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Chronic Neuropsychological Sequelae in a Patient with Nontumorous Anti-NMDA-Receptor Encephalitis

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Case Report Chronic Neuropsychological Sequelae in a Patient with Nontumorous Anti-NMDA-Receptor Encephalitis

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Anti-N-methyl-D-aspartate receptor encephalitis is a neurological, autoimmune disorder tightly conceptualized only as recently as the mid-2000s. It presents itself in a combination of psychiatric, neurological, and autonomic features. We observe a unique case with probable earlier episode (prior to the mid-2000s conceptualization of the disease) and a later relapse, accompanying a comprehensive neuropsychological profile tracked after the relapse and subsequent improvement. Neurocognitive findings revealed residual frontal deficits with mood changes even in the state after plasmapheresis. This case is the first to describe posttreatment cognition in anti-NMDAR encephalitis after probable serial autoimmune episodes.

1. Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a neurological, autoimmune disorder that presents itself in a combination of psychiatric, neurological, and autonomic features. Typical representations include generally acute personality and behavioral changes, memory loss, hallucinations, dyskinesia, dystonia, and seizures. Significant portions of the patients, up to 80%, are women with a median age in the early twenties, and ovarian teratomas and related autoimmune processes are found in approximately half of the cases [1–5]. In this case report, we present a patient with two paroxysms of anti-NMDAR encephalitis accompanied by limited cognitive abilities, frontal deficits, and mood changes.

2. Case Presentation

The patient is a 33-year-old married woman. She managed the financial aspects and business ventures of the three companies that she and her husband own. Her social history was reported normal with no incidents of significant trauma or substance abuse. Developmental history is unremarkable, and she completed one and a half years of college. The family history showed bipolar disorder in one sibling, hypertension, diabetes, and a strong presence of depression.

Upon records review, documentation revealed that the patient possibly, or rather probably, experienced her first episode of autoimmune encephalitis at the age of 24, which occurred prior to the first conceptualization documented by Dalmau et al. [3]. This episode was paired with headaches, hallucinations, delusions, violent outbursts, seizures, and then a two-month long coma. During this time, hallucinations included seeing a television on the ceiling. She was hospitalized at an inpatient psychiatric facility, but details of her clinical diagnoses at the time remain unclear. She then recovered drastically after receiving a high dose of prednisone and only reported mild to moderate residual deficits. While no formal neuropsychological measures were given at the time per report, residual deficits included low-level math computation, slowed processing speed, and short-term memory deficits, enough to a level that required supervision over daily living activities. This continued to resolve for about

| intelligence Full prior for the full of th | Domain | Function | Measure* | Standard scores | Percentile |
|--|----------------|---|------------------------------------|-----------------|------------|
| intelligence Full scale IQ WAIS-IV 75 55 Intelligence Total verbal learning CVLT-II trials 1-5 total 98 4 New learning as distraction to old learning CVLT-II trials 1 98 4 Verbal memory Short delay recall CVLT-II trials 1 98 4 Recognition CVLT-II discriminability 115 8 Visual memory Delay recall BVMT-R trials 1-3 total <65 | 1 | Estimated premorbid IQ | WRAT-4 Reading subtest | 86 | 18 |
| New learning as distraction to old learningCVLT-II trial B10766Verbal memoryShort delay recallCVLT-II short delay7877Long delay recallCVLT-II long delay8510RecognitionCVLT-II long delay8510Visual memoryDelay recallBVMT-R trials 1-3 total<65 | | Full scale IQ | WAIS- IV | 75 | 5 |
| Verbal memory Short delay recall CVLT-II short delay 78 78 Long delay recall CVLT-II long delay 85 b Recognition CVLT-II discriminability 115 88 Visual memory Delay recall BVMT-R trials 1-3 total <65 | Verbal memory | Total verbal learning | CVLT-II trials 1–5 total | 98 | 45 |
| Long delay recallCVLT-II long delay85InRecognitionCVLT-II discriminability11588Total visual learningBVMT-R trials 1-3 total<65 | | New learning as distraction to old learning | CVLT-II trial B | 107 | 68 |
| RecognitionCVLT-II discriminability1158Total visual learningBVMT-R trials 1-3 total<65 | | Short delay recall | CVLT-II short delay | 78 | 7 |
| Total visual learningBVMT-R trials 1-3 total<65<Visual memoryDelay recallBVMT-R delay<65 | | Long delay recall | CVLT-II long delay | 85 | 16 |
| Visual memoryDelay recallBVMT-R delay<65<RecognitionBVMT-R Discrimination IndexAttentionWorking memoryWAIS-IV Working Memory Index8059AttentionTrails A8820Psychomotor speed & attentionTrails B58Mental flexibilityTrails B58Response inhibitionStroop C-W9122Higher orderWCST-64 perseverative responses86executive skillsNovel problem solvingWCST-64 perseverative responses86Novel problem solvingWCST-64 perseverative errors87Processing speedWAIS-IV Processing Speed Index86SpeedRecognition speedStroop C86Verbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index83ExpressivePhonemic fluencyAnimals58ReceptiveComprehensionMAE sentencesReceptiveComprehensionMAE token1066General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index71Visuopatial constructionVisuomotor constructionClock drawingSpatial perceptionVisual perceptionJOLOGD dominant handGD dominant hand </td <td>Recognition</td> <td>CVLT-II discriminability</td> <td>115</td> <td>84</td> | | Recognition | CVLT-II discriminability | 115 | 84 |
| RecognitionBVMT-R Discrimination Index-1-AttentionWorking memoryWAIS-IV Working Memory Index8099Psychomotor speed & attentionTrails A8822Mental flexibilityTrails B5826Response inhibitionStroop C-W9122Higher orderWCST total error7877executive skillsWCST-64 perseverative responses8616Novel problem solvingWCST-64 perseverative errors8792WCST-64 categories completed-2-WCST-64 failure to maintain setProcessing speedWAIS-IV Processing Speed Index8616SpeedRecognition speedStroop C8616Verbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index8311SpeedSemantic fluencyFAS5825RespensivePhonemic fluencyFAS5825NamingBNT-264ReceptiveComprehensionMAE sentences7123ReceptiveComprehensionMAE token10666General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index7123Visuospatial constructionVisual perceptionClock drawingSpatial perceptionVisual perceptionJOLO798 | Visual memory | Total visual learning | BVMT-R trials 1–3 total | <65 | <1 |
| Attention Working memory WAIS-IV Working Memory Index 80 65 Psychomotor speed & attention Trails A 88 2 Mental flexibility Trails B 58 Response inhibition Stroop C-W 91 2 Higher order WCST total error 78 7 executive skills Worle problem solving WCST-64 perseverative responses 86 11 Novel problem solving WCST-64 categories completed - 2- WCST-64 failure to maintain set - - - Processing speed Stroop W 84 14 Speed Recognition speed Stroop C 86 14 Verbal general Verbal comprehension WAIS-IV Processing Speed Index 83 11 Expressive Phonemic fluency Animals 58 Naming BNT-2 64 Receptive Comprehension MAE token 106 6 General Perceptual reasoning WAIS-IV Perceptual Reasoning Index 71 Visuos | | Delay recall | BVMT-R delay | <65 | <1 |
| AttentionPsychomotor speed & attentionTrails A882Mental flexibilityTrails B58Response inhibitionStroop C-W912Higher order executive skillsWCST total error787Novel problem solvingWCST-64 perseverative responses861WCST-64 perseverative responses861WCST-64 categories completed-2-WCST-64 failure to maintain setProcessing speedWAIS-IV Processing Speed Index861SpeedRecognition speedStroop W841SpeedSemantic fluencyAnimals58Verbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index831ExpressivePhonemic fluencyFAS58NamingBNT-264ReceptiveComprehensionMAE sentences71Visuospatial constructionVisuomotor constructionClock drawingSpatial perceptionVisual perceptionJOLO798 | | Recognition | BVMT-R Discrimination Index | — | 1-2 |
| Psychomotor speed & attentionTrails A882Mental flexibilityTrails B58Response inhibitionStroop C-W912Higher orderWCST total error787executive skillsWCST-64 perseverative responses8611Novel problem solvingWCST-64 perseverative errors8795WCST-64 categories completed-2-WCST-64 failure to maintain setProcessing speedWAIS-IV Processing Speed Index8611SpeedRecognition speedStroop C8611Verbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index8311ExpressivePhonemic fluencyFAS58NamingBNT-264ReceptiveComprehensionMAE token1066General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index71Visuomotor constructionClock drawingSpatial perceptionVisual perceptionJOLO798 | Attention | Working memory | WAIS-IV Working Memory Index | 80 | 9 |
| Response inhibitionStroop C-W912Higher order executive skillsWCST total error787Novel problem solvingWCST-64 perseverative responses8610Novel problem solvingWCST-64 perseverative errors8725WCST-64 perseverative errors8726WCST-64 failure to maintain setProcessing speedWAIS-IV Processing Speed Index8610SpeedRecognition speedStroop W8410Verbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index8311Verbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index8311ExpressivePhonemic fluencyFAS583ReceptiveComprehensionMAE sentences713ReceptiveComprehensionMAE token1066General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index713Visuospatial constructionVisual perceptionJOLO798Spatial perceptionVisual perceptionGD dominant hand671 | | Psychomotor speed & attention | Trails A | 88 | 21 |
| Higher order executive skillsWCST total error787Higher order executive skillsNovel problem solvingWCST-64 perseverative responses8610Novel problem solvingWCST-64 perseverative errors879WCST-64 categories completed-2-WCST-64 failure to maintain setProcessing speedWAIS-IV Processing Speed Index8610SpeedRecognition speedStroop W8410Verbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index8311ExpressivePhonemic fluencyFAS5832NamingBNT-26434ReceptiveComprehensionMAE sentences7132ReceptiveComprehensionMAE token10666General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index7132Visuospatial constructionVisuomotor constructionClock drawingGD dominant hand6713330 | 0 | Mental flexibility | Trails B | 58 | .3 |
| Higher order WCST-64 perseverative responses 86 16 executive skills Novel problem solving WCST-64 perseverative errors 87 95 WCST-64 perseverative errors 87 95 <td< td=""><td>Response inhibition</td><td>Stroop C-W</td><td>91</td><td>27</td></td<> | | Response inhibition | Stroop C-W | 91 | 27 |
| executive skillsWCST-64 perseverative responses86InNovel problem solvingWCST-64 perseverative errors879WCST-64 categories completed2-WCST-64 failure to maintain setProcessing speedWAIS-IV Processing Speed Index8610SpeedRecognition speedStroop W8410Verbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index8311ExpressivePhonemic fluencyFAS58NamingBNT-264ReceptiveComprehensionMAE sentences71ReceptiveComprehensionMAE token1066General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index71Visuospatial constructionVisual perceptionJOLO798GD dominant hand671 | | Novel problem solving | WCST total error | 78 | 7 |
| WCST-64 categories completed - 2- WCST-64 failure to maintain set - - Processing speed WAIS-IV Processing Speed Index 86 14 Speed Recognition speed Stroop W 84 14 Verbal general Verbal comprehension WAIS-IV Verbal Comprehension Index 83 11 Semantic fluency Animals 58 Expressive Phonemic fluency FAS 58 Naming BNT-2 64 Receptive Comprehension MAE sentences Visuospatial Perceptual reasoning WAIS-IV Perceptual Reasoning Index Visuospatial Visual perception JOLO Spatial Visual perception JOLO GD dominant hand 67 | | | WCST-64 perseverative responses | 86 | 18 |
| WCST-64 failure to maintain setProcessing speedWAIS-IV Processing Speed Index8614SpeedRecognition speedStroop W8414Verbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index8311Verbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index8311ExpressivePhonemic fluencyFAS58NamingBNT-264ReceptiveComprehensionMAE sentences71ReceptiveComprehensionMAE token10666General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index71Visuospatial constructionVisual perceptionJOLO798GD dominant hand671 | | | WCST-64 perseverative errors | 87 | 9 |
| Processing speedWAIS-IV Processing Speed Index8614SpeedRecognition speedStroop W8414Stroop C8614Verbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index8311Semantic fluencyAnimals58Semantic fluencyFAS58Phonemic fluencyFAS58NamingBNT-264ReceptiveComprehensionMAE sentences71ReceptiveComprehensionMAE token10666General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index71Visuospatial constructionVisuomotor constructionClock drawingSpatial perceptionVisual perceptionJOLO798 | | | WCST-64 categories completed | — | 2-5 |
| SpeedRecognition speedStroop W84InVerbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index83InVerbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index83InExpressivePhonemic fluencyAnimals58ExpressivePhonemic fluencyFAS58NamingBNT-264ReceptiveComprehensionMAE sentences71ReceptiveComprehensionMAE token10666General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index71Visuospatial constructionVisuomotor constructionClock drawingSpatial perceptionVisual perceptionJOLO7986 | | | WCST-64 failure to maintain set | — | — |
| Recognition speed Stroop C 86 Intervention Verbal general Verbal comprehension WAIS-IV Verbal Comprehension Index 83 1 Semantic fluency Animals 58 Expressive Phonemic fluency FAS 58 Naming BNT-2 64 Repetition MAE sentences 71 Receptive Comprehension MAE token 106 66 General Perceptual reasoning WAIS-IV Perceptual Reasoning Index 71 Visuospatial Visuomotor construction Clock drawing Spatial Visual perception JOLO 79 86 | Speed | Processing speed | WAIS-IV Processing Speed Index | 86 | 18 |
| Stroop C86InVerbal generalVerbal comprehensionWAIS-IV Verbal Comprehension Index831Semantic fluencyAnimals58ExpressivePhonemic fluencyFAS58NamingBNT-264RepetitionMAE sentences71ReceptiveComprehensionMAE token10666General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index71Visuospatial perceptionVisuomotor constructionClock drawingSpatial perceptionVisual perceptionJOLO79GD dominant hand671 | | Recognition speed | Stroop W | 84 | 14 |
| Semantic fluencyAnimals58ExpressivePhonemic fluencyFAS58NamingBNT-264.2RepetitionMAE sentences71.3ReceptiveComprehensionMAE token1066General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index71.3Visuospatial constructionVisuomotor constructionClock drawingSpatial perceptionVisual perceptionJOLO798GD dominant hand6711 | | | Stroop C | 86 | 16 |
| ExpressivePhonemic fluencyFAS58NamingBNT-264RepetitionMAE sentences71ReceptiveComprehensionMAE token10666General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index71Visuospatial constructionVisuomotor constructionClock drawingSpatial perceptionVisual perceptionJOLO7986 | Verbal general | Verbal comprehension | WAIS-IV Verbal Comprehension Index | 83 | 13 |
| ExpressiveNamingBNT-264.4RepetitionMAE sentences713ReceptiveComprehensionMAE token10666General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index713Visuospatial constructionVisuomotor constructionClock drawingSpatial perceptionVisual perceptionJOLO798GD dominant hand6711 | Expressive | Semantic fluency | Animals | 58 | .3 |
| NamingBNT-264.3RepetitionMAE sentences713ReceptiveComprehensionMAE token10666General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index713Visuospatial constructionVisuomotor constructionClock drawingSpatial perceptionVisual perceptionJOLO798GD dominant hand6711 | | Phonemic fluency | FAS | 58 | .3 |
| ReceptiveComprehensionMAE token1066General perceptionPerceptual reasoningWAIS-IV Perceptual Reasoning Index7133Visuospatial constructionVisuomotor constructionClock drawingSpatial perceptionVisual perceptionJOLO798GD dominant hand671 | | Naming | BNT-2 | 64 | .8 |
| General perception Perceptual reasoning WAIS-IV Perceptual Reasoning Index 71 33 Visuospatial construction Visuomotor construction Clock drawing - < | | Repetition | MAE sentences | 71 | 3 |
| perception Perceptual reasoning WAIS-IV Perceptual Reasoning index 71 33 Visuospatial construction Visuomotor construction Clock drawing - - Spatial perception Visual perception JOLO 79 8 | Receptive | Comprehension | MAE token | 106 | 67 |
| construction Clock drawing - - Spatial perception JOLO 79 8 | | Perceptual reasoning | WAIS-IV Perceptual Reasoning Index | 71 | 3 |
| perception GD dominant hand 67 1 | * | Visuomotor construction | Clock drawing | _ | |
| GD dominant hand 67 1. | * | Visual perception | JOLO | 79 | 8 |
| Motor Vianual dexterity | Motor | Manual dexterity | GD dominant hand | 67 | 1.4 |
| GD nondominant hand 64 .4 | | | GD nondominant hand | 64 | .8 |

TABLE 1: Neuropsychological test scores.

*WRAT-4 Reading = Wide Range Achievement Test, 4th Edition; WAIS-IV = Wechsler Adult Intelligence Scale, 4th Edition; CVLT-II = California Verbal Learning Test, 2nd Edition; BVMT-R = Brief Visuospatial Memory Test-Revised; Trails A = Trail Making Test Form A; Trails B = Trail Making Test Form B; Stroop C = Stroop Color Subtest; Stroop W = Stroop Word Subtest; Stroop C-W = Stroop Color-Word Subtest; WCST = Wisconsin Card Sorting Test; Animals = semantic fluency; FAS = phonemic fluency; BNT-2 = Boston Naming Test, 2nd Edition; MAE = Multilingual Aphasia Examination; JOLO = Judgment of Line Orientation Test; GD = grip dynamometer.

2 years until she was able to drive and care for her children independently. However, she remained agitated and irritable compared to her baseline.

The second episode occurred nine years later and was much more severe. It involved personality changes, perseveration in behaviors and speech, impulsive financial behaviors (e.g., spending over \$10,000 on clothes in one week), paranoia, psychosis, and aggressive outbursts. She also had dressing apraxia, and her psychosis included visual hallucinations of monsters and demons, melting ceilings, delusions of her children being trapped under the bathroom tiles, and the belief that she had to free them using only her fingernails. She was under restraint during her inpatient stay for a week due to aggressive outbursts. She also developed status epilepticus 4 times, which were treated with conventional IV antiepileptic drugs.

Video EEG showed epileptic activity in the right frontoparietal region. The remainder of the workup was negative, including MRI, CT, PET, transvaginal US, and LP. MRIs of the brain and pelvis were both negative (pelvic MRI was initiated to rule out ovarian teratoma). CSF was unrevealing including T. pallidum, West Nile, IgG, albumin, cell ct/protein/glucose, cultures, cryptococcal Ag, India ink, HSV PCR, and TB. Laboratory testing by Mayo Clinic revealed that the serum anti-NMDA antibodies were negative, but CSF anti-NMDA antibodies with repeat testing were found to be positive. Treatment included bilateral salpingo-oophorectomy (but no ovarian teratoma was found), IVIG transfusion, and plasmapheresis. She was later switched to rituximab infusion and also received medications for psychosis and seizures. Final diagnosis was documented as anti-NMDA-receptor encephalitis without teratoma. A neuropsychological evaluation occurred after treatment. It showed numerous cognitive deficits such as impairments in visual memory, mental flexibility, expressive language, visuospatial skills, and motor dexterity (see Table 1). The most significant problems were present in verbal fluency (semantic and phonemic fluency, both <1st percentile), mental flexibility (<1st percentile), and elevated depression and anxiety. She continues to have compromised cognitive status along with residual frontal deficits and mood changes. She and her guardian provided consent for this case study to be published.

3. Discussion

In anti-NMDAR encephalitis, antibodies are directed towards the NR1 subunit of the NMDA receptor causing a depletion of NMDA receptors [1, 4, 6, 7]. The lack of receptors causes neuropsychiatric symptoms, attributable to ovarian teratomas and autoimmune processes in approximately half of the cases [2–4, 6, 8]. Recognizing the symptom complex is crucial to diagnosis [7]. Commonly, patients develop a multistage illness that progresses from psychiatric symptoms to more extreme global symptoms [1]. Up to half of the women diagnosed with anti-NMDAR encephalitis have an underlying ovarian teratoma [3, 8].

Treatment involves immunosuppression with steroids and intravenous administration [1, 4, 7, 9]. Many patients recover well after appropriate treatment [10]. While it is thought that there is a higher prevalence of anti-NMDAR encephalitis, data on posttreatment cognitive states remain rather limited [11, 12]. This case revealed residual frontal deficits with mood changes in the context of anti-NMDAR encephalitis. This case is the first to describe posttreatment cognition in anti-NMDAR encephalitis after probable serial autoimmune episodes.

4. Conclusion

Anti-N-methyl-D-aspartate receptor encephalitis is a neurological, autoimmune disorder tightly conceptualized only as recently as the mid-2000s. It presents itself in a combination of psychiatric, neurological, and autonomic features. This case was a unique case with probable earlier episode (prior to the mid-2000s operationalization of the disease) and a later relapse, accompanying a comprehensive neuropsychological profile tracked after the relapse and subsequent improvement. Neurocognitive findings revealed residual frontal deficits with mood changes even in the state after plasmapheresis, and these deficits do not appear to associate neatly with structural brain damage visible in imaging (or lack thereof), as clinical symptoms were likely the sequelae of a more global neuroinflammatory damage that occurred. This case is the first to describe posttreatment cognition in anti-NMDAR encephalitis after probable serial autoimmune episodes.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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