ABOUT THE AUTHORS

NIERAJ JAIN, MD: Nieraj Jain, MD is an Associate Professor of Ophthalmology at the Emory Eye Center in Atlanta, Georgia. He received his medical degree at the Duke School of Medicine, where he stayed to complete a residency and chief residency. Subsequently, he completed fellowships in vitreoretinal surgery at the University of Michigan and ophthalmic genetics at the Casey Eye Institute. His group applies novel imaging and functional testing modalities to assess disease progression and treatment outcomes for rare retinal degenerations. He also studies off-target effects of various FDA-approved therapies, and his group was the first to describe pentosan polysulfate maculopathy.

EMILY H. JUNG: Emily is a fourth-year medical student at Emory University School of Medicine and a research student of Dr. Jain. She completed her undergraduate studies in history of science at Harvard University.

Pentosan polysulfate maculopathy: keep an eye out for this masquerader

Nieraj Jain, MD and Emily H. Jung

Pentosan polysulfate sodium (PPS) (Elmiron; Janssen Pharmaceuticals), a drug used to treat bladder pain and discomfort associated with interstitial cystitis (IC), has been linked to a distinctive vision-threatening maculopathy.[1] As with the case of hydroxychloroquine maculopathy, it is worthwhile for the general ophthalmologist to be familiar with this potentially preventable condition. In this article, we briefly summarize the evidence supporting this association, review the clinical manifestations of PPS maculopathy, and provide some guidance regarding screening protocols.

Pentosan polysulfate sodium is a semi-synthetic heparin-like macromolecule that was approved by Health Canada in 1993 for treatment of interstitial cystitis. Interstitial cystitis, also known as bladder pain syndrome, is a regional pain syndrome characterized by chronic discomfort in the bladder and pelvis, in addition to urinary frequency and urgency. Studies estimate that IC may affect more than one million individuals in the United States alone.[2] IC is estimated to account for about 3% or more of all outpatient urology clinic visits in Canada.[3]

While the exact mechanism of action is unknown, the therapeutic effects of PPS for IC appear to stem from its resemblance to glycosaminoglycans and its ability to adhere to the bladder wall mucosal membrane and control cell permeability, thereby acting as a buffer between irritants in the urine and the bladder epithelium.[4] PPS is approved for oral use only, but intravesical administration has been used as an alternative.[5] The most common side effects observed with PPS include hair loss, diarrhea, nausea, stomach pain, headache, dizziness, rash, and liver function abnormality. Two serious side effects that have been reported are increased bleeding and a pigmentary maculopathy.

Our group first described a distinctive maculopathy among a series of six patients undergoing long-term treatment with PPS in 2018.[1] Since then, many additional studies across numerous centers have corroborated this finding.[6]

STRENGTH OF ASSOCIATION

Several studies have identified an association between long-term PPS use and a unique pigmentary maculopathy. In a 2019 retrospective study, 14 of 219 patients with IC at a tertiary referral eye center exhibited the characteristic maculopathy.[7] These 14 cases were exclusively among the 80 patients who reported prior PPS use; there was not a single case of this distinctive maculopathy among the 139 IC patients with no history of PPS use. Furthermore, of all medication exposures and other covariates evaluated, the only risk factor significantly associated with the presence of this pigmentary maculopathy was exposure to PPS (odds ratio 11.25, 95% CI 3.69-34.33).[7] Subsequent studies independently conducted at numerous centers have reported a significant dose-response relationship between PPS exposure and presence of maculopathy.[8-13] A study from 2020 demonstrated prevalence rates of 13%, 30%, and 42% among patients with 500-999 grams (g), 1000-1499 g, and >1500 g of cumulative PPS exposure, respectively.[8] In another study from earlier this year, researchers found prevalence rates of 46% and 83% among patients with cumulative PPS exposures of 1500-2000 g and ≥2000 g.[11]

Studies of large administrative claims databases have yielded mixed findings. In a 2019 study analyzing claims data, the authors reported that PPS exposure was significantly associated with a new diagnosis of macular disease seven years after the initiation of the drug.[14] In contrast to this, another claims database study did not find a significant association between PPS exposure and a new maculopathy diagnosis.[15] However, when assessing these studies, clinicians must be aware of the inherent limitations in these datasets, which included patient visits having taken place prior to the widespread recognition of this novel maculopathy. In the latter study, only 0.26% of the PPS users had at least five years of exposure to the drug, and only 29% of all patients had an eye examination performed.[15] It is likely that patients with early or mild disease did not have any notable findings on exam. Furthermore, eye examinations in these studies could have been performed at any time and not necessarily at the end of the observation period when the maculopathy was most likely to manifest.[16]

CLINICAL MANIFESTATIONS

Long-term use of PPS appears to be the primary risk factor in developing the characteristic maculopathy. The initial series from 2018 reported a median treatment duration of 186 months (range, 144-240 months) and median cumulative exposure of 2263 g (range, 1314-2774 g).[1] Subsequent studies have corroborated this finding, although several cases have been identified after just three years of PPS use.[17] The prevalence of this condition remains unclear, but we believe the closest estimates to date were reported from the aforementioned study from the Kaiser Permanente Northern California health system [13%, 30%, and 42% among patients with 500-999 g (4.6-9.1 years at the standard daily dose), 1000-1499 g (9.2-13.7 years), and >1500 g (longer than 13.8 years) of cumulative PPS exposure, respectively].[8]

Affected patients commonly report difficulty reading, blurry vision, and prolonged dark adaptation. While most patients have preserved visual acuity, there have been cases of loss

of visual acuity as well, typically in the setting of progressive retinal pigment epithelium (RPE) atrophy, cystoid macular edema (CME), and/or macular neovascularization. A prospective study of visual function in PPS maculopathy demonstrated that patients may suffer from prominent visual disability despite relatively preserved visual acuity, with pronounced impact on low luminance visual function.[18]

On examination, PPS maculopathy may share some resemblance to age-related macular degeneration (AMD) and macular dystrophies. A large study at our institution found that 43% and 29% of affected patients initially carried a diagnosis of macular dystrophy and AMD, respectively.[19] On closer evaluation, however, these conditions can be differentiated from each other through the use of multimodal imaging techniques.[20,21]

Dilated fundus examination (DFE) may demonstrate parafoveal pigmented spots amidst yellowish subretinal deposits in mild disease, and paracentral RPE atrophy in more advanced disease (**Figure 1**). These findings can be quite subtle in some patients, and modern fundus imaging is an essential part of the diagnostic assessment. Fundus autofluorescence (FAF) imaging demonstrates a striking pattern of densely packed hypo- and hyper-autofluorescent spots that is symmetric between eyes and typically involves the central macula. In some cases, these changes can expand well beyond the vascular arcades. Near-infrared reflectance (NIR) and optical coherence tomography (OCT) imaging can also aid in establishing a diagnosis of PPS maculopathy, particularly in milder disease. OCT imaging can help distinguish this condition from typical AMD. Eyes with PPS maculopathy often contain focal nodular thickening of the RPE that casts a shadow on the underlying choroid. These “bumps” on OCT imaging appear to be at the level of the RPE itself and differ from the typical drusen or subretinal drusenoid deposits of AMD, which appear to be below or above the RPE, respectively.[21]

To date, no other risk factors for development of PPS maculopathy have been identified. Small studies have evaluated potential risk factors, such as smoking history, diseases involving the kidney, liver, and spleen, and body mass index; however, no significant associations have been demonstrated.[7,19] Furthermore, no genetic variants associated with PPS maculopathy have been identified to date.

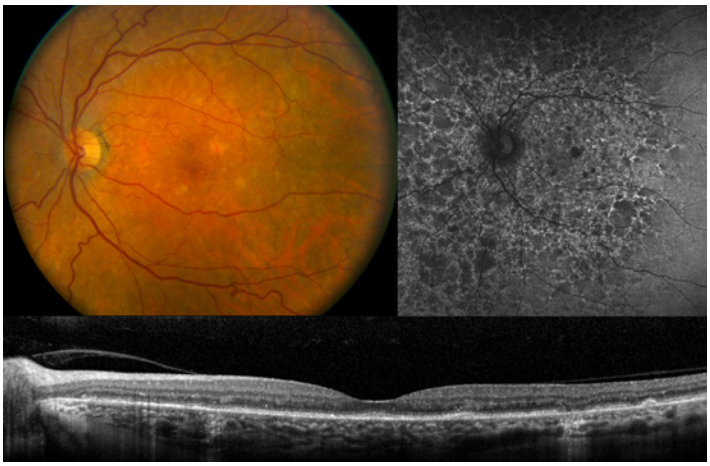

Figure 1: *Multimodal fundus imaging of the left eye of a patient with pentosan polysulfate maculopathy. (Top Left) Color fundus photo; (Top Right) fundus autofluorescence image; (Bottom) optical coherence tomography image; images courtesy of Nieraj Jain, MD*

MANAGEMENT

Currently there is no known treatment for PPS maculopathy. Thus, following a diagnosis of PPS maculopathy, patients and clinicians should have a discussion regarding drug discontinuation. If the decision is made to continue the use of PPS, patients with confirmed PPS maculopathy should continue to undergo regular comprehensive retina evaluations. It is important to note that there have been multiple reports of treatable vision-threatening sequelae, including CME and macular neovascularization.[9,19,22] Patients with CME have responded well to a wide range of therapies, including carbonic anhydrase inhibitors and anti-vascular endothelial growth factor (VEGF), and there have been reports of successful management of macular neovascularization with anti-VEGF treatment.[19,22-24]

Studies evaluating the long-term prognosis after PPS cessation have suggested that there is no disease regression. A 2020 retrospective study analyzed 11 affected patients who were followed for a median of 11.5 months after PPS cessation.[25] Eyes with atrophy at baseline demonstrated growth of atrophy at a median linearized growth rate of 0.32 mm/year (IQR, 0.13-0.38 mm/year), and some eyes without atrophy at baseline were found to have new onset incomplete RPE and outer retinal atrophy on OCT imaging.[25] For comparison, growth of atrophy in geographic atrophy, an advanced form of non-neovascular age-related macular degeneration, has been estimated at 0.33 mm/year (IQR, 0.31-0.35 mm/year).[26] Multiple case reports have found that some patients developed initial symptoms of PPS maculopathy several years (up to six years) after discontinuing PPS.[19,25,27,28]

SCREENING

In October 2019, Health Canada approved changes to the Elmiron label, noting the potential risk of pigmentary maculopathy. In June 2020, the United States Food and Drug Administration approved changes for its Elmiron label. In October 2020, Health Canada listed a personal history of any macular disease as a contraindication to PPS use and recommended that for patients with pre-existing ophthalmologic conditions, a comprehensive baseline retinal exam including color fundoscopic photography, OCT, and FAF imaging be performed prior to initiating PPS therapy.

At our institution, it is recommended that patients starting treatment with PPS undergo baseline screening and annual screening thereafter and that DFE, OCT imaging, FAF imaging, and NIR imaging be performed. Given the use of multimodal fundus imaging, retina specialists may be most comfortable performing these assessments. Clinicians should consider using the lowest dose and duration of therapy needed for disease control, and explore alternative IC therapies wherever possible.

In summary, ophthalmologists should take note of this newly recognized, preventable, vision-threatening maculopathy associated with long-term PPS use. Given that PPS has been used for decades, many under- and undiagnosed patients may already be in our clinics. Moving forward, ophthalmologists and PPS prescribers should consider implementing screening programs with multimodal fundus imaging and limiting the dose and duration of therapy wherever possible. Ongoing studies will likely refine our understanding of the prevalence and clinical manifestations of this distinctive maculopathy.

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