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Corticosteroids for shunted previously healthy patients with non-HIV cryptococcal meningoencephalitis

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Cryptococcal meningoencephalitis (CM) can cause significant morbidity and mortality in previously healthy, non-HIV-infected patients, with all-cause mortality as high as 29% at 1 year.¹ Clinical deterioration following microbiological control often results from a postinfectious inflammatory response syndrome (PIIRS). This syndrome may often result in intracranial hypertension (IH) and/or hydrocephalus (HCP).² Ventricular shunting can provide sustained relief from IH/HCP and improve neurological outcomes.³ However, persistent neurological sequelae, which occur in a subset of patients, may lead to shunt revisions and poor long-term outcomes.³ Corticosteroids have been proposed to improve outcomes in selected, relatively immunocompetent patients with CM, but are often avoided due to presumed immunosuppressive effects.^{4,5} Paradoxically, the use of corticosteroids during initial therapy of other patient populations such as HIV-associated CM has been found to result in worse overall outcomes.⁴ We hypothesised that corticosteroid salvage therapy (CST) may have specific utility in previously healthy patients with PIIRS following microbiological control with persistent neurological sequelae and report our experience in a cohort of patients who have already undergone cerebrospinal fluid (CSF) diversion.

Previously healthy patients who were evaluated and treated for cryptococcal meningitis between 2011 and 2016 at the National Institutes of Health (NIH) were identified. Informed consent to participate in clinical research was obtained from all patients (NIH protocol 93-I-0106). We limited assessment to a relatively uniform population of patients who had

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previously undergone CSF diversion. CST included induction therapy with high-dose intravenous methylprednisolone, dexamethasone or oral prednisone. Long-term maintenance therapy was established with oral prednisone (20 mg daily). Long prednisone tapers were used to mitigate adrenal insufficiency and rebound neuroinflammation. Clinical outcome data were recorded and retrospectively reviewed, including modified Rankin scores (mRS) and Glasgow Coma Scale (GCS) scores. Outcomes at 30 days and at last follow-up were analysed.

Of 30 patients treated for CM in previously healthy individuals (6 *Cryptococcus gatii*, 12 *Cryptococcus neoformans*, 12 not confirmed), 17 patients (6 female/11 male; median age 51 years, range 22–67) (26%) underwent CSF diversion (16 ventriculoperitoneal shunts, 1 endoscopic fenestration of trapped ventricle) and presented with refractory (median: 104 days from diagnosis) and severe disease (median mRS 4 (range 2–5)). Overall, patients with CSF diversion were improved at the last follow-up (median 31.7 months (range 4.8–62 months)) compared with presentation. The median mRS of the 15 surviving, shunted patients was 1.5 (figure 1A), showing significant improvement over presentation (Wilcoxon matched-pairs signed-rank, $p=0.0002$). These findings confirmed that CSF diversion is a valid first strategy for IH in CM.⁵

Thirteen patients (76%) demonstrated persistent neurological symptoms/signs following microbiological control of CM (CSF culture-negative) for which CST was initiated. Eight patients (two female/six male; median age 54 years, range 20–64) received CST at the NIH Clinical Center (NIHCC) and were included in this analysis, whereas five were treated elsewhere. The median pretreatment (before CST initiation) mRS and GCS of these eight patients were 4.5 and 14, respectively (figure 1B, C). Pretreatment neurological symptoms included headaches (five patients), altered mental status (four patients), ataxia (four patients), lethargy (four patients) and nausea/vomiting (three patients). Raised lumbar cisternal opening pressure (>20 cm H₂O) was noted in three out of eight patients, and bilateral papilledema noted in one of six patients with optic disc evaluations. CST included induction with methylprednisolone (1 g daily) or dexamethasone (12–15 mg daily) in four patients, followed by maintenance therapy using oral prednisone (20 mg daily). In the four remaining patients, oral prednisone was used for both induction (60–90 mg daily) and maintenance therapy (20 mg daily). CST duration was 1–27 months (median 8 months) and was ongoing in two patients at the time of last follow-up.

At 1 month post-CST initiation, objective neurological improvements were noted in five patients (63%). With a median mRS of 4, all patients remained at baseline mRS ($n=5$) or improved ($n=3$, 1 point). Similarly, with a median GCS of 15, patients remained at baseline GCS ($n=4$) or improved ($n=4$, 1–5 points) after CST (Figure 1). In all three patients with confirmed IH, lumbar puncture opening pressure (pretreatment range 21–69 cm H₂O) normalised after treatment (range 13–20 cm H₂O). No CST-related adverse events were noted.

Median follow-up after steroid initiation was 15.1 months (range 4.2–50 months). At last follow-up, two patients were deceased (one patient: progression of unrelated disease—Alzheimer's; one patient: haemorrhagic stroke secondary to an inflammatory vasculopathy

resulting in a haemorrhagic stroke). With concurrent fluconazole therapy, no instance of microbiological recurrence was recorded. One patient, who required assistance with all activities of daily living on presentation, experienced a full neurological recovery. Lumbar cisternal opening pressure was significantly elevated in this patient despite multiple shunt revisions (69 cm H₂O), but improved to 20 cm H₂O after treatment with corticosteroids.

Morbidity after microbiological control of cryptococcal meningitis is often related to a PIIRS. Recent analysis of CSF from previously healthy patients with CM/PIIRS has revealed expanded lymphocyte populations (CD4+ and CD8+ T cells and NK cells) and elevated pro-inflammatory cytokine levels (interferon- γ , interleukin-6 and CXCL10), associated with a biomarker of neuronal damage (neurofilament light chain).² However, steroid therapy for CM/PIIRS is often avoided due to concern for immunosuppressive effects as it is a significant risk factor for the development of CM.⁶ Additionally, CST has proven lack of efficacy in patients with HIV-associated CM.⁴ In the present analysis, including only patients with severe, refractory CM who had already undergone CSF diversion, we assessed the effect of CST on neurological outcome. We found that CST may improve functional outcome in patients with microbiological control and neurological sequelae due to PIIRS. Furthermore, we found that lumbar cisternal opening pressures reduced after treatment with corticosteroids (three of three patients). This suggests that PIIRS may be partly responsible for elevated IH in these patients.

In the setting of CM/PIIRS with elevated CSF lymphocytes and cytokines, CSF diversion appears to be an appropriate initial management option. However, for patients with persistent neurological symptoms after microbiological control, high-dose corticosteroids may be a useful salvage therapy. Overall, corticosteroids were well-tolerated and did not lead to microbiological recurrence on fluconazole maintenance therapy.

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Figure 1.

Clinical outcome measures before and after corticosteroid therapy. (A) Modified Rankin scale (mRS) scores of 15 surviving patients with cerebrospinal fluid diversion at presentation to National Institutes of Health (NIH) and at the last follow-up visit. (B) mRS and (C) Glasgow Coma Scale scores of eight patients with cryptococcal meningitis before initiation of corticosteroids and 1 month after initiation.