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Review Article

Ocular routes of neuroinvasion in fungal infections: From orbital invasion to central nervous system dissemination

Okulare Wege der Neuroinvasion bei Pilzinfektionen: Von der orbitalen Invasion zur Dissemination in das zentrale Nervensystem

Abstract

The central nervous system (CNS) is protected by highly specialized anatomical and immunological barriers that limit microbial invasion. While hematogenous dissemination, direct extension, and trans-neuronal spread are well-established routes of neuroinvasion, the eye has received comparatively little attention as a potential gateway to the brain. Owing to its developmental origin as an extension of the neural tube, the eye shares close anatomical, vascular, and immunological connections with the CNS, forming a unique eye-brain interface. Increasing evidence suggests that several invasive fungal pathogens exploit these connections to disseminate from ocular tissues to intracranial structures. Fungal infections caused by Mucorales, Aspergillus, Cryptococcus, Candida, Fusarium, and other opportunistic fungi are associated with substantial morbidity and mortality, particularly in immunocompromised individuals. These pathogens employ diverse virulence mechanisms, including tissue invasion, angioinvasion, immune evasion, extracellular enzyme production, and barrier disruption, enabling progression beyond localized ocular disease. Neuroinvasion may occur through multiple interconnected pathways, including direct orbital extension, vascular dissemination, perineural spread along the optic nerve, cavernous sinus involvement, and compromise of the blood-retinal and blood-brain barriers. Although clinical, radiological, histopathological, and experimental studies increasingly support the concept of ocular-to-CNS dissemination, the underlying mechanisms remain fragmented across the literature. This review synthesizes current knowledge on the anatomical and immunological foundations of the eye-brain interface, fungal determinants of neuroinvasion, pathogen-specific dissemination strategies, and the evidence supporting ocular routes of CNS invasion. Improved understanding of these mechanisms may facilitate earlier diagnosis, better risk stratification, and the development of targeted strategies to prevent devastating neuroinvasive complications.

Keywords: fungal neuroinvasion, eye-brain interface, central nervous system infections, ocular dissemination, invasive mycoses

Zusammenfassung

Das zentrale Nervensystem (ZNS) wird durch hochspezialisierte anatomische und immunologische Barrieren geschützt, die das Eindringen von Mikroorganismen begrenzen. Während die hämatogene Dissemination, die direkte Ausbreitung und die transneuronale Ausbreitung als etablierte Wege der Neuroinvasion gelten, wurde dem Auge als potenziellem Zugang zum Gehirn vergleichsweise wenig Aufmerksamkeit gewidmet. Aufgrund seines entwicklungsgeschichtlichen Ursprungs als Ausstülpung des Neuralrohrs weist das Auge enge anatomische, vaskuläre und immunologische Verbindungen zum ZNS auf und bildet eine einzigartige Schnittstelle zwischen Auge und Gehirn. Zunehmende Evidenz deutet darauf hin, dass mehrere invasive Pilzpathogene diese

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Verbindungen nutzen, um sich von okulären Geweben zu intrakraniellen Strukturen auszubreiten. Pilzinfektionen durch Mucorales, Aspergillus, Cryptococcus, Candida, Fusarium und andere opportunistische Pilze sind mit erheblicher Morbidität und Mortalität verbunden, insbesondere bei immungeschwächten Personen. Diese Pathogene nutzen verschiedene Virulenzmechanismen, darunter Gewebeinvasion, Angioinvasion, die Umgehung des Immunsystems, die Produktion extrazellulärer Enzyme und die Durchbrechung von Barrieren, wodurch eine Ausbreitung über eine lokalisierte okuläre Erkrankung hinaus ermöglicht wird. Eine Neuroinvasion kann über mehrere miteinander verbundene Wege erfolgen, darunter die direkte orbitale Ausbreitung, die vaskuläre Dissemination, die perineurale Ausbreitung entlang des Sehnervs, die Beteiligung des Sinus cavernosus sowie die Beeinträchtigung der Blut-Retina- und Blut-Hirn-Schranke. Obwohl klinische, radiologische, histopathologische und experimentelle Studien zunehmend das Konzept einer Dissemination vom Auge zum ZNS unterstützen, sind die zugrunde liegenden Mechanismen in der Literatur weiterhin fragmentiert dargestellt. Diese Übersichtsarbeit fasst den aktuellen Kenntnisstand über die anatomischen und immunologischen Grundlagen der Schnittstelle zwischen Auge und Gehirn, die pilzbedingten Determinanten der Neuroinvasion, pathogenspezifische Disseminationsstrategien sowie die Evidenz für okuläre Wege der ZNS-Invasion zusammen. Ein verbessertes Verständnis dieser Mechanismen könnte eine frühere Diagnose, eine bessere Risikostratifizierung und die Entwicklung gezielter Strategien zur Verhinderung verheerender neuroinvasiver Komplikationen ermöglichen.

Schlüsselwörter: pilzbedingte Neuroinvasion, Augen-Gehirn-Schnittstelle, Infektionen des zentralen Nervensystems, okuläre Dissemination, invasive Mykosen

Introduction

The central nervous system (CNS) is protected by a series of highly specialized anatomical and immunological barriers that restrict the entry of infectious agents [1]. Consequently, microbial neuroinvasion has traditionally been studied through well-recognized routes such as hematogenous dissemination, direct extension from adjacent structures, and trans-neuronal spread [2], [3]. In comparison, the eye has received relatively limited attention as a potential gateway to the brain despite its unique developmental and structural relationship with the CNS [4], [5]. As an embryological outgrowth of the neural tube, the retina represents a specialized extension of neural tissue, while the optic nerve provides direct anatomical continuity with intracranial structures [6]. Together with the blood-retinal barrier and highly regulated immune environment, these characteristics establish a complex eye-brain interface that may be exploited by invading pathogens [7], [8].

Fungal infections represent an increasingly important cause of morbidity and mortality worldwide, particularly among individuals with diabetes mellitus, hematological malignancies, organ transplantation, prolonged corticosteroid exposure, and other forms of immunosuppression [9], [10], [11]. Although many fungal pathogens initially establish infection in localized tissues, several species possess the capacity for invasive dissemination, neurovascular disruption and CNS involvement [12], [13]. Neuroinvasive fungal disease remains associated with poor clinical outcomes due to delayed diagnosis, limited therapeutic penetration into neural tissues, and extensive tissue destruction resulting from fungal invasion and host inflammatory responses [14], [15].

Like gut invasion, ocular involvement is increasingly recognized as a clinically significant feature of several invasive mycoses, including mucormycosis, aspergillosis, cryptococcosis, and candidiasis [16]. Manifestations ranging from keratitis and endophthalmitis to orbital cellulitis and optic nerve involvement may occur during disease progression. In particular, rhino-orbital-cerebral mucormycosis has highlighted the ability of fungal pathogens to traverse anatomical boundaries separating the eye, orbit, and brain [17], [18]. Accumulating clinical, radiological, and experimental evidence suggests that fungal dissemination may occur through multiple interconnected pathways, including direct orbital extension, angioinvasion, perineural spread, and disruption of ocular and cerebral barrier systems [19], [20].

Despite growing recognition of these mechanisms, the ocular route of fungal neuroinvasion remains insufficiently synthesized within the literature. Most studies focus either on ocular disease or CNS infection as separate entities, resulting in a fragmented understanding of the pathways linking them. This review examines the anatomical and immunological foundations of the eye-brain interface, the

fungal virulence determinants that facilitate dissemination, and the major mechanisms through which fungal pathogens spread from ocular tissues to the CNS. By integrating evidence across diverse fungal species, this review aims to provide a comprehensive framework for understanding ocular-to-CNS dissemination and its implications for diagnosis, pathogenesis, and future therapeutic strategies.

Method

A narrative literature review was conducted to evaluate current evidence regarding the role of the eye as a potential gateway for CNS invasion by fungal pathogens. Relevant literature was identified through searches of PubMed and Google Scholar up to June 2026. Search terms included combinations of "ocular mycosis," "fungal neuroinvasion," "rhino-orbital-cerebral mucormycosis," "eye-brain axis," "eye-brain interface," "perineural spread," "angioinvasion," "blood-retinal barrier," "ocular immune privilege," "Mucorales," "Aspergillus," "Cryptococcus," "Candida," and "fungal dissemination". Original research articles, experimental animal studies, pathological investigations, clinical reports, and review articles addressing ocular fungal infection, neuroinvasion mechanisms, blood-retinal barrier dysfunction, optic nerve and cavernous sinus involvement, immune privilege, and CNS manifestations of invasive mycoses were considered. Articles focused exclusively on non-fungal infections or unrelated ocular diseases were excluded. Additional studies were identified through manual screening of reference lists from relevant publications. The retrieved literature was synthesized thematically into five major domains:

1. Anatomical and immunological characteristics of the eye-brain interface,
2. fungal determinants enabling colonization and neuroinvasion,
3. mechanisms of ocular-to-CNS dissemination,
4. evidence from major fungal pathogens with ocular and neurological involvement, and
5. current limitations and future research directions.

Results

The eye-brain interface: Anatomical and immunological foundations

The eye occupies a unique position among peripheral organs because of its close developmental and functional relationship with the CNS. During embryogenesis, the retina arises from the neural tube and is therefore considered a specialized extension of the brain rather than a conventional sensory tissue [21]. Retinal neurons, glial cells, and vascular structures share many similarities with their counterparts in the CNS, highlighting the intimate connection between ocular and neural compartments [22]. This developmental continuity provides the foundation for understanding how pathological processes occurring within the eye may influence intracranial structures.

A key feature of the eye-brain interface is the presence of highly specialized barrier systems that regulate the movement of cells, molecules, and pathogens [23]. The blood-retinal barrier closely resembles the blood-brain barrier in both structure and function, consisting of tightly regulated endothelial and epithelial cell layers that maintain tissue homeostasis [23]. Under physiological conditions, these barriers restrict microbial entry and limit excessive inflammation. However, infection-induced inflammation, vascular injury, or direct fungal invasion can compromise barrier integrity, creating opportunities for pathogen dissemination beyond the ocular environment.

The optic nerve represents another important anatomical link between the eye and the CNS [24]. Formed by the axons of retinal ganglion cells, the optic nerve extends directly from the retina to intracranial visual pathways and is surrounded by meningeal coverings that are continuous with those of the brain [24]. This close anatomical relationship has long raised the possibility that infectious agents may spread along neural structures, particularly when local inflammation or tissue destruction disrupts normal protective mechanisms.

Beyond neural connections, the orbit contains several vascular and anatomical pathways that may facilitate communication between ocular and intracranial compartments [25]. The orbital apex, superior orbital fissure, and cavernous sinus form critical junctions through which blood vessels, cranial nerves, and connective tissues pass [26]. These structures are of particular importance in invasive fungal infections because they can serve as routes for direct extension from orbital tissues into the cranial cavity. The propensity of many pathogenic fungi to invade blood vessels further increases the risk of intracranial dissemination through these interconnected vascular networks.

The eye also possesses a specialized immune environment known as immune privilege, which helps preserve vision by limiting excessive inflammatory responses [27]. While this adaptation protects delicate ocular tissues from immune-mediated damage, it may also create conditions that allow pathogens to persist or evade complete immune clearance. Combined with anatomical continuity, barrier systems, and vascular connections, this unique immunological landscape contributes to the eye's potential role as a gateway for fungal spread to the CNS.

Taken together, the developmental origin of the retina, the continuity of the optic nerve, the similarity between ocular and cerebral barrier systems, and the presence of shared vascular and immune networks establish a biologically plausible framework for ocular-to-CNS dissemination [6]. Understanding these connections is essential for interpreting the mechanisms by which fungal pathogens exploit the eye-brain interface during neuroinvasive disease.

Fungal determinants enabling ocular colonization and neuroinvasion

Successful neuroinvasion begins long before fungal pathogens reach the central nervous system. To disseminate from ocular tissues toward intracranial structures, fungi must first establish infection, survive within hostile host environments, and overcome multiple anatomical and immunological barriers [28]. Although the specific mechanisms vary among fungal species, several shared virulence strategies enable colonization, tissue invasion, vascular spread, and persistence within the eye-brain interface.

A critical early step is the ability of fungi to adhere to host tissues and extracellular matrix components [29]. Surface adhesins facilitate attachment to epithelial cells, endothelial cells, and basement membrane proteins such as laminin and fibronectin [30]. Stable attachment allows fungal organisms to resist mechanical clearance and establish a local niche within ocular tissues [30]. Once anchored, many pathogenic fungi transition to invasive growth forms that promote tissue penetration and deeper dissemination [31]. In filamentous fungi such as *Aspergillus* and members of the Mucorales, hyphal extension enables direct invasion of surrounding tissues, allowing organisms to traverse anatomical barriers that normally restrict pathogen movement [32].

Among the most important determinants of fungal neuroinvasion is angioinvasion, the capacity to invade and damage blood vessels. This feature is particularly prominent in mucormycosis and invasive aspergillosis, where fungal hyphae penetrate vascular walls, causing endothelial injury, thrombosis, ischemia, and tissue necrosis [33]. Vascular invasion not only facilitates hematogenous dissemination but also disrupts local barrier integrity, creating additional opportunities for spread into adjacent orbital and intracranial structures. The extensive tissue destruction observed in severe fungal infections is often a direct consequence of this angioinvasive behavior.

Fungal pathogens also produce a diverse range of enzymes and metabolites that support invasion and survival within host tissues [34]. Proteases, phospholipases, and other hydrolytic enzymes contribute to degradation of extracellular matrix components and cellular barriers, thereby enhancing tissue penetration [35]. At the same time, specialized metabolic adaptations allow fungi to survive under conditions of nutrient limitation, oxidative stress, and hypoxia that are commonly encountered during infection [36]. Efficient acquisition of essential nutrients, particularly iron, is recognized as a major determinant of fungal virulence and may be especially important within inflamed ocular and neural environments.

Another key contributor to disease progression is the ability of fungi to evade or manipulate host immune responses [37]. Ocular tissues possess mechanisms of immune privilege that limit excessive inflammation to preserve vision, but these same mechanisms may inadvertently favor pathogen persistence. Several fungal species can resist phagocytic killing, alter host immune signaling pathways, or exploit specialized immunosuppressive microenvironments; paradigms increasingly recognized across immune-resistant CNS pathologies, to survive within host tissues [37], [38]. Such strategies not only prolong infection but may also facilitate dissemination to distant sites, including the CNS. In *Cryptococcus* species, survival within macrophages has been proposed to contribute to systemic spread and subsequent neuroinvasion through a so-called “Trojan horse” mechanism [3].

Recent studies have also highlighted the potential role of fungal extracellular vesicles in host-pathogen interactions. These membrane-bound structures transport proteins, lipids, nucleic acids, and other bioactive molecules that can influence immune responses, barrier function, and cellular communication [39], [40]. Although their precise role in ocular-to-CNS dissemination remains incompletely understood, extracellular vesicles are increasingly recognized as important mediators of fungal pathogenicity and may represent an emerging mechanism contributing to neuroinvasive disease.

Collectively, these virulence determinants enable fungal pathogens to establish infection, breach protective barriers, exploit vascular and neural pathways, and persist within host tissues. The interaction between fungal virulence traits and the unique anatomical features of the eye-brain interface ultimately determines the likelihood of progression from localized ocular infection to CNS involvement.

Mechanisms of ocular-to-CNS dissemination

The progression of fungal infection from the eye to the central nervous system is a complex process that rarely occurs through a single route. Instead, fungal pathogens often exploit multiple anatomical and biological pathways simultaneously, allowing them to overcome local defenses and gain access to intracranial structures. The unique relationship between the eye, orbit, vasculature, and nervous system creates several opportunities for dissemination, particularly in the setting of invasive disease.

One of the most direct mechanisms of spread is extension through contiguous tissues. Following ocular or orbital infection, fungal organisms may invade surrounding soft tissues and progressively advance toward deeper anatomical compartments [41]. This process is particularly evident in rhino-orbital-cerebral mucormycosis, where infection originating in the paranasal sinuses can rapidly involve the orbit and subsequently extend into the cranial cavity [42]. The orbital apex serves as a critical anatomical junction because it contains the optic nerve, ophthalmic vessels, and multiple cranial nerves that connect the orbit to intracranial structures. Destruction of tissue barriers by invasive hyphae allows fungal pathogens to move across these interconnected compartments with relatively little resistance.

Angioinvasion represents another major pathway of neuroinvasion. Many pathogenic fungi possess a remarkable ability to adhere to, penetrate, and damage vascular endothelial cells [29], [43]. Following invasion of blood vessel walls, fungal growth can induce thrombosis, vascular occlusion, and tissue infarction, creating areas of necrosis that facilitate further spread [44]. In addition to causing local tissue destruction, vascular invasion provides direct access to the bloodstream, allowing dissemination to distant organs including the brain [20]. Furthermore, endothelial injury can compromise the integrity of both the blood-retinal and blood-brain barriers, enabling fungal elements or inflammatory mediators to enter previously protected neural environments.

Perineural spread has emerged as an additional mechanism that may contribute to ocular-to-CNS dissemination [19]. The optic nerve is of particular interest because it represents a direct anatomical connection between the retina and the brain. Fungal invasion of the optic nerve sheath or adjacent neural tissues may permit extension toward intracranial visual pathways [45]. Although perineural dissemination is less extensively characterized than vascular invasion, clinical reports and pathological studies have documented optic nerve involvement in several invasive fungal infections, supporting its potential role in neuroinvasive disease [46].

Barrier disruption also plays a crucial role in facilitating fungal entry into the CNS. Under normal conditions, the blood-retinal and blood-brain barriers restrict the passage of pathogens and inflammatory cells. However, fungal infection can trigger endothelial injury, cytokine release, oxidative stress, and local inflammation, all of which contribute to barrier dysfunction [47]. Increased permeability allows fungal organisms, immune cells, and circulating inflammatory mediators to access neural tissues more readily. In some cases, barrier breakdown may be driven not only by direct fungal invasion but also by the host inflammatory response itself.

The cavernous sinus represents another important anatomical hub in fungal neuroinvasion. Located adjacent to the orbit, it receives venous drainage from ocular structures and contains several cranial nerves as well as the internal carotid artery [48]. Spread into the cavernous sinus can therefore provide a pathway for further intracranial dissemination while simultaneously producing severe neurological complications. Cavernous sinus involvement is frequently observed in advanced rhino-orbital fungal infections and often signals progression toward extensive CNS disease [49].

Beyond these anatomical pathways, neuroinflammation may act as a powerful amplifier of dissemination. Activation of resident immune cells, recruitment of peripheral leukocytes, and production of pro-inflammatory mediators can contribute to tissue injury and barrier disruption [50]. While these responses are intended to control infection, excessive or dysregulated inflammation may paradoxically facilitate fungal spread by weakening protective barriers and altering the local microenvironment. Emerging evidence suggests that interactions between fungal pathogens and host neuroimmune responses play a critical role in determining the extent of CNS involvement.

Taken together, direct tissue extension, vascular invasion, perineural spread, barrier disruption, cavernous sinus involvement, and neuroinflammatory amplification represent interconnected mechanisms through which fungal pathogens can exploit the eye-brain interface. The relative contribution of each pathway varies among fungal species and clinical settings, but collectively they provide a framework for understanding how localized ocular infection can progress to life-threatening CNS disease (Figure 1).

Pathogen-specific routes of neuroinvasion

Although the general mechanisms of ocular-to-CNS dissemination are shared among many fungal pathogens, individual species exhibit distinct preferences for specific neuroinvasive strategies [51], [52], [53], [54], [55]. These differences are largely determined by their virulence traits, tissue tropism, and interactions with host immune defenses. Understanding these pathogen-specific patterns is important for recognizing high-risk clinical presentations and predicting routes of disease progression (Table 1).

Despite differences in their preferred routes of dissemination, most neuroinvasive fungi ultimately exploit a combination of tissue invasion, vascular access, and barrier disruption to reach the CNS. Among these pathogens, Mucorales and Aspergillus spp. are particularly notable for their angioinvasive behavior, whereas Cryptococcus demonstrates a greater reliance on hematogenous dissemination and cellular transport mechanisms. These pathogen-specific variations highlight the diverse strategies through which fungi can exploit the eye-brain interface while ultimately converging on a common outcome: CNS invasion (Figure 2).

Evidence supporting ocular-to-CNS dissemination

Direct evidence supporting ocular-to-CNS dissemination in fungal infections remains relatively limited, largely because the process is difficult to observe in real time and often occurs in critically ill patients. Nevertheless, a growing body of histopathological, radiological, experimental, and clinical evidence supports the concept that the eye can serve as an important interface for fungal spread into intracranial structures. Collectively, these studies suggest that neuroinvasion is rarely the result of a single pathway but rather reflects the interaction of anatomical continuity, fungal virulence, and host responses.

Histopathological studies provide some of the strongest evidence for ocular-to-CNS dissemination. Examination of surgical specimens and autopsy tissues has demonstrated fungal hyphae within orbital tissues, blood vessels, optic nerves, and adjacent intracranial structures [56].

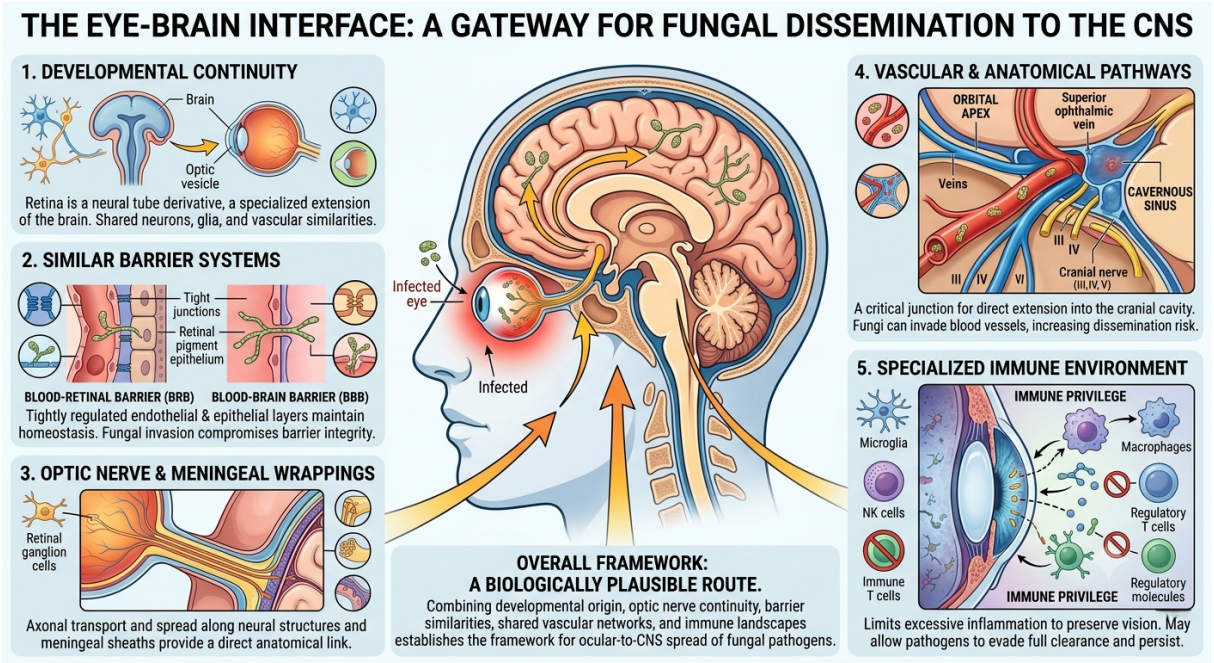


Figure 1: The eye-brain interface: The gateway for various fungal infections to disseminate to the CNS via various mechanisms

Table 1: Major fungal pathogens and their predominant ocular-to-CNS dissemination strategies

Pathogen	Common ocular manifestations	Predominant neuro-invasive route	Key virulence feature	Major CNS consequences
Mucorales	Orbital cellulitis, orbital apex syndrome, ophthalmoplegia, vision loss	Direct orbital extension, angioinvasion	Extensive vascular invasion and tissue necrosis	Rhino-orbital-cerebral mucormycosis, cerebral infarction, abscesses
Aspergillus spp.	Endophthalmitis, orbital infection, optic nerve involvement	Angioinvasion, hematogenous dissemination	Hyphal vascular invasion	Cerebral aspergillosis, hemorrhage, infarction
Cryptococcus spp.	Chorioretinitis, papilledema, optic neuropathy	Hematogenous spread, macrophage-mediated dissemination	Intracellular survival and neurotropism	Meningitis, crypto-coccomas, elevated intracranial pressure
Candida spp.	Endogenous endophthalmitis, chorioretinitis	Hematogenous dissemination	Biofilm formation and bloodstream persistence	Meningitis, cerebral microabscesses
Fusarium spp.	Keratitis, endophthalmitis	Local tissue invasion and vascular spread	Aggressive tissue penetration	Rare cerebral dissemination
Scedosporium spp.	Keratitis, orbital infection	Hematogenous and direct extension	Resistance to host defenses and antifungals	Brain abscesses, meningoencephalitis
Dematiaceous fungi	Keratitis, orbital involvement	Direct extension and hematogenous spread	Melanin-mediated immune evasion	Cerebral phaeohyphomycosis

In particular, studies of rhino-orbital-cerebral mucormycosis have repeatedly shown continuous fungal invasion extending from the orbit toward the orbital apex, cavernous sinus, and brain [57], [58]. Similar observations have been reported in invasive aspergillosis, where vascular invasion and tissue necrosis frequently accompany intracranial spread [59], [60]. These findings support the biological plausibility of both direct extension and angioinvasive dissemination.

Neuroimaging has substantially improved the understanding of fungal neuroinvasion. Modern magnetic resonance imaging (MRI) techniques can identify optic nerve involvement, orbital apex infiltration, cavernous sinus extension, vascular thrombosis, and early intracranial lesions before extensive neurological deterioration occurs. Recent advances in high-resolution orbital MRI and vessel-wall imaging have further enhanced the detection of subtle neurovascular involvement [61]. Imaging studies increasingly demonstrate that ocular, orbital, and cerebral abnormalities often coexist along anatomically connected pathways, providing indirect but compelling evidence for progressive dissemination.

Experimental models have also contributed important mechanistic insights. Animal studies have shown that invasive fungi can disrupt vascular barriers, invade neural tissues, and trigger inflammatory responses that

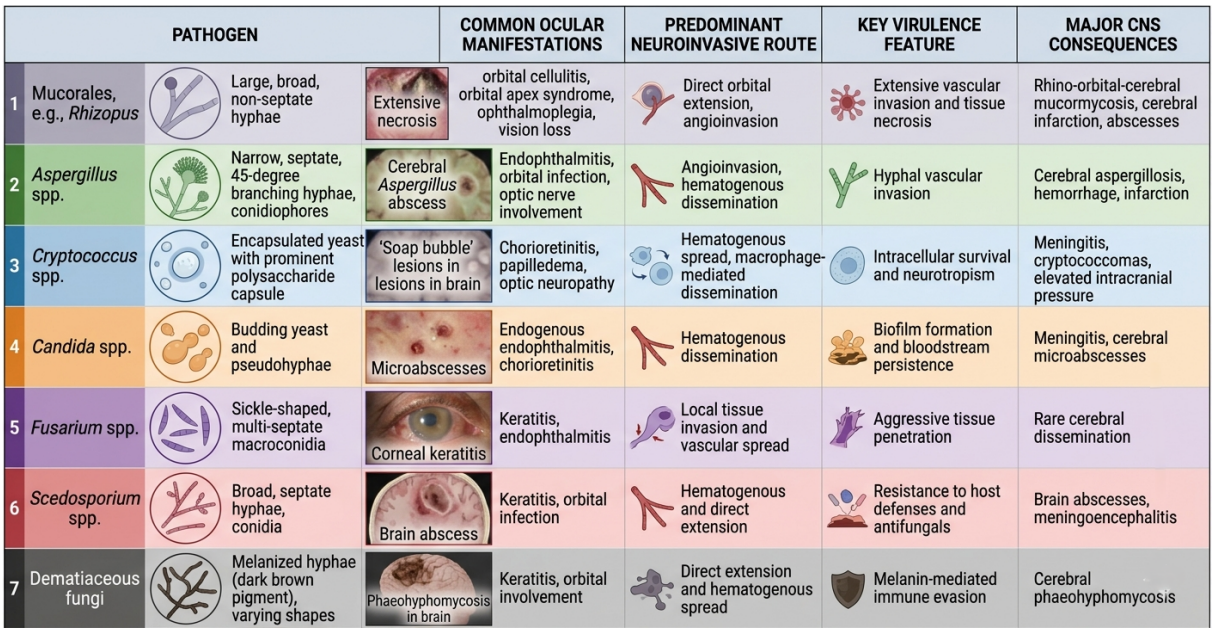


Figure 2: Various fungal pathogens, their common ocular manifestations, invasive routes, key features and the CNS consequences

facilitate dissemination [25], [29]. More recently, advances in organoid systems, microfluidic barrier models, and three-dimensional tissue cultures have enabled investigators to examine fungal interactions with retinal and neural tissues under controlled conditions [62]. Although these models cannot fully replicate human disease, they offer valuable opportunities to study barrier penetration, host-pathogen interactions, and mechanisms of neuroinvasion at cellular resolution.

Knowledge gaps and future directions

Despite growing recognition of the eye as a potential route of fungal neuroinvasion, several important questions remain unanswered. One of the major challenges is determining the relative contribution of different dissemination pathways during human infection. While direct orbital extension, angioinvasion, perineural spread, and barrier disruption have all been implicated, it remains unclear whether specific fungal pathogens preferentially utilize particular routes or whether these mechanisms operate simultaneously during disease progression. Addressing this question will require integrated clinical, imaging, and pathological studies capable of capturing the temporal evolution of infection.

Another important gap concerns the molecular interactions occurring at the eye-brain interface. The mechanisms through which fungal pathogens alter blood-retinal and blood-brain barrier integrity remain incompletely understood, as do the host signaling pathways that facilitate or restrict dissemination. Emerging evidence suggests that neurovascular cells, glial populations, and infiltrating immune cells actively shape the local microenvironment during infection, but their precise contributions to fungal neuroinvasion require further investigation. Improved understanding of these interactions may identify novel therapeutic targets capable of limiting CNS spread before irreversible neurological damage occurs.

Recent advances in single-cell sequencing, spatial transcriptomics, and high-resolution imaging provide promising opportunities to address these challenges [63]. These technologies can reveal cellular responses within infected ocular and neural tissues with unprecedented detail, enabling the identification of vulnerable anatomical niches and previously unrecognized host-pathogen interactions. Similarly, organoid systems and advanced barrier models may help bridge the gap between experimental observations and human disease by allowing direct investigation of fungal interactions with retinal and neural tissues under physiologically relevant conditions.

From a clinical perspective, earlier recognition of ocular involvement may offer an opportunity to identify patients at increased risk of CNS dissemination. Future studies should evaluate whether specific ocular findings, imaging features, or molecular biomarkers can serve as predictors of neuroinvasive disease. The integration of artificial intelligence-assisted imaging analysis and multi-omics approaches may further improve risk stratification and diagnostic accuracy [63]. Ultimately, a more comprehensive understanding of the eye-brain interface in fungal infections may not only clarify mechanisms of neuroinvasion but also support the development of strategies aimed at preventing progression from localized ocular disease to life-threatening CNS involvement.

Discussion

The present review highlights the eye as a biologically plausible but underrecognized interface for fungal neuroinvasion. Traditionally, central nervous system (CNS) invasion by fungal pathogens has been viewed primarily through the lens of hematogenous seeding or direct skull

base erosion. However, the unique developmental and anatomical relationship between the eye and the brain suggests that ocular and orbital tissues may play a more active role in neuroinvasive processes than is commonly appreciated. The retina and optic nerve represent direct embryological extensions of the CNS, while the blood-retinal barrier and ocular microenvironment share fundamental functional similarities with the neurovascular protective systems of the brain. Collectively, these features establish conditions under which opportunistic fungi can colonize local niches, evade host clearance, and traverse contiguous neural and vascular corridors.

Among the fungal pathogens reviewed, members of the Mucorales and Aspergillus species provide the most definitive evidence supporting ocular-to-CNS dissemination. Their hallmark angioinvasive behavior, rapid hyphal growth, and capacity to induce extensive tissue necrosis offer a clear mechanistic framework linking rhino-orbital disease with cavernous sinus thrombosis and intracranial infarction. In contrast, evidence for yeasts such as Cryptococcus and Candida species predominantly reflects hematogenous dissemination and cellular transport, such as macrophage-mediated persistence, rather than primary orbital extension. Meanwhile, filamentous molds such as Fusarium, Scedosporium, and dematiaceous fungi demonstrate aggressive local tissue penetration and keratitis, yet progress to cerebral phaeohyphomycosis or intracranial abscesses less frequently. These distinct patterns emphasize that the propensity for ocular neuroinvasion varies substantially across fungal taxa according to their intrinsic virulence determinants.

A recurring theme across the literature is the dual role of the specialized ocular immunological microenvironment. While ocular immune privilege is essential for preserving delicate visual architecture by dampening excessive inflammation, it can inadvertently establish a protective niche that shields invasive pathogens from robust immunological clearance. Local fungal persistence prolongs host-pathogen interactions, triggering secondary barrier disruption, chronic endothelial injury, and subsequent intracranial progression. Paradoxically, dysregulated host neuroinflammation may further accelerate dissemination by weakening tight junctions and breaking down blood-retinal barrier integrity.

Despite growing appreciation of the eye-brain interface, direct real-time visualization of fungal transit remains challenging, as human clinical evidence is frequently constrained to advanced disease stages or post-mortem specimens. Delineating the precise relative contributions of angioinvasion, contiguous soft-tissue extension, and perineural spread along the optic nerve sheath requires deeper investigation. Future translational research integrating high-resolution magnetic resonance vessel-wall imaging, microfluidic barrier models, and spatial transcriptomics will be crucial to clarify the exact molecular dynamics of barrier transit and optimize early clinical interventions before irreversible neurological damage occurs.

Conclusion

The eye represents a unique anatomical and immunological interface between the external environment and the central nervous system. Its developmental continuity with the brain, specialized barrier systems, vascular connections, and neural pathways create multiple opportunities for fungal pathogens to access intracranial structures. Although traditionally regarded as a secondary site of involvement, accumulating evidence suggests that ocular tissues may play a more active role in the pathogenesis of fungal neuroinvasion than previously appreciated. Fungal pathogens employ diverse yet overlapping strategies to exploit the eye-brain interface, including direct tissue extension, angioinvasion, perineural dissemination, and disruption of protective barrier systems. While the dominant route varies among fungal species, these mechanisms ultimately converge to facilitate CNS invasion and contribute to the severe neurological complications associated with invasive mycoses. Advances in imaging, molecular profiling, and experimental modeling are beginning to uncover the complex interactions between fungal virulence factors and host neuroimmune responses that govern disease progression. Recognizing the eye as a potential gateway to the CNS provides a valuable framework for understanding fungal dissemination and highlights the importance of early ocular assessment in patients with invasive fungal disease. Continued investigation of the cellular and molecular events occurring at the eye-brain interface may improve early diagnosis, refine risk prediction, and identify new therapeutic opportunities aimed at preventing neuroinvasive complications.

Notes

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The authors declare that they have no competing interests.

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