Missed opportunities in the diagnosis of congenital malformation: a case report

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Abstract

Genetic, metabolic or environmental disorders can cause malformations of the central nervous system (CNS) that take place during the cerebrospinal development. Congenital infections are part of environmental causes of CNS malformations. We report a case of an infant with a congenital CNS malformation, suspected of having CMV infection. Maternal use of valacyclovir during pregnancy without amniotic fluid assessment due to advanced gestational age might have prevented the virus isolation in the newborn and the identification of the cause of CNS malformation. We discuss the difficulties encountered for a diagnosis of certainty and for the child in question. Even in developed countries, congenital infections are still a great diagnostic challenge. Missed opportunities for investigation should be avoided so that the etiology becomes early recognized and, if possible, treated.

Keywords: Nervous system malformations, Diagnosis, Zika virus infection, Cytomegalovirus.
1. INTRODUCTION

Central nervous system (CNS) malformations consist of a heterogeneous group of diseases that occur during embryonic or fetal life. More than 2,000 alterations have already been described in the literature, affecting approximately one to 10 per thousand live births, and being responsible for up to 25% of perinatal deaths. Congenital infections are relevant causes of CNS malformations, amongst which cytomegalovirus (CMV) and Zika virus are included.

Herein we report the case of a child with late-diagnosed congenital CNS malformation. This report was approved by the Research Ethics Committee (protocol 4,683,559), and the child’s legal guardian signed the Informed Consent Term. We discuss the differential diagnoses and therapeutic possibilities for this patient.

2. CASE REPORT

The child was born in November 2019 to a 23-year-old pregnant woman with a non-consanguineous union. Her first trimester tests were non-reactive to HIV, syphilis, toxoplasmosis and hepatitis C, with a positive anti-HBs serology. In the seventh week of pregnancy, her first child developed fever, nausea, diarrhea and general malaise. In the following week, she presented with the same symptoms and was medicated with symptomatic drugs. In the tenth week of pregnancy, she had headache, a runny nose, facial pain. After one week, she presented with a disseminated pruritic rash, more intense on the palms and soles, that lasted for three days and was associated with vaginal bleeding. At the 14th week of pregnancy, she developed upper-respiratory symptoms lasting 15 days. In none of the aforementioned situations were laboratory tests collected.

At the 30th week of gestation, she performed morphological fetal US, where the fetus had an estimated weight of 1,823g (90th centile) and the amniotic fluid index (AFI) was adequate (169 mm). CNS showed tapering diffuse brain parenchyma associated with cortical hyperechogenicity and central-encephalic and periventricular hyperechogenicity, with ventriculomegaly, enlargement of the subarachnoid space, and thin brain parenchyma up to 0.5 cm thick, associated with cortical hyperechogenicity and central-encephalic and periventricular hyperechogenicity, with ventriculomegaly, enlargement of the subarachnoid space, and thin brain parenchyma up to 0.5 cm thick, associated with compensatory ectasia of the supratentorial ventricular system and brainstem (Figure 1 – A, B, C). Fundoscopy and Brainstem Evoked Response Audiometry (BERA) did not show alterations. During the follow-up, clinical evaluation with the geneticist ruled out a genetic etiology for the case.

At one year of age, a new BERA suggested normal hearing and fundoscopy showed bilateral pallor 1+/4+ of papilla.

Maternal and patient’s blood samples were collected at 13 months of age for Zika serology and they were both negative. A Zika plaque reduction neutralization test was also performed and it was also negative for both mother and child. This blood collection was performed since there may be cross-reactivity between zika and dengue, leading to a positive IgM during pregnancy. It was performed at this age because after 12 months there is no longer interference of maternal antibodies in the evaluation of the child’s serology.

Placental tissues, fetal membranes and umbilical cord fixed in paraffin were recovered to perform PCR for CMV and Zika, with negative results for both viruses.

After 12 months of age, the patient started with seizures. An EEG showed very frequent multifocal epileptiform paroxysms in the centromtemporal, right anterior temporal and left posterior temporal regions. Levetiracetam and baclofen were initiated, with clinical and EEG improvement.

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A cranial tomography was performed (Figure 1- D, E, F), in which a volumetric reduction of the cranial vault was verified, with marked dilation of the supratentorial ventricular system. He also presented a thinning of the cortical mantle, with effacement of the cortical sulci, associated with multiple diffuse bilateral calcifications. The corpus callosum was not characterized in this new image. As there was a midline deviation, it was decided to perform a ventriculoperitoneal bypass surgery at 17 months of age.

At 18 months of age, the patient has microcephaly below the 3rd centile, considered postnatal microcephaly, with delayed neuropsychomotor development. He underwent a progressive weight, length and head circumference velocity slowness and has z scores below -2 for the three measures.

3. DISCUSSION

We report a case of an infant with a congenital CNS malformation, suspected of having CMV infection that led to maternal use of valaciclovir during pregnancy. No virus recovery was possible neither during pregnancy nor after birth, what prevented to establish with certainty the cause of the malformation.

Microcephaly is a rare event that requires rigorous investigation to diagnose its etiology. A German study evaluated the etiology of microcephaly in 680 children, of whom 41% remained undiagnosed. In an Australian study evaluating the causes of microcephaly, 60% of the cases were idiopathic at the time of notification. In Brazil, the infectious
diagnosis was not defined in 40.3% of the children evaluated in Rio de Janeiro.

The late diagnosis of malformations of the fetus prevented amniotic fluid from being collected before valacyclovir administration and the impossibility of collecting CSF from the neonate at birth also prevented the recovery of an infectious agent at that site.

It is possible to observe that, during pregnancy, there were three moments of infection, one of them with the presence of a viral rash, and in none of them infections that could culminate in congenital malformations were investigated. Despite all recent advances in serological and molecular diagnosis of congenital infections, they are still a great challenge for obstetricians, neonatologists and pediatric infectious diseases specialists. This scenario denotes the importance of in-depth investigation in spite of the difficulty of identifying the etiology even in developed countries. The diagnosis of congenital malformation is already impacting for parents as there is a breach in the expectations of the idealized child, but the anguish becomes even greater when they are unaware of the causing event. The use of all available diagnostic apparatus is essential to minimize the absence of a diagnostic definition, which undoubtedly is a source of frustration for the investigator, but mainly for the parents.

REFERENCES