Case report

Antibody-negative autoimmune encephalitis as a complication of long-term immune-suppression for liver transplantation

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SUMMARY

Autoimmune encephalitis is a rare spectrum of disease that can be a complication of chronic immunosuppression. Diagnosis often requires the presence of antineuronal antibodies, but many causative antibodies have not yet been identified. Antibody-negative autoimmune encephalitis (AbNAE) is especially difficult to diagnose and must rely largely on exclusion of other causes. In chronically immune-suppressed transplant recipients, the differential is broad, likely resulting in underdiagnosis and worse outcomes. Here, we present a 58-year-old liver transplant recipient taking tacrolimus for prevention of chronic rejection who presented with 5 days of confusion, lethargy and lightheadedness. He was diagnosed with AbNAE after an extensive workup and recovered fully after high-dose corticosteroids. Our case highlights the importance of recognising the association between chronic immunosuppression and autoimmune encephalitis. Autoimmune encephalitis, even in the absence of characterised antibodies, should be considered when transplant recipients present with central neurologic symptoms.

BACKGROUND

Autoimmune encephalitis is a rare spectrum of disease usually associated with a viral central nervous system infection or underlying autoimmune disease. Associated symptoms include lethargy, focal deficits, seizures and changes in mentation and behaviour. Diagnosis often requires the presence of antineuronal antibodies, but many causative antibodies have not yet been identified. Antibody-negative autoimmune encephalitis (AbNAE) is especially difficult to diagnose and must rely largely on exclusion of other causes. In chronically immune-suppressed transplant recipients, the differential is broad, likely resulting in underdiagnosis and worse outcomes. Autoimmune encephalitis, even in the absence of characterised antibodies, should be considered when transplant recipients present with central neurologic symptoms, as early initiation of treatment results in better outcomes.

CASE PRESENTATION

A 58-year-old man presented with intermittent confusion, lightheadedness, lethargy and dizziness. The patient's wife reported episodes in which he forgot how to turn the lights off and forgot how to use a television remote, stating that episodes had occurred each of the last five nights. After sleeping, he returned to normal until the next evening. He was the recipient of a cytomegalovirus (CMV) positive, deceased donor liver transplant 14 years prior secondary to alcoholic cirrhosis and was maintained on tacrolimus for prevention of chronic rejection. The patient had recently made dietary and lifestyle changes due to hyperlipidaemia. He also had a sinus infection treated with amoxicillin 2 weeks prior. Other medical history included a single episode of autoimmune haemolytic anaemia (AIHA) triggered by vaccination, and a single episode of immune thrombocytopenic purpura (ITP) triggered by upper respiratory tract infection or antibiotic use. Both were refractory to steroids and required rituximab infusions but had completely resolved.

At presentation, he denied trauma, fevers, weakness or sensory changes. Physical examination revealed an alert and oriented, healthy appearing man with no focal neurological deficits. He had white, scaly patches on bilateral upper extremity extensor surfaces consistent with psoriasis. Following admission, he began having intermittent episodes of confusion which progressed to complete disorientation, inability to follow commands and agitation. He was noted to have an increased startle reflex and hyperreflexia but no nuchal rigidity or meningeal signs.

INVESTIGATIONS

Labs on admission were remarkable for a normal complete blood count, comprehensive metabolic panel with mildly low albumin (3.0) and bicarbonate level of 23.2. Tacrolimus level was 3.9 (goal 3–5) and erythrocyte sedimentation rate (ESR) was elevated (30).

Initial workup included normal thyroid stimulating hormone (TSH) and B12 levels and a negative urine drug screen. During an episode of confusion, blood glucose level was 96.

A normal CT of the brain was followed by an MRI of the brain under anaesthesia (figure 1), which revealed mild, hyperintense white matter lesions on T2 imaging of the anterior right putamen and periventricular white matter.

One-hour electroencephalogram (EEG) was performed showing mild, generalised, non-specific cerebral dysfunction without seizure tendencies and a slow, posterior dominant rhythm.

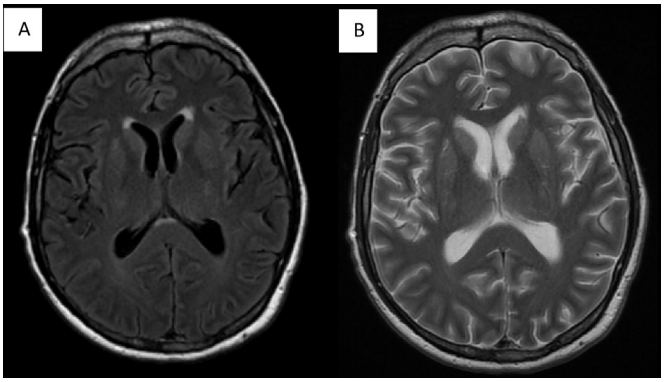

Figure 1 (A) MRI of the brain T2 fluid-attenuated inversion recovery (FLAIR) image showing hyperintense signal in the anterior aspect of the right putamen and periventricular white matter. (B) T2 fast spin echo (FSE) image.

Lumbar puncture returned colourless cerebrospinal fluid with elevated protein, IgG, albumin quotient and glucose, but infectious testing of blood and cerebrospinal fluid (CSF) was negative (table 1).

MRI of the abdomen revealed a non-specific early-enhancing lesion of the right lobe of the liver suspicious for a portosystemic shunt, but fasting arterial ammonia was normal. Serum protein electrophoresis revealed no paraproteinaemia and IgG subgroups were within normal limits.

The Mayo Clinic Laboratories Autoimmune Encephalitis Panel (ENC2) did not reveal antineuronal antibodies, but negative results do not preclude diagnosis of autoimmune encephalitis (table 2).

DIFFERENTIAL DIAGNOSIS

Central nervous system infection was highest on the differential list and we treated our patient empirically for viral encephalitis while awaiting test results. Viral, *Streptococcus*, *Cryptococcus* and toxoplasmosis testing were negative in serum and CSF.

Due to history of intermittent confusion, lifestyle and dietary changes, hemoglobin A1c (HbA1c) of 4.7% and liver transplant status, episodes of hypoglycaemic were suspected. Since transplanted livers are denervated, glucose homeostasis relies on circulating hormones and can cause slower corrections from hypoglycaemic than in patients with native livers.[1] During an episode of confusion, the patient's blood glucose was normal, and insulin and glucagon levels were within the normal ranges.

Acquired hepatocerebellar degeneration was also suspected, due to either the presence of graft dysfunction or a portosystemic shunt, which was considered on MRI of the abdomen. When paramagnetic metals such as manganese bypass biliary excretion, they can deposit in susceptible areas of the brain with similar pathogenesis to Wilson's hepatocerebral degeneration.[2–4] Our patient had normal protein and only mildly reduced albumin indicating a functioning graft. Furthermore, a portosystemic shunt was ruled out with a normal fasting arterial ammonia.

Hashimoto's encephalopathy was also on the differential since our patient's history of autoimmune disease and the clinical presentation were suggestive.[5] He had no antibodies against thyroperoxidase or thyroglobulin and had a normal thyroid stimulating hormone level.

Paraneoplastic limbic encephalitis due to onconeuronal antibodies from underlying malignancy is described similarly to

Table 1 Cerebrospinal fluid, metabolic and infectious laboratory findings

Test	Type	Serum	CSF	Reference
Cerebrospinal fluid			Colourless	Colourless
Red blood cells			0	0/HPF
White blood cells			1	0–5/HPF
Neutrophils			2%	0%–5%
Lymphocytes			0%	40%–80%
Monocytes			98%	0%–5%
Glucose			85	40–70 mg/dL
Lactic acid			24	10–22 mg/dL
Protein			133	15–45 mg/dL
Albumin			92	11–48 mg/dL
Qalbumin			23	<9
IgG			10.9	0–8.6 mg/dL
IgG index			0.5	0.00–0.70
Malignant cells			0	0/HPF
Oligoclonal bands			0	<4
Metabolic				
Glucose		93		<100 mg/dL
Hemoglobin A1c		4.70%		<5.7%
Insulin		8.8		Fasting <25 units/mL
Glucagon		107		50–150 pg/mL
8:00 cortisol		13		10–20 µcg/dL
TSH		1.85		0.50–5.0 µU/mL
Cholesterol		277		120–200 mg/dL
Triglycerides		260		10–190 mg/dL
Arterial ammonia		45		Fasting 9–55
Infectious testing				
HSV1	PCR	Negative	Negative	Negative
HSV2	PCR	Negative	Negative	Negative
Streptococcus pneumoniae	Antigen	Negative		Negative
CMV	IgM	Negative		Negative
CMV	IgG	Negative		Negative
CMV	PCR		Negative	Negative
Borrelia burgdorferi	Antibody		0.27	<0.99 Lyme index value
Cryptococcus	Antigen	Negative	Negative	Negative
Culture		Negative	Negative	Negative
Hepatitis B virus DNA	PCR	Negative		Negative
Human herpes virus 6	PCR	Negative	Negative	Negative
Varicella zoster virus	PCR		Negative	Negative
Eppestein-Barr virus	PCR		Negative	Negative
WNV	IgM		Negative	Negative
WNV	IgG		Positive	Negative
Coxsackie B1	Ab titre		<1:10	<1:10
Coxsackie B2	Ab titre		<1:10	<1:10
Coxsackie B3	Ab titre		<1:10	<1:10
Coxsackie B4	Ab titre		<1:10	<1:10
Coxsackie B5	Ab titre		<1:10	<1:10
Coxsackie B6	Ab titre		<1:10	<1:10
Coxsackie A2	Ab titre		<1:1	<1:1
Coxsackie A4	Ab titre		<1:1	<1:1
Coxsackie A7	Ab titre		<1:1	<1:1
Coxsackie A9	Ab titre		<1:1	<1:1
Coxsackie A10	Ab titre		<1:1	<1:1
Coxsackie A16	Ab titre		<1:1	<1:1

HSV, herpes simplex virus; CMV, cytomegalovirus; WNV, west Nile virus; HPF, high powered field

Table 2 Laboratory testing for autoimmune disease

Autoimmune testing	Type	Blood	Cerebrospinal Fluid	Reference
Erythrocyte sed rate	Serum	30		<10 mm/hour
Anti-Ro (anti–Sjögren's-syndrome-related antigen A)	Ab	<0.2		0–0.9 AI
Anti-La (anti–Sjögren's-syndrome-related antigen B)	Ab	<0.2		0–0.9 AI
Anti-thyroglobulin	Ab	<1.0		<1.0
Anti-thyroperoxidase	Ab	10		0–30
C3	Serum	108		80–150 mg/dL
C4	Serum	25		18–55 mg/dL
CH50	Serum	46		42–95 U/mL
Total IgG	Serum	985	10.9	700–1600 mg/dL (serum), 0.4–4.5 mg/dL (CSF)
IgG_1	Serum	444		248–810 mg/dL
IgG_2	Serum	402		130–555 mg/dL
IgG_3	Serum	58		15–102 mg/dL
IgG_4	Serum	35		2–96 mg/dL
Alpha 1 globulin	Electrophoresis	0.18		0.11–0.34 g/dL
Alpha 2 globulin	Electrophoresis	1.02		0.37–1.11 g/dL
Beta globulin	Electrophoresis	0.96		0.69–1.55 g/dL
Gamma globulin	Electrophoresis	1.24		0.73–2.00 g/dL
Aquaporin 4	Ab titre		Negative	Negative
MOG IgG_1	FACS		Negative	Negative
Mayo Clinic Laboratories Autoimmune Encephalitis Panel (ENC2)				
AMPA-R	Ab CBA		Negative	Negative
Amphiphysin	Ab titre		<1:2	<1:2
AGNA-1	Ab titre		<1:2	<1:2
ANNA-1	Ab titre		<1:2	<1:2
ANNA-2	Ab titre		<1:2	<1:2
ANNA-3	Ab titre		<1:2	<1:2
CASPR2	IgG CBA		Negative	Negative
CRMP-5	IgG titre		<1:2	<1:2
DPPX	Ab IFA		Negative	Negative
GABA-B-R	Ab CBA		Negative	Negative
GAD65	Ab		0.00	≤0.02 nmol/L
GFAP	IFA		Negative	Negative
LGI1	IgG CBA		Negative	Negative
mGluR1	Ab IFA		Negative	Negative
NMDA-R	Ab CBA		Negative	Negative
PCA-Tr	Ab titre		<1:2	<1:2
PCA-1	Ab titre		<1:2	<1:2
PCA-2	Ab titre		<1:2	<1:2

AGNA-1, antiglial nuclear antibody 1; AMPA-R, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antibody; ANNA, antineuronal nuclear antibody (ANNA-1 and 2 antibodies previously referred to as anti-Hu, anti-Ri, respectively); CASPR2, contactin-associated protein-like 2; CBA, antibody cell-binding assay; CRMP-5, collapsing response mediator protein-5; DPPX, dipeptidyl-peptidase-like protein 6; FACS, fluorescence activated cell sorting; GABA-B-R, gamma aminobutyric acid receptor type B; GAD65, glutamic acid decarboxylase 65-kd isoform; GFAP, glial fibrillar acid protein; IFA, immunofluorescence assay; LGI1, leucine-rich glioma-inactivated 1; mGluR, metabotropic glutamate receptor; MOG, myelin oligodendrocyte glycoprotein; NMDA-R, N-methyl-D-aspartate receptor; PCA, Purkinje cell cytoplasmic antibody types Tr, 1 and 2.

our patients presentation.[6] Diagnostic criteria proposed by Graus *et al* require a subacute onset, bilateral brain abnormalities highly restricted to the medial temporal lobes, at least one of the CSF pleocytosis or an EEG with epileptic or slow wave activity involving the temporal lobes, and reasonable exclusion of other causes, though the presence of specific antibodies is not required.[6] Our patient did not meet these criteria and obvious malignancy was excluded with a normal serum protein electrophoresis and benign MRI of the abdomen.

Posterior reversible encephalopathy syndrome (PRES) due to calcineurin inhibitor toxicity was considered, as it is well described after organ transplantation and is associated with significant morbidity. PRES is caused by alterations in brain perfusion secondary to excess endothelin production causing inappropriate vasoconstriction.[7] This causes disruption of the blood–brain barrier and increased leakage into the brain parenchyma, leading to hyperperfusion injury and free radical toxicity.[8 9] MRI shows subcortical white matter changes in the posterior cerebrum, which generally appear in the first month after transplantation.[7] Our patient had an MRI of the brain, which revealed white matter lesions inconsistent with PRES, and his tacrolimus level was within the desired range (3.9, goal 3.0–5.0).

Acute disseminated encephalomyelitis (ADEM) is a monophasic, multifocal demyelinating disorder precipitated by systemic infection. It is common in children and rare but reported in adults over the age of 40.[6 10] The clinical course includes the presence of encephalopathy and other new neurologic signs such as cranial nerve palsies and motor deficits, commonly haemiparesis.[6 10] Spinal cord involvement is common in adults and CSF typically shows mild pleocytosis, whereas our patient had normal CSF cell counts but elevated IgG.[6 10] While our patient's preceding history may have suggested ADEM, he did not meet MRI criteria with diffuse,

Box 1 Diagnostic criteria for antibody-negative autoimmune encephalitis[6]

- Rapid progression (<3 months) of memory deficits, altered mental status or psychologic disorders.
- Exclusion of limbic encephalitis, Birkerstaff's brainstem encephalitis and acute disseminated encephalomyelitis.
- Absence of well-characterised antineuronal antibodies in serum and CSF.
- Reasonable exclusion of other causes.
- two or more of the following:
  - MRI findings suggestive of autoimmune encephalitis.
  - Brain biopsy with inflammatory infiltrates.
  - one or more of:
    - CSF pleocytosis.
    - CSF oligoclonal bands.
    - Increased CSF IgG Index.

large, cerebral white matter lesions or deep grey matter abnormalities, which are required for diagnosis.[6] Therefore, we found another diagnosis to be most likely.

AbNAE was diagnosed using the criteria proposed by Graus *et al* (box 1). His clinical presentation was consistent with AbNAE, other causes were ruled out, and he met the required criteria with MRI findings of white matter lesions. Though his CSF IgG Index was within normal range at 0.50, (range 0.00–0.70) we believe the disease was diagnosed early in its course and his CSF IgG was elevated. Furthermore, his blood–brain barrier was disrupted as indicated by a high albumin quotient of 23 (normal <9). While his encephalitis antibody panel was negative, it is not all encompassing.[6 11–14]

TREATMENT

The patient was started on intravenous valacyclovir empirically while infectious studies were pending. After diagnosis of autoimmune encephalitis was made, he was started on intravenous methylprednisolone 1 g daily for 5 days followed by oral methylprednisolone taper from 60 mg daily for 6 weeks total duration. His tacrolimus was continued in hospital and at discharge.

OUTCOME AND FOLLOW-UP

By day 3 of high-dose steroids, the patient's mental status began to improve. He was able to follow commands but continued to have poor concentration and short-term memory loss. By day 5, he was functioning at his baseline and was discharged home after a 10-day hospitalisation.

Post discharge, the patient was followed by transplant hepatology and neuroimmunology. He remained asymptomatic and independent over the next 4 months.

DISCUSSION

To our knowledge, no other cases of AbNAE associated with chronic immune suppression for liver transplantation have been reported. In a literature search of autoimmune encephalitis related to immune suppression for liver transplant, two cases were identified. One involved a 69-year-old woman presenting with seizures. She was diagnosed with N-methyl-D-aspartate receptor (NMDAR) antibody-positive autoimmune encephalitis (AbPAE) refractory to treatment 10 years after transplantation and eventually died due to complications.[15] The other case involved a 61-year-old man 1 month post transplant with alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) AbPAE. He had complete recovery with plasmapheresis, rituximab, corticosteroids and transition from tacrolimus to cyclosporine.[16]

Rare cases have been reported of autoimmune encephalitis (AE) related to other solid organ or stem cell transplantation.[16–19] Including the liver transplant cases above, five out of six patients presented more than 6 years post transplant. Five out of six cases had Eppstein-Barr virus (EBV) DNA isolated in CSF, five patients were positive for anti-NMDAR antibodies, and one was positive for AMPAR antibodies. All six patients were maintained on mycophenolate with the addition of tacrolimus in five and methylprednisolone in one patient.

Treatment followed standard guidelines with steroids, plasmapheresis or immunoadsorption therapy as first line, followed by rituximab, then cyclophosphamide as last line treatment, and tumour removal indicated if a causative malignancy was found.[20]

Outcomes varied, with two patients dying from complications, one patient who had a mild cognitive deficiency at 3 months of follow-up, and three patients with complete recovery. Since our patient had required rituximab for refractory AIHA and ITP in the past, we suspected that escalation of therapy would be required. His family was consented for rituximab but he recovered fully with corticosteroids only.

AE is due to complement-independent antibody autoreactivity.[21] AE while on immune suppressants presents a clinical conundrum since the formation of autoantibodies should be limited.

Pathogenesis may result from long-term immune suppression causing an imbalance of B and T helper cell populations. The lack of proper immune regulation by T helper cells can predispose the development of B cells without immune tolerance.[15 21] Supporting this, our patient was on immune suppression directed only at T cells and his symptoms resolved with corticosteroids. His previous AIHA and ITP required specific anti-B-cell therapy.

The development of autoantibodies may be precipitated by an infection.[15 22] Most commonly identified are EBV and herpes simplex virus (HSV), though our patient had neither. His disease could have been precipitated by his sinus infection. Similarly, each of his previous events was precipitated by vaccination, infection or possibly his treatment with antibiotics.

This diagnosis of AbNAE is challenging for multiple reasons, and even more so in transplant patients. First, there is a range of non-specific presentations associated with autoimmune encephalitis that can lead to misdiagnosis and untimely treatment.[14] In a multicenter retrospective study of 118 patients diagnosed with AE, symptoms at onset varied even among phenotypic subgroups. Due to this, infectious encephalitis and seizure disorders were suspected more frequently than AE prior to diagnosis.[14] Subsequently, treatment was delayed for many patients, which results in worse outcomes.[11 12 14]

Many patients that are clinically diagnosed with autoimmune encephalitis lack identifiable antibodies. The same retrospective study determined that 31.4% of patients diagnosed with AE had no well-characterised antibodies identified.[14] Hence, patients diagnosed with AbNAE received treatment even further in their disease course than those with antibodies detected.[14]

Finally, there is no gold standard for diagnosis, and diagnostic algorithms are largely based on exclusion.[6 11 12 14] We used an algorithm first proposed in 2016 that included knowledge of most of the currently tested antibodies. However, even this algorithm relies on exclusion, which, in a transplant patient, requires extensive testing since they are more predisposed to a wide range of pathology.

Despite the challenges, recent developments are encouraging. While new antibodies continue to be characterised, specific biomarkers are also showing promise. In a cross-sectional study of patients with presumed AE and infectious, autoimmune and non-inflammatory controls, two potentially useful CSF biomarkers were

identified.[13] Interleukin 21, a cytokine that downregulates T regulatory cells thereby inducing autoimmunity, was found to be higher in both AbPAE and AbNAE groups. On the other hand, interferon-γ induced protein (IP10), also known as C-X-C motif chemokine 10 (CXCL10), a chemokine implicated in the helper T1 cells response to viral infection, was higher in patients with a viral infection than with AE.[13] Since chronically immune-suppressed transplant patients are also at increased risk of infectious encephalitis, these biomarkers may be especially useful.

AE, especially AbNAE, is likely underdiagnosed in transplant recipients and patients on chronic immune suppression. Those patients that are diagnosed are treated later in their disease courses. Our case highlights the importance of including AE and AbNAE as a differential and demonstrated complete recovery with early treatment. Therefore, even in the absence of well-characterised antineuronal antibodies, AE should be considered when chronically immune-suppressed transplant patients present with central neurologic symptoms.

Learning points

- Although seemingly paradoxical, chronic immune suppression is a risk factor for the development of autoimmune encephalitis.
- History of autoimmune disease, immune suppression and preceding infection are clues towards diagnosing autoimmune encephalitis.
- Autoimmune encephalitis may be diagnosed in the absence of characterised antibodies.
- There is no gold standard for diagnosis of antibody-negative autoimmune encephalitis and diagnostic algorithms are largely based on exclusion.
- Outcomes favour early treatment, so autoimmune encephalitis should be considered in any transplant recipient presenting with central neurologic symptoms.

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