Extensive Chorioretinal Atrophy in Vogt–Koyanagi–Harada Disease

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Purpose: To report extensive chorioretinal atrophy during the long-term course of Vogt–Koyanagi–Harada (VKH) disease not treated properly in the initial phase.

Cases: Four patients with VKH disease were examined more than 10 years after onset of the disease.

Observations: They presented initially with classic features of VKH disease, except 1 patient who had developed bilateral, acute angle-closure glaucoma as the initial sign. Two patients received systemic corticosteroid therapy at the acute phase of the disease. During the follow-up of 13–34 years subsequent to onset, these patients had chronic recurrent anterior uveitis with apparently stable depigmented fundus. Eventually, they developed diffuse, extensive chorioretinal atrophy that resulted in severe visual loss. One patient had an unusual familial occurrence of the disease.

Conclusions: Failure to prescribe proper corticosteroid therapy in the initial phase of VKH disease may lead to chronic recurrent uveitis. Long-standing uveitic reactions may eventually result in severe visual loss due to extensive chorioretinal degeneration.


Key Words: Chorioretinal atrophy, corticosteroid therapy, recurrent uveitis, Vogt–Koyanagi–Harada disease.

Introduction

Vogt–Koyanagi–Harada (VKH) disease is a bilateral, diffuse granulomatous uveitis that is probably due to an autoimmune pathomechanism directed against melanocytes. The acute panuveitis is usually resolved in months with early administration of systemic corticosteroid. Choroidal and extraocular depigmentation follow and there are no further episodes. However, improper initial therapy may sometimes lead to chronic recurrent anterior uveitis that may be resistant to corticosteroid therapy and cause vision-threatening complications, such as cataract, glaucoma, and subretinal neovascularization.1–6 Extensive chorioretinal atrophy is also occasionally observed many years after the onset of disease.7–9

We report herein, 4 additional cases of such late complications 13–34 years after onset of the disease. One case had a rare familial occurrence of the disease.

Case Reports

Of 135 patients with VKH disease seen between 1978 and 1997 in the Kagoshima University Hospital, the following 4 cases developed severe chorioretinal atrophies more than 10 years after onset of the disease. The clinical information of these cases is summarized in Table 1.

Case 1

A 66-year-old woman first noted acute visual blurring in 1980 at the age of 53 years and was treated subsequently by a local doctor with the diagnosis of VKH disease. The bilateral acute inflammation regressed with systemic corticosteroids tapered over 6 months. During subsequent years, the patient had exacerbations of anterior uveal reactions about twice each year, and was treated with a variable dose and
Table 1. Cases of Chorioretinal Atrophy as a Late Complication of Vogt–Koyanagi–Harada Disease

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age of Onset (y)</th>
<th>Initial Signs</th>
<th>Initial Treatment</th>
<th>Extraocular Signs</th>
<th>Clinical Course</th>
<th>Last Examination</th>
<th>Ophthalmoscopic Findings Both Eyes With Symmetric Changes</th>
<th>Remarks</th>
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<td>Sonoda, Nakao, &amp; Ohba</td>
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<tr>
<td>Case 1</td>
<td>F</td>
<td>53</td>
<td>Classic</td>
<td>Intravenous steroid dose, length unknown</td>
<td>Tinnitus, poliosis</td>
<td>+</td>
<td>(+ twice/year)</td>
<td>Cataract</td>
</tr>
<tr>
<td>Case 2</td>
<td>F</td>
<td>65</td>
<td>Acute glaucoma</td>
<td>Topical steroid</td>
<td>Tinnitus, vitiligo, hearing loss</td>
<td>+</td>
<td>Glaucoma, cataract</td>
<td>14</td>
</tr>
<tr>
<td>Case 3</td>
<td>M</td>
<td>18</td>
<td>Classic</td>
<td>Oral steroid dose, length unknown</td>
<td>Headache, poliosis</td>
<td>Unknown</td>
<td>Cataract</td>
<td>34</td>
</tr>
<tr>
<td>Case 4</td>
<td>M</td>
<td>41</td>
<td>Classic</td>
<td>Unknown</td>
<td>Headache, tinnitus, poliosis</td>
<td>+</td>
<td>Cataract, glaucoma</td>
<td>25</td>
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<td>Inomata [6]</td>
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<tr>
<td>Case 1</td>
<td>F</td>
<td>21</td>
<td>Classic</td>
<td>Steroid</td>
<td>Alopecia, poliosis, dysacusia</td>
<td>+</td>
<td>Glaucoma, rubeosis</td>
<td>26</td>
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<tr>
<td>Hayakawa [7]</td>
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<tr>
<td>Case 1</td>
<td>M</td>
<td>40</td>
<td>Classic</td>
<td>Oral steroid dose, length unknown</td>
<td>Tinnitus, loss of hairs, poliosis, vitiligo</td>
<td>+</td>
<td>(+ several times/year)</td>
<td>12</td>
</tr>
<tr>
<td>Case 2</td>
<td>M</td>
<td>33</td>
<td>Classic</td>
<td>Oral steroid dose, length unknown</td>
<td>Tinnitus, headache, poliosis</td>
<td>unknown</td>
<td>17</td>
<td>VA: 0.9, 0.4</td>
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Table 1. Continued

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age of Onset (y)</th>
<th>Initial Signs</th>
<th>Initial Treatment</th>
<th>Extraocular Signs</th>
<th>Clinical Course</th>
<th>Last Examination</th>
<th>Remarks</th>
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<td>Hayakawa³</td>
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<tr>
<td>Case 1</td>
<td>F</td>
<td>28</td>
<td>Classic</td>
<td>Oral steroid dose, length unknown</td>
<td>Tinnitus, loss of hairs, poliosis</td>
<td>–</td>
<td>12</td>
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<tr>
<td>Case 2</td>
<td>F</td>
<td>43</td>
<td>Classic</td>
<td>Steroid dose, length unknown</td>
<td>Tinnitus, loss of hairs, poliosis, dysacusia</td>
<td>+ (three times/y)</td>
<td>17</td>
</tr>
<tr>
<td>Case 3</td>
<td>F</td>
<td>42</td>
<td>Classic</td>
<td>Oral steroid dose, length unknown</td>
<td>Tinnitus, poliosis</td>
<td>+ (for 15 y)</td>
<td>23</td>
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<tr>
<td>Hayakawa³</td>
<td></td>
<td></td>
<td>Topical steroid</td>
<td></td>
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<tr>
<td>Case 1</td>
<td>M</td>
<td>36</td>
<td>Classic</td>
<td>Tinnitus, poliosis, vitiligo, dysacusia</td>
<td>+ (once/y, for 10 y)</td>
<td>Cataract</td>
<td>17</td>
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</table>

length of topical or systemic corticosteroid taper. The recurrent anterior uveitis caused a progressive decrease in bilateral visual acuity. The patient visited us 13 years after the onset of disease. On presentation, she also complained of persistent tinnitus and poliosis of the eyebrows. Best visual acuity was RE: 0.05 and LE: 0.6. Corneas were clear. Anterior chambers had +1 cells. Irides and anterior chamber angles were unremarkable. Lenses had posterior subcapsular opacities. Ophthalmoscopy revealed the characteristic orange-red appearance of both fundi. There were peripapillary chorioretinal areas of atrophy with some pigment clumps and multiple, yellow, discrete areas of chorioretinal atrophy in the midperiphery (Figure 1A).

Case 2

A 79-year-old woman had severe pain in the forehead, tinnitus, ocular pain, and bilateral visual loss in

Figure 1. Fundus photographs (A: case 1, B: case 2, C: case 3, D: case 4) illustrating extensive chorioretinal degeneration.
1981, when aged 65 years, and was referred to us 3 weeks later. She presented with features of acute angle-closure glaucoma; namely, perilimbal injection, shallow anterior chamber with numerous cells and flares, partial posterior synechiae, unidentified angle structure, and elevated intraocular pressure. Iridectomy relieved symptoms and normalized the intraocular pressure. During the acute phase of the disease no corticosteroid therapy was performed because of the delayed diagnosis of VKH disease. Six months later, ophthalmoscopy revealed the sunset-glow appearance of the posterior fundus and gray-white pigments in the periphery. At that time she had vitiligo over her head and mild hearing loss. In subsequent years, she was followed up by doctors in our affiliated hospital and had recurrent anterior uveal inflammation that was resistant to corticosteroids. The patient returned to our University Hospital in 1996 at the age of 79 years, 14 years after the onset of VKH disease. Best visual acuity was RE: blind and LE: 0.3 with aphakic correction. Anterior segments and intraocular pressure were unremarkable. Fundus changes were symmetric in both eyes. Chorioretinal atrophy was so marked in the peripapillary and juxtapapillary areas that the choroidal vessels were barely detectable. Optic disks appeared pale, being more prominent in the left eye (Figure 1B). There was multiple, ovoid, yellow-white well-circumscribed chorioretinal scarring in the inferior fundi. Figure 2 illustrates right visual field at the ages of 68 and 79 years.

Case 3

A 52-year-old man first noted bilateral acute visual loss and headache in 1964 at the age of 18 years. The disease was diagnosed as VKH disease by a local doctor. He recovered in a few months with oral corticosteroid administration, but reported that during the subsequent 30 years he had suffered slow, progressive bilateral decrease in visual acuity. From about 48 years of age, he had experienced difficulty in night vision as well, and at that time he was diagnosed as having retinitis pigmentosa by another local doctor. He visited us in 1998 at the age of 52 years because of further progressive visual losses. On presentation, he appeared physically healthy. Best visual acuity was RE: 0.2 and LE: 0.1, both eyes being pseudophakic. Panel D-15 test revealed blue-yellow defect in both eyes. Goldmann perimetry showed bilateral annular scotoma and peripheral field constriction (Figure 3). Results of scotopic electroretinogram were subnormal. Corneas were clear. A few inflammatory cells were present bilaterally in the anterior chamber. Pupils were round but sluggish to light. Irides and vitreous cavities were unremarkable. Ophthalmoscopy revealed bilateral diffuse chorioretinal atrophy, retinal pigment clumps of bone spi-
cule pattern in the midperiphery, and narrowed retinal artery (Figure 1C). Laboratory tests for HLA revealed HLA-DR4.

Case 4

A 66-year-old man complained of severe visual losses during the last 25 years. He had been followed-up by a local ophthalmologist. According to his statement, he first noted in 1964, at the age of 41 years, acute profound visual losses accompanied by headache, tinnitus, and irritable scalp hairs. At that time he was said to have bilateral severe uveitis, which regressed in a few months, leaving poliosis of scalp hairs. Whether he received corticosteroid therapy was unknown. Subsequently, inflammatory symptoms and signs recurred many times, and complicated cataracts and glaucoma had developed. The patient was referred to us in 1989 because of further progression of visual losses. The right eye was blind and the left eye had only light perception. Pupils were irregularly dilated with posterior synechiae and reacted poorly to light. No active inflammatory signs could be identified bilaterally in either the anterior or posterior ocular segments. Ophthalmoscopic examinations disclosed pale optic disks, widespread chorioretinal degenerative changes with proliferated pigment clumps, and narrow retinal vessels (Figure 1D).

There was familial occurrence of VKH disease. His son had developed acute, bilateral uveitis preceded by headache in 1989 at the age of 35 years. The disease was compatible with the clinical features of VKH disease, and it resolved in 3 months after initial high-dose intravenous corticosteroids followed by oral tapering, leaving a sunset-glow appearance of the fundi. A 4-year follow-up study showed no further episode.

The father and son, both affected by VKH disease, had no other physical ailments. There was no other contributory family history. The results of HLA typing were as follows. Affected father: A2, A24/B39, Bw54/Cw1, Cw7/DR4; nonaffected mother: A24, A31/B7, B15/Cw3, Cw7/DR1, DR4; affected son: A24, A31/Bw54, B15/Cw1, Cw3/DR4.

Discussion

The cases described above featured bilateral severe visual loss and extensive chorioretinal atrophy due to chronic recurrent uveitis. The disease is unequivocally diagnosed as VKH disease from the initial symptoms and signs, followed by the orange-red or sunset-glow appearance of the fundus and extraocular depigmentation, such as poliosis and vitiligo, VKH disease usually presents with a limited period of acute severe panuveitis and regresses in months with favorable visual recovery and no further episode, but it may sometimes show recurrences. When the disease recurs for a long time, complications, such as cataract, glaucoma, and subretinal neovascularization, may occur.1-6 Our patients had long-standing anterior uveal reactions and
eventually had severe visual losses, even complete blindness, at examinations 13–34 years after onset of the disease. A literature search enables one to identify 7 cases, all reported from Japan,7–10 whose clinical features are summarized in Table 1. The previously reported cases are consistent with our cases and indicate that they initially presented with classic features of VKH disease and that more than 10 years later they had severe visual loss due to extensive chorioretinal atrophy with pigment proliferation and migration in the retina.

Vogt–Koyanagi–Harada disease is recognized as an immune-mediated disease that primarily affects melanocytes. Hence, systemic administration of corticosteroid, first advocated in the late 1960s10 is the current therapeutic measure that significantly alters the course and prognosis of the disease. Early aggressive use of systemic corticosteroid followed by slow tapering over several months is recommended.11 However, if the timing, doses, and tapering of therapeutic regimen are not managed properly, anterior uveitis may be recurrent and become resistant to corticosteroid; in fact, some of our cases did not receive corticosteroid therapy at the early phase of disease. Chronic anterior uveitis may result in serious inflammatory events in the retina as well as choroid, as evidenced by a histopathologic study12 demonstrating that chronic inflammation of the choroid damages Bruch’s membrane and retinal pigment epithelium and, hence, leads to chorioretinal degeneration with pigment proliferation.

The incidence of extensive, severe chorioretinal atrophy in VKH disease remains undefined; it may be more uncommon after the introduction of standardized corticosteroid therapy. In any event, it is recommended that patients be followed up for many years, in particular those who had a chronic course of the disease.

The present observations warrant further discussion. One of our cases presented with distinct features of bilateral acute angle-closure glaucoma. The diagnosis of VKH disease and proper corticosteroid therapy in the early phase of the disease were delayed, which might have led to the long-standing anterior uveitis in this case; it is documented in the literature that occasional cases of VKH disease may develop acute angle-glaucoma as an initial clinical sign.13–15

As regards familial occurrence of VKH disease, an extensive literature search identifies 2 reports, each describing VKH disease in monozygotic twins.16,17 One of the cases described here, an elderly man, had a son who was affected with VKH disease. This is, to our knowledge, the first report of the disease over two successive generations. Immunogenetic predisposition to VKH disease has been well-defined for its significant association with specific HLA genes.18 It is of interest in this connection that the present familial cases shared HLA-DR4, an HLA class II antigen susceptible to VKH disease. It remains to be elucidated why the incidence of familial VKH disease is rare.

References