Acta Neurologica Belgica (2021) 121:1357–1359
https://doi.org/10.1007/s13760-021-01673-7

LETTER TO THE EDITOR

Anti-NMDA receptor encephalitis after yellow fever vaccination: a case report

Evelien Coeckelbergh[1,2] · **Tatjana Reynders**[1,2]

Received: 15 February 2021 / Accepted: 5 April 2021 / Published online: 7 May 2021

Dear Editor,

As most of us are aware, anti-N-methyl D-aspartate (NMDA) receptor encephalitis is a potentially fatal limbic encephalitis. In several cases, an underlying tumor or a preceding viral infection can be withheld. Sometimes, a previous vaccination seems to precipitate an anti-NMDA receptor encephalitis [1].

We would like to present you our patient, a 29-year-old Caucasian male without significant medical history. He received a series of vaccinations in early September, preparing for a trip around the world, including hepatitis A and B, rabies, typhoid fever and yellow fever vaccines. In the following two–three days, he presented with malaise and nausea without fever, followed on day six by dizziness, gait problems, blurry vision and cognitive complaints. A first-degree horizontal nystagmus, downward drift and rigidity of the right arm and global hyperreflexia were withheld.

Laboratory testing showed normal full blood count, ionogram, liver and renal function, glucose (Table 1). Serum and urine revealed no signs of infection. A lumbar puncture revealed one leucocyte/mm^3, normal glucose and a slightly elevated protein level (Table 1). Cerebral and spinal MRI before and after intravenous gadolinium were normal. Due to spontaneous clinical recovery and reassuring results, the patient was discharged four days after admission. One week later, the neurology service was contacted by the laboratory because of positive anti-NMDA receptor antibody titers in serum (+++) and cerebrospinal fluid (CSF) (+). At the outpatient clinic, the patient appeared to have suffered from a minor liquor hypotension syndrome, but no other symptoms. Clinical examination was normalized, aside from persisting brisk reflexes. The serum anti-NMDA receptor antibody titer was still strongly positive. A sonogram of the scrotum and whole-body PET-CT did not reveal any malignancy. Given the clinical evolution, we decided against immunosuppressive therapy. The patient had spontaneously fully recovered after three weeks, without the administration of immunosuppressive therapy, and was impatient to start his world trip.

The patient disappeared from follow-up for the next two years, during which time he consulted his generalist for cognitive dysfunction (forgetfulness, fatigue and irritability). There were no signs of epilepsy, movement disorders or other symptoms.

To our knowledge, this is the first adult case report of anti-NMDA receptor encephalitis following yellow fever vaccination. While we reported only mild clinical signs and symptoms, phenotypes limited to memory impairment, insomnia and mood instability have been reported in anti-NMDA receptor encephalitis before [2, 3]. Poorthuis reported a case of anti-NMDA receptor encephalitis in the absence of vaccination with another mild clinical picture, including vertigo, nausea and vomiting and an isolated horizontal gaze-evoked nystagmus, later followed by memory impairment and psychiatric symptoms [4]. A milder clinical image might be due to relatively lower antibody levels compared to more overt anti-NMDA receptor encephalitis cases. In our case, the anti-NMDA receptor antibody titer in the CSF was only weakly positive.

Also, the interval between vaccination and symptom onset was shorter than in the previously published case in a teenager (9 as opposed to 27 days post-vaccination [5]), suggesting that the direct triggering of antibodies might not be the only mechanism. Therefore, vaccination could unchain a pre-existing auto-immune predisposition that leads to the production of anti-NMDA receptor antibodies.

Our patient has received multiple vaccines at the same time (hepatitis A/B, typhoid fever, rabies and yellow fever) among which the yellow fever vaccine is the only live

✉ Evelien Coeckelbergh
evelien_coeckelbergh@hotmail.com

[1] Department of Neurology, University Hospital Antwerp, Edegem, Belgium

[2] Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium

attenuated one. Given the former report of a patient with NMDA receptor encephalitis after yellow fever vaccination—and no reported cases after the other vaccines—this appears to be the most probable cause.

In our opinion, the real incidence of anti-NMDA receptor encephalitis after vaccination might be higher than reported. Given the heterogeneous clinical presentation of post-vaccination reactions (among others yellow fever vaccine-associated neurotrophic disease, YEL-AND), not every physician might think to determine autoantibodies. We, therefore, suggest performing an auto-immune panel, including anti-NMDA receptor antibodies, in each patient presenting with neurological symptoms within several weeks after yellow fever vaccination. Of course, this line of thinking holds as well for other types of vaccination, live attenuated or not. Adequate diagnosis of anti-NMDA receptor encephalitis is essential, since the disease course is unpredictable and might be fatal, although admittedly, not in our case.

Appendix 1

See Appendix Table 1

Table 1 Laboratory results from serum and CSF samples during hospitalization

Test	Patient value	Reference value	Unit	Test	Patient value	Reference value	Unit
SERUM				AUTO-ANTIBODIES (serum)			
Full blood count				**Auto-immune encephalitis**			
Hb	16.6	13–17	g/dL	Anti-NMDA receptor	Strongly positive (+++)	Negative (< 1/10)	
Platelets	155	140–440	.10E9/L	Anti-Ampa1 receptor	Negative	Negative (< 1/10)	
Leucocytes	3.97	4.3–10.0	.10E9/L	Anti-Ampa2 receptor	Negative	Negative (< 1/10)	
Abs neutrophilia	1.90	2.0–7.0	.10E9/L	Anti-GABAb receptor	Negative	Negative (< 1/10)	
				Anti-CASPR2 receptor	Negative	Negative (< 1/10)	
Hemostasis				Anti-LGI1	Negative	Negative (< 1/10)	
APTT	25.8	23.0–31.0	sec				
PT	95	78.0–123	%	AUTO-ANTIBODIES (CSF)			
INR	1.04	0.90–1.20	INR	**Auto-immune encephalitis**			
				Anti-NMDA receptor	Weakly positive (+)	Negative (< 1/1)	
Biochemistry				Anti-Ampa1 receptor	Negative	Negative (< 1/1)	
Creatinine	1.02	0.62–1.10	mg/dL	Anti-Ampa2 receptor	Negative	Negative (< 1/1)	
Urea	26	13–43	mg/dL	Anti-GABAb receptor	Negative	Negative (< 1/1)	
Natrium	139	136–145	mmol/L	Anti-CASPR2 receptor	Negative	Negative (< 1/1)	
Potassium	4.3	3.5–5.1	mmol/L	Anti-LGI1	Negative	Negative (< 1/1)	
Chloride	104	101–109	mmol/L	Antineuronal antibodies			
Bicarbonate	29	21–32	mmol/L	Screening indirect Immunofluorescence	Negative	Negative (< 1/1)	
CRP	< 2.9	< 3.0	mg/dL				
Glucose	78	74–100	mg/dL	CSF			
CK	134	46–171	U/L	Glucose	57	40–70	mg/dL
AST	28	< 35	U/L				
ALT	40	< 45	U/L	Total proteins	54	15–40	mg/dL
Alkaline phosphatase	104	53–128	U/L	Albumin	38.5	< 35	mg/dL
Gamma-GT	26	< 55	U/L	Albumin index	0.008	< 0.007	mg/dL
				IgG	2.9	< 5.5	
Protein electrophoresis				IgG index	0.36	≤ 0.7	mg/dL
Normal, no M proteins				Isoelectric focusing	No oligoclonal bands in CSF nor serum		
Immunoglobulins				Leucocytes	1		/µL
IgG	10.30	7.00–16.00	g/L	Erythrocytes	< 1000		/µL
				(An)aerobic cultures	Negative		/µL

Declarations

Conflicts of interest None.

Informed consent Written informed consent for publication of clinical details was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

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