Cryptococcal Choroid Plexitis an Uncommon Fungal Disease. Case Report and Review

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**Case Report**

A 39-year-old healthy woman without a previous history of immunosuppression, lymphoreticular malignancy, corticosteroid use or sarcoidosis, developed daily moderate headache three months before admission. One month later headache increased and was associated with nausea and vomiting and she was admitted to another hospital with papilledema and bilateral paresis of sixth cranial nerve. A head CT scan was normal; on lumbar puncture cerebrospinal fluid (CSF) pressure was 300 mmH₂O, CSF analysis was reported without cells and with normal protein and glucose levels. A diagnosis of idiopathic intracranial hypertension was made and treatment with acetazolamide and furosemide started. She improved and one month later, headache relapsed with nausea, vomiting, diplopia, and confusion. A right parieto-occipital ventriculoperitoneal shunt (VPS) was placed without improvement. She became somnolent, developed urinary and fecal incontinence and then was transferred to our Institution; upon admission she was found with poor attention, mutism and perseveration, the neurological examination revealed a right central facial palsy, spared brainstem reflexes, hyperreflexia, ataxic gait and bilateral extensor plantar reflexes. Her neurological condition rapidly deteriorated and remained stuporous. The CT scan and MRI showed asymmetric hydrocephalus and ependymal enhancement with nodular areas, temporal horns were dilated producing brainstem compression (Figure 1A, B, C and D). First diagnostic

**Figure 1A:** Contrast-enhanced axial CT scan upon admission shows asymmetric hydrocephalus, lineal and nodular ependymal enhancement and brainstem compression.
considerations were diffuse central nervous system (CNS) lymphoma or a chronic infectious process. The HIV serology was negative. Emergency bitemporal craniectomies, VPS and biopsies were performed. After craniectomies a ventricular puncture yielded turbid CSF, cell count was 64 per µL (95% of lymphocytes and 5% polymorphonuclears), protein of 769 mg/dl and glucose of 14mg/dl. Biopsies of ependyma and choroid plexus revealed a granulomatous inflammatory reaction with encapsulated yeasts. The Periodic acid-Schiff (PAS) and Grocott stain confirmed *Cryptococcus* species (Figure 2). The cryptococcal antigen latex test was positive. Bacterial, mycobacterial and fungal cultures of CSF remained negative. Polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* was also negative, and CSF Adenosine-deaminase was undetectable. Corticosteroids and intravenous amphotericin B at 30 mg/day were given; a total dose of 1350mg was accumulated over 6.5 weeks. Post-operative CT scan showed resolution of hydrocephalus (Figure 3A). Her mental function improved substantially and she was discharged after 56 days in hospital. She continued her treatment with oral itraconazole 400mg per day long-term. A control MRI after eight months showed reduction of contrast enhancement in the frontal horns of the lateral ventricles while in the temporal horns enhancement of choroid plexus persisted (Figure 3B, C and D).

**RESULTS**

A MEDLINE search with key words “cryptococcal brain infections” and “choroid plexitis”, retrieved 496 articles. Only 13 were related to primary choroid plexitis and had complete clinical data. The Table summarized the 23 cases described in these articles. There were 7 women and 16 men. Mean age was 36.4 ± 17 years, range from 2 to 69 years. *Cryptococcus* was the etiologic agent in eight and aetiology was not identified in two patients. In six patients there were immunosuppressant factors such as diabetes, pulmonary fibrosis, leukemia, post-transplantation state and HIV in one case. Seven were immunocompetent and in 13 patients immunological status was not available. Of interest, in the seven immunocompetent patients the infectious agents were cryptococcus in five and nocardia in two. Clinical manifestations of choroid plexitis were variable, intracranial hypertension, headache and confusion predominated. Most common imaging findings were abnormal enhancement of choroid plexus and hydrocephalus. The
Diagnosis was made by biopsy in ten, by CSF study (cultures or immunological test) in nine, by clinical manifestation and MRI in two. Factors related to a poor outcome were delayed diagnosis, a positive HIV status and immunosuppression. Pharmacological treatment was used in 16 patients and both pharmacological and surgical treatment in the rest. The outcome was fatal in eight patients; three of these cases were due to cryptococcal infection.

**DISCUSSION**

*Cryptococcus* serotype and prevalence are quite different between immunocompromised and immunocompetent people. *C. neoformans* var *neoformans* (serotypes A and D) is associated with HIV with a prevalence from 2-10% in Europe and United States, and more than 15% in Sub-Saharan Africa,

As in tuberculosis, the lung is the primary site of infection with granulomatous inflammation, other involved organs are the skin, prostate and eyes. The neurological manifestations are

**Table: Previously reported cases of primary choroid plexitis**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Clinical manifestations</th>
<th>CSF white cells</th>
<th>Pathogen isolated</th>
<th>Outcome</th>
<th>Immunosuppressant factors</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>44</td>
<td>Intracranial Hypertension and paraplegia</td>
<td>15</td>
<td>Cryptococcus</td>
<td>Fatal</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>45</td>
<td>Intracranial hypertension</td>
<td>105</td>
<td>Cryptococcus</td>
<td>Improvement</td>
<td>None</td>
<td>63</td>
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<tr>
<td>Female</td>
<td>37</td>
<td>Headache and diplopia</td>
<td>78</td>
<td>Cryptococcus</td>
<td>Improvement</td>
<td>None</td>
<td>63</td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>Headache and fever</td>
<td>80</td>
<td>Cryptococcus</td>
<td>Improvement</td>
<td>None</td>
<td>70</td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>Headache and fever</td>
<td>720</td>
<td>Cryptococcus</td>
<td>Improvement</td>
<td>None</td>
<td>70</td>
</tr>
<tr>
<td>Female</td>
<td>69</td>
<td>Headache, vomiting</td>
<td>Nd</td>
<td>Cryptococcus</td>
<td>Fatal</td>
<td>None</td>
<td>64</td>
</tr>
<tr>
<td>Male</td>
<td>60</td>
<td>Dementia and gait disorders</td>
<td>10</td>
<td>Cryptococcus</td>
<td>Fatal</td>
<td>Nd</td>
<td>64</td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>Intracranial hypertension</td>
<td>7</td>
<td>Cryptococcus</td>
<td>Nd</td>
<td>Nd</td>
<td>45</td>
</tr>
<tr>
<td>Male</td>
<td>34</td>
<td>Meningitis</td>
<td>102</td>
<td>M. tuberculosis</td>
<td>Fatal</td>
<td>Nd</td>
<td>65</td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
<td>Fever, headache and vomiting</td>
<td>3024</td>
<td>None but imaging were compatible with M. tuberculosis</td>
<td>Improvement</td>
<td>Nd</td>
<td>66</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>Meningitis</td>
<td>252</td>
<td>M. tuberculosis</td>
<td>Improvement</td>
<td>Nd</td>
<td>70</td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>Headache, fever and vomiting</td>
<td>320</td>
<td>M. tuberculosis</td>
<td>Improvement</td>
<td>None</td>
<td>70</td>
</tr>
<tr>
<td>Female</td>
<td>33</td>
<td>Sluor and coma</td>
<td>Nd</td>
<td>N. asteroidis</td>
<td>Fatal</td>
<td>Pulmonary fibrosis and chronic use of steroids</td>
<td>45</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>Headache, fever and vomiting</td>
<td>1209</td>
<td>N. asteroidis</td>
<td>Improvement</td>
<td>None</td>
<td>43</td>
</tr>
<tr>
<td>Male</td>
<td>56</td>
<td>Headache, fever and cough</td>
<td>Nd</td>
<td>N. asteroidis</td>
<td>Improvement</td>
<td>None</td>
<td>71</td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>Meningitis and intracranial hypertension</td>
<td>58</td>
<td>None (Aseptic plexitis?)</td>
<td>Improvement</td>
<td>Nd</td>
<td>45</td>
</tr>
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<td>Male</td>
<td>2</td>
<td>Meningitis</td>
<td>Nd</td>
<td>None (Aseptic plexitis?)</td>
<td>Nd</td>
<td>Nd</td>
<td>45</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>Fever post-chemotherapy and headache</td>
<td>Nd</td>
<td>Stomatococcus mucilaginosus</td>
<td>Improvement</td>
<td>Acute myeloid leukaemia</td>
<td>67</td>
</tr>
<tr>
<td>Male</td>
<td>46</td>
<td>Fever post-chemotherapy and headache</td>
<td>Nd</td>
<td>Stomatococcus mucilaginosus</td>
<td>Improvement</td>
<td>Acute myeloid leukaemia</td>
<td>67</td>
</tr>
<tr>
<td>Female</td>
<td>44</td>
<td>Meningitis</td>
<td>5</td>
<td>Streptococcus α y β</td>
<td>Improvement</td>
<td>Diabetes mellitus</td>
<td>65</td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>Headache, fever and vomiting</td>
<td>3.3x10⁶</td>
<td>Pseudoallescheria boydii</td>
<td>Fatal</td>
<td>Pulmonary fibrosis</td>
<td>68</td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>Vertigo and confusion</td>
<td>12</td>
<td>Cytomegalovirus</td>
<td>Fatal</td>
<td>Nd</td>
<td>69</td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>Headache, fever and vomiting</td>
<td>28</td>
<td>Toxoplasma gondii</td>
<td>Fatal</td>
<td>Epstein Barr virus and HIV</td>
<td>72</td>
</tr>
</tbody>
</table>

Nd = No data available

**Figure 3A**: Non-enhanced axial CT scan one month after surgery shows bilateral craniectomies with ventriculoperitoneal shunts and hydrocephalus resolved.
sub-acute and chronic meningitis or meningoencephalitis\textsuperscript{25,26}.

Inflammation predominates in basilar meninges, occasional vasculitis or focal mass lesions are seen. Impaired resorption of CSF produces high CSF pressure and clinical manifestations include headache, papilledema and focal neurological signs, particularly of cranial nerves\textsuperscript{27}. Intracranial hypertension (ICH) is multifactorial, based on the liberation of high molecular-weight polysaccharides by the active reproduction of the yeast, leading to a higher CSF viscosity and resorption blockage. Also, D-mannitol is released and raises CSF osmolarity\textsuperscript{28-31}. These macromolecules cover the brain, the Virchow-Robin spaces and brain parenchyma, reducing the brain “compliance”\textsuperscript{32,33}. These factors produce a communicating hydrocephalus, determined by the blockage of the circulation of CSF; however, ventricular size is often normal owing to the loss of the brain “compliance” evolving to a progressive ICH. Our patient had elevated intracranial pressure (ICP) with papilledema and evidence of a focal hydrocephalus by temporal entrapment but in some patients with ICP there is not evidence of obstructive hydrocephalus\textsuperscript{34}. In AIDS patients a massive fungal burden leads to an extensive deposition of capsular polysaccharide\textsuperscript{35} that contributes to increase the CSF and interstitial fluid osmolality, promoting fluid accumulation or retention\textsuperscript{36-38}.

Diagnosis of cryptococcal choroid plexitis is a challenge for clinicians, due to non specific symptoms or an asymptomatic course, until manifestations of sub-acute or chronic meningitis, ICH and hydrocephalus appear\textsuperscript{39}.

Imaging characteristics of brain cryptococcal infection are protean. The extension of meningeal infection along perivascular spaces may produce small cysts, termed gelatinous pseudocysts in the Virchow-Robin spaces or “soap bubbles”, in the basal ganglia, thalamus, substantia nigra and periventricular regions\textsuperscript{40,41}. On MRI these structures are typically non-enhancing, hypointense lesions on T1 weighted images and hyperintense on T2 weighted images. The choroid plexus, spinal cord and nerve roots are occasionally involved\textsuperscript{6,42}. Less common manifestations are hydrocephalus and diffuse atrophy. Cryptococcomas occurred in from 4% to 11% of patients with meningitis. The pattern of contrast enhancement in cryptococcal choroid plexitis is non specific and needs to be differentiated of other infectious conditions as: \textit{Mycobacterium tuberculosis}, \textit{Cytomegalovirus}, \textit{Toxoplasma gondii}, \textit{Nocardia asteroides} and a variety of bacteria, viruses and parasites\textsuperscript{6,42-43}, differential diagnosis includes also primary neoplasm (papilloma, carcinoma, ependymoma, hemangioma, lymphoma, meningioma), metastases\textsuperscript{44,45} and several systemic disorders with CNS affection like sarcoidosis\textsuperscript{46}, xanthogranulomas\textsuperscript{47,48} and even rheumatoid nodules\textsuperscript{49}.

Antifungal drugs constitute the cornerstone of medical treatment of cryptococcal infections in patients with and without immunocompromise, amphotericin B alone, or associated with flucytosine, is effective in most cases and sterilizes CSF in 60%–90% of patients\textsuperscript{34,35}; however, the requirement of intravenous therapy for an extended period of time and the relative toxicity of the regimen, raised alternatives. A frequently used treatment consists of an induction course of amphotericin B (0.5-1mg/kg/d) with flucytosine (100mg/kg/d) for two weeks, followed by a consolidation therapy with fluconazole (400mg/d) for an additional eight to ten weeks\textsuperscript{50-54}. Our patient received amphotericin B alone at 0.4mg/kg/d for 6.5 weeks as induction and itraconazole 400mg/d as consolidation therapy. We did not use flucytosine because is not available in Mexico.

The control of ICH is another important aspect in the management of brain cryptococcosis; usual methods are
decompression by ventricular drainage, repeated lumbar punctures or medical treatment with acetazolamide or mannitol. The CSF shunts have been used to manage ICH in cryptococcal meningitis in patients with and without HIV, with good long-term outcomes. Corticosteroids sharply reduce the release of proinflammatory cytokines by monocytes/macrophages and polymorphonuclear leukocytes and they may be useful in treating associated vasculitis.

The choroid plexuses are an important target for systemic disorders and a pathway for infectious agents or toxic-metabolic disorders because of richly vascularised epithelium without the blood-brain barrier. The entrapment of the temporal horns of the lateral ventricles, hydrocephalus and intraventricular synechiae due to CSF flow obstruction are secondary to choroidal inflammation. It is still unknown why the infection in some patients persists and remains restricted to the choroid plexus. When lumbar puncture is contraindicated, the realization of CSF shunt and biopsy may be necessary for an accurate diagnosis and proper treatment.

REFERENCES


