Pigmentary Maculopathy in Interstitial Cystitis/ Bladder Pain Syndrome Treated with Oral Pentosan Polysulfate: A Review

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Abstract

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a rare and chronic bladder condition. Pentosan polysulfate sodium (PPS) is the only oral medication approved specifically for the management of IC/BPS. In 2018, Pearce et al. reported for the first time a unique pattern of ocular pigmentary maculopathy exclusively in IC/BPS patients following PPS exposure. This publication triggered several published studies, case reports, case series, and media reports claiming a link between PPS and pigmentary maculopathy; however, a clear interpretation of these data is still awaited and there are currently no prospective, well researched, confirmatory data available.

The clinical presentation of pigmentary maculopathy is characterised by moderate visual impairments and macular hyperpigmented spots, yellow-orange deposits, and/or patchy retinal pigment epithelium (RPE) atrophy. Most patients experiencing this ocular effect used high doses of PPS over an extended period, with risk of pigmentary maculopathy associated with PPS increasing with exposure. Studies that rule out prevalent retinal abnormalities are lacking. The cause of this particular maculopathy remains unclear and further research is required. The current data suggest that a median duration of 15 years of PPS exposure must elapse before

pigmentary maculopathy is detected. Furthermore, no increased incidence of any type of maculopathy is found up to a median duration of 5 years of PPS use. Thus, in line with the current European Medicines Agency (EMA) recommendation, if patients respond to therapy and a decision is made to continue PPS for longer than 6 months, a fundoscopy with optical coherence tomography (OCT) and fundus autofluorescence should be performed. In cases of no findings, the next eye examination should be after a further 5 years of PPS use; in cases of findings, continuation of the treatment should be re-evaluated by the urologist and monitored by yearly ocular fundus examinations.

This review provides a framework for evidence-based treatment with PPS in patients with IC/BPS using appropriate monitoring and gives an overview of the current understanding and evidence of the association of PPS and a specific pigmentary maculopathy.

INTRODUCTION

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic condition of unknown aetiology. Symptoms can vary but there is typically pelvic pain or discomfort perceived to be related to the urinary bladder, usually accompanied by other urinary symptoms such as the persistent urge to void or frequency. Hunner's lesions and glomerulations (mucosal bleeding after bladder overdistension) are cystoscopic disease markers. Although a prevalence of up to 500/10,000 is reported for BPS, a substantially smaller prevalence of 1–5/10,000 is assumed for patients showing cystoscopic findings of glomerulations or Hunner's lesions corresponding to classes 2X to 3C type (European Association of Urology [EAU]/ESSIC classification[1] and National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] definition).[2]

PPS is indicated for the treatment of IC/BPS, characterised by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency, and frequency of micturition. The recommended dose of PPS is 300 mg per day, taken as one 100 mg capsule orally three-times daily. It is the only oral medication specifically for the management of IC/BPS and was approved by the U.S. Food and Drug Administration (FDA) in 1996,[3] and subsequently by the EMA in 2017.[4]

In 2018, Pearce et al.[5] reported for the first time a unique pattern of ocular pigmentary maculopathy in IC/BPS patients following PPS exposure. Some patients who used the drug long-term for treating IC/BPS showed pigmented deposits that resembled little specks in the macula, associated with visual impairments. Publication of this small, retrospective case series triggered further articles discussing a possible link between PPS and pigmentary maculopathy.[6-13] These articles prompted an ongoing discussion in the media, and concern amongst patients with IC/BPS. As a result of the published findings, the summary of product characteristics[14] of PPS was updated in 2019[15] by the EMA and in 2020[16] by the FDA to include a pigmentary maculopathy warning with long-term use (>5 years), with recommendations for regular ophthalmological examinations.

This review article describes the ophthalmological features that distinguish this pigmentary maculopathy associated with PPS from other maculopathies and considers the evidence base for the nature of pigmentary maculopathy reported in patients with IC/BPS using PPS treatment.

INTERSTITIAL CYSTITIS/ BLADDER PAIN SYNDROME

IC/BPS is characterised by recurrent pain, pressure, and discomfort in the bladder and pelvic region that persists or recurs for more than 6 months in the absence of other identifiable causes.[17,18] In some patients with IC/BPS, the bladder is inflamed, ulcerated, scarred, or stiff. IC/BPS is often misdiagnosed as recurrent urinary tract infection, overactive bladder, or as prostatitis and benign prostatic hyperplasia in males.[19,20]

Pentosan Polysulfate Sodium (Elmiron)

In chemical terms, PPS is a semisynthetic sulfated polysaccharide, extracted from beechwood. Although the exact mechanism of action of PPS in the treatment of IC/BPS is not completely understood, the reported mode of action includes a local effect in the bladder where PPS binds to the deficient mucosa, protecting the urothelium from irritants and bacterial adherence to the cells.[14,21] The systemic anti-inflammatory activity of PPS supports the use of this drug to treat IC/BPS.[22,23]

Several randomised placebo-controlled studies[24-29] and meta-analyses[30-32] have shown that PPS is efficacious compared with placebo in the treatment of bladder pain, urinary urgency, and frequency of micturition in patients with IC/BPS. Its use is recommended by the guidelines of the relevant scientific societies in several countries, including EAU[33] and American Urological Association (AUA)[34] guidelines.

PPS is indicated for the treatment of IC/BPS associated with either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency, and frequency of micturition,[14] and is prescribed predominantly by urologists and gynaecologists.

PIGMENTARY MACULOPATHY IN PATIENTS WITH INTERSTITIAL CYSTITIS/ BLADDER PAIN SYNDROME

In general, maculopathy (or macular degeneration) is an ocular disease related to the central part of the retina called the macula, which is characterised by progressive loss of central vision and is irreversible in most cases. The main causes of maculopathy are age in age-related macular degeneration (AMD),[35] underlying disease like myopia, diabetes, secondary macular pucker and exudation,[36,37] genetics,[38] and drug intake.[39] Hereditary (genetic) maculopathy can be differentiated from acquired maculopathy.[40] An association between IC/BPS and retinal disease has not yet been reported.[5] From the patient's point of view, there are no differences in symptoms depending on the cause of maculopathy except for age of onset, which points towards genetic causes in younger patients.

In 2018, Pearce et al.[5] reported a unique pattern of ocular pigmentary maculopathy exclusively in six patients with IC/BPS following PPS exposure. The distinctive imaging features identified (see below) were subsequently reflected by Hanif et al.[41] and Christiansen et al.:[42]

1. Fundus photography revealing macular hyperpigmented spots, yellow-orange deposits, and/or patchy RPE atrophy;

2. Fundus autofluorescence imaging revealing a densely packed array of hyper- and hypoautofluorescent spots involving the posterior pole, centred on, and involving the fovea; and

3. OCT imaging, demonstrating focal thickening or elevation of the RPE with associated hyper-reflectance on near-infrared reflectance imaging.

This type of maculopathy resembles some aspects of AMD but, according to Christiansen et al.,[42] can be differentiated with the use of multimodal fundus imaging, and, according to Barnes et al.,[43] the same applies for a differentiation from hereditary maculopathies. In a cross-sectional study by Lyons et al.,[44] pigmentary maculopathy associated with PPS was accompanied by relevant visual function impairment that is not adequately identified by conventional visual acuity testing.

The potential mechanism of RPE damage by PPS is unknown. Whether PPS accumulates in the macular region or whether there is a mechanism comparable to the toxicity of chloroquine remains speculative.

In the following section, starting with the first report published by Pearce et al.,[5] subsequent reports are discussed including observational, cross-sectional, and case studies.

In 2018, Pearce et al.[5] reported the pattern of ocular pigmentary maculopathy in six patients with IC/BPS out of 38 patients with a diagnosis of IC/BPS and reported use of PPS on the electronic medical record system at the Emory Eye Center, Atlanta, Georgia, USA. The median age was 60 (range: 37–62) years, all patients received PPS with a median duration of exposure of 15.5 (12–20) years, and a median cumulative exposure of 2.26 (1.31–2.77) kg. Patients reported symptoms of difficulty reading and prolonged

dark adaptation without restrictions of central visual acuity and there were subtle funduscopic findings in these patients.[5]

In nearly all eyes, irregular vitelliform-like lesions were noted on funduscopic examination and OCT. Fundus autofluorescence imaging showed a well-delineated region in the posterior pole, with a highly irregular autofluorescence pattern characterised by hyperautofluorescent spots, surrounded by normal autofluorescence. The eyes of three patients had additional peripheral lesions, with a similarly irregular autofluorescence pattern, and the eyes of two patients showed patchy paracentral hypoautofluorescence, consistent with RPE atrophy. Near-infrared reflectance imaging revealed a similarly irregular reflectance pattern. OCT images from early stages demonstrated nodular excrescences at the level of the RPE and unaffected ellipsoid zones, but the clear separation between RPE/Bruch's membrane complex and the interdigitating zone was abolished. OCT in the areas of RPE defects showed loss of photoreceptors and the outer nuclear layer.[5]

In 2019, Hanif et al.[7] conducted another retrospective cross-sectional study to further evaluate the risk factors for development of the unique maculopathy among patients with IC/BPS. Eighty of 219 patients with IC/BPS in the study were on PPS and 14 showed all features of pigmentary maculopathy. The mean age was 61.3±12.2 years, the median duration of PPS intake and cumulative exposure were 18.3 (range: 3.0–21.9) years, and 2.30 (0.58–2.98) kg, respectively. There were no cases of unique maculopathy in the 139 unexposed patients and no other IC/BPS therapy showed a statistically significant association with this condition. Unfortunately, relevant demographic and anamnestic data were not provided.[7]

A further study by Hanif et al.[41] characterised the exposure and clinical manifestations of pigmentary maculopathy associated with PPS. This multi-institutional, retrospective case series included 35 patients. The median age was 60 (37–79) years, the duration of PPS intake was 15 (3–22) years, and the cumulative exposure was 1.61 (0.44–4.31) kg. Fundus examination of all eyes showed the clinical signs and imaging features of the macula outlined by Pierce et al.[5] and, in 24 eyes (36%), the lesions extended to the retinal periphery. Longitudinal evaluations in a few patients suggest dynamic changes in pigmentary abnormalities, according to Shah et al.[12]

In addition, a few single cases of potential maculopathies associated with PPS were reported in the form of case reports, but the facts presented were predominantly incomplete and unclear and not amenable to further evaluation.[45-47]

Two larger observational epidemiological studies have been conducted with respect to PPS and maculopathy in a broader context.

A retrospective, matched-cohort study was reported by Jain et al.[8] to assess a possible association between PPS use and macular disease. Defined outcome measures were any atypical maculopathy outcome and/or a diagnosis of AMD or drusen. A total of 3,012 users of PPS from a large national insurer's medical claims database in the USA were compared with 15,060 matched controls at 5 years, and 1,604 PPS users were compared with 8,017 matched controls at 7 years. Mean ages at the 5- and 7-years' time points were 52.3 and 52.8 years, respectively. At 5- and 7-years of follow-up, PPS use averaged only 10 and 13 months of prescription coverage, indicating either an incomplete database or sparse and irregular use of PPS by patients. In addition, no cumulative dose was identifiable.[8]

At the 5- and 7-year follow-up, there was no difference regarding the frequencies of atypical maculopathy. Regarding the diagnosis of AMD in addition to an atypical maculopathy, users of PPS showed no significant increase in odds ratio at 5 years ($p>0.130$), but a statistically significant increase at 7 years ($p=0.009$). Interestingly, sensitivity analyses including only patients with IC/BPS were reassuring an association for PPS and atypical maculopathy at 5 years, but not at 7 years nor in the atypical maculopathy+AMD analysis at 5 or 7 years.[8]

Ludwig et al.[13] reported a multicentre, retrospective cohort study of commercially insured patients in the MarketScan database (IBM, Endicott, New York, USA), which identified 49,899 patients with IC/BPS for whom

pharmaceutical data were available. Of those who filled a prescription for PPS (23%), the average patient filled a PPS prescription 125 days from their index IC/BPS diagnosis and filled prescriptions for 1,230 days of PPS in total.

A total of 1,335 (2.7%) patients with IC/BPS were diagnosed with maculopathy, most commonly exudative AMD (1.50%), drusen (0.80%), non-exudative AMD (0.30%), toxic maculopathy (0.10%), and hereditary dystrophy (0.04%). In unadjusted analyses, the percentage of patients who filled a PPS prescription and were subsequently diagnosed with maculopathy (2.37%) was very similar to the percentage of patients who did not fill a prescription (2.77%). Sensitivity analyses showed no significant increased risk of maculopathy following exposure to PPS. A dose-response relationship was not observed.[13]

Studies on Prevalence for a Pigmentary Maculopathy Associated with Pentosan Polysulfate Sodium

Data on prevalence are based on several prospective cohort studies

In a prospective university database cohort study by Wang et al.,[10] 741 patients on PPS were identified, of which 97 voluntarily participated in a prospective screening investigation. From among these 97 participants, 16 cases of pigmentary maculopathy associated with PPS were identified. Taking the ascertainment bias into account, a prevalence of 16.5% (16 out of 97) was cited by the study authors. Applying an intention-to-treat approach based on all exposed patients, which is common in prospective trials, showed a prevalence of 2.2% (16 out of 741). However, this might be an underestimate, as the number of patients with undetected maculopathy in the unexamined group of 644 is unknown. In an earlier interim evaluation of this study after the inclusion of 50 patients, Wang et al.[9] reported a prevalence of pigmentary maculopathy associated with PPS of 20% (10 out of 50). According to the data provided, only two of these 10 (4%) patients had pigmentary maculopathy, according to the definition given by Pearce et al.,[5] Hanif et al.,[41] and Christiansen et al.[42]

A recent retrospective chart review performed by Leung et al.[48] at a large retina-only practice showed that 33 (22%) of 148 patients with PPS exposure had signs of maculopathy. As none of these eyes fulfilled all the diagnostic criteria stipulated by Pearce et al.,[5] Hanif et al.,[41] and Christiansen et al.,[42] no further conclusions can be drawn. Moreover, genetic testing was performed in 16 out of these 33 patients and showed heterozygosity for variants of uncertain significance in 15. To note, the maculopathy group had a higher mean cumulative dose of PPS and longer duration of PPS use (1,600±849 g versus 864±852 g; $p<0.0001$; and 13.6 years versus 7.48 years; $p<0.0001$, respectively).[48]

Further indications on prevalence can be derived from the study by Ludwig et al.,[11] as described above. The percentage of patients who received PPS and were later diagnosed with maculopathy is estimated to be 2.4%. A similar prevalence of 2.0% (4 out of 216) was reported by Higgins et al.,[49] who conducted a chart review of a quaternary academic medical centre electronic medical record database. Kalbag et al.[50] described a prevalence of 1.5% (10 out of 131) based on electronic health record data.

Disease progression after cessation of pentosan polysulfate sodium usage

Retrospective data reported by Shah et al.[12] at the Emory Eye Center on 11 female patients with a total PPS exposure of 1.97 (1.55–2.18) kg, median treatment duration of 15 (3–22) years, and who were followed-up for at least 6 months after drug cessation showed that there was progression in the pattern of fundus autofluorescence changes and/or OCT findings in all eyes. No eyes exhibited a demonstrable improvement in disease after discontinuing PPS. A total of 7 eyes (32%) showed macular RPE atrophy at the baseline visit, and atrophy enlarged after discontinuation of PPS. In the absence of ongoing PPS exposure, the cause of progression of ocular disease cannot easily be explained.

Two additional case reports by Huckfeldt and Vavvas[51] and Barnett and Jain[52] each describe a potential case of pigmentary maculopathy associated with PPS, were inconclusive and the causality to PPS remains unclear.

DISCUSSION

The first report by Pearce et al.[5] of a unique maculopathy in patients with IC/BPS on PPS, more than 20 years after the launch of Elmiron (Janssen Pharmaceuticals, Beerse, Belgium), was a case series in a small number of patients in a single clinical centre, which was followed by several publications, predominantly from the Emory Eye Center[10] and other associated groups.[7,8,42,53]

Apart from several observational, cross-sectional, and case studies, there are two observational epidemiological studies,[8,13] which failed to identify a higher risk of maculopathy in patients with IC/BPS treated with PPS at 5 and 7 years. There are several inherent problems with these epidemiological studies. First, due to the broad definition of maculopathy it remains unclear which of the cases of maculopathy can be attributed to PPS. Second, the length of exposure to PPS is poorly defined. For example, the report of Ludwig et al.[13] is limited by its short follow-up and included patients with PPS who mostly had exposure of less than 5 years. Furthermore, PPS doses are often not specified. These studies, drawn from large cohorts of commercially insured patients, demonstrate a lack of a strong and reproducible association between PPS and maculopathy.

Analysis of the available information suggests an estimated prevalence of an association between PPS and maculopathy of between 2% and 4%. However, the published reports are based on highly selected cohorts and there is a significant risk that the associated data may not be representative. Thus, the true prevalence of pigmentary maculopathy associated with PPS remains speculative.

Evidence regarding disease progression or regression after cessation of PPS is limited. Imprecise characterisation of symptoms and premature drug cessation[10] currently preclude any meaningful conclusions being drawn.

Despite the lack of conclusive evidence on a causative relationship between PPS use and pigmentary maculopathy, public awareness and media interest have triggered an increase in reporting of possible side-effects. This is also reflected by the public data source for adverse events related to drugs, the FDA Adverse Event Reporting System (FAERS) database, which is used by the FDA and other entities for the post-marketing surveillance of medications and biologics. Since the launch of Elmiron in 1997, over 90% of all reports of eye disorders during PPS use were made between 2019 and 2021, and 99% of all maculopathies and retinal pigmentations were reported after the first publications in 2018.

CONCLUSION

This article reviews several case reports and case series reporting a unique maculopathy in patients with IC/BPS on PPS. The described clinical features and data from imaging studies support the notion of a new entity. However, with respect to the cause or the presumed association with exposure to PPS, the published data are suggestive but still inconsistent. Currently there are no prospective, well-researched, confirmatory data available.

A causal relationship cannot be established based on current epidemiological evidence,[53] due to variability in effect size, inconsistent diagnostic methodology, and the inability to prove temporality (the 'Bradford Hill criteria'). Most patients with the ocular finding of pigmentary maculopathy appear to have used high doses of PPS, occasionally above recommendation, over an extended period (around 15 years); however, the pathogenesis remains unexplained, and an unequivocal biological plausibility is still lacking.

The current lack of clear evidence does not exclude that this manifestation of pigmentary maculopathy is a true phenomenon; however, according to Doiron et al.,[54] several questions remain unanswered, such as are we truly observing a drug-associated toxicity or is the described maculopathy associated with another factor, e.g., another manifestation of IC/BPS itself.

Future controlled studies with sufficient follow-up to identify pigmentary changes that control for concomitant medications and comorbidities and assess for dose response are warranted. Studies should also observe the maximum daily dose of 300 mg. Consolidation of inclusion

criteria and a precise description of pigmentary maculopathy will enable the true incidence of this specific maculopathy in patients with IC/BPS who are receiving PPS.

PPS plays an important role in treatment of IC/BPS as it is the only oral drug approved for this indication. Weighing the risks and benefits of PPS use in patients with IC/BPS is essential. Clinicians should advise patients with IC/BPS of the reported potential association between PPS and pigmentary maculopathy, and to follow the recommended regimen of regular ophthalmological evaluation detailed in the product literature. Based on current evidence, PPS remains an effective, well-tolerated treatment for IC/BPS with appropriate monitoring.

Regarding ophthalmological care, recommendations are to pay particular attention to the unique ophthalmological features that single out pigmentary maculopathy from other maculopathies (described above). Screening for autofluorescence, RPE protrusions on OCT, and visual function is recommended. The value of visual field testing has not yet been established and is therefore not recommended. Liaison between ophthalmology and urology is also recommended in cases when corresponding findings are observed and ensure regular evaluation and careful monitoring of patients in cases when there is an uneventful screening.

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