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Case Report

A Neuroblastoma Case Presenting with Seizures Resistant to Anti-Epileptic Treatments

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ABSTRACT

Seizure is a rare symptom of paraneoplastic syndrome seen in neuroblastoma without a previous history. A 4-month-old male patient who was followed up with a preliminary diagnosis of an adrenal mass in pediatric oncology was admitted to hospital with a seizure. A diagnosis of undifferentiated neuroblastoma was made with a biopsy from an adrenal mass. Seizures were resistant to anti-epileptic therapy and they were completely under control with steroids on the 4th day of treatment. Electroencephalography (EEG) disturbances disappeared and no neurologic deficit was detected. This case, which presented with isolated seizure symptoms of neuroblastoma and was treated with steroids, was a very rare presentation in which symptoms and EEG disturbances disappeared. In neuroblastoma, autoimmunity may be involved in the pathogenesis of seizures, which is a rare finding of paraneoplastic syndrome and the option of immunotherapy should be considered.

Keywords: Epileptic seizure, neuroblastoma, autoantibody, steroid, paraneoplastic syndrome

Introduction

Neuroblastoma is a malignant neuroectodermal tumor and it is the most common extra-cranial solid tumor seen in childhood. Symptoms and signs are variable, depending on the localization of the tumor, metastasis, and paraneoplastic association (1). Seizure is rare as a first symptom. Paraneoplastic neurological syndromes in neuroblastoma may be associated with autoimmune epilepsy (OE) or opsoclonus-myoclonus-ataxia syndrome (OMAS). OE, in which acquired immunity plays a role, exists in the etiology of seizures. OMAS is a clinical syndrome consisting of involuntary chaotic eye movements, myoclonus of the extremities, and ataxia (1-3). As information on the role of autoimmunity and neuroinflammation in epileptogenesis has increased, immunotherapy options have begun to be offered and seizure control has begun in some patients (3,4). Although it has been discussed as to whether it is a paraneoplastic symptom or not, seizure is rare. We present a 4-month-old patient with neuroblastoma who did not respond to anti-epileptics, and whose seizure control was achieved with immunotherapy.

Case Report

A 4-month-old boy who had no previous history of seizures was referred to our center from another center with generalized clonic seizures occurring 3 times within 24 hours. The patient's neurological development and examination were normal. Among the laboratory results obtained, hemogram, liver and kidney function tests, glucose, electrolytes, and ammonia values were normal. No feature was found in cerebrospinal fluid findings. In EEG, slow waves with a generalized amplitude of 300-350 mV, showing the highest amplitude in the left occipital region, were observed at frequent intervals. The patient, who had a history of antenatal hydronephrosis, was followed up in pediatric oncology after a mass was noticed in the left surreal lobe in postnatal abdominal ultrasonography (USG). There was no infection or drug exposure in the antenatal and postnatal periods. Contrast-enhanced abdominal magnetic resonance imaging (MRI) revealed a solid mass of 5x5x5 cm in size (Figure 1). In the follow-up, a biopsy was performed

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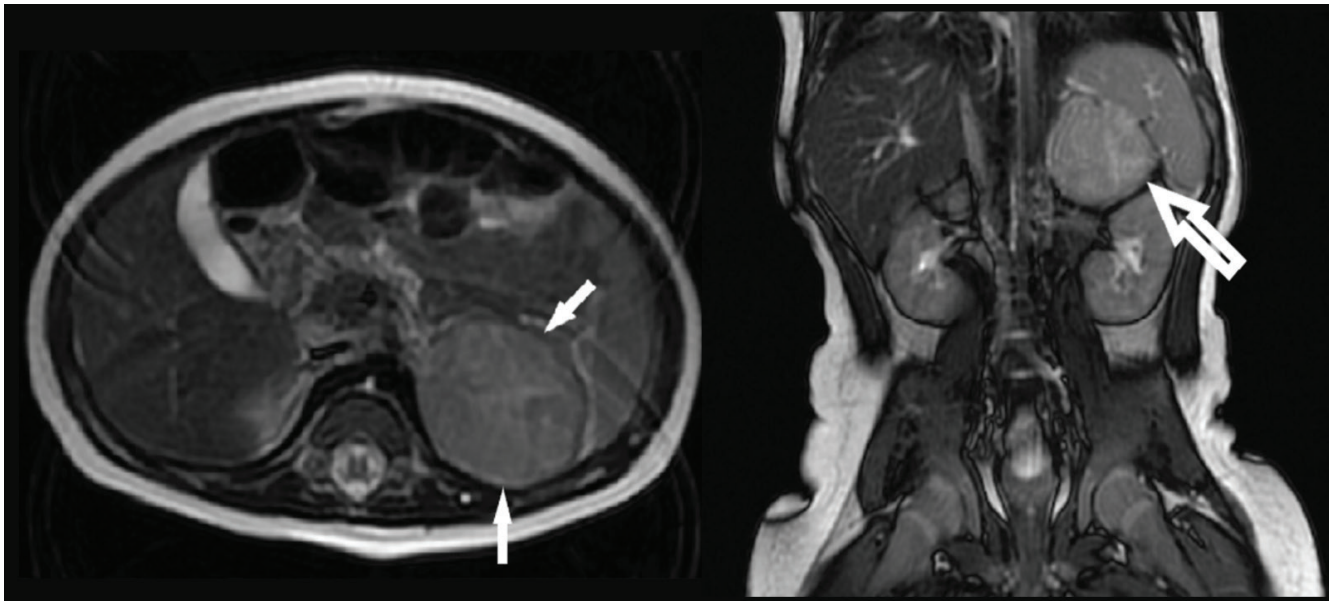

Figure 1. A homogeneous, space-occupying formation with intense contrast enhancement approximately 5x5x5 in size, in the left adrenal lobe

on the patient as an increase in the size of the mass was detected on USG and an increase in the urinary catecholamine level was observed. The biopsy of the patient's pathology resulted in a very low-risk undifferentiated neuroblastoma. The patient's age was below 18 months, n-myc amplification and 11q23 loss were negative in molecular examination, the tumor was non-metastatic and after total resection (when he was 5 months old) due to the absence of macroscopic and microscopic residues, the patient was classified as 'Very Low-Risk Group' and chemotherapy was not given to the patient.

Anti-epileptic treatment of levetiracetam, phenytoin, and topiramate was administered to the patient. In the follow-up of the patient, seizures continued intermittently despite triple anti-epileptic therapy. It was thought that paraneoplastic syndrome might play a role in the pathogenesis of the seizures, and steroid treatment was started (dexamethasone 0.4 mg/kg/day for 4 weeks). On the 4th day of steroid treatment (in the fourth month of the patient), seizures stopped and the anti-epileptic drugs, except for levetiracetam, were discontinued. Intravenous gammaglobulin was not given. Pathologies previously detected in control EEGs disappeared. Brain MRI taken for etiopathogenesis was normal. Our patient's antibody prevalence in epilepsy (APE) score was 4. The studied paraneoplastic autoantibody panel (Anti-Ri, anti-Yo, anti-Hu, anti-CV2, anti-Amphiphysin, anti-Ma2/Ta, anti-Recoverin, SOX1 antibody, Zic4, GAD65, Tr/DNER) was negative. Our patient's 'response to immunotherapy in epilepsy' (RITE) score was 5. No pathology was found in the gene panel for epilepsies of genetic origin, which is common in the infantile period. In our case with neuroblastoma, opsoclonus-myoclonus, which is a sign of paraneoplastic syndrome, was not observed either in the first application or in the 3-month follow-up. The patient was followed up by the pediatric neurology and oncology clinics and was seen to be completely healthy.

Discussion

OE, in which acquired immunity plays a role, exists in the etiology of seizures. A significant proportion of cryptogenic epilepsies have been attributed to autoimmunity, or a possible autoimmune cause (3,5,6). Discussion has started as to whether the seizures, which are rarely reported in neuroblastoma cases, are accidental or autoimmune (as a part of the paraneoplastic syndrome). OE may be isolated or be a part of the paraneoplastic syndrome (5-7).

A recent, prospective study reported serologic findings among consecutively evaluated patients presenting with epilepsy of unknown etiology. The same study also evaluated a scoring system known as the APE score as a model to predict the detection of these Abs based on the patients' clinical presentation and initial neurologic evaluation. The score was prospectively assigned to all enrolled patients before Ab testing. An APE score of ≥4 had a sensitivity and specificity of 82.6% and

82.0%, respectively (7-10). In that study, patients who received immunotherapy, autonomic dysfunction, faciobrachial dystonic seizures/oral dyskinesia, early initiation of immunotherapy, or who had the presence of antibodies targeting plasma membrane proteins (cell-surface antigens) were associated with favorable seizure outcomes. The sensitivity and specificity of an RITE score ≥7 to predict favorable seizure outcomes were 87.5% and 83.8%, respectively (7-14).

In OMAS, which is a paraneoplastic syndrome seen in neuroblastoma, movement disorders such as opsoclonus-myoclonus are detected, but seizures are not included in its definition. Among these, seizures with antibody (anti-Hu) positive OMAS were reported in only two cases. A 20-month-old infant with Turner syndrome presented with abdominal neuroblastoma and OMAS developed progressive hearing loss and seizures despite the complete removal of the tumor. Due to the disappearance of opsoclonus-myoclonus and the absence of new neurological symptoms with intravenous immunoglobulin therapy, the authors suggested that they provide direct support for the autoimmune basis of paraneoplastic symptoms associated with neuroblastoma (1,2,15). Another 11-year-old patient with anti-Hu (+) neuroblastoma first presented with epilepsy partialis continua (EPC) and later developed OMAS (16).

Although anti-Hu (+) encephalomyelitis cases have mostly been reported in association with small cell lung cancer in adulthood, pediatric encephalomyelitis cases are rarely seen (17,18). Anti-Hu (+) encephalomyelitis cases may progress as resistant epilepsy or 'Epilepsia partialis continua' in the follow-up (19,20). Only two cases of limbic encephalitis associated with neuroblastoma have been reported, and neither of these had prior OMAS (21,22). In both cases, limbic encephalitis preceded the diagnosis of the tumor and was associated with anti-Hu antibodies. Neurologic symptoms can precede the diagnosis of the neoplasm.

There are also case reports of neuroblastoma presenting with seizures without OMAS. White et al. (23) reported seizure and developmental delay in two cases without OMAS. The first case presented with infantile spasm and was diagnosed with neuroblastoma at the age of 5. In the second case, neuroblastoma was detected when the female patient was 4 weeks old, she had presented with neonatal seizure when she was 1-day old. In both cases, epilepsy resistance to antiepileptic treatments and significant growth retardation developed. The authors suggested that in these cases, epilepsy resistance to antiepileptic treatments and growth retardation may be coincidental or immune mechanisms may play a role in their pathogenesis (23).

Our case presented with seizures which did not respond to antiepileptic therapy. It was reported that he was followed up for a mass compatible with adrenal neuroblastoma in the postnatal abdominal USG. For this reason, IV dexamethasone was initiated, considering that it might be a symptom of paraneoplastic syndrome, while further investigations for seizures were performed. All seizures disappeared 4 days after steroid treatment was initiated and antiepileptic drugs were discontinued.

Paraneoplastic syndrome in neuroblastoma is most common in the age range of 18-24 months and is not expected for less than 6 months due to immune system development (24). As in our case, a case with pelvic neuroblastoma who presented with their first seizure complaint has been reported in the literature (24,25). The authors suggested that the seizure may be part of the non-classical paraneoplastic syndrome. Neuroinflammation both in the innate and acquired immune system, which plays a role in pathogenesis and epileptogenesis, is subtle and immunotherapy should be discussed (3). In our case, seizure control, improvement in EEG, and normal neurological development after steroid treatment suggest autoimmune and/or neurotransmitter-mediated paraneoplastic syndrome. Although it is thought that autoimmunity plays a lesser role when the age of the patient was taken into consideration, the disappearance of all symptoms with steroids cannot rule out the role of autoimmunity in neuroblastoma. In addition, the release of neurotransmitters, which are secreted from the tumoral tissue and play a role in epileptogenesis, may additionally contribute to the occurrence of seizures (20,26).

We present a rare case of refractory seizures and neuroblastoma with good outcomes after treatment. It would be useful to consider this relationship when evaluating seizures of unknown origin in the first years of life. Thus, in similar cases, immune-modulatory therapy may be considered primarily due to possible autoimmune etiopathogenesis.

Ethics

Informed Consent: Informed consent was obtained from the patient's parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ç.Ç.K., Design: Ç.Ç.K., A.K.A., C.Y., Data Collection and/or Processing: Ç.Ç.K., Analysis and/or Interpretation: Ç.Ç.K., Literature Search: S.A.O., M.P., Ç.Ç.K., Writing: Ç.Ç.K., M.P.

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References

1. Johnsen JI, Dyberg C, Wickström M. Neuroblastoma-A Neural Crest Derived Embryonal Malignancy. Front Mol Neurosci 2019; 12:9.
2. Berridge G, Menassa DA, Moloney T, et al. Glutamate receptor δ2 serum antibodies in pediatric opsoclonus myoclonus ataxia syndrome. Neurology 2018; 91:e714-23.
3. Tan TH, Perucca P, O'Brien TJ, Kwan P, Monif M. Inflammation, ictogenesis, and epileptogenesis: An exploration through human disease. Epilepsia 2021; 62:303-24.
4. Rudnick E, Khakoo Y, Antunes NL, et al. Opsoclonus-myoclonus-ataxia syndrome in neuroblastoma: clinical outcome and antineuronal antibodies-a report from the Children's Cancer Group Study. Med Pediatr Oncol 2001; 36:612-22.
5. Brenner T, Sills GJ, Hart Y, et al. Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. Epilepsia 2013; 54:1028-35.
6. Dubey D, Alqallaf A, Hays R, et al. Neurological Autoantibody Prevalence in Epilepsy of Unknown Etiology. JAMA Neurol 2017; 74:397-402.
7. Vincent A, Irani SR, Lang B. The growing recognition of immunotherapy-responsive seizure disorders with autoantibodies to specific neuronal proteins. Curr Opin Neurol 2010; 23:144-50.
8. Vincent A. Autoimmune channelopathies: well-established and emerging immunotherapy-responsive diseases of the peripheral and central nervous systems. J Clin Immunol 2010; 30 Suppl 1:S97-102.
9. Davis R, Dalmau J. Autoimmunity, seizures, and status epilepticus. Epilepsia 2013;54 Suppl 6:46-9.
10. Dubey D, Konikkara J, Modur PN, et al. Effectiveness of multimodality treatment for autoimmune limbic epilepsy. Epileptic Disord 2014; 16:494-9.
11. Dubey D, Pittock SJ, McKeon A. Antibody Prevalence in Epilepsy and Encephalopathy score: Increased specificity and applicability. Epilepsia 2019; 60:367-9.
12. Dubey D, Singh J, Britton JW, et al. Predictive models in the diagnosis and treatment of autoimmune epilepsy. Epilepsia 2017; 58:1181-9.
13. Sweeney M. Autoimmune Neurologic Diseases in Children. Semin Neurol 2018; 38:355-70.
14. Husari KS, Dubey D. Autoimmune Epilepsy. Neurotherapeutics 2019; 16:685-702.
15. Fisher PG, Wechsler DS, Singer HS. Anti-Hu antibody in a neuroblastoma-associated paraneoplastic syndrome. Pediatr Neurol 1994; 10:309-12.
16. Langer JE, Lopes MB, Fountain NB, et al. An unusual presentation of anti-Hu-associated paraneoplastic limbic encephalitis. Dev Med Child Neurol 2012; 54:863-6.
17. Rosenfeld MR, Dalmau J. Update on paraneoplastic and autoimmune disorders of the central nervous system. Semin Neurol 2010; 30:320-1.
18. Haberlandt E, Bast T, Ebner A, et al. Limbic encephalitis in children and adolescents. Arch Dis Child 2011; 96:186-91.
19. Aagre SV, Patel A, Choudhary M, Kataria P, Baldaniya K. Paraneoplastic encephalitis as a first evidence of recurrent neuroblastoma: A rare case entity. J Pediatr Neurosci 2015; 10:404-7.
20. Sweeney M, Sweney M, Soldán MM, Clardy SL. Antineuronal Nuclear Autoantibody Type 1/Anti-Hu-Associated Opsoclonus Myoclonus and Epilepsia Partialis Continua: Case Report and Literature Review. Pediatr Neurol 2016; 65:86-9.
21. Jarius S, Arnold S, Linke R, et al. Long term survival in anti-Hu associated adult neuroblastoma. J Neurol Sci 2009; 284:205-8.
22. Meyer JJ, Bulteau C, Adamsbaum C, Kalifa G. Paraneoplastic encephalomyelitis in a child with neuroblastoma. Pediatr Radiol 1995; 25 Suppl 1:S99-101.
23. White AV, Manson JI, Toogood IR. Neuroblastoma associated with seizures and arrested development. Pediatr Neurol 2000; 22:57-9.
24. Martins CL, Monteiro JP, Pereira F, Calhau P, Fonseca MJ. Seizures as a presentation of a pelvic neuroblastoma in a 5-month-old infant. J Child Neurol 2014; 29:84-7.
25. Pranzatelli MR, Tate ED, McGee NR. Demographic, Clinical, and Immunologic Features of 389 Children with Opsoclonus-Myoclonus Syndrome: A Cross-sectional Study. Front Neurol 2017; 8:468.
26. Werner F-M, Coveñas R. Neuropeptides and Neurotransmitters Involved in Generalized Epilepsy: How Can the Antiepileptic Effect be Improved? J Neurol Neurophysiol 2015; 6:4.