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BRIEF REPORT

Anti-NMDAR encephalitis: a new, severe and challenging enduring entity

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Abstract Two girls, 15- and 17-year old, were consecutively and involuntarily admitted to the local child and adolescent psychiatric hospital with severe first onset psychosis. Due to refractory agitation, ongoing psychosis and insomnia, catatonic features, autonomic instability and the need for one-on-one guidance, the first girl was transferred to the PICU of an academic tertiary hospital and anti-NMDA receptor encephalitis was diagnosed. Given this experience nursing staff suspected, due to similarities in the clinical presentation and course, anti-NMDA receptor encephalitis in the second girl also and this proved to be true. The main clinical features, pharmacological and non-pharmacological treatment strategies and outcomes are presented and discussed. Perhaps, one ought to suspect anti-NMDA receptor encephalitis in every case of severe first onset psychosis with catatonic features.

Keywords Anti-*N*-methyl-D-aspartate receptor encephalitis · First episode psychosis · Critical illness · Diagnostic tools · Refractory insomnia · Refractory agitation

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Dedication The authors wish to dedicate this paper to H. Michielsen, a devoted child and adolescent psychiatrist.

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Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis refers to a new disorder with a mortality of 8–10 %. It progresses from a non-specific viral-like prodromal phase that is reported in up to 86 % of patients into a psychotic phase [1, 2]. Due to the primary neuropsychiatric manifestation in the early phase, 77 % of patients are first seen by a psychiatrist [1]. However, psychiatrists and other clinicians do not consider anti-NMDAR encephalitis until obvious neurological symptoms occur. Subsequent phases are characterized by impaired consciousness, lethargy, seizure-like episodes, dyskinesias, hypoventilation and autonomic instability [1, 3, 4].

The exact prevalence and incidence of the disease remain unknown. Although the median age of onset is 23 years, it ranges from 3 to 76 years [1, 5]. The preponderance is female. In slightly more than half of the patients anti-NMDAR encephalitis is associated with an underlying ovarian (or testicular) teratoma [1, 6]. In this brief report we present two cases of adolescent girls to illustrate the typical course of anti-NMDAR encephalitis and highlight some remarkable characteristics of the disease.

Case vignettes

Between January and April 2012, two severely psychotic adolescent girls were admitted to our tertiary paediatric

Table 1 Case vignettes

	Patient 1	Patient 2
General information		
Gender	Female	Female
Age	15 years	17 years
Race	Caucasian	Caucasian
Intelligence	Average intelligence	Average intelligence
Medication use	None	Oral anticonception
Previous history for psychiatry	None	None
Family history for psychiatry	None	None
Possible trigger	Traumatic break-up with boyfriend one week before onset of symptoms	Possible one-time use of XTC[a] and/or GHB[b] 1 week before onset of symptoms
Prodromal symptoms	None	Insomnia; fatigue; malaise
Neuropsychiatric symptoms	Insomnia, confusion, agitation, aggression, delusions, visual and tactile hallucinations	Decreased consciousness, insomnia, confusion, anxiety, agitation, aggression, disinhibition, visual hallucinations
	Catatonic features: mutism, echolalia, catalepsy	Catatonic features: hypo- and hyperkinesias, posturing, mutism
Neurological symptoms	Seizure-like episodes, orofacial dyskinesia, regression, dyspraxia	Generalized tonic–clonic seizure, dysarthria, hypersalivation, orofacial dyskinesia, unstable body balance, incontinence for urine and faeces, regression, dyspraxia
Other symptoms	Tachycardia, high diastolic blood pressure, limited intake, imminent exhaustion	Perspiration
	Secondary amenorrhoea	Secondary amenorrhoea
Initial diagnosis	First episode psychosis	First episode psychosis
Additional diagnostic tests	Venapuncture, lumbar puncture, cerebral MRI, abdominal ultrasound, abdominal MRI, total body MRI, EEG	Venapuncture, lumbar puncture, cerebral CT, cerebral MRI, abdominal and vaginal ultrasound, abdominal MRI, EEG
Positive results on additional diagnostic tests	Venapuncture/lumbar puncture: positive for NMDAR antibodies	Venapuncture/lumbar puncture: positive for NMDAR antibodies
		EEG: slow background activity and the presence of delta waves
Days to diagnosis	24	13
Tumour detected	No	No
Admission to PICU[c]	Yes	Yes
Scores at admission	Day 18 after onset of symptoms	Day 13 after onset of symptoms
GCS[d]	3-5-1, decreased consciousness	3-5-1, decreased consciousness
PAED[e]	15/20, paediatric delirium	15/20, paediatric delirium
MMSE[f]	Impossible to score	Impossible to score
PANSS[g]	158 points, severely ill	88 points, moderately ill
PIM[h] [15]	1.3 %	0.8 %
PRISM[i] [16]	2.5 %	0.7 %
Scores at discharge	Day 92 after onset of symptoms	Day 61 after onset of symptoms
GCS	4-6-5, normal consciousness	4-6-5, normal consciousness
PAED	2/20, no paediatric delirium	4/20, no paediatric delirium
MMSE	21/30, mild cognitive impairment	19/30, mild cognitive impairment
PANSS	80 points, moderately ill	58 points, mildly ill

[a] Ecstasy

[b] Gamma-hydroxybutyrate acid

[c] Paediatric intensive care unit

[d] Glasgow Coma Scale

[e] Paediatric Anaesthesia Emergence Delirium scale

[f] Mini-mental state examination

[g] Positive And Negative Syndrome Scale

[h] Paediatric index of mortality

[i] Paediatric risk of mortality

Table 2 Treatment Characteristics

	Patient 1		Patient 2	
I. Pharmacological Treatment				
1. Agitation (probable side effects)	Risperidone (acute dystonia tongue)	1 dd 2.5 mg p.o.	Risperidone (hypnosedation; coarse tremor left hand)	2 dd 1 mg p.o.
Max dosage and route of administration	Haloperidol (low grade fever and CPK[a] >1200 U/L: possibly NMS[b])	3 dd 0.25 mg IV	Methotrimeprazine	1 dd 25 mg p.o.
	Methotrimeprazine	5 mg/h IV	Haloperidol (parkinsonism)	3 dd 0.2 mg p.o.
2. Insomnia (probable side effects)	Promethazine (tachycardia)	25 mg incidentally p.o.	Promethazine	25 mg incidentally p.o.
Max dosage and route of administration	Oxazepam	10 mg incidentally p.o.	Temazepam	2 dd 10 mg p.o.
	Lorazepam	1 dd 2 mg p.o.	Lorazepam	2 dd 2.5 mg p.o.
	Methotrimeprazine	5 mg/h IV	Trazodon	1 dd 150 mg p.o.
	Melatonin	1 dd 3 mg p.o.	Methotrimeprazine	1 dd 25 mg p.o.
	Trazodon	1 dd 100 mg p.o		
	Methadone	3 dd 2.5 mg p.o.		
3. Anti-NMDAR encephalitis	Methylprednisolone	1 dd 1000 mg p.o.	Prednisone	2 dd 30 mg p.o.
Max dosage and route of administration	IVIG[3]	2 g/kg every 2 weeks IV	IVIG	2 g/kg every 2 weeks IV
	Rituximab	725 mg 2 courses IV	Plasmapheresis	Daily
			Cyclophosphamide	1 dd 150 mg p.o.
4. Additional pharmacological treatment	Midazolam	5 mg incidentally IV	Levetiracetam	2 dd 500 mg p.o.
Max dosage and route of administration	Morphine	20 mcg/kg/h IV		
	Propofol	2 mg/kg/h IV		
II. Non-pharmacological treatment				
5. Agitation	Behaviour reversal		Holding the patient tightly	
	Closed bed		Closed bed	
	Familiar objects in the room		Familiar objects in the room	
6. Insomnia	Light therapy		Light therapy	
	Mobilization		Mobilization	
	Day-to-day programme		Day-to-day programme	
	Sleep hygiene		Sleep hygiene	

[a] Creatinephosphokinase

[b] Neuroleptic malignant syndrome

[c] Intravenous immunoglobulin

intensive care unit (PICU). A detailed qualitative and quantitative description of their cases is provided in Table 1. Both the girls experienced an acute onset of neuropsychiatric symptoms and presented themselves to their general practitioner first. Within few days they were admitted involuntarily to a local child psychiatric hospital. They were diagnosed with first episode psychosis, and treatment with antipsychotics was commenced. Despite antipsychotic treatment the patients' psychiatric and somatic state deteriorated. Based on their recent experience

with patient 1, nursing staff taking care of patient 2 quickly suspected anti-NMDAR encephalitis. In both the cases one of us (J.S.) was consulted. Given his previous experience with this disease [4], he considered anti-NMDAR encephalitis to be an important differential diagnosis. Due to their severe neuropsychiatric symptoms, autonomic instability and need for one-on-one guidance transferral to the PICU was arranged for both the patients. Sleep disorders, agitation and aggression complicated the patients' stay at the PICU. These symptoms were treated with medication and non-pharmacological interventions (see Table 2). Several days within their stay NMDAR antibodies proved to be positive in serum and cerebrospinal fluid (CSF), and neuroimmunologic treatment was commenced. Both the girls were transferred to a local rehabilitation centre 3 and 2 months, respectively, after the onset of neuropsychiatric symptoms. At present both the patients have almost completely regained their premorbid level of functioning. Patient 1 has returned to school and patient 2 recently resumed her studies. They are no longer treated with psychotropics and they have both regained their menstrual cycle.

Discussion

These cases show similarities as well as differences with regard to the symptomatology, diagnosis and time-delay, treatment and course in time (Tables 1, 2). In both the patients an academically based child psychiatrist was consulted 5 and 7 days prior to diagnosis. His previous experience led him to quickly suspect anti-NMDAR encephalitis [4]. This illustrates that patients benefit significantly from awareness and knowledge of anti-NMDAR encephalitis among child psychiatrists, nurses and other clinicians alike as it reduces diagnostic and therapeutic time-delay and contributes to the improved prognosis [7].

Diagnosis of anti-NMDAR encephalitis relies on the detection of antibodies against the glycine-binding NR1 subunits of the NMDA receptor in serum and/or CSF. Antibodies against these subunits reduce the number of receptors on cell surfaces and in postsynaptic dendrites, and result in hypofunction of the NMDA-receptor system, which, among others, is thought to be associated with schizophrenia, as postulated in the glutamate hypothesis of schizophrenia [8, 9]. Zandi and colleagues [10] reported that in a set of patients ($N = 46$) with first episode psychosis, 6.5 % ($N = 3$) of the patients tested positive for NMDAR antibodies and these three patients met the DSM-IV criteria for schizophrenia. However, up to date other research has not been able to reproduce this [11].

Due to their severe neuropsychiatric symptoms, autonomic instability and need for one-on-one guidance both the patients were considered to be critically ill and were transferred to the PICU. Sleep disorders, agitation and aggression complicated their stay, as they required specialized psychiatric care and treatment. Therefore close cooperation with a consultant liaison psychiatric service is mandatory.

The before mentioned neuropsychiatric symptoms were often refractory to the standard treatment. Both pharmacological and non-pharmacological interventions were implemented. As shown in Table 2 the patients' psychotic symptoms and agitation were treated with typical as well as atypical antipsychotics. Risperidone and haloperidol are preferred in the treatment of positive psychotic symptoms, as they are both potent. They are available as oral liquids and thus can be administered in a low dose and titrated slowly. Moreover, haloperidol can be administered intravenously. As there appeared to be a marked sensitivity to often asymmetrical, extrapyramidal side effects "start low, go slow" is applied. In contrast with this sensitivity, high doses of sedative psychotropics, e.g., methotrimeprazine and benzodiazepines, were often necessary (see Table 2). By treating the patients with two differently targeted psychotropics, we were able to appropriately treat the symptoms that were of main concern.

Both the patients fulfilled the criteria of a catatonic disorder due to a general medical condition, a common diagnosis in anti-NMDAR encephalitis [3, 4]. Catatonia was treated with benzodiazepines and in patient 1 electroconvulsive therapy (ECT) was considered, but due to a sudden overnight improvement ECT was not applied eventually. Perhaps one can generally state that: in every agitated, psychotic patient with catatonia anti-NMDAR encephalitis should be considered.

Psychometric evaluation of the patient's symptoms and response to treatment is vital. The psychometric scales we used are the GCS, PAED scale, MMSE and PANSS. Scoring our patients during their treatment provided us with a structured and clear overview of their recovery (see Table 1).

Conclusion

Anti-NMDAR encephalitis is a new and severe neuropsychiatric disorder in which major challenges occur concerning diagnosis, pharmacological therapy and other non-pharmalogical interventions. Anti-NMDAR encephalitis deserves an important place in the child psychiatric differential diagnosis of first episode psychosis.

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Conflict of interest None.

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