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ORIGINAL CONTRIBUTION

Anti-NMDA receptor encephalitis presenting as atypical anorexia nervosa: an adolescent case report

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Abstract Since 2007, more than 600 patients have been diagnosed with anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis, with almost 40 % of those affected being children or adolescents. In early phases of the illness, this life-threatening disease is characterized by psychiatric symptoms, such as depression, anxiety, obsessions, hallucinations or delusions. Consequently, a high percentage of patients receive psychiatric diagnoses at first, hindering the crucial early diagnosis and treatment of the anti-NMDA receptor encephalitis. We report on a 15-year-old girl initially presenting with pathological eating behaviour and significant weight loss resulting in an (atypical) anorexia nervosa (AN) diagnosis. Her early course of illness, diagnostic process, treatment and short-term outcome are described. This case report aims to raise awareness about the association between anorectic behaviour and anti-NMDA receptor encephalitis and highlight the importance of multidisciplinary teams in child and adolescent services.

Keywords Anti-NMDA receptor encephalitis · Atypical anorexia nervosa · Child and adolescent psychiatry · Paediatrics

Introduction

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune disease which was first described by Dalmau et al. [1]. The average age of onset for anti-NMDA receptor encephalitis is around 21 years, whereby almost 40 % of those affected are under the age of 18 [2]. The recovery process can take several years and full premorbid functioning is achieved only in a small percentage of patients. Around 80 % show a substantial improvement and about 10 % of patients pass away [2]. In those affected, antibodies are targeting the NR1 subunit of postsynaptic NMDA receptors, resulting in inhibited functioning of these receptors. In some cases, these synaptic modifications seem partly reversible when treated effectively, suggesting the absence of permanent structural neuronal damage [3].

A definite diagnosis can be achieved by showing the presence of antibodies against the NR1 subunit in the serum and/or cerebrospinal fluid (CSF). In addition, the white blood cell count and protein levels in the CSF can be slightly increased. Abnormal electroencephalographic (EEG) activity can arise in the form of uni- or bilateral slow rhythm patterns. In around half of the cases, the cranial magnetic resonance imaging (MRI) T2-weighted analyses reveal nonspecific local hyperintensities [4]. Tumours, especially ovarian teratoma, are present in about 35 % of female patients

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above 12 years of age and in six percent of females under 12 years of age [2]. Therefore, it is critical to check for the presence of potential neoplasm immediately after the diagnosis of anti-NMDA receptor encephalitis and when necessary, to initiate tumour removal and associated treatment. The anti-NMDA receptor encephalitis is targeted first-line with methylprednisolone accompanied by either intravenous immunoglobulin (IVIG) therapy or plasma exchange. Due to its less invasive nature, the second-line treatment is often chosen in children instead, which is the administration of either rituximab or cyclophosphamide or both [5].

Anti-NMDA receptor encephalitis is characterized by five different disease stages with different symptomatology: (1) the shorter prodromal stage presents with cold-like symptoms, such as fever and/or headaches; (2) the second stage often leads to psychiatric diagnoses, due to symptoms like social withdrawal, sleeping difficulty, depression, anxiety, obsessions, delusions, hallucinations, amnesia and/or seizures; (3) the unresponsive stage shows catatonic-like behaviour, dystonic postures, and/or bizarre smiling; (4) symptoms of autonomous dysregulation, such as orolingual dyskinesia, hyperthermia, tachycardia, and/or bradycardia, characterize the hyperkinetic stage; (5) finally, there is a treatment stage with gradual recovery or in some cases death [6]. Important to note, patients often exhibit the clinical symptoms of the different disease stages in the reverse direction during treatment and recovery [5]. The psychiatric symptoms observed during the second disease stage have been slowly expanded during recent years [7]. This case report is the first to describe anorectic eating behaviour in an adolescent patient with anti-NMDA receptor encephalitis and hopes to raise awareness for this clinical presentation of anti-NMDA receptor encephalitis, especially amongst child and adolescent psychiatrists.

Case report

A 15-year-old female patient was presented (day 0) to the eating disorder outpatient unit with severe underweight (BMI = 15.7 kg/m^2, 2nd BMI-percentile). Her parents reported a loss of 7 kg within a period of 7 weeks (premorbid BMI = 18.7 kg/m^2, 26th BMI-percentile). The patient exhibited highly selective and limited food intake and increased physical activity. She described her body as "normal" despite clear underweight, suggesting the presence of a body image distortion. Secondary amenorrhoea was not present. Her parents described the patient as exhausted, pensive and short-tempered. In addition, the patient herself reported weakness and drowsiness, flush symptoms, cold fingers, symptoms of depression and sleeping difficulties. Taken together, these symptoms led to the probable diagnosis of (atypical) anorexia nervosa and the patient was seen on a weekly basis in our eating disorder outpatient unit. On a follow-up visit 2 weeks later (day 15), the patients weight had already increased by 4 kg (BMI = 16.8 kg/m^2, 6th BMI-percentile) and her parents reported a return to non-pathological eating behaviour.

On day 19, the patient was unexpectedly admitted to our paediatric emergency room due to a second complex partial and secondary generalized tonic–clonic seizure. The subsequent cranial magnetic resonance imaging (MRI) and angiography showed no neurological abnormalities. Additionally, electroencephalography (EEG) showed no epileptoform discharges. The seizures were interpreted as dissociative and the patient was admitted to the child and adolescent psychiatry inpatient unit and kept under multidisciplinary neuropaediatric and psychiatric supervision. Her cerebrospinal fluid (CSF) and serum (day 22) showed no indication for viral encephalitis related to the following infections (see Table 1): herpes simplex virus (HSV), human herpesvirus-6 (HHV-6), enterorvirus, Epstein-Barr-virus (EBV) or varicella-zoster virus (VZV). Moreover, a wide range of autoimmune diseases tested negative as well, indicated by her negative antinuclear antibody (ANA) test and extractable nuclear antigens (ENA) panel. Furthermore, neuroborreliosis could be excluded (Table 1). However, her CSF showed an increased cell count (32/μl) and borderline level of protein (35 mg/dl) and was positive for oligoclonal immunoglobulin (IgG) bands.

During inpatient treatment, acoustic hallucinations occurred (day 23), her sleep cycle was disturbed, her orientation to place, time and person was impaired, and she suffered from delusions of reference. Moreover, the patient showed increased motor activity, recurring states of physical excitation, increased associative looseness and flight of ideas. Treatment with antipsychotics, at first olanzapine and levomepromazine, followed by a switch to risperidone, only led to a minimal improvement. Furthermore, the patient started experiencing orofacial dyskinesia (day 29). Due to a conspicuous ultrasound report of the thyroid gland (day 31), Hashimoto's encephalopathy was considered as differential diagnosis and treatment with methylprednisolone was started. Laboratory analyses did not confirm the diagnosis of Hashimoto's encephalopathy or other differential diagnoses, such as human immunodeficiency virus (HIV) encephalopathy or influenza A-H1N1-encephalitis (day 35). The simultaneously heightened levels of antibodies for VZV, rubella and measles (see Table 1), a so-called MRZ reaction, suggest the presence of a chronic inflammatory disease of the central nervous system, such as multiple sclerosis (MS). However, MS was ruled out due to the inconspicuous MRI results. A prolonged infection with the measles virus could lead to subacute sclerosing panencephalitis (SSPE); the patient's symptomatology however did not indicate the presence of SSPE.

Table 1 Overview of laboratory results for differential diagnoses

Day	Sample	Analysis	Value	Unit	Reference range	Result
22	Serum	Enterovirus-IgM/-IgA	–	–	–	Negative
	Serum	HHV-6-IgM	–	–	–	Negative
	CSF	HHV-6 (PCR)	–	–	–	Negative
	CSF	HSV-IgG	–	–	–	Negative
	CSF/serum	Varicella-zoster virus-IgG	1.1	AI	<1.5	
	CSF/serum	Epstein-Barr virus-IgG	1.1	AI	<1.5	
	Serum	Borrelia-IgM/-IgG (ELISA)	5.6	U/ml	<16.0	
	CSF	Borrelia-IgM/-IgG (ELISA)	–	–	–	Negative
	CSF	M. pneumonia-IgA/-IgG (ELISA)	–	–	–	Negative
	Serum	IgG bands	1,050	mg/dl	509–1,580	
	CSF	IgG bands			–	Positive
35	Serum	Anti-TPO antibodies	<10	U/ml	<60	
	Serum	Thyroglobulin antibodies	<10	U/ml	<60	
	Serum	TSH receptor antibodies	<1.0	U/l	<1	
	Serum	HIV1/2 p24	–	–	–	Negative
	NP	Influenza-A/-B (RT-PCR)				Negative
	NP	Influenza-A H1N1 (RT-PCR)				Negative
	Serum	TPHA	–	–	–	Negative
	CSF/serum	Varicella-zoster virus-IgG	7	AI	<1.5	
	CSF/serum	Rubella-IgG	6	AI	<1.5	
	CSF/serum	Measles-IgG	38.2	AI	<1.5	

IgM immunoglobulin M, *IgA* immunoglobulin A, *IgG* immunoglobulin G, *HHV*-6 human herpesvirus 6-DNA, *CSF* cerebrospinal fluid, *PCR* polymerase chain reaction, *HSV* herpes simplex virus, *AI* antibodies index, *ELISA* enzyme-linked immunosorbent assay, *U* enzyme unit, *M. pneumonia Mycoplasma pneumonia*, *TPO* thyroid peroxidase, *TSH* thyrotropin, *HIV* human immunodeficiency virus, *NP* nasopharyngeal swab, *TPHA* treponema pallidum haemagglutination assay

Finally, on day 36, a definite diagnosis of anti-NMDA receptor encephalitis could be made after confirming the presence of NMDA receptor antibodies in the CSF [positive at 1:32; immunofluorescence test (IFT), normal values ≤1:10] and serum (positive at 1:100; IFT, normal values ≤1:10). Parallel to the corticosteroid therapy, which was tapered stepwise, IVIG treatment was started and resulted in slow daily improvement of symptoms. A total of 90 grams IVIG (2 g/kg bodyweight) was given to the patient over the course of 4 days. The multidisciplinary team and the patient's parents decided against a treatment with rituximab for the time being. The neoplasm screening via a transvaginal ultrasound and a whole-body positron emission tomography-computed tomography (PET-CT) scan was negative. On day 73, the patient could be transferred to a rehabilitation centre with a stable, but low, weight (BMI = 17.2 kg/m^2, 9th BMI-percentile). Under continued IVIG therapy with two doses of 30 g every 4 weeks for 10 months, she has since remained largely symptom-free (NMDA-NR1 receptor antibodies in CSF positive at 1:10, and serum is negative) and was able to return to school successfully. An extensive neuropsychological examination 2 years after disease onset confirmed that the patient was almost at her premorbid cognitive level and did not experience residual cognitive impairments.

Discussion

Despite the presence of psychiatric symptoms being typical for anti-NMDA receptor encephalitis, the anorectic symptoms presented by this case report are a peculiarity. The anorexia nervosa criteria were largely fulfilled, except for the amenorrhoea criteria. However, first doubts regarding the diagnosis arose after the rapid increase in weight seen in this patient. The subsequent neurological symptoms and notable CSF cell count and borderline protein level, led to the consideration of several differential diagnoses.

Except for the case report by Perogamvros et al. (2012), anorectic symptoms had not been previously associated with anti-NMDA receptor encephalitis, therefore causing a delay in obtaining the correct diagnosis and appropriate treatment. Our patient was able to benefit from our multidisciplinary neuropaediatric and psychiatric team. Since those affected often visit psychiatric departments first, it is vital that adult as well as child and adolescent psychiatrists are familiar with anti-NMDA receptor encephalitis and are able to potentially recognize its symptoms [8, 9], especially since an early diagnosis and fast treatment have been shown to reduce relapse and are associated with a better outcome.

A potential explanation for the anorectic behaviour seen in our patient is the specific role that NMDA receptors play in mediating food intake. Animal models for eating

behaviour show that NMDA receptor antagonists lead to reduced food intake and consequently, a reduction in body weight [10]. A similar association between anti-NMDA receptor encephalitis and pathological eating behaviour was described in a young adult who experienced both an anorectic phase after her encephalitis diagnosis, followed by a hyperphagia phase during her treatment [11]. In addition, hyperphagia has been previously reported as a potential symptom of anti-NMDA receptor encephalitis [5].

Our adolescent case of anti-NMDA receptor encephalitis underlines the importance of multidisciplinary teams in child and adolescent services. More importantly, it led to the first description of the association between anorectic symptoms and anti-NMDA receptor encephalitis, which widens its clinical spectrum even more and will hopefully improve the speed of the diagnostic process for these patients.

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Conflict of interest The authors declare that they have no conflict of interest.

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