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Congenital Lymphocytic Choriomeningitis Virus: When to consider the diagnosis

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Abstract

Lymphocytic Choriomeningitis Virus (LCMV) is a rodent-borne arenavirus that can cause congenital infection affecting the developing central nervous system. When the infection occurs during pregnancy, the virus targets the fetal brain and retina potentially causing ventriculomegaly, hydrocephalus, chorioretinitis, and neurodevelopmental abnormalities. It has been previously suggested that lymphocytic choriomeningitis virus be added to the list of congenital infections currently included in the TORCH acronym (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes,

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Author Contribution: JA, KL and PL identified the case and provided clinical care to the patient under the supervision of FSC. Along with FSC, PL developed the project. JA and KL drafted the manuscript, which was then critically reviewed and approved by all authors. LT and CS evaluated and diagnosed the patients. LT performed all optical examinations and visual evoked potential recordings and CS provided all the neuro-radiological inputs. TY, PL, CS, FSC worked in evaluation, diagnosis, and follow-up of the patients.

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Ethical Approval

Informed consent was gained from the parents for publication of the case report.

and Syphilis). We present two neonates with antenatally known ventriculomegaly that were diagnosed with congenital lymphocytic choriomeningitis virus infection after birth. In addition to ventriculomegaly, one had non-immune hydrops fetalis and the other had intracranial hemorrhage. In view of the seroprevalence of lymphocytic choriomeningitis Virus (4.7–10%), our findings suggest that screening for congenital lymphocytic choriomeningitis virus infection should be considered in fetuses and newborns with ventriculomegaly as well as other abnormal neuroimaging findings such as intracranial hemorrhage.

Keywords

ventriculomegaly; hydrocephalus; congenital lymphocytic choriomeningitis Virus (LCMV)

Introduction

Lymphocytic choriomeningitis virus (LCMV) is an enveloped single-stranded RNA virus in the Arenaviridae family. Wild mice are the natural host and principal reservoir of lymphocytic choriomeningitis virus, but the virus can also be found in pet hamsters, golden hamsters, and guinea pigs. Human infection occurs via contact with fomites contaminated with infectious virus recently shed by rodents, aerosolized virus inhalation, transplanted organs, or intrauterine transmission. Acquired postnatal infection ranges from asymptomatic to a brief, nonspecific flu-like illness to critical yet self-resolving neurological disease, predominantly consisting of aseptic meningitis or meningoencephalitis (1–4).

Lymphocytic choriomeningitis virus can cause intrauterine infection from either vertical transmission across the placenta or from exposure to maternal vaginal secretions or blood during maternal viremia (1). Although less than 100 cases are described in the literature, the majority of published reports suggests that the virus is selectively neurotropic when transmitted in utero, targeting the brain and retina in 87.5% of cases (1–7). In animal models, Bonthius et al. demonstrated several mechanisms that explain the effect of the virus on the fetal brain: a) The virus exhibits a strong tropism for neuroblasts, b) disturbs the migration of neurons, and c) triggers an inflammatory response, driven by cytotoxic T lymphocytes. The gestational age of the fetus also significantly affects the “patterns of infection and pathology within the brain”. (1).

In contrast to postnatal lymphocytic choriomeningitis virus infection that usually targets meninges and choroid plexus, prenatal lymphocytic choriomeningitis virus infects brain parenchyma usually without detectable systemic effects (1,4,8). Common sequelae of congenital lymphocytic choriomeningitis virus infection include structural cerebral anomalies, such as microcephaly, neuronal migration anomalies, periventricular calcifications, pachygyria, porencephalic cysts and periventricular cysts (1,3,5). Hydrocephalus, seizures, and subsequent neurodevelopmental disability are also common (1–6,9,10). Eye findings include chorioretinal lacunae, panretinal pigment epithelium atrophy, bilateral optic nerve dysplasia or atrophy, and reduced caliber of retinal vessels (1–5). Other common findings are nystagmus and strabismus eso- or exo- tropia (2).

Congenital lymphocytic choriomeningitis virus infection is often misdiagnosed as other infectious, neurologic, ophthalmologic, or chromosomal syndromes, or is lethal in utero (2,9,10). It has therefore been previously suggested that lymphocytic choriomeningitis virus be added to the list of congenital infections currently included in the TORCH acronym (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, and Syphilis) (1–3,6,10). In this case study, we present two neonates with congenital lymphocytic choriomeningitis virus infection that had unusual antenatal ultrasound findings, including ventriculomegaly, intracranial hemorrhage, and hydrops fetalis.

Case Report 1

Our first case involves an infant with suspected non-immune hydrops fetalis detected on screening ultrasound two weeks prior to delivery. The patient's mother was a 24yo woman with two prior full-term, uncomplicated pregnancies. The pregnancy was uneventful prior to the finding of non-immune hydrops on ultrasound at 32 weeks estimated gestation. A subsequent fetal magnetic resonance image confirmed hydrops fetalis and also revealed ventriculomegaly, polyhydramnios, and a large amount of ascites (Figure 1A). Fetal karyotype was normal (46,XY). Maternal indirect Coombs test was negative. Maternal serum titers were negative for congenital toxoplasmosis, syphilis, and rubella. Amniotic fluid was negative for cytomegalovirus, toxoplasmosis, and Listeria. Testing for lymphocytic choriomeningitis virus was not performed.

The infant was delivered at 34 weeks estimated gestation via cesarean section secondary to active labor and hydrops fetalis. The infant's birth weight was 3060 grams (97th percentile), length was 46 cm (50th percentile) and head circumference was 30 cm (10th percentile). The physical exam revealed non-dysmorphic features. The anterior fontanel was soft and flat. He had a distended abdomen with probable ascites.

Postnatal evaluation investigating the etiology of the patient's anasarca, CNS findings, and ophthalmologic findings included testing for infectious, metabolic, and genetic diseases. Initial hemoglobin concentration was 16.6 gm/dl, and the blood type was Rh negative, indicating non-immune hydrops. Tests for inborn errors of metabolism, including lysosomal storage disorders, were negative. Chromosomal microarray and L1 cell adhesion molecule (L1CAM) sequencing showed no mutations. Urine Cytomegalovirus culture and serum Toxoplasmosis titers were negative. Testing for lymphocytic choriomeningitis virus was positive with serum Immunoglobulin G titers > 1:256 and Immunoglobulin M titers 1:20, consistent with a diagnosis of congenital lymphocytic choriomeningitis virus infection.

His initial head ultrasound showed marked dilation of the lateral ventricles with normal third and fourth ventricles. Postnatal brain magnetic resonance imaging showed severe ventriculomegaly involving the lateral ventricles and a thin mantle of cortical parenchyma with scattered periventricular foci consistent with hemorrhage or calcification (Figure 1B). At one month of age, a ventriculoperitoneal shunt was placed for progressive ventriculomegaly.

The initial ophthalmologic evaluation revealed lacunar chorioretinopathy congregated mainly within the vascular arcades (maculas) in both eyes. Ophthalmologic examination at

12 months of age showed unchanged bilateral optic nerve dysplasia and lacunar chorioretinopathy. Pupillary responses to light were brisk in both eyes. Visually-evoked potential testing showed normal response latencies (less than 100 msec) but amplitudes reduced to ~ 33% of normal for age. Tracking and fixation were markedly subnormal with frequent conjugate upgaze deviation

At one year of age, his length was 50th percentile, weight was 5th percentile, and head circumference was 6 standard deviations below the 5th percentile. He also had global developmental delay and spastic quadriplegia. He had a normal hearing screen at birth and at one year of age.

Case Report 2

Our second case involves an infant with ventriculomegaly and intrauterine growth restriction (IUGR) identified on second trimester screening fetal ultrasound. The patient's mother was a 24yo woman with one prior full-term, uncomplicated pregnancy. Fetal brain magnetic resonance imaging at 28 weeks estimated gestation revealed fetal intraparenchymal and periventricular hemorrhage, microcephaly, cortical volume loss and ventriculomegaly (Figure 2A). Amniocentesis showed normal karyotype (46,XY). Amniotic studies for Herpes simplex virus (HSV), toxoplasmosis, and Cytomegalovirus were negative. Testing for lymphocytic choriomeningitis virus was not performed.

The infant was born at 34 weeks estimated gestation via cesarean section secondary to growth restriction (<5th percentile), reversed diastolic flow in the placenta, and increased left-sided fetal ventriculomegaly. The infant's birth weight was 1.74 kg (10th percentile), length was 42.5 cm (10th percentile), and head circumference was 31.6 cm (50th percentile). The initial physical examination revealed non-dysmorphic features.

The initial head ultrasound confirmed marked enlargement of both lateral ventricles and showed mild enlargement of the third ventricle. Brain magnetic resonance imaging showed markedly dilated lateral ventricles, mildly enlarged third ventricle, normal fourth ventricle, thin cortical mantle, and no hemorrhage or infarction of brain parenchyma (Figure 2B). At one week of life, a ventriculoperitoneal shunt was placed in the left occipital region for management of the infant's hydrocephalus.

The postnatal infectious evaluation included a negative Cytomegalovirus urine culture and cerebral spinal fluid polymerase chain reaction (PCR), negative serum Toxoplasma titers and cerebral spinal fluid polymerase chain reaction, and negative cerebral spinal fluid polymerase chain reaction for herpes simplex virus, Epstein-Barr virus (EBV), and enterovirus. Cerebral spinal fluid for lymphocytic choriomeningitis virus titers were positive for Immunoglobulin M (1:16) and negative for Immunoglobulin G (<1:1). Serum lymphocytic choriomeningitis virus titers were positive for Immunoglobulin G (>1:256) and negative for Immunoglobulin M (<1:20). These findings were consistent with a diagnosis of congenital lymphocytic choriomeningitis virus infection. Maternal lymphocytic choriomeningitis virus titers were not performed.

The initial ophthalmologic exam revealed bilateral lacunar chorioretinopathy with bilateral optic nerve dysplasia. He had normal eye alignment without manifest strabismus or nystagmus and a mild myopia in both eyes. The ophthalmologic examination at six months still showed bilateral optic nerve dysplasia and lacunar chorioretinopathy. The lacunar lesions occupied the macular region of both eyes (causing a white pupil-leukocoria appearance in facial flash photographs) and the retinal periphery. Pupillary responses to light were brisk in both eyes. Visually-evoked potential testing showed normal response latencies (~ 95 msec) but amplitudes reduced to ~ 25% of normal for age. Optokinetic tracking could be elicited when viewing with either eye. The tracking was superimposed on a baseline, intermittent horizontal, conjugate jerk nystagmus (sensory-anomaly nystagmus).

At 12 months of life, his length and weight were in 5th percentile, and head circumference is 6 standard deviations below 5th percentile. Auditory testing still revealed profound peripheral hearing loss on the left and severe hearing loss on the right. Structural ear anatomy was normal, and tympanography was normal. He has bilateral hearing aids and had global developmental delay.

Discussion

We presented two infants that had antenatally diagnosed ventriculomegaly, a finding in up to 1% of fetuses (13,14); in addition, one infant had intracranial hemorrhage and the other hydrops fetalis. In both cases, antenatal investigation included evaluation for traditional TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, and Syphilis) infections without consideration for lymphocytic choriomeningitis virus. There are no prior reported cases of Lymphocytic choriomeningitis virus infection with fetal intracranial hemorrhage and only one prior case with non-immune hydrops fetalis (10). There are also no epidemiological studies examining the incidence of lymphocytic choriomeningitis virus infections in pregnant women or newborns. Lymphocytic choriomeningitis virus seroprevalence in humans is estimated to be between 4.7 and 10% (4). The seroprevalence of conventional TORCH infections ranges from syphilis (0.71%) to toxoplasmosis (11%). (11,12). It is well known that cytomegalovirus (CMV) can have a seroprevalence that ranges from 45–100% (15). In view of lymphocytic choriomeningitis virus seroprevalence, our findings suggest that Lymphocytic choriomeningitis virus infection should be considered when fetal ventriculomegaly, intracranial hemorrhage, or hydrops is detected.

There are numerous reports in the literature of ventriculomegaly and/or hydrocephalus secondary to congenital lymphocytic choriomeningitis virus infection (1–4). Sheinbergas originally studied 40 children under the age of one diagnosed with hydrocephalus and noted that 30% had positive lymphocytic choriomeningitis virus titers (6). Bonthius et al used a mouse model to support several proposed mechanisms for congenital lymphocytic choriomeningitis virus infection causing the development of ventriculomegaly and hydrocephalus (1–3). Several authors have also suggested that congenital lymphocytic choriomeningitis virus infection, as a cause of ventriculomegaly, is common enough to warrant its inclusion in the diagnostic considerations for fetal ventriculomegaly (1–6,9,10). However, when ventriculomegaly or hydrocephalus has been suspected based on fetal

neuroimaging (ultrasound and/or magnetic resonance), diagnostic practices often neglect testing for lymphocytic choriomeningitis virus (5,9).

To our knowledge, this is the first described case of fetal intraparenchymal hemorrhage associated with maternal-fetal lymphocytic choriomeningitis virus infection. In view of the lack of evidence for a bleeding disorder in the mother, fetal coagulation abnormalities, problems with placental circulation, evidence of intrauterine hypoxia, alterations in maternal blood pressure, recent trauma, drug use, maternal hepatic disease, or the presence of a cerebral vascular malformation, this finding was likely associated with the intrauterine lymphocytic choriomeningitis virus infection. Further research is needed to elucidate the incidence of congenital lymphocytic choriomeningitis virus infection in infants with intracranial hemorrhage considered to be of unknown etiology. Intracranial hemorrhage, and particularly intracranial hemorrhage in the context of other findings consistent with congenital lymphocytic choriomeningitis virus on antenatal imaging, should prompt consideration of testing for lymphocytic choriomeningitis virus infection.

This is the second case described in the literature of an infant who presented with hydrops fetalis and was subsequently diagnosed with congenital lymphocytic choriomeningitis virus (9). Meritet et al diagnosed an infant with congenital lymphocytic choriomeningitis virus who was suspected of having hydrops fetalis on prenatal imaging. This mother elected to terminate the pregnancy at 29 weeks. The mother worked in a pet store, which raised suspicion for lymphocytic choriomeningitis virus, and the investigators confirmed their suspicions with a postmortem examination and reevaluation of maternal serology and polymerase chain reaction (10). It has also been suggested that lymphocytic choriomeningitis virus should be added to the list of causes of non-immune hydrops (10), especially when there is unexplained hydrops fetalis and/or possible maternal contacts with rodents or other members of the arenavirus family. These cases highlight the importance of obtaining a detailed maternal history and the importance of avoiding contacts with rodents when pregnant.

Congenital lymphocytic choriomeningitis virus is not yet a part of the TORCH acronym (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, and Syphilis) that guides clinicians in the care of the mother, fetus, and newborn (1–5,9,10). Congenital lymphocytic choriomeningitis virus infection may be difficult to differentiate from congenital infection secondary to TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, and Syphilis) infections, especially cytomegalovirus, toxoplasmosis, or rubella. However, unlike the other classic TORCH congenital infections, few infants congenitally infected with lymphocytic choriomeningitis virus have organ involvement outside the central nervous system and rarely include signs of systemic infection, hepatosplenomegally or rash (1,2,3,8). Table 1 shows the most common characteristics of congenital lymphocytic choriomeningitis virus infection as they compare to the other TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, and Syphilis) infections (Table 1).

Auditory deficits are rare in infants diagnosed with congenital lymphocytic choriomeningitis virus (1). One of the children that we described had significant bilateral sensorineural hearing loss that required hearing aids. Based on Bonthius et al's animal models we

hypothesis that the insult of the injury may have occurred earlier in gestation. Furthermore, the lack of auditory deficits reported in infants with the congenitally acquired virus may be due to under-diagnosis. We recommend that all infants suspected of congenital acquired lymphocytic choriomeningitis virus should not only receive an ophthalmological evaluation, but undergo a baseline auditory evaluation as well.

Due to the diverse clinical presentations for congenital lymphocytic choriomeningitis virus infection and the small number of cases described in the literature, further epidemiologic studies are needed to elucidate the natural history of congenital lymphocytic choriomeningitis virus infection, and to develop guidelines for inclusion of lymphocytic choriomeningitis virus in prenatal testing. These are the necessary steps to take to substantially reduce the risk of LCMV infection, since there is no treatment or vaccine to prevent the infection in pregnant women or their offspring (1–5). Our cases suggest that congenital lymphocytic choriomeningitis virus infection should, at least, be considered in the diagnostic evaluation of fetal ventriculomegaly.

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Figure 1. Magnetic Resonance Imaging (MRI) for Patient 1

A). Fetal: Thin mantle of cortex. Lateral ventricles dilated bilaterally. Scalp edema consistent with hydrops fetalis. B) Postnatal: Thin mantle of cortical parenchyma. Severe hydrocephalus with ventriculomegaly. Periventricular foci of increasing T1 signal consistent with calcifications.

Figure 2. Magnetic Resonance Imaging (MRI) for Patient 2

A). Fetal: Thinning of the cortex. Periventricular T1 hyperintensity in the parenchyma consistent with hemorrhage. Enlarged lateral ventricles. B) Postnatal: Marked lateral ventriculomegaly. Thin cortical mantle. Normal signal intensity, no acute infarct or hemorrhage.

Table 1

Common Manifestations of congenital infections

Manifestations	Hydrocephalous	ICH	Calcifications	Micro/Macrocephaly	Retinopathy	Deafness	HSM	Cardiac	NI hydrops
LCMV	+	+	+	+	+	+/-*			+
TOXO	+		+	+	+	+	+		+
Rubella			+	+	+	+	+	+	+
CMV			+	+	+	+	+		+
Herpes			+	+	+		+		+
Syphilis	+		+		+	+	+		+

Note: NI Hydrops = Non-Immune Hydrops. ICH = Intracranial Hemorrhages. HSM = Hepatosplenomegaly. (+) = positive findings in the literature.

* We report one case of auditory pathology in a patient with LCMV, but it is rarely reported in the literature.