(1-3)-β-D-Glucan in Cerebrospinal Fluid Is Useful for the Diagnosis of Central Nervous System Fungal Infections

To the Editor—A definitive diagnosis of invasive fungal infection (IFI) remains difficult in immunocompromised hosts. Thus, fungal markers such as galactomannan (GM) or (1-3)-β-D-glucan (BG) are useful for the diagnosis of probable IFI in high risk patients [1]. Detection of GM in cerebrospinal fluid (CSF) has been studied and is now considered diagnostic for central nervous system (CNS) aspergillosis in high-risk patients with a compatible neurological disease [1, 2].

Serum BG, major constituent of fungi other than the Mucorales, is being used for noninvasive diagnosis of fungal infection, and has been included as microbiological criterion for the diagnosis of probable IFI in the revised definitions of IFI of the European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) [1]. BG has been widely studied in serum, but only 1 animal study has analyzed its levels in CSF in a

Table 1. Clinical Characteristics of Patients With Cerebral Invasive Fungal Infections

<table>
<thead>
<tr>
<th>Patient/ Sex, Age</th>
<th>Underlying Disease</th>
<th>Diagnosis</th>
<th>Clinical Signs and Symptoms</th>
<th>Radiological Signs</th>
<th>Serum GM* (ODI)</th>
<th>Serum Glucan* (pg/mL)</th>
<th>CSF GM (ODI)</th>
<th>CSF Glucan (pg/mL)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/ F, 48</td>
<td>Myelodysplastic syndrome, allogeneic HSCT</td>
<td>Probable cerebral and pulmonary aspergillosis</td>
<td>Confusion, seizures, aphasia</td>
<td>Focal hypodense lesion</td>
<td>1.044</td>
<td>158</td>
<td>&gt;12</td>
<td>&gt;523</td>
<td>Deceased 1 d after lumbar puncture</td>
</tr>
<tr>
<td>2/ F, 50</td>
<td>Acute lymphoblastic leukemia, allogeneic HSCT</td>
<td>Probable cerebral aspergillosis</td>
<td>Confusion, hemiparesis, aphasia</td>
<td>Focal hypodense lesion</td>
<td>0.11</td>
<td>19</td>
<td>1.14</td>
<td>&gt;523</td>
<td>Alive</td>
</tr>
<tr>
<td>3/ F, 45</td>
<td>Acute myelogenous leukemia, relapsed after allogeneic HSCT</td>
<td>Probable cerebral aspergillosis</td>
<td>Aphasia</td>
<td>Meningeal enhancement and hypodense lesions</td>
<td>0.061</td>
<td>94</td>
<td>0.82</td>
<td>103</td>
<td>Deceased 7 d after lumbar puncture</td>
</tr>
<tr>
<td>4/ M, 39</td>
<td>Immunocompetent</td>
<td>Proven cerebral histoplasmosis</td>
<td>Seizures</td>
<td>Focal lesion with ring enhancement</td>
<td>0.124</td>
<td>33</td>
<td>0.13</td>
<td>282</td>
<td>Alive</td>
</tr>
<tr>
<td>5/ F, 37</td>
<td>SLE treated with high-dose corticosteroids and MMF</td>
<td>Proven cryptococcal meningitis</td>
<td>Coma and fever</td>
<td>Meningeal enhancement</td>
<td>0.166</td>
<td>&lt;7</td>
<td>0.27</td>
<td>331</td>
<td>Alive</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; GM, galactomannan; HSCT, hematopoietic stem cell transplant; MMF, mycophenolate mofetil; ODI, optical density index; SLE, systemic lupus erythematosus.

* On the day of lumbar puncture, except for patients 1 and 3, in whom serum sample was drawn 2 days before lumbar puncture.
nonneutropenic rabbit model of experimental hematogenous Candida meningoencephalitis [3].

The aim of this study was to assess the utility of BG in CSF in patients with cerebral IFI, particularly aspergillosis. Five patients with CNS IFI, for whom CSF was available, were included in the study: 3 patients with probable CNS aspergillosis; 1 patient with proven cerebral histoplasmosis, and 1 with proven cryptococcal meningitis. Aspergillosis was classified according to 2008 EORTC/MSG criteria, with positive GM in CSF and compatible cerebral lesions in case of probable CNS aspergillosis [1]. CSF samples from 19 patients without IFI were included as controls.

BG and GM testing were performed with Fungitell (Associates of Cape Cod, Inc, Falmouth, Massachusetts), and Platelia Aspergillus (Bio-Rad, Paris, France) assays, respectively, according to the manufacturers’ instructions. Values >80 pg/mL for BG and 0.5 optical density index for GM were considered positive.

Clinical characteristics of patients with cerebral IFI are shown in Table 1. CSF was positive for BG in all 5 patients with CNS IFI, with a mean concentration of 352 pg/mL and a median concentration of 331 pg/mL (range, 103–523 pg/mL); 18 of 19 control patients had negative results for BG with a mean concentration of 37.1 pg/mL and a median concentration of 32 pg/mL (range, 7–115 pg/mL). The test showed a high specificity, and the only 1 positive BG in a control patient had a low concentration (115 pg/mL).

Cryptococcus has been reported to release low levels of BG [4], even 10 times lower than Candida [5]. Whereas 2 studies found BG to be consistently negative in patients with cryptococcosis (5 and 3 cases, respectively) [6, 7], others reported serum BG positivity in some or all cases of cryptococcosis (3 of 12, 5 of 6, and 3 of 3 [8–10]).

In conclusion, BG is useful for the diagnosis of different cerebral IFIs, including aspergillosis, histoplasmosis, and probably some cases of cryptococcosis. Our results suggest that a positive BG in CSF might be included in the EORTC/MSG microbiological criteria for the diagnosis of CNS IFI in high-risk patients.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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