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Refractory inflammatory hydrocephalus: A case report of a rare and complicated delayed sequelae following cerebral hemispherectomy surgery for epilepsy

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ABSTRACT

Hydrocephalus is a known complication following surgical resection of a cerebral hemisphere for refractory epilepsy, yet the pathological mechanism remains poorly understood. We present a case of refractory aseptic inflammatory hydrocephalus following cerebral hemispherectomy surgery for refractory epilepsy treated with a combination of cerebral spinal fluid (CSF) diversion and immunosuppression via IL-1 receptor agonist, Anakinra. At 6 month follow up, the patient had returned to neurologic baseline, with improvement in school and physical therapy performance. Further investigation into the beneficial role of immunosuppressive therapy is needed to better understand the relationship between neuro-inflammation and improving outcomes following epilepsy surgery.

Introduction

Hydrocephalus is a known complication following surgical resection of a cerebral hemisphere for refractory epilepsy, occurring in up to 20 % of cases, despite advances in operative techniques and post-operative management [1]. The pathological mechanism remains poorly understood, and multiple studies have identified heterogeneous factors associated with the disease. Many theories center on exposure of the ventricular system to prolonged inflammation following surgery [1].

We present a case of refractory aseptic inflammatory hydrocephalus following cerebral hemispherectomy surgery for refractory epilepsy treated with a combination of cerebral spinal fluid (CSF) diversion and immunosuppression.

Case report

A 14-year-old boy with history of left hemimegaloencephaly with hemispheric refractory epilepsy presented now 5 years since last surgery with recurrent staring spells, eye twitching, worsening memory, emotional lability, and cognitive decline. He underwent initial disconnective hemispherotomy at 5 years of age, complicated by seizure recurrence, treated with revision anatomic hemispherectomy at age nine. These new symptoms had overlap with preoperative seizures, though careful evaluation with video EEG was carried out and symptoms were confirmed as non-epileptic. He was maintained on his anti-seizure medication as well. Magnetic Resonance Imaging (MRI) of the brain revealed progressive ventriculomegaly compared to previous studies. The decision was made to place a ventriculoperitoneal (VP) shunt for CSF drainage given the concern for symptomatic hydrocephalus. In the following 9 months after the initial left frontal adjustable VP shunt insertion, the patient returned 4 times with symptoms of shunt failure including headaches, nausea, lethargy, incontinence, and imaging consistent with worsening ventriculomegaly, each return resulting in a revision of the shunt system using both programmable and fixed-pressure shunt systems. No evidence of infection was found at any point during revision, and the etiology was attributed to cloudy and xanthrochromic fluid clogged in the proximal valve-catheter system. Ipsilateral and contralateral placement of the intracerebral portion of the shunt was attempted without success.

High resolution MRI showed a cystic membrane within the third

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ventricle, allowing communication of cystic fluid and CSF through but not past the supratentorial ventricular system (Fig. 1a-c). An endoscopic third ventriculostomy was attempted. This was unsuccessful due the heavy opacity and viscosity of the patient's CSF. An intraoperative image at the junction of the septum pellucidum and foramen of Monro showed a pedunculated membrane remaining as a cast of the previously midline crossing ventricular catheter (Fig. 1b). CSF analysis revealed extreme proteinosis (>1000 mg/dL) in the absence of pleocytosis or infection, concerning for an hypersecretory process (Fig. 2). Several attempts were made to divert CSF using larger caliber shunt valves and even valveless systems, which all failed proximally, leading to prolonged shunt externalization via ventriculostomy.

Suspecting an inflammatory etiology, consultation was made to dermatology and rheumatology. Neuroaxial imaging was obtained to rule out occult neoplastic disease. Allergies to shunt system materials were ruled out via patch testing. CSF cytokine panel showed markedly elevated interleukin (IL) 6 and soluble IL-2 receptor (IL2R) levels. The patient was started on high dose dexamethasone, and daily CSF sampling revealed decreasing protein and cytokine levels following administration. Additional immunosuppressive therapy was initiated with anakinra (Kineret, Swedish Orphan Biovitrum [Sobi], Stockholm, Sweden), which further decreased protein levels (Fig. 2). Following optimization of anakinra dosing to twice daily administration, the patient's shunt was reinternalized, requiring use once again of a valveless shunt system to maintain patency. At 6 month follow up, the patient had returned to neurologic baseline, with improvement in school and physical therapy performance. Post-operative imaging at 3 and 6 months showed improving ventricular caliber and stable drainage of the shunt system.

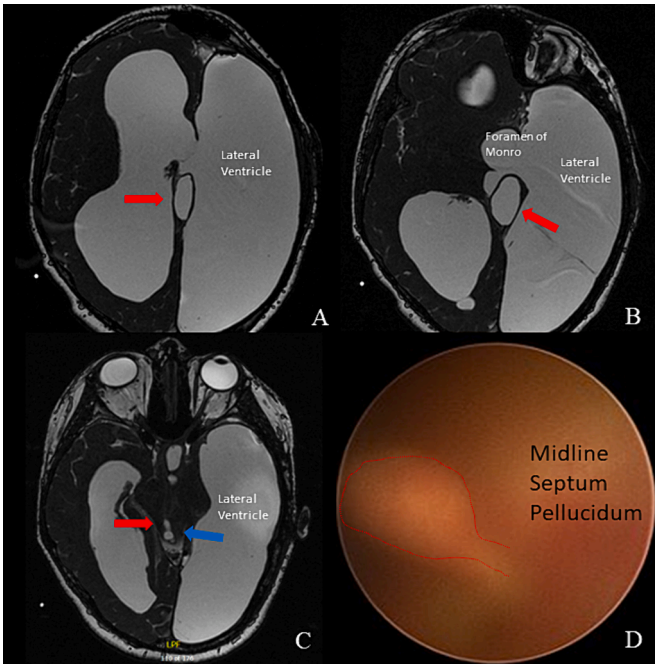

Fig. 1. (A-C) High-resolution constructive interference in steady state (CISS) gradient-echo sequences shows formation of a postoperative obstructive cyst (red arrows) at the origin of the cerebral aqueduct (blue arrow) with patent communication of the lateral and 3rd ventricles. (D) Endoscopic findings during attempted third ventriculostomy show a membranized peduncle (outlined in red) in the cast of the previous intraventricular catheter, poorly visualized through the cloudy CSF. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Discussion

There are few reports of aseptic inflammatory presentations of hydrocephalus previously published. This case may represent an extreme manifestation of a common underlying inflammatory mechanism leading to the development of hydrocephalus in patients undergoing cerebral hemispherectomy.

Superficial cerebral hemosiderosis (SCH) is a rare condition that results from chronic microhemorrhage and deposition of hemosiderin into subpial regions of the brain, cranial nerves and spinal cord [2]. Persistent bleeding overwhelms the chelation of free iron in the CNS and eventually leads to inflammatory neurotoxicity resulting in cognitive decline, cranial neuropathies, ataxia, and in some cases hydrocephalus [2]. In our experience with anatomical hemispherectomy, a procedure which exposes the ventricular system to significant blood and has been associated with the development of SCH, we have noted the formation of membranous cysts within the hemisphere following surgery. When the dominant cyst is walled off from the functional ventricle in the contralateral hemisphere, typically the secretory process remains limited to the resection cavity with limited pathological consequence [3]. When the cyst communicates with the choroid plexus or form below the foramen of Monro, the pathologic process results in hydrocephalus. Despite the limited findings of hemosiderin deposition on MRI, xanthochromic CSF appearance, pro-inflammatory profiles found on CSF analysis, along with extensive membranous formation throughout the ventricular cavity leads us to believe that the etiology of the inflammatory hydrocephalus was the result of SCH [2].

Anakinra is an IL-1 receptor antagonist which inhibits the inflammation driven by IL-1β. The low molecular weight allows for favorable blood–brain barrier penetration. It is reported effective in the treatment of inflammatory epilepsy and cerebral autoinflammatory syndromes [4]. Anakinra is administered as a subcutaneous injection with limited side-effects and is generally well tolerated by patients. Limited data exists on the optimal use and indications for anakinra therapy in hypersecretory inflammatory hydrocephalus, though prior studies have demonstrated that anakinra decreases CSF pleocytosis, opening pressure, protein, and pro-inflammatory cytokine levels [4]. Similar findings were seen in this case as the patient's hyperproteinosis improved following anakinra initiation. We plan to trend CSF inflammatory markers and protein levels as a guide in reducing dosage of anakinra for our patient in the future.

There is an association between the incidence of hydrocephalus and aseptic meningitis [1]. We hypothesize that suppressing inflammatory milieu via immunomodulation following hemispherectomy surgery could have benefit in limiting the exposure of the ventricular system to oxidative stress and the sequelae of chronic inflammatory structures such as hemorrhagic membranes. Targeted suppression of the immune system based off abnormal cytokine panels and inflammatory markers may optimize therapy while reducing unintended complications. A better understanding of the beneficial role of immunosuppressive therapy is needed to better understand the relationship between neuroinflammation and improving outcomes following epilepsy surgery. Finally, further investigation into the predictive value of CSF inflammatory markers for impending hydrocephalus may allow for better management and surveillance of patients recovering after surgical hemispherectomy.

CRediT authorship contribution statement

Akshay Sharma: Writing – original draft, Data curation, Conceptualization. **Efstathios Kondylis:** Writing – review & editing, Data curation, Conceptualization. **Shaarada Srivatsa:** Writing – review & editing, Data curation, Conceptualization. **Nehaw Sarmey:** Writing – review & editing, Data curation, Conceptualization. **Deepak Lachhwani:** Writing – review & editing, Supervision, Conceptualization. **Laura Nedorezov:** Writing – review & editing, Supervision,

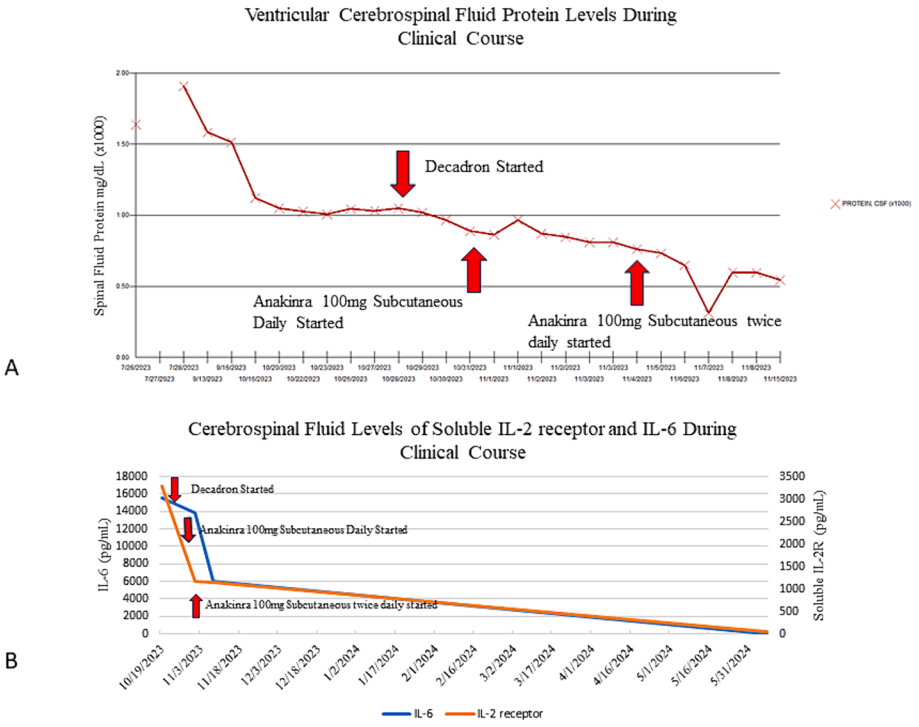

Fig. 2. Prior to administration of any immunosuppressive therapy protein levels remained above 1000 mg/dL in the CSF, and IL-6 and soluble IL-2 receptor were markedly elevated. High dose dexamethasone (13 mg oral twice daily) was started initially and after limited response, additional immunosuppression with Anakinra was added. Following optimization of dosing of anakinra to 100 mg subcutaneously twice daily, significant therapeutic response in the CSF protein level (A) and (B) IL-6 and IL2R were recorded. Steroids were tapered off over 4 weeks following the increase of Anakinra.

Investigation, Formal analysis, Data curation, Conceptualization. **William Bingaman:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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