Unfolding the Mystery of Endemic Eye Disease of Nepal: Fifty Years of SHAPU, the Seasonal HyperAcute PanUveitis

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Half a century on, first reported in 1975 by Professor (Prof.) Doctor (Dr.) Om Krishna Malla as Seasonal Endophthalmitis (Malla OK, 1978; Malla OK, 2005); and named as Seasonal HyperAcute PanUveitis (SHAPU) in 1979 by Prof. Dr. Madan Prasad Upadhyay (Upadhyay et al., 1979), the mystery of SHAPU continues to unfold, but the enigma persists. As another potential outbreak of SHAPU is expected this year, let this be a call to action: to collaborate, to increase awareness, to investigate, to establish pathogenesis, to treat, and be prepared to manage this endemic disease of Nepal efficiently and effectively; ultimately, to protect the vision of the vulnerable.

The SHAPU remains one of the most puzzling and devastating ocular diseases confronted by the ophthalmologists of Nepal, occurring predominantly in young children. The SHAPU has a unique seasonal pattern, typically emerging in the post-monsoon period (August to December) every alternate year and is clinically characterised by unilateral red eye with white glow with hypopyon, fibrinous reaction, non-dilating pupil, rapidly progressing vitritis, retinal vasculitis, retinitis, and fulminant diffuse inflammation. The aggressive nature of the disease, affecting predominantly one eye and sparing the other, only deepens the mystery. The fact that most patients are healthy children under the age of 10 years usually after contact with white moth (*Gazalina* species) raises concerns about unknown environmental exposures or immune vulnerabilities in this age group (Manandhar, 2011). Without immediate intervention, rapid progression to phthisis bulbi or total blindness is common (Koirala et al., 2004).

Financial Interest : Nil
Conflict of Interest : Nil

Received : 22.07.2025
Accepted : 04.08.2025

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Access this article online
Website: www.nepjol.info/index.php/NEPJOPH
DOI: https://doi.org/10.3126/nepjoph.v16i2.85099
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ISSN: 2072-6805, **E-ISSN:** 2091-0320
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What we achieved and came to know in half a century can be summarised as follows:

1. **Risk factors:** Different studies have shown moth as a risk factor (Upadhyay et al., 1984; Malla,1978; Shrestha, 2010; Upadhyay et al., 2019; Kharel Sitaula, et al., 2020; Upadhyay et al., 2021), and one of those study also showed physical contact with livestock (Upadhyay et al., 2021).

2. **Demographics**: Although it was known from the beginning that children are predominantly affected, now it is confirmed that about seven out of 10 cases would be children. Other than from the Kaski district, cases are found to come from many other districts of Nepal. In one of the largest outbreaks, cases came from 29 districts of Nepal according to Epidemiology and Disease Control Division (EDCD), Ministry of Health and Population (MoHP) records. Hilly areas of Nepal are most commonly affected. Besides the classic autumn outbreaks, small summer outbreaks, and sporadic cases from pre and post-outbreaks are also identified (Manandhar et al., 2018; Gurung et al., 2021). Now it is confirmed that it is found in Bhutan (Rai et al., 2020; Tamang et al., 2024) and India as well (Manandhar et al., article accepted for publication).

3. **Clinical features**: Discovery of hair follicles/setae inside the eye, suggestive of moth setae, is reported (Manandhar et al., 2018; Kharel Sitaula et al., 2020; Goh et al., 2025). More clinical findings like decreased or lost corneal sensation in slightly more than 50% cases, oedematous cornea, iris atrophy in few cases, shifting hypopyon, vitreous consistency, and colour have been described (Manandhar et al., 2018). Fundus of SHAPU cases was described for the first time in 2008 (Manandhar et al., 2008), which has been later studied in more detail (Manandhar et al., 2018).

4. **Classification of SHAPU:** The SHAPU is divided into mild, moderate, and severe SHAPU (Kharel Sitaula et al., 2022; Khatri et al., 2017). The same study showed another category of classification named as "Suspected SHAPU" where the individuals living in endemic regions of Nepal with a dramatic surge in the population of white moths present with mild redness with or without moth hairs in the ocular surface and no intraocular reactions (Kharel Sitaula et al., 2022).

5. **Metagenomic and interleukin (IL) analysis**: The high technology to Metagenomic sequencing and IL analysis from the vitreous sample had been undertaken to understand the aetiology of SHAPU (Sitaula et al., 2024). It showed the raised level of IL-6/IL-10 ratio in the vitreous sample, suggestive of inflammatory cascades within the eye.

6. **Studies on microbes:** Based on the isolation of bacteria from vitreous, Culture positive and negative SHAPU were identified. Since the first reporting of the bacterial isolation from vitreous of few SHAPU cases in 2008 (Manandhar et al., 2008), 14-39.8% of cases have proven to be vitreous culture positive for mainly *Streptococcus pneumoniae* (Manandhar et al., 2018; and a paper

under submission by same author). Whole genome sequencing recovered bacterial sequence in 90% of vitreous samples of SHAPU cases (86% *Streptococcus pneumoniae*), despite 44% of the samples being culture negative (Nakamura and Manandhar et al., article under submission). Another recent study has also observed *Streptococcus pneumoniae* in two out of 10 vitreous samples, confirmed by quantitative polymerase chain reaction (qPCR) (Sitaula et al., 2024). These findings strongly suggest that SHAPU could be mostly bacterial endophthalmitis as historically suggested. Negative polymerase chain reaction (PCR) for Herpes group of virus: Herpes simplex virus (HSV), Varicella-Zoster virus (VZV), Cytomegalo virus (CMV) in a large number of samples has now ruled out the possibility of herpes virus as the cause of SHAPU, although one case of SHAPU was reported to have been due to Herpes Zoster caused by (VZV) (Kathil et al., 2005). There has also been detection of Human Herpes Virus 7 (HHV-7) in the aqueous sample of a SHAPU patient of 2019 outbreak (paper under review by Sitaula et al.). Isolation of Torque Teno Virus (TTV)/ Anellovirus from significant number of vitreous samples of SHAPU cases is significant for its clinical features suggestive of endophthalmitis. It could be a biomarker of the severity of infection in SHAPU, just like in post-operative endophthalmitis cases, since its pathogenicity is still questionable (Lee et al., 2015).

7. **Treatment protocol:** The treatment protocol is based on the clinical spectrum and severity of the disease. Discovery of good outcome with pars plana vitrectomy (PPV) (Byanju et al., 2003; Shrestha, 2010) was made long time back. Other reports suggest the treatment of mild stage with topical antibiotics and topical steroids; moderate stage with periocular and intraocular antibiotic and steroid injections and severe stage with PPV (Khatri et al., 2017; Kharel-Sitaula et al., 2025). In an outbreak of 66 cases, slightly less than 50% cases were treated with intravitreal antibiotics and dexamethasone while rest of the cases needed additional PPV. No additional benefit of antiviral treatment over antibiotics treatment alone was noted. None of the cases were treated just with topical steroid and antibiotic in that outbreak (Manandhar et al., 2018). Although visual prognosis remains guarded and many eyes progress to phthisis despite aggressive treatment, with prompt treatment, recovery of vision >6/18 is expected in at least two out of 10 eyes (Manandhar et al., 2018).

8. **Complications:** Other than phthisis bulbi, iris discolouration, recurrent hyphema, corneal opacification, rhegmatogenous retinal detachment, optic atrophy with severe vascular attenuation, and chronic hypotony have been seen (Manandhar et al., 2018, and the article accepted for publication). Newer complications like scleritis (Kharel-Sitaula paper under review) and scleral necrosis have been detected (Shrestha et al., 2024).

9. **Public awareness:** There have been increased public awareness and there are plenty of articles in national and local newspapers; and talk programmes/

interviews in radios and social media. Community education campaigns and seasonal surveillance could aid in early detection and improved outcomes. With the help of World Health Organisation (WHO) funding, the collaborative effort resulted in the development of two factsheets on SHAPU, one each for the health professionals and for the general public in 2018. The EDCD and National *Health Education, Information and Communication Centre* under the MoHP have been supporting in the community awareness activities in various provinces of Nepal.

10. **Integration with the Wider Health System within the country:** Most of the eye care in Nepal is provided by Non-governmental organisations (NGOs) and University Hospitals. There is a lack of integration into the Nepal Government Health Structure. Even if so, the SHAPU has been placed in the Early Warning and Reporting System (EWARS) and Surveillance Outbreak Response Management and Analysis System (SORMAS) by EDCD, MoHP, the Government of Nepal. This includes coordinating with the Primary Health care Centres (PHC), MoHP and also epidemiologists, environmentalists, entomologists, and infectious disease specialists. Eye care systems also need to ensure that patients have access to necessary resources, such as medication and transportation, to ensure adherence to treatment plans. NOS is also advocating for the inclusion of SHAPU in the list of Neglected Tropical Diseases (NTDs) or Zoonotic Disease of Nepal. One health approach is best suited for SHAPU.
11. **Collaboration with International Organisations:** Nepal Ophthalmic Society (NOS) is a member of International Council of Ophthalmology (ICO), Asia Pacific Association of Ophthalmology (APAO), International Association of Prevention of Blindness (IAPB), and South Asian Academy of Ophthalmology (SAO). In all these international forums, NOS and Nepali ophthalmologists have actively participated and familiarised the world about this endemic disease of Nepal – SHAPU. The NOS collaborates with these international organisations, and also WHO, to share information about SHAPU and implement prevention and treatment strategies. This collaboration helps in strengthening public health systems and addressing challenges related to this rare disease, endemic to our country, Nepal.
12. **Collaborative study with the entomologists:** The occurrence of the SHAPU outbreak in a predetermined post-monsoon season, along with a striking temporal congruence with the emergence pattern of adult female white moths, has been recently proven. A triad interaction has been identified between a specific host insect (*Gazalina chrysolopha*), a specific host plant (*Alnus nepalensis*), and a susceptible human host, in the presence of regional ecosystems. (Goh et al., 2025). This possible connection between SHAPU outbreaks and environmental exposures was established through collaborative studies with entomologists and forestry experts.

There are different aetiological theories like Insect-Associated Hypothesis (Shrestha et

al., 2007), Hypersensitivity Reactions (Joshi et al., 2005); Toxin-Triggered Inflammation (Upadhyay and Bajracharya, 2001). However, the high IL-6/IL-10 ratio seen in few SHAPU cases hints towards more of infectious nature of the disease (Sitauala RK et al, 2024). After the effort of so many researchers, the mystery of SHAPU has started unfolding. Now SHAPU can be described as a seasonal bacterial endophthalmitis most likely to be triggered by toxins of a specific white moth called Gazalina species. However, the complex interlink between the moth toxins and bacteria (mostly *Streptococcus species*), the reason why it affects children predominantly and is always unilateral, and the toxicological evidence, are yet to be found out. The multidisciplinary investigation and region-specific health care strategies (Goh YY et al., 2025; Sitaula RK et al., 2025) are necessary.

There are some interrelationship between animal - white moth, environment - the *Alnus nepalensis* (Utis tree), and the onset of disease in human eye – SHAPU (Khanal et al., 2022; Srivastava et al., 2006). The One Health approach recognises the interconnectedness of human, animal, and environmental health (Prata et al., 2022). The concept of One Health approach is being implemented to promote balanced ecosystems and improve the overall health and well-being of communities (Lerner and Berg, 2015). One Health will play a crucial role in addressing and preparing for the future outbreaks of SHAPU – a multifaceted link between human, animal, and environment. The SHAPU is also a subject of further research and requires a One Health approach to understand its aetiology and develop better prevention and treatment strategies. As climate change alters ecosystems and human-animal-insect interactions, diseases like SHAPU may become more frequent, more widespread, or more severe. Understanding SHAPU today may help prevent more such diseases tomorrow.

The public health implications and socio-economic impact of SHAPU is profound. The SHAPU often results in irreversible blindness in the affected eye, deeply impacting the lives of children and their families. Unlike more common causes of paediatric blindness, SHAPU is acutely traumatic - its progression measured not in weeks or months, but in hours and days. The SHAPU is not just a clinical oddity; it is a public health challenge and a call to action.

Nepal stands at the forefront of this mystery, and with support from the global scientific community, could lead the way in solving it. The SHAPU challenges our understanding not only of ocular diseases but of how environmental, infectious, and immunologic factors intersect in unexpected ways.

A possible route of ocular exposure could be the dispersion of the moths' setae in the air during attraction to artificial lights, the exposure to inflammatory agents of the setae in our human environment is a possible hypothesis of SHAPU causation. Hence, SHAPU is now better appreciated as a disease of "One Health System" caused by a relationship between the environment and human activities; hence ophthalmologists need to expand their tie-up with the entomologists, zoologists, forestry experts, and ecologists for inclusive act to reduce SHAPU blindness in future.

Despite SHAPU's 50-year history, basic and translational research on SHAPU and risk

classification has been hampered by the lack of high-quality, standardised epidemiological datasets, including clinical and environmental biomarkers. This also makes it more difficult to understand the aetiology, host-vector interactions, and treatment responses of SHAPU.

Hence, the need of the hour is coordinated research: combining ophthalmology, entomology, immunology, and environmental science to unravel the root causes of this devastating illness. Establishing surveillance systems in endemic districts: the national SHAPU registry, investing in community education, and improving early referral pathways could mitigate the damage while research continues.

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