Ocular Manifestations of Juvenile Paget Disease

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Objectives: To determine the prevalence and spectrum of retinal changes in juvenile Paget disease.

Methods: Observational case series and literature review with analysis. Patients with clinical and molecular evidence of juvenile Paget disease were recruited by members of the International Hyperphosphatasia Collaborative Group. Participants underwent ophthalmic examinations consisting of at least best-corrected Snellen visual acuity and dilated fundal examination or color fundus photography. A MEDLINE literature search was performed, and all identified case reports were reviewed for information regarding ocular phenotype.

Results: Fourteen eyes from 7 patients were examined. The mean (SD) patient age was 22 (8) years, and 4 patients were female. Retinal abnormalities were evident in 12 of 14 eyes and were reported among an additional 12 patients in the literature. Retinal abnormalities included mottling of the retinal pigment epithelium, peripapillary atrophy, angioid streaks, and choroidal neovascularization. Cumulative number of retinal abnormalities was strongly associated with increasing age.

Conclusions: Juvenile Paget disease is associated with progressive retinopathy characterized by the development of angioid streaks, which may be complicated by choroidal neovascularization, the predominant cause of visual loss. Osteoprotegerin or its signaling pathway may have a role in calcification of Bruch membrane and in the pathogenesis of angioid streaks. Retinopathy in patients with juvenile Paget disease may be a sign of a more generalized vascular disorder.


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Juvenile Paget disease, or idiopathic hyperphosphatasia, is a rare recessively inherited disorder characterized by greatly accelerated bone turnover throughout the skeleton. Since the condition was first described in 1956, approximately 50 cases have been reported worldwide. Affected individuals are healthy at birth but manifest progressive long-bone deformity, kyphoscoliosis, growth impairment, and fractures in infancy or early childhood. The skull is also involved, and patients typically have massive thickening of the calvaria and sensorineural hearing loss. Life expectancy is reduced largely because of severe restrictive lung disease secondary to chest wall deformity. Bony changes are the consequence of increased activity of osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells). Juvenile Paget disease results from deletions or loss-of-function mutations in the TNFRSF11B gene (OMIM *602643), which encodes the protein osteoprotegerin, a key regulator of bone turnover.

Because skeletal features predominate, other manifestations of the disorder have received little attention. Retinal changes and blindness have been described in some patients, but the literature regarding ocular manifestations of juvenile Paget disease is limited, and most case reports do not indicate whether the eyes were examined. The objectives of this study were to determine the prevalence and natural history of retinopathy in juvenile Paget disease and to characterize the spectrum of retinal changes.

Methods

Patients with juvenile Paget disease were recruited by members of the International Hyperphosphatasia Collaborative Group in Argentina, Turkey, the United States, and New Zealand. The sole inclusion criterion was clinical and molecular diagnosis of juvenile Paget disease. There were no exclusion criteria. The age at diagnosis, presence or absence of visual symptoms, duration of visual symptoms, extraocular phenotypic features, and a detailed family history were obtained for each patient. Ophthalmic examinations consisted of at least best-corrected Snellen visual acuity and dilated binocular indirect ophthalmoscopy by an ophthalmologist (N.M.K. and A.L.V.) or color

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fundus photography through pharmacologically dilated pupils. At a minimum, fields were required from the posterior pole and the peripheral retina. Because of skeletal manifestations of this disorder, specifically limited cervical flexion and extension, standardized photography was not practical. Where possible, patients underwent full examination by an ophthalmologist consisting of best-corrected Snellen visual acuity, visual fields to confrontation, brightness sense, red perception, pseudoisochromatic color Ishihara plates, pupillary assessment, slit-lamp biomicroscopy, Goldmann applanation tonometry, and dilated funduscopy. All patients provided peripheral blood samples for genomic DNA analysis as reported previously.3 Informed consent was obtained from all participants, and the study complied with the tenets of the Declaration of Helsinki.

A literature search was performed using MEDLINE (January 1, 1950, to present) for the terms juvenile Paget disease, osteoprotegerin deficiency, and idiopathic hyperphosphatasia. All identified case reports were reviewed for information regarding the ocular phenotype.

RESULTS

Seven patients with juvenile Paget disease were identified, and all but 1 had retinal abnormalities. Three patients were siblings (patients 3, 6, and 7); clinical details of all study patients are summarized in Table 1. The mean age at presentation was 5 years; most patients manifested difficulty in walking and long-bone deformities with or without fractures. The mean (SD) patient age at the time of study was 22 (8) years (age range, 13-31 years). All patients had sensorineural hearing loss and biochemical evidence of increased bone turnover. All were homozygous for probable loss-of-function mutations in TNFRSF11B. Details of the skeletal and genetic findings in 6 of these patients have been published previously.3 The ophthalmic findings are summarized in Table 2. All patients had best-corrected visual acuity of 20/30 Snellen or better. Results of optic nerve function clinical tests (visual fields to confrontation, brightness sense, red perception, pseudoisochromatic color Ishihara plates, and pupillary assessment) and slitlamp examinations of the anterior segment were normal in patients 3, 6, and 7. Slitlamp examination could not be performed in patients 1 and 2.

All patients underwent dilated fundal examination by an ophthalmologist or color fundus photography of the posterior pole and peripheral retina through pharmacologically dilated pupils. The fundus was normal in only 1 patient examined. Optic nerve pallor was evident in 4 patients, and 4 patients had peripapillary atrophy. Five patients had mottling of the retinal pigment epithelium, and an equal number had angioid streaks. These changes are shown in Figure 1. In patient 7 (Table 2), angioid streaks were complicated by peripapillary choroidal neovascularization. Shortly after undergoing retinal examination as part of this study, patient 4 was seen with signs of cavernous sinus syndrome, including bilateral chemosis and convergent strabismus secondary to bilateral sixth nerve palsy. Magnetic resonance imaging revealed large bilateral intracavernous aneurysms of the internal carotid artery (Figure 2).

We identified 40 case reports of juvenile Paget disease describing 55 patients in the literature. Ocular manifestations were described in 12 patients, including se-
Angioid streaks were the most common ocular abnormality. They were found in almost all patients by the end of the second decade of life and seemed to be a precursor to the development of choroidal neovascularization, which occurred in more than half of those with angioid streaks. Subsequent involvement of the macula by disciform scarring was the predominant cause of visual loss. Two patients with long-term serial follow-up developed blindness due to choroidal neovascularization and disciform scarring.

The nonspecific finding of mottling of the retinal pigment epithelium was observed less frequently and was more common in older patients. Peripapillary atrophy and optic nerve pallor were less frequent observations across all age groups. Electrophysiologic studies were undertaken in 4 patients, and all results were abnormal, showing diminished photoreceptor function. There was a striking correlation between cumulative number of retinal abnormalities and increasing age (Figure 3).

To our knowledge, this is the largest systematic study of ophthalmic manifestations of juvenile Paget disease reported to date. It confirms that juvenile Paget disease is associated with distinctive retinopathy that is detectable in most patients by the end of the second decade of life. Cumulative number of retinal abnormalities is strongly associated with older age, suggesting that this is a progressive disorder. The earliest changes seem to be optic nerve pallor and mottling of the retinal pigment epithelium. This is followed by the development of angioid streaks, choroidal neovascularization, and ultimately disciform scarring and visual loss. Among patients in whom electrophysiologic studies were undertaken, this seems to correlate with altered retinal function. Two published case reports of patients studied serially provide evidence that severe visual loss can occur. Both patients had mild skeletal phenotypes. Because they have the longest life expectancy, such patients may paradoxically be at greatest risk of visual loss.

Juvenile Paget disease results from deletions or loss-of-function mutations in TNFRSF11B, which encodes osteoprotegerin. Osteoprotegerin is a soluble homodimeric glycoprotein, secreted by osteoblasts and osteoblast precursors, that has an important role in regulating bone turnover. Osteoprotegerin is a decoy receptor for receptor activator of nuclear factor-κB ligand (RANKL), which dampens the stimulus to bone resorption; therefore, osteoprotegerin deficiency is characterized by unrestrained bone remodeling activity.

Patients with juvenile Paget disease have greatly expanded skull bones, so it is possible that the optic nerve pallor and atrophy we observed could result from bony compression of the optic nerve at the orbital apex. Mottling of the retinal pigment epithelium seems to be an early sign and may represent changes in underlying Bruch membrane. Angioid streaks were a common finding. These are linear gray or dark red lesions that typically extend radially from the optic disc and run beneath the retinal vessels. They are seen in a wide variety of systemic conditions and are of significance because they may be complicated by choroidal neovascularization in up to 86% of cases. Although recognized as breaks or dehiscence in a thickened, calcified, and abnormally brittle Bruch mem-

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**Table 3**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Follow-up Duration (years)</th>
<th>Ocular Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>12</td>
<td>Angioid streaks, choroidal neovascularization, disciform scarring</td>
</tr>
<tr>
<td>Patient 2</td>
<td>15</td>
<td>Angioid streaks, choroidal neovascularization, disciform scarring</td>
</tr>
<tr>
<td>Patient 3</td>
<td>18</td>
<td>Angioid streaks, choroidal neovascularization, disciform scarring</td>
</tr>
</tbody>
</table>
brane, their exact pathogenesis remains unknown. Therefore, osteoprotegerin deficiency may provide new insights about pathogenesis of angioid streaks. Osteoprotegerin is expressed in many tissues, including the eye and vascular endothelium. Animal investigations have shown that osteoprotegerin-deficient mice develop calcification of the internal elastic lamina of the aorta and renal arteries, suggesting that osteoprotegerin acts as an inhibitor of calcification of elastic fibers. Angioid streaks have not been described in the analogous bone condition of familial expansile osteolysis, which results from constitutive activation of RANK due to tandem duplications within its TNFRSF11A gene. This suggests that osteoprotegerin deficiency causes angioid streaks through a system independent of RANK activation. Osteoprotegerin may prevent vascular calcification by inhibiting apoptosis of endothelial cells caused by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL).

### Table 3. Patients in the Literature Having Juvenile Paget Disease With Ocular Features

<table>
<thead>
<tr>
<th>Patient/Source</th>
<th>Sex/Age, y</th>
<th>Best-Corrected Visual Acuity, Snellen Equivalents</th>
<th>Visual Fields</th>
<th>Retinal Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Iancu et al., 1978</td>
<td>F/5</td>
<td>20/40</td>
<td>20/40</td>
<td>. . .</td>
</tr>
<tr>
<td>B/Bakwin and Eiger, 1965</td>
<td>F/5</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>C/Iancu et al., 1978</td>
<td>M/7</td>
<td>Normal</td>
<td>Normal</td>
<td>. . .</td>
</tr>
<tr>
<td>D/Thompson et al., 1969</td>
<td>M/9</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>E/Mitsudo, 1971</td>
<td>M/9</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>F/Bakwin et al., 1964</td>
<td>F/11</td>
<td>20/90</td>
<td>20/90</td>
<td>Normal</td>
</tr>
<tr>
<td>G/Bakwin et al., 1964</td>
<td>F/14</td>
<td>. . .</td>
<td>. . .</td>
<td>Grossly constricted with relative central scotomas</td>
</tr>
<tr>
<td>H/Thompson et al., 1969</td>
<td>F/19</td>
<td>20/70</td>
<td>20/200</td>
<td>. . .</td>
</tr>
<tr>
<td>I/Mitsudo, 1971</td>
<td>M/17</td>
<td>Diminished</td>
<td>Diminished</td>
<td>. . .</td>
</tr>
<tr>
<td>J/Sharif et al., 1989</td>
<td>M/10</td>
<td>20/20</td>
<td>20/20</td>
<td>. . .</td>
</tr>
<tr>
<td>J/M13</td>
<td>20/20</td>
<td>HM</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>J/M18</td>
<td>20/60</td>
<td>20/120</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>K/Whyte et al., 2007</td>
<td>M/31</td>
<td>20/16</td>
<td>20/120</td>
<td>. . .</td>
</tr>
<tr>
<td>K/Mlate 30s</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>K/M41</td>
<td>20/30</td>
<td>20/80</td>
<td>Generalized constriction of visual fields, paracentral relative scotomas</td>
<td>Midperipheral and peripheral white speckled retinal lesions</td>
</tr>
<tr>
<td>M/60</td>
<td>Legally blind</td>
<td>Legally blind</td>
<td>Central scotoma</td>
<td>. . .</td>
</tr>
</tbody>
</table>

Abbreviations: CNVM, choroidal neovascular membrane; ellipses, not reported; ERG, electroretinogram; F, female; HM, hand motion; M, male; PPA, peripapillary atrophy; RPE, retinal pigment epithelium.
deed, it has been shown that osteoprotegerin protects endothelial cells from apoptosis induced by serum withdrawal and nuclear factor-κB inactivation. Therefore, osteoprotegerin deficiency may lead to angiod streaks through loss of inhibition of calcification in the elastin-rich middle elastic layer of Bruch membrane, with subsequent formation of cracks. Whether susceptibility of the choriocapillaris endothelium to apoptosis contributes to this process requires further investigation.

Angiod streaks may be a marker or indicator of calcification in the systemic vasculature. Association between juvenile Paget disease and vascular calcification has been clinically observed. Mitsudo reported that calcium deposits were found in the intima of all muscular arteries at the time of autopsy in a 17-year-old boy with juvenile Paget disease who died of intracerebral hemorrhage. Furthermore, a temporal artery biopsy specimen from a 6-year-old boy with the disease revealed calcification of the internal elastic lamina. These findings are in keeping with results of animal investigations showing that osteoprotegerin-deficient mice develop early arterial calcification. In our study, a patient investigated for signs of cavernous sinus syndrome was found to have intracavernous internal carotid artery aneurysms that were identical to those recently described by Allen et al in an 11-year-old boy with a severe form of juvenile Paget disease due to complete deletion of TNFRSF11B. Compared with extracranial arteries, intracranial arteries have an attenuated tunica media and lack an external elastic lamina, rendering them vulnerable to aneurysm formation.

Results of studies indicate that the skeletal phenotype of juvenile Paget disease can be ameliorated with intensive bisphosphonate treatment to inhibit bone turnover. However, neither systemic therapy with antireportive agents nor drugs specifically targeting the RANKL–osteoprotegerin–RANK system seem effective in modifying the ocular phenotype. Furthermore, response to choroidal neovascularization photodynamic therapy has been disappointing, and there are no published reports of treatment with intravitreal anti-VEGF agents. Newer agents such as denosumab that mimic the effects of osteoprotegerin may influence the ocular phenotype; however, their efficacy remains to be proven. Given the rarity of this disease, it is unlikely there will ever be an “evidence-based” treatment.

Based on our findings, we recommend that patients with juvenile Paget disease be examined by an ophthalmologist at diagnosis and then on a regular basis according to the severity of ocular involvement. Patients should be warned about the risk of visual loss and should be advised to immediately report any changes in vision. Furthermore, patients with angiod streaks should be informed of the possibility of subretinal hemorrhage after even minor ocular trauma. The regular use of a macular Amsler grid to screen for metamorphopsia, which may be the first sign of choroidal neovascularization, may be beneficial. Prophylactic laser treatment of angiod streaks is discouraged by some authorities because of the risk of choroidal neovascular membrane formation.

We conclude that juvenile Paget disease is associated with progressive retinopathy characterized by optic nerve pallor, motting of the retinal pigment epithelium, and subsequent development of angiod streaks. The latter may be complicated by choroidal neovascularization, the predominant mechanism of visual loss. Retinal changes are evident by the end of the second decade of life, and the severity of retinopathy increases with age. Paradoxically, patients with a mild skeletal phenotype may be at greatest risk of ocular complications. With early use of potent bisphosphonates, amelioration of the skeletal disease could lengthen the lifespan of affected patients, increasing the risk of retinal disease development. Retinopathy associated with juvenile Paget disease seems to be part of a more generalized vascular disorder, suggesting that osteoprotegerin or its signaling pathway has an important role in inhibition of vascular calcification.

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REFERENCES


