Journal of Neuroimmunology 325 (2018) 29–31

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short communication

Confusional state in a pregnant woman: A case of NMDA receptor encephalitis during pregnancy

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ABSTRACT

We report the case of a pregnant female presenting with behavioral change and hallucinations followed by focal seizures with impaired awareness. EEG revealed generalized slowing interspersed with extreme delta-brush pattern and MRI brain was normal. Both Serum and CSF anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies were positive. Patient had a prolonged hospital stay with full recovery and delivered a healthy baby, highlighting the significance of early diagnosis and management in this disorder.

1. Introduction

A paraneoplastic immune-mediated syndrome was first described in four young females with ovarian teratomas, presenting with acute psychiatric symptoms, seizures, and central hypoventilation (Vitaliani et al., 2005). Autoantibodies to the *N*-methyl D-aspartate receptor (NMDAR) were demonstrated in these and eight other patients with similar presentation, seven of whom also had ovarian teratomas (Dalmau et al., 2007). This syndrome was subsequently also reported in patients without an associated tumor. Anti-NMDAR encephalitis has been described as a multistage illness that usually begins with a prodrome of flu-like illness that progresses to psychosis, memory deficits, seizures, and language disintegration into a state of unresponsiveness with catatonic features often associated with abnormal movements and alternating with periods of agitation, and autonomic instability and hypoventilation (Izuka et al., 2008; Sansing et al., 2007; Dalmau et al., 2011). Despite Anti-NMDAR encephalitis being more common in young aged females (Median age of onset of 21 years and M: F ratio 4:1) reports of this illness during pregnancy are sparse and treatment paradigms are uncertain. We report the first case of NMDA receptor encephalitis in pregnancy from India with its long-term outcome.

2. Case report

A 25-year-old pregnant lady at 16 weeks of gestation was admitted to our hospital with history of aggressive behaviour, decreased sleep and visual hallucinations for a period of three weeks prior to presentation. A week after the onset of these symptoms, the relatives noticed decreased verbal output with undue repetition of words and phrases. Two weeks into the illness, she developed involuntary jerky movements of right side of body with facial twitching and oral automatisms, which occurred multiple times a day, following which she had become minimally responsive with fluctuating consciousness, five days prior to admission. She had no previous history of any medical illness or exposure to any psychotropic drugs or medications.

On examination, she was drowsy and localizing painful stimuli. No meningeal signs were elicitable. There was intermittent focal facial twitching and lip smacking. Pupils were equal in size and reacting to light. She was moving all four limbs and deep tendon reflexes were brisk and plantars were flexor. There was no evidence of neck stiffness. Systemic examination was normal.

A brain magnetic resonance imaging (MRI) was done which was normal. Lumbar puncture revealed 5 cells per cubic mm (100% lymphocytes), 30 mg % protein and 104 mg/dl sugar with no organisms on Gram stain and India Ink, negative cryptococcal antigen test and negative CSF bacterial and fungal cultures. CSF PCR for HSV 1, 2 and CMV was negative. Transabdominal ultrasonography showed single live intrauterine foetus with no evidence of any adnexal mass. CT abdomen and pelvis was not done as the patient was pregnant. Ultrasound of abdomen was done every 2 weeks for fetal well being. EEG was suggestive of asymmetric diffuse 2 Hz to 5 Hz slowing (Right > Left) with extreme delta brush pattern (Fig. 1).

She was started empirically on pulse steroids (Intravenous Methylprednisolone 1 g for 5 days) and anti-epileptics (Levetiracetam 1 g IV BD, Tab Lacosamide 50 mg BD and Tab Clobazam 20 mg/day).Intravenous immunoglobulin (IVIg) (2 g/kg over five days) was started on day four of methylprednisolone in view of no improvement. By day nine, there was substantial decline in the facial twitching, however the patient continued to have oral dyskinesias and fluctuations in sensorium. Decision against termination of pregnancy was taken in

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https://doi.org/10.1016/j.jneuroim.2018.10.008
Received 18 September 2018; Received in revised form 17 October 2018; Accepted 17 October 2018

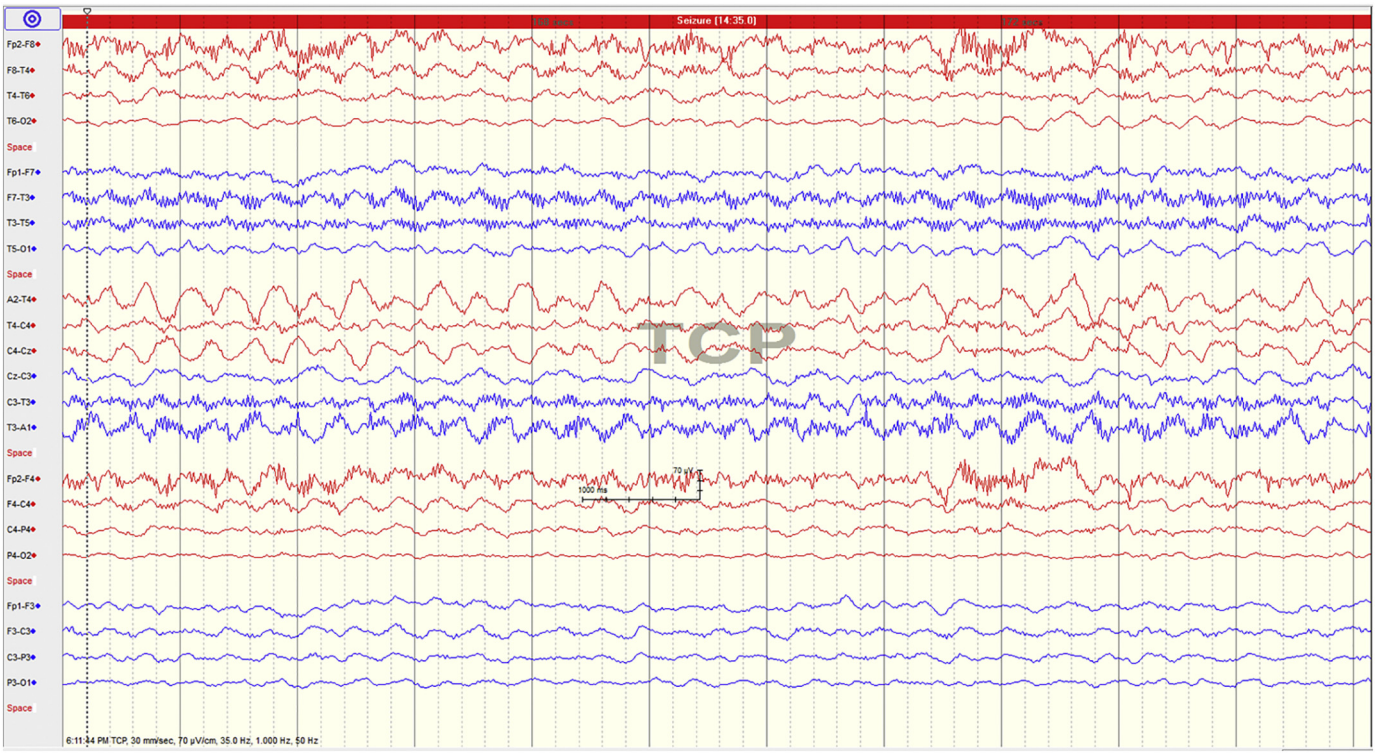

Fig. 1. EEG- Extreme delta brush.

view of advanced age of foetus and absence of any established evidence- based guidelines for the same. Reports of both serum and CSF NMDA receptor antibodies came to be positive. In view of persistent neuro-behavioral abnormalities after 2 weeks of IVIg, after well-informed consent of caregivers she was given Inj. Rituximab (500 mg) on day 24 of admission followed by weekly for 4 weeks. By day 40 (two weeks after Rituximab), she was able to recognize her relatives and give coherent response to commands. She started taking orally by day 45 and was discharged in stable condition on day 47 at a period of 23 weeks of gestation. She delivered a healthy male child weighing 2.1 kg at term. At the time of writing this report the child was 11 months of age and is able to walk with support and can say “ma”, “pa” with the intervening milestones being attained normally and no evidence of developmental delay. There has been a continuous improvement in the mothers' cognition and behaviour and follow-up modified Rankin Scale (mRS) score at six months of 0, even though detailed neuropsychological assessment was not done.

3. Discussion

Our case represents the first case of Anti-NMDAR encephalitis in pregnancy to be reported from India. A total of 15 such cases have been reported in the literature so far. The details of these patients are given in Table 1. Ovarian teratoma was detected in 6 out of 15 patients reported at the time of pregnancy. Ultrasonography was contributory for diagnosis in only one of these six patients. MRI abdomen-pelvis was contributory in another patient. In one patient the adnexal mass was detected only at the time of LSCS (lower segment caesarean section), despite a prior ultrasonography and MR pelvis. Pelvic CT detected the adnexal mass in 4 out of these patients (two of which had miscarriage and one had termination of pregnancy). Mizutamari et al. in their case noted that although ultrasonography and MRI can be used safely to evaluate adnexal masses during pregnancy, it is difficult to differentiate ovarian tumors from luteal cysts during early pregnancy, and although right ovarian cystic lesion was detected on USG, they proceeded with a reduced dose noncontrast pelvic CT for their patient at 16 weeks of gestation. After detection, teratoma resection/oophorectomy was performed in two of the patients in the second trimester. Although faster recoveries and improved outcomes are associated with early surgical removal of teratomas, both the role of Pelvic CT for detection and early surgery in the context of pregnancy is unclear.

Regarding the outcome of pregnancy, one patient had medical termination of pregnancy, two had spontaneous abortion, four delivered by caesarean section while eight had a normal vaginal delivery. All abortions occurred in patients diagnosed with NMDAR encephalitis in the first trimester. Our patient had a term vaginal delivery.

There is a distinct possibility that maternal NMDAR antibodies by transplacental transfer may affect brain development of the fetus. By the end of second trimester the fetal blood-brain barrier is functional and hence there is a possibility that offspring of patients who develop disease later in the course of pregnancy may have less adverse outcomes. Blood or CSF NMDAR antibodies were tested in four of the new-borns, two of which were positive (Jagota et al., 2014, Lamale-Smith et al., 2015). The titres were same as that of mother and eventually declined in both cases without any overt clinical manifestation in one of the case reports. However the other child had global developmental delay and seizures and was detected to have focal cortical dysplasia at 3 years of age (Jagota et al., 2014). The remaining new-borns have a maximum follow-up of six months to 1 year and are reportedly normal. There is a need for more data to ascertain the consequences of prenatal trans-placental exposure of NMDAR antibodies as NMDA receptors are known to play a role in brain development (Hughes et al., 2010).

The initial management in these case reports includes methylprednisolone (MPS) in 14 out of the 15 cases, with recovery occurring in two cases with this intervention alone, whereas all other patients required multiple second line agents. Plasma exchange was tolerated and performed in 8 out of 15 patients. Post-delivery, rituximab was used in two of the patients. Early immune therapy hastens recovery. Plasmapheresis may be superior to other treatment modalities, as it can be safely used in pregnancy and has an added advantage of being able to remove foetal antibodies. In our case, in view of restlessness and irritability of the patient, plasma exchange was not attempted. In view

Table 1
Case reports Anti- NMDA receptor encephalitis in pregnancy.

Reference	Age (years)	Gestational age (weeks)	Symptom	Ovarian Teratoma	Mode of delivery	Treatment	Outcome Mother	Outcome Child
Kumar et al., 2010	19	14	Headache, Seizure, Delusions	+	LSCS 38th week	MPS, IVIg, PE Oophorectomy	Recovery	Normal
Kumar et al., 2010	20	8	Abnormal behavior Orofacial dyskinesias	+	Abortion 10th week	MPS, IVIg Tumor resection	Recovery	–
Kumar et al., 2010	19	17	Abnormal behavior Seizures	–	Delivery 37th week	MPS	Recovery	Normal
Ito et al., 2010	19	17	Oral dyskinesia Abnormal behavior	–	Delivery 37th week	MPS	Recovery	Normal
McCarthy et al., 2012	32	8	Psychosis Catatonia	+	LSCS 32ndweek	MPS, PE, Azathioprine	Recovery	Normal
Magley et al., 2012	24	Before Pregnancy	Choreoathetosis Abnormal behavior	–	Delivery 35th week	IVIg	Recovery	Strabismus Torticollis
Jagota et al., 2014	18	9	Oral dyskinesias, Fever	–	Delivery 34th week	MPS IVIg	Died	GDD Seizures
Lamale-Smith et al., 2015	24	20	Abnormal behavior Catatonia	–	LSCS 28th week	MPS, IVIg, PE Oophorectomy	Recovery	Normal
Chan et al., 2015	23	First trimester	Fever, hallucinations, Behavior changes	+	Miscarriage	MPS, PE Rituximab	Recovery	–
Lu et al., 2015	36	2	Hallucination, psychosis	–	Delivery At term	MPS, PE	Recovery	Normal
Shahani, 2015	26	22	Headache, delusions, abnormal behavior	–	Delivery 37th week	MPS, PE	Recovery	Normal
Mathis et al., 2015	21	10	Abnormal behavior Orofacial dyskinesia	–	Delivery 40th week	MPS, IVIg	Recovery	Normal
Kim et al., 2015	28	7	Abnormal behavior, Seizures	+	Miscarriage	MPS, PE Tumor resection Rituximab	Recovery	–
Mizutamari et al., 2016	30	15	Headache, Altered Sensorium	+	Delivery 40th week	PE,MPS, IVIg Tumor resection	Recovery	Normal
Xiao et al., 2017	24	28	Hallucinations, Seizures	–	LSCS 33rd week	MPS, IVIg	Recovery	Normal

MPS: Methylprednisolone; IVIg: Intravenous immunoglobulin; PE: Plasma exchange; LSCS: Lower segment Caesarean section. GDD: Global developmental delay.

of poor response to MPS and IVIG, rituximab was offered to our patient after an informed consent and was efficacious and well tolerated.

All except one patient had favourable outcome. Most of the newborns underwent delivery at term. These cases point towards a generally favourable prognosis for both the mother and the child, provided a early diagnosis and good supportive care is provided.

4. Conclusion

This case highlights the importance of considering Anti-NMDAR encephalitis as one of the differential diagnosis in a pregnant female presenting with altered sensorium, seizures or abnormal behaviour. A rapid recognition, diagnosis, medical and supportive treatment can ensure a good recovery of mother and the child.

Conflict of interest

There are no conflicts of interest in submission of this manuscript.

Informed consent was obtained from the patient included in the manuscript.

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