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Devic syndrome and pregnancy: A case series

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Abstract

Background: Devic syndrome or neuromyelitis optica is an autoimmune neurological condition characterized by relapsing symptoms of optic neuritis and transverse myelitis. Women with neuromyelitis optica suffer from adverse pregnancy outcomes and high relapse rates during pregnancy and the postpartum period.

Methods: This case series describes 13 pregnancies in four women with neuromyelitis optica managed at a tertiary hospital in Toronto, Canada.

Results: In most cases, neurologic symptoms either worsened or developed for the first time during pregnancy or the postpartum period, and often responded to a combination of steroids, immunosuppressant medications, plasma exchange and intravenous immunoglobulin. The 13 pregnancies resulted in two miscarriages, three preterm and eight term births. One fetus whose mother was on gabapentin, prednisone and spironolactone, had congenital malformations (aplastic lung and fused fingers).

Conclusions: Despite high frequency of relapses in pregnancy and the postpartum period, with multidisciplinary team management, outcomes for women with neuromyelitis optica are encouraging.

Keywords

Complications, high-risk pregnancy, maternal-fetal medicine, drugs (medication), autoimmune demyelinating disease

Introduction

Devic syndrome or neuromyelitis optica (NMO) is a recurrent antibody-mediated inflammatory disorder characterized by clinical presentations of optic neuritis and transverse myelitis. It is differentiated from multiple sclerosis (MS) using the Wingerchuck criteria developed in 2006, and requires the presence of optic neuritis, transverse myelitis and at least two of: continuous spinal cord lesions extending more than 3 vertebral segments on magnetic resonance imaging (MRI), a brain MRI not meeting diagnostic criteria of MS, or presence of serum NMO-immunoglobulin G anti-aquaporin 4 antibodies (AQP4).[1] Furthermore, the Wingerchuck criteria[1] provide guidance on management of the disease.

Although there are less than 150 reported cases of NMO in pregnancy in the literature, there is evidence that pregnancy may be associated with disease exacerbation, relapse, and adverse maternal and fetal outcomes.[2–5] In this paper, we describe outcomes of 13 pregnancies in four patients with NMO.

Methods

Patients with NMO were identified using a Special Pregnancy Program database that enlists medical, surgical, and obstetric diagnoses of all patients attending the Maternal-Fetal Medicine and High-Risk Obstetric clinics at Mount Sinai Hospital, Toronto, between the years 2000 and 2015. Preconception counseling, neurology, internal medicine, antepartum, intrapartum, and postpartum records were retrieved and maternal demographics including age, ethnicity, gravidity, parity, comorbidities, past obstetric history as well as details on neurological symptoms and disease progression were collected. Clinical outcomes such as NMO disease activity, maternal neurologic symptoms, development of preeclampsia, mode of delivery, fetal loss, preterm birth, infant's status at birth and neonatal intensive care unit (NICU) admission status were retrieved from patient records and documented. A descriptive account of the four cases and 13 pregnancies is presented below.

Case series

Case 1 (Figure 1)

A 24-year-old African woman presented with balance and vision symptoms following termination of her first pregnancy. Her symptoms resolved spontaneously and she was not investigated further. Two years later she presented with complete lower extremity paralysis after a second pregnancy and spontaneous vaginal delivery (SVD) of a healthy male (M) infant. She remained hospitalized for six weeks

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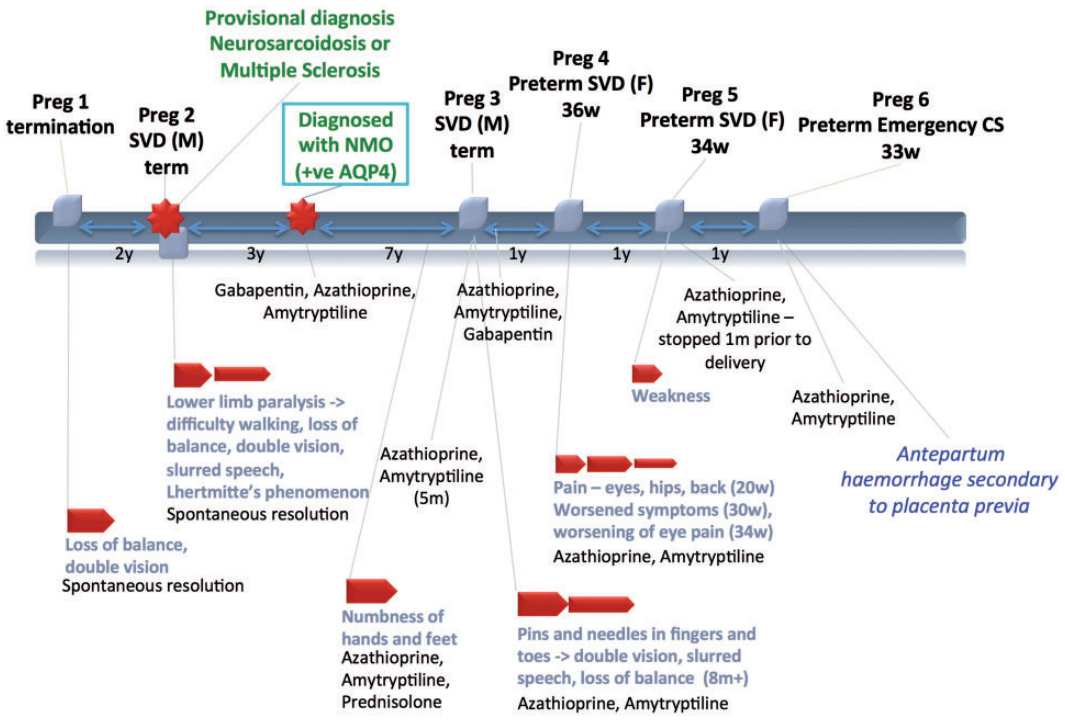

Figure 1. Case 1.
IV: intravenous; CS: cesarean section; SVD: spontaneous vaginal delivery.

over which time she had a relapsing-remitting course of symptoms. A provisional diagnosis of MS was made. Three years later her serum tested positive for AQP4 antibodies and her diagnosis was revised to NMO. She was treated with azathioprine, amitriptyline, and gabapentin with complete remission for seven years. She then had recurrence of paresthesias and was treated with prednisone.

During her third pregnancy, she was taken off gabapentin and experienced recurrence of peripheral paresthesias, visual complaints, and imbalance. She was treated successfully with azathioprine and amitriptyline. She had an uncomplicated term SVD of a healthy male infant and no further NMO-related symptoms. Gabapentin was added postpartum.

During her fourth pregnancy, she experienced visual and pain symptoms that were managed with azathioprine and amitriptyline. The symptoms progressively worsened until 36 weeks, when she delivered a preterm but healthy female (F) infant.

In her fifth pregnancy, she self-discontinued amitriptyline and her only symptom was generalized weakness. This pregnancy also resulted in preterm SVD at 34 weeks.

During her sixth pregnancy, the patient experienced third trimester antepartum hemorrhage believed to be secondary to placenta previa. She required emergency caesarean section (CS) at 33 weeks due to placental abruption, and delivered a preterm but healthy infant. There were no NMO-related symptoms in this pregnancy.

Case 2 (Figure 2)

A 26-year-old African-American woman initially presented with symptoms concerning for cauda equina. An MRI showed hyperintensities of unclear significance at the T4–T6 vertebral levels and exploratory spinal surgery found no apparent cause. Her symptoms responded partially to IV corticosteroids but there was progression to complete lower extremity paralysis within three months. She was eventually diagnosed with NMO when anti-AQP4 antibodies were detected in her serum. Over the next two years, her sensory deficits continued, however, her motor symptoms gradually recovered following courses of IV immunoglobulin (IVIG), azathioprine, prednisone, and extensive physical rehabilitation.

Many years later she underwent a healthy first pregnancy but experienced postpartum exacerbation of NMO requiring treatment with prednisone and azathioprine.

Prior to her next pregnancy, she came off all immunosuppressants and had an uncomplicated second pregnancy without NMO symptoms.

Case 3 (Figure 3)

A 21-year-old African woman who had previously been diagnosed with generalized seizures, presented with hemiparesis, loss of vision, and bladder symptoms over a three-week period. After a complete workup, she was diagnosed with NMO and started prednisone therapy with good response. Her only subsequent neurologic symptoms included a seizure four years later, and later recurrence of visual symptoms. MRIs performed in subsequent years revealed signal loss within the cervical discs on T2-weighted imaging and signal hyperintensity in the thoracic T3 and T4 vertebrae.

The patient later conceived but had first trimester spontaneous abortion. During her second pregnancy, she experienced recurrence of NMO symptoms with progressively worsening visual complaints and hemiparesis requiring use of a walker. She was treated with gabapentin and prednisone and eventually delivered a healthy infant at term by CS for failure to progress. There was no progression of symptoms postpartum.

During her third pregnancy she was maintained on a regimen of gabapentin and prednisone. Although her symptoms persisted, in late third trimester, she had exacerbation of weakness now involving both upper limbs and experienced new headaches. No changes were made to her medications, and she eventually delivered a female infant by

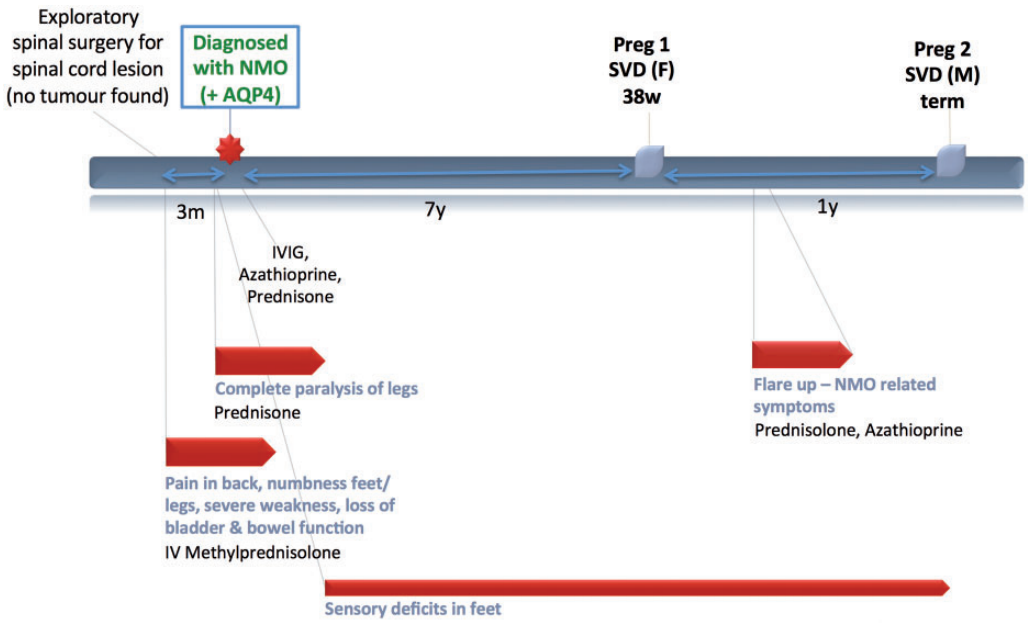

Figure 2. Case 2.

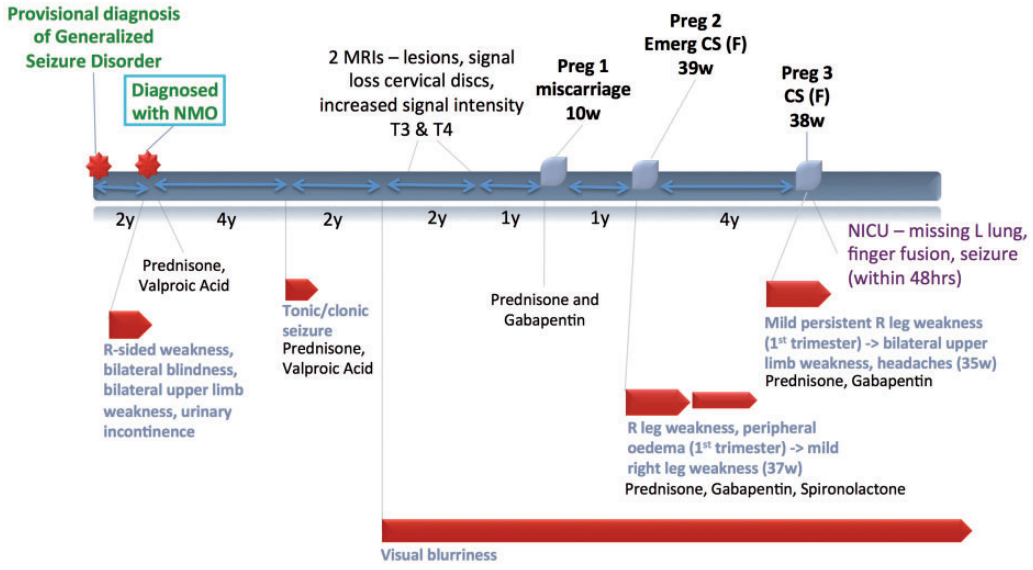

Figure 3. Case 3.

CS at term. The infant had congenital fusion of her digits and left lung aplasia. She went on to require NICU admission for respiratory failure and seizures.

Case 4 (Figure 4)

A 28-year-old woman with a prior uncomplicated pregnancy presented in her first trimester with transient progressive visual symptoms that spontaneously resolved. Three months later she was admitted to hospital with progressive neck and arm paresthesias. Despite treatment with azathioprine and plasma exchange, she progressed to dysesthesias involving upper and lower extremities, gait changes, hiccups and vomiting, and eventually had complete lower limb paralysis with bladder and bowel incontinence. MRI studies revealed extensive signal abnormalities in her medulla and thoracic spine. Cerebrospinal fluid (CSF) tested positive for AQP4. During the course of the pregnancy, her symptoms fluctuated with motor and sensory involvement, even after high doses of IV methylprednisolone, numerous cycles of plasma exchange, IVIG, and azathioprine. Notably, fetal surveillance was always reassuring throughout. She went on to deliver a healthy infant by CS at term. Postpartum, azathioprine was stopped, steroids tapered and Mitoxantrone started, along with physical rehabilitation.

Over the next six months the patient had fluctuating but gradually improving symptoms and was eventually walking with assistance. Azathioprine and monthly IVIG were used for sustained improvement. Bladder and bowel continence was eventually regained. By 18

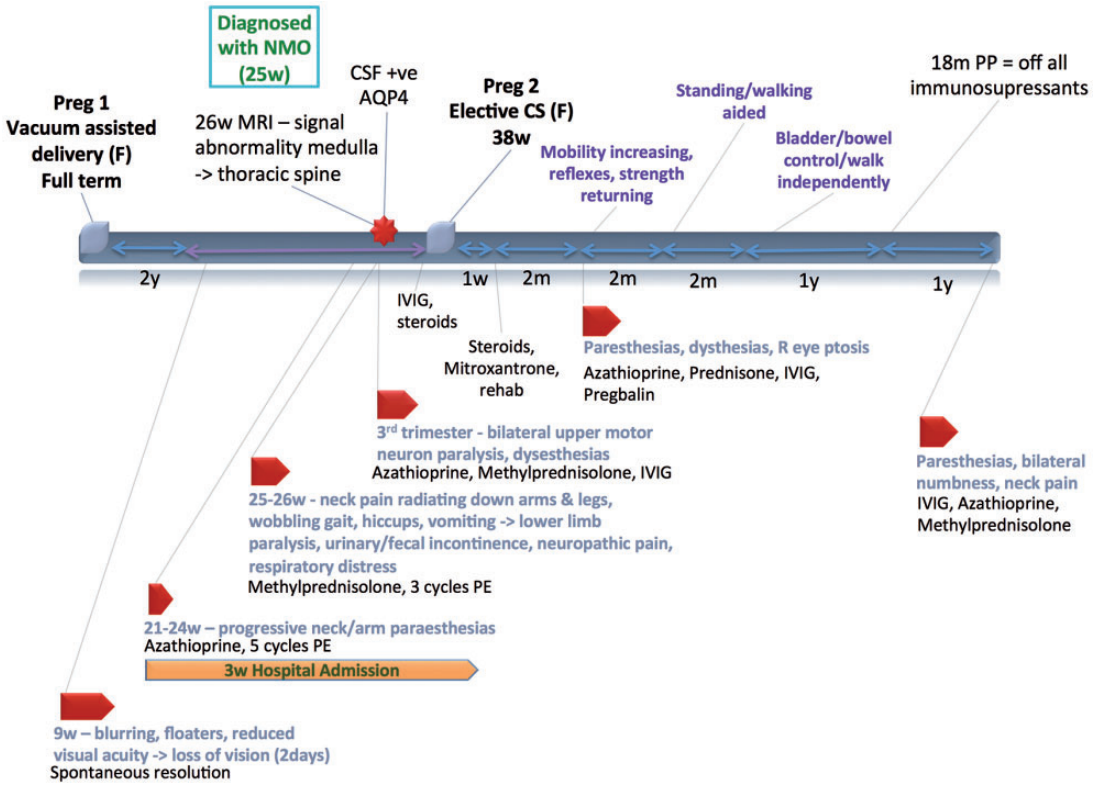

Figure 4. Case 4.

months, she was walking independently and off immunosuppressive therapy in complete remission.

She relapsed again two years later with similar symptoms to her initial presentation. MRIs revealed hyperintensities at the T11 vertebral level. She was restarted on IV methylprednisolone, IVIG, azathioprine, and prednisone with some recovery.

Discussion

Devic syndrome in pregnancy was first reported in 1985[6] in the case of a woman who successfully delivered without complications after multiple treatments with plasmapheresis. Her symptoms included optic neuritis and limb weakness progressing to paralysis. In our case series, we describe four patients with 13 pregnancies that were managed at a tertiary care hospital in Toronto, Canada. Three of the four patients showed either a relapsing and remitting pattern or progressive worsening during their respective pregnancies. In two of the four patients, NMO-related symptoms appeared de-novo, during or soon after a pregnancy.

NMO is known to have a higher prevalence in women of Asian, African American, and Hispanic descent.[1] We observed this trend in our case series, with three of the four women being African or African American. Most published observational studies show a median age of onset in the late 30s–40s, however, in our case series, the median age of disease onset was lower at 27 years (24.75–28.25). With a higher index of suspicion for the disease, likely leading to earlier diagnosis, there is an opportunity to better examine the relationship between NMO and pregnancy prospectively over time.

Studies suggest that NMO exacerbates in pregnancy[2,7,8] but unlike MS, where a specific immune target has yet to be identified, NMO is a distinct autoimmune disease with a specific antibody target. Unlike most other autoimmune diseases that improve in pregnancy, NMO can develop *de novo* or worsen in pregnancy and the postpartum period, as was seen in three out of four of our cases. In fact, of the 13 total reported pregnancies, only four pregnancies did *not* develop NMO-related symptoms during pregnancy or postpartum.

There are some possible explanations for increased NMO activity in pregnancy, including rising AQP4 titers during the third trimester and postpartum,[9] accelerated demyelination of astrocytes due to their susceptibility in pregnancy and a potential role of the hyperestrogenemic or hyperprolactenemic states of pregnancy. Other suggested hypotheses include changes in T-helper cell function in pregnancy, akin to diseases such as systemic lupus[10] or Sjogren's, both of which are actually more common in patients with NMO.[11]

With regard to the effect that NMO has on pregnancy, we showed that 15% of the pregnancies studied resulted in miscarriage, which is comparable to the 13% spontaneous miscarriage rate seen in a retrospective cohort of AQP4 positive women from the National NMO Service (Oxford, UK)[5] and higher than expected given that the median age of our patients was 27 years old. Three of the 8 pregnancies were preterm live births occurring at 36, 34, and 33 weeks (mean gestational age 34.3 weeks, SD 1.25).

Regarding fetal and neonatal outcomes, we observed one case of multiple congenital anomalies (aplastic left lung and fusion of fingers) in a female infant delivered at 38 weeks, who then experienced a seizure two days after birth. Although the mother received gabapentin, spironolactone and prednisone during the pregnancy, none of these medications have been previously associated with the observed fetal anomalies or neonatal seizures.

In our case series, six treatment strategies were used including oral and intravenous corticosteroids, azathioprine, IVIG, plasma

Table 1. Medication use in pregnancy.

Medication	Evidence for use in pregnancy	Evidence for use in breastfeeding
Corticosteroids (e.g. prednisone, methylprednisolone)	• Associated with oral cleft lip, cleft palate, and possible impaired fetal growth in early first trimester[12–14]	• No adverse effects to infants during breastfeeding with avoidance of nursing for a few hours after dose is taken[25]
IVIG	• No adverse effects in pregnancy[16]	• Immunoglobulins are a normal component of breast milk, thus safe
Amitriptyline	• No increase in risk of miscarriage, stillbirth, or congenital malformations compared to general population[26] • No difference in neurodevelopmental IQ & behavior differences in children exposed antenatally[27]	• Breastfeeding likely to be safe[28]
Azathioprine	• Small association with atrial or ventricular septal defects in a small group of exposed children, not conclusive whether this was due to maternal disease, other medications, or chance[29] • When used to treat autoimmune disease, no effects on the infant immune system[30,31] • Lower incidence of neonatal complications in mothers treated for inflammatory disease compared to those that were untreated[32,33]	• No adverse effects on growth or development in infants exposed during breastfeeding[34,35]
Mitoxantrone	• IUGR reported in a single patient with multiple sclerosis[36]	• No adverse outcomes reported in infants when used by mother while breastfeeding[37]
Gabapentin	• Very few reported congenital malformations in monotherapy[38,39] • No increase in congenital defects in first trimester use[40]	• No adverse effects to infants with breastfeeding[41]

IUGR: intrauterine growth restriction; IQ: intelligence quotient.

exchange, gabapentin/pregabalin, and mitoxantrone. Other drugs such as amitriptyline were also used as adjuvant analgesics for neuropathic pain. A summary of the evidence for use of these modalities in pregnancy and lactation is shown in Table 1. Corticosteroids such as prednisone are commonly used during pregnancy, are generally considered safe outside of the first trimester,[12–15] and formed the mainstay of treatment for NMO. IVIG was also used successfully in two pregnancies in our series and has also shown promise in several other reports of NMO in pregnancy.[16] Plasma exchange is deemed safe in pregnancy[17] and was used successfully in one of our reported pregnancies. Azathioprine is an immunosuppressant with benefits generally believed to outweigh the risks in pregnancy when used for disease modulation.[18] It was successfully used in 7 of the 13 pregnancies in our series and has also been shown in other reports to reduce disease progression and disability in NMO in pregnancy.[19] Gabapentin has routinely been used for the treatment of neuropathic pain associated with NMO,[20] and is generally considered safe in pregnancy.[21] In our series gabapentin was used in four pregnancies. Of these, two relapsed with recurrence of symptoms, one patient delivered an infant with congenital anomalies and neonatal seizures and one resulted in a miscarriage. Although the adverse fetal outcomes cannot directly be attributed to gabapentin, its efficacy in managing symptoms of NMO remains uncertain. Pregabalin is believed to be more effective than gabapentin in the treatment of neuropathic pain in NMO patients[22] and could be considered as an alternative. We report two pregnancies in which no medications were taken due to stable ongoing disease activity that resulted in two healthy term deliveries. A study by Shi et al.[19] showed similar outcomes with eight pregnant women with NMO, with stable disease activity that resulted in eight live births without complications. After careful discussion of the risks and benefits and the knowledge that symptoms of NMO often worsen in pregnancy, an approach involving conservative (non-medicated) management may be an option for those with stable disease activity.[23,24]

Our case series is a limited examination of the relationship between NMO and pregnancy since it involves 13 pregnancies in four women, some of which were not managed at our hospital. The data, which were obtained retrospectively from a chart review, have limitations characteristic of a retrospective analysis. Some of these limitations include missing data and insufficient information with regards to doses, duration of therapies, and details on some clinical outcomes. Furthermore, the relapsing and remitting nature of the disease in some pregnancies poses a challenge when trying to accurately assess trends in progression, recovery, response to therapy, and when trying to establish associations.

To our knowledge, our case series is the first Canadian series describing pregnancy outcomes in women with NMO. It adds important information to the limited existing literature on the topic pertaining to the effect pregnancy has on NMO and the course of the disease during pregnancy. With multidisciplinary management, the prognosis for pregnancies in women with NMO is reassuring. This study also highlights a need for prospective data gathering on pregnancy outcomes in women with NMO, possibly through establishment of an international registry. Information gleaned from such a registry would be vital in assisting healthcare providers in the management of pregnancies in these women.

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Guarantor

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Contributorship

All authors have contributed to the production of this paper.

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