Clinical Reasoning:

An 82-year-old woman with dissociated aphasia followed by amnesia

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SECTION 1

An 82-year-old right-handed woman presenting with a sudden-onset language deficit was initially evaluated in a regional hospital, with an unremarkable head MRI with gadolinium and progressive full recovery of the language deficit. Two hours later, she presented a second episode of aphasia and was transferred to our department for evaluation of IV thrombolysis (within a European time window of 4 hours and 30 minutes), arriving 1 hour and 40 minutes after symptom onset.

Examination revealed global aphasia with reduced spontaneous speech, deficits in naming, and impaired comprehension, with jargon and semantic paraphasia in French. Conversely, in this bilingual (French and

German) patient of German origin, only slightly disrupted language production and entirely intact comprehension in German were observed. Neurologic examination was unremarkable otherwise (NIH Stroke Scale 2).

Blood pressure and heart rate were within normal range with a cardiac sinus rhythm. Blood glucose was also normal (5.6 mmol/L). Initial laboratory testing including electrolytes, leukocyte count, and C-reactive protein was normal.

Questions for consideration:

1. What is your differential diagnosis at this point?
2. Would you administer IV thrombolysis?

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Figure EEG at admission

Brief left frontotemporal semi-rhythmic theta-delta slowing (highlighted by the orange frame) with superimposed sharply contoured transients and maximum negativity over F7-T1-T3 compatible with the patient's language dysfunction. Referential (average) montage, right over left, 20 mm/s, 10 μ V/mm, high-frequency filter 70 Hz, low-frequency filter 1 Hz.

SECTION 2

Differential diagnosis for recurrent sudden-onset aphasia includes stroke and epileptic seizures; less frequently, this picture may also be due to amyloid spells or psychogenic origin. Amyloid spells refer to recurrent, stereotyped, spreading focal symptoms seen in cerebral amyloid angiopathy, mainly due to microbleeds and possibly subsequent electric phenomena.¹ Dissociated aphasia with selective impairment of one

language in multilingual patients is more often associated with circumscribed vascular lesions. Since focal epileptic seizures usually affect larger cortical areas, they are less prone to causing dissociated aphasia.

Substantial fluctuation of the aphasia observed immediately after normal cranial CT at the emergency department including CT angiogram and perfusion imaging during the second episode and absence of diffusion-weighted signal restriction on the MRI performed during the first episode rendered stroke unlikely. Thrombolysis was not administered. Focal status epilepticus with recurrent dysphasic seizures was suspected and the patient received 1 mg of IV clonazepam followed by an IV load of 2,000 mg of levetiracetam. Status epilepticus management includes a benzodiazepine (e.g., lorazepam, midazolam, or—in some countries—clonazepam) as first-line compound, followed by a nonsedative antiepileptic agent (e.g., fosphenytoin, valproic acid, or levetiracetam).² Waking up from moderate somnolence after clonazepam administration, no language deficit but circumstantial amnesia was noted.

EEG after admission to inpatient unit showed a left focal, frontotemporal, semi-rhythmic theta-delta slowing with superimposed sharply contoured transients and maximum negativity over F7-T1-T3 (figure) that disappeared after levetiracetam was increased from 500 mg to 1,000 mg twice daily. Nonetheless, anterograde and partial retrograde amnesia persisted.

Questions for consideration:

1. Where would you localize the cognitive deficit and what diagnoses have to be considered?
2. Which is your next diagnostic step?

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SECTION 3

Anterograde and retrograde amnesia point to dysfunction in mesiotemporal regions, specifically the hippocampi. Persistence of focal status epilepticus seemed unlikely in view of a normal EEG. Generally, with deeper epileptic foci, disruption of normal waveforms or some slow rhythmic alteration would be expected. Absent memory improvement despite normalization of the EEG and disappearance of language deficits points to another underlying cause.

New-onset epilepsy in elderly patients is often due to lesions such as stroke or brain tumor. Yet, in the present case, normal initial and repeat MRI after 2

days excluded both. New-onset mesiotemporal dysfunction and epileptic seizures suggest viral or autoimmune limbic encephalitis. A lumbar puncture was performed and CSF analysis revealed 5 leukocytes/mm³ (92% lymphocytes), slightly elevated protein at 516 g/L, and normal glucose and lactate. Oligoclonal bands were positive and cytology was negative for malignant cells.

Questions for consideration:

1. Would you initiate an acyclovir IV treatment at this point and, if yes, why?
2. Do additional diagnostic tests need to be performed?

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SECTION 4

In the present case, herpes simplex virus (HSV) encephalitis is not formally excluded by brain MRI or the CSF profile (5 cells/mm³, with a usual cutoff of 4 cells/mm³) since during the first days, MRI and even HSV PCR can be normal, and lower CSF leukocyte count may be encountered. Possible immunosuppression also needs to be taken into account.

Eventually, the level of clinical suspicion will determine whether empirical IV acyclovir will be introduced, and repeat lumbar puncture may be indicated. In the present case, we opted for acyclovir treatment and the second lumbar puncture showed 11

cells/mm³ (90% lymphocytes). However, PCR on both CSF samples came back negative for HSV-1, HSV-2, varicella virus, and enteroviruses.

A screen for immune-mediated encephalitis including antineuronal antibodies yielded positive results for anti-Hu and anti-Sry-like high-mobility group box (SOX) 1 antibodies. Limbic encephalitis with anterograde and retrograde amnesia and temporal-onset aphasic epileptic seizures was diagnosed.

Questions for consideration:

1. What further investigations are indicated?
2. What would be your therapeutic approach?

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SECTION 5

Autoimmune limbic encephalitis is often paraneoplastic (the involved antibodies cross-react with tumoral and cerebral antigens) and implies an extensive workup for a primary tumor. In our patient, thoracic CT, total body PET-CT, gynecologic examination, and tumor markers (CA-125, NSE) were all normal. Since limbic encephalitis may precede the diagnosis of a primary tumor by several years, repeat whole-body imaging was recommended every 3 months during the first year, then every 6 months for 4 years.

Methylprednisolone was administered, starting IV (1,000 mg daily for 5 days), then orally at 60 mg per day. In the absence of significant neuropsychological improvement after 1 month, therapy was progressively stopped. On follow-up at 3 months, the patient still presented substantial memory deficits.

DISCUSSION Selective impairment of one language in multilingual subjects is termed dissociated aphasia. While the literature on bilingualism reports numerous cases of dissociated aphasia during acute stroke or its recovery, only a few cases of epileptic origin have been documented to date.^{3,4} Clinical distinction between stroke and epilepsy may be extremely difficult, especially in the context of rapid therapeutic decision-making regarding IV thrombolysis or antiepileptic medication.

In bilingual individuals, both the age at which the second language is learned and the learning mode impact neural correlates. Secondary languages acquired at later stages in life are represented in perisylvian regions topographically slightly distinct from areas processing the maternal language.⁴ Dissociated postictal aphasia affecting the second language as in the present case has been previously described in 2 late bilingual patients.⁴ Nonconvulsive status epilepticus with impaired language function, also termed aphasic status epilepticus, can thus contribute to the understanding of brain topography.

Temporal lobe seizures and memory dysfunction evoke infectious or autoimmune inflammation of the limbic system, with HSV encephalitis being the most dangerous condition. HSV encephalitis may prove particularly difficult to diagnose in its initial stage, since brain MRI and even CSF PCR for HSV may be unremarkable.⁵ Therefore, in the presence of a compatible CSF profile or in immunocompromised patients, empiric acyclovir treatment and repeat lumbar puncture and brain imaging are recommended. EEG may prove sensitive on days 2–14 after symptom onset, most commonly showing temporal lateralized periodic discharges (LPDs).⁶ Typical clinical symptoms of

autoimmune limbic encephalitis comprise alterations in personality traits, irritability, epileptic seizures, and memory dysfunction. Precise clinical markers with high specificity are still missing. Diagnosis is therefore challenging. In paraneoplastic encephalitis, symptom onset may frequently precede the detection of cancer.⁷ LPDs on EEG and circumscribed unilateral or bilateral hyperintensities on T2 or fluid-attenuated inversion recovery (FLAIR) MRI sequences, slight increase of CSF leukocyte count (usually <10 cells/mm³), and eventually positive antineuronal antibodies may point towards the diagnosis.⁸ The antibodies comprise 2 classes differentiable by their target components: (1) Hu, Ma2, CV2/CRMP5, SOX, and others as intracellular or typical paraneoplastic antigens; and (2) voltage-gated potassium channels and NMDA receptors as cell membrane antigens. This second group of antibodies is directly pathogenic and may respond well to immunotherapy when the underlying cause is autoimmune. However, if these antibodies are paraneoplastic, prognosis is dictated by the underlying tumor.⁹

The type of antineuronal antibodies may specifically indicate the associated neoplastic origin. Our patient's CSF was positive for anti-Hu and anti-SOX1 antibodies, both related to small-cell lung cancer. Anti-Hu antibodies are also associated with gynecologic and gastric carcinoma. SOX protein is an established as marker of early neurogenesis and belongs to the class of DNA-binding transcriptional factors.¹⁰ Negative findings on initial workup for neoplasia are frequent and regular imaging follow-up required.

Tumor removal is essential in treating paraneoplastic encephalitis. The presence of intracellular vs surface antigens yields important implications for therapy and prognosis. Encephalitis due to antibodies targeting membranous antigens is significantly more responsive to immunotherapy (IV immunoglobulin, plasma exchange, corticosteroids, cyclophosphamide, rituximab), while if intracellular antigens are found, prognosis is less favorable, and tumor discovery remains crucial. Our approach was to attempt a glucocorticoid treatment as first line, but in the absence of favorable response, a second-line immunosuppression (e.g., azathioprine) was not considered useful.⁹ Anti-Hu-associated limbic encephalitis is mainly mediated by cytotoxic T cells, but improvement is rarely observed, even with drugs targeting cellular immunity.⁹

AUTHOR CONTRIBUTIONS

E. Eskiolglou acquired, analyzed, and drafted the content of this clinical reasoning including medical writing. R.A. Du Pasquier and A.O. Rossetti revised the manuscript for content and performed supervision of this clinical reasoning. A.A. Sokolov acquired, analyzed and revised the content of this manuscript, and performed supervision of this clinical reasoning.

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The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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