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Case Report

Absence of serum anti-NMDAR antibodies in anti-NMDAR encephalitis mother predicts having healthy newborn

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1. Introduction

In the common clinical practice, it has been known that for diagnosis of the patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, it is important to show the presence of the antibodies against NMDAR in the cerebrospinal fluid (CSF) as well as serum.

Accumulating evidences have suggested anti-NMDAR encephalitis often attacks on women and even patients complicated with pregnancy. At present, however, the best way of how to treat pregnant cases of anti-NMDAR encephalitis and how to manage their fetuses remained to be elucidated [1–3].

In this study, we examined serial changes of anti-NMDAR antibodies titers in sera as well as CSF of an anti-NMDAR encephalitis mother. Moreover, we succeeded in examining the positivity of the antibody in sera and CSF from her neonate. We also searched for previously reported similar and dissimilar pregnant women suffering from NMDAR encephalitis in the literature who had healthy or complicated neonates. The data strongly suggest that her negative serum but not CSF anti-NMDAR antibodies appeared to be well-correlated to the favorable outcome of the present mother such as having normal newborn.

2. Case report

A 22-year-old woman at 22 weeks' gestation was admitted to our hospital complaining of high fever and disturbed consciousness. She also exhibited oro-lingual-facial dyskinesia, choreoathetosis, intractable convulsions and required respiratory support due to central hypoventilation till caesarean section. CSF examination revealed increased IgG index (Table 1). An electroencephalogram (EEG) was also abnormal (Table 1). Imaging studies revealed no abnormal findings including ovaries except for increased blood flow in the left temporal lobe on brain single photon computed tomography. Laboratory examinations revealed positive anti-NNMDAR antibodies in the patient's serum and CSF (Fig. 1), but no other autoantibodies including paraneoplastic antibodies listed in the Table 1. Therefore, we tentatively diagnosed her with anti NMDAR encephalitis and started sequential intravenous immunoglobulin (IVIg, 0.4 g/kg/day for 5 days), along with one course of methylprednisolone pulse therapy (1 g/day for 3 days) followed by seven times plasma exchange (PE) treatments, none of which resulted in the immediate recovery. She had been managed without stronger immunosuppressive agents because of the possible adverse effects on her fetus and we performed a caesarean section at 35 weeks' gestation. Fortunately, a healthy boy was born. Surprisingly, the patient's medical and neurological symptoms abruptly improved after the caesarean section. At 1 month after caesarean section, she became asymptomatic and normalized in EEG findings and was discharged to her home. Her son has been followed up by a pediatrician and is now 14 months old. He has achieved normal developmental milestones thus far.

Immunocytochemistry was performed with a kit from EUROIMMUNE AG (Luebeck, Germany) following the manufacturer's instruction. Under the informed consent from her husband and immediate relatives, we obtained maternal serum and CSF samples at

Abbreviations: CSF, cerebrospinal fluid; ANA, nuclear antibody; Tg, thyroglobulin; TPO, thyroid peroxidase; IgG, Immunoglobulin G; MONO, Monocytic cells; PCR, polymerase chain reaction; HSV-1, Herpes simplex virus 1; HSV-2, Herpes simplex virus 2; VZV, varicella-zoster virus; CMV, cytomegalo virus; HHV-6, human herpesvirus 6; HHV-7, human herpesvirus 7; EEG, electroencephalogram

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Table 1
Whole blood, Serum, CSF and EEG Findings.

Measure	Result	Reference Range
Whole blood		
White blood cell count	8600/μL	4500–11000/μL
Red blood cell count	2.8 × 10^6/μL	3.9–5.5 × 10^6/μL
Hemoglobin	8.9 g/dL	14.0–17.5 g/dL
Hematocrit	25.0%	41–50%
Platelet count	219 × 10^3/μL	150–350 × 10^3/μL
Serum		
C-reactive protein	< 0.3 mg/dL	0.008–3.1 mg/dL
Sodium	137mEq/L	136–142 mEq/L
Creatinine	0.31 mg/dL	0.6–1.2 mg/dL
ANA (Nucleolar pattern)	×80	×0–19
Anti-Tg antibody	17IU/mL	< 28IU/mL
Anti-TPO antibody	< 5IU/mL	< 16IU/mL
Anti-Hu antibody	negative	
Anti-Yo antibody	negative	
Anti-Ri antibody	negative	
Anti-CV2 antibody	negative	
Anti-Ma1 antibody	negative	
Anti-Ma2 antibody	negative	
Anti-Amphiphysin antibody	negative	
CSF		
Opening pressure	22 cm/H_2O	6–18 cm/H_2O
Glucose	56 mg/dL	45–75 mg/dL
Protein	28 mg/dL	10–40 mg/dL
IgG	4 mg/dL	< 4 mg/dL
IgG index	1.73	< 0.73
Red Blood cells	0/μL	0/μL
Nucleated cells	21/μL (Mono 100%)	< 5/μL
Bacterial culture	negative	
Herpes virus real time PCR (HSV-1, HSV-2, VZV, CMV, HHV-6, HHV-7)	negative	
EEG	background 3–4 Hz, 70–100 μV no lazy activity, no spike activity	

various time points and the infant's serum at 1 day after birth and CSF 3 at days after birth, respectively. Stained cells were visualized using a Carl Zeiss LSM710 fluorescence microscope (Oberkochen, Germany) (Fig. 1). This study was approved by the ethics committee of Fujita Health University.

Maternal serum and CSF obtained at admission (at 22 weeks' gestation) were both positive (Fig. 1C, D). However, serum antibody became negative at 26 weeks' gestation (2 weeks after first IVIg replacement therapy) and remained negative at subsequent time points (Fig. 1E–G), whereas at 35 weeks' gestation the mother's CSF was still anti-NMDAR antibodies-positive, although the titer slightly decreased (Fig. 1H–J). There was no anti-NMDAR antibody in either serum or CSF of the newborn (Fig. 1K, L). Moreover, immunohitochemical examination on rat hippocampus and cerebellum with EUROIMMUNE AG kit supported the data from the cell-based assay (data not shown).

3. Discussion

Thus far, there have been few reports on NMDAR encephalitis in pregnant women [1–3]. IgG subclasses 1 and 3 are known to cross the placenta by binding with an Fc receptor present in syncytiotrophoblasts from 13 weeks of gestation onward [4], although the transfer of the antibodies seems very limited at the initial stage. The largest amount of IgG transplacentally transferred to fetus is achieved in the third trimester of the pregnancy [5]. Serum titer of anti-NMDAR antibodies in the present case turned negative at the latest within the second trimester.

An interesting and pertinent case was recently reported by Jagota et al. [1]. A mother with NMDAR encephalitis and positive serum anti-NMDAR antibodies gave birth to an infant whose serum was also anti-NMDAR antibodies–positive and who later developed cortical dysplasia. Unfortunately, they did not examine the infant's CSF. Moreover, Hilderink et al. reported a case in some way opposite to the present case, in that case passive transfer from a mother in remission with remaining serum antibodies to her child was shown [2].

There are reports of healthy neonates born to mothers with anti-NMDAR encephalitis [2,3], information on the positivity of anti-NMDAR antibodies in newborn CSF has been unavailable except one newborn case, although the authors did not comment on this finding [3]. The neonate of the present case did not exhibit anti-NMDAR antibodies in both serum and CSF at birth, even though his mother's CSF but not serum was positive for anti-NMDAR antibodies at the time of delivery. Therefore, we speculate that the absence of anti-NMDAR antibodies in maternal serum from 26 weeks' gestation onward, at the latest, to the delivery might prevent the large amount of the antibodies transfer to the fetus.

4. Conclusions

The present case strongly indicates that especially in pregnant cases, quick reduction of serum anti-NMDAR antibody titers with immunological therapies might be good clue for having healthy newborns from pregnant women suffering from anti-NMDAR encephalitis. In the good agreement with this assumption, a recent report suggested that serum NMDAR antibodies-positive pregnant woman resulted in giving birth of a complicated newborn. The antibodies in maternal CSF did not seem to affect the outcome of new born babies, although we cannot exclude the possibility that other factor(s) unidentified in the present study might be involved in the good outcome of the newborn of the present mother. Anyhow, the present study highlighted the significance of testing serum antibodies for the prediction of the consequences of delivered baby.

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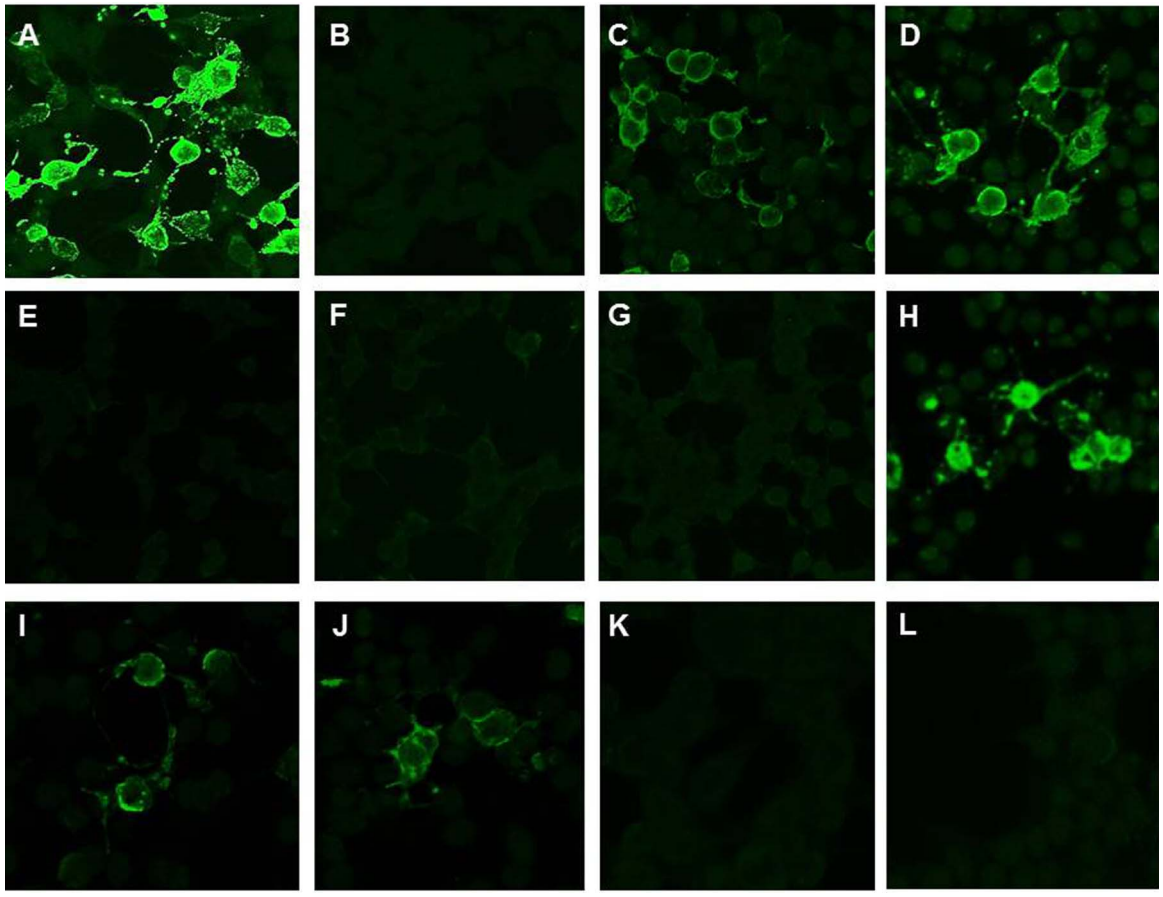

Fig. 1. CSF and serum reactivity in a mother with anti-NMDAR encephalitis and in her neonate. Immunocytochemistry was performed with Autoimmune Encephalitis Mosaic 1 (EUROIMMUNE AG, Luebeck, Germany) as described in the text. Maternal and neonatal CSF was undiluted and serum was diluted 1:10 in PBS-Tween. Cells were incubated with primary antibodies for 30 minutes at room temperature, then incubated with secondary anti-human antibodies conjugated with fluorescein for 30 minutes at room temperature. To determine the titer of the antibody in the sample which was positive in initial screening at the dilution of 1:10, serum was sequentially diluted in PBS-Tween according to the protocol by the manufacturer. (A) Positive control: human anti-NMDAR antibody, provided by the kit (type NMDA; subunit NR1). (B) Negative control: autoantibody-negative, human provided by the kit. (C) Maternal serum during the acute phase of encephalitis at 22 weeks' gestation. The titer was determined to be 1:100. (D) Maternal CSF during the acute phase of encephalitis at 22 weeks' gestation. The titer was 1:1000. (E) Maternal serum after IVIg, at 26 weeks' gestation. The antibody became negative. (F) Maternal serum after PE therapy, at 28 weeks' gestation. Note that the antibody is negative. (G) Maternal serum before caesarean section, at 32 weeks' gestation. Note that the antibody is negative. (H) Maternal CSF taken at 2 weeks after first IVIg (26 weeks' gestation). The titer was 1:1000. (I) Maternal CSF after PE therapy at 28 weeks' gestation. The titer decreased to 1:100. (J) Maternal CSF before caesarean section at 32 weeks' gestation. The titer was still 1:100. (K) Neonatal serum at 1 day after caesarean section. Note that the antibody is negative. (L) Neonatal CSF at 3 days after caesarean section. Note that the antibody is negative.

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