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Practical Management of Congenital Zika Syndrome

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Zika Virus was initially discovered in monkeys in Republic of Uganda in 1947 [1]. This was followed by the virus identification in humans in Republic of Uganda and the United Republic of Tanzania in 1952 [1]. Since 2007, Zika virus infections have been reported in the Americas, Africa, Asia and Oceania [2]. The first mosquito-transmitted, locally acquired cases of Zika virus in Europe were reported in October 2019 [3].

Zika Virus is an RNA Flavivirus belonging to the family Flaviviridae, which includes Dengue Virus, West Nile Virus, Hepatitis C virus, Yellow Fever Virus, Classical Swine Fever Virus, and Japanese Encephalitis Virus [4]. Mosquito-borne transmission is the primary mechanism for epidemic spread [5]. *Aedes aegypti* mosquito is the major vector for horizontal transmission of Zika Virus to humans [5]. It is the same mosquito that transmits Yellow Fever and Dengue Virus [6]. Moreover, Zika Virus can be transmitted to humans by non-vector borne mechanisms such as blood and blood products transfusions, sexual contact and through transplacental transmission leading to Zika Virus Congenital Infection [6]. Despite various reports of viable Zika virus detection in human breast milk, there has been limited evidence to confirm transmission through breastfeeding [7]. The early post-partum cases of infants infected with Zika virus are most likely due to transplacental transmission [7].

Zika Virus Disease in children and adults follows an incubation period of 3 - 14 days [1]. Most people infected with Zika Virus are asymptomatic (approximately 80%) [8]. The infection presents with mild symptoms including fever, malaise, maculopapular rash, non-purulent conjunctivitis, muscle ache, joint pain, and headaches [8]. The illness usually last for 4 - 7 days [1,8]. Guillain-Barre Syndrome (GBS) is strongly linked to Zika Virus Disease as it was epidemiologically linked during the Zika Virus outbreak in the Americas [9]. However, the cause effect relationship is yet to be proved [10]. Other less frequently reported neurological complications include encephalitis; meningoencephalitis; acute disseminated encephalomyelitis; myelitis; cerebrovascular complications (ischemic infarction; vasculopathy); seizures; encephalopathy; sensory polyneuropathy and sensory neuronopathy [11,12]. Pregnant women constitute the main target for preventive measures because of association of transplacental transmission with intrauterine Zika virus CNS infection leading to congenital malformations, microcephaly and foetal death [13].

Transplacental transmission of Zika Virus leads to Congenital Zika Syndrome (CZS). This is a combination of birth defects with microcephaly as its main feature [13]. The microcephaly in CZS is usually severe (more than 3 SD below the mean) and can be accompanied by findings consistent with fetal brain disruption sequence (FBDS) [14]. This, in turn, is characterized by severe microcephaly, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, in addition to severe neurologic impairment [13]. Other brain anomalies associated with CZS include subcortical calcifications; ventriculomegaly; marked cortical thinning; abnormal gyral patterns; absent or hypoplastic Corpus Callosum; diminished myelination; cerebellar and cerebellar vermis hypoplasia; brainstem hypoplasia; basal ganglion and brainstem calcifications [14-16]. The intracranial range of anomalies in CZS resembles that of Congenital Cytomegalovirus (CMV). However, the distribution of intracranial calcifications is different as it is typically subcortical in CZS and periventricular in CMV [14]. Ophthalmic anomalies associated with CZS have been frequently reported with posterior ocular defects as the most prevalent findings

[13]. Chorioretinal atrophy, focal pigmentary mottling as well as Optic Nerve Hypoplasia and Atrophy are the usual findings [13]. The pathogenesis of the posterior ocular lesions has not been established but is very likely to be due to direct cellular damage by Zika virus or the inflammatory sequelae [13]. Other ocular anomalies include microphthalmia; iris coloboma; cataracts; congenital glaucoma; lens subluxation and intraocular calcifications [13].

The spectrum of Congenital Zika Syndrome is evolving with emerging reports from all over the world. Congenital contractures involving one or multiple joints of varying severity have been reported very frequently. These musculoskeletal contractures are usually associated with severe early hypertonia or hypotonia and extrapyramidal movements [13]. Arthrogryposis multiplex congenita, isolated clubfoot and bilateral congenital hip dislocation are the usual presentations [17]. Other described anomalies in other organ systems include the cardiovascular system; genitourinary system (ambiguous genitalia and bilateral cryptorchidism; gastrointestinal system (dysphagia); small for gestational age (SGA); hearing abnormalities and unilateral diaphragmatic paralysis [18].

Time of transplacental transmission

The available evidence indicates the most common timing of maternal Zika Virus infection leading to CZS is late 1st and early 2nd trimester [13]. However, 3rd trimester maternal infection is also reported among affected newborns [13]. It has been observed that 1st and 2nd trimester infections have the highest risk of developing central nervous system anomalies, compared to 3rd trimester infections [19].

Diagnosis of zika virus infection during pregnancy:

A. For symptomatic pregnant women who had recent travel to areas with active dengue transmission and a risk of Zika:

    1. Specimens should be collected as soon as possible after the onset of symptoms up to 12 weeks after symptom onset [20]. The following diagnostic tests should be requested: Dengue and Zika virus Nucleic Acid Amplification Tests (NAAT) on a serum specimen, and urine for Zika virus NAAT, plus IgM testing for Dengue only.

    2. Zika virus IgM is not recommended as Zika IgM antibodies can persist for months - years following infection. Therefore, detecting Zika IgM might not indicate a recent infection.

    3. There is a significant cross-reactivity between Dengue IgM and Zika IgM in serologic tests. Recent Dengue IgM antibodies can cause the Zika IgM to be falsely positive.

    4. If the Zika NAAT is positive on a single specimen, the Zika NAAT should be repeated on newly extracted RNA from the same specimen to rule out false-positive NAAT results. Adequate evidence of a Dengue infection is provided by a positive Dengue NAAT and further testing for Zika virus is not indicated.

    5. A positive IgM for Dengue is adequate evidence of a Dengue infection, and no further testing is indicated.

B. Pregnant women who have a foetuses with antenatal ultrasound findings consistent with congenital Zika virus infection who live in or travelled to areas with a risk of Zika during the pregnancy:

    1. Zika virus NAAT and IgM testing should be performed on maternal serum and NAAT on maternal urine.

    2. If the Zika virus NAAT is negative, and the IgM is positive, confirmatory Plaque Reduction Neutralization Test (PRNT) should be performed against Zika virus and Dengue.

3. If amniocentesis is performed, Zika virus NAAT testing of amniocentesis specimens should be performed. It is unknown how sensitive or specific RNA NAAT testing of amniotic fluid is for congenital Zika virus infection and what proportion of fetuses will develop CZS following the Zika virus infection.

4. Testing of placental and fetal tissues should be considered.

Practical management of CZS:

A. The role the family doctor (General practitioner):

1. The family doctors should be proactive in advising their patients who live in or travel to areas with active Zika transmission.

2. The family at risk of Zika infection should be advised to take the following measures:

    - Prevention of mosquito bites by using appropriate insect repellents and covering skin.
    - Prevention of Zika sexual transmission by using condoms during all sexual acts (oral, vaginal, or anal) or by not having sex during pregnancy.
    - Decreasing the risk of Zika infection by staying in places with air conditioning, window and door screens, or sleeping under a mosquito bed net.
    - Controlling mosquitoes inside and outside.
    - Reporting the travel and any incidence to the family doctor after return from areas with active Zika transmission.
    - Be aware of symptoms of Zika Virus Disease, including headache, rash, joint pain, red eyes etc.

B. The role of the obstetrician:

1. The Obstetric Department should have a clear pathway for assessing pregnant women with a history of travel during pregnancy to geographical areas with risk for Zika virus transmission.

2. The Obstetrician should review pregnant women reporting clinical illness consistent with Zika Virus Disease during or within 2 weeks of travel or sexual contact with potentially infectious partner. Maternal serum for Zika and Dengue NAAT plus Dengue IgG and IgM should be sent without delay. A urine sample should be sent as well for Zika virus NAAT if within 21 days of symptoms. The family should be offered baseline foetal ultrasound screening.

3. Patients with positive Zika virus NAAT, on a single specimen, should have the Zika NAAT repeated on newly extracted RNA from the same specimen to rule out false-positive NAAT results.

4. Patients with confirmed positive Zika or abnormal ultrasound findings (e.g. small head, ventriculomegaly or intracranial calcifications etc) or other concerns, should be referred to the Foetal Medicine Department.

5. All cases where the diagnosis of maternal Zika Virus Disease is suspected should be promptly communicated to the Neonatal team.

6. CZS should be suspected in all cases with unexplained severe microcephaly detected during the routine antenatal anomaly scan as well as in cases with antenatal cerebral subcortical calcifications. Appropriate travel and sexual history should be ascertained. NAAT for Zika virus should be arranged if indicated.

C. The rule of the neonatologist:

1. The Neonatologist should establish effective communications with the Obstetric and Foetal Medicine department to identify confirmed and potentially infected newborn born to parents who had travelled to areas with active Zika virus transmission.

2. A plan for Zika virus testing and other management lines should be explained to the parents and a plan agreed in ample time before delivery. This should be preceded by a detailed antenatal counselling including short and long term outcomes. The parents must be made aware of the lack of any antiviral treatment for Zika virus infection, and all the lines of management to the baby are supportive to deal with the consequences of the infection.

3. The delivery should be attended by an accredited Neonatal Resuscitation Provider. The medical team should follow the agreed pre-birth plans.

4. The placenta and 10 cm of the umbilical cord should be sent for histopathological examination of the placenta as well as Zika virus NAAT for both tissues.

5. The baby should be examined thoroughly at birth with specific reference to head circumference; dysmorphic features; joint contractures, microphthalmia; cataract; glaucoma; lymphadenopathy; hepatosplenomegaly; rash or other skin abnormalities. A detailed neurological examination is essential. Length and weight should be documented. Local admission guidelines should be followed in babies who are premature or unwell. The provisional diagnosis of ZVS is not an indication by itself for admission in well looking term or near term babies.

6. Suitable lactation support should be arranged. Breastfeeding should be encouraged. Many babies have feeding difficulties, but this usually improve within few days-weeks. Gastric tube feeding may be required. The local unit hypoglycaemia protocol should be followed in babies with concomitant IUGR or risk factors for hypoglycaemia.

7. Vitamin K administration and routine neonatal vaccinations including BCG and Hepatitis B should be provided without delay.

8. The first baby check should be within 12 - 24 hours of birth to ascertain baby wellbeing, support the family and answer their questions. The baby should be re-examined and any new or overlooked earlier finding discussed with the parents and documented. The hearing screening should be arranged before hospital discharge.

9. Serum Zika NAAT should be arranged in all babies with positive maternal Zika NAAT, or suspicious clinical features (i.e. Severe microcephaly, or a combination of microcephaly of any degree with ophthalmic findings or joint contractures).

10. Appropriate diagnostic tests for Syphilis, Toxoplasma, Rubella, Cytomegalovirus and Herpes Simplex Virus infections should be arranged in every baby with antenatal or post-natal abnormalities consistent with CZS. In addition; full blood count; clotting, urea and electrolytes; liver function tests and C-reactive protein; should be arranged.

11. A cranial Ultrasound should be performed before discharge in all babies with microcephaly, maternal confirmed Zika during pregnancy or suggestive antenatal cerebral findings.

12. An MRI should be planned as inpatient or out-patient in all cases of microcephaly or if intracranial abnormalities are detected on cranial ultrasound scan.

13. An ophthalmic evaluation, including examination of the retina is mandatory in all babies if the diagnosis of CZS is a possibility. The Ophthalmologist should arrange the suitable follow up.

14. Targeted specialised hearing tests should be arranged in babies who do not pass the initial hearing screening test.

15. Individualized plans should be made for the differential diagnosis of microcephaly as per the clinical assessment. Consideration should be given to chromosomal microarray, genetic referral, and metabolic screen.

16. Multidisciplinary coordination is advisable with the Geneticist, Infectious Disease Consultant, Paediatric Neurologist, Paediatric Endocrinologist, Paediatric Physiotherapist and Developmental Paediatrician according to the findings.

17. Follow up arrangements: all babies with confirmed CZS or where Zika virus infection cannot be excluded or a normal looking baby with laboratory evidence of Zika virus infection should have a planned follow up with a Consultant Paediatrician, Developmental Paediatrician, and a Paediatric Neurologist. Follow up Zika virus testing should be arranged in unconfirmed cases as per the advice of the Infectious Disease Consultant.

D. The role of the paediatrician:

1. The Paediatricians should raise and maintain their awareness of the relation between maternal Zika virus infection during pregnancy and neurodevelopmental delay in children, especially those with microcephaly. Appropriate tests should be carried out in children who fit the clinical spectrum but were not investigated in the past.

2. The Paediatrician in liaison with the Developmental Paediatrician should plan the necessary follow up and support for children with confirmed CZS as well as children in whom the diagnosis could not be excluded: The arrangements should include:

    - 3 monthly follow up. The follow up may be discontinued at the age of one year in normal children who are followed up due to suspicion about diagnosis of CZV.

    - Regular ophthalmic and auditory assessment in all children with suspected or confirmed CZS. The frequency of the assessment should be dictated by the findings and the expert opinion of the relevant departments.

3. The Paediatrician should arrange early referral to Community Paediatric team for neuro-developmental assessment and long-term support.

4. Follow-up of children with CZS should be continued into childhood to identify and monitor long-term adverse sequelae. Preschool as well as educational and family support are required.

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