



Fulminant acute disseminated encephalomyelitis in renal transplant patient treated by decompressive craniectomy: a case report

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Abstract

Background: Acute disseminated encephalomyelitis (ADEM) is a rare demyelinating disease of the central nervous system that most commonly afflicts children and young adults and may be rarely seen in renal transplant patients. Most cases resolve with medical management; however, in some instances, the initial episode may evolve into a fulminant illness with malignant cerebral edema and elevated intracranial pressure that can result in a herniation syndrome with possible fatal consequences. Immediate relief of intracranial pressure is a priority and medical therapies alone may not suffice or may be precluded by compromised renal function.

Case description: A case is presented of fulminant ADEM in a pediatric renal transplant patient associated with intracranial hypertension and an acute herniation syndrome with rapid neurological decline that was effectively treated with a decompressive craniectomy. The procedure was life-saving and resulted in a favorable outcome without inflicting any additional morbidity.

Conclusion: Decompressive craniectomy is an effective way to rapidly reduce intracranial pressure in patients with malignant cerebral edema associated with fulminant ADEM and rapid neurological decline.

Keywords: ADEM, cerebral edema, herniation, renal transplant, craniectomy

Introduction

Acute disseminated encephalomyelitis (ADEM) is an acute post-infectious demyelinating disorder involving the white matter of the brain and spinal cord that commonly affects children or young adults of both sexes [1,2,20]. Although rare, ADEM may be seen in organ transplant patients on chronic immunosuppressive therapy [3]. The first case of ADEM after renal transplantation was reported in 1998 [4].

The diagnosis of ADEM is made by the temporal relationship between the onset of acute neurological deficits or encephalopathy and a recent illness or vaccination, and the presence of diffuse, non-confluent, white matter abnormalities in the brain and spinal cord [5,20]. A prodrome of fever, headache, nausea, and vomiting just prior to neurologic decline is usually

seen, but in approximately 20-30% of patients, this may be absent [1,5-8,20]. Presentation of ADEM varies depending on location of the lesions; Motor weakness, sensory loss, cranial nerve palsies, optic neuritis with visual loss, speech deficits, spinal cord or pyramidal signs, and mental status changes have been reported, and symptoms evolve over a period of hours to days [1,20].

At times, a fulminant form of ADEM with intracranial hypertension may occur heralded by increasing drowsiness or somnolence. We describe a child who had previously undergone renal transplantation who developed fulminant ADEM with rapid neurological decline associated with significant mass effect on cranial imaging studies. An emergent decompressive craniectomy was effective in rapidly reducing intracranial

pressure and proved life-saving.

Case presentation

This 6-year-old right-handed boy underwent bilateral nephrectomies and successful cadaveric renal transplantation for end stage renal disease secondary to focal segmental glomerulosclerosis. He was on chronic immunosuppressive therapy with twice a day dosing of cyclosporine 100 mg, tacrolimus 0.5 mg, and mycophenolate 420 mg. He presented approximately one year after transplantation with bilateral lower extremity weakness and urinary retention. He had no visual complaints or symptoms or signs suggestive of elevated intracranial pressure. Craniospinal axis MRI demonstrated several non-confluent, T2-hyperintense supratentorial lesions with mild edema but no mass effect (**Figure 1A**). Similar lesions were noted within the central gray matter of the spinal cord extending from T4 to the conus medullaris. Lumbar puncture opening pressure was not recorded. Analysis of CSF was significant for oligoclonal bands, elevated myelin basic protein, Mycoplasma pneumonia IgM and IgG, and Coxsackie virus A/B antibodies; other parameters included Glucose 62 mg/dL, Protein 108 mg/dL, white blood cell count 49 cells/ μ L and red blood cell count 31,010 cells/ μ L. A provisional diagnosis of ADEM was made based on clinical presentation, laboratory and imaging findings. He was treated with intravenous (IV) methylprednisolone followed by oral prednisone taper over 3 weeks and responded well with recovery of lower extremity and bladder functions. On examination, he was noted to have near normal strength in his lower extremities, mild residual ankle clonus and mild spasticity of gait.

Two months later, he presented with an acute decline in his level of alertness associated with bilateral lower extremity weakness, loss of bowel and bladder control, and somnolence. He was intubated. Cranial magnetic resonance imaging (MRI) demonstrated multiple supratentorial lesions with pronounced edema and mass effect with evidence of subfalcine herniation (**Figure 1B**). On examination, he had pinpoint, non-reactive pupils, and only moved his extremities to painful stimulus. The rapid decline in his neurological status prompted the need for urgent intervention. Given his prior history of renal transplantation and the significant mass effect noted on his cranial imaging studies, a decision was made to perform a decompressive craniectomy.

An emergent bifrontal craniectomy revealed a tense dura which was opened to reveal swollen edematous frontal lobes that herniated out rapidly through the dural opening. A right frontal corticectomy allowed biopsies of leptomeninges, white and gray matter in a region of MRI abnormality. The dura was closed in a loose, patulous fashion with a pericranial graft and the bone flap stored for later replacement. Pathology findings revealed loss of myelin and numerous CD68 positive macrophages with focal perivascular and parenchymal lymphocytes (CD3/CD5>>CD20) consistent with ADEM. No viral, fungal, or bacterial pathogens were detected.

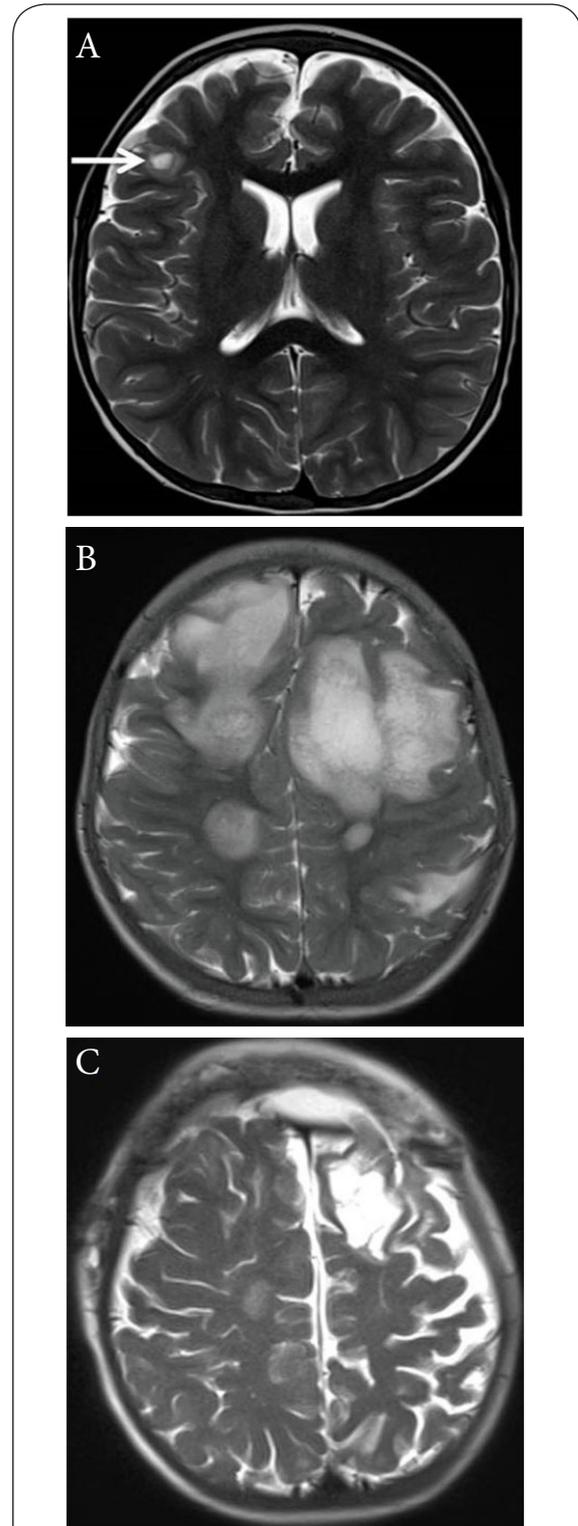


Figure 1. Craniospinal axis Magnetic Resonance Imaging. (A) Several non-confluent, T2-hyperintense supratentorial lesions with mild edema but no mass effect. (B) Multiple supratentorial lesions with pronounced edema and mass effect. (C) Resolution of the cerebral edema and intracranial abnormalities.

Following surgery, his neurological examination gradually improved. A week after surgery, following extubation, he was awake and alert with equal and reactive pupils and moved all four extremities well. He received five days of IV Methylprednisolone (225 mg twice a day) followed by 36 days of tapered oral Prednisolone. At one year from surgery, he was doing well with a normal neurological examination and resolution of the cerebral edema and intracranial abnormalities (**Figure 1C**).

Discussion

Acute disseminated encephalomyelitis (ADEM) is an auto-immune-mediated disorder characterized by an inflammatory response affecting the subcortical and deep white matter and occasionally the gray matter, particularly the thalami and basal ganglia [1,20]. The presentation commonly follows an episode of infection, predominantly of the upper respiratory tract; ADEM has been associated with viral and bacterial illnesses as well as following vaccinations [1,2,5,20]. The diagnosis is based on a variety of neurological and radiological findings as defined by the International Pediatric Multiple Sclerosis Study Group [1,20]. The pattern of distribution of lesions on MRI studies in ADEM and multiple sclerosis is distinct [2,12]. Lesions in ADEM tend to spare periventricular areas which are characteristically affected with multiple sclerosis. In addition, lesions in ADEM have an asymmetric distribution unlike the diffuse and symmetric pattern frequently observed in a variety of leukodystrophies and toxic leukoencephalopathies [2,12]. Spinal cord involvement in ADEM ranges from 25% to 80% [1,12]. Patients present with signs of myelopathy and thoracic spinal cord involvement is most common [2,8]. Fulminant ADEM presents with more acute symptoms ranging from behavioral changes, confusion, and irritability to altered mental status and coma. Our patient presented with fulminant encephalopathic symptoms two months after his initial presentation with spinal cord dysfunction. This second episode was distinct in time and anatomical region of the CNS that was involved; it therefore met criteria for multiphasic ADEM [1,2,5,20].

The pathogenesis of ADEM is presumed to be an inflammatory process affecting the central nervous system (CNS) secondary to direct inoculation by a neurotropic pathogen or due to an auto-immune response. This mimics animal models of experimental autoimmune encephalomyelitis, with short amino-acid epitopes of viral or bacterial pathogens resembling host myelin proteins instigating the attack [1,5,8]. Chronic immunosuppression following organ transplantation is usually achieved with steroids, or medications such as tacrolimus, cyclosporine and mycophenolate mofetil. Immunosuppressant drugs increase the risk of viral or bacterial opportunistic infections of the CNS and are associated with aberrant T-cell reactivity against myelin basic protein. Tacrolimus is a calcineurin inhibitor and has been associated with adverse neurotoxic side-effects including weakness, ataxia, seizures, psychosis

and posterior reversible encephalopathy syndrome (PRES) following transplantation [10]. It disrupts the blood-brain barrier affecting permeability by endothelial damage leading to vasogenic edema, vasoconstriction and microangiopathy [10].

Treatment of ADEM generally consists of supportive therapy and intravenous corticosteroids during the acute phase transitioning to oral corticosteroids tapered over 3-6 weeks. Both IV methylprednisolone (10-30 mg/kg/day up to maximum dose of 1g/day) and IV dexamethasone (1 mg/kg/day) have been used over a period of 3-10 days; then switched to oral prednisolone (1-2 mg/kg/day) or deflazacort (3 mg/kg/day) for an average of 10 days followed by 4-6 week taper [8]. Most patients respond within a few days and require no further intervention. In cases of poor or no response to steroids, the next step in management of ADEM is intravenous immunoglobulin (IVIG, 0.4 g/kg over 5 days), followed by plasmapheresis. Immunosuppressive therapy with cyclophosphamide and mitoxantrone has been reported in severe cases of adult ADEM [1,5,6,8,11]. With treatment, resolution of lesions is noted in 37-75% of patients and careful follow up for at least five years is recommended [8,12].

Hyperacute variants of ADEM, which represent 2% of cases, are associated with rapid symptom progression, malignant brain edema, and high mortality rates [1,5]. Patients present with irritability and headache that progresses to stupor, decerebrate rigidity, coma, respiratory failure, or death due to herniation from severe intracranial hypertension [9,13,14]. The initial management consists of intubation and controlled ventilation, elevation of the head of the bed, administration of analgesics, sedatives and paralytics, and IV mannitol (1 gm/kg) with placement of an ICP monitor. Mannitol is an osmotic diuretic administered as a hypertonic solution that is used to treat intracranial hypertension [15]. Generally, it is freely filtered by the glomerulus and does not undergo tubular reabsorption. However, in patients with compromised renal function, it may be retained in the circulation leading to extracellular fluid volume expansion, dilutional hyponatremia and metabolic acidosis, and hyperkalemia. Doses in excess of 200-300 grams/day may also precipitate acute kidney injury and failure [15].

Intracranial hypertension refractory to these measures requires either induction of electroencephalogram burst suppression with barbiturate administration, or surgical decompression. Barbiturates may cause hypotension or cardiovascular and respiratory collapse and have limited use in patients with compromised renal function. Decompressive craniectomy provides instant relief of intracranial hypertension with minimal morbidity [16]. In this procedure, a large area of calvarial bone is removed and stored for future replacement. The dura is opened and reclosed with a large patulous auto-logous or synthetic graft. At times, if the brain is significantly swollen and herniating out of the bony opening, infarcted cerebral tissue is evacuated or a portion of the frontal and temporal cortex removed [16]. It is effective in rapidly reducing intracranial hypertension associated with ischemic cerebral

infarction, intracerebral hemorrhage, post-traumatic cerebral edema, subarachnoid hemorrhage, and post-inflammatory cerebral edema [16]. It is relatively simple to perform and is not associated with significant risks or complications. The effectiveness of decompressive craniectomy with hyperacute forms of ADEM has been reported [7,17-19]. It is particularly effective in acute neurological deterioration associated with significant mass effect and brain herniation, particularly in patients with compromised or at risk renal function, in whom the use of osmotic diuretics or other measures to control intracranial pressure may be limited. It is safe and effective and replacement of the cranial bone flap can be easily accomplished after the acute cerebral edema has subsided.

In the case described in this report, the patient had a precipitous decline in his neurological status associated with significant progression of the intracranial lesions and increased mass effect with evidence of subfalcine herniation. While standard measures to combat elevated intracranial pressure may be considered, the acuity of the situation demanded immediate intervention and the decompressive craniectomy was very effective in this regard. In addition, it did not subject his renal function to any risk from infusions of mannitol, and obviated the need to administer other medications such as barbiturates that may have compromised his renal function further. With resolution of his intracranial hypertension, the bone flap was replaced uneventfully and he made an excellent recovery.

Conclusion

Fulminant ADEM is an acute demyelinating CNS disorder that can be seen in renal transplant patients and have fatal consequences despite medical management particularly in patients with significant intracranial edema and mass effect. With rapid neurological decline and clear evidence of mass effect and herniation on cranial imaging studies, neurosurgical intervention in the form of a decompressive craniectomy and duraplasty can be life-saving. It is particularly effective in instances where medical management of intracranial hypertension may be precluded by compromised or at-risk renal function. The immediate relief of intracranial hypertension maximizes the likelihood of a better functional outcome and should be considered in these circumstances.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	DS	DVD	MS	AWB	ES	VCP
Research concept and design	✓	✓	✓	✓	✓	✓
Collection and/or assembly of data	✓	✓	✓	--	--	--
Data analysis and interpretation	✓	✓	✓	--	--	--
Writing the article	✓	✓	✓	✓	✓	✓
Critical revision of the article	--	--	--	✓	✓	✓
Final approval of article	✓	--	--	--	--	✓
Statistical analysis	--	--	--	--	--	--

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