AANP DSS 2014
Case 8

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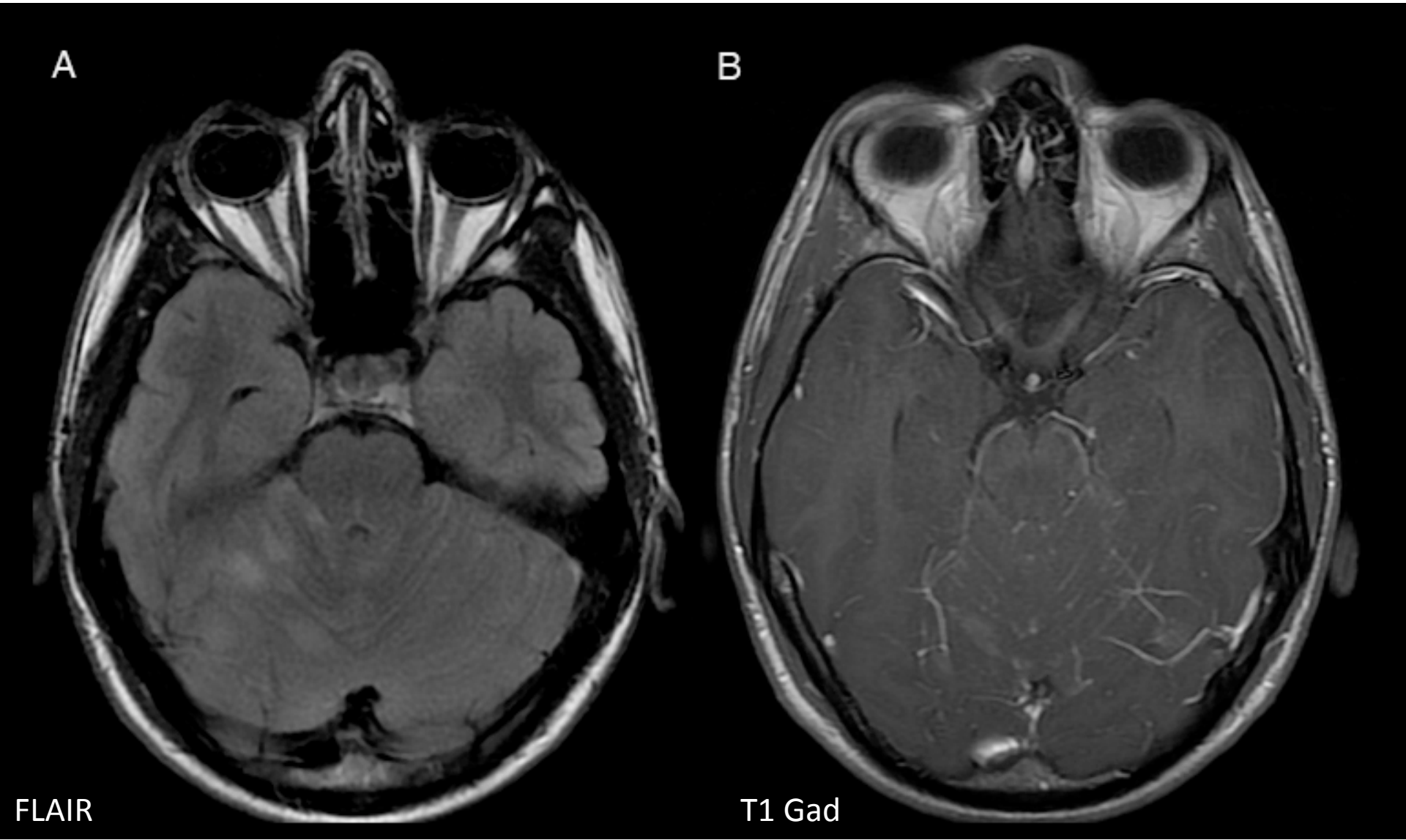
No conflicts of interest to disclose

DSS
Case 8

- previously well 18 yo male, 2 month h/a, clumsiness, difficulty walking
- neurological exam: nystagmus, dysarthria, ataxia

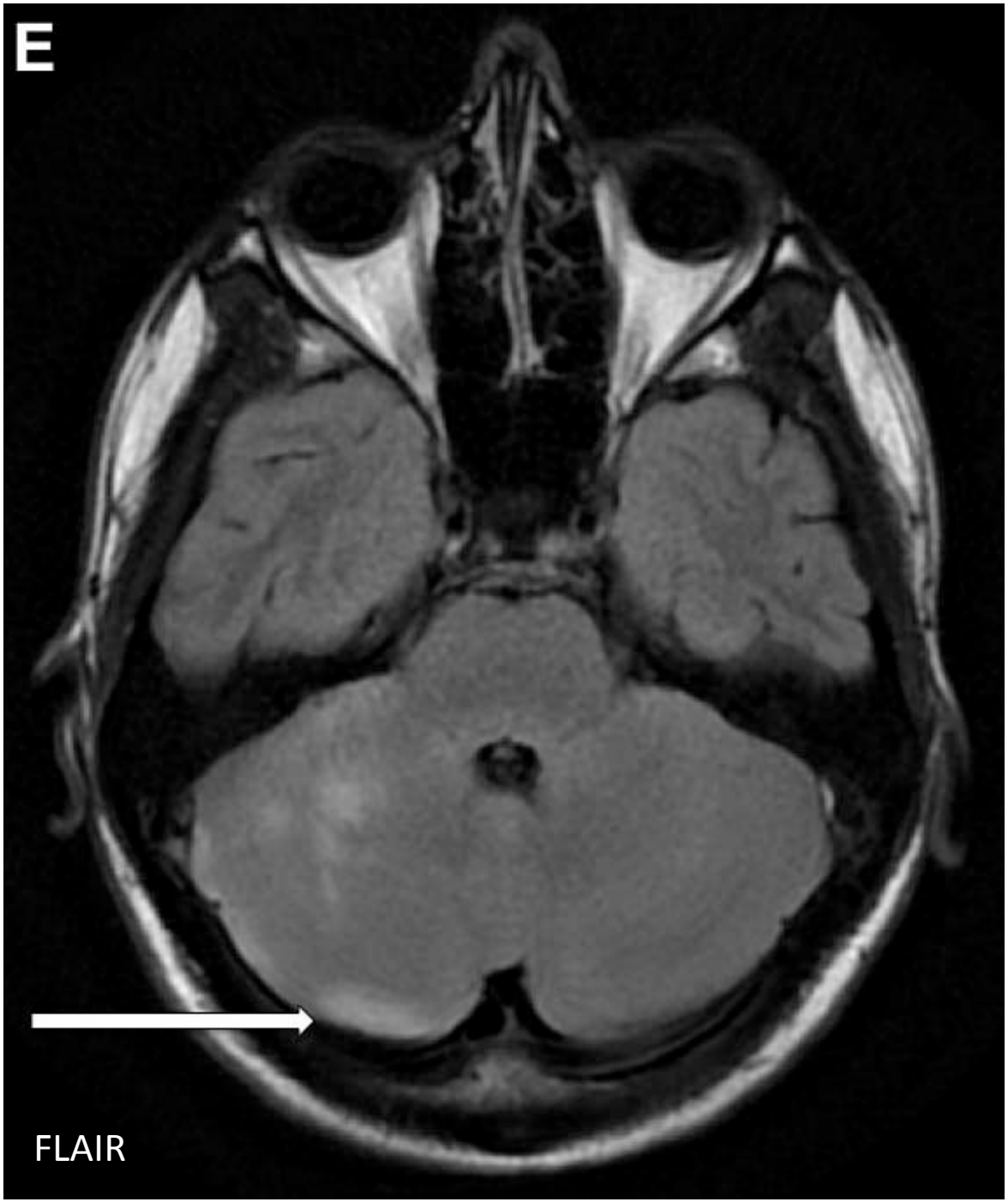


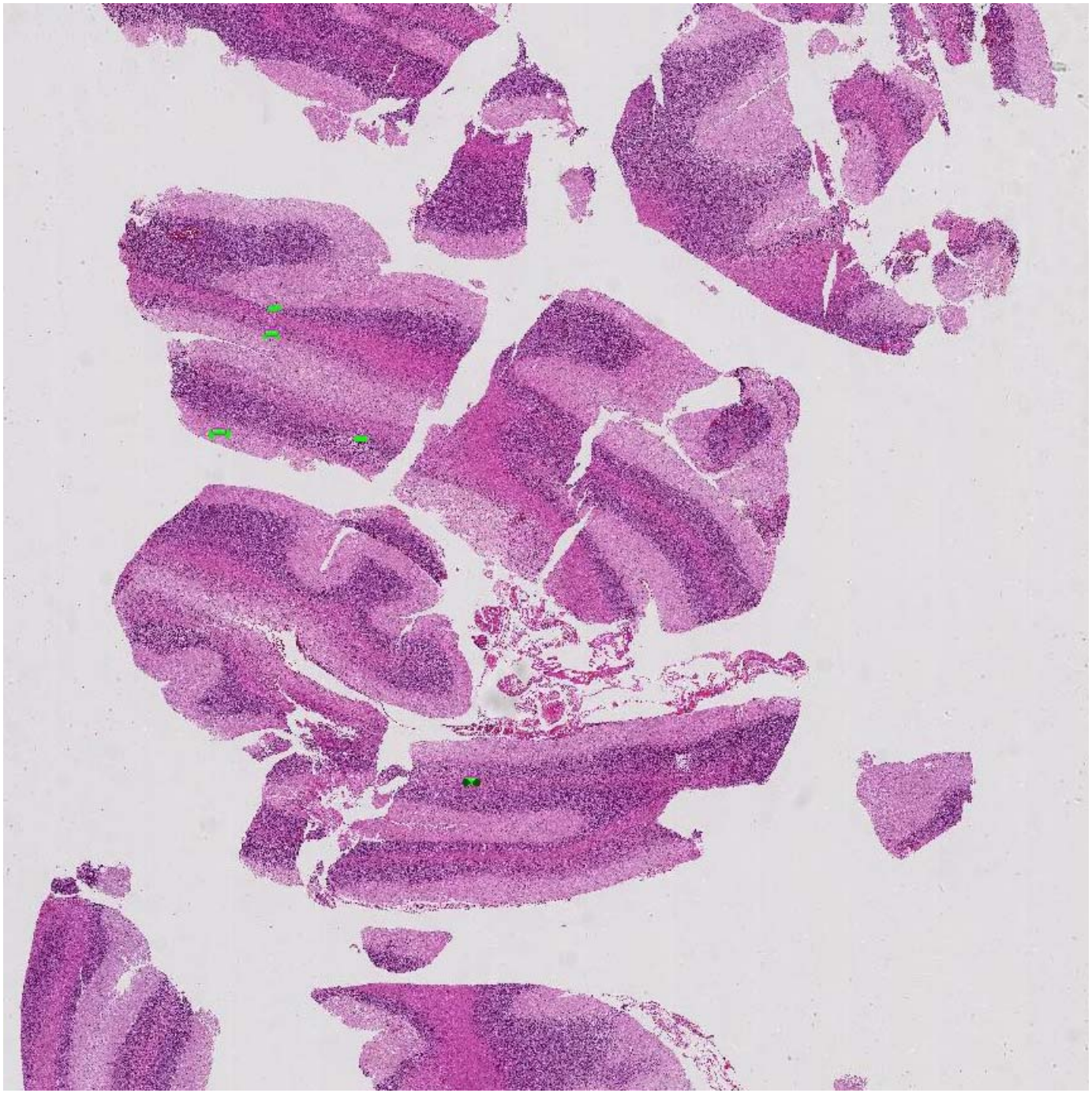
DSS
Case 8

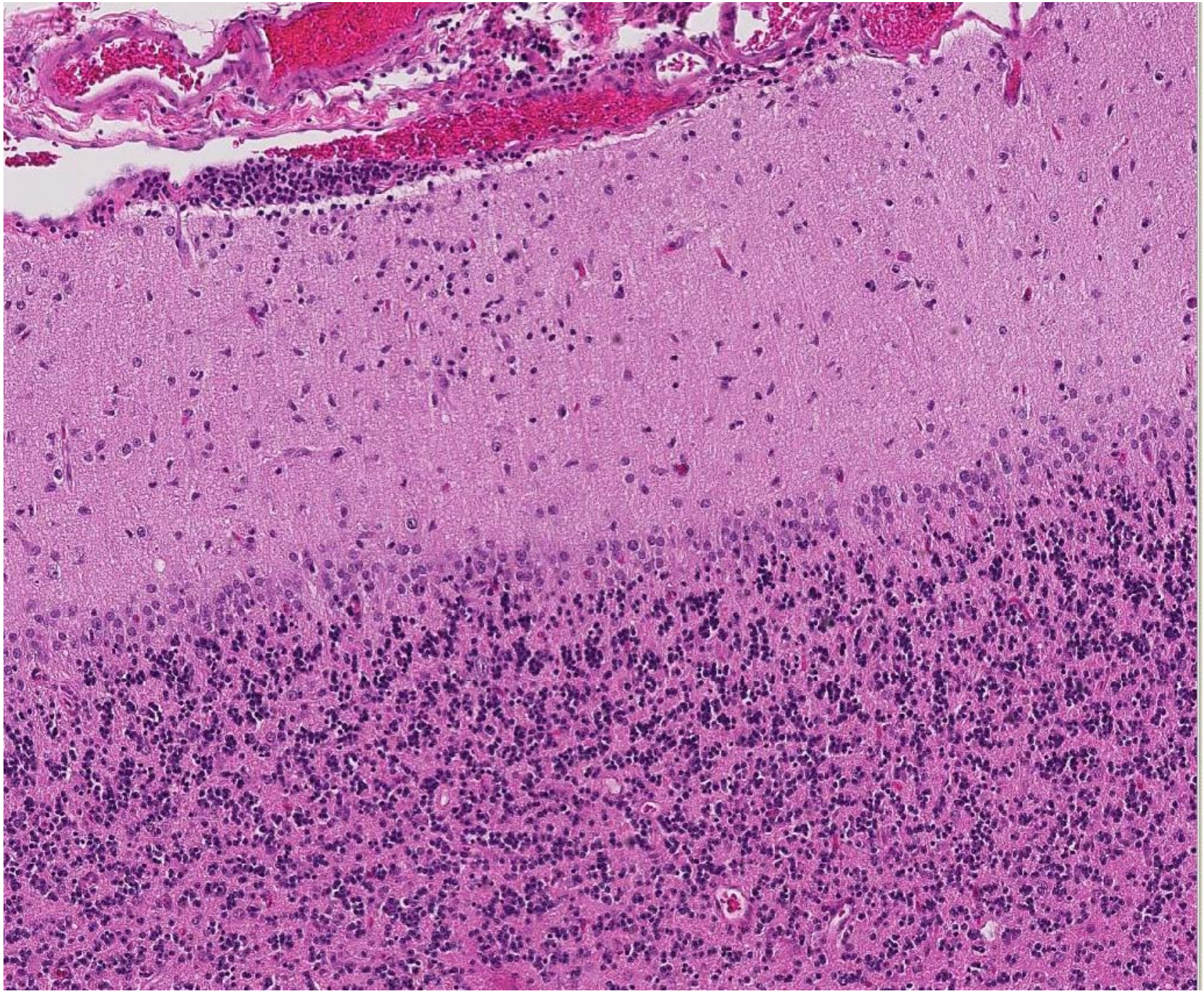
- CSF:
  - 69 WBC/hpf, ↑pro (0.468 g/L)
  - negative micro, cytology, flow cytometry
- DDx:
  - viral cerebellitis
  - lymphoproliferative disorder
  - (when worsened with cog dysfunction, visual hallucinations) added paraneoplastic, autoimmune
    - CT chest abdo pelvis, testicular U/S, PET scan were normal
    - serum samples were sent for measurement of autoantibodies*
      - NMDA (NR1), VGKC (LGI1, CASPR2), Amphiphysin, GAD-65, CV2/CRMP5, Recoverin, SOX1, Titin, Hu, Yo, Ri and PNMA2 (Ma2, Ta)

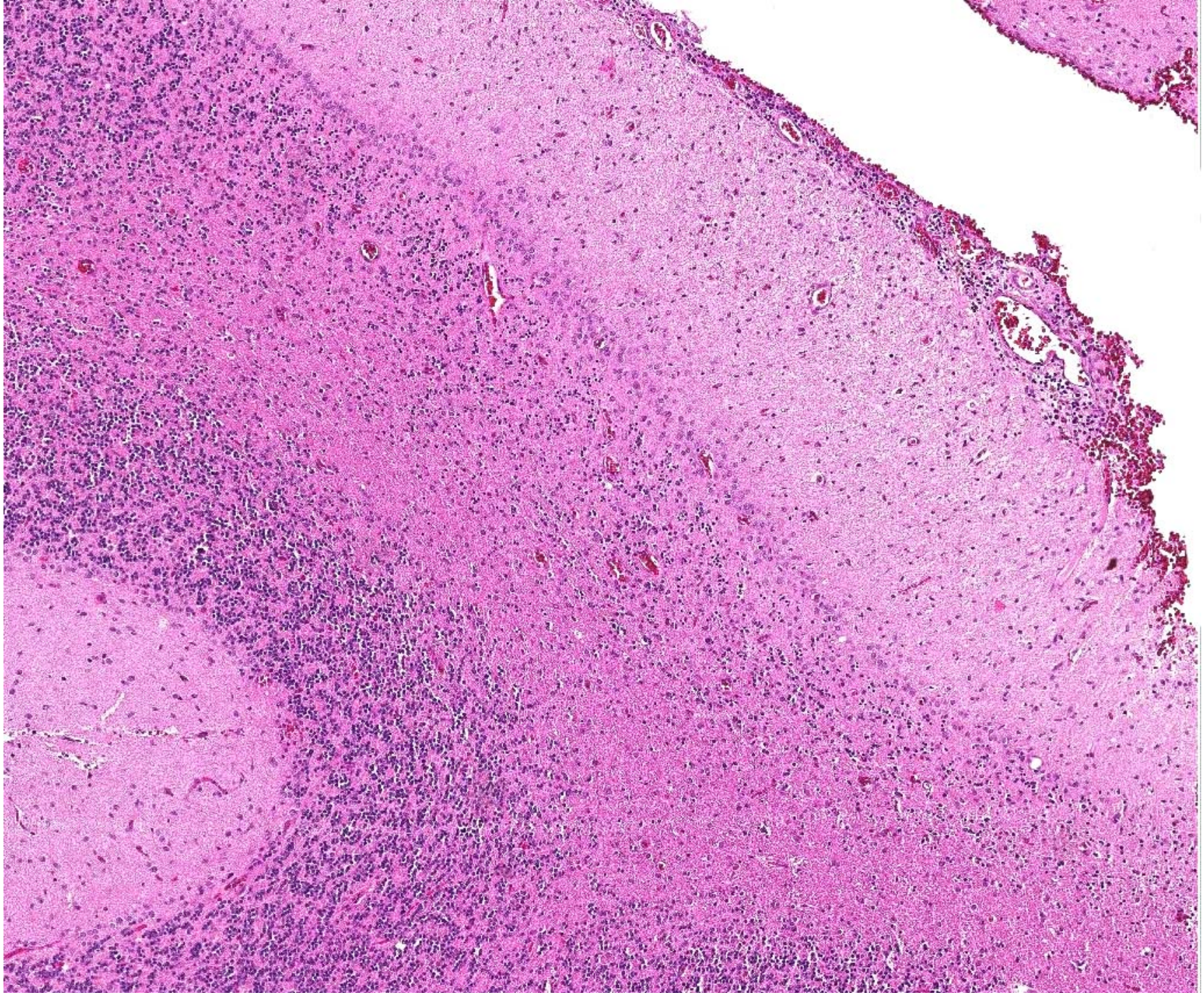
*Mitogen Diagnostics, Calgary, Alberta, Canada

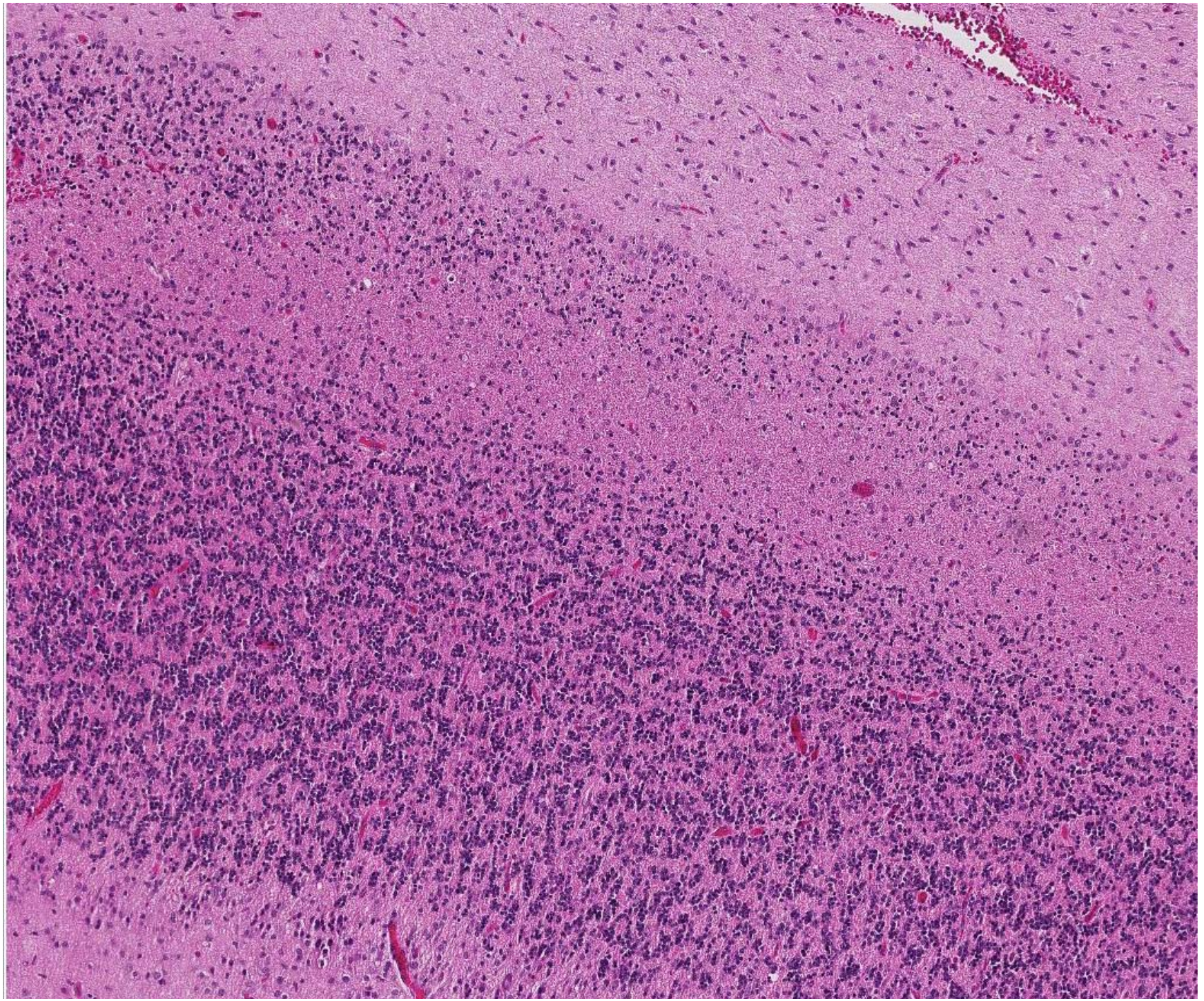
DSS
Case 8





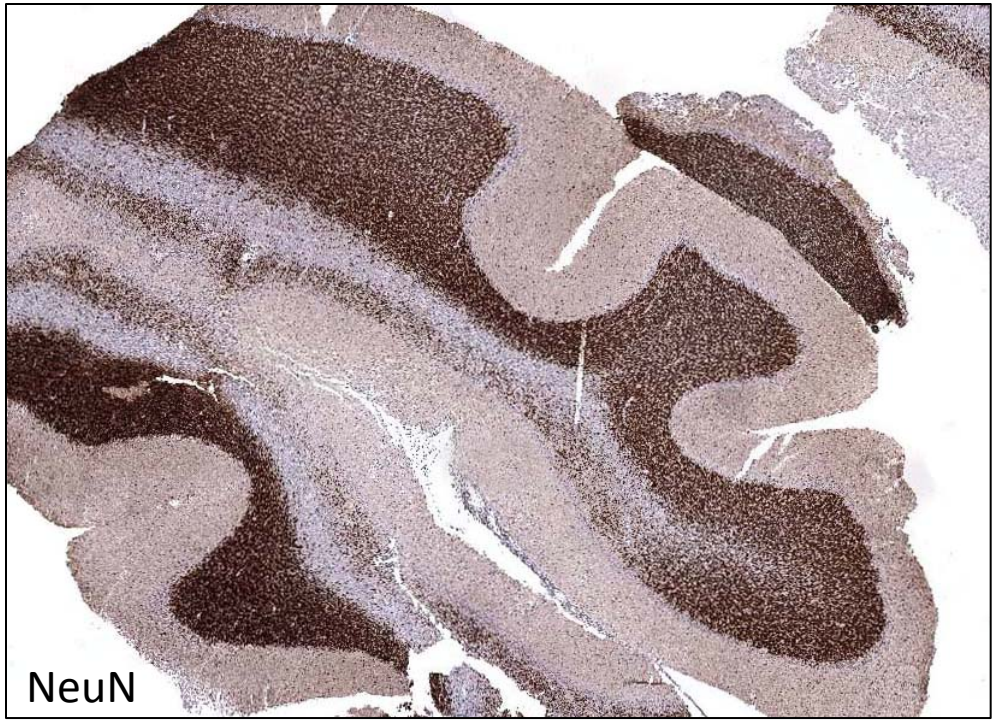


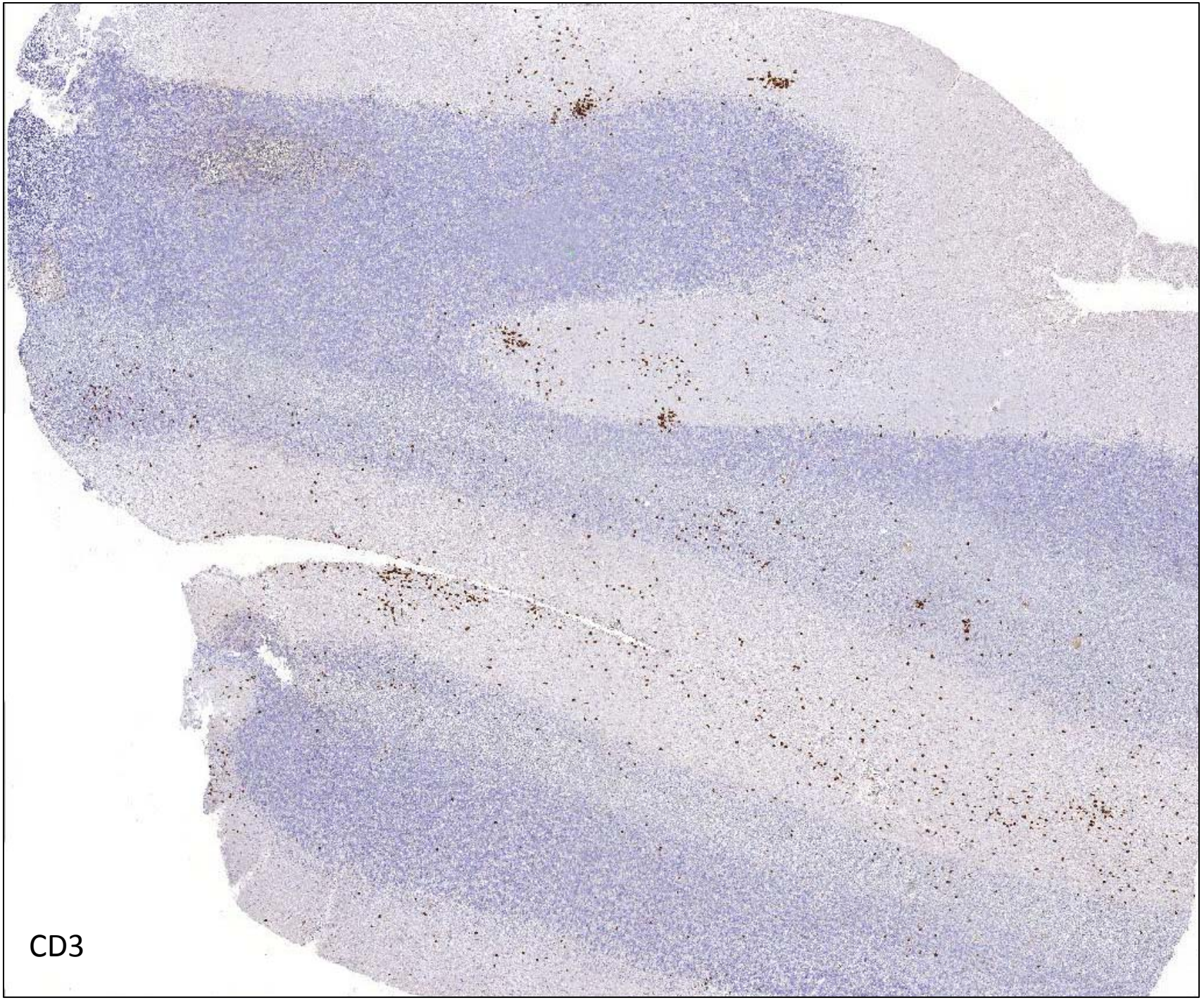




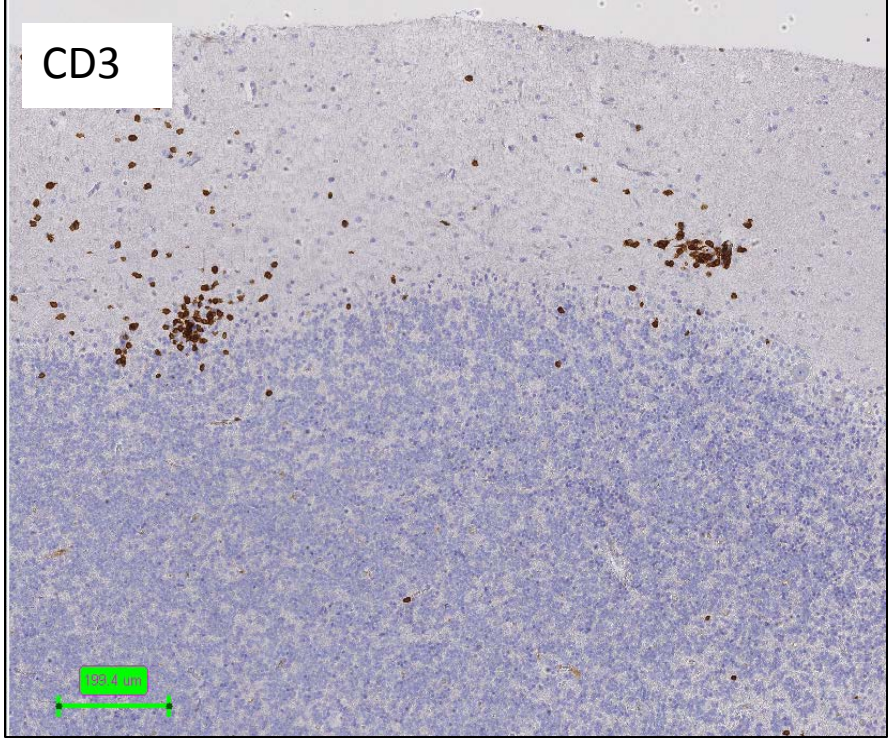
Audience comments?

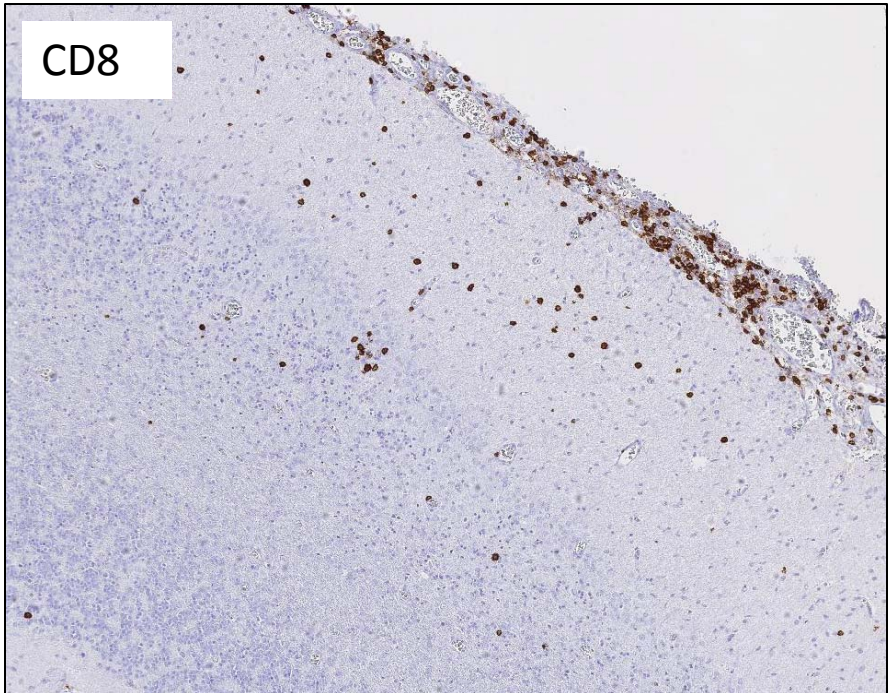

NeuN


NeuN


CD3


CD20
200.0 um


CD3
199.4 um


CD8

Additional path findings and DDx

- No evidence of malignancy
- Infectious
  - no microglial nodules, viral inclusions, organisms
  - JCV? No PML, SV40 negative
- Neurodegenerative
  - clinical (young, acute), inflammation, no spongiosis, p62 negative
- Autoimmune encephalitis
- Paraneoplastic cerebellar degeneration
  - usually selective Purkinje cell loss

Clinical course

- During the days following bx the patient declined
  - ↓ LOC
  - generalized myoclonus
  - prominent involuntary movements of orofacial musculature

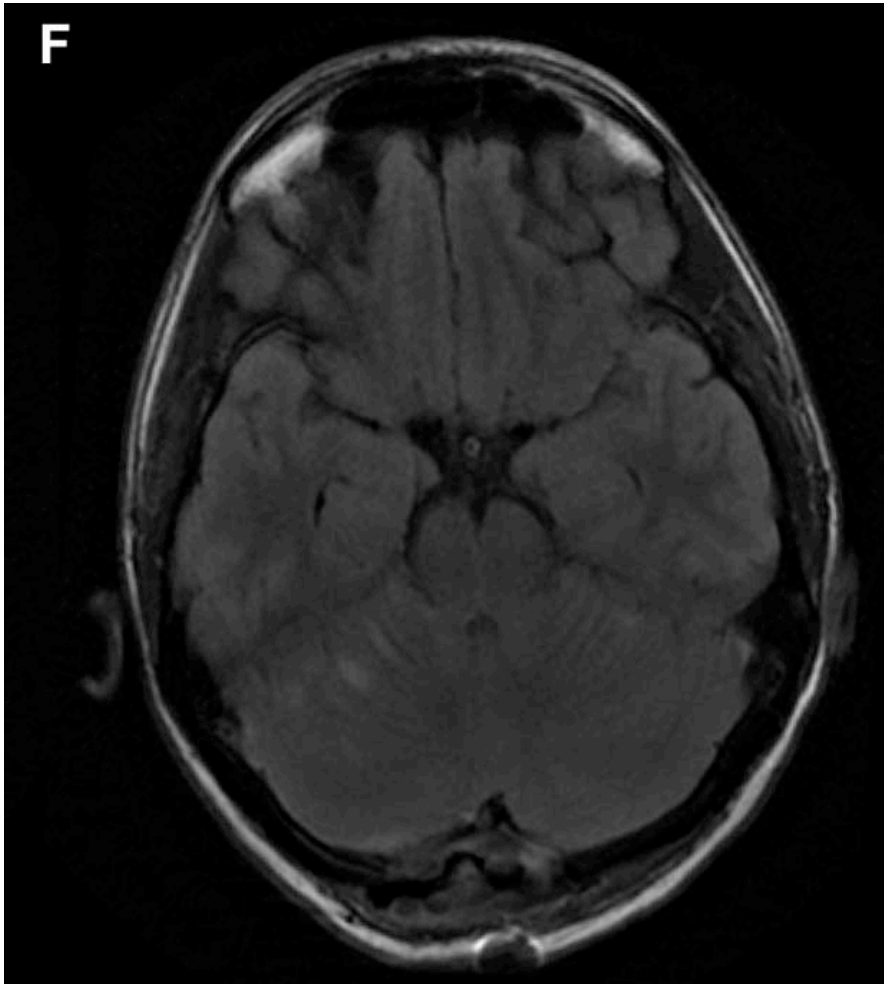
Diagnosis

- 4 weeks following presentation (5 days post biopsy) results from the serum autoantibodies:
  - **LGI1 autoantibodies present in serum**

LGI1 Ab associated encephalitis with presenting symptoms and signs localized to the cerebellum

Clinical course

- Treated with IVIg
- 24 hours after IVIG completed LOC improved and myoclonus resolved
- Repeat MRI brain showed improvement in cerebellar lesions
- Discharged home 3 weeks later (cognitively intact with mild ataxia)
- Normal 9 months later



Neuro-Oncology

Neuro-Oncology 16(6), 771–778, 2014
doi:10.1093/neuonc/nou030
Advance Access date 16 March 2014

Autoimmune encephalitis update

Josep Dalmau and Myrna R. Rosenfeld

Antibody associated CNS disorders

Paraneoplastic disorders

- Ab target intra-cellular neuronal Ag, T cell mediated, poor Rx response

Autoimmune encephalitis

- +/- tumour, Ab target neuronal cell surface or synaptic receptors, Ab cause primary pathogenic effect, good Rx response

Neuro-Oncology

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Autoimmune encephalitis update

Josep Dalmau and Myrna R. Rosenfeld

Table 2. Autoimmune encephalitis associated with antibodies against neuronal cell-surface or synaptic proteins

Antigen Target	Syndrome	Cancer Association if Present	Observations
NMDA receptor	Characteristic neuropsychiatric syndrome with movement disorders, seizures, autonomc dysfunction	Age-related association with ovarian teratoma	Predominantly affects young adults, adolescents, and children
AMPA receptor	Limbic encephalitis, psychosis	Lung, breast, thymus in ~70% of cases	Frequent coexisting autoimmunities
$GABA_B$ receptor	Limbic encephalitis with early, prominent, and severe seizures	SCLC or other neuroendocrine tumor of lung in ~50% of cases	Frequent coexisting autoimmunities
LGI1	Limbic encephalitis, seizures, hyponatremia, myoclonus	Thymoma in <10% of cases	Frequent tonic seizures that may be misdiagnosed as myoclonus or startle
Caspr2	Encephalitis and/or peripheral nerve hyperexcitability	Rarely thymoma	Symptoms of overlapping immune disorders such as myasthenia have led to misdiagnosis of motor neuron disease
$GABA_A$ receptor	Status epilepticus or refractory seizures and encephalitis	None	Frequent coexisting autoimmunities; extensive and often multifocal MRI abnormalities
DPPX	Encephalopathy, agitation, tremor, startle with muscle rigidity, seizures, and gastrointestinal dysfunction	None	Severe gastrointestinal symptoms can mislead diagnoses
Glycine receptor	Stiff-person, hyperekplexia, PERM, and encephalitis	Rare associations with cancer but usually not paraneoplastic	
mGluR1	Cerebellar ataxia	Hodgkin lymphoma	
mGluR5	Limbic encephalitis	Hodgkin lymphoma	Known as Ophelia syndrome
Dopamine-2 receptor	Basal ganglia encephalitis, Sydenham chorea	None	
Amphiphysin	Stiff-man syndrome	Breast, SCLC	
GAD	Stiff-man syndrome at times with cerebellar ataxia, refractory seizures	Rarely thymoma or other tumors	Have been reported in other syndromes, such as limbic encephalitis and epilepsy; frequent coexisting autoimmunities

Leucine-rich Glioma Inactivating Protein 1

ASN NEURO REVIEW ARTICLE

ASN NEURO 5(3):art:e00115.doi:10.1042/AN20120095

OPEN ACCESS

LGI proteins in the nervous system

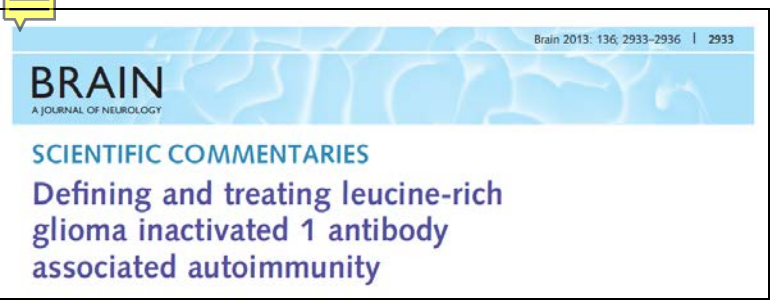
Linde Kegel*, Eerik Aunin*, Dies Meijer*[1] and John R. Bermingham, Jr†[1,2]

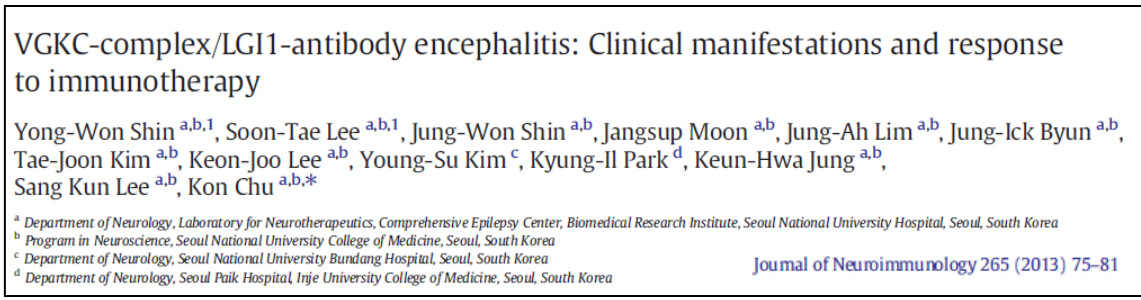
The Journal of Neuroscience, November 13, 2013 • 33(46):18161–18174 • 18161

Neurobiology of Disease

Autoantibodies to Epilepsy-Related LGI1 in Limbic Encephalitis Neutralize LGI1-ADAM22 Interaction and Reduce Synaptic AMPA Receptors

Toshika Ohkawa,[1,2] Yuko Fukata,[1,2] Miwako Yamasaki,[3] Taisuke Miyazaki,[3] Norihiko Yokoi,[1,2] Hiroshi Takashima,[4] Masahiko Watanabe,[3,5] Osamu Watanabe,[4]* and Masaki Fukata[1,2]*





Typical LGI1 encephalitis presentation:

- Faciobrachial dystonic seizures, then insidious cognitive impairment
- 10% associated teratoma

REVIEW

J Neurol Neurosurg Psychiatry 2012;**83**:638–645

Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition

Luigi Zuliani,[1,2] Francesc Graus,[3] Bruno Giometto,[1] Christian Bien,[4] Angela Vincent[2]

Criteria for 'possible neuronal surface antibody syndrome' warranting Ab testing:

1. Acute or subacute onset of sx
2. Exclusion of other causes (infectious, toxic, metabolic, tumour, trauma, demyelinating)
3. Evidence of CNS inflammation:

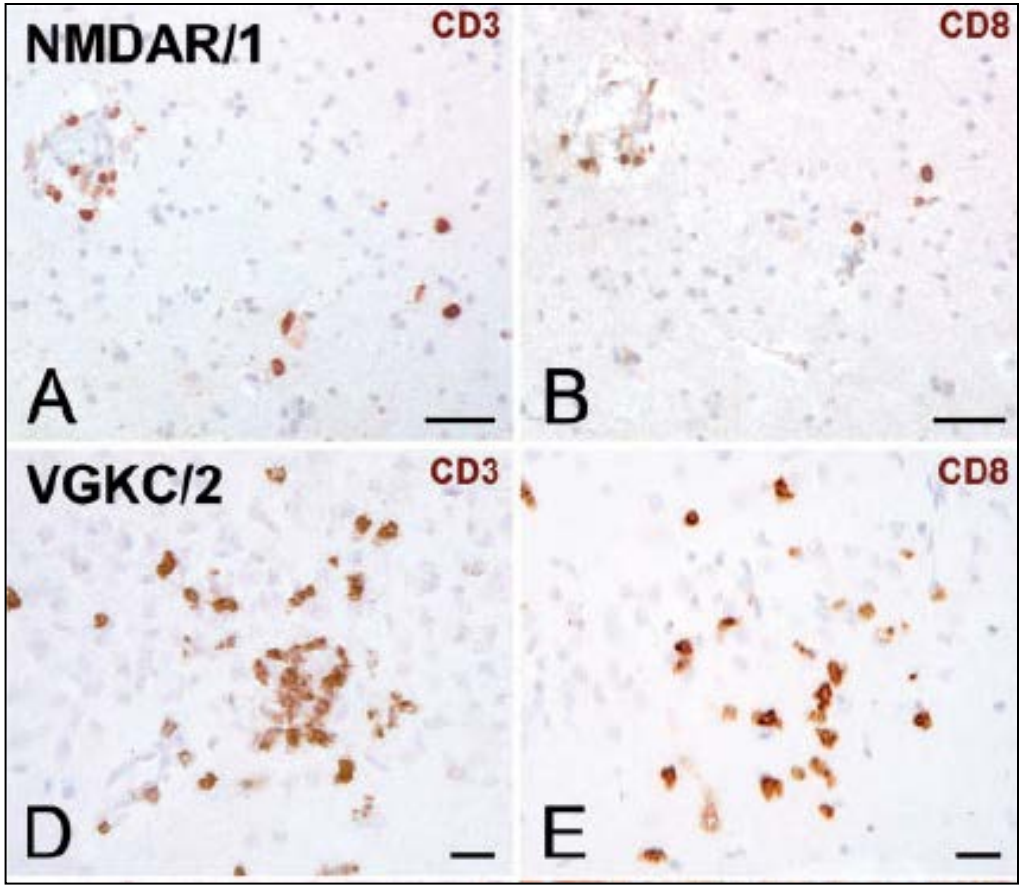
   - either on CSF, imaging or **inflammatory neuropathology**

doi:10.1093/brain/aws082 Brain 2012: 135; 1622–1638 | 1622

BRAIN
A JOURNAL OF NEUROLOGY

Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis

Christian G. Bien,[1] Angela Vincent,[2] Michael H. Barnett,[3] Albert J. Becker,[4] Ingmar Blümcke,[5] Francesc Graus,[6] Kurt A. Jellinger,[7] David E. Reuss,[8] Teresa Ribalta,[9] Jürgen Schlegel,[10] Ian Sutton,[11] Hans Lassmann[12] and Jan Bauer[12]



- Compared pathology of 17 Ab mediated encephalitis cases
- pts w Ab to cell surface R had:
  - variable T lymph inflammation (LGI1 had more than NMDA)
  - LGI1 had cortical neuronal loss

Age and Ageing 2006; **35:** 536–537
doi:10.1093/ageing/afl045
Published electronically 8 June 2006

CASE REPORTS

Autoimmune limbic encephalitis causing fits, rapidly progressive confusion and hyponatraemia

EDMUND JAMES DUNSTAN[1], JOHN B. WINER[2]

European Journal of Neurology 2007, **14:** e5–e6

LETTER TO THE EDITOR

An autopsy case of limbic encephalitis with voltage-gated potassium channel antibodies

D. C. Park[a], D. L. Murman[a], K. D. Perry[b] and L. A. Bruch[c]

- 2 autopsy case reports describing
  - mild limbic encephalitis, T lymphocytic
  - one emphasizes extensive neuronal loss in mesial temporal structures – *can look degenerative*

Dx: **LGI1 Ab associated encephalitis**

with presenting symptoms and signs localized to the cerebellum

- Take-home points:
  - Remarkable response to immunotherapy
  - What is the neuropathologist's role in the identification of biopsied atypical cases?

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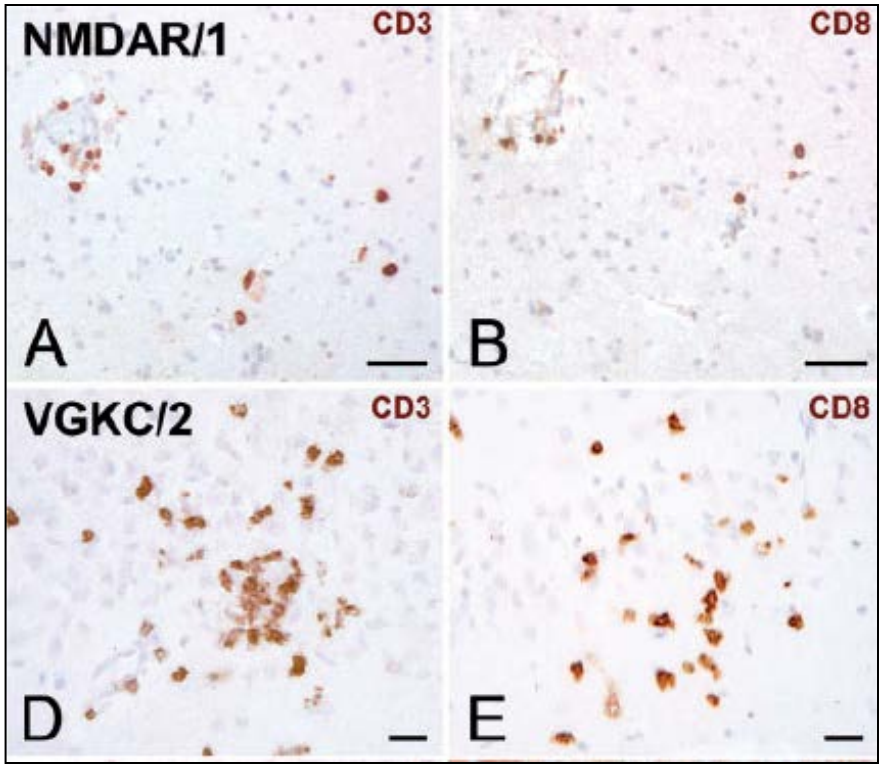
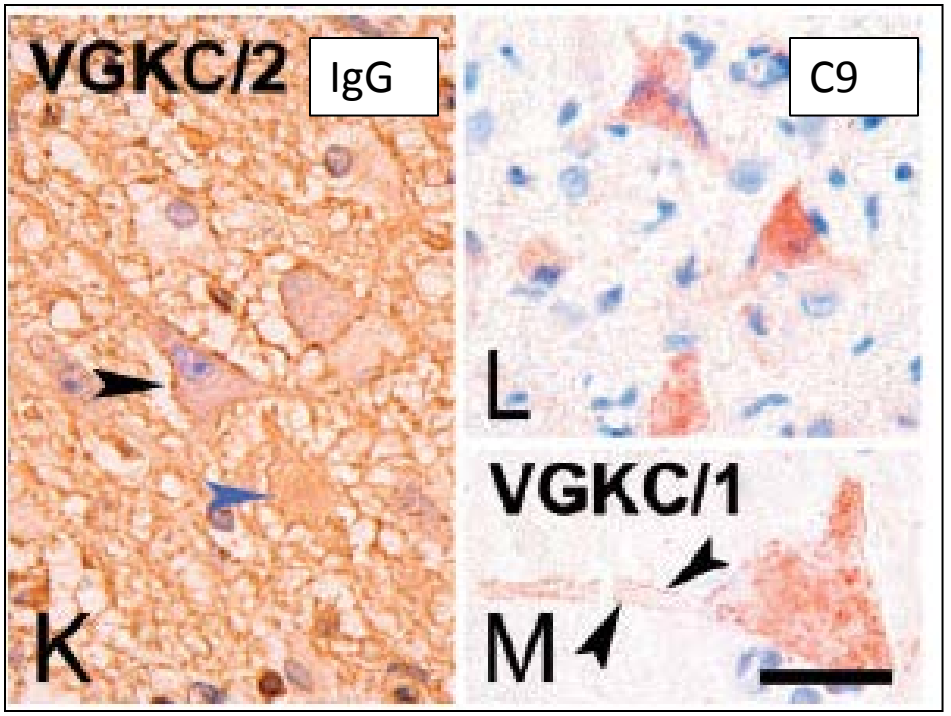
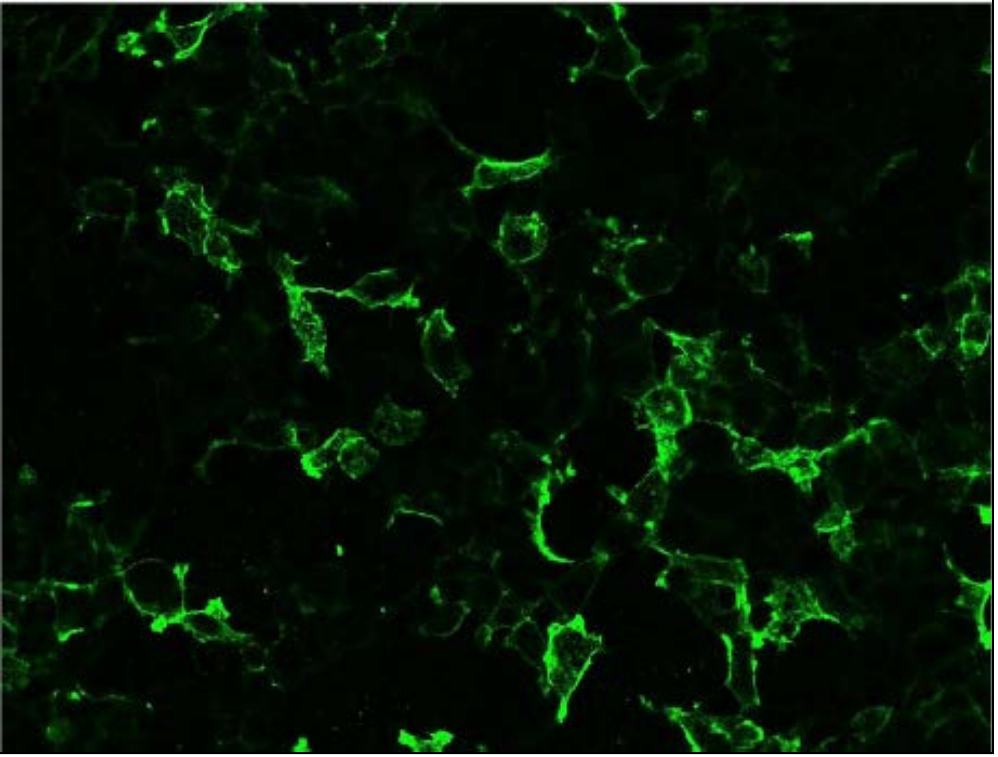
- Compared neuronal loss and immunopathology of 17 Ab mediated encephalitis cases
- patients with LGI1 encephalitis had variable T lymphocytic inflammation, *cortical neuronal loss*, plus IgG and compliment deposition







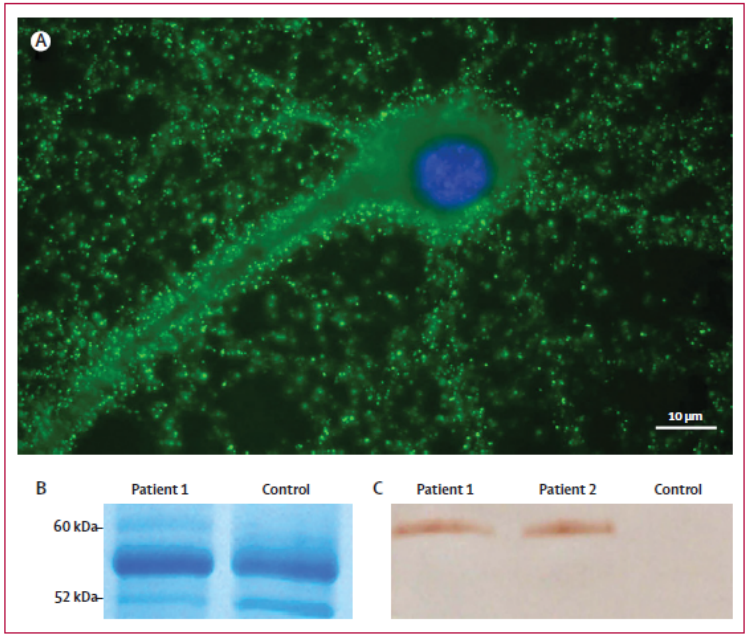


Figure 1: **Immunocytochemistry and immunoprecipitation of LGI1 with sera from patients with limbic encephalitis previously attributed to voltage-gated potassium channels**

(A) Immunolabelling of a rat hippocampal neuron with serum of a patient (patient 1) with antibodies previously attributed to voltage-gated potassium channels. The nucleus of the neuron is visualised with DAPI.

(B) Immunoprecipitates obtained using serum from a patient and a control individual were separated by gel electrophoresis and the gel stained with coomassie blue. A band of about 60 kDa was detected in the sample from the patient and, by mass spectrometry, was identified as LGI1. This band was not present in the sample from the control individual. The protein bands at 55 kDa and 52 kDa correspond to fragments of human IgG. (C) Immunoblot of the precipitates obtained with the sera from patient 1, another patient (patient 2), and a control individual (control). LGI1 was present in the neuronal immunoprecipitates obtained using sera from both patients but not the control individual. The antibody used in this analysis was a polyclonal LGI1 antibody that is commercially available.