

Early Diagnosis of Anti-N-Methyl-D-Aspartate Receptor (Anti-NMDAR) Encephalitis with Predominant Cognitive Symptoms: A Case Study

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Abstract

Anti-NMDAR encephalitis is an autoimmune syndrome primarily affecting young women and often associated with bilateral ovarian teratoma. As the hallmark clinical manifestations of this condition are neuropsychiatric symptoms, the diagnosis is often delayed, potentially leading to irreversible brain damage. We present the unique case of a 30-year-old female with an acute emergence of memory impairment ultimately diagnosed as caused by anti-NMDAR encephalitis and highlight the potential use of cognitive assessment as a sensitive tool for analyzing the clinical course and prognosis of autoimmune mediated encephalitis.

Keywords: Anti-NMDAR autoimmune encephalitis; Recognition; Familiarity; Recollection

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Introduction

The most common type of autoimmune encephalitis, Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis [1] was first described by Dalmau et al. [2] and has been shown to frequently affect young women with ovarian teratomas [3,4] While this autoimmune encephalitis is treatable, it can be life-threatening if not caught early on. Since the most prominent initial presenting symptoms are neuropsychiatric [5,6], early diagnosis is often difficult. Additional clinical presentations may include epileptic seizures, behavioral and consciousness changes, and cognitive decline [7]. This case study demonstrates the complexity of diagnosis and differential diagnosis.

Case Presentation

L.L. is a 30-year-old, female, social worker. Her past medical and psychiatric history was uneventful except for the diagnosis of attention deficit hyperactivity disorder at the age of 10. L.L. was hospitalized in the neurology department due to her complaints of elevated anxiety, clouded and confused thinking, "blackouts" and mood changes. Her husband reported that during the two weeks prior to her hospitalization, L.L. seemed very nervous, unfocused and unable to recall events throughout the day. He further explained that L.L. was behaving oddly, such as asking the same question over and over again and needing frequent reminders in carrying out basic daily tasks such as teeth brushing and showering. Eight months before her admission, during the COVID-19 pandemic, L.L. had a normal childbirth delivery and reported feeling more lonely, sad and anxious than usual. Due to her change in mood, L.L. began meeting with a psychologist regularly. L.L. remembers retrospectively speaking coherently during this time, although her psychologist noticed a change in her train of thought and attributed these changes to possibly postpartum depression. Throughout the neuropsychological (NP) evaluation examination, L.L. appeared very stressed. She cried and repeatedly asked if she was going to die. Nevertheless, a formal testing measure (TOMM) indicated normal cooperation indices. The NP exam revealed preserved performance in language functions and visual

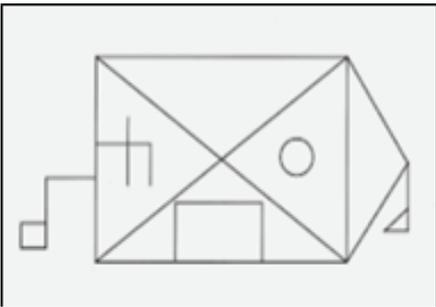
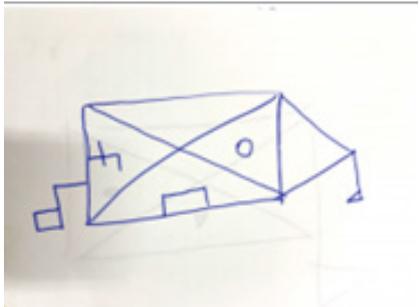
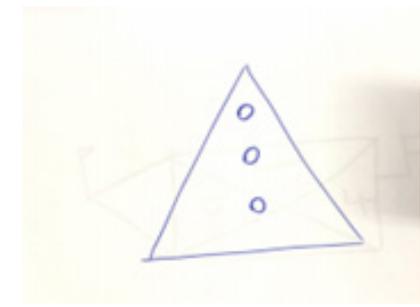
perception. The immediate recall of information was within the norm. A noticeable impairment was observed in L.L.'s episodic memory when presented with verbal and visual material (Benson

test, RAVLT, Logical memory). However, when L.L. performed NP tasks relying on recognition (RAVLT, TOMM), her performance partially improved, as seen in Tables 1&2.

Table 1: L.L.'s neuropsychological exam scores at two time points: (1) upon her initial hospitalization and (2) after treatment.

Neuropsychological Exam									
	MoCA	TOMM	Benson Complex Figure 10-min Delay	Logical Memory Immediate Recall	Logical Memory Delayed Recall	RAVLT Learning Curve	RAVLT After Short Distraction	RAVLT Delayed Recall	RAVLT correct Recognition/ Wrong Recognition
First Evaluation (2.12.2020)	21/30 41/50 47/50 46/50	0/17	11	1	9,9,9,8,9	4	2	12:18	
Final Evaluation (post-treatment) (24.12.2020)	28/30	50/50 50/50 50/50	16/17	15	15	9,11,11,12,11	11	11	12:04

Table 2: L.L.'s copy and recall during the Benson Complex Figure Test upon first evaluation.

Benson Complex Figure Test at First Evaluation		
Original Benson Figure	Copy of Benson Figure at First NP Evaluation	Benson Recall After 10-min Delay
		

The diagnostic work up

The blood count, electrolytes, glucose, renal, liver, thyroid function tests, serum vitamins B12 and folate, lipid profile, autoimmune serology antibodies, neoplastic markers, serology for CMV, EBV, WNV, COVID-19, HIV, syphilis and Mycoplasma and MRI of the brain were normal. CSF analysis revealed 4 lymphocytes and protein and glucose levels were normal. Cytology, virology (HSV, HZV, and enterovirus) and bacteriology (syphilis, cryptococcal antigen) of CSF were negative. The oligoclonal band was negative. EEG depicted bitemporal epileptiform discharges as more prominent on the left. A panel of paraneoplastic and non-paraneoplastic antibodies in blood and CSF revealed positive antibodies for NMDAR. Gynecologic ultrasonography revealed polycystic ovaries with bilateral dermoid cysts up to 15mm with hyperechoic areas.

Diagnosis & treatment

L.L. was diagnosed with anti-NMDAR autoimmune encephalitis. Treatment included IV Methylprednisolone (4 grams for 4 days) followed by plasmapheresis (5 alternate-day treatments) and bilateral dermoid cystectomy.

Discussion

We present the case study of a young woman with anti-NMDA receptor encephalitis presenting with behavioral changes and memory impairment. The NP testing was an integral part of the anti-NMDA receptor encephalitis diagnosis. Furthermore, by using NP testing, we were able to realize that while L.L.'s ability to acquire and retrieve new information was impaired, her ability to perform recognition tasks relying on familiarity memory processes were relatively intact. We believe that this finding in the NP evaluation can help shed light on the understanding of how memory processes work. For this reason, we would now like to elaborate on the cognitive processes of recognition, familiarity, and recollection. It is well accepted that recognition memory reflects the contribution of two separable memory retrieval processes, recollection, and familiarity. Recollection is a specific type of memory process that occurs when a "test stimulus prompts retrieval of what one was doing, thinking, or feeling when the stimulus was previously encoded" [8]. "Familiarity refers to knowing that an item was presented earlier, with no additional contextual information retrieved" [9]. It is assumed that in familiarity, the process of remembering relies on the perceived memory strength of the recognized stimulus [10].

The Dual-Process theories of recognition suggest that the two processes, recognition and familiarity, depend on separate neural substrates [11-25]. Recollection mainly dependent on the hippocampus, while familiarity mainly depending on outside the hippocampus substrates [26,27]. A different explanation to the recollection-familiarity discrepancy is offered by The Single-Process View, which suggests that the neural substrates for recollection and familiarity are nearly the same, differing only in their degree of involvement and the strength of memory encoding single-process view [28-32].

Since L.L's cognitive profile in the NP assessment revealed a specific deficit in recollection memory (RAVLT, Logical memory, and Benson Complex Figure) and intact familiarity (Test of Malingering – TOMM test, a 50 item, two-alternative forced-choice test), we believe that NMDAR encephalitis could serve as a suitable clinical platform for future anatomo-functional research in examining "single" or "dual-process" recognition-recollection memory process.

Conclusion

LL's case demonstrates the value of incorporating early NP testing and cognitive functioning exams in neurological evaluations. In addition, to the best of our knowledge, this is the first time that the cognitive processes of familiarity and recollection are examined in a case of anti-NMDA receptor encephalitis.

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