Understanding the Patient Experience of Erythropoietic Protoporphyria and X-Linked Protoporphyria: A Qualitative Study

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Background

- Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) are rare genetic disorders of the heme biosynthetic pathway that result in accumulation of protoporphyrin in the blood, erythrocytes, and tissues.[1]
- The photodynamic protoporphyrin molecules absorb light radiation, resulting in painful phototoxicity upon exposure to sunlight, as well as some types of artificial light.[1,2]
- EPP and XLP are primarily managed by avoidance of sunlight and wearing sun-protective clothing, which leads to decreased social activity and considerable decrements in quality of life.[3,4]

Objective

- The objective of the interviews was to explore the patient experience of living with EPP or XLP and views on potential benefits of treatment outcomes as part of a vignette health-utility estimation study to quantify the quality-of-life impact of EPP and XLP.

Methods

- Qualitative interviews were conducted via web conference in the United States (US) and United Kingdom (UK) with adults with EPP or XLP recruited from patient organizations and with clinical and patient experts.
- The interviews were conducted according to a semistructured interview guide and were audio recorded and transcribed.
- Participants were asked to describe the experience of living with EPP or XLP day-to-day, as well as the triggers, symptoms, and impact of having adverse reactions to light, from initial prodromal symptoms to a full phototoxic reaction.
- Participants were also asked to provide feedback on the anticipated benefits of taking a hypothetical treatment that would allow an additional 30, 55, and 90 minutes of light exposure before experiencing prodromal symptoms. Participants with EPP/XLP were asked to consider this time as additional to the amount of time they were currently (or before treatment) able to be exposed to light; expert advisors were asked to consider this time as additional to an "average" light tolerance time (approximately 20 minutes).
- Content analysis was conducted on interview field-note data, supplemented by the transcripts as needed.

Results

Sample Characteristics

- The interview sample included 8 individuals with EPP/XLP (4 US, 4 UK; Table 1) and 4 expert advisors (2 US, 2 UK), including 2 clinicians with expertise in EPP/XLP and 2 representatives from porphyria patient organizations.

Table 1. Characteristics of Interview Participants With EPP or XLP

Sample Characteristic	US EPP/XLP Sample (n = 4)	UK EPP/XLP Sample (n = 4)	Total EPP/XLP Sample (N = 8)
EPP/XLP diagnosis, n (%) XLP	1 (25.0)	1 (25.0)	2 (25.0)
Gender, n (%) female	2 (50.0)	2 (50.0)	4 (50.0)
Age in years, mean (range)	42.0 (26-52)	35.5 (24-45)	38.8 (24-52)
Ethnicity, n (%) White	4 (100.0)	4 (100.0)	8 (100.0)
Age at EPP/XLP diagnosis, mean (range)	11.0 (3-22)	8.8 (0.8-18)	9.9 (0.8-22)
Age at first EPP/XLP symptoms, mean (range)	2.9 (0.5-6.5)	3.3 (0.8-8.0)	3.1 (0.5-8.0)
Minutes in daylight to first symptom, mean (range)	9.8 (1.0-22.7)	16.0 (1.5-30.0)	12.9 (1.0-30.0)
Current/past treatment, n (%)			
Antihistamines	0 (0)	2 (50.0)	2 (25.0)
Beta-carotene	2 (50.0)	3 (75.0)	5 (62.5)
Dersimelagon [a]	1 (25.0)	0 (0)	1 (12.5)
Phototherapy	1 (25.0)	3 (75.0)	4 (50.0)
Afamelanotide [b]	2 (50.0)	1 (25.0)	3 (37.5)
Long-term health impacts related to EPP/XLP, n (%)			
Skin-related issues	1 (25.0)	2 (50.0)	3 (37.5)
Anemia	2 (50.0)	3 (75.0)	4 (62.5)
Vitamin D deficiency	3 (75.0)	3 (75.0)	6 (75.0)
Gallbladder issues	1 (25.0)	0 (0)	1 (12.5)
Liver damage or failure	0 (0)	2 (50.0)	2 (25.0)
Mood or anxiety disorders	1 (25.0)	0 (0)	1 (12.5)

[a] Investigational treatment in clinical trials for EPP and XLP.
[b] Food and Drug Administration approved for the treatment of EPP only.

EPP and XLP Phototoxic Reactions

- The patient experience of triggers, symptoms, and impacts of adverse reactions to light is illustrated in Figure 1.
- Illustrative quotes from interview participants are presented in Table 2.

Triggers of Phototoxic Reactions

- Interview participants reported a range of natural and artificial sources of light that could trigger or exacerbate a phototoxic reaction: direct sunlight (n = 12), reflected or scattered light (e.g., surfaces, water, clouds) (n = 12), light through windows (n = 8), artificial lighting (e.g., fluorescent, LED) (n = 7), and electronic devices (e.g., computers, tablets, smartphones, TVs) (n = 3) (Figure 1).
- Direct sunlight was reported to be the most intense trigger; sensitivity to artificial lighting (e.g., fluorescent or LED lighting) and electronic devices was more likely once a reaction had already started to occur.
- Environmental factors such as weather conditions, time of year, geographical location and climate, and amount of previous exposure were important factors that influenced the frequency, severity, and onset of symptoms.

Prodromal Symptoms

- Interview participants reported a range of initial warning symptoms at the onset of a reaction, most commonly tingling or prickling (n = 11), itching (n = 9), and burning (n = 8) (Figure 1).
- The onset of these initial symptoms served as a warning sign of an impending reaction, signaling the urgent need to move indoors or seek shade, with disruption to daily activities, family life, and social participation, and caused anxiety and frustration.

Figure 1. Patient Experience of the Triggers, Symptoms, and Impacts of Adverse Reactions to Light

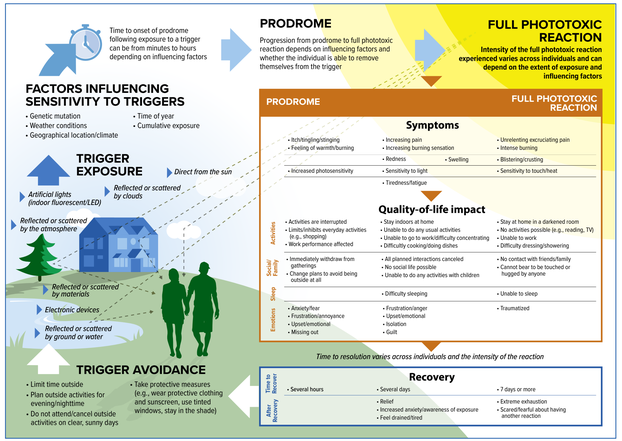

Table 2. Representative Statements From Interview Participants on the Triggers, Symptoms, and Impacts of Adverse Reactions to Light

Aspect of EPP/XLP	Representative Statements
Reaction triggers	"…for someone with EPP, it's a reaction, it's triggering a reaction in their blood, which is linked to a tissue. So that chemical reaction, so most typically, it is sunlight that impacts someone. For some people, a smaller percentage of the population, it is artificial lighting, but the difference is that once you have a reaction from sunlight, artificial lighting exacerbates it." [Expert Advisor] "Yeah, so it depends on a lot of different factors. It depends on the weather. It depends on where you're located at if you're in the southern hemisphere or the northern hemisphere. It depends upon if it's hot outside, if it's colder outside, if there's wind, if there's no wind. There's a lot of different factors that play into it." [Patient with EPP]
Prodromal symptoms	"So the progression of a reaction for EPP or XLP, the first thing that someone would feel upon exposure is a stinging, burning, tingling, itching sensation, and those are the words that typically characterize the prodrome at the outset of this." [Expert Advisor] "It's like having a lightning siren right when you're hot, and you're at a ball field or something, and the lightning siren goes off. It's like, okay, you've got to get indoors, stops the game, whatever. You're constantly on alert." [Patient with XLP]
Full phototoxic reaction	"Excruciating burning oil, fire pain that is relentless." [Patient with EPP] "… it starts off with almost like pins and needles, like somebody has got tiny little pins and they are just pricking you all over, and then as it gets worse—it's almost as if someone's got a kettle, and they are pouring, like, boiling hot water over you." [Patient with XLP]
Impact of prodrome and phototoxic reactions	**Activities** "It's impossible to do anything. You just end up sat in a darkened room a lot of the time. You can't even watch TV or look at your mobile phone even because the light from them is so painful." [Patient with EPP] **Social/Family** "… we couldn't plan for days out, that sort of thing, and if we did, it quite often used to end up backfiring where I was then in pain, and obviously, then, that impacted on the relationship with my wife and children." [Patient with EPP] **Sleep** "Like there's no sleep because you can't have anything touching it, but you're exhausted." [Patient with EPP] **Emotions** "To be honest, I felt kind of depressed because, obviously, it literally took like my whole life away, and I couldn't do anything. Because your whole life is on hold, like, you can't do anything until it's gone, and there's nothing to help it get better." [Patient with XLP]
Recovery	"I would say the anxiety is always there because then you know it's amplified even more because you just went through another trauma, and you don't want that again, so then it's super anxious." [Patient with EPP]

Figure 2. Participant Feedback on the Impact of EPP/XLP and the Anticipated Benefits of Additional Light Tolerance Times With Treatment

[a] Participants with EPP/XLP considered the time as additional to their current (or before treatment) light tolerance time; expert advisors considered the time as additional to approximately 20 minutes.
[b] Participants with EPP/XLP reported light tolerance times (amount of time able to be exposed to light before experiencing symptoms) of between 1 and 30 minutes (Table 1).

Full Phototoxic Reactions

- Phototoxic reactions were described as debilitating and, for some, traumatic events, characterized by feelings of intense burning and excruciating relentless pain that cannot be relieved by painkillers (Table 3 and Figure 1).
- A full phototoxic reaction was reported to last on average 2 to 7 days, during which time patients typically stay at home, often in a darkened room.
- Participants described a total cessation of normal life during the reaction due to the debilitating nature of the reaction itself and the need to avoid any further light exposure until complete resolution.
- Key reported impacts included being unable to conduct any usual daily activities, go to work, socialize, or do any activities with family and friends, either inside or outside, as well as difficulties sleeping.
- Following recovery, participants reported feeling emotionally and physically drained and being in a heightened state of anxiety and hypervigilance.

Table 3. Reported Symptoms of a Full Phototoxic Reaction

Symptom	Participants With EPP/XLP (n = 8)	Expert Advisors (n = 4)
Burning	8 (100.0)	4 (100.0)
Pain	7 (87.5)	4 (100.0)
Sensitivity to touch	7 (87.5)	4 (100.0)
Swelling	5 (62.5)	4 (100.0)
Tiredness/fatigue	4 (50.0)	3 (75.0)
Redness	4 (50.0)	2 (50.0)
Temperature sensitivity	3 (37.5)	3 (75.0)
Increased photosensitivity	4 (50.0)	1 (25.0)
Blistering/crusting	2 (25.0)	2 (50.0)
Itching	2 (25.0)	2 (50.0)
Purple spots/bruising	2 (25.0)	1 (25.0)
Tingling	1 (12.5)	0 (0.0)

Results - Living With EPP or XLP and Anticipated Benefits of Treatment

Overall Impact of Living With EPP or XLP

- Between reactions, the impact of living with EPP or XLP day-to-day centers on the need to limit exposure to light to avoid having a phototoxic reaction.
- The fear and anxiety of having a phototoxic reaction, the need to be constantly aware of their environment, and the frequent need to take evasive action have wide-reaching effects on all aspects of life and severely curtail opportunities to participate in normal everyday activities that require going outside.
- Key reported impacts included restricted participation in outdoor activities, impaired relationships, social isolation/withdrawal, and detriments to psychological well-being and mental health (Figure 2).

Anticipated Benefits of Treatment

- Participants provided feedback on the anticipated benefits of a hypothetical treatment that would provide 30, 55, and 90 minutes of additional light exposure time before experiencing symptoms.
- Key potential benefits of additional light tolerance included increased freedom to participate in normal everyday activities; greater opportunities for life experiences; and reduced anxiety (Figure 2).
- Illustrative quotes from interview participants on the impact of EPP/XLP and the anticipated benefits of treatment are presented in Table 4.

Table 4. Representative Statements From Interview Participants on the Impact of EPP and XLP and the Anticipated Benefits of Treatment

Aspect of EPP/XLP	Representative Statements
Impact of EPP/XLP	"I wear gloves as much as I can, but… obviously you look a bit strange… I am conscious of it. It's horrible to do because it doesn't look normal." [Patient with EPP] …but when the sun would change or the weather would change, I'd have to go in the house and watch all my friends and family having a party without me in the backyard. I'd be in my bedroom with the shades drawn… It's very sad, very lonely when stuff like that happens." [Patient with EPP] "I get very frustrated that I can't do the things that most people would consider to be normal. I get times where I'm literally in floods of tears because I can't go and do something." [Patient with EPP] "…so it's definitely affected my life choices as far as, like, where I want to live geographically, as far as, like, who I hang out with and what they do…" [Patient with EPP]
Anticipated benefit of treatment (i.e., additional daylight exposure without symptoms)	**Additional 30 minutes** "I'm constantly kind of running from place to place and it would just give me that extra buffer, that extra time that I wouldn't have to worry about anything." [Patient with XLP] **Additional 55 minutes** "Just the ability to be able to go and do basic things—you know, go to the shops without having to worry about having a reaction, maybe saying to the kids, 'Let's go and have an hour in the park.'" [Patient with EPP] " I think it would have definitely helped my anxiety, that constant fear and always being in protection mode. It would have helped that a lot." [Patient with EPP] **Additional 90 minutes** "I would just feel more normal. I'd be able to do what everyone else does without having to think about it or plan it." [Patient with XLP] "I could have done a lot more outdoor activities, which I love. It would have really decreased that anxiety for me." [Patient with EPP]

Conclusions

- **The interviews provided key insights into the patient experience of living with EPP or XLP.**
- **Phototoxic reactions are associated with debilitating, relentless, and excruciating symptoms that have a devasting impact on normal functioning.**
- **For many, prodromal symptoms signaled the urgent need to move inside or seek shade to avoid an impending reaction.**
- **Living with EPP or XLP day-to-day centers on the continual drive to avoid the pain and trauma of phototoxic reactions, with associated impacts on all aspects of quality of life.**
- **Treatments that result in modest increases in light-exposure tolerance have the potential to substantially improve patients' lives.**

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