Bilateral Acute Depigmentation of the Iris: Report of 26 New Cases and Four-year Follow-up of Two Patients

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Purpose: To report new cases of bilateral acute depigmentation of the iris (BADI), a recently described clinical entity, and to report the 4-year follow-up of 2 patients that was published previously.

Design: A retrospective case series.

Participants: Twenty-six Turkish patients who were diagnosed with BADI between 2006 and 2008 and 2 patients who were reported previously.

Methods: We reviewed the patients’ charts and clinical photographs. Observation procedures included clinical examination, anterior segment color photography, laser flare photometry, and pupillometry. We performed an anterior chamber tap in 2 patients for polymerase chain reaction (PCR) to demonstrate the DNA of herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV) in the aqueous samples.

Main Outcome Measures: Demographic features, presenting symptoms, laboratory findings, changes in iris stromal pigment and architecture, and time to resolution of pigment dispersion in the anterior chamber.

Results: Nineteen patients were female, and 7 patients were male. Mean age was 32.3 ± 8.6 years. All had bilateral involvement. Twenty patients (76.9%) presented with photophobia and red eyes, and 4 patients (15.4%) presented with a recent change in eye color. Ten patients (38.5%) had flu-like symptoms preceding the onset of ocular symptoms. Diagnostic laboratory workup, viral serology, and PCR analysis of the aqueous humor were unrewarding. Diffuse depigmentation of the iris stroma from the collarette to the iris root was seen in 16 patients, and geographic areas of depigmentation were seen in 10 patients. There was heavy pigment deposition in the trabecular meshwork in all patients. Anterior chamber flare was elevated in eyes with circulating pigment. The pupil was not affected. Twenty patients received topical corticosteroids. Pigment dispersion resolved in 1 to 16 weeks (median, 9 weeks). The intraocular pressure was elevated in 8 steroid-treated eyes but was controlled with antiglaucomatous medications. In 2 patients reported previously, the depigmented iris stroma became repigmented after 4 years.

Conclusions: Patients with BADI present with bilateral, symmetrical, nontransilluminating depigmentation of the iris stroma and pigment discharge into the anterior chamber. Young female persons are more commonly affected. The cause remains unknown. After 4 years, the ocular findings in 2 patients normalized.

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Materials and Methods

Between August 2006 and August 2008, 28 patients with BADI were seen at 3 university clinics, 2 state hospitals, and 1 private practice in Turkey. One patient with a history of unilateral uveitis associated with Behçet’s disease and another patient with a history of unilateral viral iridocyclitis were excluded from the study. We reviewed the medical records and color photographs of 26 patients for the purpose of this study. Informed consent of the patients was obtained. The study was approved by the Ethical Committee of Istanbul Faculty of Medicine, Istanbul University. The study was conducted according to the tenets of the Declaration of Helsinki.

A detailed history was obtained from each patient at the initial visit, including ocular symptoms and ocular and medical histories.
A complete ocular examination was performed at each visit, including best-corrected visual acuity, slit-lamp biomicroscopy, tonometry, and indirect ophthalmoscopy. Gonioscopy was performed in all patients. Color photographs of the anterior segment were taken in each patient. We used the Vision Monitor WIN8000E (Metrovision, Perenchies, France) to perform pupillometry and the Kowa FC-2000 (Kowa Company, Ltd, Tokyo, Japan) laser flare photometer to measure anterior chamber flare in patients followed at the Uveitis Service of the Department of Ophthalmology, Istanbul Faculty of Medicine. The pupil diameters were measured under photopic and scotopic conditions before and 1 hour after the instillation of apraclonidine 0.5% (Iopidine, Alcon, Turkey) 1 drop in each eye. Laser flare photometry readings were obtained after pupillary dilation.

Diagnostic laboratory workup included erythrocyte sedimentation rate, complete blood count, and biochemistry. Serum immunoglobulin (Ig)-G and M antibodies against herpes simplex virus (HSV) I and II, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus, and Parvovirus were measured in 10 patients. In 2 patients who gave consent to an anterior chamber tap, aqueous humor was collected 3 and 6 days after the onset of ocular symptoms. Aqueous samples were sent to the Virology Laboratory at Hopital Saint Vincent-de-Paul Hospital, Paris, France, for polymerase chain reaction (PCR) analysis to demonstrate the DNA of HSV, VZV, and CMV.

Patients were treated with topical corticosteroids when they had acute symptoms or ongoing pigment dispersion in the anterior chamber. Empirical treatment with oral acyclovir 2400 mg/d was given in the first 5 patients with recurrent symptomatic pigment dispersion. We used only topical corticosteroids in subsequent cases with recurrences. In patients with an intraocular pressure (IOP) more than 21 mmHg, topical antiglaucomatous medications were used.

The main outcome measures were demographic features, presenting ocular and systemic symptoms, laboratory findings, changes in iris stromal pigment and architecture, and time to resolution of pigment discharge in the anterior chamber.

Two patients reported previously1 returned for a follow-up visit 50 months after the initial presentation. Color photographs were taken and compared with the initial photographs in these 2 patients.

We used the Statistical Package for the Social Sciences 11.5 for Windows (SPSS Inc., Chicago, IL) for analysis of data. Wilcoxon signed-ranks test was used for comparison of pupil diameters before and after instillation of apraclonidine 0.5%. A P value less than 0.05 was considered significant.

Results

Nineteen new patients were female and 7 patients were male. The mean age at the diagnosis of BADI was 32.3 ± 8.6 years (range, 18–52 years). Seven patients were seen once or had a follow-up of less than 1 month. In the remaining 19 patients, the mean follow-up was 6.5 ± 6.7 months (range, 1–23 months). All patients had bilateral involvement. The demographic and clinical characteristics of the patients are shown in Table 1.

Presenting Ocular Symptoms

Twenty patients (76.9%) had an acute onset of severe photophobia, red eyes, and ocular pain. Severe photophobia was the most prominent symptom. Both eyes were involved simultaneously or within a few days. Time from onset of acute symptoms to presentation ranged from 1 to 4 days in 11 patients and from 10 days to 6 weeks in 9 patients. Those who presented late were receiving topical corticosteroids prescribed elsewhere with a diagnosis of acute iridocyclitis. Four patients (15.4%) presented because of a recent change in eye color noticed by the patients themselves or by others. All stated that their brown eyes had turned gray. Only 1 of them recalled an episode of photophobia and red eyes 5 months before presentation. In the remaining 2 patients (7.7%), BADI was diagnosed during routine ocular examination. Only 1 of them recalled an episode of photophobia and red eyes 4 months before the diagnosis of BADI.

Ocular History

In all patients, ocular history was unremarkable. None of them had undergone ocular surgery.

Systemic Symptoms and Medical History

In 11 patients (42.3%), medical history was unremarkable. Ten patients (38.5%) had a history of upper respiratory tract infection or flu-like illness preceding the onset of ocular symptoms, and all had prescriptions of oral antibiotics, including moxifloxacin in 8 patients and amoxicillin clavulanate in 2 patients. One of them had a diagnosis of Crohn’s disease without previous ocular involvement. Five patients had a history of recurrent fever blisters. Only 1 of them had fever blisters at the onset of ocular symptoms. Two patients had oral and genital ulcers. In both of these patients, HSV I DNA was found by PCR of the scrapings of genital ulcers at the Dermatology Department. One patient had undergone rhinoplasty 1 month before the onset of ocular symptoms.

Results of Laboratory Workup

Diagnostic workup was unrewarding. Viral serology performed in 10 patients did not support the presence of active systemic infections because the IgM antibodies were negative and IgG antibodies were not elevated. All had IgG antibodies against CMV. In 2 patients, PCR analysis of the aqueous humor was found to be negative for HSV, VZV, and CMV.

Ocular Findings at Presentation

All patients had 20/20 vision in both eyes. Bulbar conjunctival and episcleral injection was more pronounced than ciliary injection in eyes with conjunctival hyperemia. Fine pigment keratic precipitates (KPs) were seen in 16 patients (32 eyes). There was circulating pigment in the anterior chamber in both eyes of 20 patients and was graded from 0.5+ to 3+ at slit-lamp examination. Depigmentation of the iris stroma was seen at the initial visit in 22 patients and at the second or third-week visit in 4 patients. The latter was mistaken for pigment dispersion syndrome until iris stromal change was noticed. The iris stroma was diffusely depigmented and had a granular appearance from the collarette to the iris root bilaterally in 16 patients (Fig 1; available at http://aaojournal.org). There were 1- to 2-mm extensions of the depigmented area toward the pupil in 4 eyes and patches of healthy stroma within the depigmented area in several eyes. There were geographic areas of depigmentation and granularity preferentially affecting the superior peripheral iris in both eyes of 10 patients (Fig 2; available at http://aaojournal.org). One of them had depigmentation of only the superior peripheral iris in 1 eye and more extensive depigmentation in the other eye. Other patients had symmetrical involvement of both irides. All patients originally had brown irides, and the depigmented areas caused a dull grayish discoloration. None of the patients had transillumination defects or posterior synechiae. The pupil was round in all but 1 eye of a patient that had slight irregularity. We did not see pigment deposition on the surface of
the lens in any patient. The corneal sensation was intact, the vitreous was clear, and the fundus was normal in all patients. The IOP was elevated bilaterally in only 1 patient (25 mmHg in the right eye and 24 mmHg in the left eye). On gonioscopy, there was heavy pigment deposition especially in the inferior angle in all patients. Laser flare photometry was performed at the initial visit in 13 patients. The highest flare reading was 21 ph/ms (Table 1).

Pupillometry Findings

Pupillometry was performed in 12 patients (Table 1). One hour after instillation of apraclonidine 0.5%, there was a significant change in pupil diameter under photopic conditions (P = 0.812 and P = 0.414 for the right and the left eyes, respectively), but the mean pupil diameter was significantly smaller compared with the pre-apraclonidine diameter under scotopic conditions (P = 0.002 and P = 0.003 for the right and left eyes, respectively). We did not observe dilation of the pupil in any eye under scotopic conditions after the instillation of apraclonidine.

Treatment and Follow-up

Topical corticosteroids were used in 20 patients who had circulating pigment in the anterior chamber. In 9 patients, tapering or discontinuation of topical corticosteroids at 1 to 4 weeks resulted in immediate relapse of ocular symptoms, conjunctival hyperemia, flare rise (up to 143 ph/ms), and a high grade of pigment discharge in the anterior chamber. There was no change in the area of involvement of the iris in any of the patients who experienced relapses. At the onset of relapse, there was a reduction of IOP by 7 to 10 mmHg in 4 eyes of 3 patients. Topical corticosteroids were restarted or the dose was increased in all, and oral acyclovir 2400 mg/d was administered to 5 patients for 2 to 5 weeks. On reinsti-
tution of topical corticosteroids,ocular symptoms and conjunctival hyperemia disappeared immediately; the IOP returned to previous levels, and flare values declined rapidly; but the resolution of pigment dispersion took several weeks. The IOP increased to 23 to 37 mmHg in 8 eyes of 5 patients at 1 to 8 weeks after the presentation. All were receiving topical corticosteroid therapy at the time of IOP increase. The IOP was controlled rapidly with topical antiglaucomatous medications and remained at normal levels after discontinuation of antiglaucomatous therapy after 2 to 8 weeks in all. Time from onset of ocular symptoms to complete resolution of pigment in the anterior chamber was 8.1 ± 4.6 weeks (median, 9 weeks; range 1–16 weeks) in 19 patients. Topical corticosteroids were slowly tapered and discontinued when there was no circulating pigment in the anterior chamber. One patient

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Table 1. Demographic and Clinical Features of 26 Patients (52 Eyes) with Bilateral Acute Depigmentation of the Iris

<table>
<thead>
<tr>
<th>Age (Mean±SD; Range)</th>
<th>32.3±8.6; 18–52 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 patients (73.1%)</td>
</tr>
<tr>
<td>Male</td>
<td>7 patients (26.9%)</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
</tr>
<tr>
<td>Photophobia/red eyes/ocular pain</td>
<td>20 patients (76.9%)</td>
</tr>
<tr>
<td>Change in eye color</td>
<td>4 patients (15.4%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2 patients (7.7%)</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>26 patients (100%)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>0</td>
</tr>
<tr>
<td>Visual acuity</td>
<td></td>
</tr>
<tr>
<td>20/20</td>
<td>52 eyes (100%)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td></td>
</tr>
<tr>
<td>Pigment keratic precipitates</td>
<td>16 patients (61.5%)</td>
</tr>
<tr>
<td>Circulating pigment in the anterior chamber</td>
<td>20 patients (76.9%); 40 eyes (76.9%)</td>
</tr>
<tr>
<td>Posterior synechiae</td>
<td>0</td>
</tr>
<tr>
<td>Iris stromal depigmentation</td>
<td>26 patients (100%); 52 eyes (100%)</td>
</tr>
<tr>
<td>Bilateral diffuse</td>
<td>16 patients (61.5%)</td>
</tr>
<tr>
<td>Bilateral segmental</td>
<td>10 patients (38.5%)</td>
</tr>
<tr>
<td>Pigment deposition in the angle</td>
<td>26 patients (100%); 52 eyes (100%)</td>
</tr>
<tr>
<td>IOP at presentation (mean±SD; range)</td>
<td></td>
</tr>
<tr>
<td>Right eye</td>
<td>14.0±3.8 mmHg; 7–25 mmHg</td>
</tr>
<tr>
<td>Left eye</td>
<td>13.4±3.8 mmHg; 6–24 mmHg</td>
</tr>
<tr>
<td>Anterior chamber flare measured in 13 patients (mean±SD; range) (ph/ms)</td>
<td></td>
</tr>
<tr>
<td>In eyes with 2+ pigment (N = 12)</td>
<td>11.4±4.9; 4.3–21</td>
</tr>
<tr>
<td>In eyes with 0.5+ to 1+ pigment (N = 10)</td>
<td>7.7±3.4; 4.0–13.2</td>
</tr>
<tr>
<td>In eyes with no circulating pigment (N = 4)</td>
<td>3.4±0.2; 3.1–3.6</td>
</tr>
<tr>
<td>Pupil diameter measured in 12 patients (mean±SD) (mm)</td>
<td></td>
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<tr>
<td>Before apraclonidine</td>
<td></td>
</tr>
<tr>
<td>OD (photopic/scotopic)</td>
<td>2.56±0.33/5.11±1.03</td>
</tr>
<tr>
<td>OS (photopic/scotopic)</td>
<td>2.39±0.19/4.96±0.86</td>
</tr>
<tr>
<td>After apraclonidine</td>
<td></td>
</tr>
<tr>
<td>OD (photopic/scotopic)</td>
<td>2.55±0.30/4.41±0.82</td>
</tr>
<tr>
<td>OS (photopic/scotopic)</td>
<td>2.43±0.25/4.23±0.78</td>
</tr>
<tr>
<td>Elevation of IOP &gt;21 mmHg during follow-up</td>
<td>5 patients (19.2%); 8 eyes (15.4%)</td>
</tr>
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IOP = intraocular pressure; OD = right eye; OS = left eye; SD = standard deviation.
with pigment dispersion at presentation did not have follow-up. In 4 patients who had 12 to 23 months of follow-up, iris depigmentation was still noticeable at the final visit; however, previously depigmented areas were less granular and the eye color was more brown than gray.

Four-year Follow-up of Two Patients

Two patients, a 20-year-old female and a 15-year-old female (cases 3 and 4 in the previous publication1), returned for a follow-up visit 50 months after the initial diagnosis of BADI. In both patients, the previously depigmented areas of the iris stroma became repigmented and resumed a normal architecture (Fig 3A, B). There was an iris nevus in the previously depigmented stroma in 1 eye of each patient. The patients stated that they had not had any ocular symptoms after the initial episode and that it had taken more than 2 years for their eye color to return to normal. Pigment deposition in the anterior chamber angle was less than that found at the time of their initial presentation, IOP was normal, and there was no cupping of the optic disc.

Discussion

An increased awareness of BADI among Turkish ophthalmologists resulted in the report of new cases from different institutions in Turkey. Data on 26 new cases of BADI are consistent with our previously reported observations in the first 5 cases.1 Young female patients were predominantly affected. Patients had bilateral symmetrical involvement, acute depigmentation of the iris stroma without transillumination defects, pigment deposition in the angle, and a self-limited course. Four-year follow-up of 2 patients showed that the iris changes were reversible.

Ocular findings that helped us differentiate BADI from acute iridocyclitis included diffuse episcleral injection that was more pronounced than ciliary injection, presence of pigment particles but not inflammatory cells in the aqueous humor, heavy pigment deposition in the trabecular meshwork, and stromal depigmentation of the iris. It was interesting that even in eyes with very high flare readings at the onset of an acute episode, we did not see inflammatory cells in the anterior chamber or inflammatory KPs on the corneal endothelium.

Herpetic iridocyclitis without associated keratitis is a distinct entity characterized by unilateral recurrences in the same eye, sectoral or patchy atrophy of the iris, and an acute IOP increase at exacerbations2,3; it is a clinical diagnosis in most cases.4 Aqueous humor analysis showed that HSV was the most common cause of this entity followed by VZV.2 Sectoral iris atrophy may rarely be seen in immunocompetent patients with CMV anterior uveitis as well.5,6 Sectoral atrophy that results from ischemic necrosis of the iris and loss of function of the sphincter muscle may cause pupillary distortion sometimes associated with iris spiraling. Transillumination caused by the loss of iris pigment epithelium may be seen in the absence of apparent iris stromal atrophy.2,3 Posterior synechiae develop in more than 50% of the cases.2 There were several features that helped us differentiate patients reported here from those with herpetic iridocyclitis. All patients with BADI had bilateral symmetrical involvement, whereas bilateral involvement has rarely been reported in herpetic iridocyclitis.7 Fine pigment precipitates on the corneal endothelium and circulating pigment in the anterior chamber were seen in patients with BADI, but not inflammatory KPs or inflammatory cells as in viral iridocyclitis. The IOP did not increase, but decreased at acute exacerbations. Subsequent IOP increase was presumed to be due to the clogging of the trabecular meshwork with heavy pigment deposition. However, corticosteroid-induced IOP increase could not be excluded in some patients. Pupillary distortion was absent, and no spiraling of the iris or posterior synechiae was seen. The depigmented iris did not transilluminate and looked different from the atrophic patches seen in herpetic iridocyclitis. Apart from the recurrences associated with early withdrawal of topical corticosteroids, patients experienced a single episode and a self-limiting course. This was also a feature that differentiated patients reported here from the recently described chronic or recurrent CMV anterior uveitis with secondary glaucoma.8 There was a slow but substantial recovery with repigmen-

Figure 3. Color photographs of the right eye of a 15-year-old female patient show diffuse depigmentation and grayish discoloration of the iris with sparing of a peripupillary band at presentation (A) and normal iris color and a new iris nevus after 4 years (B).
Bilateral peripheral iris depigmentation has been rarely reported in Vogt-Koyanagi-Harada disease. Additional findings reported in Vogt-Koyanagi-Harada, including transillumination of the iris, seclusio pupillae, choroidal depigmentation, and chronic intraocular inflammation, were not seen in patients in the present series.

Disruption of the sympathetic stimulation of the melanocytes in the superficial stroma of the iris can lead to ipsilateral hypochromia, a well-known feature of congenital Horner’s syndrome. Sym pathetic deficit in adulthood may also rarely cause acquired hypochromia. Unilateral involvement and other features of the syndrome, such as miosis and ptosis, suggest the diagnosis, and pharmacologic tests are often used to confirm the diagnosis. Apraclonidine 0.5% causes dilation of the miotic pupil and reversal of anisocoria in eyes with denervation supersensitivity. It shows no affect or may cause constriction of the pupil in healthy eyes. Patients with widespread autonomic neuropathy can develop bilateral Horner’s syndrome. Anisocoria may not be apparent in such cases, and pupillary redilation lag may help the diagnosis. We considered sympathetic denervation in the pathogenesis of the iris depigmentation in patients with BADI. Although the patients had conjunctival hyperemia, which may be associated with loss of the vasoconstricting affects of the sympathetic innervation, they did not have miosis or ptosis. Apraclonidine 0.5% did not cause pupil dilation in any of the patients tested in the present series.

We have not been able to identity the cause of BADI. A possible association with a herpetic infection was initially suspected. Two of the first 5 patients reported previously and 5 patients in this series had a history of frequently recurring fever blisters. Two additional patients had herpetic oral and genital ulcerations. None of these patients had a history of atopy. Although 10 patients described a preceding viral illness, the cause remained unknown. Viral serology in 10 patients and PCR analysis of the aqueous humor in 2 patients were unrewarding. It could be an emerging virus that may cause upper respiratory tract disease in some and subclinical infection in others. Reversibility of the iris changes suggests that depigmentation may not be associated with active viral infection and inflammation of the iris tissue but may be due to a neuropathic effect. Because we could not perform iris angiography, an ischemic process could not be excluded.

In conclusion, BADI is a new entity that is being increasingly recognized in Turkey. It is more common in women than men. The diagnosis of BADI is currently based on a distinct constellation of ocular findings, including an acute onset of bilateral symmetrical depigmentation of the iris stroma, pigment discharge into the anterior chamber, and pigment accumulation in the trabecular meshwork. Topical corticosteroids are useful for relief of symptoms. It is a self-limiting condition. Four-year follow-up of 2 patients suggested reversibility of iris depigmentation in the long-term. The etiopathogenesis of BADI remains to be elucidated.

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References


Footnotes and Financial Disclosures

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Figure 1. Color photograph of the right eye of a 41-year-old female patient shows diffuse depigmentation and granular appearance of the iris stroma. Please note sparing of the sphincter region and a patch of healthy iris at the temporal periphery.

Figure 2. Color photograph of the right eye of an 18-year-old female patient shows depigmentation and granular appearance of the superior peripheral iris from 10 to 2 o'clock. There is also a narrow band of depigmentation at the inferior iris root.