Autoimmune limbic encephalitis in association with acute stroke

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A 60-year-old woman with no known medical history presented with acute-onset altered mental status and aphasia. She was in her usual state of health until the time of presentation. She was found to have left middle and posterior cerebral artery (MCA and PCA) acute ischemic strokes and subsequently developed refractory status epilepticus. CT angiography showed moderate stenosis of the proximal left internal carotid artery (ICA), occlusion of the right ICA at its origin, and near-complete occlusion of the left vertebral artery (figure). Strokes were attributed to large-vessel atherosclerotic disease in the setting of multiple vascular risk factors including diabetes (A1c 13.5%), hypertension, and hyperlipidemia (low-density lipoprotein 244 mg/dL).

PRACTICAL IMPLICATIONS

Consider autoimmune encephalitis in the differential diagnosis of persistent encephalopathy of uncertain etiology following acute ischemic stroke.

Continuous EEG demonstrated left-sided focal seizures with left posterior temporal sharp waves and spikes as well as right temporal sharp transients. Seizures resolved by admission day 14 with multiple antiepileptic drugs (later transitioned to levetiracetam and phenytoin). Evaluation for refractory seizures included a normal CSF profile on day 10 (1 white blood cell/cm³, protein 33 mg/dL, negative viral, bacterial, and fungal studies) and a negative serum paraneoplastic panel on day 21 (table). Despite resolution of clinical and electrographic seizure activity, her mental status remained profoundly abnormal for weeks. Her examination was notable for periods of wakefulness with occasional visual tracking and intermittent localization to pain in the left upper extremity; however, she did not attempt to vocalize, follow commands, or move spontaneously, consistent with a modified Rankin Scale (mRS) of 5. Subsequent EEGs showed generalized delta slowing, more pronounced in the left temporal region, without epileptic activity. Repeat brain MRI showed stable, evolving multifocal infarcts within the left MCA/PCA territories including the left insula and mesial temporal lobe with associated enhancement (figure). The extent of encephalopathy was thought to be out of proportion to the ischemic stroke burden.

Serum erythrocyte sedimentation rate (ESR) was persistently elevated above the level of detection (>130 mm/h), and C-reactive protein was elevated to 20.5 mg/dL (normal <0.5 mg/dL). Additional rheumatologic studies were normal. CT of the chest, abdomen, and pelvis as well as PET/CT scan of the entire body did not demonstrate occult malignancy.

Because the patient's profound encephalopathy persisted without explanation through day 60, a second serum paraneoplastic panel was sent, which demonstrated multiple positive antibody titers, with voltage-gated potassium channel (VGKC) antibody detected at the highest level (table). Anti-contactin-associated protein-like 2 (anti-CASPR2) antibodies were detected in the serum by cell-based assay, which was repeated for confirmation (Mayo Medical Laboratories, Rochester, MN). Given disparate results, a third serum panel was sent after initiation of steroid treatment, which was similarly abnormal (table), though cell-based assay for anti-CASPR2 was negative in this sample. The family declined lumbar puncture for CSF antibody testing. She was treated with IV methylprednisolone 1,000 mg daily for 5 days. By day 3, she

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Figure MRI of the brain and CT angiography of the cerebral vasculature

Diffusion-weighted imaging from the outside hospital on admission day 9 demonstrates small regions of acute infarction in the left mesial temporal lobe (A) and left insula (B). Fluid-attenuated inversion recovery images (C, D) and T1 postcontrast images (E, F) from follow-up MRI on admission day 42 show evolution of infarct with associated contrast enhancement. CT angiography (G) shows occlusion of the right internal carotid, with absent flow-related enhancement of the distal cervical and intracranial right internal carotid artery. There is hairline opacification of the left vertebral artery to the level of the C2 vertebral body, after which the left vertebral artery is not visualized. There is focal stenosis of the proximal left internal carotid artery.

moved all extremities spontaneously, followed commands, and answered questions appropriately. She was diagnosed with definite anti-CASPR2 limbic encephalitis.¹ At hospital discharge, she was alert and oriented to self and place and able

to follow simple commands (mRS 4). At 6-month follow-up, she remained seizure-free with normal EEG; she was oriented to self, place, and time, followed complex commands, and ambulated with assistance (mRS 4).

Table Antibodies detected from the patient’s serum by paraneoplastic testing (Mayo Medical Laboratories, Rochester, MN)

Antibody (reference range, nmol/L)	Admission day 21	Admission day 60	Admission day 72
Voltage-gated potassium channel antibody (<0.02)	0.01	0.37	0.45
N-type calcium channel antibody (<0.03)	0.02	0.18	0.08
P/Q type calcium channel antibody (<0.02)	0.01	0.08	0.06
Anti-contactin-associated protein-like 2 (CASPR-2) detected by cell-based assay	No	Yes	No

All testing was performed by immunofluorescence assay except for CASPR-2 testing in the final row, which was performed by cell-based assay. All numerical results are measured in nmol/L.

Discussion

Varied clinical presentations have been described with antibodies for proteins associated with or part of the VGKC complex, with half of VGKC-seropositive patients possessing antibodies against either of 2 identified associated proteins: leucine-rich glioma-inactivated-1 and CASPR2.^{1–3} Autoimmune limbic encephalitis is a well-described presentation for both.¹

Persistent encephalopathy following multifocal strokes and status epilepticus may represent a unique presentation of anti-CASPR2 limbic encephalitis.^{3–5} One prior report described autoimmune limbic encephalitis and VGKC antibody detection following an acute ischemic stroke.⁶ It is speculated that blood–brain barrier compromise may play a role in pathogenesis. Here, the inciting event (acute ischemic stroke involving the insula and medial temporal lobe) and neuronal death may have caused antigen exposure with subsequent immune response to multiple neuronal antigens. The clinical presentation of seizures, persistent encephalopathy, electrographic temporal lobe slowing, and dramatic steroid response supports a limbic encephalitis diagnosis; however, the transient appearance of anti-CASPR2 and lack of CSF and alternate confirmatory testing lend uncertainty in this complex case, as the serum CASPR2 cell-based assay is highly, but not completely, specific.⁷ Autoimmune limbic encephalitis should be considered in the differential diagnosis of persistent encephalopathy of uncertain etiology following acute stroke, as altered mental status may be misattributed to sequelae of ischemic insult or medical complications in the post-stroke period.

Author contributions

B. Kaas: drafted original manuscript. S.R. Zeiler: critical revision of manuscript for intellectual content. M.N. Bahouth: critical revision of manuscript for intellectual content. R.H.

Llinas: critical revision of manuscript for intellectual content. J.C. Probasco: critical revision of manuscript for intellectual content.

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