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REVIEW ARTICLE

Ocular sequelae of snakebite envenoming: a review of the indirect effects of snakebite envenoming on the eye

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ABSTRACT

Snakebite envenoming is a major public health issue in developing, often agricultural-based, tropical countries, which causes substantial mortality and morbidity. Most studies have been conducted on well-known toxic effects such as neurotoxicity, cytotoxicity, and hemotoxicity, however, there is scarce information on their indirect effects on the eye. In this review, we provide an overview of ocular pathologies caused by snakebite envenoming. In total, 65 cases, described in 42 case reports and series, were identified in the PubMed and Embase databases. Most reported ocular toxicities/disorders after snakebite envenoming were ophthalmoplegia (12 cases), intra- and peri-ocular hemorrhages (9 cases), and acute glaucoma (13 cases). We also discuss the possible mechanisms for these ocular pathologies. Interestingly, optic neuropathy might be an adverse effect of antivenom instead of directly being caused by envenoming. We prompt recognition of this largely overlooked topic within the field of snakebite, and further stress the need to combat this neglected tropical disease.

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Introduction

There are circa 4000 species of snakes (Serpentes) around the world. Certain lineages possess specialized oral glands that produce a complex mixture of proteinaceous toxins, referred to as venom (Uetz and Hošek 2022). Venom is only found in advanced snakes (Caenophidia), a superfamily consisting of over 2500 species. These include Viperidae (e.g. true vipers and pitvipers), Elapidae (e.g. true cobras, king cobras, mambas, kraits, and sea snakes), and Colubridae (e.g. boomslang and twig snakes) (Pyron *et al.* 2013). Venom is predominantly used for facilitating prey capture, although spitting cobras deter aggressors by ejecting venom toward their eyes (Jalink 2020, Kazandjian *et al.* 2021). Prey capture is facilitated by interference with vital homeostatic processes, ultimately resulting in incapacitation or death of the prey (Gutiérrez *et al.* 2017).

Human envenoming happens mostly under accidental events, causing substantial mortality and morbidity, particularly affecting (sub)tropical regions (Kasturiratne *et al.* 2008, Longbottom *et al.* 2018). Hence, snakebite envenoming was designated as a neglected tropical disease by the World Health Organization in 2017. Snake venom toxins generally cause three distinct pathological effects: neurotoxicity, cytotoxicity, and hemotoxicity (Gutiérrez *et al.* 2017). Neurotoxicity is caused by the disruption of neurotransmission, leading to muscle paralysis and respiratory failure. Cytotoxicity is caused by disruption of cell membranes, causing cell death, which mainly results in local tissue necrosis, blistering, and edema. Hemotoxicity is associated with different hemostatic alternations including hemorrhage and coagulopathy, caused by the breakdown of capillary walls, thrombocytopenia, and interference with the coagulation cascade. This can lead to venom-induced consumption coagulopathy (VICC) (Isbister 2010). Another regularly observed effect is acute kidney injury, either caused by direct cytotoxic effects or by toxic intracellular proteins that enter circulation after related muscle damage (i.e., rhabdomyolysis).

There is a significant lack in our knowledge on the ocular pathologies caused by snakebite envenoming.

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The likelihood of developing ocular complications depends on many circumstances such as the species of snake, present toxins, treatment, and condition of the patient. Therefore, certain eye pathologies are more common in certain regions of the world. For example, in one study from India, a country where on average 200 000 people are bitten by snakes every year, an estimated 27.3% of venomous snakebites led to ocular symptoms (Das *et al.* 2015). Examples of snake species causing ocular symptoms after snakebite can be found in Figure 1. Most scientific literature, however, is limited by case reports or series that describe a seemingly heterogeneous group of symptoms, including ophthalmoplegia, proptosis, red eyes, loss of central or peripheral vision, and painful eye movements. Severe ocular complications such as endogenous endophthalmitis, retrobulbar hemorrhage, and retinal hemorrhages are reported.

It is of clinical importance that healthcare workers know which ocular symptoms and/or diagnoses are to be expected when dealing with a patient with snakebite envenoming. Severe complications should be treated promptly. Quick recognition, and (if possible) referral to an ophthalmologist, may help preserve vision. The aim of this article is to gather scientific literature to give an ophthalmologic overview of all possible ocular symptoms that have been recorded after snakebite envenoming. This review highlights the wide diversity of ocular pathologies that can be observed in patients with snakebite envenoming.

This paper includes symptoms pertaining to the ocular adnexa, like eyelid and orbit. Ophthalmoplegia, ptosis, and cerebral visual impairment pertain mainly to the realm of neurology. This review focused solely on ophthalmologic sequalae, but found studies on these neurologic disorders were included in the results because of their effects on vision/visual acuity. Ophthalmoplegia and ptosis are recognized as an (early) expression of general neurotoxicity. For example, in Common krait (*Bungarus caeruleus*) envenoming, partial or complete ptosis is reported in 70–100% of patients with mild neurotoxicity and complete ophthalmoplegia was seen in 82.4% of patients with severe neurotoxicity (Kularatne 2002, Silva *et al.* 2016a). Ptosis in mild neurotoxicity is reported in both elapids (e.g. Indian cobra, *Naja naja* and Common krait, *Bungarus caeruleus*) and vipers (e.g. Death adders, *Acanthophis* spp. and Russell's viper, *Daboia*

Figure 1. Examples of snake species causing ocular symptoms after snakebite envenoming. A: Russell's viper (*Daboia russelii*) in Mysore District, Karnataka, India. B: Spectacled Cobra (*Naja naja*) in Karnataka State, India. C: Common Lancehead (*Bothrops atrox*) on Brownsberg, Brownsweg, Suriname. D: Saw-scaled viper (*Echis carinatus*) in Tamil Nadu, India. Photo A, B and D courtesy of Wolfgang Wüster. Photo C courtesy of Maarten B. Jalink.

russelii) (Johnston *et al.* 2012, Kularatne *et al.* 2009, Silva *et al.* 2016b). Scientific literature that discusses ocular complications caused by a snakebite directly to the eye or its adnexa, or by direct inoculation with venom was not included in this review, as those injuries are not caused by systemic envenoming. Ocular injury caused by spitting cobras and direct ocular injury caused by snakebites has been discussed separately (Chu *et al.* 2010, Jalink 2020, Jalink and Wisse 2022).

Methods

In March 2022, a search in the PubMed and Embase databases was performed using the broad terms "snake" and "eye". There were 455 (PubMed) and 642 (Embase) studies, of which the title and abstract were screened for suitable articles. Inclusion criteria were reports and studies discussing ocular symptoms caused by systemic snakebite envenoming. Non-human reports were excluded. The majority of studies that were not included discussed a completely different topic than this review (e.g. studies on snake eye anatomy or ophthalmologic drugs derived from snake venom). After discarding fourteen duplicates, 34 relevant studies were selected. Eight studies could not be retrieved online. Two studies were retracted and were therefore not included in our results. A multi-language search was performed. The references of all found studies were then cross-checked, resulting in eighteen additional sources. In total, 42 relevant studies were retrieved and incorporated into our analysis. A comprehensive overview can be found in Figure 2.

Results

A total of 65 separate cases were described across 42 studies. A summary can be found in Tables 1, 2, and 3. The majority of patients were male (72.3%), and

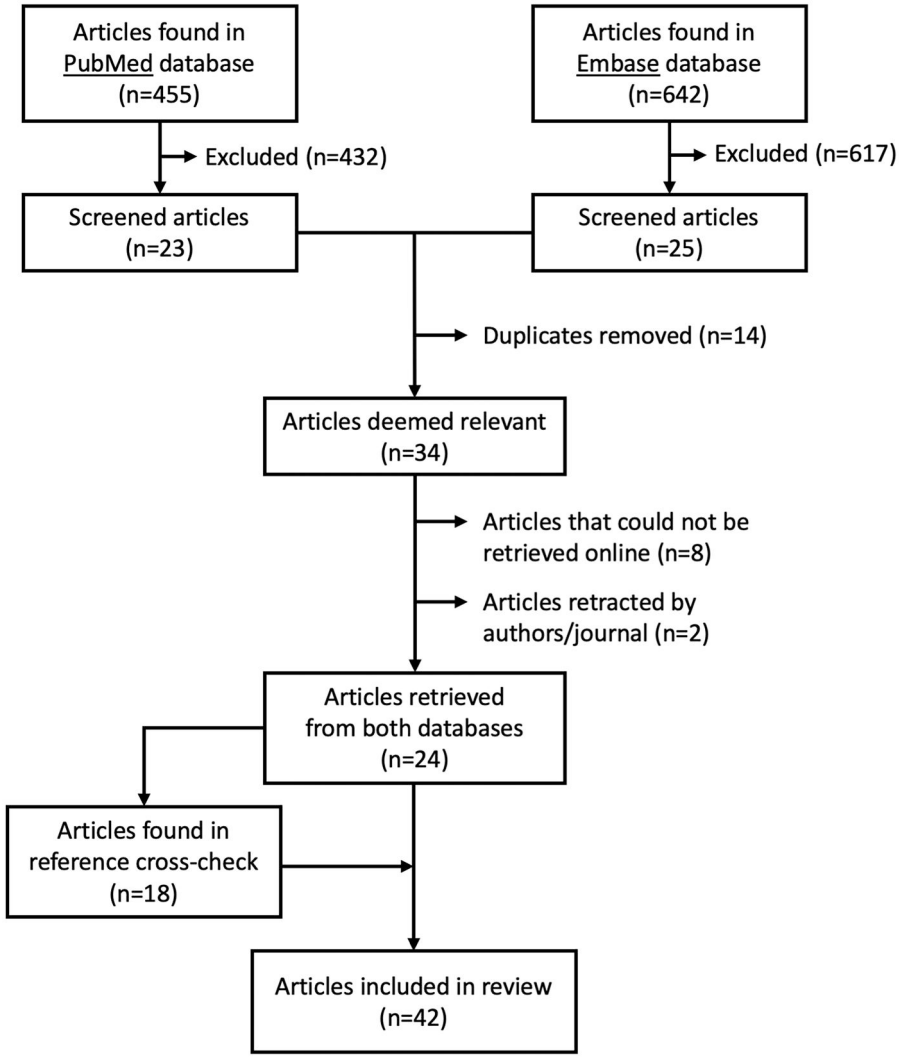

Figure 2. Flow chart of literature search.

Table 1. Summary of cases of neurotoxic effects on the eye.

Ophthalmologic diagnosis	Age	Sex	Country	Species of snake	Anti-venom	Authors (year)
Ophthalmoplegia	23	male	South Korea	*Gloydius halys*	no	Ari (2001)
Ophthalmoplegia	51	male	Japan	*Gloydius blomhoffi*	yes	Takeshita *et al.* (2003)
Ophthalmoplegia	51	female	South Korea	*Gloydius halys*	yes	Lee and Lee (2004)
Ophthalmoplegia	59	male	South Korea	*Gloydius halys*	no	Kim *et al.* (2009)
Ophthalmoplegia	49	male	Japan	*Gloydius blomhoffi*	no	Igari *et al.* (2010)
Ophthalmoplegia	21	female	Zimbabwe	*Bitis atropos*	yes	Montgomery (1959)
Ophthalmoplegia	19	male	Zimbabwe	*Bitis atropos*	yes	Montgomery (1959)
Ophthalmoplegia	22	male	Italy	*Vipera aspis*	yes	Re *et al.* (1999)
Ophthalmoplegia	12	male	Thailand	*Trimeresurus macrops*	yes	Sontichai *et al.* (2015)
Ophthalmoplegia	36	female	India	unspecified elapid	yes	Praveen Kumar *et al.* (2015)
Ophthalmoplegia	43	male	India	unspecified elapid	yes	Praveen Kumar *et al.* (2015)
Ophthalmoplegia	8	female	India	*Bungarus caeruleus*	yes	Bawaskar *et al.* (2017)
Optic neuropathy	51	male	Nigeria	*Echis carinatus*	yes	Davenport and Budden (1953)
Optic neuropathy	40	male	Israël	*Macrovipera lebetinus*	yes	Guttmann-Friedmann (1956)
Optic neuropathy	50	male	India	*Naja naja*	yes	Menon *et al.* (1997)
Optic neuropathy	35	female	India	unspecified	yes	Sahai and Sinha (1978)
Optic neuropathy	7	female	South Africa	*Naja nigricollis*	yes	Schwersenski and Beatty (1982)
Optic neuropathy	24	female	India	*Naja naja*	yes	Dhabhar *et al.* (2021)
Optic neuropathy	35	male	India	unspecified viper	yes	Praveen Kumar *et al.* (2015)
Optic neuropathy and uveitis	20	male	India	unspecified viper	yes	Nayak *et al.* (2007)
Neuroretinal toxicity	26	Male	India	unspecified	no	Jalali *et al.* (2013)

Table 2. Summary of cases of hemotoxic effects on the eye.

Ophthalmologic diagnosis	Age	Sex	Country	Species of snake	Anti-venom	Authors (year)
Central retinal artery occlusion	20	female	India	*Echis carinatus*	yes	Bhalla *et al.* (2004)
Central retinal artery occlusion	17	female	India	unspecified viper	yes	Singh *et al.* (2007)
Central retinal artery occlusion	32	male	Thailand	*Daboia russelii*	yes	Tungpakorn (2010)
Central retinal artery occlusion	24	male	India	unspecified	no	Jalali *et al.* (2013)
Central retinal artery occlusion	30	female	India	unspecified viper	yes	Naik *et al.* (2017)
Central retinal artery occlusion	17	male	India	unspecified viper	yes	Patel *et al.* (2018)
Cerebral visual impairment	6	male	India	*Naja naja*	yes	Dhaliwal (1999)
Cerebral visual impairment	46	male	Martinique	*Bothrops lanceolatus*	yes	Merle *et al.* (2005)
Cerebral visual impairment	54	female	Sri Lanka	*Daboia russelii*	yes	Subasinghe *et al.* (2014)
Vitreous hemorrhage	46	male	India	unspecified viper	yes	Rao (1977)
Vitreous hemorrhage with ghost cell glaucoma	44	male	Colombia	*Bothrops athrox*	no	Rojas *et al.* (2001)
Vitreous hemorrhage	13	female	India	unspecified	yes	Thomas *et al.* (2017)
Retinal hemorrhage	62	female	South Korea	unspecified viper	yes	Kweon *et al.* (2009)
Retinal hemorrhage	22	female	India	*Daboia russelii*	yes	Dutta *et al.* (2011)
Retinal hemorrhage	42	male	India	unspecified viper	yes	Omprakash *et al.* (2016)
Retrobulbar hemorrhage	15	male	Nigeria	*Echis ocellatus*	yes	Mustapha *et al.* (2010)
Retrobulbar hemorrhage	10	male	Nigeria	unspecified viper	yes	Katibi *et al.* (2015)
Anterior segment ischemia	60	male	India	unspecified viper	yes	Sivakumar and Rao (2016)
Anterior segment ischemia	30	male	India	unspecified viper	yes	Sivakumar and Rao (2016)
Anterior segment ischemia	54	male	India	unspecified viper	yes	Sivakumar and Rao (2016)
Anterior segment ischemia	55	male	India	unspecified viper	yes	Sivakumar and Rao (2016)
Anterior segment ischemia	45	male	India	unspecified viper	no	Sivakumar and Rao (2016)
Anterior segment ischemia	60	male	India	unspecified viper	yes	Sivakumar and Rao (2016)
Anterior segment ischemia	50	male	India	unspecified viper	yes	Sivakumar and Rao (2016)
Conjunctival hemorrhage	32	male	India	unspecified	yes	Praveen Kumar *et al.* (2015)

ages ranged between 6 (Dhaliwal 1999) and 76 years (Aye *et al.* 2018) with an average of 38.7 years (standard deviation 22.6 years). The oldest case was reported in 1953 (Davenport and Budden 1953). In 86.2% of all cases, antivenom was given, mostly for non-ophthalmologic reasons such as bleeding diathesis or respiratory arrest. The majority of studies, 78.6%, were from Asia, with 47.6% from India alone. Furthermore, 14.3% was from Africa, 4.7% from South America, and 2.4% (one case) was reported from Europe (Italy). Remarkably, there were no reported cases from North America or Australia. Snake species were identified in various questionable manners, e.g. recognized by a patient or family/acquaintance, the snake specimen killed and brought to the primary care physician, or an educated guess. About three-quarters of all cases were reported to be caused by snakes from different genera of the Viperidae family, although not every study reported the species of snake (Figure 3). Other snakes that were found to cause ocular morbidity were members of the Elapidae family. All cases were categorized according to the most prominent ocular symptom caused by systemic envenoming.

Neurotoxicity

We have identified symptoms related to neurotoxicity in 21 separate cases. An overview can be found in Table 1.

Table 3. Summary of other effects on the eye.

Ophthalmologic diagnosis	Age	Sex	Country	Species of snake	Anti-venom	Authors (year)
Painful eye movements	27	female	South Africa	*Atractaspis bibronii*	no	Tilbury and Branch (1989)
Uveitis	60	male	India	*Daboia russelii*	yes	Nayak *et al.* (2007)
Uveitis	25	male	India	unspecified viper	yes	Praveen Kumar *et al.* (2015)
Exsudative retinal detachement	13	male	India	Unspecified	yes	Praveen Kumar *et al.* (2015)
Acute glaucoma	30	male	India	unspecified viper	yes	Srinivasan *et al.* (2005)
Acute glaucoma	42	female	India	unspecified viper	yes	Srinivasan *et al.* (2005)
Acute glaucoma	53	male	India	unspecified viper	yes	Kulkarni *et al.* (2014)
Acute glaucoma	36	male	India	unspecified viper	yes	Kulkarni *et al.* (2014)
Acute glaucoma	16	male	India	unspecified viper	yes	Kulkarni *et al.* (2014)
Acute glaucoma	67	female	Türkiye	*Macrovipera lebetinus*	yes	Olcaysu *et al.* (2015)
Acute glaucoma	53	male	India	unspecified viper	yes	Praveen Kumar *et al.* (2015)
Acute glaucoma	45	male	India	*Naja naja*	yes	Praveen Kumar *et al.* (2015)
Acute glaucoma	43	female	India	unspecified viper	yes	Praveen Kumar *et al.* (2015)
Acute glaucoma	52	male	India	unspecified viper	yes	Praveen Kumar *et al.* (2015)
Acute glaucoma	48	male	India	unspecified viper	yes	Praveen Kumar *et al.* (2015)
Acute glaucoma	38	male	India	unspecified	yes	Praveen Kumar *et al.* (2015)
Acute glaucoma	76	male	Myanmar	unspecified viper	yes	Aye *et al.* (2018)
Endogenous endophthalmitis	50	male	Pakistan	unspecified	no	Iqbal *et al.* (2009)
Endogenous endophthalmitis	39	male	India	*Naja naja*	yes	Ganesan *et al.* (2021)

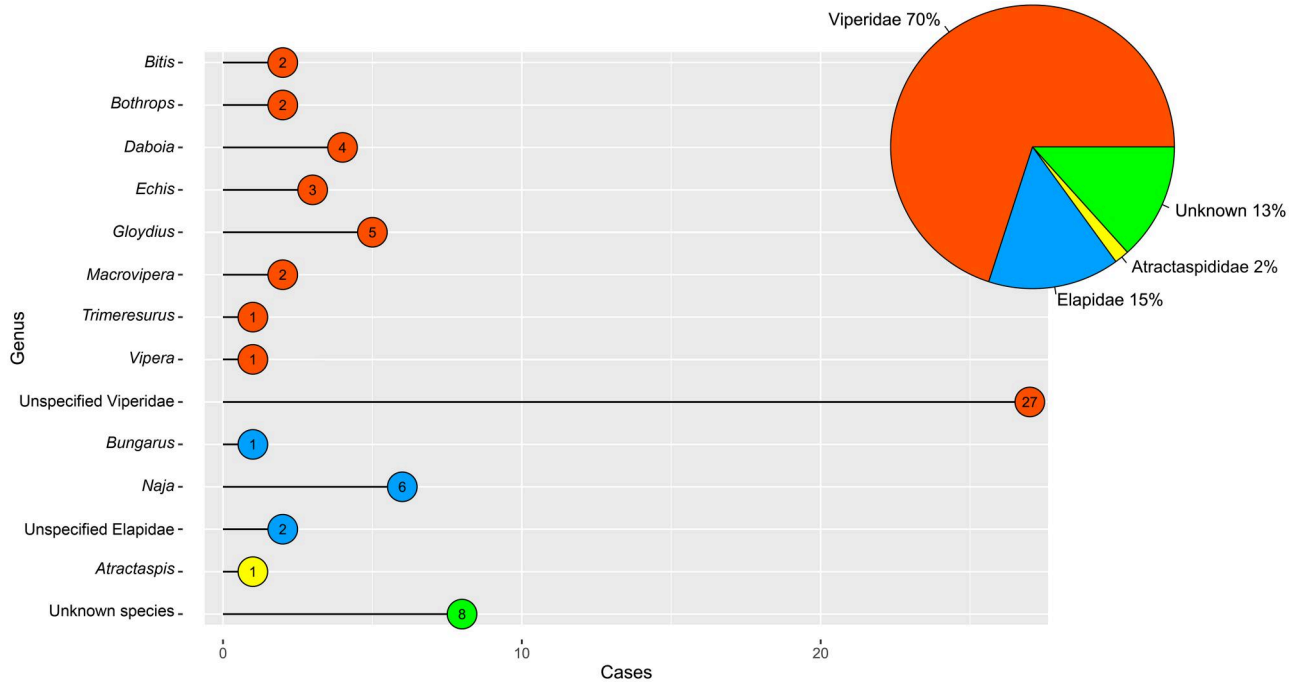

Figure 3. Distribution of published case reports and case series on the development of ocular effects following various snake genera.

Ophthalmoplegia

There were twelve reports of paresis of the extra-ocular muscles, leading to ophthalmoplegia and ptosis. Three quarters of the cases were caused by vipers and the rest by elapids. Two members of the viperid genus *Gloydius* (Mamushi, *Gloydius blomhoffi,* in Japan, and the Halys Viper, *Gloydius halys* in South Korea, reported under the previous names *Agkistrodon blomhoffi* and *Agkistrodon halys* respectively) was identified in five separate cases (Ari 2001, Takeshita *et al.* 2003, Lee and Lee 2004, Kim *et al.* 2009, Igari *et al.* 2010). Each bite caused paresis within a few hours up to three days, ranging from single muscle paresis (Igari *et al.* 2010) to bilateral comitant exotropia with equal paresis of all muscles (Kim *et al.* 2009).

Paresis is triggered by neurotoxins that cause pre-synaptic and post-synaptic interference in the neuromuscular junction, leading to symptoms comparable to ocular myasthenia (Igari *et al.* 2010). In cases involving Asian pitvipers (*Gloydius spp.*), this could be explained by the presence of presynaptic phospholipase A2 (PLA2) neurotoxins in their venoms (Chen *et al.* 1987, Tang *et al.* 1998, Yang *et al.* 2015). Extra-ocular muscles are more susceptible to paresis than larger

striated muscles because of a higher ratio of nerve to muscle fibers, so a smaller dose of toxin is needed to inhibit them (Lee and Lee 2004, Kim *et al.* 2009). Two of five cases received antivenom and the other three were treated conservatively; all cases were orthophoric and had normal ocular motility after two to fourteen days.

Bites of other vipers can also induce total ophthalmoplegia (Montgomery 1959, Re *et al.* 1999, Sontichai *et al.* 2015). In addition, a bite of a Berg Adder (*Bitis atropos*) caused pupillary dilatation and difficulty with accommodation (Montgomery 1959). In contrast, a bite of an Asp Viper (*Vipera aspis*) additionally led to facial diplegia (Re *et al.* 1999). This is particularly interesting since both species represent rare examples of vipers known to cause neurotoxicity (Ferquel *et al.* 2007, de Haro *et al.* 2009, van der Walt and Muller 2019, Youngman *et al.* 2021). Their neurotoxic effects, again, have been attributed to the presence of presynaptic PLA2 neurotoxins (van Zyl *et al.* 2001, Jan *et al.* 2002, Guillemin *et al.* 2003). In one case of ophthalmoplegia with exotropia after a snakebite in Thailand, ocular and systemic symptoms persisted after the patient received antivenom for various brown-colored snakes (true cobras, Malayan pitviper, and Russell's viper), since he reported to be bitten by a dark snake (Sontichai *et al.* 2015). Symptoms quickly improved after switching to Green pitviper (*Trimeresurus macrops*) antivenom, underlining that a clinician should be aware of erroneous memory recollection (Meyer *et al.* 2015). We found three cases of ophthalmoplegia that were caused by the bite of an elapid, two unknown species and a Common krait (*Bungarus caeruleus*) (Praveen Kumar *et al.* 2015, Bawaskar *et al.* 2017). An 8-year-old girl from India who was bitten in her neck by a Common krait while in bed suffered from a complete myasthenic face including dilated pupils, ptosis and ophthalmoplegia that recovered within three days after treatment with anti-venom (Bawaskar *et al.* 2017). Common kraits are well-known for the presence of both postsynaptic neurotoxins (e.g. three-finger toxins; 3FTX) and presynaptic neurotoxins (e.g. PLA2) in their venom (Oh *et al.* 2017). In conclusion, ophthalmoplegia in all cases could be explained by the presence of presynaptic PLA2 neurotoxins in each of these species of snake.

Optic neuropathy

Optic neuropathy is a broad diagnosis that has a wide variety of etiologies, including toxins, auto-immune disease, and trauma. In found literature, both the terms "optic neuropathy" and "optic neuritis" were used to describe the same clinical picture of central and/or peripheral vision loss in association with papilledema, pupillary defects, dilated retinal veins, and peripapillary hemorrhages after snakebite envenoming. Since "optic neuritis" refers to a specific auto-immune condition, the term "optic neuropathy" is used in this review. Most cases are bilateral, though severity per eye is variable. There is rapid progression to optic atrophy, with severely diminished visual fields or complete loss of sight, within weeks and there is a somewhat bleak prognosis (Davenport and Budden 1953, Guttmann-Friedmann 1956, Menon *et al.* 1997, Sahai and Sinha 1978, Schwersenski and Beatty 1982). Full recovery has been reported as well (Dhabhar 2021). Optic neuropathy was observed following bites from various snakes of the Viperidae (i.e. Saw-scaled viper, *Echis carinatus*, Lebetine Viper, *Macrovipera lebetinus*) and Elapidae families (i.e. Indian cobra, *Naja naja,* Black-necked spitting cobra, *N. nigricollis*). The clinical outcomes are difficult to predict because of the different combinations of treatments applied (e.g. antivenom, and steroids). In six out of seven cases of optic neuropathy, ocular symptoms started at day six after the bite (Davenport and Budden 1953, Guttmann-Friedmann 1956, Menon *et al.* 1997, Sahai and Sinha 1978, Praveen Kumar *et al.* 2015, Dhabhar 2021), while systemic neurotoxicity usually presents within 3 min to 19 h (Nayak *et al.* 2007). This suggests that not the venom causes optic neuropathy, but that other factors may be involved. A hypothesis is that optic neuropathy – at least those presenting at a later stage – is not caused by the snake venom itself, but by antivenom instead. The conventional antivenoms are composed of antibodies (IgG) or antibody fragments (such as the fragment antigen binding region, or Fab) against snake venom toxins, that are derived from the plasma of hyperimmunized animals such as horses or sheep (Gutiérrez *et al.* 2017). All mentioned cases that developed complaints on day six were treated with anti-venom; the type of antivenom was rarely reported. Interestingly, we found another case of similar clinical features of transient papilledema that also originated six days after a patient received antivenom. However, this patient was bitten by a non-venomous snake (which was confirmed since the snake was killed and brought in) and received anti-venom as a precautionary measure (Mathur 1959). This report supports the second hypothesis. Furthermore, in some cases, optic neuropathy is accompanied by anterior uveitis, which is also linked to the use of antivenom (Nayak *et al.* 2007, Praveen Kumar *et al.* 2015). This suggests a previously unknown adverse effect of the current generation of antivenoms.

Retinal neurotoxicity

In just a single case, venom-induced intra-ocular neurotoxicity is suspected (Jalali *et al.* 2013). A 26-year-old male from India was bitten by an unknown snake, was treated by a traditional healer and did not receive any antivenom. After three days, best-corrected visual acuity dropped to 20/80 and visual field test showed severe peripheral field loss in both eyes. He presented to the ophthalmologist one month after the event. Visual evoked potentials and magnetic resonance imaging of the brain were normal, but the electroretinogram suggested an inner retinal layer dysfunction involving mainly the rod pathways.

Hemotoxicity

In 25 separate cases, we have identified hemotoxic effects after snakebite envenoming. An overview can be found in Table 2.

Central retinal artery occlusion

Six cases of unilateral central retinal artery occlusion (CRAO) were reported, all from India and Thailand (Bhalla *et al.* 2004, Singh *et al.* 2007, Tungpakorn 2010, Jalali *et al.* 2013, Naik *et al.* 2017, Patel *et al.* 2018). Five cases were caused by vipers (Saw-scaled viper, *Echis carinatus,* and Russell's viper, *Daboia russelii*); in the other case, the species of snake was unknown (Jalali *et al.* 2013). All cases of CRAO happened within 24 h after the bite, and most led to legal blindness. In one case, CRAO was recognized fast and was treated with acetazolamide and ocular massage (Naik *et al.* 2017). Visual acuity eventually improved from 2/60 to 6/9.

Various theories about the etiology of the arterial occlusions have been proposed. First, procoagulant toxins might cause either direct emboli and/or venom-induced consumption coagulopathy (VICC). Furthermore, certain cytotoxins or hemotoxins might cause vasospasm or vasculitis, and certain other toxins (e.g. ACE inhibitors) might induce hyperviscosity secondary to hypovolemia or hypotension, or finally, a preexisting procoagulant state (Singh *et al.* 2007, Tungpakorn 2010, Naik *et al.* 2017). These toxins are commonly present in vipers, including Saw-scaled vipers and Russell's viper (Slagboom *et al.* 2017). However, none of these theories have been confirmed.

Cerebral visual impairment

Three patients suffered from cerebral visual impairment after snakebite envenoming (Dhaliwal 1999, Merle *et al.* 2005, Subasinghe *et al.* 2014). Although these sequelae are not truly ophthalmologic, they were included because they led to bilateral legal blindness in two cases caused by an Indian cobra (*Naja naja*) and a Russell's viper (*Daboia russelii*) (Dhaliwal 1999, Subasinghe *et al.* 2014). The other case, in which a transient homonymous quadrantanopia developed, was caused by a Martinique Lancehead (*Bothrops lanceolatus*) (Merle *et al.* 2005). Cerebral visual impairment is not caused by neurotoxicity, but rather by multiple (occipital) infarctions. As with CRAO, various causes for these infarctions are postulated (see previous paragraph). In one case, diffuse intravascular coagulopathy was suspected (Merle *et al.* 2005).

Vitreous hemorrhage

Three cases of vitreous hemorrhage after snakebite envenoming, all bilateral, have been reported (Rao 1977, Rojas *et al.* 2001, Thomas *et al.* 2017). All patients underwent vitrectomy because of non-clearing hemorrhage. There was significant patient delay in two cases, which made it hard to determine the etiology of these hemorrhages (Rao 1977, Thomas *et al.* 2017). In one case, caused by an unknown species, platelet count was normal at the time of presentation (Rao 1977). However, the 46-year-old patient had been unconscious for 20 days, probably as the result of a subarachnoid hemorrhage, and had been treated by a traditional healer. It was theorized that the vitreous hemorrhage was secondary to the subarachnoid hemorrhage (Terson's syndrome). Another patient, a 13-year-female, presented three months after being bitten by an unknown species of snake (Thomas *et al.* 2017). Besides vitreous hemorrhage, B-scan ultrasonography showed total retinal detachment in both eyes, for which she underwent pars plana vitrectomy in conjunction with belt buckling, endolaser, and silicone oil tamponade in the left eye. Peroperatively, proliferative retinopathy of the posterior pole was observed. This indicates a different pathophysiological mechanism, possibly secondary to retinal ischemia or vasculitis directly caused by cytotoxins. The third case, a 44-year-old male from Colombia with bilateral vitreous hemorrhage two days after being bitten by a Common Lancehead (*Bothrops atrox*), also suffered from retinal detachment, but this was of rhegmatogenous origin and happened after the initial vitrectomy; there was no mention of retinopathy (Rojas *et al.* 2001).

Retinal hemorrhage

Retinal hemorrhages were seen in three patients with low platelets and increased titers of fibrin degradation products and D-dimer after being bitten by viperid snakes, one of which was identified as a Russell's viper (*Daboia russelii*) (Kweon *et al.* 2009, Dutta *et al.* 2011,

Omprakash *et al.* 2016). These hemotoxic effects could be explained by the diverse hemotoxins (e.g. snake venom metalloproteinases, snake venom serine protease) commonly present in viper venoms including Russell's vipers (Slagboom *et al.* 2017). All presented with a combination of different types of hemorrhage in both eyes; pre-retinal, retinal, and subretinal hemorrhages and Roth's spots. Only one eye had complete visual recovery (Dutta *et al.* 2011); one patient deceased due to systemic complications (Omprakash *et al.* 2016).

Retrobulbar hemorrhage

Bilateral retrobulbar hemorrhage was observed in two separate cases from Nigeria (Mustapha *et al.* 2010, Katibi *et al.* 2015). Both patients were young boys (10 and 15 years) that were bitten by viperid snakes; one was identified as an Ocellated Carpet Viper (*Echis ocellatus*). Patients had spontaneous bleedings (from nose and gums respectively) and subgaleal hematoma with increased head circumference. In one case, clotting time was confirmed to be prolonged (>20 min) (Mustapha *et al.* 2010). Hemorrhaging and incoagulable bleedings are common systemic pathologies in Saw-scaled viper (*Echis* spp.) envenomings, and thus also can affect the eye (Warrell *et al.* 1977). Proptosis, chemosis, and vision loss occurred at two and seven days post-bite. Both patients had no light perception in both eyes at the time of presentation and no treatment options could be offered.

Anterior segment ischemia

Sivakumar and Rao (2016) published a study on seven snakebite victims with anterior segment ischemia, that were seen in a uveitis clinic in South India between 1996 and 2007. All patients were healthy, male farmers between 30 and 60 years old. They were bitten by unknown viper species, but presumably Russell's viper (*Daboia russelii*) or Saw-scaled viper (*Echis carinatus*). All patients developed systemic hypotension; this led to renal failure in six patients, for which five patients eventually needed dialysis. Six patients had received antivenom from their primary care physician. Patients presented at the clinic between one and eighteen months after the snakebite. In total, twelve eyes presented with the clinical picture of ciliary hyperemia, flare, superficial iris atrophy, mid-dilated pupil, pigment dispersion, low intra-ocular pressure, and cataracts. Posterior segment anomalies were absent. Seven eyes underwent cataract extraction. Most patients had a guarded visual prognosis; on three month follow-op, five out of fourteen eyes had developed phthisis. The authors theorize that anterior segment ischemia is caused by systemic hypotension in combination with vasoconstriction in the anterior uveal vascular bed caused by (cholinergic) neurotoxins. However, based on the observed pathologies, and the assumed Indian viper species, the systemic hypotension is likely induced by hemotoxins (e.g. bradykinin potentiating peptides, snake venom metalloproteinases, snake venom serine protease) present in their venom (Slagboom *et al.* 2017). Anterior segment ischemia has not been reported in any other paper.

Miscellaneous

Various other ophthalmologic diagnoses have been briefly reported after snakebite envenoming, such as anterior uveitis and serous retinal detachment (Nayak *et al.* 2007, Praveen Kumar *et al.* 2015) (Table 3). Acute glaucoma and endogenous endophthalmitis were described more comprehensively. Only one case, with minor symptoms was caused by a member of the Atractaspididae family; a 27-year-old female from South Africa reported "painful eye movements" after being bitten by a Bibron's Stiletto Snake (*Atractaspis bibronii*), which was treated conservatively (Tilbury and Branch 1989).

Acute glaucoma

Acute glaucoma, reported in fourteen cases, is the most common ocular complication after snakebite envenoming (Rojas *et al.* 2001, Srinivasan *et al.* 2005, Kulkarni *et al.* 2014, Olcaysu *et al.* 2015, Praveen Kumar *et al.* 2015, Aye *et al.* 2018). Three different mechanisms for the acute rise of intra-ocular pressure have been identified. The first is ghost cell glaucoma, which is a form of secondary glaucoma that is caused by blockage of the trabecular meshwork by degenerated erythrocytes that migrated from the vitreous. This was reported in the previously mentioned patient from Colombia with bilateral vitreous hemorrhages (see section *Vitreous hemorrhage*) (Rojas *et al.* 2001). Intra-ocular pressure was 28 mmHg OD and 40 mmHg OS, and aqueous tap confirmed ghost cells in both eyes. Pressure normalized with topical therapy. The second mechanism demonstrates a similar phenomenon; blockage of the trabecular meshwork by hyphema caused by bleeding diathesis. A 56-year-old male from Myanmar was bitten by an unspecified viper species. He was then hospitalized because of coagulopathy and renal failure, for which he received antivenom and dialysis (Aye *et al.* 2018). Periorbital edema prevented him from opening his eyes until the

sixth day. By then, visual acuity was light perception, and subconjunctival hemorrhages, hazy corneas, and hyphema were noticed. The anterior chamber was deep, suggesting no structural abnormalities. Intra-ocular pressure was normal (10 mmHg in both eyes) at the time. Ultrasonography ruled out vitreous hemorrhage. When the corneas cleared after two weeks, mid-wide fixated pupils and cataract with glaucomflecken were seen, indicative of a prior increase in intra-ocular pressure. The third mechanism is acute angle closure (Srinivasan *et al.* 2005, Kulkarni *et al.* 2014, Olcaysu *et al.* 2015, Praveen Kumar *et al.* 2015). Kulkarni *et al.* (2014) analyzed the records of 119 snakebite victims that were admitted to the intensive care unit of a hospital in southern India between May 2012 and May 2013. In total, 47 patients showed hemotoxic sequelae (e.g. prolonged clotting time) of which fifteen underwent hemodialysis for acute renal failure. Seven of these patients had capillary leak syndrome of which three (2.5% of all patients) developed bilateral acute angle closure glaucoma, with intra-ocular pressure up to 60 mmHg. In two cases, fibrinous exudates were seen in the anterior chamber. The writers theorized that capillary leak led to ciliary body edema, which in turn resulted in anterior rotation of the ciliary processes, causing angle closure. Other authors have postulated a similar etiology (Srinivasan *et al.* 2005, Olcaysu *et al.* 2015). In these cases, comparable clinical features of increased intra-ocular pressure, angle closure, and fibrinous reaction in the anterior chamber were seen (Srinivasan *et al.* 2005). With the exception of an Indian cobra bite (*Naja naja*), all cases of angle closure glaucoma were attributed to the bite of a viper, although on only two accounts the species was identified properly (Common Lancehead, *Bothrops atrox*, and Lebetine Viper, *Macrovipera lebetinus*) (Rojas *et al.* 2001, Olcaysu *et al.* 2015, Praveen Kumar *et al.* 2015).

Endogenous endophthalmitis

As with all bite wounds, the site of a bite can act as a portal of entry for bacteria. In two cases, unilateral endogenous endophthalmitis developed within three and seven days after a snakebite (Iqbal *et al.* 2009, Ganesan *et al.* 2021). Both patients were initially treated with antivenom. However, presentation at the ophthalmologist was relatively late (two days and three weeks after first ocular symptoms respectively), leading to permanent loss of vision. In one case, a 39-year-old male from India that was bitten in his index finger by an Indian cobra (*Naja naja*), corneal melting and scleral necrosis had developed and eye movement became restricted (panophthalmitis) (Ganesan *et al.* 2021). The eye was eviscerated and bacterial culture showed *Bacillus cereus*, a bacterium that is part of the normal oral flora found in Indian snakes (Shaikh *et al.* 2017). In the other case, vitreous tap culture was negative for bacteria (Iqbal *et al.* 2009). The eyeball could be preserved with systemic and intravitreal antibiotics and steroids.

Discussion

Ocular pathologies caused by systemic snakebite envenomings are relatively rare, but can lead to severe loss of vision. Ocular complications like CRAO, cerebral visual impairment, and endophthalmitis can cause long term effects, with permanent blindness being the most serious (Waiddyanatha *et al.* 2019). In this review, we discuss all ocular sequelae that have been reported in medical literature. The most prominent pathologies include ophthalmoplegia, intra- and peri-ocular hemorrhages, and acute glaucoma. This work could be used by both primary care physicians and ophthalmologists as an overview as to what to expect when dealing with snakebite envenoming, as well as by biomedical scientists, to study underlying mechanisms and potential treatments.

Based on available literature, we advise primary care physicians working with snakebite victims to take ophthalmologic complaints (e.g. pain, vision loss, or ophthalmoplegia) seriously, since the ocular effects can be severe. Patients should be seen by an ophthalmologist as soon as the setting permits. Given the acute nature of some sequelae however, doctors working in an emergency setting should acquaint themselves with basic acute ophthalmologic diseases like acute glaucoma and retrobulbar hemorrhage. Ocular pressure can easily be manually checked by palpation. Retrobulbar hemorrhage should be recognized promptly so that lateral canthotomy be performed as soon as possible. The etiology of endophthalmitis after a snakebite is still unclear. Systemic antibiotics as a prophylaxis for endogenous endophthalmitis could be considered in patients with snakebite wounds. However, there is no evidence on whether this effectively prevents such disseminated infections.

Ophthalmologic treatment was symptomatic in most cases, as plasma concentration lowers over time. There is no convincing evidence for use of antivenom for isolated ocular symptoms. In most cases, antivenom was already given at the primary hospital, mostly for non-ophthalmologic reasons, and was not a decision of the reporting ophthalmologist. It is noted that the use of systemic antivenom might lead to severe

optic neuropathy, however this side effect is not yet fully documented and understood. The administration of antivenom should not be taken lightly, since there is a 2–33% chance of anaphylaxis (Sharma *et al.* 2019). Administration should therefore be given under strict monitoring, like in an intensive care unit, and should not be done at an ophthalmology clinic. Likewise, systemic treatment of snakebites – wound treatment, antibiotics, tetanus prophylaxis, laboratory work-up, etc. – should be reserved for those with experience.

Our study is limited by the fact that the literature search only encompassed ophthalmologic complications in general. Ocular symptoms that are part of a broader array of systemic and neurologic complaints (e.g. ptosis), although not excluded per se, may not have shown in our search strategy. The main goal, however, was not to quantify these symptoms, but rather to provide a summary of different ocular sequelae caused by snakebite envenoming.

We show that a wide variety of ocular pathologies can occur after systemic snakebite envenoming. These are either directly, or indirectly, induced by toxins that specifically affect the nervous system (by interfering with neuromuscular transmission) or cardiovascular system (by inducing hemorrhage, coagulopathy, and/or hypotension). More research is needed to elucidate the exact mechanisms underlying these ocular complications. Additionally, our finding suggests that optic neuropathy is likely not caused by venom toxins, but rather as an adverse effect of the current generation of antivenoms. This further stresses the need to develop safer and better treatments, and we prompt better registration and screening of serious complications like optic neuropathy associated with antivenom. Ultimately, this review provides clinical relevance to this largely overlooked topic within the field of snakebite, and further stresses the need to combat this neglected tropical disease.

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References

Ari, A.B., 2001. Patient with purely extraocular manifestations from a pit viper snakebite (Agkistrodon halys brevicaudus). *Military medicine*, 166 (7), 667–669. Jul

Aye, M.T.H., Naing, T., and Myint, K.T., 2018. Unusual ocular manifestations following viper bite. *British medical journal case reports*, 2018, bcr2018225040.

Bawaskar, H.S., Bawaskar, P.H., and Bawaskar, P.H., 2017. Pathophysiology of dilatation of pupils due to scorpion and snake envenomation and its therapeutic value: clinical observations. *Indian journal of ophthalmology*, 65 (1), 67–70.

Bhalla, A., *et al.*, 2004. Central retinal artery occlusion: an unusual complication of snakebite. *Journal of venomous animals and toxins including tropical diseases*, 10 (3), 311–314.

Chen, Y.C., *et al.*, 1987. Characterization of the structure and function of three phospholipases A2 from the venom of Agkistrodon halys pallas. *Toxicon : official journal of the international society on toxinology*, 25 (4), 401–409.

Chu, E.R., *et al.*, 2010. Venom ophthalmia caused by venoms of spitting elapid and other snakes: Report of ten cases with review of epidemiology, clinical features, pathophysiology and management. *Toxicon : official Journal of the international society on toxinology*, 56 (3), 259–272.

Das, S., Samaddar, S., and Jana, S., 2015. Ocular manifestation and long standing visual impairment following venomous snake bite. *Journal of evolution of medical and dental sciences*, 4 (46), 7919–7923.

Davenport, R.C., and Budden, F.H., 1953. Loss of sight following snake bite. *The British journal of ophthalmology*, 37 (2), 119–121.

de Haro, L., *et al.*, 2009. Asp Viper (Vipera aspis) envenomation: experience of the Marseille poison centre from 1996 to 2008. *Toxins*, 1 (2), 100–112.

Dhabhar, J., Mehta, V., and Desai, N., 2021. Optic neuritis after a snakebite: a diagnostic dilemma. *Ochsner journal*, 21 (1), 90–92.

Dhaliwal, U., 1999. Cortical blindness: an unusual sequela of snake bite. *Indian journal of ophthalmology*, 47 (3), 191–192.

Dutta, J., *et al.*, 2011. An unusual case of bilateral retinal haemorrhage following snakebite. *Journal of ocular biology, diseases, and informatics*, 4 (4), 159–160.

Ferquel, E., *et al.*, 2007. Reappraisal of Vipera aspis venom neurotoxicity. *PLOS One*, 2 (11), e1194.

Ganesan, S., Agarwal, A.A.K., and Subramanian, K., 2021. A rare case of Panophthalmitis due to cobra bite. *European journal of ophthalmology*, 33 (1), 51–54.

Gutiérrez, J.M., *et al.*, 2017. Snakebite envenoming. *Nature reviews. Disease primers*, 3 (1), 17063.

Guttmann-Friedmann, A., 1956. Blindness after snake-bite. *The British journal of ophthalmology*, 40 (1), 57–59.

Sahai, A.S., and Sinha, R.H., 1978. Bilateral blindness following snake bite. *Indian journal of ophthalmology*, 26 (3), 16.

Guillemin, I., *et al.*, 2003. Sequences and structural organization of phospholipase A2 genes from Vipera aspis aspis, V. aspis zinnikeri and Vipera berus berus venom. Identification of the origin of a new viper population based on ammodytin I1 heterogeneity. *European journal of biochemistry*, 270 (13), 2697–2706.

Igari, R., *et al.*, 2010. Binocular diplopia and ptosis due to snakebite (Agkistrodon blomhoffi "mamushi")-a case

report. *Brain and Nerve = Shinkei Kenkyu No Shinpo*, 62 (3), 273–277.
Iqbal, M., Khan, B.S., and Ahmad, I., 2009. Endogenous endophthalmitis associated with snake bite. *Pakisthan journal of ophthalmology*, 25, 114–116.
Isbister, G.K., 2010. Snakebite doesn't cause disseminated intravascular coagulation: coagulopathy and thrombotic microangiopathy in snake envenoming. *Seminars in Thrombosis and Hemostasis*, 36 (4), 444–451.
Jalali, S., *et al.*, 2013. Visual loss with inner retinal dysfunction, after snake bite: two case reports. *Documenta ophthalmologica. Advances in ophthalmology*, 127 (2), 155–163.
Jalink, M.B., 2020. Ocular complications of spitting cobra venom. *Indian journal of ophthalmology*, 68 (11), 2632–2633.
Jalink, M.B., and Wisse, R.P.L., 2022. A Guide to direct (Peri)ocular injuries caused by snakes: systematic review and treatment advice. *The American journal of tropical medicine and hygiene*, 107 (5), 968–973. Epub ahead of print.
Jan, V., *et al.*, 2002. Toxicity evolution of Vipera aspis aspis venom: identification and molecular modeling of a novel phospholipase A(2) heterodimer neurotoxin. *Federation of European biochemical societies letters*, 527 (1–3), 263–268.
Johnston, C.I., *et al.*, 2012. Death adder envenoming causes neurotoxicity not reversed by antivenom–Australian snakebite project (ASP-16). *PLOS Neglected Tropical Diseases*, 6 (9), e1841.
Katibi, O.S., *et al.*, 2015. Blindness and scalp haematoma in a child following a snakebite. *African health sciences*, 15 (3), 1041–1044.
Kasturiratne, A., *et al.*, 2008. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. *PLOS medicine*, 5 (11), e218.
Kazandjian, T.D., *et al.*, 2021. Convergent evolution of pain-inducing defensive venom components in spitting cobras. *Science*, 371 (6527), 386–390.
Kim, H.D., Jung, M.S., and Kim, S.Y., 2009. Exotropia caused by pit viper snakebite. *Journal of AAPOS: the official publication of the American Association for pediatric ophthalmology and strabismus*, 13 (4), 424–425.
Kularatne, S.A., 2002. Common krait (Bungarus caeruleus) bite in Anuradhapura, Sri Lanka: a prospective clinical study, 1996-98. *Postgraduate medical journal*, 78 (919), 276–280.
Kularatne, S.A., *et al.*, 2009. Epidemiology, clinical profile and management issues of cobra (Naja naja) bites in Sri Lanka: first authenticated case series. *Transactions of the royal society of tropical medicine and hygiene*, 103 (9), 924–930.
Kulkarni, C., *et al.*, 2014. Acute angle closure glaucoma with capilllary leak syndrome following snake bite. *Journal of clinical and diagnostic research*, 8 (10), VC01–VC03. Oct
Kweon, E.Y., *et al.*, 2009. Vision loss following snakebite in a patient with controlled aplastic anemia. *Journal of venomous animals and toxins including tropical diseases*, 15 (1), 163–167.
Lee, S.Y., and Lee, Y.C., 2004. Intermittent exotropia as the presenting sign of pit viper snakebite to an extremity: A case report. *Journal of AAPOS: the official publication of the American Association for pediatric ophthalmology and strabismus*, 8 (2), 206–208.
Longbottom, J., *et al.*, 2018. Vulnerability to snakebite envenoming: a global mapping of hotspots. *Lancet*, 392 (10148), 673–684.
Mathur, S.P., 1959. Allergy to antivenine serum. *The British journal of ophthalmology*, 43 (1), 50–51.
Menon, V., *et al.*, 1997. Optic neuritis following snake bite. *Indian journal of ophthalmology*, 45 (4), 236–237.
Merle, H., *et al.*, 2005. Occipital infarction revealed by quadranopsia following snakebite by Bothrops lanceolatus. *The American journal of tropical medicine and hygiene*, 73 (3), 583–585.
Meyer, M.M., Bell, R., and Buchner, A., 2015. Remembering the snake in the grass: threat enhances recognition but not source memory. *Emotion*, 15 (6), 721–730.
Montgomery, J., 1959. Two cases of ophthalmoplegia due to berg adder bite. *The Central African journal of medicine*, 5 (4), 173–177.
Mustapha, S.K., Mubi, B.M., and Askira, B.H., 2010. Bilateral blindness following snakebite. *tropical Doctor*, 40 (2), 117–118.
Naik, A.S., Ranjan, R., and Manayath, G.J., 2017. Transient central retinal artery occlusion following viperine snake bite. *Canadian journal of ophthalmology. Journal canadien d'ophtalmologie*, 52 (6), e205–e208.
Nayak, S.G., *et al.*, 2007. Uveitis following anti-snake venom therapy. *Journal of venomous animals and toxins including tropical diseases*, 13 (1), 130–134.
Oh, A.M.F., *et al.*, 2017. Venomics of Bungarus caeruleus (Indian krait): Comparable venom profiles, variable immunoreactivities among specimens from Sri Lanka, India and Pakistan. *Journal of proteomics*, 164, 1–18.
Olcaysu, O.O., *et al.*, 2015. Unilateral optic neuropathy and acute angle-closure glaucoma following snake envenomation. *Case reports in ophthalmological medicine*, 2015, 687829.
Omprakash, T., *et al.*, 2016. Ocular manifestations following snakebite. *Delhi journal ophthalmology*, 26, 188–189.
Patel, R., Gopalakrishnan, M., and Haris, E.M., 2018. Central retinal artery occlusion following viperine snake bite. *Ophthalmology retina*, 2 (2), 172–173.
Praveen Kumar, K.V., *et al.*, 2015. Ocular manifestations of venomous snake bite over a one-year period in a tertiary care hospital. *Korean journal of ophthalmology*, 29 (4), 256–262.
Pyron, R.A., Burbrink, F.T., and Wiens, J.J., 2013. A phylogeny and revised classification of Squamata, including 4161 species of lizards and snakes. *bmc evolutionary biology*, 13 (1), 93.
Rao, B.M., 1977. A case of bilateral vitreous haemorrhage following snake bite. *Indian journal of ophthalmology*, 25 (2), 1–2.
Re, G., Trisolino, G., and Miglio, F., 1999. Eye muscle paralysis after Vipera aspis envenomation. *Journal of accident & emergency medicine*, 16 (6), 458–458.
Rojas, L., *et al.*, 2001. Ghost cell glaucoma related to snake poisoning. *Archives of Ophthalmology*, 119 (8), 1212–1213.
Schwersenski, J., and Beatty, D.W., 1982. Unusual features in a case of snakebite, presumably due to a Cape cobra (Naja nigricollis). *South African medical journal*, 61 (16), 597–598.
Shaikh, I.K., *et al.*, 2017. Assessment of cultivable oral bacterial flora from important venomous snakes of india and

their antibiotic susceptibilities. *Current microbiology*, 74 (11), 1278–1286.

Sharma, S.K., *et al.*, 2019. Acute severe anaphylaxis in nepali patients with neurotoxic snakebite envenoming treated with the VINS polyvalent antivenom. *Journal of tropical medicine*, 2019, 2689171–12.

Silva, A., *et al.*, 2016a. Neuromuscular effects of common krait (Bungarus caeruleus) Envenoming in Sri Lanka. *PLoS Neglected Tropical Diseases*, 10 (2), e0004368.

Silva, A., *et al.*, 2016b. Neurotoxicity in Russell's viper (Daboia russelii) envenoming in Sri Lanka: a clinical and neurophysiological study. *Clinical toxicology*, 54 (5), 411–419. Jun

Singh, J., *et al.*, 2007. Macular infarction following viperine snake bite. *Archives of Ophthalmology*, 125 (10), 1430–1431.

Sivakumar, R.R., and Rao, N.A., 2016. Anterior segment ischemia in viper bite. *Ocular Immunology and Inflammation*, 24 (1), 49–54.

Slagboom, J., *et al.*, 2017. Haemotoxic snake venoms: their functional activity, impact on snakebite victims and pharmaceutical promise. *British journal of haematology*, 177 (6), 947–959.

Sontichai, W., *et al.*, 2015. Neurological involvement and hepatocellular injury caused by a snake with hematotoxin envenomation. *Wilderness & environmental medicine*, 26 (3), 366–370.

Srinivasan, R., Kaliaperumal, S., and Dutta, T.K., 2005. Bilateral angle closure glaucoma following snake bite. *The Journal of the Association of Physicians of India*, 53, 46–48.

Subasinghe, C.J., *et al.*, 2014. Bilateral blindness following Russell's viper bite - a rare clinical presentation: a case report. *Journal of medical case reports.*, 8, 99.

Takeshita, T., *et al.*, 2003. Case report: extraocular muscle paresis caused by snakebite. *The Kobe journal of medical sciences*, 49 (1–2), 11–15.

Tang, L., Zhou, Y.C., and Lin, Z.J., 1998. Crystal structure of agkistrodotoxin, a phospholipase A2-type presynaptic neurotoxin from agkistrodon halys pallas. *Journal of molecular biology*, 282 (1), 1–11.

Thomas, N.R., *et al.*, 2017. A rare case of bilateral tractional retinal detachment following snakebite. *Indian journal of ophthalmology*, 65 (11), 1238–1240.

Tilbury, C.R., and Branch, W.R., 1989. Observations on the bite of the southern burrowing asp (Atractaspis bibronii) in Natal. *South African medical journal*, 75 (7), 327–331.

Tungpakorn, N., 2010. Unusual visual loss after snakebite. *Journal of venomous animals and toxins including tropical diseases*, 16 (3), 519–523.

Uetz P, Hošek J. The Reptile Database. Accessed February 1, 2022. http://www.reptile-database.org

van der Walt, A.J., and Muller, G.J., 2019. Berg adder (Bitis atropos) envenoming: an analysis of 14 cases. *Clinical toxicology*, 57 (2), 131–136.

van Zyl, H.M., Müller, G.J., and van der Merwe, M., 2001. Purification and properties of two phospholipase A2 enzymes from berg adder (Bitis atropos) venom. *South African Journal of Science*, 97 (9), 437–444.

Waiddyanatha, S., *et al.*, 2019. Long-term effects of snake envenoming. *Toxins*, 11 (4), 193.

Warrell, D.A., *et al.*, 1977. Poisoning by bites of the saw-scaled or carpet viper (Echis carinatus) in Nigeria. *Quarterly journal medical ethics*, 46 (181), 33–62.

Yang, Z.M., *et al.*, 2015. Transcriptome and proteome of the highly neurotoxic venom of Gloydius intermedius. *Toxicon: official journal of the international society on toxinology*, 107 (Pt B), 175–186.

Youngman, N.J., *et al.*, 2021. Widespread and differential neurotoxicity in venoms from the bitis genus of viperid snakes. *Neurotoxicity research*, 39 (3), 697–704.