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Clinical Note: Spontaneous intracranial hypotension-hypovolemia associated with tacrolimus

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Abstract

There is little precedent for a medication-induced spontaneous intracranial hypotension/CSF hypovolemia (SIH). This case history of a woman with low CSF pressure, orthostatic headache, and radiographic findings consistent with SIH but without a detectable leak was notable for its association, both onset and resolution, with the use of the calcineurin inhibitor tacrolimus (FK506). A literature review for potential causes of a tacrolimus-induced CSF hypotension suggests many potential mechanisms of action, including effects on blood brain barrier and dural compliance, and supports further vigilance for this condition in the medically complex setting of tacrolimus use.

Keywords

headache; low pressure syndrome; tacrolimus

Introduction

Spontaneous intracranial hypotension-hypovolemia (SIH) is a disorder of intracranial cerebrospinal fluid (CSF) hypovolemia^{1–3}. The common clinical presentation of SIH is orthostatic headache, including the prompt onset of dull head pain upon arising from sitting or lying down, usually with prompt resolution of pain upon recumbency. Clinical investigation of SIH is notable for a low opening pressure on lumbar puncture, is usually accompanied by a constellation of MRI findings, including diffuse dural enhancement, dural venous dilatation, and a sagging appearance of the posterior fossa structures with flattening of the pons. The clinical spectrum of SIH is variable, and can be life-threatening⁴. A high-volume lumbar autologous epidural blood patch is often curative, even without a clear localization of the leak, but a more localized approach is thought to increase the likelihood of successful treatment. CT myelography, and more recently MRI myelography, can localize the presumptive CSF leak, which is most commonly found at the mid-thoracic spine, in

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association with an arachnoid cyst, an incompetent nerve root sleeve, a ventral transdural osteophyte, or herniated disc⁵. Occasionally an open surgical procedure is necessary to close the dural defect. However, in a significant number of patients, despite detailed imaging studies and clinical features of SIH, no apparent CSF leak is detected. We present such a case of SIH/CSF hypovolemia, notable for its marked association with tacrolimus.

Case report

This 50-year-old woman, notably without a prior headache history, underwent orthotopic cadaveric liver transplant, and concurrently started tacrolimus immunosuppression. Within two weeks of the transplant, in the setting of normalizing markers of liver function, the patient had the new onset of a dull orthostatic headache. Notably, and with a similar onset, the patient had the new onset of episodic headache attacks, characterized by throbbing holocephalic head pain accompanied by nausea, vomiting, photophobia, phonophobia, and exacerbation of pain with exertion. Despite the resolution of the orthostatic headache within 8 months, these acute episodic attacks remained severe and frequent, three or more times per week, with a consistent response to rizatriptan.

The referring neurologist noted the hallmarks of SIH on MRI of the brain, but radionuclide cisternography did not provide evidence for a leak. Two presumptive autologous lumbar epidural blood patches produced marked but only temporary reduction of the frequent migrainous headaches. Repeat MRI of the brain at our institution revealed the persistence of diffuse dural enhancement, dural venous dilatation, and a flattened pons (Fig. 1A). MRI of the entire spine did not localize a dural lesion suggestive of a CSF leak. Upon CT myelogram of the spine an opening pressure of 0 mm of water was obtained, verifying an abnormally low pressure, but failed to detect extradural extravasation of contrast, even after delayed imaging. On successive studies, three repeated high-volume autologous epidural blood patches at the lumbar, thoracic, and cervical levels provided extended but only temporary headache-free periods of 4–8 weeks.

We hypothesized that the myelogram failed to localize the leak because there was insufficient pressure within the dural sac to move contrast, and infused Elliot's B artificial CSF through an intrathecal catheter, immediately prior to concurrent radionuclide cisternography and CT myelography. Bolus infusions of artificial CSF restored normal pressure only after a total volume of 40cc, and whose pressure-volume curve was suggestive of a functional hypovolemia (Figure 1C). However, neither cisternography nor myelography localized the leak, and a large volume epidural blood patch again only temporarily reduced the headache frequency, and did not result in any interval changes on repeated MRI of the brain.

The patient was medically managed with caffeine and vitamin A for an additional 10 months without a change in her episodic headaches, until the patient's immunosuppression was switched from tacrolimus to mycophenylate mofetil. The patient's headache attacks promptly became less frequent, and resolved completely within two months. At six months after the withdrawal of tacrolimus, MRI of the brain showed substantial normalization of the

meningeal enhancement and other structural changes noted above (Fig. 1B). There have been no further headaches in the subsequent three years.

Discussion

Although orthostatic headache is not always present in SIH² it was an early and prominent feature of this patient's headache. When present, the orthostatic aspect of the headache often gradually declines despite the persistence of the underlying hypotension-hypovolemia. Here, the persistence of abnormally low CSF opening pressures and characteristic hallmarks of SIH on MRI of the brain were clearly documented, even after the resolution of the orthostatic sign. The enduring feature of this woman's headache and associated SIH were frequent episodic attacks consistent with the diagnosis of migraine without aura, which is also common in this condition². In addition, remissions from the migrainous attacks following epidural blood patch is highly consistent with the relationship of these attacks to the SIH. The infusion of artificial CSF prior to diagnostic myelogram revealed a pressure-volume curve (Fig. 1C) that confirmed a functional under-filling of this CSF-filled space.

Headache is a common side effect of tacrolimus immunosuppression⁶, and its evaluation is particularly challenging because it occurs amidst a host of potential causes for neurological complications after transplantation⁷, and tacrolimus-related encephalopathy and long term cognitive changes are well-documented⁸. Moreover, in the perioperative setting of compromised hepatic function the presence of intracranial *hypertension* is the more common finding, and would obscure the existence of a more subtle opposing effect by tacrolimus.

If present, there are several potential mechanisms underlying a tacrolimus-induced CSF hypovolemia. Tacrolimus interacts with a large family of conserved proteins called immunophilins, which are implicated in a broad range of biochemical processes, including protein folding, receptor signaling, protein trafficking, and transcription⁹. Tacrolimus forms a complex with the major immunophilin, FK506-binding protein (FKBP), and inhibits calcineurin, a key signaling enzyme in T-lymphocyte activation¹⁰.

Because the immunophilins and calcineurin are both present at high levels in discrete regions of the brain¹¹, it is presumed that the CNS effects of tacrolimus act through one of the many potential actions of these proteins. There are many potential mechanisms, including an increase in cerebrovascular tone¹², a change in blood brain barrier function¹³, or a suppression of nitric oxide production^{6, 14}. Direct modes of action of tacrolimus could include the inhibition of CSF production, the facilitation of its absorption, or a change of vascular tone that could cause a subtle disruption of the CSF compliance of the thecal sac around the spinal cord.

Conclusions

This single-case association of SIH with tacrolimus is purely hypothetical, as many cases of SIH arise and resolve spontaneously without a detectable leak. However, the onset and resolution of the headache and MRI findings coincide remarkably with the start and discontinuation of tacrolimus. Although our current understanding of the mechanism of tacrolimus action does not explain its association with SIH/CSF hypovolemia, we suggest it

is important to consider the potential role of tacrolimus and other medications when evaluating a patient with this condition.

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Figure 1.

(A) Sagittal T1WI without contrast demonstrates effacement of the pre pontine cistern, downward displacement of the floor of the third ventricle, mamillary bodies, and cerebellar tonsils, as well as horizontal orientation of the infundibular stalk of the pituitary gland. Note compression of the basilar artery by the pons. Prominence of the dural venous sinuses is also present. Inset: Coronal T1 with gadolinium demonstrates diffuse dural enhancement and subdural effusions. These findings are consistent with intracranial CSF hypovolemia (SIH). (B) Sagittal T1WI MR without contrast, twenty-two months following initial scans, and 6 months following withdrawal of tacrolimus, demonstrates a normalization of the downward displacement seen in multiple prior studies. Inset: Coronal T1 with gadolinium demonstrates marked resolution of the dural enhancement and subdural effusion. (C) Pressure volume curve during the infusion of Elliot's B artificial CSF prior to CT myelogram and radionuclide cisternography. A slow overnight infusion at 15 cc per hour for 10 hours did not markedly change CSF pressure, but bolus infusion of 10 cc and 30 cc of CSF demonstrated a pressure-volume relationship consistent with a functional hypovolemia.