The Risk Factors of Seasonal Hyperacute Panuveitis

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ABSTRACT

Background: Seasonal Hyperacute Panuveitis (SHAPU) is an eye disease of unclear aetiology occurring cyclically during the autumn in odd years in Nepal causing blindness within a week. This study is the first of its type to investigate the risk factors of SHAPU.

Methods: A multicentric national level case–control study was performed during the 2017 SHAPU outbreak. Cases were matched to controls in a 1:3 ratio based on age, sex and geographic area.

Questionnaire-based personal interview was used and risk factors were categorized as biological and behavioral. For univariate analysis, frequency, median and interquartile range was calculated. Chi-squared test with/without continuity correction and Fisher's exact test were used. Multivariate conditional logistic regressions were used for all the independent variables for p <0.1 in the univariate analyses.

Results: We identified 35 cases and 105 controls; 71.4% were children≤16 years (38-day infant to 50-year-old). All were immunocompetent individuals, males were 57.1% and females 42.9%. Potential risks such as visible moths/butterfly activity, contact with livestock, and attending mass gatherings of people were not reported more frequently in cases vs controls in univariate analyses. Differences in possibly protective factors such as self-reported mosquito net use, light off at night while sleeping, and habit of hands/face washing after physical contact/touch with any insects/butterflies/birds were not statistically significant between both groups. In multivariate model, SHAPU cases were significantly more likely than controls to report physical contact with butterflies/white moths (Adjusted OR:6.89; CI:2.79–17.01,p < .001).

Conclusions: Direct physical contact with butterflies/moths was associated with significantly increased odds of SHAPU cases.

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Background

Seasonal Hyperacute Panuveitis (SHAPU) is an eye disease of unknown aetiology with grave prognosis, reported only in Nepal. The first case was reported in 1975.[1–3] SHAPU is characterized by unilateral red eye with significant vision impairment, with no prior history of surgery or trauma. Hypopyon, fibrinous exudates in the anterior chamber, massive vitreous exudation producing a "White Pupil In Red Eye" and inability to visualize the retina are characteristic features of SHAPU.[4]

SHAPU occurs cyclically during the autumn season soon after monsoon (August–November) and usually ends with the peaking of winter in December or January.[4] The disease mostly affects children and is almost always unilateral, with rapid and profound vision loss.[4–6] The loss of sight is followed by cosmetic disfigurement due to phthisis bulbi, which can have a significant emotional impact on the patient.

Clinical and laboratory tests performed at the treating hospitals have identified a variable and confusing array of bacteria and viruses isolated from the aqueous and vitreous fluid samples from the eyes of affected patients.[4] In some cases, *Streptococcus pneumoniae* and *Acinetobacter*, have been grown.[5,7] However, viruses such as human Anelloviruses and Varicella zoster have also been reported in the vitreous fluid, but with no clear clinical significance,[8,9]while in many cases no organisms could be identified. Thus, various organisms have been

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reported by different authors,[5,8,9] but lack of consistency in organisms reported makes it difficult for final attribution.

In the 1980s, exposure to Tussock moths was reported as the primary risk factor for the disease, and at this point, the disease was named as seasonal endophthalmitis.[10] But later, other studies reported Gazalina moths as the suspect.[7,11] Though tiny hairs of the moths have been identified in ocular structures in few patients,[5] neither Tussock nor Gazalina has been proven as the culprit. Moreover, no field-based epidemiological studies have been attempted to trace the cause of the disease. Hence, we performed this multicenter, national case–control study to identify possible risk factors for SHAPU during the 2017 outbreak in Nepal.

Methods

A case–control study was conducted between 1stJuly 2017 to 31st December 2017 among 4/7 provinces of Nepal. SHAPU cases were identified through the medical record database from the following centers: Tribhuvan University B.P. Koirala Lions' Centre for Ophthalmic Studies (BPKLCOS) Kathmandu; BP Eye Foundation – Hospital for Children, Eye ENT and Rehabilitation Services (CHEERS) Bhaktapur, Tilganga Institute of Ophthalmology (TIO) Kathmandu and Himalaya Eye Hospital (HEH) Pokhara. Data abstraction was performed by the research assistants on paper forms and later entered in the study database.

In order to be considered a case for this study,the patient needed to have the following characteristics: seasonal occurrence, unilateral sudden redness with no history of trauma or surgery, profound vision loss, presenting with dense anterior chamber reaction with leukocoria and vitreous exudation that was later confirmed with ultrasonography [4](Figure 1).

The differential diagnosis of suspected SHAPU cases, often presenting with hypopyon uveitis, includes endogenous endophthalmitis, HLA-B27- associated uveitis, and Behçet's disease. These alternative aetiologies were excluded on the basis of detailed clinical history, review of systems, as well as appropriate ancillary testing such as blood/urine/nasopharyngeal cultures and HLA-typing. All patients presenting with suspected SHAPU were nonetheless treated with intravitreal antibiotics (vancomycin 1 mg/0.1 mL and ceftazidime 2.25 mg/0.1 mL), with or without intravitreal corticosteroids (dexamethasone 0.4 mg/0.1 mL) for possible endogenous endophthalmitis. If there was no sign of improvement by the 3rd day, pars plana vitrectomy was performed for diagnostic and therapeutic purposes. The vitreous sample was sent for Gram staining and bacterial culture.

For each case of SHAPU, we identified three controls who were age±1 year matched; sex-matched, and geographical districts matched. The controls should have no prior ocular and systemic problems. They were selected by systematic random sampling in which every 5th house from the right side of the SHAPU case house during July–December 2017 were included.

Once the outbreak was completed by Dec 2017, the survey was conducted to all the cases and controls at their homeplace during January 2018.

An expert panel of ophthalmologists and epidemiologists developed a semi-structured questionnaire and was pretested for validity and reliability among uveitis cases. The questionnaire included a broad array of possible risk factors. The questionnaire was administered to cases and controls by a team of investigators: one epidemiologist, one enumerator with public health background, and WHO Emergency District Support (WEDS) officers, and the enumerator with public health background was only involved in the questionnaire asking. For participants aged <16 years, the questionnaire was administered to their legal guardian.

Risk factors were categorized as biological or behavioral for both groups. Biological risk factors were an unusual flow of butterflies/moths/birds around the area, physical contact with insects or livestock, bushes around the house/school/playground/workplace and unusual

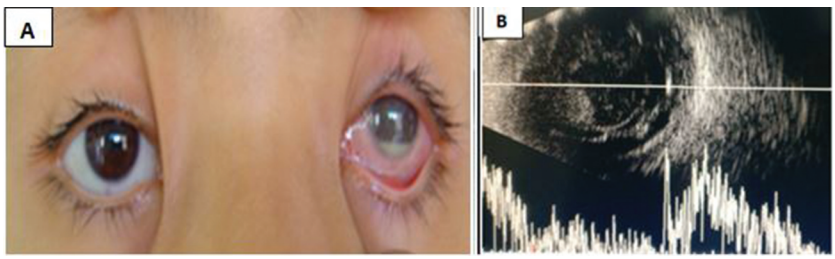

Figure 1. SHAPU Case with Unilateral Red Eye, Leukocoria and Hypopyon (A) and Ocular Ultrasonography showing Dense Hyperechoic Shadows in Vitreous with Thickened Retinochoroidal Complex (B).

movement of people (mass migration, floods, landslides). Behavioral risk factors included not sleeping under a mosquito net; hand washing after touching insects/birds, leaving lights on in the room while sleeping or in the corridor at nighttime; and attending mass gatherings (wedding/festival/religious pilgrimages) where Hindu Nepalese put Tika made from vermillion powder mixed with grains of uncooked rice on the forehead as a sign of blessings from the seniors.

Demographic data were collected using the same questionnaire. Socioeconomic status was assessed using a measure of the family's food security – whether the family was able to procure enough food during the past 12 months. Families often unable to obtain enough food (low food security) were categorized as "poor"; families that usually had just enough food (marginal food security) were categorized as "low middle-class"; and families that always had a surplus (high food security) were categorized as "upper middle-class/rich".

Data analysis

We performed an analysis using Statistical Package for Social Science (SPSS)-21. Univariate and multivariate analyses were performed. For univariate analysis, frequency, median and interquartile range was calculated. We used chi-square, chi-square with continuity correction and Fisher's Exact Test to select variable for logistic regression. To determine the effect adjusted for each of the other potential explanatory variables, multivariate conditional logistic regressions were used for all the independent variables where p-value was <0.1, except for age, sex, geography and socioeconomic status as they were matched variables. We calculated odds ratios and 95% confidence intervals. A statistician not involved in the study preparation reviewed the final analysis program.

The study adheres to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the participants ≥16 years and from the legal guardians of the participants <16 years. The research was approved by Nepal Health Research Council (NHRC), Institutional Review Board of Institute of Medicine, Tribhuvan University and the Review Committee of the WHO Nepal country office. All SHAPU cases reporting to the hospitals were given financial support for the laboratory investigation (partially supported by NHRC) and hospital bed charges (supported by the individual hospitals).

Results

During the 2017 SHAPU outbreak, 45 cases were reported from all participating hospitals across the nation. Careful scrutiny revealed that nine patients were seen at multiple hospitals, resulting in duplicate reporting and one parent refused to participate. Thus, the findings are based on 35 cases and 105 controls (1:3 ratio).

Most cases were from Kaski district, Pokhara valley or its neighbouring districts (65.7%). A few cases were scattered across the eastern and western regions of Nepal (Figure 2). The majority of SHAPU cases were reported during the post-monsoon period (July–

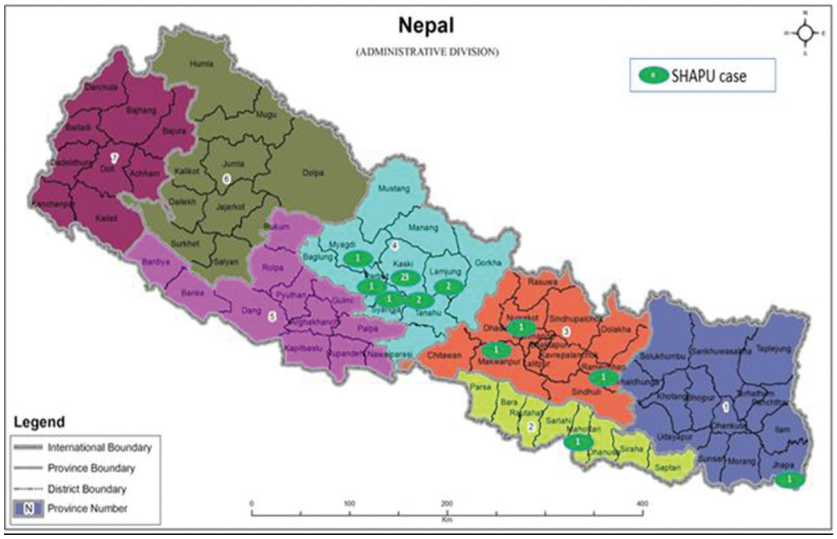

Figure 2. Map of Nepal showing the district-wise distribution of cases over 7 provinces during the 2017 SHAPU epidemic.

Table 1. Demographic characteristics of study participants.

Variables	Cases (%)	Controls (%)
Ethnicity		
Dalit	6 (17.1)	17 (16.2)
Janajati	11 (31.4)	46 (43.8)
Madhesi	2 (5.7)	8 (7.6)
Brahmin Chhetri	16 (45.7)	32 (30.5)
Others	0 (0.0)	2 (1.9)
Sex		
Male	20 (57.1)	60 (57.1)
Female	15 (42.9)	45 (42.9)
Age		
≤ 1 year	7(20)	19(18.1)
1–5 years	9(25.7)	38(36.2)
6–15 years	9(25.7)	18(17.1)
≥16 years	10(28.6)	30(28.6)
Generation		
Up to 15 years	25 (71.4)	75 (71.4)
More than 15 years	10 (28.6)	30 (28.6)
Family Size		
Family Size < 4	20(57.1)	52(49.5)
Family Size ≥ 4	15(42.9)	53(50.5)
Socioeconomic status		
Poor and lower class	24 (68.6)	75 (75.0)
Upper class and Rich	11 (31.4)	25 (25)
Birth weight		
Birth Weight <2500 grams	1(4.8)	3(5.2)
Birth Weight ≥2500 grams	15(95.2)	44(94.8)

September) with the last reported at the beginning of December. The detailed characteristics of the cases are reported below in Table 1.

SHAPU cases mostly had good general and eye health prior to developing the disease. The mean ± standard deviation of age was 10.99 ± 11.90 years for cases and 11.06 ± 11.83 years for controls. The youngest case was a 38 day-old infant and the oldest case was a 50 year-old man. Over 50% of the cases reported the first occurrence of symptoms during morning hours between 6 am–12 pm.

There were no differences in gender, gestational age, birth weight, birth place or ethnicity among cases and controls (Table 2). History of recent physical contact with white moths (Figure 3) was reported in 48.6% of the SHAPU versus 11.4% of controls (with adjusted OR of 6.89; 95% CI: 2.79–17.01).

Table 2. Univariate analysis of potential risk factors of SHAPU.

Factors	Cases (%)	Controls (%)	OR (95% CI)	*p*-value
Bushes around home/playground/office				
Yes	26 (74.3)	87 (82.9)	0.60 (0.24–1.49)	0.269
No	9 (25.7)	18 (17.1)	1.00	
Unusual flow of butterflies/moths around the area				
Yes	26 (74.3)	71 (67.6)	1.38 (0.58–3.27)	0.460
No	9 (25.7)	34 (32.4)	1.00	
Unusual movements of people				
Yes	4 (11.4)	3 (2.9)	4.39 (0.93–20.67)	0.117*
No	31 (88.6)	102 (97.1)	1.00	
Physical contact with butterflies/moths				
Yes	17 (48.6)	12 (11.4)	7.32 (2.99–17.91)	**<0.001**
No	18 (51.4)	93 (88.6)	1.00	
Attended mass gathering				
Yes	9 (25.7)	23 (21.9)	1.23 (0.51–2.99)	0.642
No	26 (74.3)	82 (78.1)	1.00	
Physical contact (touch) with livestock				
Yes	13 (37.1)	23 (21.9)	2.1 (0.92–4.82)	0.077
No	22 (62.9)	82 (78.1)	1.00	
Regular mosquito net use while sleeping				
Yes	6 (17.1)	21 (20.0)	0.83 (0.30–2.25)	0.711
No	29 (82.9)	84 (80.0)	1.00	
Regular light on in room/corridor while sleeping at night				
Yes	9 (25.7)	27 (25.7)	1.00 (0.41–2.40)	1.00
No	26 (74.3)	78 (74.3)	1.00	

*Note: *Chi square with continuity correction*

Risk factors analysis

Univariate and multivariate analyses of possible risk factors for developing SHAPU are shown in Tables 2 and 3 respectively. Cases were 6.89 times more likely to report coming in contact with moths and butterflies. Physical contact with livestock was also associated with being a case (p value-0.077), while regular use of a mosquito net while sleeping had no significant association with the occurrence or protection against moth exposure (p value −0.71). Regular use of a mosquito net during sleeping was not associated with SHAPU status. In addition, there was no difference in reported direct physical contact with butterflies/moths between users (14.8%) and non-users (22.1%). There were no reported differences in bushes around the home/playground/office; unusual flow of butterflies/moths around the area; washing of the hands/face after physical contact with insects/butterflies/birds; unusual movements of people; and attendance at mass gatherings between cases and controls.

Co-variates unusual movement of people, physical contact with butterfly and physical contact with livestock (all with $p < .1$ in bivariate analysis) were put in logistic regression model which showed that the patients with SHAPU were 6.89 times (CI = 3.03–19.38, $p < .001$) more likely to have reported exposure to white moths. The model was fit ($p = .943$, $r^2 = 0.207$).

Discussion

SHAPU is a devastating inflammatory eye disease that often leads to severe, irreversible vision loss within a week of onset. Till date, SHAPU has only been reported in Nepal. The disease is peculiar in its own as many ophthalmologists in the world have no experience about SHAPU. The etiopathogenesis of this disease is yet not confirmed so definite treatment protocol is lacking. Herein, we have attempted to identify the risk factors of SHAPU which can lead to disease aetiology establishment.

Geographical preponderance of SHAPU in Nepal

Consistent with prior epidemics, most cases during this outbreak originated from Pokhara valley, Kaski and its

Figure 3. The female white moth with brownish hairs behind surrounding the yellow eggs.

Table 3. Multivariate conditional logistic regression analysis among the most potential risk factors of SHAPU.

Factors	Cases (%)	Controls (%)	COR (95% CI)	p-value	AOR (95% CI)	p-value
Physical contact with butterflies/moths						
Yes	17 (48.6)	12 (11.4)	7.32 (2.99–17.91)	<0.001	6.89 (2.79–17.01)	<0.001
No	18 (51.4)	93 (88.6)	1.00		1.00	
Physical contact (touch) with livestock						
Yes	13 (37.1)	23 (21.9)	2.1 (0.92–4.82)	0.077	1.74 (0.70–4.31)	0.230
No	22 (62.9)	82 (78.1)	1.00		1.00	

Note: Here, variables with p-values <0.1 from above analyses were included in a multivariate logistic regression analysis to determine the effect adjusted for each of the other potential explanatory variables.

neighboring districts. Interestingly, all outbreaks, since the first one reported in 1975[4] also occurred in this area. This suggests that there may be something about the area that is conducive to this disease. Hence, it would be interesting to conduct future epidemiological studies focused on the climatic, rainfall, humidity, and vegetation of Pokhara and its five districts which make it vulnerable to SHAPU.

Characteristics of SHAPU cases

The 2017 SHAPU outbreak followed a 44-year long trend of occurring in odd years during the post-monsoon season (August to November). All cases were immunocompetent with no prior history of systemic or ocular illness/trauma. For 97.1% cases, it was the first time for them to have had any eye problem.

In over half of the cases, initial symptoms were reported in the morning. This is not entirely surprising given that most individuals sleep at night and symptoms are likely to go unnoticed, particularly since SHAPU is painless, and the limited discomfort or pain is not sufficient to wake the patient up. It is also possible that patients were exposed to the causative agent(s), moths most likely, the previous night or evening and manifested the disease the next morning. Home emerged to be the commonest site before developing ocular symptoms. This may be associated with the attraction of a large number of moths around the illuminated bulb inside the house.

Demographic characteristics

Consistent with other reports, the cases of SHAPU in this study were primarily children (71.4%).[4,11] Although an earlier report identified a 9 month old infant as the youngest case of SHAPU, the present study reports SHAPU in a neonate of 38 days old, making it the youngest case seen to date.[12] No gender predilection has been identified in SHAPU.[4]

Caste, ethnicity, and birth weight were studied for the first time; however, none of them were significantly associated with the disease.

Primary factors associated with SHAPU

Butterflies/Moths. While a sudden increase in the prevalence of white moths was reported for both cases and controls, SHAPU cases were 6.89 times more likely to report a history of direct contact with these white moths, making it the most important factor found in this study. The fact that physical contact with the moth was much more common in cases suggests that mere exposure to moths does not cause the condition, but that physical contact with the moth is necessary for developing SHAPU. This has been further confirmed by the clinical detection of the moth hairs in the cornea of a SHAPU case confirmed with the anterior segment OCT.[13] Interestingly, we had history from two brothers from the same family in this study who were both exposed to moths. The elder brother rubbed the moths on his whole body, but the younger brother observed the moth but did not rub it on his body. Only the elder brother developed redness of the eye with decreased vision the next day, while the younger one was fine. We hypothesize that either the toxins released by the moth or the fine hairs that protect the egg sac may lead to SHAPU.

Two types of white moths have been considered as the vector for SHAPU. An early report suggested that the Tussock moth was the likely culprit.[10] However, more recently, the Gazalina moth has been considered more likely the moth that causes SHAPU for several reasons.[5] Unlike Tussock moth, *Gazalina* live in habitats near human settlements. They remain inactive during day, resting in gardens, tree bark, leaves, lawns, and walls and emerging at night, attracted by bright light.[14,15] The adults of *Gazalina chrysolopha* emerge from mid-July to mid- August[16]which matches with outbreak period of SHAPU in Nepal. Though Gazalina chrysolopha remains the strongest suspect, future moth studies are warranted to prove its role in disease causation.

Pathophysiology of SHAPU

There are many possible ways in which the moths may cause SHAPU. One possibility is that the moths might serve as vectors, carrying plant material acquired during their feeding time and this material may be the responsible agent that can induce infective and/or immunological reactions within hours of contact. Alternatively, female moth spines and setae bear toxic materials for the natural protection of their eggs. These toxic materials include histamine, acetylcholine, formic acid, venom, pro-inflammatory products of cyclo-oxygenase, and nitric oxide, proteins with trypsin-like activity and vaso-degenerative and fibrinolytic effects, serine proteases and pro-coagulant toxins.[15] Some of these venoms and toxins are capable of causing hypersensitivity reactions in susceptible individuals. Some species cause immediate hypersensitivity reactions, others cause delayed-type hypersensitivity, and some appear capable of causing both.[4,15,17] Given the rapid onset of SHAPU, type 1 hypersensitivity reaction may be the most plausible explanation as histamine, a mediator of type 1 hypersensitivity is one of the substances that moths carry. Additional research is needed in this area, including the need for toxins & immunobiomarkers analysis of the moth particles and its comparison with the ocular fluid samples of SHAPU.

Since the 1977 SHAPU epidemic, parents or patients reported a history of contact or being near the moths[4]; however, no systematic investigation to determine whether there was an increased chance of exposure to moths in cases compared to the general population. This study provides strong support for the theory that the white moth is an important correlating factor for SHAPU. Hence, futher studies targeting the moth species, its lifecycle, its toxins, microbiomes and mode of transmission of the disease need to be answered in future studies.

The major limitation of this study is its retrospective nature as the prospective study would have allowed us to correlate the disease progression in presence of its risk factor. Recall bias of our participants (cases & controls)

due to the retrospective nature of this study is a point to be noted though the enumerator provided enough time to recall the information asked. But recall bias can be influenced by sensory distractions, emotional responses, personal beliefs and more We are also aware that the extent of recall might be differential in cases and controls, with cases being more likely to (accurately or inaccurately) recall exposure to a suspected risk factor, and controls are less likely to recall the risk factor.

Another limitation of the study is the relatively small number of cases. However, our sample size was limited by the number of cases during the most recent outbreak.

While we work to establish the cause, it will be necessary to have a consensus on a common diagnostic protocol harnessing the opportunities offered by newer molecular technologies for bacteria, viruses, and parasites. But the availability of facilities of molecular, genomic, immunological and toxicological study in Nepal is the main issue to reach to the depth of SHAPU mystery. In future, a systematic epidemiological, clinical, microbiological, immunological and entomological study will hopefully clarify these issues. Our team has requested that the government make SHAPU a notifiable disease and put a surveillance system in place within the Epidemiology and Disease Control Division (EDCD) of Department of Health Services to prepare for future outbreaks. Dissemination of the results of this study with the Nepalese government stakeholders, ophthalmologists (national & international), epidemiologists and local people has increased the awareness of SHAPU. A prospective study during the subsequent outbreaks should focus on SHAPU-Moth saga and SHAPU-Microbiome saga thereby solving the mystery of SHAPU etiopathogenesis.

Conclusions

SHAPU remains an idiopathic severe inflammatory eye disease occurring in alternate years in Nepal. Understanding its cause would be the first step in developing reduction strategies and/or treatments. To date, most of the data suggesting aetiopathogenesis has been anecdotal or based on case reports and case series. This retrospective, survey-based case–control study examining risk factors for SHAPU is the first large-scale nationwide epidemiologic study of its kind. Based on a multivariate analysis of potential risk factors, the study shows that individuals with SHAPU are more likely to recall having physical contact with white moths compared to controls. However, more than 50% of cases do not recall having direct physical contact with moths. Future studies focused on moth SHAPU saga including moth lifecycle, toxin analysis, hypersensitivity reactions, genotyping, phenotyping and identifications of its biomarkers are warranted.

Abbreviations

BPKLCOS	B.P. Koirala Lions' Centre for Ophthalmic Studies
CHEERS	Hospital for Children, Eye, ENT and Rehabilitation ServicesEDCD - Epidemiology and Disease Control Division
HEH	Himalaya Eye Hospital
NHRC	Nepal Health Research Council
SHAPU	Seasonal Hyperacute Panuveitis
TIO	Tilganga Institute of Ophthalmology
WEDS	WHO Emergency District Support

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Authors' contributions

MPU and RKS designed the study, SNJ, AM, PK, HG, IM, RKS were involved in evaluating and managing the case.MPU, RKS, EWG, BRK and AM were involved in report writing

and data analysis. MPU, SNJ, BRK and EWG are involved in critical analysis and review of manuscript. RKS, EWG were involved in drafting the manuscript. All authors have read the manuscript carefully and approved its submission.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Obtained.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Ethical approval for the study was obtained from the Nepal Health Research Centre (NHRC) and consent to participate was obtained from all the cases and controls.

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