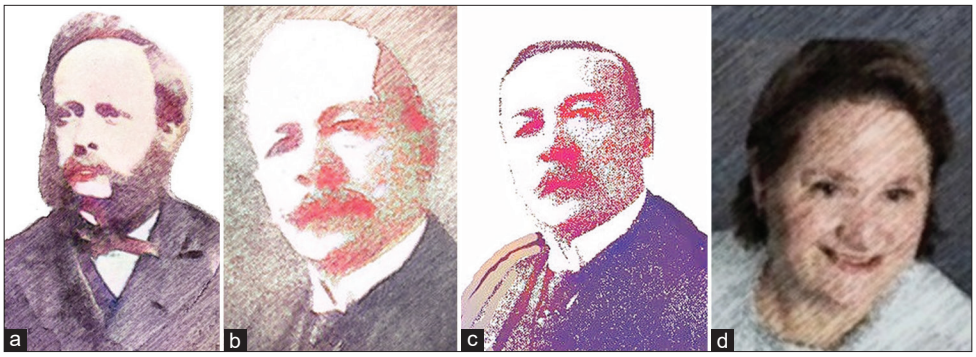

Figure 1: (a) John Zachariah Laurence (1829–July 1870), an English ophthalmologist from London. (b) Robert Charles Moon (1844–1914), an ophthalmologist who worked in England and the United States. (c) Arthur Biedl (October 04, 1869–August 26, 1933), a Hungarian pathologist who was born in Romania. (d) Susan J. Moore, a Canadian pediatrician

French physician, and Arthur Biedl [Figure 1c], a Hungarian pathologist. They suggested that the condition is a distinct clinical entity during the 1920s.

Georges Louis Bardet was a French medical student at the University of Paris in 1920 when he described a case of an obese child with hexadactyly and retinitis pigmentosa and called the syndrome adiposo-genital dystrophy in his medical degree thesis. In 1922, Arthur Biedl a Hungarian pathologist further described the condition in two sisters.

In 2005, Canadian pediatrician Susan J. Moore [Figure 1d] and her research team published a comprehensive clinical genetic and epidemiology study of BBS, further emphasizing the phenotypic similarities between BBS and Laurence-Moon syndrome.

Despite these similarities, BBS and Laurence-Moon syndrome are clinically distinguishable by the absence of polydactyly in Laurence-Moon syndrome and the presence of spasticity.[1]

In 2002, I reported the first patient with BBS in Iraq. The boy had polydactyly, obesity, retinal degeneration, and was hospitalized at the University Hospital in Al-Kadhimiyia because of the development of chronic renal failure.[2] In 2023, he described the second case of BBS in Iraq.[1]

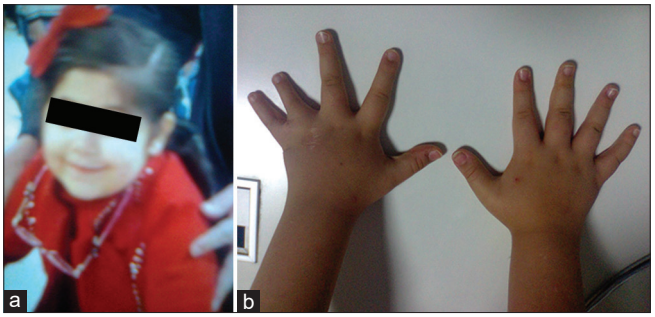

Figure 2: (a) The second case of Bardet–Biedl syndrome in Iraq was a Kurdish girl. (b) The patient's extra-digits were removed surgically

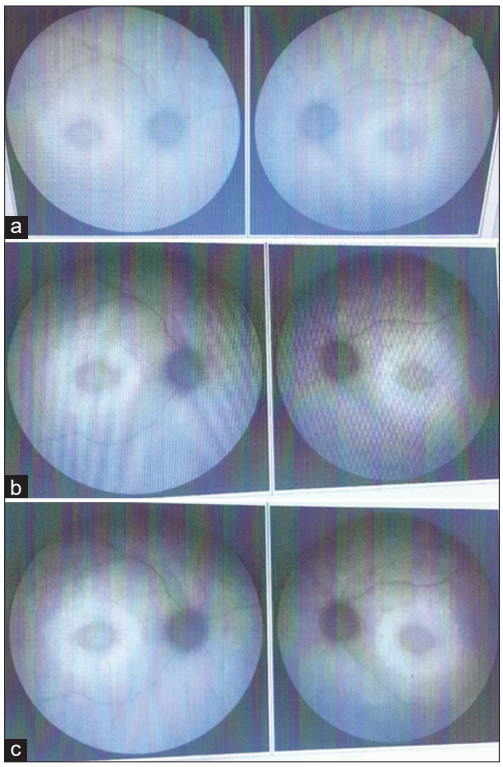

Figure 3: (a) Fundus autofluorescence (February 21, 2023). (b) Fundus autofluorescence (February 21, 2023). (c) Fundus autofluorescence (February 21, 2023)

MATERIALS AND METHODS

This study describes the second known case of BBS in Iraq, reported in a Kurdish girl [Figure 2a] born on August 05, 2013. Initially, the patient

presented with polydactyly of the hands and feet and decreased visual acuity, initially attributed to myopia, which was partially corrected with eyeglasses. The parents were non-consanguineous, and her younger sister also had polydactyly of the feet but no other family members exhibited the condition. Both sisters had their extra-digits removed surgically [Figure 2b].

At the time of presentation, the patient was in the fourth grade with no reported learning disabilities. Routine urinalysis and renal function tests were normal. Ophthalmological examination, including fundus autofluorescence [Figure 3], showed normal optic discs and retinal peripheries, with no evidence of retinitis pigmentosa. However, the foveal reflex was noted to be abnormal.

To confirm the diagnosis, electroretinography (ERG) was performed on February 21, 2023. Previous research by Prosperi *et al*. emphasized the value of ERG in the early diagnosis of BBS, detecting retinal degeneration not always visible via ophthalmoscopy during childhood.[3]

Main ERG Abnormal Findings [Figure 4] Included

Scotopic ERG (rod function)

Markedly reduced or absent rod function (0.01 ERG), with reduced a- and b-wave amplitudes, with delayed implicit times indicating impaired combined rod-cone response (3.0 ERG [combined rod and cone response]).This points to significant dysfunction in both rods and cones in dim light conditions.

Scotopic 10.0 ERG: Further reduced responses, reinforcing rod system dysfunction.

Photopic ERG (cone function)

Diminished cone activity under bright light (3.0 ERG) with delayed implicit times, suggesting cone degeneration. Photopic 3.0 ERG (cone response) showed decreased amplitudes of the b-wave with delayed implicit times, indicating diminished cone activity under bright light conditions. 30 Hz Flicker (cone function) showed reduced amplitudes and possibly delayed timing, suggesting global cone dysfunction.

Oscillatory potentials

Reduced amplitudes of oscillatory potentials in the scotopic 3.0 ERG, indicating inner retinal dysfunction (e.g., bipolar cells). The parents, concerned about the progressive nature of the patient's ocular condition, were informed that her vision would likely deteriorate and that she might become blind before the age of 30.

The refractive error assessment and keratometry conducted on December 09, 2023, revealed significant astigmatism in both eyes [Table 1].

RESULTS

Visual Acuity and Refractive Error

- Initial Visual Acuity (August 24, 2017)
  - Right eye (RE): 6/12, left eye (LE): 6/12
- Progressive visual deterioration
  - March 2024: RE: 6/60, LE: 6/60
  - Significant decline observed between June 2021 (RE 6/18, LE 6/18) and January 2023 (RE 6/24, LE CF 4 m).

The patient showed progressive deterioration in visual acuity, especially after 2021, consistent with advancing retinal degeneration. The refractive error also worsened over time, with myopia increasing and astigmatism remaining stable.

Refractive Error Summary

Spherical (Sph) values: Initial (August 2017): RE: −2.00, LE: −2.00 (consistent myopia).

Progressive increase in myopia, reaching RE: −3.00 in March 2023 and maintained afterward.

LE showed higher Sph error by December 2023: −2.50 compared to the RE (−1.00).

Cylindrical and axis values: Consistent astigmatism of −0.50–−0.75 over the years, with the axis remaining at or near 180°, indicating regular astigmatism.

The girl experienced marked deterioration in visual acuity especially in January 2023, suggesting potential progression of retinal or optic nerve-related issues. She also experienced steady progression of myopia.

Clear worsening of myopia over time, more pronounced in the LE by December 2023.

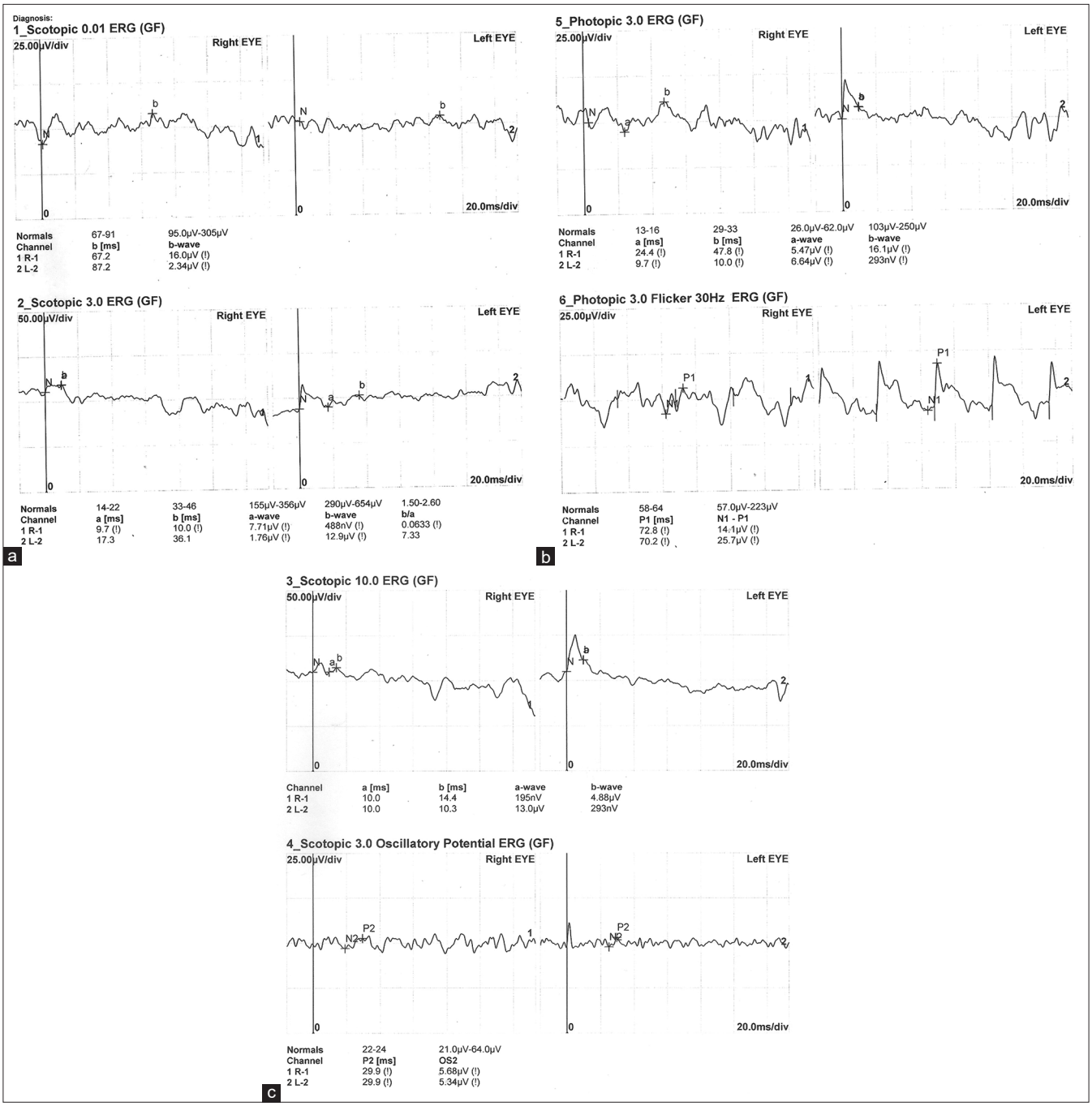

Figure 4: (a) Electroretinography (February 21, 2023). (b) Electroretinography (February 21, 2023). (c) Electroretinography (February 21, 2023)

Minimal fluctuation in astigmatism values, indicating that the primary issue is progressive myopia rather than irregular corneal changes.

The significant drop in visual acuity, particularly in early 2023, suggests advancing retinal degeneration as a hallmark feature of the disease's ocular progression.

The worsening acuity suggests progressive retinal degeneration consistent with retinitis pigmentosa, a hallmark of BBS. The presence of retinitis pigmentosa can cause a slow but steady decline in both central and peripheral vision.

Eye Examination and Findings (December 09th, 2023)

Ocular motility: Normal (no strabismus or abnormal eye movements).

Retinoscopy: Bone spicule appearance of the retinal pigment epithelium which is characteristic of retinitis pigmentosa.

Table 1: Refractive error and Keratometry of eye

Eye	Refractive error	Keratometry
Right eye	Sphere (−1.00) (mild nearsightedness)	Flattest corneal curvature: 8.30 mm (41.00D)
	Cycle (−3.00) with an axis of 180°	Steepest corneal curvature: 7.98 mm (42.25D)
	Significant astigmatism	Irregular corneal curvature (Astigmatism)
Left eye		Flattest corneal curvature: 8.25 mm (41.00D)
	Cycle (−2.25) with an axis of 175°	Steepest corneal curvature: 7.98 mm (42.25D)
	Moderate astigmatism	Similar astigmatism to the right eye

Images from the Wavelight Allegro Oculyzer [Figure 5] revealed the following specific abnormalities:

1. The sagittal (anterior) curvature (topography) map showed an irregular pattern with areas of steepening (yellow/orange) and flattening (green/blue), especially in the LE (oculus sinister [OS]), indicating irregular corneal curvature and corneal astigmatism.
   Asymmetric steepening: The steepening is not evenly distributed, suggesting abnormal corneal biomechanics, which may be linked to corneal ectasia or dystrophy.
2. The posterior elevation map showed areas of abnormal elevation relative to the reference

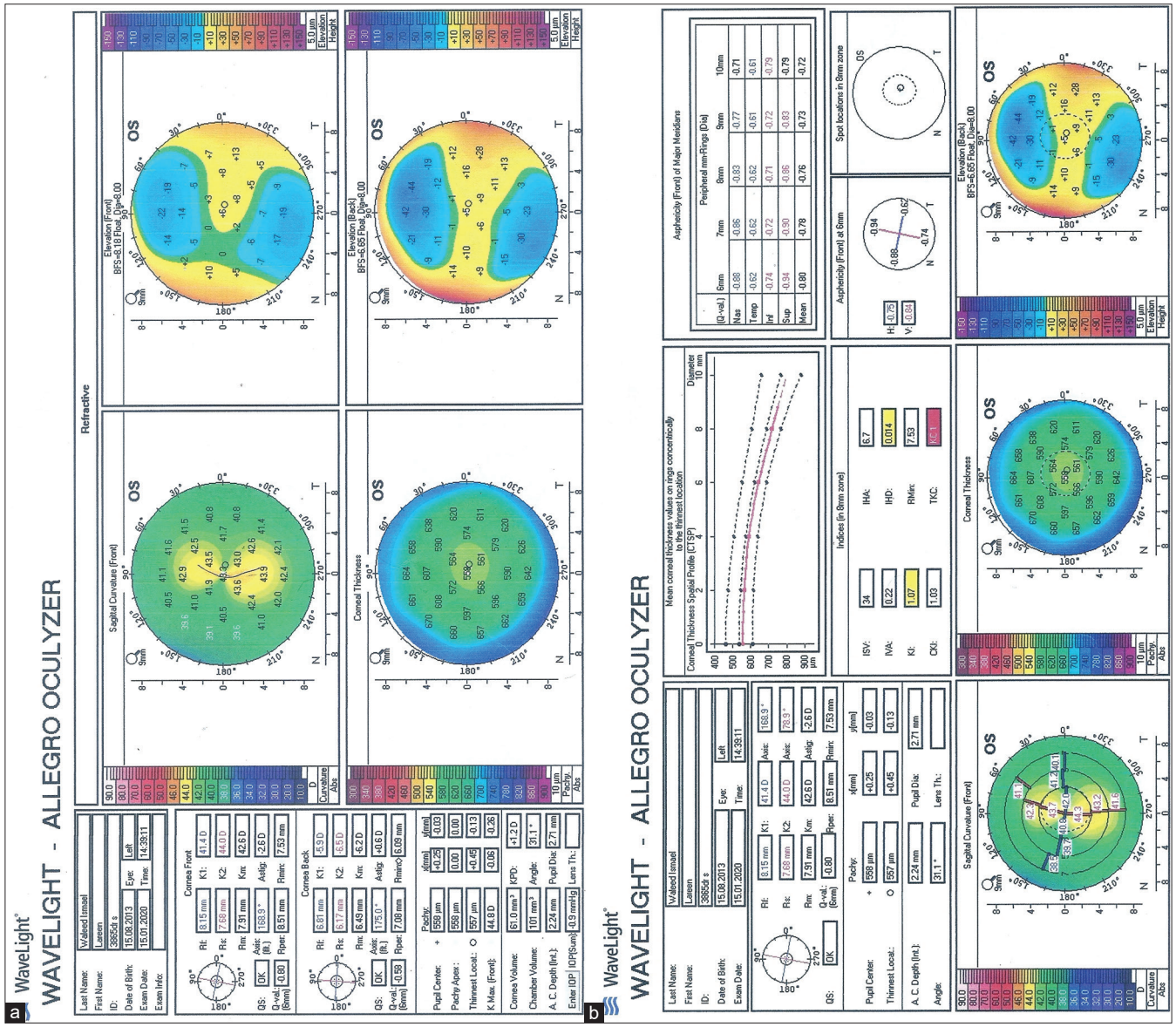

Figure 5: (a) Wavelight Allegro Oculyzer. (b) Wavelight Allegro Oculyzer. (c) Wavelight Allegro Oculyzer

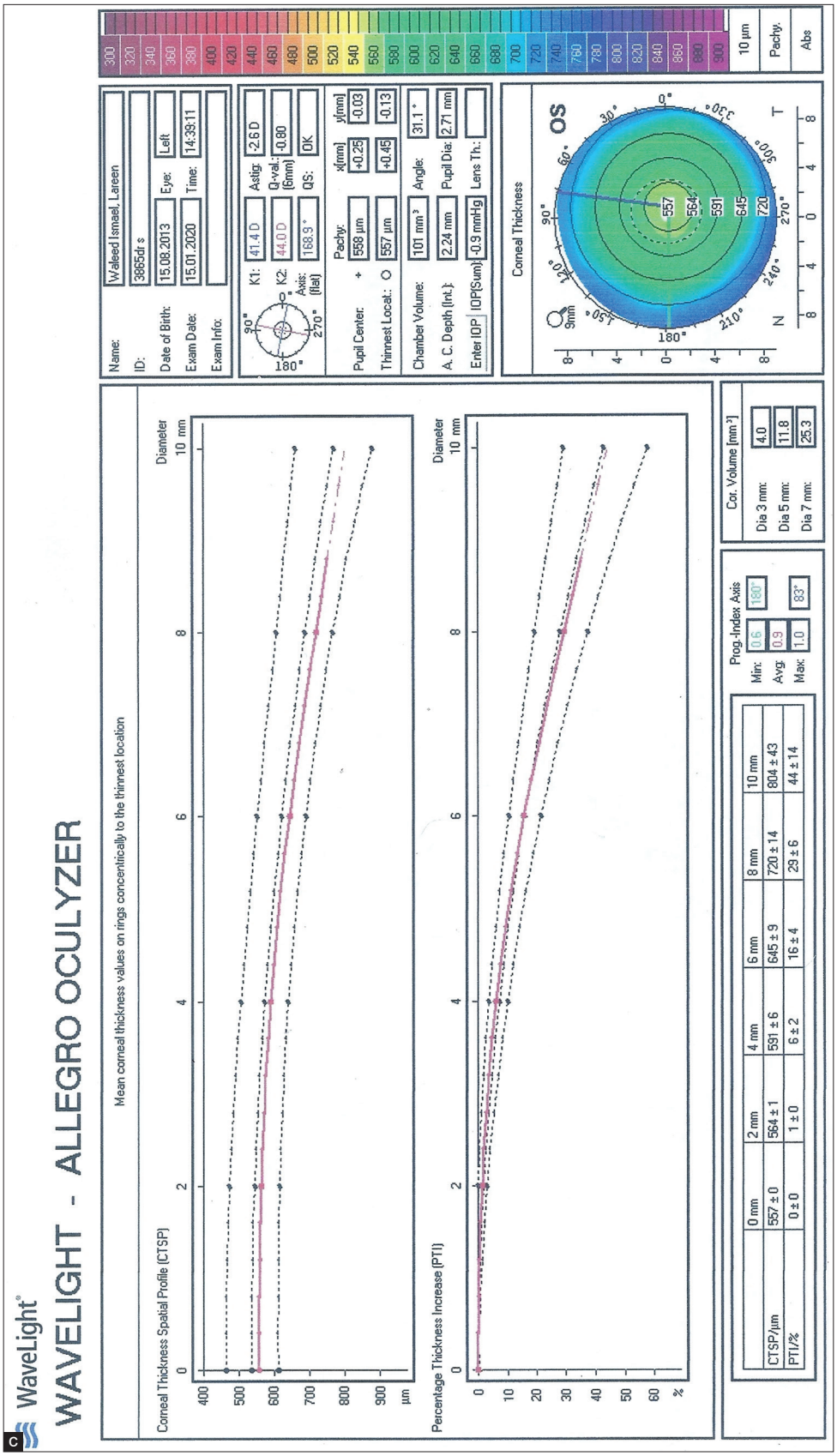

Figure 5: *(Continued)*

sphere (yellow/orange zones). The deviations from normal posterior corneal elevation are significant.

These could suggest early signs of ectasia or subclinical keratoconus, common in syndromic disorders.

3. The pachymetry map showed generalized corneal thinning with reduction of the central corneal thickness, likely below the normal range (~530–550 µm in healthy individuals). The thinning is more pronounced toward the periphery, indicated by the blue/green zones on the map.

The asymmetric thickness profile further supports irregular corneal structure.

4. The asphericity (Q-values) and indices of surface irregularity likely show deviations, as can be inferred from the shape of the corneal curvature maps. These are the key indicators of abnormal corneal morphology.
5. There is a clear difference between the two eyes (oculus dextrus vs. OS) in terms of corneal shape, thickness, and posterior elevation. This asymmetry is abnormal and suggests irregular biomechanics.
6. The corneal thickness spatial profile (CTSP) graph shows a steeper drop-off in thickness from the center to the periphery compared to normal eyes. This is consistent with corneal thinning or ectasia.

These findings strongly suggest irregular astigmatism, generalized corneal thinning, and possible subclinical keratoconus, which can occur as part of BBS due to its effects on connective tissue and corneal integrity.

Pentacam Findings Included

Pentacam 4 maps refractive [Figure 6a]

1. Axial/sagittal map showed evidence of asymmetry in corneal curvature and possible steepening of the cornea, suggesting ectatic changes.
2. Elevation front/back maps showed increased

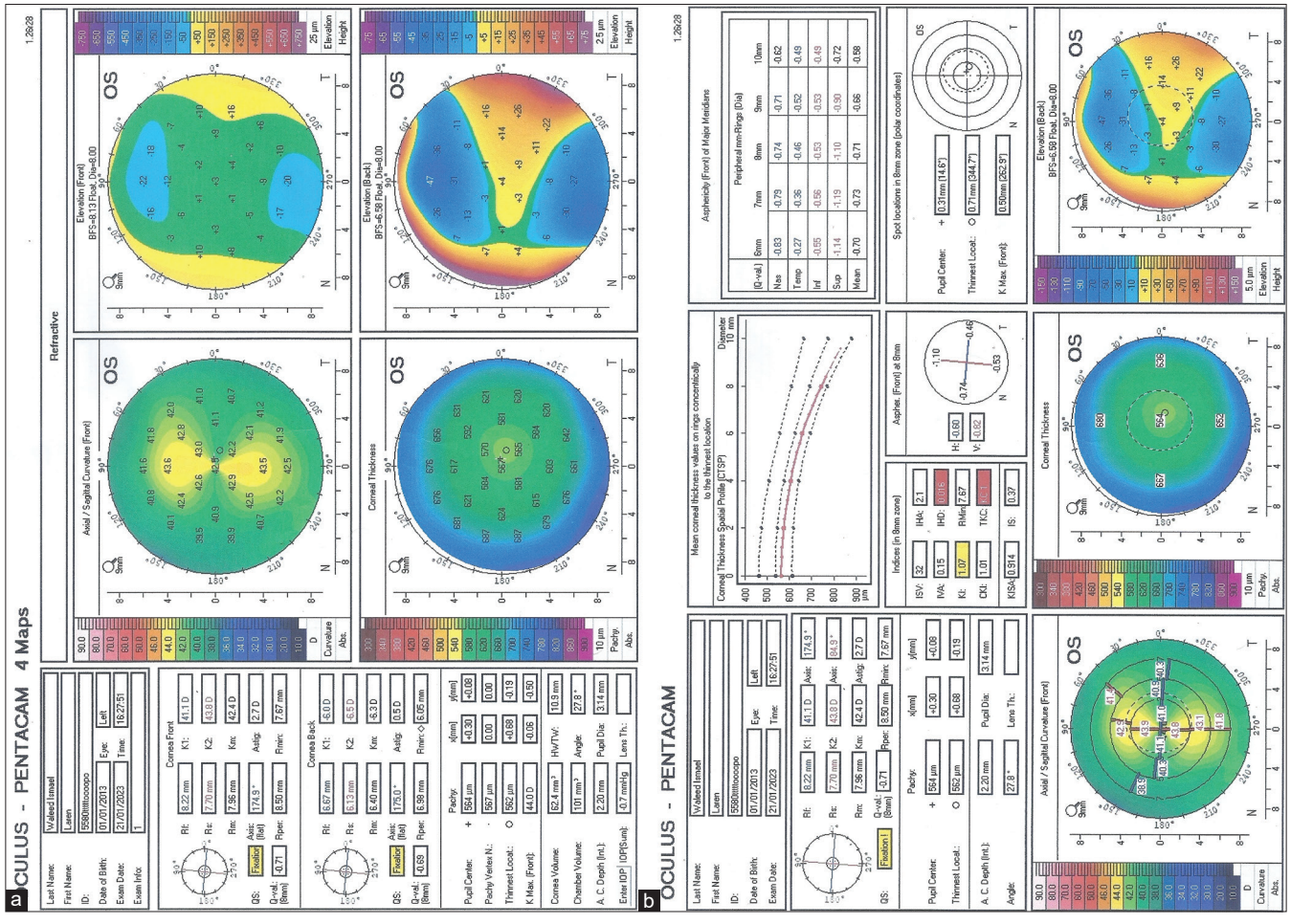

Figure 6: (a) Pentacam 4 maps refractive. (b) Pentacam refractive analysis. (c) Pentacam pachymetric analysis

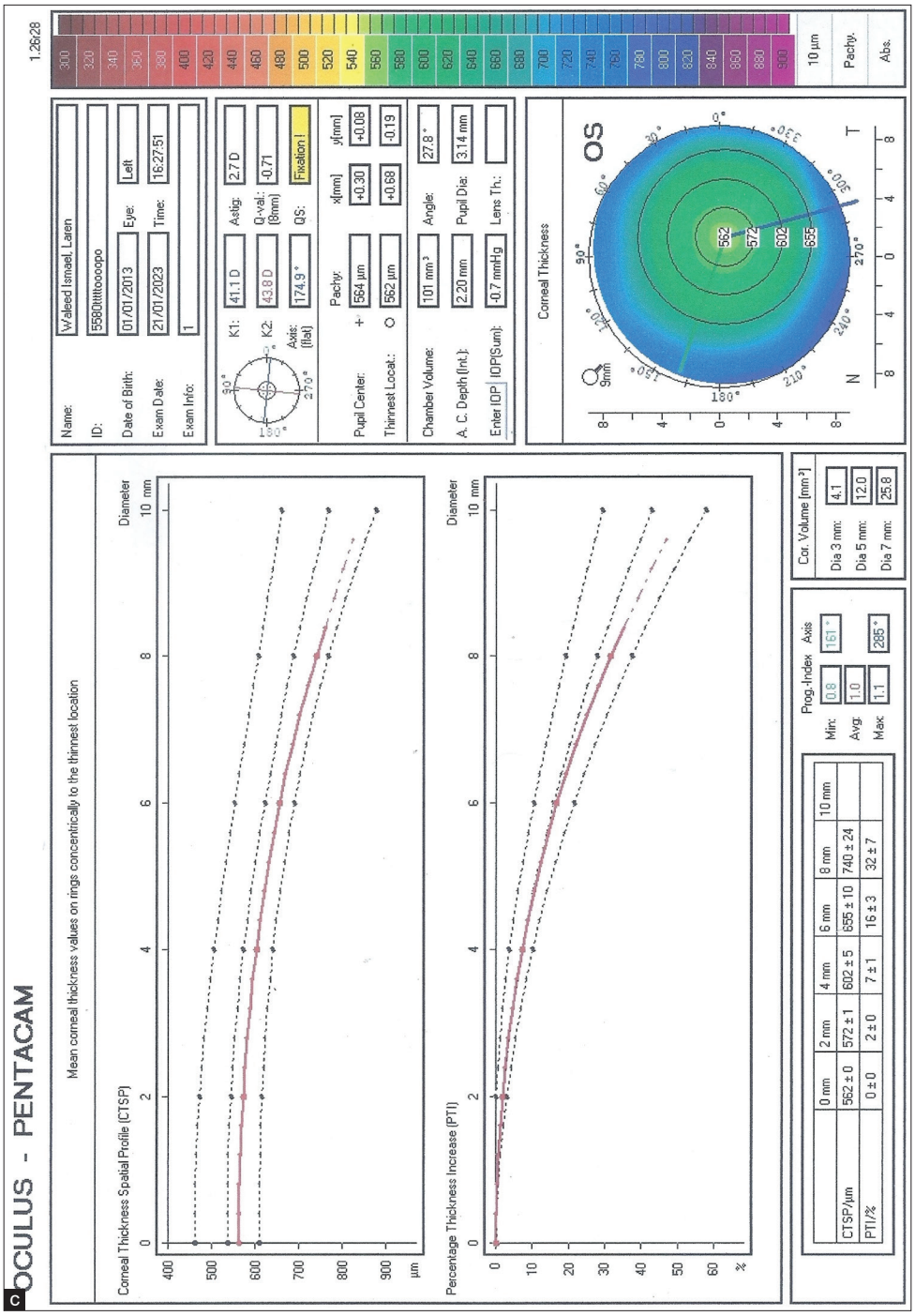

Figure 6: *(Continued)*

elevation values, particularly on the posterior map, which may indicate keratoconus or early ectasia.

3. Corneal thickness (pachymetry) showed marked reduction of thinnest point appears a key sign in keratoconus.

Pentacam refractive analysis [Figure 6b]

1. Corneal asphericity (Q-value): Abnormal Q-value (either very negative or deviating significantly from normal), often seen in keratoconus
2. Wavefront analysis: High values of coma or other higher-order aberrations typically associated with irregular corneal surfaces
3. Refraction and curvature: Signs of irregular astigmatism or significant anisotropy in

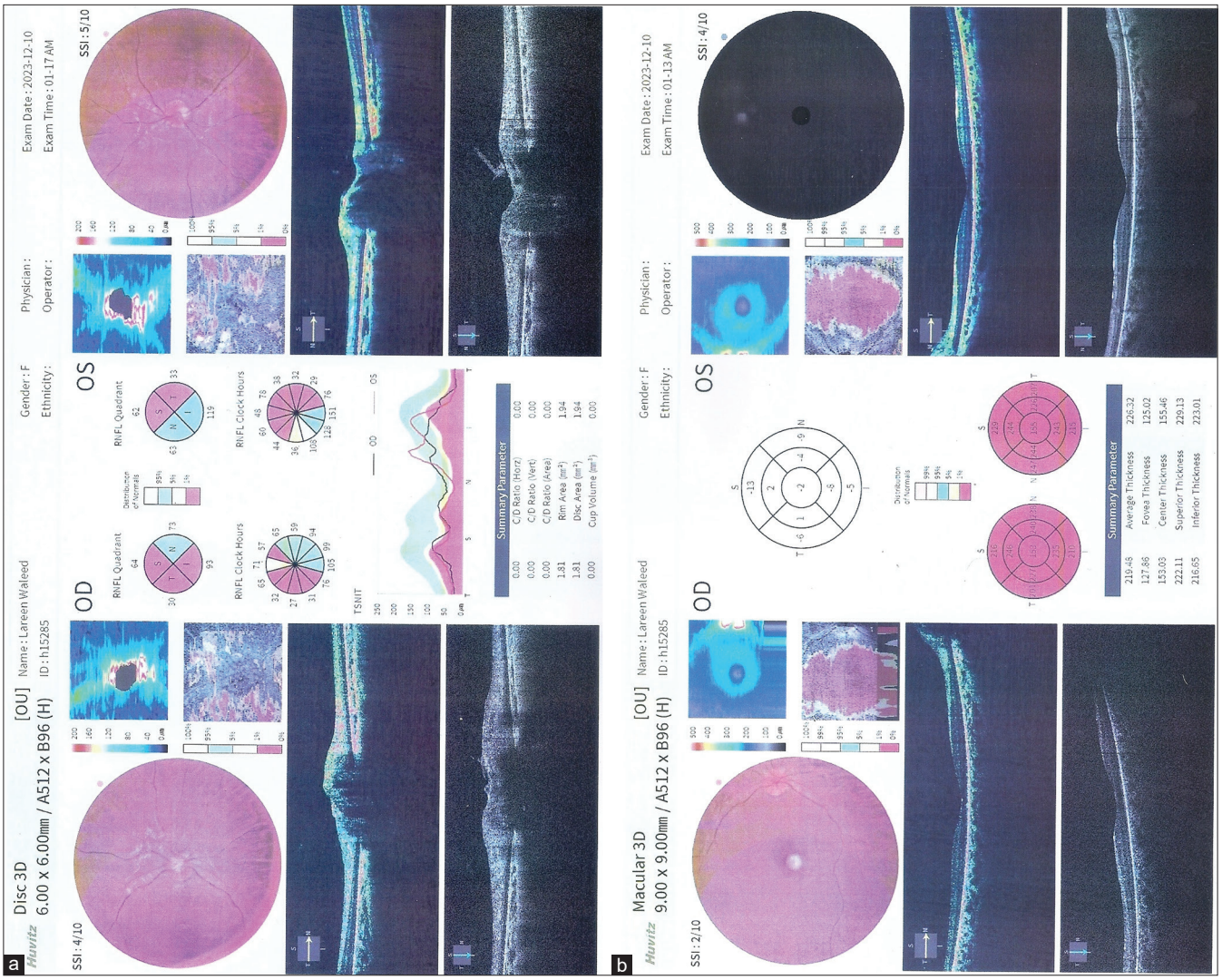

Figure 7: (a) Optical coherence tomography (December 10, 2023). (b) Optical coherence tomography (December 10, 2023)

curvature.

Pentacam pachymetric analysis [Figure 6c]

1. CTSP: Thinning of the corneal center compared to peripheral zones, with deviation from normal thickness patterns
2. Increased pachymetric progression index values suggesting a higher likelihood of ectasia
3. Corneal thickness distribution: Thinnest pachymetric point is displaced, a typical finding in keratoconus.

The pentacam findings indicate keratoconus or a similar corneal ectatic disorder. In the context of BBS, secondary ectasia due to systemic or genetic factors could also be considered.

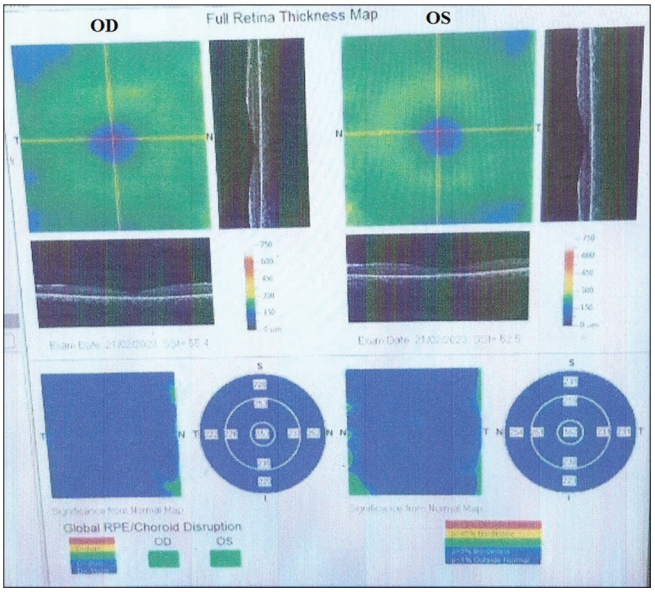

Figure 8: Full thickness map

Table 2: Bilateral symmetric changes

Bilateral Symmetric Changes	Description
Marked retinal thinning (blue and green zones)	Thinning is particularly observed in the perifoveal and macular regions
Disruption of retinal layers	Irregularity of the outer retinal layers especially in the photoreceptor and retinal pigment epithelium is revealed by B-scan cross-sectional images
Loss of foveal contour	The macular region lacks the normal depression (foveal contour), indicating structural changes in the central retina
Global retinal pigment epithelium/choroidal disruption	The bottom panel shows global abnormal in the retinal pigment epithelium/choroidal representing scattered colors deviating from the normal pattern, indicating atrophy or the degeneration of the retinal pigment epithelium.

Figure 9: The girl was seen on February 13th, 2024

Optical coherence tomography [Figure 7] performed on the December 10th, 2023:

The thickness map which shows a color-coded thickness distribution revealed generalized retinal thinning particularly in the central foveal area region which is common in progressive retinal degeneration like BBS. Macular thickness map showed areas of reduced macular thickness, indicated by cooler colors (blue/green). This suggest atrophy of the photoreceptor layer and retinal pigment epithelium which is a hall mark of retinal dystrophy of BBS. There was also thinning and disruption of the outer retinal layers (photoreceptors and retinal pigment epithelium).

The findings of full thickness map [Figure 8] showed bilateral symmetric changes that are typical of genetic dystrophy [Table 2].

The girl [Figure 9] was seen on February 13th, 2024, follow-up visual acuity):

RE: 6/36 (uncorrected) LE: 6/36 (uncorrected).

Both eyes have worsened further, with uncorrected visual acuity dropping to 6/36 (20/120) in both eyes. This indicates that her vision is significantly impaired, and she may be approaching the advanced stages of retinitis pigmentosa, where central and peripheral vision loss is more pronounced.

A drop in both eyes to 6/36 could suggest that the retinal degeneration is progressing symmetrically. In retinitis pigmentosa, central vision is often the last to go, but as the disease advances, both central and peripheral vision can be affected, leading to profound visual impairment.

Refractive Error (February 10th, 2024)

The patient is 3 diopters myopic (nearsighted) (Sphere: −3.0) in both eyes, meaning that she requires a prescription for clear distance vision.

Optical coherence tomography performed on the February 13th, 2024:

The cross sectional scan showed disruption or thinning of the outer retinal layer (photoreceptor layer and retinal pigment epithelium), especially in the central region which is consistent with retinal dystrophy.

These findings reflect degenerative changes affect the retina, and are consistent with retinitis pigmentosa changes, a key feature of BBS.

Optical coherence tomography also showed thinning of the retinal nerve fiber layer which suggests optic nerve atrophy, a potential complication of BBS.

The main findings of the optical coherence tomography [Figure 10] which was perfumed on the February 13th, 2024) included: Generalized retinal thinning, especially in the central foveal region, characteristic of retinal dystrophy. Macular thickness and outer retinal layer disruption confirmed retinal degeneration. Bilateral symmetric changes were observed, which are typical of genetic retinal dystrophies.

Eyeglass prescription (February 13th, 2024): RE: −1.0 (sphere), −3.0 (astigmatism), axis 180° (horizontal astigmatism). LE: −1.0 (sphere), −3.0 (astigmatism), axis 180° (horizontal astigmatism).

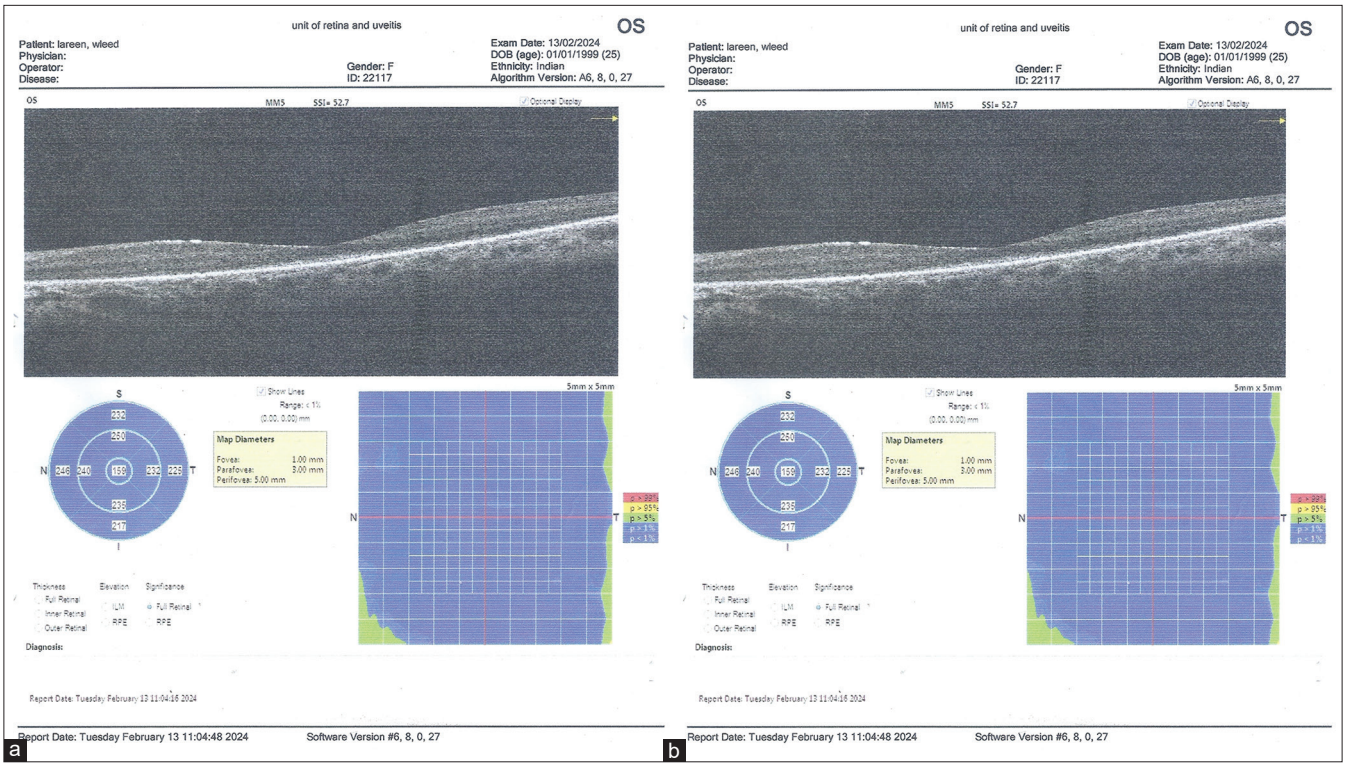

Figure 10: (a) Optical coherence tomography (February 13, 2024). (b) Optical coherence tomography (February 13, 2024)

The corrected visual acuity with eye glasses was 6/24 and the LE visual acuity was 6/18. The eye glasses were not changed.

The patient has myopia and astigmatism in both eyes, which can contribute to reduced visual acuity if not corrected. However, the primary cause of her vision deterioration is likely the progressive retinal degeneration associated with BBS rather than refractive error. Her eyeglass prescription appears to correct for her refractive error adequately. However, the worsening uncorrected acuity indicates that her vision loss is primarily due to retinitis pigmentosa. The astigmatism (with the axis at 180°) is relatively common and is effectively addressed with her glasses.

The child's relative, Dr. Omeed Abdullah who is a pediatrician, requested considering the possibility of using preventive therapies to preserve her vision. Therefore, safe evidences-based therapies were considered.

An initial 1 month course of 10 doses of intramuscular citicoline was given followed by long-term supplementation with lutein, co-enzyme Q10 and oral citicoline. Thereafter, oral citicoline was replaced by topical citicoline ophthalmic preparation, and later oral goji berry was added, both medications were brought from outside Ira.

DISCUSSION

BBS and Laurence-Moon syndrome are progressive disorders with overlapping features. For our patient, the progressive nature of her retinal degeneration aligns with the typical progression of retinitis pigmentosa, a hallmark of BBS.

Although there is no established cure for retinal degeneration in these syndromes, various therapies have been explored to slow the progression and preserve vision.

Before delving into the available evidence-based new potential therapies relevant to the ocular abnormalities of BBS, it is imperative to underscore the principles of evidence-based medicine, where research evidence is integrated with clinical expertise and patient values to optimize patient care.

Updating and innovating medical practices and patient care should, ideally be based on strong evidence, but this is not always possible, and there is no best evidence to deal with many of the medical problems that have no known effective or satisfactory treatment.

Therefore, the medical community has increasingly relying on the most expert doctors who can

judiciously use less strong evidence from published research including evidence from controlled and uncontrolled trials, and even the evidence available from published case reports.[4-6]

Given the lack of robust evidence for a universal therapeutic regimen, treatment strategies often rely on expert opinion, case reports, and emerging research.

Recent studies suggest the potential role of antioxidants and neuroprotective agents, such as citicoline, coenzyme Q10, lutein, and goji berry, in managing retinal degeneration. These therapies are believed to provide neuroprotective effects, reduce oxidative stress, and improve mitochondrial function, all of which are crucial in conditions like BBS.[7-11]

For this patient, a combination therapy regimen consisting of goji berry (*Lycium barbarum*), coenzyme Q10, lutein, and topical citicoline was initiated based on evidence suggesting their effectiveness in retinal protection. These supplements may help protect the retina from oxidative damage and slow the progression of retinal degeneration. Although not universally available in Iraq, these therapies were sourced externally for the patient.

Our recommendation was based on the emerging evidence (Chan *et al*., 2019, Bahrami *et al*. 2006; Mao *et al*., 2016; Parravano *et al*., 2020; Zhang *et al*., 2017) suggesting the potential therapeutic role of goji berry (*L. barbarum*) citicoline, Coenzyme Q10, and lutein in the treatment of various retinal and ocular conditions, including those affecting children, such as myopia or retinal degeneration.[7-11]

The work Chan *et al*., 2019 and Bahrami *et al*., 2006 specifically addressed the possible role of goji berry, and lutein respectively in the treatment of retinitis pigmentosa. However, it was not possible initially to adopt this recommended therapeutic approach because of non-availability of some items.[7,8]

In this patient, we used citicoline based on our extensive experience with use of citicoline in children which was summarized in a book entitled "Citicoline research progress" which has been translated into several languages.[12]

An article entitled "The use of citicoline in ophthalmology" summarized the evidence supporting the use of citicoline in this patient.[13]

Citicoline (cytidine diphosphate-choline) is a naturally occurring compound involved in the synthesis of phospholipids, which are essential for cell membrane structure, particularly in the central nervous system and retina. It has been suggested that citicoline can improve retinal function, slow the progression of vision loss, and protect against further damage through supporting retinal cell integrity by promoting phospholipid synthesis, enhancing mitochondrial function, and protecting retinal cells from oxidative stress.

These mechanisms are particularly relevant for conditions such as BBS, where retinal cell degeneration is a central concern.[12,13]

In 2019, Chinese researchers led by Henry Chan Ho-lung suggested that Goji berry (*L. barbarum* L), a Chinese plant polysaccharides supplement could have a neuroprotective effect on the retina that could possibly used to delay deterioration in vision in patients with retinitis pigmentosa.

They reported a placebo-controlled study which included 42 patients with retinitis pigmentosa. Twenty-three patients were treated with oral goji berry supplement for 1 year and 19 received placebo. Treatment prevented thinning of the macular layer occurred in the patients who received placebo ($P = 0.008$).

Treatment was not associated with important adverse effects. They suggested that goji berry supplement has a neuroprotective effect on the retina and can be used to slow or minimize cone degeneration.

Goji berries are known for their antioxidant properties and have been shown to improve retinal health and function by enhancing retinal blood flow and reducing inflammation. For our patient, goji berries could help protect the retina from oxidative damage, improve retinal blood circulation, and potentially slow the progression of retinal diseases, including conditions like retinitis pigmentosa or macular degeneration.[7]

Lutein is a carotenoid known for its antioxidant properties, and has been shown to be particularly beneficial for protecting the retina from oxidative

damage. Lutein accumulates in the macula of the eye, where it helps filter harmful blue light and protect retinal cells from oxidative stress.

According to ophthalmologist Hossein Bahrami and his colleagues from the United States, lutein supplementation has been studied in the context of retinitis pigmentosa, where it showed potential in preserving vision and slowing disease progression.[8]

Coenzyme Q10 is an antioxidant that plays a critical role in mitochondrial function and energy production. It has been shown to have neuroprotective effects, particularly in diseases that involve retinal degeneration including retinitis pigmentosa. CoQ10 helps mitigate oxidative stress and improves cellular energy metabolism in the retina, which is crucial for maintaining retinal cell integrity and function.

In 2017, Zhang *et al*. from the United Kingdom and Italy reviewed the literature and underscored the findings of previous studies which showed treatment with CoQ10 can improve visual function through beneficial effects on function of inner retina and improving visual cortical response.

They emphasized that oxidative stress plays an important role in the pathogenesis of retinitis pigmentosa, and thus CoQ10 is a therapeutic target for the conditions. Zhang *et al*. also emphasized the accumulating evidence supporting a role of CoQ10 in retinal diseases through preventing the production of reactive oxygen species and preventing neuroretinal cells oxidative damage.[11]

It is hoped that the combination therapy (goji berry, citicoline, lutein, and co-enzyme-Q 10) will exert a synergistic effect.

Citicoline could address neural and retinal cell integrity, CoQ10 would provide mitochondrial support and reduce oxidative stress, lutein would protect the retina from light-induced damage, and goji berry could support retinal health through its anti-inflammatory and antioxidant properties.

Our patient is suffering from myopia and early retinal degeneration; the combination therapy might help by:

Slowing myopia progression through improved retinal and optic nerve function by citicoline. Protecting the retina from oxidative damage and improving retinal cell function and integrity through CoQ10 and lutein.

Enhancing retinal health and possibly delaying the progression of retinal degenerative diseases via goji berry and lutein.

CONCLUSION

BBS presents the significant challenges in terms of both diagnosis and management. This case illustrates the importance of early diagnosis, including the use of ERG, and the role of innovative, evidence-based therapies in managing the ocular complications of BBS. While the current treatment options are not curative, they may help slow progression and preserve vision. The combination of citicoline, Goji berry, coenzyme Q10, and lutein represents a promising approach for the management of retinal degeneration in BBS patients, although further clinical trials are needed to confirm their efficacy.

ACKNOWLEDGMENT

The girl and her parents happily accepted the publication of the patient photos. Some of the sketches (figures) in this book have been included in a previous publication. The author has the copyright of the sketches (figures) included in this book.

CONFLICT OF INTEREST

None.

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