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A Case of Wernicke-Korsakoff Syndrome Initially Diagnosed as Autoimmune Limbic Encephalitis:

Differential Diagnosis of Delirium and Short-Term Memory Deficits

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Wernicke encephalopathy is a condition that classically presents with a triad of symptoms characterized by oculomotor dysfunction, cerebellar dysfunction, and delirium. The incidence of all 3 symptoms in patients is rare (≈17%), and many patients present with delirium alone.[1] The altered cognition of Wernicke encephalopathy can progress to Wernicke-Korsakoff syndrome (WKS), with key neuropsychological features of anterograde amnesia and temporally graded retrograde amnesia.[2] The clinical manifestation of antibody-mediated limbic encephalitis (ALE) is primarily defined by the subacute onset of short-term memory loss, seizures, confusion, and psychiatric symptoms, suggesting involvement of the limbic system.[3] As both delirium and short-term memory impairment can be presenting symptoms in both conditions, the potential of misdiagnosis and delayed treatment can occur.[1] We present the case of a patient recently treated for ALE, admitted to our facility for similar symptoms, and longitudinally diagnosed with WKS.

Case Report

Ms A was a 66-year-old white woman who presented to our emergency department in August 2019 with "altered mental status and short-term memory loss." Three months earlier, she presented to an outside hospital with a similar chief complaint. At that time, cerebrospinal fluid (CSF) evaluation was remarkable for elevated protein and lymphocytic pleocytosis, although paraneoplastic panel results were unremarkable. Magnetic resonance imaging (MRI) of the brain demonstrated increased T2-weighted fluid-attenuated inversion recovery (FLAIR) involving bilateral temporal lobes, specifically moderately extensive abnormal increased T2 signal through the cortex and subjacent white matter of the anterior and anterior medial right temporal lobes, extending throughout the right hippocampus and contiguously into the right insular cortex. While some mild swelling of the anterior temporal lobe was possible, prominent atrophy appeared to be present. Atrophy was noted in the right mammillary bodies and anterior thalamic nuclei. She was diagnosed with ALE and treated with intravenous immunoglobulin (IVIg). Reportedly, her cognition returned to baseline level.

According to family and unbeknownst during the prior admission, Ms A had been misusing alcohol for 3 decades. Blood alcohol, urine drug screen, and thiamine levels were not assessed at admission despite repletion of the latter beginning on hospital day 1. When measured on hospital day 23, her thiamine level was within normal limits. Despite treatment, the patient remained confused, and we were consulted at that time.

On our evaluation, Ms A was oriented to person only, with vacillating mentation. The Confusion Assessment Method (CAM)[4] for delirium was positive. As mentioned, MRI of the head was remarkable for extensive bilateral anterior/anteromedial temporal lobe disease, mainly gray matter. Otherwise, complete blood count, complete metabolic profile, C-reactive protein, and infectious workup results were unremarkable.

Ms A restarted a course of 5 IVIg treatments and then rituximab. Upon completion, the CAM was negative, although she had residual anterograde amnesia and retrograde amnesia. Table 1 shows the results of cognitive testing and follow-up.[5–7] The patient was discharged on hospital day 40.

While details of Ms A's prior hospitalization were scant, there was no history of ictal episodes or behavioral changes. Thus, it would appear that the patient's primary symptoms for both prior and current admission were delirium followed by short-term memory deficits. Prior CSF evaluation was remarkable for elevated protein (elevated in ~50% of LE patients)[8] and lymphocytic pleocytosis despite the paraneoplastic panel not identifying an antigenic target. Interestingly, it has been reported that in alcohol use disorder, ~6% of patients have a slightly elevated CSF protein (up to 75 mg/dL), while 2.3% have a moderately elevated level (up to 100 mg/dL).[9] Our patient's CSF protein level was 73.1 mg/dL.

MRI of the head at this admission was interpreted as improved but nonspecific temporal lobe disease, compatible with ALE. Most patients with ALE have unilateral or bilateral increased T2/FLAIR signal in the medial temporal lobes

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Table 1. Anterograde and Retrograde Amnesia: General Overview and Results for Ms A[5–7]

	Anterograde Amnesia	Retrograde Amnesia
Definition	Impairment in forming new memories after "lesion/onset"	Loss of memories acquired prior to lesion/onset: Autobiographical: typically divided into semantic and episodic components: AS: refers to "facts" that are not tied to a single event, for example, knowing that you used to go camping on holidays AE: refers to personal events that a person is able to reexperience in a detailed spatial and temporal context SM: memory for factual knowledge that has been learned, but for which specific "time and place" information about the source of the original experience is typically not known
Pathophysiology	Lesion(s) in hippocampus→ fornix→ mammillary bodies→ anterior thalamic nuclei via MTT	AS, SM: lesion in perirhinal cortex→ mediodorsal thalamic nuclei through VAFP AE: lesion in hippocampus→ fornix→ mammillary bodies→ anterior thalamic nuclei via MTT
Korsakoff syndrome: memory symptoms	+++	AE, AS: temporal gradient–recent > early adulthood > childhood SM: relatively preserved
Autoimmune/limbic encephalitis: memory symptoms	+++	AE: temporal gradient–recent > early adulthood > childhood AS: recent > early adulthood = childhood
Ms A: memory symptoms	+++ The Montreal Cognitive Assessment (MoCA) score was 22, with Ms A being unable to retrieve 4 of 5 words even with recognition. One month later, the MoCA score was 23, with Ms A scoring 1 point on delayed recall.	AE, AS: temporal gradient–recent > early adulthood > childhood SM: relatively preserved Ms A was asked about major life events from 3 periods of time: childhood, young adulthood, and recent. Her recall of childhood events had more detail and familiarity than young adulthood and recent time periods.

Abbreviations: AE = autobiographical episodic, AS = autobiographical semantic, MTT = mammillothalamic tract, SM = semantic memory, VAFP = ventroamygdalofugal pathway.
Symbols: → = efferent projection, +++ = markedly affected.

without contrast enhancement or abnormal diffusion-weighted images.[10] Alternatively, diencephalon disease (mammillary body and thalamus) also described in the MRI of Ms A is more consistent with WKS. Neuroimaging in both ALE and KS has been reviewed elsewhere,[11] although, in summary, the former has findings of unilateral/bilateral T2/FLAIR signals in the medial temporal lobe, while the latter has principle findings of atrophy in thalami, mammillary bodies, and the frontal cortex.[12]

Discussion

While WKS could explain Ms A's symptoms, her cognition was reported by her family to have returned to baseline after IVIg treatments during the initial hospitalization, and improvement during our hospitalization after little change was noted with thiamine supplementation. First, it is possible that Ms A may have been experiencing the effects of both ALE and WKS. For instance, neuroimaging findings of anteromedial temporal and diencephalon disease support ALE and WKS, respectively. Second, as there was no objective evaluation of the patient's cognition, such as the Mini-Mental State Examination, the reports by family were their subjective opinion. Additionally, Ms A's presentation with delirium could have been that of Wernicke encephalopathy. Notably, even with thiamine supplementation, mental status changes and acute encephalopathy often gradually recede in Wernicke encephalopathy.[13] Thus our patient's cognitive improvement with IVIg could have been coincident with the predicted response course of Wernicke encephalopathy with thiamine. Finally, prolonged and excessive use of alcohol may lead to structural and functional brain damage, leading to alcohol-related dementia. The *DSM-5* classifies this diagnosis as alcohol-induced major/mild neurocognitive disorder. Ms A presented at age 66 years with a 30-year history of alcohol use disorder. Thus, alcohol-related dementia also should be included in her differential diagnosis.[14]

Therefore, as our patient demonstrates, if ALE is not manifest in its full form, the symptoms are often not specific. Furthermore, most oligosymptomatic courses show a wide overlap with established neuropsychiatric conditions,[15] although specific parts of our case that point toward the diagnosis of WKS include preservation of semantic memory, lack of behavioral disturbance, negative paraneoplastic panel, and lack of identifiable tumor. Therefore, combined with similarities in imaging and even CSF protein, KS should be considered in the differential diagnosis of ALE.[6,7]

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Patient consent: The patient and her family verbally consented to publish this case report, and information has been de-identified to protect anonymity.

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