ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

CASE SERIES

Evaluation of galactomannan and 1,3-β-d-glucan assays as diagnostic tools for intracranial fungal infection: A case series

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Abstract

Fungal infections of the central nervous system have dramatically surged over the past decade, particularly in semitropical regions such as Karachi. Herein, we retrospectively evaluated the diagnostic potential of galactomannan (GM) and 1,3-β-d-glucan (BDG) assays for intracranial fungal infections (IFI) at a tertiary care facility in Karachi. A total of 12 patients (3 immunocompromised and 9 immunocompetent) aged 18 – 60 years underwent serum fungal biomarker testing, imaging studies, and cerebrospinal fluid (CSF) analysis. Suboptimal GM and high BDG titers indicated invasive mycoses. Computed tomography scan revealed fungal sinusitis, and magnetic resonance imaging revealed brain parenchyma involvement. Fungal biomarkers helped rule out a neoplastic etiology. Normal GM and high BDG titers negated the probability of aspergillosis. Further, culture tests helped identify the causative organisms and tailor the treatment. Our findings emphasize the diagnostic value of GM and BDG assays in IFIs. Furthermore, we recommend the use of CSF specimens for fungal biomarker assays in future diagnostic protocols.

Keywords: Intracranial fungal infection; Galactomannan; Fungal sinusitis; d-glucan; 1,3-β-d-glucan

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Citation: Kumar S, Rehman Z, Akhlaq A, Khan TBA, Bullo N, Afzal M. Evaluation of galactomannan and 1,3-β-d-glucan assays as diagnostic tools for intracranial fungal infection: A case series. *INNOSC Theranostics and Pharmacological Sciences*. 2025;8(2):96-101.
doi: 10.36922/itps.4528

Received: August 15, 2024

Revised: November 10, 2024

Accepted: December 11, 2024

Published online: December 3, 2025

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1. Background

The incidence of fungal infections in the central nervous system (CNS) has increased over the past decade and is primarily attributed to the growing population of immunocompromised individuals. The fungal species predominantly responsible for these infections include yeasts (e.g., *Candida* spp.), molds, and filamentous fungi (e.g., *Aspergillus* spp.).[1] *Candida albicans*, which typically spreads through the hematogenous route, is a common cause of CNS infections that often present as meningitis. In addition, it sometimes manifests as chronic meningitis. It can lead to brain abscesses, spinal infections, ventriculitis, or mycotic aneurysms and vasculitis, ultimately leading to cerebral infarctions.[2] The underlying mechanism for *Candida* meningitis is the invasion of fungi through the blood–brain barrier (BBB).[3]

Aspergillus fumigatus and *Aspergillus flavus* are strongly associated with invasive aspergillosis (IA) and fungal sinusitis, respectively.[4] *Aspergillus* infections are primarily transmitted through spores, and the lungs, head, and neck – particularly the paranasal

sinuses (PNSs), orbit, and cranial areas – are the primary disease sites.[5] Disease progression in these regions is accompanied by pain, fever, ophthalmic complications, epistaxis, and cough.[6] The symptoms progress gradually and often include proptosis, monocular blindness, congestion, classic meningitis symptoms, and hemorrhage.[7] Owing to its angioinvasive properties, *Aspergillus* can affect the branches of the internal carotid artery (ICA) in the ethmoidal or orbital regions, leading to microaneurysms and cerebral emboli.[8] Furthermore, bone destruction is observed in 30 – 50% of patients with sinus infections.[9]

The European Organization for Research and Treatment of Cancer and the Mycoses Study Group have included galactomannan (GM) and 1,3-β-d-glucan (BDG) assays as microbiological criteria for diagnosing fungal infections.[10] GM, a polysaccharide antigen primarily found in the cell walls of *Aspergillus* spp., can be detected using the Platelia *Aspergillus* enzyme immunoassay (Bio-Rad Laboratories, Inc., headquartered in Hercules, California, USA). This method utilizes serum or bronchoalveolar lavage fluid samples. However, cerebrospinal fluid (CSF) can be used to treat cerebral aspergillosis.[10-12]

BDG, a cell wall component of most fungi (excluding *Cryptococci*, *Zygomycetes*, and *Blastomyces dermatitidis*), is a panfungal serological marker. Although BDG is not specific to IA, it can be used to diagnose invasive candidiasis.[10-12] Of the four available BDG detection assays (Fungitell, Wako, Fungitec-G, and Maruha), only Fungitell (Associates of Cape Cod, Inc., 124 Bernard E. Saint Jean Drive, East Falmouth, Massachusetts 02536-4445, USA) has been FDA-approved for use with serum.[10]

Pakistan faces unique challenges because of its humid climate, which fosters fungal growth and widespread immunosuppressive therapy use. Furthermore, owing to limited data on intracranial fungal infections (IFIs) and restricted availability and affordability of neuroimaging or CSF analysis, diagnoses are delayed or missed. Consequently, the timely detection of fungal infections must be improved by assessing specific diagnostic parameters such as GM and BDG assays, which can enhance the diagnostic accuracy and facilitate prompt treatment. Given the low socioeconomic status of patients in our setup, we must focus on targeted diagnostic markers to streamline patient and healthcare provider processes.

This study contributes to the existing literature on IFIs by presenting a case series of patients with IFIs who were admitted to the Jinnah Postgraduate Medical Center, a tertiary care hospital in Karachi, Pakistan, between November 2022 and May 2023. We aimed to evaluate the potential role of serum fungal biomarkers as an adjunct to early diagnostic tools in resource-limited low- and middle-income countries such as Pakistan.

2. Case series

We retrospectively reviewed the medical records of patients with clinically suspected IFI. Only patients with fungal assay data (GM and BDG levels), neuroimaging studies (computed tomography [CT] of the PNS and magnetic resonance imaging [MRI]), and CSF analysis results were included in this study. We solely focused on the diagnostic approach for suspected cases of IFI from a single center and did not address the treatment regimens or management outcomes. The interpretation of the BDG and GM index values is provided in Table 1.

2.1. Case 1

A 48-year-old man presented with headaches, vertigo, left-sided visual loss, and hearing loss 2 months after surgical excision of a parasellar space-occupying lesion. CSF analysis revealed an elevated protein level, a decreased glucose level, and an increased white blood cell (WBC) count (lymphocytes, 95%). The serum was positive for BDG, whereas Gram and acid–fast bacteria staining yielded negative results.

Contrast-enhanced MRI of the brain revealed an intracranial extra-axial mass in the right parasellar region. The mass extended into both cavernous sinuses and involved the right supraclinoid ICA, cerebellar peduncle, and brainstem.

2.2. Case 2

A 51-year-old man with fungal sinusitis presented with swelling in the left maxillary region 8 months after a craniotomy. GM and BDG fungal biomarker assays were positive. Contrast-enhanced MRI of the brain revealed changes in the left maxillary sinus with ipsilateral intraorbital and intracranial extensions. The CT PNS confirmed the findings of chronic left maxillary sinusitis with osteomyelitis.

2.3. Case 3

A 61-year-old man with hepatitis C and uncontrolled type-2 diabetes presented with proptosis, pain, lacrimation, and

Table 1. Cutoffs for the serum fungal diagnostic assays and their interpretation

Tests	Cutoff	Interpretation
β-d-glucan	<60 pg/mL	Negative
	60–80 pg/dL	Intermediate*
	>80 pg/dL	Positive
Galactomannan	<0.5	Negative

Notes: *Repeat test-recommended; **GMI >0.5 in two consecutive samples.

rhinorrhea of the right eye, which progressed to painless visual loss. CT PNS exhibited thickening of the soft tissues along the right optic canal, further compressing the optic nerve. The serum was positive for BDG.

2.4. Case 4

A 30-year-old woman presented with a 3-month history of headaches and vomiting. A plain CT PNS revealed a complete opacification of the sphenoid sinus, right posterior ethmoid air cells, and right frontal sinus, indicating superadded fungal colonization. The serum BDG titers were elevated.

2.5. Case 5

A 40-year-old woman presented with headaches. The fungal assay was positive, revealing elevated BDG levels. CSF analysis revealed a normal glucose, an elevated protein level, and 20% polymorphs. The gram staining and cryptococcal antigen test yielded negative results.

2.6. Case 6

A 32-year-old man presented with headache, right eyelid drooping, diplopia that progressed to complete ophthalmoplegia and visual loss. A plain CT PNS revealed mucosal thickening in the right maxillary sinus and right posterior ethmoidal air cells, indicating a fungal sinus disease with intracranial extension. The fungal biomarkers were negative. CSF analysis revealed a normal glucose, an increased protein level, and 90% lymphocytes.

2.7. Case 7

A 35-year-old man presented with headaches and left eye pain. Serum fungal biomarkers were negative. Gadolinium-enhanced brain MRI revealed sinonasal fungal colonization with intraorbital and intracranial extensions.

2.8. Case 8

A 40-year-old man presented with chronic headaches. CSF analysis revealed a markedly elevated protein level, normal glucose level, and 95% lymphocytes. The fungal potassium hydroxide prep yielded a negative result, and the serum was positive for BDG.

2.9. Case 9

An 18-year-old woman presented with headache, eye pain, blurred vision, nasal blockage, and shortness of breath. The serum was positive for BDG. CT PNS revealed sinus opacification and cribriform plate erosion, indicating intracranial extension. Brain MRI confirmed the presence of pansinusitis with fungal colonization and cortical erosion.

2.10. Case 10

A 36-year-old woman presented with a headache and left maxillary swelling. The fungal assays revealed positive GM and BDG titers. Consistent with the clinical features, magnetic resonance angiography, and venography revealed abnormal signal intensity of fungal colonization, infiltrative soft tissue thickening, optic nerve encasement, and ICA attenuation.

2.11. Case 11

A 35-year-old man presented with chronic right-sided headaches. The serum was positive for BDG. CSF analysis revealed an elevated protein level, normal glucose level, and 95% lymphocytes. Brain MRI revealed fungal sinusitis with cribriform plate erosion and orbital apex extension.

2.12. Case 12

A 27-year-old man presented with a chronic history of headaches, facial numbness, burning sensation over the upper right side of the face, diplopia, and fever. CT PNS revealed sphenoid sinus opacification and cavernous sinus extension. Brain MRI revealed sinonasal polyposis with fungal colonization and skull base involvement. The serum was positive for GM and BDG. CSF analysis revealed a turbid fluid, high protein content, 90% neutrophils, and markedly low glucose level.

(The clinical profile and fungal assays of the patients are listed in Table 2).

3. Discussion

The CNS is an immunologically privileged site with a specialized comparatively impermeable BBB. However, immunocompromised states predispose individuals to opportunistic and pathogenic mycosis. CNS manifestations typically arise from hematogenous or disseminated invasion from pulmonary, intestinal, or cardiac sites. Nevertheless, direct intracranial spread can occur from the paranasal sinuses, intraorbital extension, petromastoid area, and retropharyngeal spaces. Furthermore, the colonization of ventricular drains, shunts, and central venous lines placed during trauma management, as well as the colonization during craniotomies, facilitate direct mycosis implantation.[13]

In 2017, Jabeen *et al*. reported that approximately 1.78% of individuals suffer from serious fungal infections, excluding oral candidiasis, allergic fungal sinusitis, and cutaneous infections.[14] However, the actual burden of fungal infections, particularly IFIs, remains unknown because of the lack of centralized surveillance. Compared with fungal infections, which are usually rare, IFIs are rarer. However, they are relatively common in

Table 2. Characteristics and serum fungal biomarker levels of the included patients

Case	Age (years)	Sex	Comorbidities	Headache	Serum fungal biomarker		CSF analysis		
					GM index (OD)	BDG levels (pg/mL)	Glucose (mg/dL)	Protein (mg/dL)	WBCs (×10E9/L)
1	48	M	Parasellar space-occupying lesion (postsurgical status)	Yes (acute)	0.098	408.442	24	109	0.012
2	51	M	Fungal sinusitis (postsurgical status)	No	3.016	523.438	23	189	0.315
3	61	M	Type-2 diabetes mellitus and hepatitis C	No	0.269	170.833	-	-	-
4	30	F	None	Yes (chronic)	0.533	523.438	-	-	-
5	40	F	None	Yes (acute)	0.361	159.899	62	62	0.012
6	32	M	None	Yes (acute)	0.119	10.708	61	47	0.008
7	35	M	None	Yes (acute)	0.22	7.812	-	-	-
8	40	M	None	Yes (chronic)	0.488	298.994	60	408	0.085
9	18	F	None	Yes (acute)	0.212	236.771	-	-	-
10	36	F	None	Yes (chronic)	1.324	500	-	-	-
11	35	M	None	Yes (chronic)	0.160	500	51	99	0.340
12	27	M	None	Yes (chronic)	0.781	500	11	97	0.071

Notes: Green: Indicates positive result; Red: Indicates negative result.
Abbreviations: BDG: 1,3-β-d-glucan; F: Female; GM: Galactomannan; M: Male; OD: Optic density.

immunocompromised individuals. If such infections go unnoticed or the management is delayed, they can be fatal. In our case series, all patients were healthy, except for three patients. During presentation, our patients had no history of fungal, pulmonary, or dermatological mycotic infections.

Sarwar *et al.* (2020) highlighted the diagnostic benefits and efficacy of fungal markers (GM and BDG) in the early identification of IA and concluded that BDG is sensitive while GM is specific for IA.[15] Our study focused on using the same serological markers to timely detect IFIs. Among the three immunocompromised patients, one exhibited positivity for GM and BDG and two exhibited positivity for BDG. In addition, among the immunocompetent patients, two yielded negative results for serum fungal biomarkers, five exhibited positivity for BDG, and two exhibited positivity for GM and BDG.

Although CSF fungal culture was not performed in all patients, fungal infection was evident in those who underwent the test. In most patients, normal GM levels and high BDG levels negated the risk of aspergillosis.

In patients clinically suspected to have IVI but without typical meningitis signs, the combination of CSF analysis and other investigations can help establish a provisional diagnosis of fungal infection even when fungal assays are negative; this indicates that with further studies on this approach, a single CSF specimen could be sufficient for fungal biomarker analyses, general analysis, and culture tests. The combination of serological and CSF fungal biomarker assays and the clinical interpretation of CSF analysis and culture tests may be a promising noninvasive diagnostic approach for patients, especially those with an atypical presentation or any contraindication to radiological imaging.

Although biopsy is the gold standard for making a final diagnosis, imaging modalities such as CT and MRI are invaluable for diagnosing IFIs. CT PNS is the preferred noninvasive investigation for making a presumptive diagnosis. At this stage, fungal biomarkers may help differentiate neoplastic lesions from infectious lesions. On CT, fungal sinusitis with intracranial extension appears as near-complete opacification of the infected sinus, expansion of the involved sinus, and remodeling and thinning or erosion of the sinus wall.[16] MRI is more specific for CNS parenchymal mycoses, exhibiting hypo-to-iso-intense signals on T1-weighted images, extremely hypo-intense signals on T2-weighted images, and bright homogenous enhancement on postgadolinium images.[17,18]

Radiographic imaging remains the preferred diagnostic tool for IFIs. However, serological fungal markers (GM and BDG) and CSF analysis are crucial adjuncts for prompt diagnosis and early onset of treatment, providing morbidity- and mortality-related benefits.

This study has certain limitations. Our institution is a government tertiary care hospital with limited research facilities, which limit long-term patient follow-up. Thus,

only the importance of fungal markers in early diagnosis could be assessed and not treatment efficacy.

4. Conclusion

Given the limited data on fungal infections in Pakistan and the lack of IFI-centered studies, the epidemiology is largely unknown. Consequently, the diagnostic approach is suboptimal. Although imaging studies and biopsy are the gold standards for IFI diagnosis, the gap in noninvasive modalities must be assessed. Our findings highlight the importance of serological fungal biomarkers (GM and BDG) and CSF analysis as adjuncts to the gold standard diagnostic tools. Furthermore, we propose the inclusion of fungal biomarker assays using CSF specimens in future diagnostic protocols.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Suneel Kumar, Zuhaa Rehman
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Ethics approval and consent to participate

This study was approved by the Institutional Review Board Committee of JPMC under the IRB number NO.F.2-81/2023-GENL/92/JPMC.

Consent for publication

The retrospective case series was conducted using deidentified data from the department registry. Hence, consent for publication was not required.

Availability of data

The data can be shared on request.

Further disclosure

Part of or the entire set of findings has been presented in a conference – 9th Annual Neuroscience Conference. The paper has been uploaded to ResearchGate (doi: 10.13140/RG.2.2.33961.61287).

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