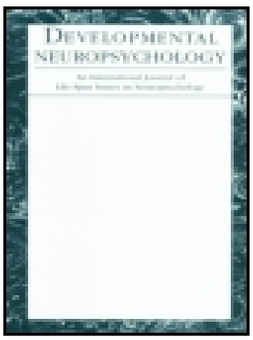

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Two Case Reports of Neuropsychological Outcomes following Pediatric anti-*N*-methyl *D*-aspartate Receptor Autoimmune Encephalitis

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ABSTRACT

Anti-NMDAR autoimmune encephalitis is a rare neurological condition. Limited existing pediatric case studies have shown mild, but persisting, neuropsychological impairments. This report described neuropsychological functioning in two patients treated for anti-NMDAR autoimmune encephalitis. Patient A is a 16-year-old male (10 months after symptom onset) and Patient B is a 5-year-old female (45 months after symptom onset). Contrary to expectations, their cognitive profiles were largely intact, raising the possibility of minimal cognitive implications for some pediatric patients with this condition. Additional research is needed to identify factors that contribute to better cognitive outcomes in children with anti-NMDAR autoimmune encephalitis.

N-methyl-*D*-aspartate receptors (NMDARs) are glutamate receptors that are involved in normal neural network formation throughout the central nervous system and play a vital role in synaptic plasticity, memory, and learning (Komuro & Rakic, 1993; Lynch, Anegawa, Verdoorn, & Pritchett, 1994). Anti-NMDAR autoimmune encephalitis is a rare autoimmune condition that was first characterized in 2007 (Dalmau et al., 2008). Although the mechanisms that initiate this condition are largely unknown, the course of recovery indicates immune-mediated neuronal dysfunction, rather than irreversible degeneration. This dysfunction is thought to occur when antibodies that were produced to attack neoplastic cells cross-react and instead destroy NMDARs (Dalmau et al., 2008; Dalmau, Lancaster, Martinez-Hernandez, Rosenfeld, & Balice-Gordon, 2011). In total, 120 cases of anti-NMDAR autoimmune encephalitis were reported in the literature (Day, High, Cot, & Tang-Wai, 2011). However, the exact incidence remains largely unknown. Women are thought to account for 80% of known patients and many documented cases have been associated with ovarian teratoma (Dalmau et al., 2011; Florance et al., 2009). There are fewer reports of childhood cases, although Florance et al. (2009) suggested that it may occur more frequently than is currently thought.

The acute clinical presentation of anti-NMDAR autoimmune encephalitis has been well characterized. However, given the heterogeneity of presenting symptoms and the overlap with other psychiatric and neurological conditions, anti-NMDAR autoimmune encephalitis may often be misidentified (Florance et al., 2009). Adults often present with memory problems, difficulty using everyday objects, depression, anxiety, paranoia, hallucinations, delusions, confusion, and inappropriate laughing and crying (Finke et al., 2011; Miya, Takahashi, & Mori, 2014; Titulaer et al., 2013). In children, initial symptoms may include temper tantrums, behavioral disturbance, motor problems,

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hyperactivity, agitation, memory deficits, and speech deterioration (Florance et al., 2009; Guo et al., 2014). These symptoms often progress to altered mental status and seizures (Finke et al., 2011; Miya et al., 2014). Electroencephalogram (EEG) is abnormal in 77% of patients and characterized by non-specific, slow, and disorganized activity (Dalmau et al., 2008, 2011). In about 50% of cases, magnetic resonance imaging (MRI) is unremarkable and typically not associated with the emergence of cognitive problems (Houtrow, Bhandal, Pratini, Davidson, & Neufeld, 2012). Patients are typically hospitalized for 3–4 months and subsequently require outpatient rehabilitation, including physical, speech, and/or behavioral therapies. Treatment includes corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange. If untreated, the risk of mortality is high (Dalmau et al., 2011).

Past research has also documented the medical course of recovery after the acute period. Factors associated with better neurological outcome include early diagnosis, aggressive immunosuppressive therapy, the presence of a detectible tumor, participation in rehabilitation services, and longer rehabilitation length of stay (Dalmau et al., 2008; Houtrow et al., 2012; Tailor et al., 2013; Titulaer et al., 2013). A multi-site study of children and adults found that 81% of patients showed significant neurological improvement within the first 2 years of the initial symptom onset. Twelve percent of patients relapsed and required continued immunotherapy. Those who did not recover often remained severely disabled or died (Titulaer et al., 2013). In a study of children, 29% of patients had a full recovery and returned to all previous activities, 45% had substantial improvement/mild functional deficits, and 26% showed limited improvement/minimal change in neurological status from acute phase of illness (Florance et al., 2009). With respect to psychiatric symptoms, Chapman and Vause (2011) documented mild persisting agitation, anxiety, social withdrawal, and inappropriate affect in a 16-year-old male who was 3 months post-hospitalization. In another case study of adolescents, there were mild anxiety symptoms 2–6 months after symptom onset. Anxiety symptoms were minimal at a 6–24-months' follow-up. Those who endorsed mild depressive symptoms in the acute phase reported minimal symptoms at the 2–6 months' and the 6–24 months' follow-ups, suggesting that emotional problems resolved with time (Hinkle et al., 2016).

Few studies have examined cognitive outcomes after treatment for anti-NMDAR autoimmune encephalitis. Adolescent and adult patients often self-report persisting difficulties with memory, attention and executive functioning (Chapman & Vause, 2011; Dalmau et al., 2008). Finke et al. (2011) assessed nine adult patients (eight of which were female) with a history of anti-NMDAR autoimmune encephalitis. Participants were 21–44 years of age and were assessed 23–69 months after their initial diagnosis. Eight of the nine patients had cognitive impairments on formal testing, including deficits in attention, visual and auditory working memory, verbal learning and memory, and planning. Earlier medical intervention was associated with better neuropsychological outcomes (Finke et al., 2011). A separate case report of six children (five of which were female) showed persistent difficulties at 1–2 years following inpatient rehabilitation, including mild impulsivity, slowed processing speed, learning, inattention, and deficits in language and short-term memory (Houtrow et al., 2012). Hinkle et al. (2016) reported neuropsychological outcomes in three female adolescents. In the acute phase (4–6 weeks after symptom onset), all three patients demonstrated substantial cognitive impairments on neuropsychological testing. At the post-acute phase (2–6 months after symptom onset), executive functioning and processing speed ranged from low average to severely impaired. One patient had impaired to severely impaired problem solving. Another showed low average to impaired verbal memory. At the long-term follow-up (6–24 months after symptom onset), two patients showed weaknesses in fine motor skills (low average to impaired ranges) and memory (low average to impaired). All three showed continued weaknesses in executive functioning, specifically problem solving, inhibition, working memory, planning, and organization (low average to impaired). Based on these findings, the authors concluded that there are mild, but persisting cognitive problems, primarily in the areas of memory, processing speed, fine motor skills, and executive functioning.

Other factors may influence cognitive recovery after treatment for anti-NMDAR autoimmune encephalitis. Seizures are a common consequence of this condition (Miya et al., 2014). The presence

of seizures may place patients at elevated risk for cognitive problems, most notably learning and attention (Seidenberg, Pulsipher, & Hermann, 2007). Age at onset may be another relevant consideration. In clinical populations that are characterized by diffuse neurological insult, early childhood is a time of increased neural vulnerability (Ewing-Cobbs, Prasad, Landry, Kramer, & DeLeon, 2004). This is particularly true of frontal regions (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002). This may result in various cognitive impairments, most notably attention and executive functions (Bellgrove, Hester, & Garavan, 2004).

This case report described neuropsychological functioning in two culturally diverse pediatric patients with a history of anti-NMDAR autoimmune encephalitis. As an additional contribution to the literature, this report included a male and a younger child, which are demographics for which the current literature is particularly limited. In view of prior research (Dalmau et al., 2008; Hinkle et al., 2016), it was hypothesized that learning and memory would be particularly affected. Because the frontal areas are particularly vulnerable in conditions that disrupt early neural development (Anderson et al., 2002; Hinkle et al., 2016), it was also expected that attention and executive functions would be impacted.

Evaluation procedures

Two pediatric patients with a history of anti-NMDAR autoimmune encephalitis participated in comprehensive outpatient neuropsychological evaluations. Parents/guardians consented for their child's de-identified clinical information to be used for research and educational purposes. Neuropsychological test data was interpreted using the qualitative descriptions of performance that were offered by Wechsler (1997).

Patient A

Patient A is a 16-year, 4-month-old, right-handed, Native American male who was referred by his neurologist. This evaluation was conducted 10 months after the symptom onset. Initial symptoms included headaches, inappropriate giggling, seeing "shadows" that others could not see, problems with attention, and slowed speed of cognitive processing. One month after the symptom onset, Patient A had two periods of confusion, and receptive and expressive aphasia. He eventually sought emergency medical services and a cerebrospinal fluid (CSF) culture confirmed the anti-NMDAR autoimmune encephalitis diagnosis. While hospitalized, there was a 5-week period of confusion and disorientation. Computerized tomography (CT) and MRI of the brain were normal. An EEG was abnormal and characterized by suppressed background activity and occasional bilateral frontal slowing. There was no evidence of epileptiform activity. Patient A was treated with IVIG and hospitalized for 8 weeks. He subsequently received outpatient occupational, physical, and speech/language therapies. At the time of this evaluation, he was no longer receiving these services.

With respect to current concerns, Patient A and his mother ("Ms A") described persisting fatigue. Patient A also reported problems with attention, distractibility, and slowed processing speed for academic tasks. These concerns were not present before his illness. Patient A also described anxiety about his health and problems with behavioral dysregulation. For example, Patient A was recently suspended from school after a physical altercation with another student. Ms A reported that this behavior was atypical for him.

Birth, developmental, medical, and psychiatric histories prior to onset of anti-NMDAR autoimmune encephalitis were unremarkable. Patient A was adopted by Ms A and her spouse shortly after his birth. Relevant biological family history was unknown. Patient A's biological and adoptive parents identified as Native American. Patient A and his adoptive parents were bilingual (English and Tewa). All of Patient A's education was in English. He reported that he prefers and has a better command of English overall. Throughout his education, Patient A was enrolled in a general education setting. There were no preexisting concerns about learning. After his hospitalization, a Section 504 Plan was implemented, which provided him with extended time for exams, a quiet testing environment, and reduced homework load.

Results

Patient A presented casually dressed and well groomed. Affect was euthymic. Motor skills and language were unremarkable. He worked slowly, particularly on academic tasks. Later in the morning on the first day of testing, Patient A expressed fatigue. Therefore, testing was completed over the course of two morning testing sessions on separate days.

Neurobehavioral data are reported in Table 1. On the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV; Wechsler, 2008), all of the indices were in the average range. Performances were average to high average on measures of verbal and visual learning and memory (Wechsler Memory Scale, Fourth Edition; Wechsler, 2009), grip strength (Lafayette Instruments, 2004), fine motor coordination (Grooved Pegboard; Lafayette Instruments, 2002), sustained visual attention (Continuous Performance Test-II; Conners & MHS Staff, 2002), and processing speed (Delis, Kaplan, & Kramer, 2001; Wechsler, 2008). Executive functions were somewhat variable, although many aspects were also within age expectation. On the Delis–Kaplan Executive Functioning System (D-KEFS; Delis et al., 2001), performances were average to high average on tests of inhibition/switching, speed of word reading, category fluency, category set shifting, and spatial planning. Letter fluency was in the borderline range and color naming was low average. Expressive vocabulary (Wechsler, 2008) was also low average.

Using age-based norms for the Woodcock Johnson Test of Achievement – Fourth Edition (WJ-IV; Schrank, McGrew, Mather, Wendling, & LaForte, 2014), math, spelling, and written expression were average to high average. Reading skills were variable. On the WJ-IV, brief reading fluency was average and single-word reading was low average. When reading longer passages on the Nelson-Denny Reading Test (Brown, Fishco, & Hanna, 1993), reading rate and comprehension were borderline to impaired.

On the Behavior Assessment System for Children – Second Edition (BASC-2; Reynolds & Kamphaus, 2004), Patient A endorsed mild concerns about attitudes toward school, sense of inadequacy, social stress, attention, hyperactivity, and atypicality. Ms A reported mild problems with attention. Patient A's teacher reported mild problems with hyperactivity, anxiety, somatization, attention, learning and atypicality. Elevations on the atypicality subscales per self and teacher report may represent atypical experiences during Patient A's recent illness. Patient A reported significant anxiety on the self-report version of the Multidimensional Anxiety Scale for Children – Second Edition (MASC-2; March, 2013). Ms A similarly reported clinically significant symptoms of anxiety.

Patient B

Patient B is a 5-year, 11-month-old, right-handed, Hispanic female who was referred by her neurologist. This evaluation was conducted 45 months' post-treatment. Symptoms of anti-NMDAR autoimmune encephalitis were first noted when Patient B was 26 months of age. Initial symptoms included problems with sleep, reduced appetite, and crying more than usual. Her mother ("Ms B") described possible atypical perceptual experiences as evidenced by pointing and responding to visual stimuli that was not seen by others. Prior to that time, Patient B was typically developing with respect to speech and toilet training. There were mild preexisting concerns about gross motor skills, which were attributed to low muscle tone. Patient B briefly received occupational therapy at 18 months of age and these concerns resolved shortly thereafter. After the onset of symptoms, she "stopped talking," toileting accidents became more frequent, and gross motor problems re-emerged (e.g., unable to walk without holding on to furniture for balance). Per medical records, Patient B had two seizures that were characterized by bilateral convulsions and lack of awareness. An EEG that was completed during her hospitalization was mildly abnormal and characterized by diffuse slowing and multifocal spikes. Brain MRI was normal. A CSF culture confirmed the anti-NMDAR antibody and Patient B was treated with corticosteroids and IVIG. She was hospitalized for 2 months. After discharge, she struggled to

Table 1. Test results.

Patient A: 16-year, 4-month old, right-handed male				Patient B: 5-year, 11-month old, right-handed female			
10 months after initial symptom onset				45 months after initial symptom onset			
Measure	Index/subtest	Score	Performance classification	Measure	Index/subtest	Score	Performance classification
Intellectual							
WAIS-IV	**Full Scale Intelligence Quotient (StS)**	100	Average	WPPSI-IV	**Full Scale Intelligence Quotient (StS)**	89	Low average
	Verbal Comprehension Index (StS)	98	Average		**Verbal Comprehension Index (StS)**	93	Average
	Vocabulary (ScS)	7	Low average		Information (ScS)	9	Average
	Similarities (ScS)	14	Superior		Similarities (ScS)	9	Average
	Information (ScS)	8	Average		**Visual Spatial Index (StS)**	89	Low average
	Perceptual Reasoning Index (StS)	109	Average		Block Design (ScS)	8	Average
	Block Design (ScS)	10	Average		Object Assembly (ScS)	8	Average
	Visual Puzzles (ScS)	12	High average		**Fluid Reasoning Index (StS)**	82	Low average
	Matrix Reasoning (ScS)	13	High average		Matrix Reasoning (ScS)	7	Low average
	Working Memory Index (StS)	92	Average		Picture Concepts (ScS)	7	Low average
	Digit Span (ScS)	8	Average		**Working Memory Index (StS)**	103	Average
	Arithmetic (ScS)	9	Average		Picture Memory (ScS)	8	Average
	Processing Speed Index (StS)	100	Average		Zoo Locations (ScS)	13	High average
	Coding (ScS)	8	Average		**Processing Speed Index (StS)**	97	Average
	Symbol Search (ScS)	12	High average		Bug Search (ScS)	10	Average
					Cancellation (ScS)	9	Average
Academics							
WJ-IV	Letter-Word Identification (StS)	85	Low Average	WJ-IV	Letter-Word Identification (StS)	102	Average
	Applied Problems (StS)	109	Average		Applied Problems (StS)	113	High average
	Spelling (StS)	94	Average		Spelling (StS)	109	Average
	Calculation (StS)	99	Average		Word Attack (StS)	113	High average
	Writing Samples (StS)	110	High Average				
	Sentence Reading Fluency (StS)	85	Low Average				
	Math Facts Fluency (StS)	100	Average				
	Sentence Writing Fluency (StS)	100	Average				
Nelson- Denny	Timed Comprehension (%)	5	Borderline				
	Extended Time Comprehension (%)	4	Borderline				
	Reading Rate (%)	1	Extremely Low				
Language							
				NEPSY-II	Comprehension of Instructions (ScS)	11	Average
				CELF-5	Formulated Sentences (ScS)	9	Average
Attention							
CPT-II	Omissions (T)	44	Low	K-CPT	Omissions (T)	47	Average
	Commissions (T)	43	Low		Commissions (T)	48	Average
	Hit Reaction Time (RT) (T)	43	A Little Fast		Hit RT (T)	50	Average

(*Continued*)

Table 1. (Continued).

Patient A: 16-year, 4-month old, right-handed male				Patient B: 5-year, 11-month old, right-handed female			
10 months after initial symptom onset				45 months after initial symptom onset			
Measure	Index/subtest	Score	Performance classification	Measure	Index/subtest	Score	Performance classification
	Hit RT Standard Error (SE) (T)	46	average		Hit RT SE (T)	52	Average
	Variability (T)	52	Average		Variability (T)	54	Average
	Detectability (d') (T)	47	Average		Detectability (d') (T)	55	High average
	Response Style (B) (T)	46	Average		Response Style (B) (T)	70	Very elevated
	Perseverations (T)	45	Average		Perseverations (T)	51	Average
	Hit RT Block Change (T)	49	Average		Hit RT Block Change (T)	20	Atypically fast
	Hit SE Block Change (T)	57	High average		Hit SE Block Change (T)	31	Low
	Hit RT Inter-Stimulus Interval (ISI) Change (T)	50	Average		Hit RT ISI Change (T)	34	Atypically fast
	Hit SE ISI Change (T)	61	Elevated		Hit SE ISI Change (T)	35	Low
Executive Functions							
D-KEFS	Verbal Fluency: Letter (ScS)	5	Borderline	CCT	Total (T)	36	Borderline
	Verbal Fluency: Category (ScS)	8	Average	NEPSY-II	Word Generation: Semantic (ScS)	12	High average
	Verbal Fluency: Switch Correct (ScS)	8	Average		Inhibition: Naming Time (ScS)	9	Average
	Verbal Fluency: Switching Accuracy (ScS)	9	Average		Inhibition: Naming Total Errors (%)	26–50	Average
	Color-Word: Color Naming (ScS)	7	Low Average		Inhibition: Inhibit Time (ScS)	9	Average
	Color-Word: Word Read (ScS)	8	Average		Inhibition: Inhibit Errors (%)	11–25	Borderline
	Color-Word: Inhibition (ScS)	8	Average				
	Inhibition Errors (ScS)	13	High Average				
	Color-Word: Inhibit/Switch (ScS)	8	Average				
	Inhibit/Switch Errors (ScS)	12	High Average				
	Tower: Total Achievement (ScS)	9	Average				
Learning and Memory							
WMS-IV	Logical Memory I (ScS)	10	Average	ChAMP	Lists (ScS)	10	Average
	Logical Memory II (ScS)	9	Average		Lists Delayed (ScS)	11	Average
	Logical Memory II Recognition (%)	10–16	Low Average		Lists Recognition (ScS)	15	Superior
	Visual Reproduction I (ScS)	12	High Average		Objects (ScS)	13	High average
	Visual Reproduction II (ScS)	10	Average		Objects Delayed (ScS)	13	High Average
	Visual Reproduction II Recognition (%)	26–50	Average				
Visual-Motor							
Grooved Pegboard	Dominant (right) (Z)	−1.06	Low Average	Beery VMI	VMI (StS)	96	Average
	Non-dominant (left) (Z)	0.13	Average		Visual Perception (StS)	111	High average

(*Continued*)

Table 1. (Continued).

Patient A: 16-year, 4-month old, right-handed male				Patient B: 5-year, 11-month old, right-handed female			
10 months after initial symptom onset				45 months after initial symptom onset			
Measure	Index/subtest	Score	Performance classification	Measure	Index/subtest	Score	Performance classification
Grip Strength	Dominant (right) (Z)	−0.09	Average		Motor Coordination (StS)	86	Low average
	Non-dominant (left) (Z)	−0.01	Average				
Behavioral and Emotional Functioning							
BASC-2: Mother	Hyperactivity (T)	41	Non-clinical	BASC-3: Mother	Hyperactivity (T)	50	Non-clinical
	Aggression (T)	38	Non-clinical		Aggression (T)	42	Non-clinical
	Conduct Problems (T)	42	Non-clinical		Anxiety (T)	46	Non-clinical
	Anxiety (T)	36	Non-clinical		Depression (T)	40	Non-clinical
	Depression (T)	41	Non-clinical		Somatization (T)	37	Non-clinical
	Somatization (T)	47	Non-clinical		Attention Problems (T)	67	At-risk
	Atypicality (T)	52	Non-clinical		Atypicality (T)	42	Non-clinical
	Withdrawal (T)	38	Non-clinical		Withdrawal (T)	47	Non-clinical
	Attention Problems (T)	64	At-risk		Adaptability (T)	46	Non-clinical
	Adaptability (T)	68	At-rick		Social Skills (T)	44	Non-clinical
	Social Skills (T)	50	Non-clinical		Functional Communication (T)	46	Non-clinical
	Leadership (T)	49	Non-clinical		Act of Daily Living (T)	37	Non-clinical
	Activities of Daily Living (T)	45	Non-clinical				
	Functional Communication (T)	57	Non-clinical				
BASC-2: Self	Attitudes to School (T)	63	At-risk				
	Attitudes to Teachers (T)	53	Non-clinical				
	Sensation Seeking (T)	51	Non-clinical				
	Atypicality (T)	65	At-risk				
	Locus of Control (T)	44	Non-clinical				
	Social Stress (T)	62	At-risk				
	Anxiety (T)	53	Non-clinical				
	Depression (T)	55	Non-clinical				
	Sense of Inadequacy (T)	68	At-risk				
	Somatization (T)	44	Non-clinical				
	Attention Problems (T)	63	At-risk				
	Hyperactivity (T)	60	At-risk				
	Relations with Parents (T)	57	Non-clinical				
	Interpersonal Relations (T)	52	Non-clinical				
	Self-esteem (T)	50	Non-clinical				
	Self-reliance (T)	35	Non-clinical				
BASC-2: Teacher	Hyperactivity (T)	68	At-risk				
	Aggression (T)	54	Non-clinical				
	Conduct Problems (T)	56	Non-clinical				
	Anxiety (T)	68	At-risk				

(*Continued*)

Table 1. (Continued).

Patient A: 16-year, 4-month old, right-handed male				Patient B: 5-year, 11-month old, right-handed female			
10 months after initial symptom onset				45 months after initial symptom onset			
Measure	Index/subtest	Score	Performance classification	Measure	Index/subtest	Score	Performance classification
	Depression (T)	57	Non-clinical				
	Somatization (T)	60	At-risk				
	Attention Problems (T)	63	At-risk				
	Learning Problems (T)	66	At-risk				
	Atypicality (T)	81	Elevated				
	Withdrawal (T)	44	Non-clinical				
	Adaptability (T)	43	Non-clinical				
	Social Skills (T)	57	Non-clinical				
	Leadership (T)	51	Non-clinical				
	Study Skills (T)	39	Non-clinical				
	Functional Communication (T)	36	Non-clinical				
MASC-2: Mother	Total (T)	64	Slightly Elevated				
	Separation Anx/Phobias (T)	65	Elevated				
	GAD Index (T)	69	Elevated				
	Social Anxiety (T)	55	High average				
	Obsessions & Compulsions (T)	54	Average				
	Physical Symptoms (T)	62	At-risk				
	Harm Avoidance (T)	57	high Average				
MASC-2: Self	Total (T)	78	Very elevated				
	Separation Anx/Phobias (T)	60	At-risk				
	GAD Index (T)	72	very elevated				
	Social Anxiety (T)	68	Elevated				
	Obsessions & Compulsions (T)	82	Very elevated				
	Physical Symptoms (T)	65	Elevated				
	Harm Avoidance (T)	65	Elevated				

WAIS-IV = Wechsler Adult Intelligence Scale-Fourth Edition; WJ-IV = Woodcock Johnson IV Tests of Achievement; CPT-II = Continuous Performance Test 2nd Edition; D-KEFS = Delis–Kaplan Executive Function System; WMS-IV = Wechsler Memory Scale Fourth Edition; BASC-2 = Behavior Assessment System for Children, Second Edition; MASC-2 = Multidimensional Anxiety Scale for Children 2nd Edition; WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition; NEPSY-II = A Developmental Neuropsychological Assessment-2nd Edition; CELF-5 = Clinical Evaluation of Language Fundamentals, Fifth Edition; K-CPT = Kiddie Continuous Performance Test; CCT = Children's Category Test; ChAMP = Child and Adolescent Memory Profile; Beery VMI = Beery-Buktencia Developmental Test of Visual-Motor Integration; StS = Standard Score; ScS = Scaled Score; *T* = *T*-Score; *Z* = *Z*-Score.

return to her previous level of functioning, including walking, talking, and feeding herself. From 3 to 5 years of age, she received outpatient speech/language, occupational, and physical therapies. Since her hospitalization, she was healthy and follow-up EEGs were normal. At the time of this evaluation, she was not receiving any therapies.

Birth and pre-illness medical history were unremarkable. At the time of the evaluation, she was enrolled in a general education kindergarten class with no formal academic accommodations. Her biological family history was reportedly unremarkable.

With respect to current concerns, Ms B described hyperactivity and inattention. Although she was not offered a formal diagnosis of an attentional disorder, Patient B was prescribed Adderall (20 mg) by her primary care physician. Patient B took this medication for 3 weeks before it was discontinued because of stomachaches. At the time of this evaluation, she was not prescribed any medications. According to Ms B, academic skills were at grade expectation, although there were mild concerns about slow acquisition. Ms B speculated that this was related to inattention. Additional mild concerns were related to gross (e.g., sometimes clumsy) and fine (e.g., difficulty buttoning and zipping clothing) motor skills.

Results

Patient B presented casually dressed and well groomed. Affect was euthymic. Motor functioning and language were unremarkable. Per observation, attention and activity level were within normal limits.

Neurobehavioral data are reported in Table 1. On the Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV; Wechsler, 2012), the Verbal Comprehension, Working Memory, and Processing Speed indices were average. The Visual Spatial Index was at the upper end of the low average range. The Fluid Reasoning Index was low average. Across neuropsychological measures, expressive (Clinical Evaluation of Language Fundamentals-Fifth Edition; Wiig, Semel, & Secord, 2013) and receptive (NEPSY-2; Korkman, Kirk, & Kemp, 2007) language, visual perception, visual motor integration (Beery-Buktenica Developmental Test of Visual-Motor Integration – Sixth Edition; Beery & Beery, 2010), sustained visual attention (Kiddie Continuous Performance Test; Conners, 2001), working memory, processing speed (WPPSI-IV), verbal and visual learning and memory (Child and Adolescent Memory Profile; Sherman & Brooks, 2015), and rapid word generation (NEPSY-2 Word Generation subtest) were all average. Motor coordination was low average (Beery & Beery, 2010). On the WJ-IV, basic reading (Letter-Word Identification and Word Attack subtests), spelling, and math (Applied Problems subtest) skills were average to high average for her age.

Patient B evidenced relative weaknesses in aspects of her early executive skills. On the Children's Category Test (CCT; Boll, 1993), complex problem solving with the aid of corrective feedback was at the upper end of the borderline range. On a task of inhibition, she appeared to compromise accuracy for speed and errors were in the borderline range (NEPSY-2; Korkman et al., 2007). On the Behavior Assessment System for Children –Third Edition (BASC-3; Reynolds & Kamphaus, 2015), Ms B reported mild (at-risk) concerns about attention.

Discussion

This case report examined neuropsychological functioning in two pediatric patients with a history of anti-NMDAR autoimmune encephalitis. In both cases, the acute clinical presentation (e.g., initial symptoms and abnormalities on EEG) and the course of treatment (e.g., medication, IVIG, hospitalization, and rehabilitation) were consistent with the existing literature (Finke et al., 2011; Hinkle et al., 2016; McKeon et al., 2017; Miya et al., 2014). Specifically, Patient A had unusual perceptual experiences, aphasia, and problems with attention and processing speed. Patient B had regressions in her speech and gross motor skills and behavioral changes.

As reviewed above, limited prior research has documented neuropsychological impairments in adults and children with a history of anti-NMDAR autoimmune encephalitis (Finke et al., 2011; Hinkle et al., 2016). From a cognitive perspective, the existing pediatric literature suggests long-term deficits, primarily in the areas of memory, processing speed, fine motor skills and executive functioning (Hinkle et al., 2016). Contrary to our hypotheses and what would be expected given these prior findings, the patients in this case study were largely intact cognitively. This suggests either minimal impact of anti-NMDAR autoimmune encephalitis on cognitive functioning or adequate functional recovery after the illness. Although not as impaired as the case studies reported by Hinkle et al. (2016), there were weaknesses in executive functioning in one of our pediatric patients.

Patient A showed weaknesses in aspects of reading, most notably comprehension and rate. Letter fluency was an additional area of weakness, which is notable as this has been associated with reading ability (Buil-Legaz, Aguilar-Mediavilla, & Rodríguez-Ferreiro, 2015). However, there are several issues that complicate the interpretation of these cognitive and academic weaknesses. As an individual of Native American decent, cultural bias may have contributed to the relatively lower test scores in Patient A's cognitive profile. Although the effect of culture on neuropsychological testing has been documented for verbal and nonverbal measures across diverse populations (Rosselli & Ardila, 2003), research in Native American samples has shown that bias is particularly prominent on verbal measures (Verney, Bennett, & Hamilton, 2015). As an additional consideration, single-word reading and expressive vocabulary are often considered crystallized abilities and are therefore resistant to decline in cases of neural insult (Satz, Cole, Hardy, & Rassovsky, 2011). From that perspective, it is unlikely that reading and expressive vocabulary were impacted by anti-NMDAR autoimmune encephalitis. Instead, it is possible that Patient A had unrecognized reading and language weaknesses before his illness. These preexisting weaknesses were potentially exacerbated by the circumstances of his illness. Specifically, Patient A was absent from school for 2 months because of his illness and hospitalization. Reduced participation in school may have resulted in limited academic gains during that time. Fatigue, which the family identified as an area of concern since the illness, may have influenced test performance, particularly on the speeded measures of reading fluency and letter fluency.

Anxiety is common following neurological insult, including anti-NMDAR autoimmune encephalitis (Hinkle et al., 2016), and often contributes to long-term disability after neurological insult (Koponen et al., 2002). Consistent with this, anxiety was an area of concern for Patient A. Specifically, there were clinically significant symptoms of anxiety on the parent- and self-report versions of the MASC-2. In contrast, reports of anxiety on the BASC-2 were in the normal range. In considering the discrepancy between these measures, the MASC-2 is a more comprehensive assessment of anxiety whereas the BASC-2 anxiety subscale includes only a few general items.

Patient B also produced a largely intact cognitive profile. Early executive skills, specifically inhibitory control and problem solving, were relatively weak. In the interview and on a standardized behavioral rating, Patient B's mother endorsed mild concerns about attention. Patient B's weaknesses in attention and executive functioning are consistent with prior research that has shown that young children with neurological insults are at particularly high risk for difficulties in these areas (Anderson et al., 2002; Bellgrove et al., 2004). In children, the development of attention and executive skills relies heavily on functioning of the entire brain (Benjamin et al., 2007). It is possible that these areas were mildly impacted because Patient B's illness occurred during a time of rapid neural development.

Recent research has found that obtaining some low scores on neuropsychological testing is common in typically developing children. For example, Brooks, Sherman, and Iverson (2010) administered a comprehensive neuropsychological test battery to healthy children and adolescents. Low scores were common in children between the ages of 7 and 16 years, although it was rare that the number of low scores was five or more. It is possible that the relative weaknesses in these case studies were the result of expected variability in neuropsychological test performance.

However, each patient produced a pattern of relative weaknesses that was generally consistent with their presenting concerns. Therefore, expected variability alone was not thought to explain these test results.

Overall, these case studies suggest that it is possible for pediatric patients with anti-NMDAR autoimmune encephalitis to remain largely intact after their illness. Considering the existing literature (Hinkle et al., 2016; Miya et al., 2014) along with these case studies, long-term outcomes are nonetheless variable. In these case studies, Patient A presented with elevated anxiety and weaknesses in reading and language, whereas Patient B presented with weaknesses in early executive functioning. These differences in cognitive presentation between patients may be due to individual factors, including age of symptom onset, possible premorbid differences, and time since symptom onset. At this time, the role of individual and anti-NMDAR-related factors remains unclear. McKeon et al. (2017) found that individual (e.g., age and sex) and anti- NMDAR-related factors (e.g., disease etiology, the use of more aggressive immunotherapies, abnormal MRI and/or EEG, the presence of life-threatening symptoms, and seizure activity) were weak predictors of long-term outcome. In view of these case studies and the findings of McKeon et al., additional research is needed to increase our understanding of factors that are associated with long-term medical, psychiatric, and cognitive outcomes.

There are limitations of these case studies. Firstly, there are considerations when using common neuropsychological measures to assess the abilities of patients from diverse populations. Many neuropsychological measures, including those used in these evaluations, were normed and developed on primarily white, middle-class examinees. Neuropsychological measures may therefore not account for the unique cultural characteristics of individuals from diverse backgrounds. As a result, many neuropsychological measures underestimate the abilities of examinees from diverse populations (Ardila, Rodriguez-Menéndez, & Rosselli, 2002). This possible underestimation provides further evidence to suggest that these patients were generally intact from a cognitive perspective. As an additional consideration, neither patient had previous cognitive testing, which limits our understanding of premorbid ability. Therefore, we are unable to determine if the patterns of relative weakness were attributable to anti-NMDAR autoimmune encephalitis or if they were preexisting. Finally, generalizability is a limitation given the nature of a case report.

These case studies contribute to the currently limited literature that has examined outcomes following anti-NMDAR autoimmune encephalitis. These findings are particularly valuable because there are few known studies of neuropsychological outcomes in pediatric patients with a history of anti-NMDAR autoimmune encephalitis and even fewer that included data on patients from diverse populations, males (Patient A), and younger children (Patient B). Overall, considered with the existing literature, these case studies suggest that outcomes after anti-NMDAR autoimmune encephalitis are variable, although it is possible for pediatric patients to remain largely cognitively intact after their illness. In view of this variability in cognitive outcome, comprehensive neuropsychological assessment is an important part of treatment planning and intervention. From a research perspective, there is a need for research that improves our understanding of factors that contribute to better medical and cognitive outcomes in a larger sample of patients.

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References

Anderson, V. A., Anderson, P., Northam, E., Jacobs, R., & Mikiewicz, O. (2002). Relationships between cognitive and behavioral measures of executive function in children with brain disease. *Child Neuropsychology*, *8*(4), 231–240. doi:10.1076/chin.8.4.231.13509

Ardila, A., Rodriguez-Menéndez, G., & Rosselli, M. (2002). Current issues in neuropsychological assessment with Hispanics/Latinos. *Minority and Cross-Cultural Aspects of Neuropsychological Assessment*, 161–179.

Beery, K. E., & Beery, N. A. (2010). *Beery VMI* (6th ed.). Bloomington, MN: Psych Corp.

Bellgrove, M. A., Hester, R., & Garavan, H. (2004). The functional neuroanatomical correlates of response variability: Evidence from a response inhibition task. *Neuropsychologia*, *42*(14), 1910–1916. doi:10.1016/j.neuropsychologia.2004.05.007

Benjamin, C., Anderson, V., Pinczower, R., Leventer, R., Richardson, M., & Nash, M. (2007). Pre-and post-encephalitic neuropsychological profile of a 7-year-old girl. *Neuropsychological Rehabilitation*, *17*(4–5), 528–550. doi:10.1080/09602010601130927

Boll, T. (1993). *Children's category test*. San Antonio, TX: The Psychological Corporation.

Brooks, B. L., Sherman, E. M., & Iverson, G. L. (2010). Healthy children get low scores too: Prevalence of low scores on the NEPSY-II in preschoolers, children, and adolescents. *Archives of Clinical Neuropsychology*, *25*(3), 182–190. doi:10.1093/arclin/acq005

Brown, J. I., Fishco, V. V., & Hanna, G. S. (1993). *Nelson-Denny reading test*. Rolling Meadows, IL: Riverside.

Buil-Legaz, L., Aguilar-Mediavilla, E., & Rodríguez-Ferreiro, J. (2015). Reading skills in young adolescents with a history of Specific Language Impairment: The role of early semantic capacity. *Journal of Communication Disorders*, *58*, 14–20. doi:10.1016/j.jcomdis.2015.08.001

Chapman, M. R., & Vause, H. E. (2011). Anti-NMDA receptor encephalitis: Diagnosis, psychiatric presentation, and treatment. *American Journal of Psychiatry*, *168*(3), 245–251. doi:10.1176/appi.ajp.2010.10020181

Conners, C. K. (2001). *Conner's Kiddie continuous performance test*. North Tonawanda, NY: Multi-Health Systems.

Conners, C. K.; MHS Staff. (2002). *Conner's continuous performance Test- II*. North Tonawanda, NY: Multi-Health Systems.

Dalmau, J., Gleichman, A. J., Hughes, E. G., Rossi, J. E., Peng, X., Lai, M., … Lynch, D. R. (2008). Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. *The Lancet Neurology*, *7*(12), 1091–1098. doi:10.1016/S1474-4422(08)70224-2

Dalmau, J., Lancaster, E., Martinez-Hernandez, E., Rosenfeld, M. R., & Balice-Gordon, R. (2011). Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *The Lancet Neurology*, *10*(1), 63–74. doi:10.1016/S1474-4422(10)70253-2

Day, G. S., High, S. M., Cot, B., & Tang-Wai, D. F. (2011). Anti-NMDA-receptor encephalitis: Case report and literature review of an under-recognized condition. *Journal of General Internal Medicine*, *26*(7), 811–816. doi:10.1007/s11606-011-1641-9

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan executive function system*. San Antonio, TX: The Psychological Corporation.

Finke, C., Kopp, U. A., Prüss, H., Dalmau, J., Wandinger, K. P., & Ploner, C. J. (2011). Cognitive deficits following anti-NMDA receptor encephalitis. *Journal of Neurology, Neurosurgery & Psychiatry, 83:195-198*.

Florance, N. R., Davis, R. L., Lam, C., Szperka, C., Zhou, L., Ahmad, S., … Glaser, C. A. (2009). Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Annals of Neurology*, *66*(1), 11–18. doi:10.1002/ana.21756

Guo, Y. H., Kuan, T. S., Hsieh, P. C., Lien, W. C., Chang, C. K., & Lin, Y. C. (2014). Rehabilitation for a child with recalcitrant anti-N-methyl-d-aspartate receptor encephalitis: Case report and literature review. *Neuropsychiatric Disease and Treatment*, *10*, 2263.

Hinkle, C. D., Porter, J. N., Waldron, E. J., Klein, H., Tranel, D., & Heffelfinger, A. (2016). Neuropsychological characterization of three adolescent females with anti-NMDA receptor encephalitis in the acute, post-acute, and chronic phases: An inter-institutional case series. *The Clinical Neuropsychologist*, 31(1):1–21.

Houtrow, A. J., Bhandal, M., Pratini, N. R., Davidson, L., & Neufeld, J. A. (2012). The rehabilitation of children with Anti-NMDA-receptor encephalitis: A case series. *American Journal of Physical Medicine & rehabilitation/Association of Academic Physiatrists*, *91*(5), 435. doi:10.1097/PHM.0b013e3182465da6

Komuro, H., & Rakic, P. (1993). Modulation of neuronal migration by NMDA receptors. *Science-New York Then Washington*, *260*, 95. doi:10.1126/science.8096653

Koponen, S., Taiminen, T., Portin, R., Himanen, L., Isoniemi, H., Heinonen, H., … Tenovuo, O. (2002). Axis I and II psychiatric disorders after traumatic brain injury: A 30-year follow-up study. *American Journal of Psychiatry*, *159*(8), 1315–1321. doi:10.1176/appi.ajp.159.8.1315

Korkman, M., Kirk, U., & Kemp, S. (2007). *NEPSY* (2nd ed.). San Antonio, TX: Harcourt Assessment, Inc.

Lafayette Instruments. (2002). *Grooved pegboard user instructions*. Lafayette, IN: Author.

Lafayette Instruments. (2004). *Hand dynamometer user instructions*. Lafayette, IN: Author.

Linda Ewing-Cobbs, Mary R, Prasad, Susan H, Landry, Larry, & DeLeon, Rosario. (2004). Executive functions following traumatic brain injury in young children: a preliminary analysis. *Developmental Neuropsychology*, *26* (1), 487-512. doi: 10.1207/s15326942dn2601_7

Lynch, D. R., Anegawa, N. J., Verdoorn, T., & Pritchett, D. B. (1994). N-methyl-D-aspartate receptors: Different subunit requirements for binding of glutamate antagonists, glycine antagonists, and channel-blocking agents. *Molecular Pharmacology*, *45*(3), 540–545.

March, J. S. (2013). *Multidimensional anxiety scale for children* (2nd ed.). North Tonawanda, NY: Multi-Health Systems.

McKeon, G. L., Robinson, G. A., Ryan, A. E., Blum, S., Gillis, D., Finke, C., & Scott, J. G. (2017). Cognitive outcomes following anti-N-methyl-D-aspartate receptor encephalitis: A systematic review. *Journal of Clinical and Experimental Neuropsychology*, 40(3): 1–19.

Miya, K., Takahashi, Y., & Mori, H. (2014). Anti-NMDAR autoimmune encephalitis. *Brain and Development*, *36*(8), 645–652. doi:10.1016/j.braindev.2013.10.005

Reynolds, C. R., & Kamphaus, R. W. (2004). *Behavior assessment system for children* (2nd ed.). Bloomington, MN: Psych Corp.

Reynolds, C. R., & Kamphaus, R. W. (2015). *Behavior assessment system for children* (3rd ed.). Bloomington, MN: Psych Corp.

Rosselli, M., & Ardila, A. (2003). The impact of culture and education on non-verbal neuropsychological measurements: A critical review. *Brain and Cognition*, *52*(3), 326–333.

Satz, P., Cole, M. A., Hardy, D. J., & Rassovsky, Y. (2011). Brain and cognitive reserve: Mediator (s) and construct validity, a critique. *Journal of Clinical and Experimental Neuropsychology*, *33*(1), 121–130. doi:10.1080/13803395.2010.493151

Schrank, F. A., McGrew, K. S., Mather, N., Wendling, B. J., & LaForte, E. M. (2014). *Woodcock-Johnson IV tests of achievement*. Riverside Publishing Company. Rolling Meadows, IL

Seidenberg, M, Pulsipher, D. T, & Hermann, B. (2007). Cognitive progression in epilepsy. *Neuropsychology Review*, *17* (4), 445-454. doi: 10.1007/s11065-007-9042-x

Sherman, E. M. S., & Brooks, B. L. (2015). *Child and adolescent memory profile*. Lutz, FL: PAR Inc.

Tailor, Y. I., Suskauer, S. J., Sepeta, L. N., Ewen, J. B., DeMatt, E. J., Trovato, M. K., … Slomine, B. S. (2013). Functional status of children with encephalitis in an inpatient rehabilitation setting: A case series. *Journal of Pediatric Rehabilitation Medicine*, *6*(3), 163–173. doi:10.3233/PRM-130248

Titulaer, M. J., McCracken, L., Gabilondo, I., Armangué, T., Glaser, C., Iizuka, T., … Aguilar, E. (2013). Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. *The Lancet Neurology*, *12*(2), 157–165. doi:10.1016/S1474-4422(12)70310-1

Verney, S. P., Bennett, J., & Hamilton, J. (2015). Cultural considerations in the neuropsychological assessment of American Indians/Alaska Natives. In Richard Ferraro (Ed.), Minority and Cross-Cultural Aspects of Neuropsychological Assessment: Enduring and Emerging Trends, 2nd edition. New York, NY: Psychology Press.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale – Third edition: Administration and scoring manual*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2008). *Wechsler adult intelligence scale* (4th ed.). Bloomington, MN: Pearson Clinical Assessment.

Wechsler, D. (2009). *Wechsler memory scale* (4th ed.). Bloomington, MN: Pearson Clinical Assessment.

Wechsler, D. (2012). *Wechsler preschool and primary scale of intelligence* (4th ed.). Bloomington, MN: Pearson Clinical Assessment.

Wiig, E. H., Semel, E., & Secord, W. A. (2013). *Clinical evaluation of language fundamentals* (5th ed.). Bloomington, MN: Psych Corp.