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CASE REPORT

Anti-*N*-methyl-D-aspartate receptor encephalitis in a pre-teenage girl: a case report

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Abstract Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an auto-immune and paraneoplastic encephalitis which generally affects young adults. It is a multistage illness, with prominent extrapyramidal, neuropsychiatric and autonomic symptoms. The syndrome is frequently associated with an ovarian teratoma. Recently, it has become evident that anti-NMDAR encephalitis is more common in children and adolescents than was previously believed. Prognostic factors that determine a good outcome are presence of a tumour, prompt treatment and no need for admission to an intensive care unit. Increased awareness among paediatricians of this potentially life-threatening disease is important because early recognition and treatment will improve the patients' chances of a good clinical outcome. In this case report, we describe a 9-year-old girl with behavioural changes and severe extrapyramidal symptoms due to anti-NMDAR encephalitis associated with an ovarian teratoma. She was treated with a variety of immunomodulating therapies and made a slow, but good recovery.

Keywords Anti-*N*-methyl-D-aspartate receptor · Encephalitis · Teratoma · Children

Abbreviations

Anti-NMDAR	Anti-*N*-methyl-D-aspartate receptor
CSF	Cerebrospinal fluid
NMDAR	*N*-methyl-D-aspartate receptor
PICU	Paediatric intensive care unit

Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an auto-immune and paraneoplastic encephalitis. Antibodies targeted at the NR1 subunit cause capping and internalisation of the NMDAR and subsequent decline in NMDAR-mediated synaptic function, resulting in a characteristic neuropsychiatric syndrome [2, 3].

Initially, anti-NMDAR encephalitis was believed to primarily affect young female adults; however, recent studies have shown that the disease is more common in children and adolescents than was previously believed [3, 4]. Between 37 and 65 % of all cases occur in children (<18 years) [5, 8]. Furthermore, it was recently noted that anti-NMDAR encephalitis is an over four times more frequent cause of encephalitis in patients less than 30 years of age compared to well-known viral causes like herpes simplex virus 1, West Nile virus and Varicella Zoser virus [5].

Anti-NMDAR encephalitis is a multistage disease that usually (70 %) begins with prodromal symptoms such as

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headache, fever, vomiting and nausea. Within a few days, patients develop psychiatric symptoms including anxiety, insomnia, fear, delusions, mania and paranoia. During this stage, patients are often misdiagnosed with a primary psychiatric disorder and anti-NMDAR-mediated psychosis is missed. The following stage is characterised by a state of unresponsiveness where abnormal movements and autonomic instability dominate the clinical picture [3]. Anti-NMDAR encephalitis is frequently associated with a malignancy, most often an ovarian teratoma [2]. Treatment consists of a combination of immunosuppressive agents and, in case of presence of a teratoma, surgical removal of the tumour. Early removal of the tumour results in better outcome and fewer relapses [4, 7, 8]. The prognosis is good in 75 % of patients, but recovery generally takes a long time. Improvement may still occur after 24 months [8]. 25 % remain severely disabled or die. Mortality is estimated to be 7 % [8]. Prognostic factors that determine a good outcome are prompt treatment, no need for admission to an intensive care unit and the presence of a tumour [2, 4, 6, 8]. Also, a longer follow-up was associated with a better outcome [8]. In this case report, we describe a 9-year-old patient with anti-NMDAR encephalitis associated with an ovarian teratoma.

Case presentation

A 9-year-old girl had suffered from frontal headaches and vomiting for several days. This was followed by a change in behaviour, consisting of agitation, anxiety and emotional liability. Within 1 week, her condition worsened as she became both verbally and physically aggressive and experienced visual hallucinations. She was initially diagnosed with a psychosis and subsequently admitted for observation and started on midazolam. She continued to deteriorate and, under suspicion of a neuropsychiatric syndrome, was transferred to our hospital where haloperidol was started after which she began to experience extrapyramidal symptoms. On clinical examination, the patient was delirious and displayed aggressive behaviour. Her speech was incoherent and marked orofacial dyskinesias, hypersalivation, muscle rigidity and choreatic movements of the arms were noted.

Routine laboratory investigations, including thyroid function and Epstein–Barr virus antibodies, and a computed tomography scan of the brain were unremarkable. The electroencephalography showed slowed frontal activity with no epileptic activity. A lumbar puncture showed a lymphocytic pleocytosis (70 cells per microliter) with normal protein and glucose values (Table 1).

Table 1 Lumbar puncture results

Leucocytes	70/μl (99 % mononuclears)
Glucose	3.4 mmol/l
Total protein	0.38 g/l

We considered anti-NMDAR encephalitis the most likely diagnosis. Because viral encephalitis could not be ruled out at that point, immunomodulating drugs were not started yet and she was started on aciclovir 10 mg/kg thrice daily. Aciclovir was stopped 2 days later when the polymerase chain reaction for herpes simplex virus came back negative. She was subsequently started on methylprednisolone (1 mg/kg) in combination with intravenous immunoglobulin (400 mg/kg per day). Meanwhile, the patient had been transferred to the paediatric intensive care unit (PICU) because of uncontrollable anxiety, agitation and automutilation requiring intense sedation with midazolam and propofol, and later, mechanical ventilation. Using pelvic and transvaginal ultrasound, an ovarian tumour with a maximum diameter of 2.5 cm was found. A diagnostic laparoscopy with complete tumour removal was performed. The pathologic diagnosis was an immature teratoma stage 1. The cerebrospinal fluid came back positive for anti-NDMAR antibodies which confirmed the diagnosis of anti-NMDAR encephalitis caused by an ovarian teratoma [1, 8].

During her stay at the PICU, frequent cardiac dysrhythmias (bradycardia) were noted as well as cardiac pauses, which were attributed to either vagal stimulation or autonomic dysregulation related to the autoantibodies [2], and for which she received a temporary pacemaker. Despite immunomodulating treatment, no improvement of the neurological symptoms was noted. Therefore, the patient was additionally treated with plasmapheresis (eight sessions) and 500 mg rituximab twice. Six weeks after the start of the disease, she slowly began to improve. Mechanical ventilation could be discontinued and the pacemaker was removed. She was transferred to the paediatric ward, where she stayed an additional 13 weeks before being discharged home with severe residual symptoms. She is currently treated with prednisolone to prevent relapse, which occurs in 20–25 % of all patients [3]. Prognostic factors that determine a lower relapse frequency are presence of a tumour and long-term treatment with immunotherapy [8]. Recently, at her 3-month follow-up visit, the patient had shown a remarkable recovery. She was able to perform daily routine tasks independently and her speech had completely recovered. Although she still suffered from difficulties with concentration and occasional disorderly behaviour, she had begun to attend school again.

Discussion

Anti-NDMAR encephalitis is a potentially life-threatening disease with a broad spectrum of symptoms. After a prodromal phase, the disease quickly progresses in different stages. Starting with memory deficits, seizures and psychiatric symptoms resembling psychosis, a patient may eventually deteriorate to a state of unresponsiveness with abnormal movements, autonomic and breathing instability. Although occurring in all age groups, the disease mostly affects children and young adults. It may be associated with a tumour, usually an ovarian teratoma. Tumours are predominantly found in older patients and are more likely to occur in Asian and black patients [8]. The younger the patient, the less likely a tumour will be present [4]. In children less than 12 years of age, the frequency of a tumour is under 10 % [4]. Similar to adults, the presence of a tumour is associated with a better prognosis. Treatment consists of tumour resection (if applicable) and immunotherapy. Prompt removal and immunotherapy results in early improvement decreases relapse frequency. First-line treatment consists of corticosteroids, intravenous immunoglobulin and/or plasma exchange. Cyclophosphamide, rituximab or both may be given as second-line therapy. Second-line therapy improves the outcome and reduces the amount of relapses of non-responders to first-line therapy [8]. No response to first-line therapy is not uncommon and occurs in about half the patients (47 %) [8]. Supportive measures like sedation or mechanical ventilation may necessitate admission to an intensive care unit. Recovery occurs in more than 75 % of the patients, but may take up months. Characteristically, there is a temporal pattern in improvement, inasmuch that symptoms which came last are often the first to disappear [3]. In conclusion, anti-NMDAR encephalitis should be considered in a child who presents with acute psychotic symptoms, especially when prodromal or extrapyramidal symptoms are present.

Consent The parents of the patient gave informed consent for publication of this case report.

Conflict of Interest The authors declare that they have no competing interests.

References

1. Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR (2007) Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 61(1):25–36
2. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR (2008) Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 7(12):1091–1098
3. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R (2011) Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 10(1):63–74
4. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, Campen CJ, Moss H, Peter N, Gleichman AJ, Glaser CA, Lynch DR, Rosenfeld MR, Dalmau J (2009) Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 66(1):11–18
5. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA (2012) The frequency of autoimmune *N*-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis 54(7):899–904
6. Mirza MK, Pogoriler J, Paral K, Ananthanarayanan V, Mandal S, Mazin A, Baron B, Richa E (2011) Adjunct therapeutic plasma exchange for anti-*N*-methyl-D-aspartate receptor antibody encephalitis: a case report and review of literature. J Clin Apher 26(6):362–365
7. Naoura I, Didelot A, Walker F, Luton D, Koskas M (2011) Anti-*N*-methyl-D-aspartate receptor encephalitis complicating ovarian teratomas: a case report. Am J Obstet Gynecol 205(4):6–8
8. Titulaer MT, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, Honig LS, Benseler SM, Kawachi I, Martinez-Hernandez E, Aguilar E, Gresa-Arribas N, Ryan-Florance N, Torrents A, Saiz A, Rosenfeld MR, Balice-Gordon R, Graus F, Dalmau J (2013) Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 12:157–165