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Original Article

Anti-N-Methyl-D-Aspartate receptor (NMDAR) encephalitis during pregnancy: Clinical analysis of reported cases

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ABSTRACT

Objective: To analyze the clinical features of 13 pregnant patients with anti-N-Methyl-D-Aspartate receptor (NMDAR) encephalitis.

Materials and methods: Retrospective review of thirteen reported cases was conducted for anti-NMDAR encephalitis patients during pregnancy. The clinical data were collected from papers published in PubMed prior to 16 February 2016. Statistical analysis of the data was performed, which encompasses the patients' age, past medical history, onset of symptoms, concomitant with ovarian teratomas, immunotherapy, outcomes of mothers and newborns.

Results: Thirteen cases were reported in 11 articles with a median age of 23 (interquartile range, 19–27) years old. There were eight cases in which the onset periods of gestation happened in the first trimester and five cases in the second trimester. Among 13 cases, five patients had a past medical history, one concomitant with autoimmune Graves' hyperthyroidism, one with bilateral ovarian teratomas removed history, one with anti-NMDAR encephalitis five years before pregnancy and two with psychiatric symptoms. Five patients were found with ovarian teratomas. Seven patients responded to first-line immunotherapy whereas all of two patients responded to second-line immunotherapy when the first-line immunotherapy failed. Following up all the 13 patients, most experienced a substantial recovery, except one had spasticity and dystonia in one hand, and one died of a superimposed infection. Three fetuses were miscarried or aborted in total. Most newborns were healthy, except two cases (2/10) with abnormal neurologic signs.

Conclusions: Clinical analysis of the data indicates that most patients respond to first-line immunotherapy. A second-line immunotherapy is effective when first-line immunotherapy fails. It has also been found that most mothers and newborns can have good outcomes.

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was first reported in 2005 in four patients with ovarian teratoma [1]. It is a type of autoimmune synaptic encephalitis, and it is known that the NMDAR antibody is principally associated with the antigen against NR1 subunit of the NMDAR [2]. This disease is reversible upon removal of patients' antibodies [3]. Despite the severity of the disorder, most patients have substantial recoveries.

More recently [4,5], anti-NMDAR encephalitis in pregnant women has been more frequently reported with an increasingly concerned by gynecologists and neurologists. Diagnosis and treatments are challenging in pregnancy because little data exists for reference. So we have made a review of reported cases of anti-NMDAR encephalitis during pregnancy. Here we report our study on 13 cases with anti-NMDAR encephalitis focusing on pathogenesis, immunotherapy and prognosis of mother and newborn. To the best of our knowledge, this is the first report of a review of anti-NMDAR encephalitis during pregnancy.

Methods

Literature search and data analysis

An extensive search in PubMed was carried out for case reports which were published prior to 16 February 2016, using the search terms 'anti-nmda receptor encephalitis' and 'pregnancy'. During the search there was no language restrictions applied. For example,

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a paper published in Japanese was included. The search using those criteria generated 16 articles in total. Among them, 11 articles containing 13 cases of anti-NMDAR encephalitis during pregnancy were found to be relevant. A review of these articles was performed. Firstly, the titles and abstracts of all articles were evaluated by two neurologists to determine whether each case report should be considered. When there were different opinions between these two neurologists, a third neurologist was invited to further assess the case. We contacted authors to make a further clarification when the information provided in their publications was not clear enough. The gestation time was used in weeks at a symptom onset which was divided into first trimester ($0–13^{+6}$ weeks) and second trimester (14th week-27^{+6} weeks). First-line immunotherapy is defined as the use of steroids, IVIg or plasmapheresis singly or in combination, and second-line immunotherapy includes rituximab or cyclophosphamide singly or in combination.

Results

General clinical data of patients

The median age at the time of onset was 23 (interquartile range 19–27) years old. Most patients (8/13) were registered with a healthy medical history with a remainder of five patients being unhealthy (one concomitant with autoimmune Graves' hyperthyroidism which was relieved during pregnancy and relapsed postpartum [6], one with anti-NMDAR encephalitis five years before pregnancy whose symptoms remained stable throughout pregnancy but deteriorated postpartum [7], one with a bilateral ovarian teratomas removed history [8], and two with psychiatric symptoms which may be an early symptom of anti-NMDAR encephalitis [4,9]). The onset period of gestation for the most (8/13) was during the first trimester, five cases happened in the second trimester. Five patients were diagnosed with ovarian teratomas. Among them, two mothers gave birth to healthy babies [8,10], two suffered from miscarriage with unclear causes [8,9], and one was aborted due to the mother's recurrent bilateral ovarian teratomas and serious clinical conditions such as sinus bradycardia, status epilepticus and respiratory depression [8] (Table 1).

Main clinical symptoms of patients

The main clinical symptoms discovered consist of seizures, psychiatric disorders, extrapyramidal symptoms, hypoventilation, autonomic disturbance and decreased consciousness. All patients initially presented psychiatric symptoms such as hallucination, anxiety, depression and memory disturbance. The survey also reveals that most patients had severe conditions. It should be pointed out that 53.8% (7/13) patients presented with hypoventilation required the implementation of intubation, tracheotomy or mechanical ventilation. Nevertheless a follow-up study indicated that the majority of the patients had recovered well. Table 1 illustrates that 84.6% (11/13) patients had slight deficits or full recovery whilst one suffered from spasticity in right hand, dystonia and dysphonia [7], another died of superimposed infection, however her neuropsychiatric condition was improved significantly postpartum [5].

The onset periods of gestation and conditions of fetuses or newborns

Among thirteen fetuses studied, two were miscarried with unclear causes and one was aborted due to the mother's recurrent bilateral teratomas [8,9]. All of these happened within the first trimester of gestation. The other ten babies were labored and most of them (8/10) were healthy, but one baby with respiratory and neuromuscular depression whose NMDAR antibody of the fetal cord blood was tested positive [4]. However, after one year follow-up, the baby was found to do well and be developmentally appropriate [4]. Two babies (2/10) were unhealthy with delayed development, seizure, torticollis and strabismus [5,7]. The number of miscarried/aborted fetuses and unhealthy babies was five in total and four of their mothers underwent hypoventilation. Among ten newborns, only two had been extensively evaluated for antibodies which were both positive [4,5]. Their mothers initially developed symptoms at the gestation of the first trimester in one case [5] and the second trimester in the other case [4].

Effects of immunotherapy

The data in Fig. 1 reveals that seven patients with anti-NMDAR encephalitis were responsive to first-line immunotherapy. In all remaining two cases, second-line immunotherapy was found to be effective when the first-line therapies were unsuccessful [9,10]. Nine patients' conditions were improved after the delivery and/or ovarian teratomas removal. Only one patient's neuropsychiatric symptoms deteriorated postpartum [7]. One patient's neuropsychiatric symptoms improved postpartum, but she became hyperthyroid which was secondary to recurrence of Graves' disease [6].

Discussion

The causes of anti-NMDAR encephalitis during the pregnancy have not yet been fully addressed. One feature of such disease is that it predominantly affects women of reproductive age [15,16], and exists a frequent association with ovarian teratomas [2,8,17,18]. We found nearly a quarter of anti-NMDAR encephalitis pregnant patients concomitant with ovarian teratomas. So we presume that the pregnant patients predispose to anti-NMDAR encephalitis may relate to the ovarian teratomas too. And anti-NMDAR encephalitis and other variants in the autoimmune synaptic protein encephalopathy syndromes spectrum exhibit a female predominance (female-to-male ratio 4:1), primarily targeting women of childbearing age [16]. If the same mechanisms apply as in other autoimmune conditions, the effect of sex hormones on autoreactive T and B cells may provide an insight [19]. Estrogen has the general effect of stimulating B cell survival and antibody production, whereas it can suppress T cell expansion when present at high levels (as seen in pregnancy). Such observations explain why autoantibody disorders may flare with pregnancy [20]. We discovered 84.6% patients initially presented during the first trimester. The presence of the embryo or placenta may have triggered an antigenic signal and/or antibody through inappropriate immunological modulation [12]. The NMDAR is known to be expressed in ovum at higher levels in adults [6,21]. Increasing number of documents suggest that antibodies formed in response to a number of possible stimuli (i.e., tumor, infection), cross-react with the NMDAR [17]. Embryo or placenta may be a stimulus, and most patients' conditions improved after delivery which confirmed this hypothesis. One case is concomitant with Graves' disease [6], both are autoimmune disorders that may have shared the same mechanism of pathogenesis. As in some other autoimmune diseases, the disease may remit in pregnancy and relapse postpartum [10].

The treatment is extremely challenging as little data exist to guide managements. Currently, there are no established guidelines, first-line immunotherapy is well tolerated in pregnancy [7,9,12,17], as well as tumor removal if a paraneoplastic process is involved [17,22]. Second-line immunotherapy is usually effective when first-line immunotherapy does not work [4,14,22]. In light of harmful effect on fetus of second-line immunotherapy, clinicians usually avoid it except that the fetus is aborted or miscarried. For treatments of refractory symptoms, second-line immunotherapy such as rituximab

Table 1
The general clinical data of patients.

Reference	Age	Past medical history	Onset of symptoms	OT	HPV	GA	Immunotherapy		Neurological Sequelae	
							1st-line	2nd-line	Mother	Baby
Lamale-Smith et al. [4]	24	Psychiatric symptoms	Catatonia, disoriented, confused	No	Yes	2nd trimester	Steroids, IVIg, Plasmapheresis	No	Slight disinhibition and memory deficits	Normal
Jagota et al. [5]	18	Healthy	Orolingual movements, eye deviation, fever	No	Yes	1st trimester	Steroids, IVIg	No	Died	Delayed in global development, seizure
Lu et al. [6]	36	Graves' disease	Hallucination, psychosis	No	No	1st trimester	Steroids, Plasmapheresis	No	Slight subjective memory impairment	Normal
Magley et al. [7]	24	Anti-NMDAR encephalitis	Choreoathetosis, bradykinesia, weakness, depression, obsessive thoughts	No	No	1st trimester	Steroids, IVIg, Plasmapheresis	No	Spasticity in right hand, dystonia and dysphonia	Torticollis, strabismus
Kumar et al. [8]	19	Healthy	Headache, malaise, abnormal behavior	Yes	Yes	2nd trimester	IVIg, Plasmapheresis	No	Substantial recovery	Normal
Kumar et al. [8]	20	Bilateral OT	Abnormal behavior	Yes	Yes	1st trimester	IVIg	No	Minimal deficits	Aborted
Kumar et al. [8]	19	Healthy	Abnormal behavior	No	No	2nd trimester	Steroids	No	Normal	Normal
Chan et al. [9]	23	Psychiatric symptoms	Fever, hallucinations, disinhibited behavior, confusion	Yes	Yes	1st trimester	Steroids, Plasmapheresis	Yes	Normal	Miscarried
Kim et al. [10]	28	Healthy	Epileptic, abnormal behavior	Yes	Yes	1st trimester	Steroids, IVIg, plasmapheresis	Yes	Slight cognitive function deficits	Miscarried
Mathis et al. [11]	21	Healthy	Abnormal behavior	No	Yes	1st trimester	Steroids, IVIg	No	Slight memory disturbance	Normal
Shahani [12]	26	Healthy	Headache, delusions, abnormal behavior	No	No	2nd trimester	Steroids, Plasmapheresis	No	Normal	Normal
McCarthy et al. [13]	32	Healthy	Psychotic, catatonia, autonomic disturbance.	Yes	No	1st trimester	Steroids, Plasmapheresis	No	Normal	Normal
Ito et al. [14]	19	Healthy	Oral dyskinesia, abnormal behavior	No	No	2nd trimester	Steroids	No	Normal	Normal

OT = Ovarian teratoma, HPV = hypoventilation, GA = gestational age.

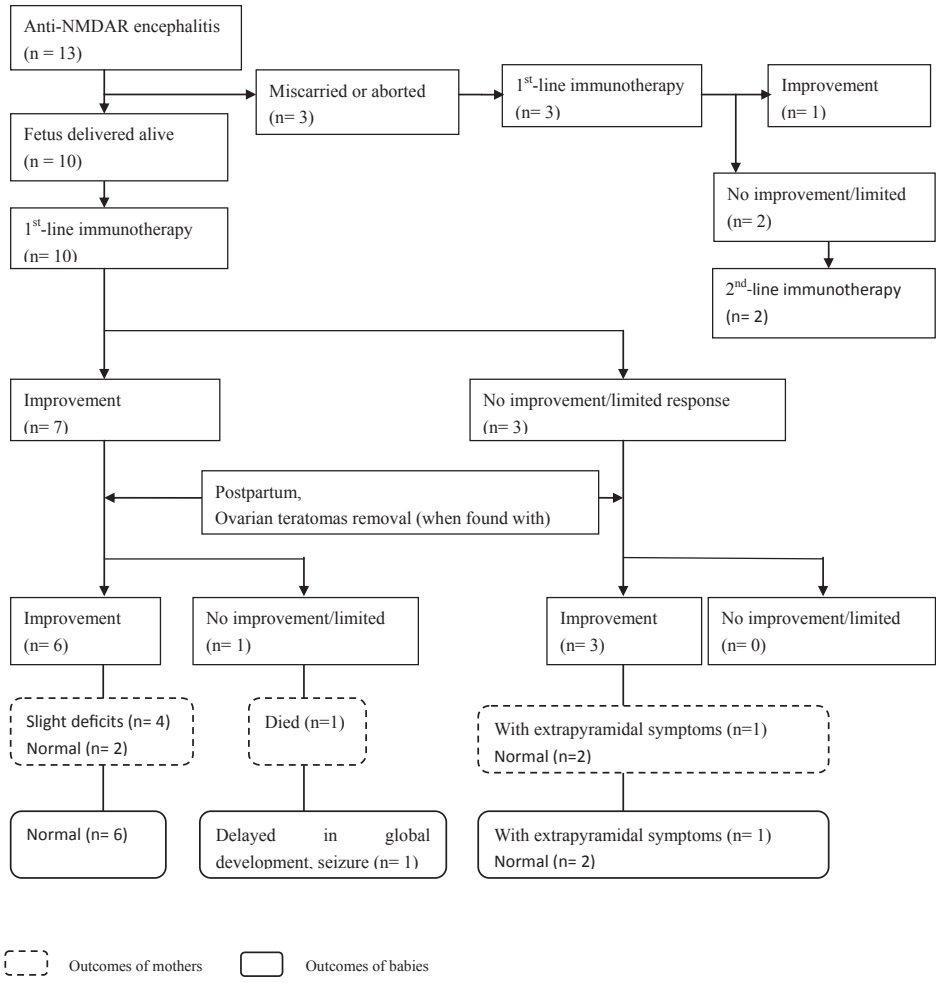

Fig. 1. Flowchart of therapeutic effects.

may be considered in pregnancy, whereas azathioprine and cyclophosphamide should be avoided [10]. Plasmapheresis can be used safely in pregnant patients [9], however, hypotension may occur which can decrease fetal perfusion [18]. In addition, it is necessary for clinicians to carefully position the patient to avoid compression of the inferior vena cava in the latter half of pregnancy [18]. Many cases reported that delivery or termination of pregnancy can accelerated recovery [7,9,13]. We found 85% patients recovered well postpartum. So a planned preterm birth may be considered to improve maternal outcomes and decrease fetal exposure to maternal antibodies. But one patient miscarried in first trimester and she underwent a prolonged recovery period which included four months of an intensive care unit stay [14]. Some thought pregnancy itself may not worsen or cause disease relapse [10]. Further study is needed to characterize the disease responses postpartum. Clinicians have come to agreement that early surgical removal of the teratoma has been associated with faster recovery and improved outcome [2,8,23]. Additional reports have described recovery after oophorectomy in normal-appearing ovaries and accelerated recovery after delivery or termination of pregnancy [2,18,23]. Recently, one study has discovered normal ovum expresses NMDARs [21]. It is supposed that bilateral oophorectomy may expedite recovery [7], because this can remove the ectopic antigen. There are reports of microteratomas only identified on histopathologic evaluation [18,24]. However, empiric surgical oophorectomy in the absence of a confirmed teratoma remains controversial [25].

Despite the severe condition, most mothers and newborns can have good outcomes. Two newborns were tested for NMDAR antibodies, both were positive. That confirmed transfer of maternal antibodies to fetal circulation [7,13]. Placental transfer of maternal antibodies occurs through IgG1 and IgG3 binding to the neonatal Fc receptor in syncytiotrophoblasts [23]. This process starts slowly at the end of the first trimester and early second trimester and progressively increases until term. Additionally, by the end of the second trimester, the fetal blood–brain barrier is functional [7]. As mentioned above, the test indicated that the newborn with NMDAR antibody in serum whose mother initiated anti-NMDAR encephalitis early at the 9th weeks of gestation within the first trimester [13], contained a higher titer (1:450), compared with the other newborn (1:20) whose mother at the 20th weeks of gestation [7]. The miscarried or aborted fetuses were all within the first trimester of gestation [4,8,14]. But those cases came from different centers with different laboratories performing the determination of antibodies, further studies are needed to characterize the potential effect of transplacental transfer of antibodies to the newborn.

We speculate the unfortunate prognosis of babies or fetuses may relate with mother's hypoventilation which can affect growth and development of fetus. The good outcome of newborns may relate to the period of transplacental transfer of IgG and fetus's blood–brain barrier function [23,26]. As with previous reports of anti-NMDAR encephalitis in pregnancy, maternal and fetal outcomes can be excellent [4].

This paper provides us with more understanding the characteristics of anti-NMDAR encephalitis during pregnancy. However, there are only thirteen reported cases available in this review. There may have some other cases which have not been published, or published in journals outside PubMed. Therefore it may be a challenge to use this limited number of cases to represent the whole onset population.

Conflict of interest

There was no conflict of interest for all the authors.

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