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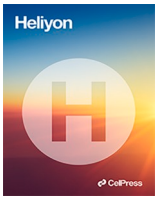

Case report

Organ donation after brain death from autoimmune glial fibrillary acidic protein astrocytopathy: A case report

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ABSTRACT

Background: No reports of organ donation have been documented in patients suffering from severe autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy.

Case presentation: A 27-year-old male patient developed a fever and headache, followed a week later by weakness and unsteadiness in his limbs. He attended his local hospital, but no cause was found. Thirteen days later, he became unconscious and was promptly moved to the intensive care unit for symptomatic support treatment, with no improvement. He was then transferred to our hospital, where he suffered a cardiac arrest on the same day. The family abandoned treatment and opted for organ donation, for financial reasons. Cell-based assays demonstrated GFAP antibodies in the cerebrospinal fluid. Two kidney recipients and one liver recipient showed no abnormal reactions 15 months after receiving organ transplants.

Conclusions: We report a case of organ donation following brain death in a patient diagnosed with GFAP astrocytopathy, highlighting the need for vigilance regarding the potential occurrence of cardiac arrest in patients with this condition. Considering the potential of GFAP astrocytopathy is crucial when observing deteriorating symptoms, seizures, and consciousness disturbances subsequent to a suspected viral infection. Successful organ donation from patients with GFAP astrocytopathy may be feasible given the exclusion of systemic infection and the absence of peripheral organ involvement.

1. Introduction

Autoimmune astrocytopathy, specifically linked to glial fibrillary acidic protein (GFAP), is characterized by the detected presence of GFAP autoantibodies within the central nervous system [1]. Common clinical manifestations encompass fever, headache, involuntary movement, myelitis, encephalopathy and optic papillitis [1]. The current literature reports that patients with GFAP generally have mild disease and a favorable prognosis [1,2]. In contrast, severe disease is relatively rare, and no cases of organ transplantation from these patients have been reported. The possibility of organ transplantation for autoimmune diseases' donors is still under debate,

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and there is currently no unanimous consensus. In this study, we showcase an organ donation case of a patient diagnosed with GFAP astrocytopathy.

2. Case presentation

2.1. Organ donor medical history

A 27-year-old previously healthy male patient presented with nausea and vomiting and headache after a rain shower. He developed a fever of 39 °C the next day, followed by gradual onset of limb weakness and unsteadiness within 3 days. He was admitted to the local hospital on the fifth day of illness. Cerebral computed tomography (CT) findings were unremarkable, but cranial magnetic resonance imaging suggested inflammatory changes in the meninges and splenium of corpus callosum (Fig. 1A–D). The patient was immediately treated with acyclovir, dexamethasone, and mannitol.

The cerebrospinal fluid (CSF) examination revealed elevated intracranial pressure (>300 mmH2O), increased protein level of 2.48 g/L, and a high white blood cell count of 79 × 10^6/L, with normal glucose and chloride levels. No pathogens were identified in either the CSF or blood, but NGS including DNA and RNA detected Streptococcus pneumoniae (sequence number 12) in the sputum. One week later, the patient became unconsciousness with limb twitching and straightening, eye rolling and staring, teeth clenching, and intermittent apnea episodes, which resolved spontaneously after a few seconds. A repeat brain CT scan still showed no abnormal findings, but he was moved to the intensive care unit for further treatment. He received tracheal intubation with ventilator-assisted ventilation, acyclovir, ceftriaxone, dexamethasone, intracranial pressure reduction, and antiepileptic treatment. His heart rate exhibited frequent episodes of bradycardia, with a minimum rate of 10 beats per minute, often observed during nursing roll-ups and back pats. An electrocardiogram (ECG) indicated the presence of complete right bundle branch block, but bedside cardiac ultrasound showed no significant abnormality. He subsequently received isoprenaline and atropine, and his heart rate recovered to 80 beats/min. However, his level of consciousness gradually worsened to a moderate coma. The CSF pressure increased again (290 mmH_2O) and the CSF protein level reached 1.93 g/L. Repeat NGS still found no pathogens in the CSF. He was hospitalized for further treatment in our facility.

Examination revealed that the patient was in a comatose state, with no expression of pain despite pressure on the orbits. His bilateral direct and indirect light reflexes were absent, his left corneal reflex was blunted and right corneal reflex was absent. No limb muscle contraction was observed upon painful stimulation, accompanied by absent tendon reflexes in all four limbs. Additionally, the patient presented with bilateral negative Babinski signs in both lower limbs and positive meningeal stimulation signs. On the day of admission, the patient suffered two cardiac arrests, and arterial blood gas potassium tests showed levels of 5.0 and 4.3 mmol/L, respectively. A bedside ECG suggested complete right bundle branch block. His heart rate recovered to 90 beats/min within 2 min after

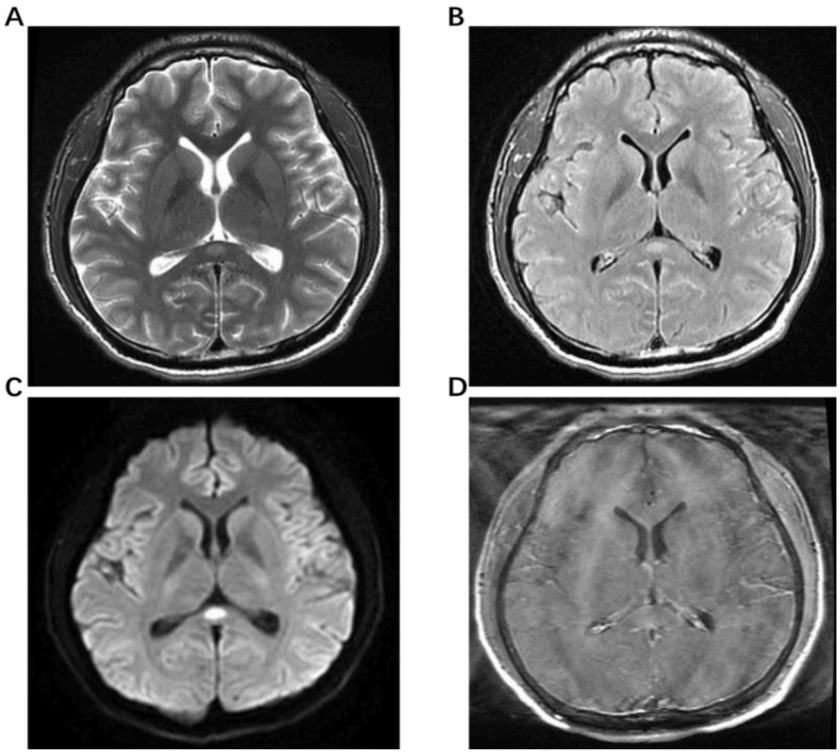

Fig. 1. Cerebral magnetic resonance imaging.

both cardiopulmonary resuscitation sessions. The following day, the patient's heart rate rose to 160–180 beats/min, and a bedside ECG showed atrial flutter and complete right bundle branch block, and a temporary bedside pacemaker was placed after communication with the family. On the third day, the patient's bilateral pupil dilatation was fixed and bilateral direct and indirect light reflexes, bilateral corneal reflexes, and head-eye reflexes had disappeared. Considering the patient's critical condition and poor prognosis and the family's poor financial situation, they chose to stop active treatment and were willing to donate the patient's organs.

Cranial CT angiography showed diffuse edema of the brain tissue, suggesting an inflammatory response, with no intracranial arterial visualization and poorly visualized veins. GFAP IgG antibodies were found in the CSF at a dilution of 1:32 using a cell-based assay, but were not detected in the serum (Fig. 2A–F). A tissue-based indirect immunofluorescence assay suggested a positive result in the CSF but not in serum, indicating fluorescent signals in cerebellar and hippocampal regions and significant astrocyte signals, indicating positivity for anti-GFAP antibody (Fig. 3A–D). Other IgG autoantibodies were tested in both the CSF and serum, including N-methyl-D-aspartatic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), gamma-aminobutyric acid subtype A (GABAA), gamma-aminobutyric acid type B (GABAB), aquaporin-4 (AQP4), myelin oligodendrocyte glycoprotein (MOG), ganglionic nicotinic acetylcholine receptor (ganglionic AChR), myelin basic protein (MBP), glutamic acid decarboxylase 2 (GAD65), dopamine receptor 2 (DRD2), leucine-rich glioma inactivated 1 (LGI1), and contactin-associated protein-like2 (CASPR2) were all negative. Oligoclonal bands were found in the CSF but were absent in the serum. No pathogens were detected in the CSF, alveolar lavage fluid, urine, or blood by NGS. Alveolar lavage fluid smears for antacid bacilli and rapid fluorescence staining for deep fungi, and Aspergillus tests were all negative.

Hospital Organ Procurement Organizations use the ABC-HOME assessment to evaluate patients for eligibility as potential organ donors. The patient was judged to be brain dead according to the Chinese Adult Brain Death Determination Criteria and Practice Guidelines, and organ harvesting was carried out according to standard protocols by the hospital surgeons. Two patients successfully received kidney transplants and one patient received a liver transplant.

2.2. Organ recipient medical history

The two kidney transplant recipients, aged 56 and 50 years respectively, suffered from chronic renal insufficiency in the uremic phase. Their pre-transplant blood creatinine levels peaked at 506 and 1002 μmol/L, respectively, and both had creatinine fluctuating from 118 to 191 μmol/L in the 15 months after transplantation, with regular anti-rejection medication. One recipient had a serum creatinine level of 191 μmol/L at the 13th month after transplantation, with no clinical discomfort; however, this was considered as an immune rejection response and anti-rejection treatment was intensified for 10 days. In this report, his serum creatinine fluctuated between 115 and 133 μmol/L.

A male patient who was 23 years old with hepatocellular carcinoma diagnosed 6 months previously due to anemia detected at a local hospital, received a liver transplant. His maximum alanine aminotransferase levels were 1082 U/L before transplantation and 84 U/L 1 week after transplantation, but increased again to 446 U/L 1 month later. He was readmitted to hospital with suspected acute rejection and was treated with tacrolimus 2.5–3 mg and liver protection. His alanine aminotransferase was maintained at 24–40 U/L over the following 15 months.

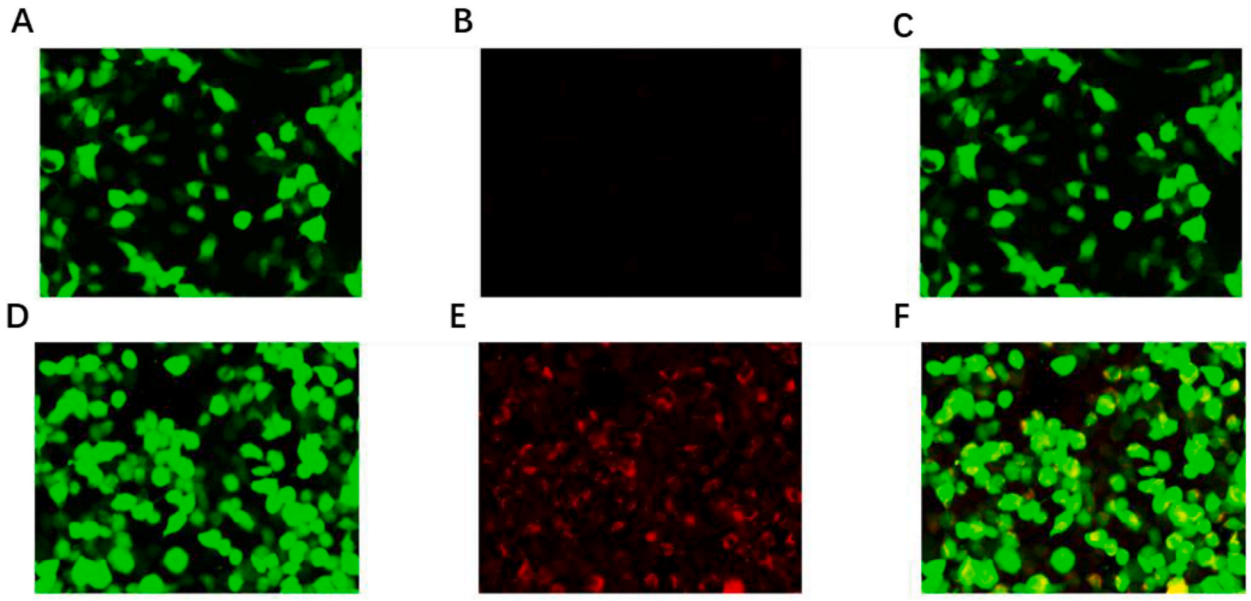

Fig. 2. GFAP by transfected cell-based assay in serum and CSF.

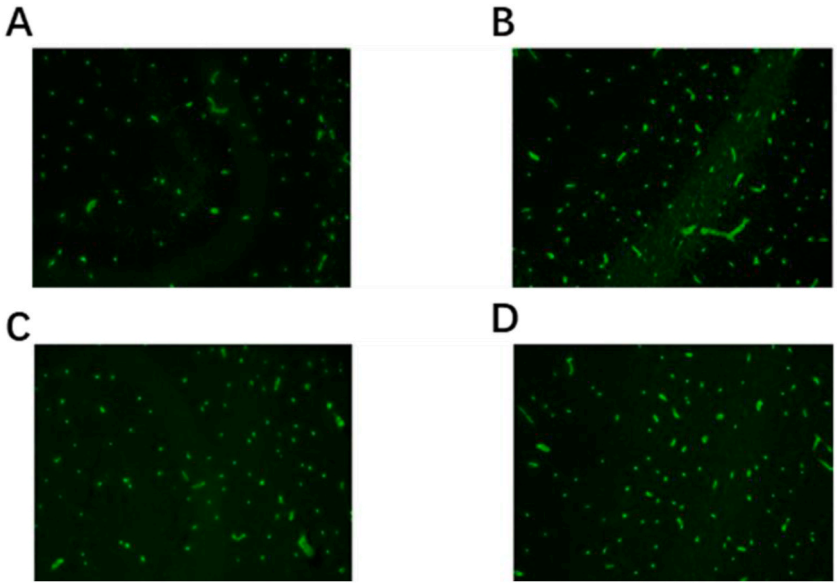

Fig. 3. GFAP by tissue-based indirect immunofluorescence assay in serum and CSF.

3. Discussion

At present, GFAP astrocytopathy lacks standardized diagnostic criteria. Generally, diagnosing GFAP astrocytopathy involves detecting GFAP antibodies in either the CSF or serum, serving as a biomarker for a distinctive form of corticosteroid-responsive autoimmune meningoencephalomyelitis, which occasionally presents as a paraneoplastic syndrome [1]. Several previous case reports have shown good results and prognosis of GFAP astrocytopathy following hormonal treatment [3,4]. The patient we report received a 7-day treatment at an external hospital, with daily intravenous injections of 10mg dexamethasone and 20g intravenous immunoglobulin. Due to rapid deterioration of the condition and unclear initial diagnosis, high-dose methylprednisolone therapy was not administered. Few cases of progressive exacerbation have been reported, but Allen et al. reported a patient who tested positive for GFAP and subsequently developed acute flaccid paralysis and respiratory failure [5]. We present a case of a patient who had multiple cardiac arrests resulting in fatality, which were inconsistent with the imaging findings. The patient's cardiac ultrasound, ECG, and electrolyte results did not support cardiac arrest due to heart disease, and we consider that autonomic dysfunction, caused by GFAP astrocytopathy, led to a brain–heart syndrome, which has not previously been reported. Yamamoto et al. presented a case study involving a child with GFAP astrocytopathy, who exhibited bradycardia without experiencing cardiac arrest [6]. Unfortunately, the patient suffered multiple cardiac arrests and had to have a temporary pacemaker implanted, and was unable to complete cranial magnetic resonance imaging to follow the evolution of the lesion. The current case highlights the need to treat GFAP astrocytopathy seriously and to be aware of the possibility of cardiac arrest, which may occur multiple times and require aggressive installation of a temporary pacemaker.

The reason why the current, previously healthy, young patient showed obvious signs of GFAP astrocytopathy after being caught in the rain remains unknown. Cheng and colleagues documented a case in which GFAP astrocytopathy developed after viral encephalitis, implying a potential association between viral infection and the development of GFAP astrocytopathy [2]. This association may stem from an immune response triggered by neuronal lysis and subsequent antigen release after viral infection [2,7]. Further studies are needed to investigate the susceptibility to GFAP astrocytopathy and its relationship with cardiac function. However, in this particular case, the deterioration of the patient's condition following a suspected viral infection, accompanied by symptoms such as seizures and consciousness disturbances, necessitated prompt investigation into the possibility of autoimmune encephalitis, such as GFAP astrocytopathy. Timely initiation of adequate steroid treatment was crucial.

Furthermore, in autoimmune GFAP astrocytopathy, typical brain MRI findings include lesions exhibiting linear or radial perivascular enhancement signals commonly observed in the cerebellum, basal ganglia, brainstem, meninges, and subcortical white matter. In our case, early MRI findings revealed inflammatory changes in the meninges and splenium of corpus callosum. There have been a few reports of cases of GFAP brain disease with Reversible Splenium of corpus callosum lesion (RESLES) [8,9]. RESLES typically presents as mild encephalitis/encephalopathy, associated with squamous cell carcinoma [8]. The mechanism of GFAP astrocytopathy associated with RESLES remains unclear but may be related to secondary changes following viral infection. Unfortunately, we were unable to obtain subsequent cranial MRI scans for the patient to dynamically observe changes in inflammation of the splenium of the corpus callosum post-treatment. In cases of GFAP astrocytopathy, it is crucial to closely monitor cranial MRI for changes in the region where the splenium region of the corpus callosum is located and investigate potential squamous cell carcinoma.

Furthermore, GFAP astrocytopathy typically presents as prodromal symptoms of viral infection, with intracranial pressure usually within the normal range. However, several reported cases of mild intracranial hypertension in GFAP astrocytopathy patients have been

noted. Fang et al. reported elevated cerebrospinal fluid pressure measuring 29.8 cm H2O in a GFAP astrocytopathy patient [10]. Chen et al. reported two cases of GFAP astrocytopathy patients with mildly elevated CSF pressures measuring 265 mmH2O and 298 mmH2O, concurrent with increased CSF cell count and protein levels [11]. These findings suggest a potential link between elevated CSF protein levels and increased intracranial pressure. Canissario described a case of GFAP astrocytopathy in a patient aged thirty-one, who presented with severe intracranial hypertension, revealing an opening pressure of 54 cmH2O during lumbar puncture, accompanied by lymphocytosis and heightened protein levels [12]. Despite the link between autoimmune encephalitis and elevated intracranial pressure, the exact underlying mechanism remains unclear, with proposed mechanisms including inflammatory disruption of cerebrospinal fluid reabsorption [12]. Our patients did not exhibit communicating hydrocephalus on MRI imaging. However, they presented with elevated CSF pressure, increased protein, and cell count during their hospital admission. This suggests a potential correlation between these factors and increased intracranial pressure, warranting further research into the underlying causes of intracranial hypertension in these cases.

GFAP IgG identifies a distinct autoimmune meningoencephalomyelitis that is responsive to corticosteroids, with occasional paraneoplastic features. Although rare, there is a potential risk of transmitting severe illness from donors who have succumbed to meningitis or encephalitis to recipients with compromised immune systems during transplantation [13,14]. However, there have been many cases of successful transplantations after anti-infective treatment. Douchy et al. reported on the donation of solid organs following the donor's death from Listeria encephalitis, suggesting that donors should receive adequate antibiotics and sterile blood cultures should be confirmed as a prerequisite for donation [15]. In the present patient, NGS analysis of the CSF on three separate occasions revealed the absence of any detectable pathogens. Although Streptococcus pneumoniae was initially detected in sputum, it was not detected in alveolar lavage fluid, urine, or blood after anti-infective treatment. Moreover, we followed up the three transplant recipients and found no manifestations of underlying donor infection. We therefore recommend that patients with GFAP astrocytopathy may act as organ donors, after ruling out the possibility of infectious encephalitis or underlying systemic infection. Nevertheless, the organ functional status of the recipients still needs to be tracked and monitored to ensure their safety.

In addition, there is concerned about whether GFAP antibodies might affect extracerebral organs. The safety of organ donation from individuals with autoimmune diseases has always been controversial. A previous study reported that GFAP was a coimmunogen in certain occult neoplasms, such as lymphoma, driving immune responses against this antigen [1]. GFAP immunoreactivity has also been reported in some neoplasms, including carcinoid, pleomorphic adenoma of the salivary gland, teratoma, prostate cancer and melanoma [1,16–18]. Antibodies to tumor markers and blood and CSF tests for paraneoplastic syndrome were negative in the current patient. In addition, the surgeon performed a puncture biopsy of the organs to be transplanted prior to organ procurement, and no heterotypic cells were found in the biopsies. However, the recipients need to be observed for longer. In the current patient however, we carried out the corresponding autoimmune tests and found no abnormal results. In this case, we considered that the GFAP antibodies may not have involved extracerebral organs, but tumors and other autoimmune diseases still need to be strictly excluded prior to transplantation. The recipients of organs from this case thus still need to be monitored and followed-up to detect any secondary tumors.

4. Conclusions

We report a case of organ donation following brain death in a patient diagnosed with GFAP astrocytopathy, highlighting the need for vigilance regarding the potential occurrence of cardiac arrest in patients with this condition. Considering the potential of GFAP astrocytopathy is crucial when observing deteriorating symptoms, seizures, and consciousness disturbances subsequent to a suspected viral infection. Successful organ donation from patients with GFAP astrocytopathy may be feasible given the exclusion of systemic infection and the absence of peripheral organ involvement.

Ethics statement

Their proxies granted consent for publishing anonymized case details and images.

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Data Availability Statement

Data will be made available on request.

CRediT authorship contribution statement

Jinbiao Li: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Cunzhou Shen:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Yixin Chen:** Writing – review & editing, Writing – original draft,

Investigation, Conceptualization. **Huixing Zeng:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Liqian Cui:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Huiyu Feng:** Writing – review & editing, 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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