Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 113; No. 6; P101

Diagnostic Limitations in Congenital Zika Virus Infection

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Abstract

This is the first documented case of an infant with congenital Zika virus infection (ZVI) born in Ireland. A term infant was delivered with an antenatal diagnosis of severe microcephaly. First trimester bloods confirmed maternal ZVI and although the infant did not have Zika virus RNA or Zika-specific IgM in her blood or urine, she had multiple clinical features of congenital ZVI and Zika virus RNA was present in the placenta.

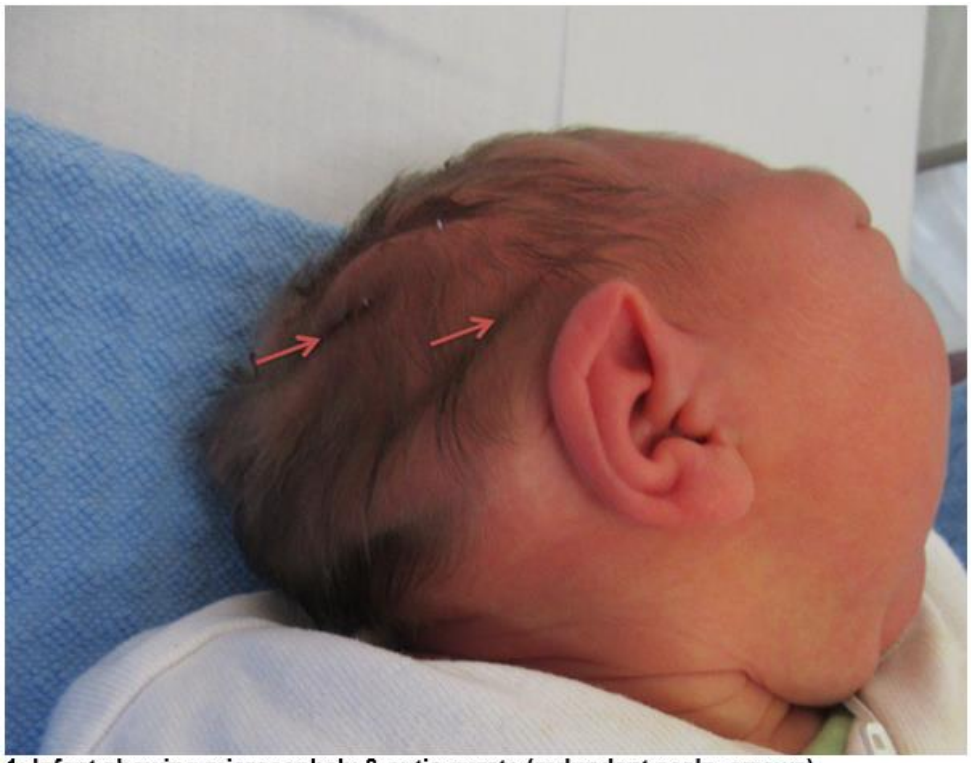
Introduction

Zika virus is a mosquito borne flavivirus, whose infectious manifestations vary greatly from asymptomatic infection to disabling neurological impairment and death[1]. The World Health Organization declared ZVI a public health emergency in 2016 due to concerns of severe postnatal neurological complications following congenital ZVI[1].

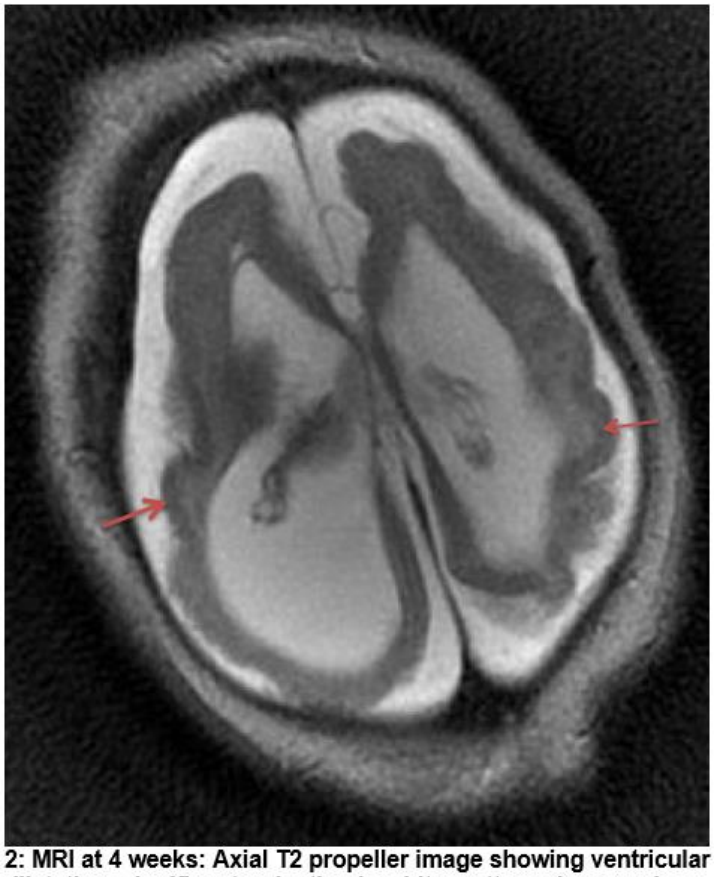
Case Report

The infant's 20 week fetal scan showed normal biometry but borderline ventriculomegaly. Her head circumference at 31 week scan was 22.1cm, < 3rd centile. A maternal history of myalgia and fever, whilst travelling in her native country Brazil during the first trimester, prompted re-examination of maternal 11 weeks gestation booking bloods. This confirmed the presence of Zika virus RNA (Altona Diagnostics, GmbH, Hamburg, Germany) and Zika-specific IgG (Euroimmun, Lübeck, Germany) and the presence of Dengue virus IgG but absence of Dengue IgM. Maternal Zika-specific IgG persisted at 31 weeks gestation but Zika virus RNA was no longer detectable.

Examination of the term infant at delivery showed severe microcephaly and cutis gyrate (image 1), but an otherwise normal examination. Her head circumference was 26cm, <<< 0.4th centile (normal 32-37cm), whilst her weight was 2505g, 2nd centile, and her length was 45cm, < 2nd centile. She had clear responses on otoacoustic emission hearing screen. An ophthalmology assessment showed bilateral retinal abnormalities; chorioretinal pigmentary disturbances and paramacular chorioretinal atrophy. Day of life 2 neonatal urine was negative for Zika virus RNA, whilst paired serum samples were positive for Zika-specific IgG but negative for RNA and Zika-specific IgM (Euroimmun, Lübeck, Germany). The placenta tested positive for Zika virus RNA (Altona Diagnostics, GmbH, Hamburg, Germany). MRI brain showed microcephaly, ventricular dilatation, reduction in white matter volume, simplified gyral pattern with polymicrogyria and multiple areas of calcification (image 2).



1: Infant showing microcephaly & cutis gyrate (redundant scalp, arrows)



2: MRI at 4 weeks: Axial T2 propeller image showing ventricular dilatation, significant reduction in white matter volume and simplified gyral pattern with polymicrogyria (arrows)

At 6 weeks of age, the infant showed significant peripheral hypertonia and dystonic posturing of the upper limbs. At 14 months of age her head circumference showed interval growth (35cm, normal 43.5-47.8cm). She developed multifocal epilepsy, spastic-dystonic quadriplegic cerebral palsy, irritability, visual impairment and showed severe global developmental delay, for which she requires multidisciplinary healthcare team care.

Discussion

Guidance regarding testing for and diagnosing congenital ZVI has changed over the last 4 years. Moore et al have put forward 5 features to help clinically differentiate congenital Zika syndrome from other congenital infections including (1) severe microcephaly with partially collapsed skull, (2) thin cerebral cortices with subcortical calcifications, (3) macular scarring and focal pigmentary retinal mottling, (4) congenital contractures and (5) marked early hypertonia with symptoms of extrapyramidal involvement[2]. Our infant showed 4 of these 5 features.

The period of detectability of Zika virus RNA, Zika specific IgM and IgG in serum and other bodily fluids is highly variable[3,4]. This, along with the availability of multiple diagnostic assays[5], and the cross-reactivity with other flaviviruses including dengue complicates the laboratory diagnosis of ZVI[3].

A diagnosis of congenital ZVI is based on clinical, epidemiological and laboratory test criteria. Positive Zika virus RNA in infantile blood, urine, or CSF within the first few days of life clinches the diagnosis from a laboratory perspective[6]. A probable congenital ZVI diagnosis can be made if the infant is Zika virus-specific IgM positive but RNA negative[6]. Identification of Zika virus in maternal bloods during pregnancy or the placenta at birth confirms maternal but not congenital ZVI. Though our infant was negative for Zika virus RNA and IgM, she had many of the clinical features consistent with congenital ZVI and maternal ZVI during pregnancy was confirmed.

Infantile CSF identification of Zika virus could have aided the laboratory diagnosis of congenital ZVI for this infant. The persistence of Zika IgG at 18 months of age, when maternal antibodies should have disappeared will assist the laboratory confirmation of our largely clinical diagnosis for this infant.

This case highlights the deficiencies in the current laboratory diagnostic criteria for congenital ZVI and the need for expert consultation whilst investigating possible cases.

Consent:
Consent received from parent.

Declaration of Conflicts of Interest:
The author has no conflicts of interest to declare.

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