NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

CASE REPORT

Arch Neuropsychiatry 2022;59:338–341
https://doi.org/10.29399/npa.28018

Permanent Impairment of Language Functions in an Adolescent Case of Autoimmune Encephalitis

Elif Şanlı[1], Merve Savaş[2], Gülten Öztürk[3], Onur Tuğçe Poyraz Fındık[3], Sezin Başoğlu[4], Hakkı Akbeyaz[3], Erdem Tüzün[1], Dilşad Türkdoğan[3]

[1]İstanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Neuroscience, İstanbul, Turkey
[2]İstanbul Atlas University, Faculty of Health Sciences, Department of Speech and Language Therapy, İstanbul, Turkey
[3]Marmara University, Faculty of Medicine, Department of Pediatrics, Division of Child Neurology, İstanbul, Turkey
[4]Biruni University, Faculty of Health Sciences, Department of Speech and Language Therapy, İstanbul, Turkey

ABSTRACT

Introduction: In pediatric and adolescent population, autoimmune encephalitis (AE) may present with a wide variety of symptoms including cognitive regression accompanied with loss of language skills. Despite its high prevalence in AE, linguistic functions have not been investigated in extensive detail.

Case: A 12-year-old girl with no significant premorbid history and normal school performance presented with fever, hypersomnia, nocturnal myoclonus and behavioral changes. Although neurological examination was normal, psychiatric evaluation revealed euphoria, mild irritability and visual hallucinations. Cranial MRI was normal, whereas cerebrospinal fluid (CSF) analysis showed elevated protein concentration and lymphocyte count, electroencephalogram (EEG) showed diffuse slow waves. A panel for anti-neuronal antibodies demonstrated glutamic acid decarboxylase (GAD) antibodies in the serum. Following immunotherapy, all neurological and behavioral symptoms vanished. However, the patient suffered from significant worsening of school performance. Psychiatric evaluation revealed severe depression. Assessment of intelligence done on the 10th and 18th month of follow-up yielded significantly low scores at mental retardation level. Linguistic assessment showed significant impairment in all domains but especially in semantics.

Conclusion: Our case emphasizes the fact that AE may cause permanent cognitive dysfunction and language impairment even in patients with normal MRI/neurological examination findings and relatively mild treatment-responsive disease course.

Keywords: Autoimmune encephalitis, language impairment, immunotherapy

Cite this article as: Şanlı E, Savaş M, Öztürk G, Poyraz Fındık OT, Başoğlu S, Akbeyaz H, et al. Permanent Impairment of Language Functions in an Adolescent Case of Autoimmune Encephalitis. Arch Neuropsychiatry 2022;59:338–341.

INTRODUCTION

In pediatric and adolescent population, autoimmune encephalitis (AE) may present with a wide variety of symptoms including epileptic seizures, sleep dysfunction, behavioral abnormalities, catatonia and cognitive impairment (1). Seizures and fever are usually the initial symptoms in AE and may be followed by psychiatric signs, insomnia and movement disorders. Orofacial dyskinesia and language impairment are often encountered in the advanced stages of disease (1,2).

Language dysfunction tends to be reported relatively more often in children with AE and is observed in around 1/3 of pediatric and adolescent anti-N-methyl-D-aspartate receptor (NMDAR)-encephalitis patients mostly during hospitalization (2,3). Language impairment, along with mutism, sleep dysfunction, catatonic state and seizures predicts anti-NMDAR encephalitis and help clinicians distinguish it from other autoimmune encephalopathies (2). Language impairment is often accompanied by other typical AE symptoms such as seizures, altered consciousness, movement disorders and abnormal magnetic resonance imaging (MRI) findings (4). In the pediatric population, AE may result in developmental regression characterized with loss of expressive language skills (5–8).

Highlights

- **Language impairment is a common finding in OE.**
- **Cognitive dysfunction and language impairment may be permanent in treatment-responsive OE.**
- **OE-induced language dysfunction may take longer to resolve.**
- **Language impairment without cognitive, somatic, radiological findings is important.**

Impairment of language, memory and other cognitive functions is frequently observed even in pediatric AE cases with low modified Rankin scores (mRS) and normal bedside cognitive test scores. Moreover, language impairment appears to persevere months after the acute encephalitis episode despite improvement of other somatic and cognitive neurological signs (4,9). To our knowledge, despite its high prevalence in AE, linguistic functions have not been investigated in extensive detail in

Correspondence Address: Elif Şanlı, İstanbul Universitesi, Aziz Sancar Deneysel Tıp Araştırma Enstitüsü, Sinirbilim Anabilim Dalı. Vakıf Gureba Cad. No: 69, Fatih, İstanbul, Turkey • **E-mail:** elifsanli12@gmail.com
Received: 15.09.2021, **Accepted:** 05.10.2021, **Available Online Date:** 18.10.2022

Table 1. Cognitive assessment of the patient

WISC-4	Index Scores	Comment
Verbal comprehension (Similarities, Vocabulary, Comprehension, Information, Word Reasoning)	56/64	MR/MR
Perceptual reasoning (Block Design, Picture Concepts, Matrix Reasoning, Picture Completion)	49/52	MR/MR
Working storage (Digit Span, Letter-Number Sequencing, Arithmetic)	56/67	MR/MR
Processing speed (Coding, Symbol Search, Cancellation)	59/61	MR/MR
Full scale IQ	40/43	MR/MR

MR: Mental Retardation; WISC-4: Wechsler Intelligence Scale for Children Fourth Edition.
All results are denoted in the form of 10th month of follow-up / 18th month of follow-up.

AE cases, except for one recently reported 2.5-year-old boy with putative glial fibrillary acidic protein (GFAP)-encephalitis presenting with motor seizures and permanent severe cognitive/linguistic dysfunction (10).

CASE

We have recently encountered an adolescent AE case with preferential impairment of behavioral and linguistic functions. Written consent was obtained from patient's family. This 12-year-old girl presented with a 3-day history of fever, hypersomnia, nocturnal myoclonus and episodes of sudden uncontrollable and inappropriate laughing. Several days before the onset of her symptoms she had developed temporary upper respiratory system infection symptoms. She denied paranoid or suicidal thoughts but described visual hallucinations. She was born to non-consanguineous parents with normal vaginal delivery and showed normal childhood development. Her school performance was described as normal by her parents. A pediatric psychiatrist, who had evaluated the patient 4 months ago due to increased day-time sleepiness reported normal psychiatric, cognitive and neurological status. Her time, space, person orientation and neurological examinations were normal. Neuropsychological and psychiatric evaluation revealed euphoria, mild irritability, impaired short-term memory and normal abstraction.

While cranial MRI and whole-body computed tomography (CT) with contrast enhancement (for screening of a putative underlying tumor) were normal, cerebrospinal fluid (CSF) analysis showed elevated protein concentration (124 mg/dL; normal <45 mg/dL) and lymphocyte count (57/mm^3). Total blood count and blood chemistry were normal. Thyroid autoantibodies, antibody panel for rheumatologic diseases, several blood/CSF culture studies and antibody panel for viral encephalitis were unrevealing. Electroencephalogram (EEG) showed diffuse slow waves with no epileptic discharges. A panel for anti-neuronal antibodies demonstrated low levels of glutamic acid decarboxylase (GAD) antibodies in the serum (20 IU/mL; normal <10 IU/mL) but not in the CSF. Serum/CSF antibodies to NMDAR, alpha-amino-3-hidroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), gamma-aminobutyric acid B receptor ($GABA_BR$), leucine-rich, glioma inactivated 1 (LGI_1) and contactin-associated protein-like 2 (CASPR2) were negative (all done with a cell based assay kit, Euroimmun, Luebeck, Germany).

Following treatment with pulse methylprednisolone (1 g/day ´ 5 days) and intravenous immunoglobulin (2 g/kg), behavioral symptoms promptly regressed. In less than four weeks, all neurological and behavioral symptoms vanished, CSF analysis showed no cells and normal protein concentration, EEG examination was normal and cranial MRI did not show atrophy or lesions. GAD antibody was negative in serum and CSF. She was discharged without any immunosuppressive treatment due to absence of symptoms and pathological laboratory findings (mRS=0). Although none of her admission symptoms appeared again during 18-month of follow-up, her parents reported significant worsening of school performance and deterioration in reading, writing and arithmetic skills. She had demonstrated more than 1 standard deviation of reduction

Table 2. Linguistic assessment of the patient

TOLDP-4:T		Index Scores	Comment
Listening (Picture Vocabulary, Syntactic Understanding)		84/82	BA/BA
Organizing (Relational Vocabulary, Sentence Imitation)		67/71	VP/P
Speaking (Oral Vocabulary, Morphological Completion)		79/81	P/BA
Grammar (Syntactic Understanding, Sentence Imitation, Morphological Completion)		82/83	BA/BA
Semantics (Picture Vocabulary, Relational Vocabulary, Oral Vocabulary)		63/65	VP/VP
Over all language ability		68/71	VP/P
TNRT	Correct score for a whole word (total score: 16)	Correct score for only the consonants (total score: 72)	
	14/15	71/72	

BA: Below Average; P: Poor; TNRT: Turkish Non-word Repetition Test; TOLDP-4:T: Test of Language Development Primary - Fourth Edition: Turkish Version; VP: Very Poor.
All results are denoted in the form of 10th month of follow-up / 18th month of follow-up.

in marks after hospital discharge, which was compatible with school failure (11). Moreover, psychiatric evaluation revealed major depressive disorder that required anti-depressant treatment.

Assessment of intelligence done with Wechsler Intelligence Scale for Children Fourth Edition on the 10th and 18th month of follow-up showed significantly low scores at mental retardation level. A detailed linguistic assessment done at the same time by Turkish Non-Word Repetition Test (12) and Test of Language Development-Primary: Fourth Edition Turkish Version (13) showed significant impairment in all domains but especially in semantics and organizing skills (Table 1 and 2).

Non-word repetition test, which includes repetition of meaningless words and does not require semantics skills, was not affected suggesting relative preservation of linguistic processes of encoding, storage and production governed by phonological working memory. Linguistic and intelligence tests also did not show any progressive deterioration in mental capacity during the follow-up period.

DISCUSSION

In the pediatric population, AE may present with atypical findings that do not strictly fulfill the relevant criteria constructed for adult patients (14). Likewise, our case presented predominantly with behavioral and cognitive/linguistic symptoms in the absence of cardinal AE manifestations of seizures, psychosis, movement disorders and hippocampal lesions. Nevertheless, several frequently observed and highly characteristic AE findings including short-term memory loss, hallucinations, inflammatory CSF features, slow waves on EEG and fever at onset were present in our case. More importantly, these findings were promptly reversed following immunotherapy.

School failure, depression and abnormal linguistic assessment results were the permanent adverse consequences of the acute encephalopathy episode. The patient was concluded to have developed mental deterioration after the encephalopathy episode on the basis of significant reduction in school marks and low Wechsler Intelligence Scale for Children (WISC) scores. WISC scores have been closely associated with academic achievement and low WISC scores have been related with poor language comprehension, reading, writing and arithmetic skills (15). Since patient's parents report normal school performance before hospital admission, it is safe to assume that the patient had a higher intelligence score before the encephalopathy episode. Maintenance immunotherapy was not considered in our patient, since it is generally recommended for pediatric AE patients with a severe or relapsing clinical course, treatment resistance or prolonged hospitalization (16). More importantly, there is little experience and evidence for maintenance therapy in pediatric and/or antibody-negative AE patients. Maintenance immune suppression could have been considered if detailed cognitive and linguistic tests had been performed during or shortly after the acute encephalopathy episode and perhaps prevented the development of cognitive dysfunction. Thus, our case emphasizes the significance of linguistic tests in treatment decision paradigm of pediatric AE.

There are several reported GAD-antibody positive pediatric limbic encephalitis cases with permanent residual mental problems in the literature (7,8). However, in contrast with our case, these patients have often displayed severe somatic neurological findings, epileptic seizures, MRI lesions and higher GAD-antibody levels (>1000 IU/mL) (8). Low titer seropositivity for GAD-antibody in the absence of CSF GAD antibodies should be interpreted cautiously, since this combination may be found in a small percentage of healthy individuals and non-autoimmune disorders (17). Thus, only serum GAD antibodies at high titers are genuinely associated with autoimmune neurological disorders, especially if coupled with CSF GAD antibody positivity (14,17). Therefore, in all likelihood, our case may be considered as an antibody negative AE.

Febrile infection-related epilepsy syndrome (FIRES) starts with fever and low titer serum anti-neuronal antibodies are found in epileptic encephalopathies (18,19). However, these disorders were disregarded due to absence of evident and permanent proof of clinical and electrophysiological epilepsy, monophasic nature of the clinical presentation and lack of progressive neurological disability. Particularly in the absence of any other identifiable metabolic or infectious etiology, AE was considered as the most likely diagnostic option.

Our case emphasizes the fact that AE may cause irreversible neuronal damage and permanent cognitive dysfunction even in patients with normal MRI/neurological examination findings and treatment-responsive, relatively mild disease course (7). Thus, normalization of mRS or similar disability scores in AE following immunotherapy should not necessarily suggest amelioration of cognitive, social, behavioral and neurodevelopmental complications that may particularly occur in pediatric patients. Although, non-effective immunotherapy, coma and intensive care unit admission are variables associated with poor prognosis in AE (6), our patient exhibited permanent cognitive/linguistic dysfunction in the lack of any well-known risk factors, indicating the vulnerability of language-related brain regions.

Importantly, other previously reported AE cases with linguistic dysfunction have exhibited clinical features that may have interfered with the functioning of language networks such as seizures, attention deficit, diffuse slow waves on EEG, extensive brain lesions and brain atrophy (6–8). Presence of profound language impairment in the absence of any of these factors indicates that biological factors (i.e. glial activity, plasma cell infiltration and antibody deposition) targeting language-specific brain regions are sufficient to generate linguistic dysfunction (20).

The neuropsychological tests showed significant impairment in all cognitive domains with particularly enhanced deterioration of semantics. Successful completion of the non-word repetition test, which requires an intact working memory, suggested that impairment of language functions cannot be solely explained by deterioration of attention and short-term memory. According to the dual stream model of language processing, semantics is regulated through bilateral posterior-medial temporal gyrus and posterior-inferior temporal gyrus regions, whereas auditory-motor transformation, repetition of words, verbal working memory and auditory attention are modulated through left temporal plane and left posterior frontal lobe (21). Results of the linguistic assessment suggests that the former semantics network (posterior temporal gyrus) was more preferentially affected in our patient.

Overall, our observations imply that language impairment is frequent in AE, may be long-lasting and may interfere with school performance. Occurrence and persistence of language dysfunction in the absence of other somatic, cognitive and radiological findings of neurological involvement may conceal its hazardous impact. Thus, routine screening and treatment of language dysfunction is recommended in pediatric AE cases.

Informed Consent: Written informed consent form was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ET, HA, DT; Design – ET, HA, DT, GÖ, MS; Supervision – ET, HA, DT; Resource – DT, HA, OTPF, GÖ; Materials – GÖ, EŞ, MS; Data Collection and/or Processing – DT, HA, OTPF, GÖ, SB, MS, EŞ; Analysis and/or Interpretation – ET, MS, HA, SB; Literature Search – ET, HA, DT, SB, OTPF, GÖ, MS, EŞ; Writing – DT, ET, HA, SB, OTPF, GÖ, MS, EŞ; Critical Reviews – ET, HA, DT.

Conflicts of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: The authors received no financial support for the research, authorship or publication of this article.

REFERENCES

1. Hon KLE, Leung AK, Au CC, Torres AR. Autoimmune encephalitis in children: from suspicion to diagnosis. Cureus 2021;13:e13307. [Crossref]
2. Ursitti F, Roberto D, Papetti L, Moavero R, Ferilli MAN, Fusco L, et al. Diagnosis of pediatric anti-NMDAR encephalitis at the onset: A clinical challenge. Eur J Paediatr Neurol 2021;30:9–16. [Crossref]
3. Gurrera RJ. Recognizing psychiatric presentations of anti-NMDA receptor encephalitis in children and adolescents: A synthesis of published reports. Psychiatry Clin Neurosci 2019;73:262–268. [Crossref]
4. Hou R, Wu J, He D, Yan Y, Li L. Anti-N-methyl-D-aspartate receptor encephalitis associated with reactivated Epstein-Barr virus infection in pediatric patients: Three case reports. Medicine (Baltimore) 2019;98:e15726. [Crossref]
5. Kim SY, Choi SA, Ryu HW, Kim H, Lim BC, Hwang H, et al. Screening autoimmune anti-neuronal antibodies in pediatric patients with suspected autoimmune encephalitis. J Epilepsy Res 2014;4:55–61. [Crossref]
6. Raja P, Shamick B, Nitish LK, Holla VV, Pal PK, Mahadevan A, et al. Clinical characteristics, treatment and long-term prognosis in patients with anti-NMDAR encephalitis. Neurol Sci 2021;42:4683–4696. [Crossref]
7. Wright SK, Wood AG. Neurodevelopmental outcomes in paediatric immune-mediated and autoimmune epileptic encephalopathy. Eur J Paediatr Neurol 2020;24:53–57. [Crossref]
8. Haberlandt E, Bast T, Ebner A, Holthausen H, Kluger G, Kravljanac R, et al. Limbic encephalitis in children and adolescents. Arch Dis Child 2011;96:186–191. [Crossref]
9. Shim Y, Kim SY, Kim H, Hwang H, Chae JH, Choi J, et al. Clinical outcomes of pediatric Anti-NMDA receptor encephalitis. Clinical outcomes of pediatric anti-NMDA receptor encephalitis. Eur J Paediatr Neurol 2020;29:87–91. [Crossref]
10. Savaş M, Tzartos J, Küçükali Cİ, Dursun E, Karagiorgou K, Gezen-Ak D, et al. Glial fibrillary acidic protein (GFAP)-antibody in children with focal seizures of undetermined cause. Acta Neurol Belg 2021;121:1275–1280. [Crossref]
11. Gauffin K, Vinnerljung B, Fridell M, Hesse M, Hjern A. Childhood socio-economic status, school failure and drug abuse: a Swedish national cohort study. Addiction 2013;108:1441–1449. [Crossref]
12. Topbaş S, Kaçar-Kütükçü D, Kopkalli-Yavuz H. Performance of children on the Turkish Nonword Repetition Test: Effect of word similarity, word length, and scoring. Clin Linguist Phon 2014;28:602–616. [Crossref]
13. Savaş M, Tunçer AM, Çokar AÖ, Demirbilek AV, Tüzün E. Impact of epilepsy on language and discourse: Two self-limited focal epileptic syndromes of childhood. Epilepsy Behav 2020;102:106671. [Crossref]
14. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15:391–404. [Crossref]
15. Mayes SD, Calhoun SL. Analysis of WISC-III, Stanford-Binet: IV, and academic achievement test scores in children with autism. J Autism Dev Disord 2003;33:329–341. [Crossref]
16. Nosadini M, Thomas T, Eyre M, Anlar B, Armangue T, Benseler SM, et al. International Consensus Recommendations for the Treatment of Pediatric NMDAR Antibody Encephalitis. Neurol Neuroimmunol Neuroinflamm 2021;8:e1052. [Crossref]
17. Saiz A, Blanco Y, Sabater L, González F, Bataller L, Casamitjana R, et al. Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain 2008;131:2553–2563. [Crossref]
18. Specchio N, Pietrafusa N. New-onset refractory status epilepticus and febrile infection-related epilepsy syndrome. Dev Med Child Neurol 2020;62:897–905. [Crossref]
19. Tekturk P, Baykan B, Erdag E, Peach S, Sezgin M, Yapici Z, et al. Investigation of neuronal auto-antibodies in children diagnosed with epileptic encephalopathy of unknown cause. Brain Dev 2018;40:909–917. [Crossref]
20. Tüzün E, Zhou L, Baehring JM, Bannykh S, Rosenfeld MR, Dalmau J. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. Acta Neuropathol 2009;118:737–743. [Crossref]
21. Hickok G, Poeppel D. The cortical organization of speech processing. Nat Rev Neurosci 2007;8:393–402. [Crossref]