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Author's Accepted Manuscript

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Chang Yanyu, Shu Yaqing, Sun Xiaobo, Xu Chengfang, He Dan, Fang Ling, Chen chen, Hu Xueqiang, Allan Kermode, Qiu Wei



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Ectrodactyly in a Chinese patient born to a mother with neuromyelitis optica spectrum disorder
Chang Yanyu^{a1}, Shu Yaqing^{a1}, Sun Xiaobo^a, Xu Chengfang^b, He Dan^c, Fang Ling^a, Chen chen^a, Hu
Xueqiang^a, Allan Kermode^{d,e}, Qiu Wei^{a*}

^aDepartment of Neurology, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou
Guangdong, China

^bDepartment of Obstetrics, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou,
Guangdong, China

^cDepartment of Pathology, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou,
Guangdong, China

^dCentre for Neuromuscular and Neurological Disorders, University of Western Australia,
Department of Neurology, Sir Charles Gairdner Hospital, Queen Elizabeth II Medical Centre,
Nedlands, Perth, Western Australia, Australia

^eInstitute of Immunology and Infectious Diseases, Murdoch University, Perth, Western Australia,
Australia

changyyu@163.com (Chang YY),

shuyaqing@126.com (Shu YQ),

sister_555@163.com (Sun XB),

lindaxu2011@qq.com (Xu CF),

hedan76@126.com (He D),

lingf0313@qq.com (Fang L),

chen931691670@qq.com (Chen C),

hxq245600@qq.com (Hu XQ),

kermode@me.com (A. Kermode),

qiuwei120@vip.163.com(Qiu W)

*Corresponding author.

Abstract

¹ Department of Neurology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China Chang YY and Shu YQ contributed equally to this manuscript.

NMOSD develops primarily in women of childbearing age, and several previous studies have shown that the disorder may increase the risk of miscarriage. However, there are no reports, to our knowledge, of fetal malformation, other than neonatal hydrocephalus, related to NMOSD. We report a 30-year-old woman who experienced recurrent neuritis and who was seropositive for AQP4-IgG. She became pregnant, and the fetus was found to have ectrodactyly. Histological analysis of the placenta showed moderate inflammatory infiltration; however, whether fetal malformation in NMOSD is related to inflammation and AQP4-IgG remains to be determined.

Keywords: Neuromyelitis optica spectrum disorder; AQP4-IgG; Fetal malformation; Ectrodactyly

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the central nervous system, and circulating antibodies against aquaporin 4 (AQP4, AQP4-IgG) is a critically important feature of NMOSD (Papadopoulos and Verkman, 2012). NMOSD develops primarily in women of childbearing age; therefore, research to determine whether NMOSD affects pregnancy outcomes has received increasing attention. Several animal studies and some clinical cases have shown that AQP4-IgG may increase the risk of miscarriage in NMOSD patients (Huang et al., 2017; Nour et al., 2016; Ratelade et al., 2011; Saadoun et al., 2013); however, to our knowledge, there are no previous reports of fetal malformation related to NMOSD (Huang et al., 2017; Nour et al., 2016). We report a Chinese NMOSD patient whose fetus suffered malformation during pregnancy, and discuss the placental pathological findings.

2. Case report

Fetal malformation was identified in a 30-year-old southern Chinese female NMOSD patient based on ultrasound examination at 24-weeks' pregnancy in May, 2017. She had no family history of fetal malformation, had no contact with poisonous substances or radioactivity during pregnancy, and she was not infected by *Toxoplasma* or viruses. Her symptoms first appeared as right eye vision impairment when she was 17-years old, in 2004. In 2013, she suffered repeat optic neuritis of the right eye at 4-weeks' gestation when she elected induced abortion and began to take continuous low-dose glucocorticoid therapy. In July, 2014, she experienced right eye

vision loss for the third time. Her serum AQP4-IgG titer was positive (1:32), and she was diagnosed as having NMOSD and began to take azathioprine 50mg and methylprednisolone 8mg per day. In preparation for pregnancy, she discontinued azathioprine while continuing methylprednisolone 8mg daily, in August 2016. She also began to take folic acid and Vitamin E in September, 2016. Her last menstrual period before becoming pregnant was September 16th, 2016. In February 2017, she experienced transient mild vaginal bleeding and was diagnosed with threatened abortion. Dydrogesterone 10mg was prescribed every 8 hours for 2 weeks, and methylprednisolone was added at 16mg per day until March, 2017, when it was reduced to 12mg per day. On May 31st, 2017, the fetus was found to have ectrodactyly, based on ultrasound examination, and the patient elected induced labor on June 6th. The fetus' height and weight were within normal range in same gestational age (Height 32cm, Weight 0.885kg) and the appearance of face and trunk were normal, too. However, it had ectrodactyly in both hands and the left foot (Fig. 1A,B,C). Macroscopic pathological examination revealed a normal placenta, and histological examination of the placenta showed moderate inflammation (Fig. 1D,E,F,G,H). Chromosomal analysis of the infant showed no deficiency or repetition of chromosome fragments larger than 0.4Mbp, and fluorescence in situ hybridization found no aneuploidy of chromosome 21, 18, 13, X, or Y. Whole exome sequencing of the fetus revealed no clinically relevant causal variant. This study was approved by the Ethics Committee of The Third Affiliated Hospital of SUN Yat-sen University. Written informed consent was obtained from the patient to donate the placenta and publish her case report and accompanying images.

3. Discussion

To our knowledge, this is the first case report describing fetal limb malformation in NMOSD. Ectrodactyly is a rare congenital disorder in which the development of the hands and feet are disturbed. Ectrodactyly can be isolated or associated with other anomalies in some syndromes, including single gene mutations, chromosomal rearrangements, and possibly digenic inheritance, as well as early amnion rupture disruption sequence (Kalathia et al., 2013; Wilcox et al., 2015). While in this case, there was no causal variant found in the fetus. Exposure to certain drugs was also reported to cause limb malformations (Sanders et al., 1991). There was one infant born with preaxial polydactyly to a mother taking azathioprine throughout pregnancy reported

before(Williamson and Karp., 1981), but several studies showed that the use of azathioprine may not increase the rate of fetus malformation, even in early pregnancy(Cleary and Kallen., 2009; Saavedra et al., 2015; Hoeltzenbein et al., 2012). Besides in this case, the patient discontinued azathioprine before pregnancy, therefore the possibility that the malformation was associated with the use of azathioprine was low.

AQP4-IgG-seropositive patients may have a higher risk of miscarriage. Saadoun et al showed in animal experiments that AQP4-IgG can bind placental AQP4, activate complement, and cause inflammatory cell infiltration then miscarriage (Saadoun et al., 2013). Placental immunostaining from an NMOSD patient who had a spontaneous miscarriage showed complete loss of AQP4 and diffuse, mainly perivascular, deposits of membrane attack complexes in the syncytiotrophoblasts (Reuss et al., 2009). Cases of neonatal hydrocephalus in NMOSD patients have also been reported (Huang et al., 2017; Nour et al., 2016). Neonatal hydrocephalus may be caused by disturbances in fetal CNS fluid balance related to AQP4-IgG, but this has not been confirmed, pathologically. In our case, placental AQP4 loss was not obvious, but moderate inflammatory cell infiltration was seen.

In early gestation, multiple aquaporin proteins are expressed in the human embryo, and these play important roles in embryonic development(Xiong et al., 2013). AQP4-IgG can reach the fetal circulatory system through the placenta; however, it is not known whether AQP4-IgG can disturb fetal development and cause fetal malformation.

In conclusion, it is important to be aware of NMOSD-related fetal malformation. Further study is needed to determine whether NMOSD can cause fetal malformation by AQP4-IgG-induced inflammation and its sequelae.

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Declaration of Conflicting Interests

The Authors declares that there is no conflict of interest.

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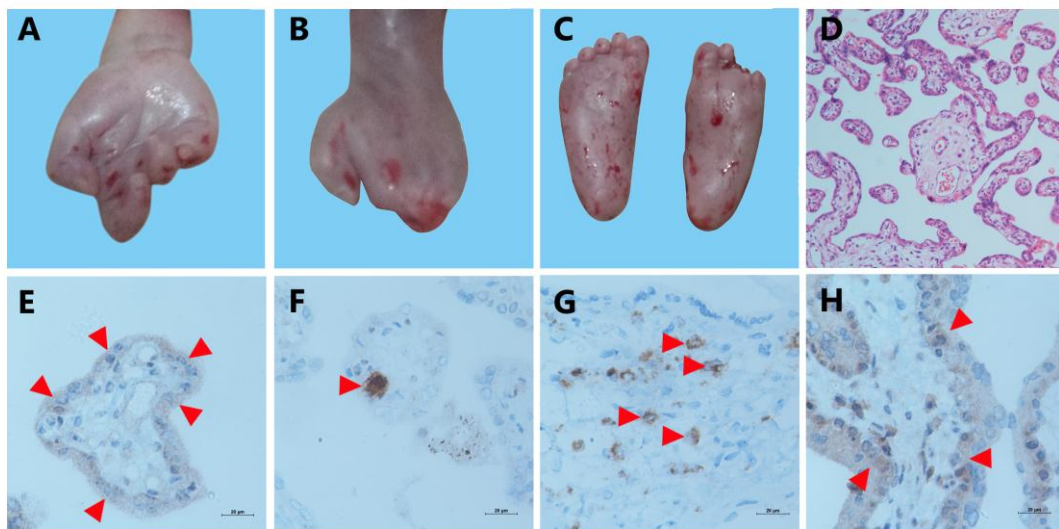
The Authors declares that there is no conflict of interest.

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Fig.1 Macroscopical manifestation of the fetus and histological evaluation of the placenta. A–C. Hands and feet of the fetus showing deficiencies in the proximal and intermediate phalanges of the 3rd, 4th, and 5th fingers of the right hand (A), 2nd, 3rd, 4th, and 5th fingers of the left hand (B), and 3rd, 4th, and 5th toes of the left foot (C). D. Photomicrograph of hematoxylin and eosin staining of the placenta showing normal structure of the chorionic villi ($\times 100$); E. AQP4 immunostaining showing no obvious loss of immunoreactivity in trophoblasts (arrows indicate AQP4-immunostaining-positive trophoblast cells, $\times 400$); F. CD20 immunostaining showing B-lymphocyte infiltration into villi (arrow indicates a typical CD20-immunostaining-positive cell, $\times 400$); G. CD68 immunostaining showing macrophage infiltration into villi (arrows indicate typical CD68-immunostaining-positive cells, $\times 400$); H. c5b-9 immunostaining showing moderate complement deposit in trophoblasts (arrows, $\times 400$)



Highlights

- This is the first case report describing fetal limb malformation in NMOSD.
- Moderate inflammatory infiltration was found in the patient's placenta.
- Whether fetal malformation in NMOSD is related to inflammation and AQP4-IgG remains to be determined.
- We should be aware of NMOSD-related fetal malformation.

Accepted manuscript