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ORIGINAL ARTICLE

Serologic biomarkers in *Candida* and *Aspergillus* infections of the central nervous system: A comparison of galactomannan, mannan and β-1,3-D-gucan testing from serum and cerebrospinal fluid

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Abstract

Background: The incidence of *Aspergillus* and *Candida* CNS infection, which are characterised by high mortality rates, is underestimated. This underdiagnosis presumably results from the limitations of available diagnostic tools and the need for invasive sampling. Little is known about the role of serologic biomarkers in the setting of CNS aspergillosis and candidiasis.

Patients, materials and methods: Serum and cerebrospinal fluid (CSF; 10) samples of 19 patients, whose CNS specimens yielded growth of *Aspergillus* or *Candida*, were analysed for different biomarkers for fungal infection, that is galactomannan (GM), galactomannoprotein (GP), mannan, anti-mannan-antibodies and β-1,3-D-glucan (BDG). Serum and CSF specimens of time-matched patients (two each for every case of fungal CNS infection) were included as controls.

Results: Galactomannan, GP and BDG seropositivity was found in one, two and three of five cases of CNS aspergillosis. BDG and mannan/anti-mannan-antibody sensitivity in proven CNS candidiasis was 40% and 20%, respectively. Applying the serum cut-off, sensitivity in CSF testing was 100% for GM and BDG and 50% for mannans. While serum specificity for all assays ranged from 89 to 97%, specificity for CSF BDG was only 70%. No false-positive GM results from CSF were obtained.

Conclusion: Sensitivity for diagnosing CNS aspergillosis and CNS candidiasis from serum is mediocre for all serological biomarkers. GM testing in CSF proved excellent performance. With a sensitivity of 100% but a specificity of only 70%, CSF BDG might be most useful when used in patients with a high pre-test probability.

KEYWORDS
CNS, CSF, invasive aspergillosis, invasive candidiasis, invasive fungal infection, meningitis

Johannes Wagener and Karl Dichtl contributed equally to the manuscript.

1 | INTRODUCTION

Severe fungal infections continue to increase causing an estimated total of 1.5 million deaths per year.[1,2] Hundreds of thousands of fatal outcomes per year are attributable to the basidiomycete yeast *Cryptococcus*, which is the most common cause of fungal meningoencephalitis.[1,2] However, other fungal pathogens, including *Aspergillus* and *Candida* species, can also cause central nervous system (CNS) infections, which are associated with devastating outcomes.[3]

Invasive candidiasis (IC) can manifest with a wide spectrum of clinical presentations ranging from candidemia to infections of virtually all organ systems including the CNS.[3–5] Mortality rates, which are reported to range from 10% to 70% in IC, increase to 90% upon CNS involvement.[5] The two major risk factors for CNS candidiasis are intracranial procedures, for example neurosurgery or implantation of ventricular drains and candidemia.[3,5] The rate of haematogenous dissemination into the brain during candidemia is estimated to be as high as 6% in adults and >60% in neonates.[5] Following *Cryptococcus* spp. and *Coccidioides immitis*, *Candida* is the third most common causative agent of fungal meningoencephalitis accounting for 8% of cases.[3] However, the disease often remains undetected, and autopsy studies suggest that CNS candidiasis is an underdiagnosed disease.[3,5] This might be attributable to diagnostic challenges: CT imaging is typically negative, and MRI findings are mostly non-specific.[5] Since there is still a lack of solid data on the use of molecular methods for the detection of CNS candidiasis, cultural detection from CNS samples remains the gold standard to date.[3,5]

Invasive aspergillosis (IA) is the most common mould infection, which is a particular threat for immunocompromised patients.[1,2] Typically, the disease manifests in the lungs, which are the primary entry point for the ubiquitous, airborne *Aspergillus* spores.[1,2] Contrarily, CNS aspergillosis is either caused by secondary haematogenous dissemination or by contiguous growth originating from the paranasal sinuses.[6–9] Notably, some authors report CNS involvement in up to 20% of IA cases.[5] In contrast to pulmonary IA, diagnosis of CNS aspergillosis is particularly challenging: clinical presentation is non-specific and can vary between brain abscess, cerebritis, meningitis, cranial sinus thrombosis, mycotic aneurysm, infarction and ventriculitis.[6,8] The definitive diagnosis is made by histologic and microbiologic examination of an image-guided stereotactic brain biopsy, a resource-intensive and invasive procedure.[6]

Besides microscopy, culture and molecular methods, the fourth pillar of microbiological diagnostics that can be applied is serology. While commercial assays for the detection of serum biomarkers such as galactomannan (GM) for IA,[6,10] anti-*Candida*-antibodies and mannan antigen (MAN) for IC,[11] and the panfungal marker β-1,3-D-glucan (BDG)[6,10,11] are well established, very limited data exist on the performance of these tests for diagnosing CNS infections directly in CSF.

In this study, we aimed to evaluate the performance of five different serologic assays for the detection of non-*Cryptococcus* fungal CNS infections from blood and CSF samples.

2 | PATIENTS, MATERIALS AND METHODS

In this retrospective analysis, we included serum (n = 19) and CSF (n = 10) samples of nineteen patients with fungal growth from CNS specimens and time-matched control specimens: nineteen sera each of patients with culture-proven bacterial meningoencephalitis and without evidence for CNS infection, and ten CSF samples each of inpatients and outpatients. All sera were sampled within one and all CSF specimens were sampled within 2 weeks from the sampling date of the culture-positive specimen. Patients were treated at the University Hospital of Ludwig Maximilians University (LMU) Munich.

β-1,3-D-glucan testing was conducted at the Institut für Hygiene und Mikrobiologie (Julius-Maximilians-Universität Würzburg). All other analyses were performed at the Max von Pettenkofer Institute, Munich. Antigen testing was conducted using the Wako β-Glucan Test (FUJIFILM Wako Chemicals Europe) at a cut-off of 7 pg/ml, the Serion ELISA antigen Candida-kit at a cut-off of 2.6 U/ml (Institut Virion\Serion, Würzburg, Germany), and two *Aspergillus* antigen ELISAs with a cut-off optical density index (ODI) of 0.50 for the Platelia *Aspergillus* GM EIA (Bio-Rad Laboratories) and the Euroimmun Aspergillus Antigen ELISA (Euroimmun Medizinische Labordiagnostika AG). An indirect hemagglutination assay (IHA) was applied for the detection of anti-*Candida* antibodies (Hemkit Candida IHA, Ravo Diagnostika) at a cut-off titre of 1: 320. All assays were performed according to the manufacturers' instructions. CSF was processed analogously to serum.

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. This retrospective study was reviewed and approved by the local ethics committee (Ethikkommission der Medizinischen Fakultät der LMU München). A waiver of informed consent was granted. Sample processing and data analysis were performed anonymously. Clinical information and reference standards results were not available to the performers and readers of the assay.

3 | RESULTS

Nineteen patients with CNS specimens growing *Candida*[14] or *Aspergillus fumigatus*[5] were included in this study (Table 1). Despite recovery of *Candida* from CNS specimens, four patients did not meet the criteria for a proven invasive fungal infection (IFI) according to the EORTC/MSG consensus criteria,[12] since there were no clinical or radiological abnormalities consistent with an infectious disease process. A favourable outcome despite the omission of antifungal therapy confirmed the hypothesis of contamination in these four patients. This group will subsequently be referred to as 'presumably false-culture positive'. The majority of CNS IFIs was related to cranial surgery. Underlying diseases were heterogeneous with haemato-oncologic malignancy, which represents a major risk factor for invasive fungal infections, being only present in three cases.

TABLE 1 Patient and sample characteristics

	All cases	*Candida*	*Aspergillus*
n	19	14	5
Mean age	56	55	60
Female sex	6	5	1
Clinical diagnosis of IFI	15	10	5
Aetiology			
Cranial surgery[a]	12	11	1
Hem. Dissemination[a]	4	5	1
per continuitatem	3	0	3
Underlying conditions			
Neoplasia	11	9	2
Haemato-oncologic	3	3	0
Other neoplastic diseases[b]	8	6	2
Intracranial tumour/ meningeosis	9	8	1
Intracranial haemorrhage	2	2	0
Immunosuppression	2	0	2
Primary infection (no risk factors identified)	2	1	1
DM and PD	2	2	0
Intracranial procedures			
Tumour resection	8	7	1
Non-oncologic intracr. Surgery	4	4	0
None	7	3	4
Culture-positive specimens			
CSF	11	10	1
Intracranial swabs	5	3	2
Cerebral biopsy	2	0	2
Vitreous sample	1	1	0
Species			
A. fumigatus	5	-	5
C. albicans	12	12	-
C. dubliniensis	1	1	-
C. parapsilosis	1	1	-

Abbreviations: DM, type II diabetes mellitus; Hem, hematogenous; Intracr. intracranial; PD, Parkinson's disease.

[a]In two cases of *Candida* infection, it remained unclear, whether the CNS infection was a consequence of haematogenous dissemination or of cranial surgery. Hence, the two cases are included in both categories.

[b]Other neoplastic diseases included meningioma, adenoma of the pituitary gland, chordoma and paranasal sinus adenocarcinoma.

Only 5/15 sera (33%) from patients with CNS IFI were BDG positive with concentrations ranging from 7 to 17,000 pg/ml (Table 2). Serum BDG and GM resulted positive in 3/5 and 1/5 CNS IA patients. In addition to the serological gold standard, that is the Platelia GM EIA, another EIA was assessed (Euroimmun), which resulted positive in 2/5 CNS IA cases. The MAN EIA identified only 1/10 cases of CNS IC, which was also one of the four anti-*Candida* antibody-positive cases. Notably, none of the presumably false-culture positive *Candida* patients was seropositive in any test.

All seven CSF samples from patients with proven CNS IFD yielded BDG concentrations above the serum cut-off ranging from 9 to 777 pg/ml (median: 48 pg/ml). The three available CSF samples of CNS IA cases were highly reactive in the GM EIA with optical density indices in all three significantly above the cut-off recommended for serum (range 3.8–6.0). Contrarily, results were more heterogeneous in the *Candida* group: 2/4 patients with the clinical diagnosis of *Candida* meningitis had test results far above the serum cut-off and two had no reactivity in the MAN EIA.

Of the three presumably false-culture positive patients with available CSF samples, BDG was detected in 1/3 cases (27 pg/ml), low-level reactivity in the MAN EIA (1.2 U/ml) was detected in another, and the third was negative in both tests.

In matched cases without cultural evidence, specificity of serum GM and combined serum MAN/anti-*Candida*-antibody testing was 97% and 89%. The only MAN positive control was also *Candida* Ab positive. Serum BDG testing demonstrated a specificity of 95%.

In twenty CSF controls, minor GM EIA reactivity beneath the serum cut-off was detected in one sample (0.38), while there was no reactivity in the other 19 samples. Contrarily, BDG was detected in seven samples (three inpatients and four outpatients). Six samples yielded BDG concentrations above the serum cut-off of 7 pg/ml with a maximum of 487 pg/ml (median of 14 and mean of 98 pg/ml). BDG was detected in CSF sampled from inpatients and outpatients (three and four cases, respectively).

4 | DISCUSSION

To date, the diagnosis of CNS infections caused by *Candida* and *Aspergillus* spp. remains a challenge that already begins with the choice of the appropriate specimen: while for CNS candidiasis, analysis of CSF represents the gold standard, the definite diagnosis of CNS aspergillosis requires an even more invasive and elaborate procedure, that is stereotactic brain biopsy.[3,5,6] Two reasons might account for the low sensitivity of CSF culture in the setting of CNS aspergillosis: first, CNS aspergillosis typically does not present as meningitis, which might explain the absence of *Aspergillus* from CSF. Second, even upon the presence of fungal cells in CSF, aspiration through a canula might be hindered by the filamentous nature of mould cells. Classic microbiological techniques like microscopy and culture perform poorly in the setting of CNS IFI, for example culture positivity in CNS aspergillosis was reported to be as low as 9–24%.[3,7–9] Molecular methods like PCR have also not fulfilled the hopes placed in them to date.[13,14] Contrarily, antigen testing is a well-established tool for diagnosis of IFI and can be performed from an easily available specimen, that is serum.[11,15]

TABLE 2 Sensitivities and specificities of the different assays in serum and CSF (using the respective serum cut-offs)

			Aspergillus ag		*Candida* serology		
	n	BDG	GM	GP	Ag/Ab	Man	Ab
Sensitivity (%)							
Serum							
All culture pos. Cases	19	26	-	-	-	-	-
Proven CNS IFI	15	33	-	-	-	-	-
Proven CNS IA	5	60	20	40	-	-	-
All *Candida* pos. Cases	14	14	-	-	29	7	29
Proven CNS IC	10	20	-	-	40	10	40
CSF							
All culture pos. Cases	10	80	-	-	-	-	-
Proven CNS IFI	7	100	-	-	-	-	-
Proven CNS IA	3	100	100	-	-	-	-
All *Candida* pos. Cases	7	71	-	-	-	29	-
Proven CNS IC	4	100	-	-	-	50	-
Specificity (%)							
serum							
All controls	38	95	97	-	89	97	89
Bacterial CNS infections	19	95	95	-	95	100	95
Without CNS infection	19	95	100	-	84	95	84
CSF							
Without CNS infection	20	70	100	-	-	-	-

Abbreviations: ag, antigen; BDG, Wako β-Glucan Test; GM, Platelia *Aspergillus* Ag EIA; GP, Euroimmun Aspergillus Antigen ELISA; Ag/Ab, combined results of mannan antigen and anti-*Candida*-IgG testing; Man, SERION ELISA *antigen* Candida; Ab, Hemkit Candida IHA;

Besides few anecdotal reports, data on the performance of serum biomarkers for the diagnosis of CNS aspergillosis and CNS candidiasis are scarce: in 2015, Salvatore and colleagues presented a small case series including two cases of CNS aspergillosis and seven cases of CNS candidiasis, of which one and six cases were characterised by BDG seropositivity.[16] Very recently, Chaussade analysed serum samples of 14 patients suffering from CNS candidiasis, demonstrating BDG seropositivity of 100%.[17] For combined MAN/anti-*Candida*-antibody testing, the sensitivity was 71%. Therefore, despite the small overall number of 15 cases, which meet the EORTC/MSG criteria for proven CNS infection,[12] we think that the results of our study contribute to the knowledge in this field. Interestingly, all serum biomarkers demonstrated sensitivities of only 20–40% in our study. In the case of CNS candidiasis, this seropositivity primarily relied on antibody rather than on antigen testing (40% vs. 10%). The underwhelming sensitivity of serum GM and BDG testing might be attributable to the brain blood barrier, which inhibits spillover of intrathecally synthesised antigens.

In contrast to the limited literature for serum biomarkers, there are a number of case reports describing the analysis of CSF biomarkers for the diagnosis of CNS infections due to *Candida* and *Aspergillus*. Importantly, none of the available respective fungal antigen tests is certified or recommended for the analysis of CSF. Particularly for GM, several case reports and small case series about the utility of CSF GM testing had been published.[18] A very recent review of the literature indicates a sensitivity of 80%.[3] Notably, the 2017 ESCMID-ECM-ERS guideline includes a grade B recommendation for GM testing from CSF but at the same time warns of low evidence and a lacking cut-off.[15] Superiority of CSF BDG testing over culture was evidenced in experimental models (haematogenous *Candida* meningitis in nonneutropenic rabbits).[19] Our results for CSF BDG are in good agreement with current estimates for BDG sensitivity, which range from 64 to 90%.[5,8] BDG sensitivity can be increased by repetitive CSF sampling or by performing ventricular instead of lumbar puncture.[20] Interestingly, CSF BDG was shown to be a useful marker for therapy monitoring in CNS candidiasis.[21] Less information is available for *Candida*

antigen testing with only two very recent studies investigating CSF mannan in five and three cases, respectively.[17,20] The results in those studies (in total: 6/8 cases CSF mannan positive) are again comparable to our findings.[17,20]

While the GM ELISA remained negative in all controls, BDG specificity was only 70%. Notably, this study relies on the Wako β-Glucan Test, which is even characterised by higher specificity than other BDG assays.[22] Still, BDG testing is known for lower specificity compared with other fungal antigens.[23] The combination of low test specificity and low disease prevalence raises concerns that a CSF BDG-based workup in case of CNS IFI suspicion may lead to a high rate of false-positive diagnoses. Nevertheless, due to the high sensitivity CSF BDG testing may still be a useful tool in a setting of high pre-test probability, that is upon clinical suspicion of CNS IFI. Given the fact that the assay did not miss a single case of CNS IFI in this study, one could speculate that in clinical practice a negative BDG result might allow to omit the suspicion of fungal disease. Notably, attempts to establish a better discriminating CSF cut-off based on our findings failed because of the wide distribution of false-positive results.

There are several possible explanations for false-positive CSF BDG results, including cross reactivity with other polymers or bacterial metabolites.[24,25] Furthermore, it is conceivable that systemic IFI without CNS involvement but with high BDG serum concentrations could lead to BDG leakage from the bloodstream to the CSF. Depending on the materials used for CSF puncture, for example wipes used for disinfection or tubes that are not glucan-free, contamination during collection could also be a possible reason for positive results. Lastly, elevated CSF BDG levels have been described in HIV infected patient populations with leaky gut and neurocognitive impairment but without fungal disease, indicating that in some patient populations with chronic diseases that result in microbial translocation in the gut, CSF BDG may actually serve as a marker of the gut brain axis and neurocognitive impairment.[26]

The current study has a number of limitations. With regard to the 30% BDG positive CSF samples in the control group, it cannot be excluded (though it is highly unlikely) that a patient suffered from undiagnosed fungal infection. The study suffers from a very small number of cases, which is further divided into two subgroups of only 14 (IC) and 5 (IA) cases. Additionally, our cases do not necessarily represent the typical risk population, for example none of the CNS IA cases suffered from haemato-oncologic malignancy. Subsuming the two subgroups (IC and IA) is difficult, since those very different disease entities require different assays for diagnosis. It was not possible to test the samples with every serologic assay, or even with additional tests like PCR. This is because of the significant sample volume required for most antigen tests (≥ 300 µl). Therefore, more and larger studies are necessary to identify contributing factors and to evaluate reliability of CSF biomarkers.

In summary, our data suggest low sensitivity for diagnosing CNS aspergillosis and CNS candidiasis for all serology biomarkers in blood samples. Testing for CSF GM could be a promising tool for the diagnosis of CNS aspergillosis. With a sensitivity of 100% but a specificity of only 70%, CSF BDG might be most useful when used in patients with a high pre-test probability.

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AUTHORS' CONTRIBUTIONS

Johannes Forster and Karl Dichtl contributed to conceptualisation, supervision and project administration. Johannes Wagener and Karl Dichtl contributed to methodology, formal analysis and investigation. Sebastian Suerbaum, Johannes Wagener and Karl Dichtl contributed to resources. Martin Hoenigl and Karl Dichtl contributed to writing—original draft. Johannes Forster, Martin Hoenigl, Sebastian Suerbaum, Johannes Wagener and Karl Dichtl contributed to writing—review and editing. Karl Dichtl contributed to visualisation.

CONFLICT OF INTERESTS

The manufacturers had no role in the study design, data collection, analysis, interpretation, decision to publish, in the writing of the manuscript or in the decision to submit the manuscript for the publication. JF reports report grants to the institution and non-financial support from Fujifilm Wako Chemicals Europe. MH received research funding from Gilead, Astellas, MSD, Scynexis, F2G and Pfizer. JW reports grants to the institution and non-financial support from Fujifilm Wako Chemicals Europe and Euroimmun Medizinische Labordiagnostika and speaker honoraria for lectures from Pfizer. KD reports grants to the institution and non-financial support from Fujifilm Wako Chemicals Europe and Euroimmun Medizinische Labordiagnostika. SS has nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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