

## Case Series

# Brain Involvement in Congenital Syphilis: Case Series and Brief Literature Review

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**Submitted:** 12 June 2020

**Accepted:** 23 June 2020

**Published:** 25 June 2020

**ISSN:** 2373-9312

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**OPEN ACCESS****Keywords**

- Congenital syphilis
- *Treponema pallidum*
- Newborn
- Brain

**Abstract**

Syphilis, one of the most common sexually transmitted infections globally, is caused by the spirochete, *Treponema pallidum*. It can be transmitted from an infected mother via the placenta to the fetus. Untreated syphilis during pregnancy has a transmission rate nearing 100%, but treatment with penicillin is 98% effective at preventing congenital syphilis. Most of the infants born with congenital syphilis are asymptomatic at the time of birth and are identified only by routine prenatal screening. We present three newborns infants born to mothers infected with syphilis who presented with abnormal neuroimaging findings at the time of birth.

**ABBREVIATIONS**

AZT: Zidovudine; CNS: Central Nervous System; CUS: Cranial Ultrasound; CPAP: Continuous Positive Airway Pressure; DNA: Deoxyribonucleic Acid; DOL: Day Of Life; EEG: Electroencephalogram; ER: Emergency Room; FTA-ABS: Fluorescent Treponemal Antibody Absorption Test; HIV: Human Immunodeficiency Virus; IVH: Intraventricular Hemorrhage; MRI: Magnetic Resonance Imaging; PPV: Positive Pressure Ventilation; PCR: Polymerase Chain Reaction; PVL: Periventricular Leukomalacia; RNA: Ribonucleic Acid; RBC: Red Blood Cells; ROP: Retinopathy Of Prematurity; RPR: Rapid Plasma Regain; TORCH: Toxoplasma, Other Viruses, Rubella, Cytomegalovirus, Herpes; VDRL: Venereal Disease Research Laboratory; WBC : White Blood Cells

**INTRODUCTION**

Syphilis is a sexually transmitted infection caused by a spirochete, *Treponema pallidum*. It can be transmitted to the fetus during pregnancy through the placenta. There has been an increase in the rate of syphilis in the pregnant women to 1.1 cases per 100,00 women and in the number of cases of congenital syphilis to 11.6 cases per 100,000 live births in the United States [1].

Untreated maternal syphilis has a transmission rate nearing 100%, but treatment with penicillin is 98% effective at preventing congenital syphilis [1]. Most infected infants are asymptomatic at birth and are identified only by routine prenatal screening. Routine screening of all pregnant women should be done at the

first visit, at 28 weeks gestation and at delivery [1]. Clinical signs appear in approximately two-thirds of affected infants at 3 to 8 weeks of life and in most cases by three months of age [2].

Primary central nervous system (CNS), involvement is rare. We are reporting 3 cases of congenital syphilis that presented with CNS imaging findings at birth.

**CASE 1**

An ex 32 2/7 weeks female infant born to a 24-year-old G4P3 mother via C-section, with limited prenatal care, recent human immunodeficiency virus (HIV) diagnosis, syphilis and chlamydia, and history of drug abuse. Fetal ultrasound (US) showed head circumference <1%, no posterior fossa structures appreciated, multiple small cystic structures in posterior aspect of the brain. Birthweight was 1,380 grams (21% on Fenton growth chart), length 36cm (<3%), head circumference 27 cm (10%).

Maternal rapid plasma reagin (RPR), 1 week prior to delivery was 1:64 with reactive fluorescent treponemal antibody absorption (FTA-ABS) test. She received 2 doses of penicillin. At delivery, her titers were 1:256 with reactive FTA-ABS and HIV viral load of 76000 and CD4 482. She was started on Truvada and Tivicay. TORCH titers were negative.

Infant's Apgar scores were 6 and 6 at 1 and 5 minutes, respectively. The infant required positive pressure ventilation (PPV), in the delivery room and continuous positive airway pressure (CPAP), for 3 weeks after birth. On physical exam infant had hepatosplenomegaly and a generalized fine petechial rash over abdomen, palms and soles were noted. Infant's RPR

titers were 1:4. HIV1 DNA polymerase chain reaction (PCR), was positive with absolute CD4 count 2506 and HIV RNA 3876 copies/mL. The infant was started on penicillin, Zidovudine, Nevirapine, Lamivudine and Raltegravir.

The baby was noted to have neutropenia, thrombocytopenia and conjugated bilirubin of 6.9 with total bilirubin of 9.1mg/dL on day of life (DOL) 2. Cerebrospinal fluid (CSF), showed red blood cell (RBC), count of 143,500/cumm, white blood cell (WBC) count 131/cumm (18% segments, 67% lymphocytes, 15% monocytes/histiocytes), glucose 48mg/dL and protein >1000 mg/dL, VDRL was not obtained.

Eye exam performed on DOL 3 reported no retinopathy. Radiographs of the long bones showed metaphyseal lucency and irregularity most pronounced in the distal femurs bilaterally (Figure 1). Abdominal US showed hepatosplenomegaly. Cranial US (Figure 2), on DOL 1 showed multiple cystic lesions seen within the midline posterior fossa slightly superior to the cerebellar vermis, which may be seen in the setting of congenital TORCH infections; possible grade 1 germinal matrix hemorrhage in the left caudothalamic groove and a heterogeneous lesion in the right cerebellar hemisphere (Figure 2). Brain magnetic resonance imaging (MRI) (Figure 3), on DOL 6 was significant for large right cerebellar hemorrhage with mass effect on the 4<sup>th</sup> ventricle. Repeat brain MRI a month later showed decreased hemorrhage, with stable to slightly decreased associated mass effect on 4<sup>th</sup> ventricle (Figure 4).

Baby received 14 days of intravenous penicillin G and was discharged home after 8 weeks on antiretroviral therapy and Bactrim prophylaxis. Repeat RPR and lumbar puncture (LP) at 6 months of age resulted as non-reactive/negative.

## CASE 2

Ex 27 week old male infant born to a 24-year-old mother G3P3 via vaginal delivery in the emergency room (ER) when mother arrived fully dilated in preterm labor. There was no prenatal care. The mother was hospitalized two weeks prior to delivery due to an assault. Mother used cocaine and cannabis during pregnancy, was positive for gonococcus and had a reactive RPR. The infant's birthweight was 1,030 grams (60%), length 36 cm (<20%), and head circumference 27 cm (20%).

At birth, the infant required PPV, chest compressions, intubation, epinephrine and normal saline bolus and was admitted to the NICU on mechanical ventilation. Apgar scores were 4, 2 and 6 at 1, 5 and 10 min respectively.

On physical exam, the baby had alopecia in right temporal area, mild frontal bossing and bruises on the face. The liver was palpable 3 cm below the right costal margin and the spleen 1 cm below the left costal margin. Eye exam showed retinopathy of prematurity (ROP) stage I-II, Zone III, no plus disease.

Maternal RPR titer 2 weeks prior to delivery was 1:64. The baby's serum RPR was 1:64, *Treponema pallidum* was reactive. CSF showed RBC 57, WBC 30 (12% neutrophils, 57% lymphocytes, 27% mono/histiocytes), glucose 85, protein 270, VDRL was reactive. TORCH titers were negative.

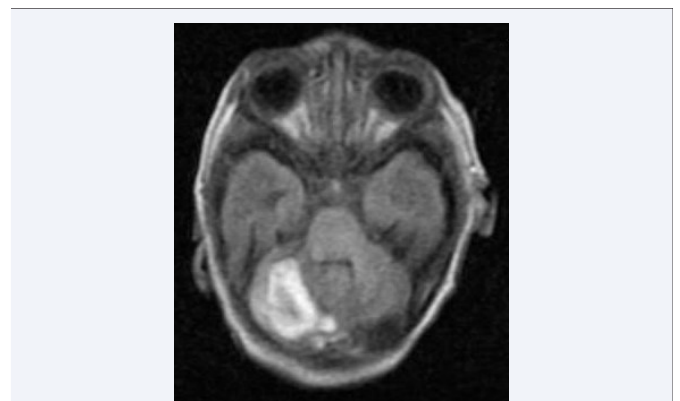
Radiograph of the long bones (Figure 5), showed the typical



**Figure 1** X-ray of the lower extremities demonstrated metaphyseal lucencies with irregular (sawtooth) distal metaphysis.

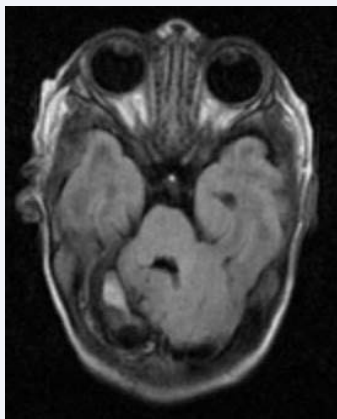


**Figure 2** Ultrasound of the right cerebellum with a large hypochoic area replacing the normal folia pattern of the cerebellar hemisphere.



**Figure 3** Brain MRI demonstrating large right cerebellar hemorrhage.

lesions of congenital syphilis. Abdominal US showed liver within normal limits. Cranial ultrasound (CUS) showed (Figure 6), small right grade 2 IVH and an 11 cm area of increased echogenicity in the right cerebellum which was thought to be hemorrhage vs focal cerebritis. Brain MRI (Figure 7), showed decreased volume of the right cerebellar hemisphere with residual blood product. Infant was noted to have abnormal EEG with bilateral independent central temporal positive sharp waves.



**Figure 4** Follow up Brain MRI showing decreased hemorrhage and hemispheric volume.



**Figure 5** X-ray showing diffuse metaphyseal lucencies and irregularity with periostitis consistent with intrauterine TORCH infection.

Infant was treated with Penicillin for 14 days. Repeat RPR at almost 3 months of age was 1:1. Infant was discharged from the NICU on home oxygen.

**CASE 3**

A 35 weeks male infant born to a 34-years-old mother G6P4 via vaginal delivery complicated by placenta previa with hemorrhage, seizure disorder, drug abuse, genital HSV and syphilis. Mother had scant prenatal care with history of cocaine and marijuana use. Fetus was noted to have hydrops, hepatosplenomegaly, ascites and cerebellar lesion on antenatal US. Mother’s RPR titers 1:64 with adequate treatment with penicillin prior to delivery. Infant’s birthweight 2160 g (<25%); length, 41 cm (<5%); and head circumference 30 cm (10%). Apgar scores were 6 and 8 at 1 and 5 minutes.

Physical exam was notable for hepatosplenomegaly. No skin rashes. Increased tone was noted DOL 1 but resolved by day 2. Ophthalmology evaluation showed megalodiscus with no chorioretinitis.

The baby’s RPR titer was 1:8. His CSF VDRL and HSV PCR were negative, but CSF protein was elevated at 214 mg/dL, RBC 0/cumm, WBC 0-9/cumm (neutrophils 7%, lymphocytes 28%, monocytes/histiocytes 64%). TORCH titers and HIV were negative.

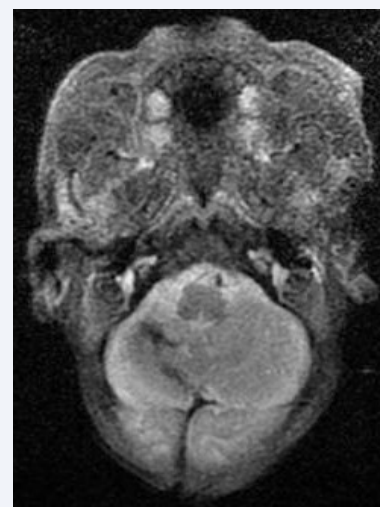
Radiographs of the lower extremities showed diffuse metaphyseal lucencies (Figure 8). Abdominal US showed small amount of ascites near the liver and possible sludge in gallbladder. Cranial US on DOL 1 showed a hypoechoic lesion in the left cerebellar hemisphere (Figure 9). A brain MRI (Figure 10), showed an atrophic left cerebellar hemisphere with old blood products, most likely due to vascular event leading to infarction caused by in utero infection. Also noted was an abnormal myelination pattern of the posterior limbs of internal capsules and leptomeningeal enhancement surrounding the medulla.

He was treated with penicillin G for 14 days and was discharged home on DOL 19.

When patient was nine years old, he suffered a severe headache and a brain MRI was done in the ER demonstrating marked loss of left cerebellar parenchymal volume (Figure 11).

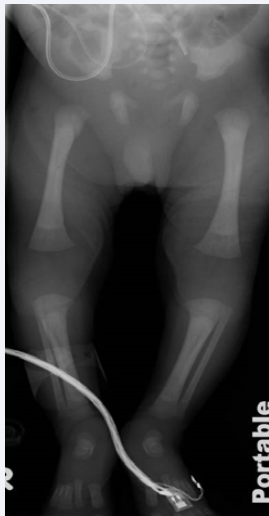


**Figure 6** Head US showing are of increased echogenicity in the right cerebellum representing hemorrhage vs focal cerebritis..



**Figure 7** Head MRI demonstrating an atrophic right cerebellum with subacute blood products.

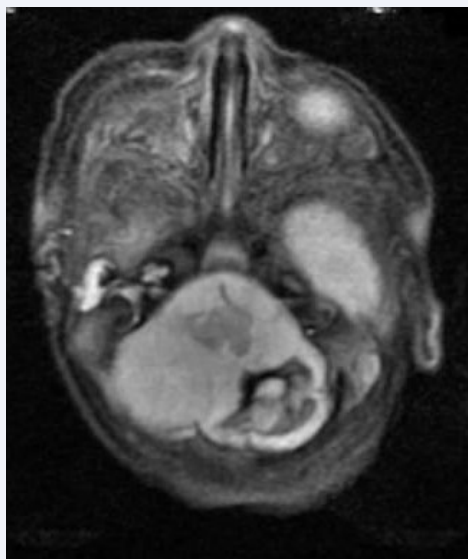




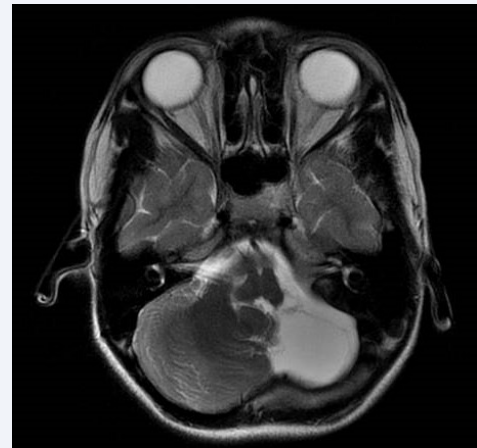
**Figure 8** X-ray of the lower extremities with marked metaphyseal lucencies.



**Figure 9** Cranial US- hypochoic lesion in the left cerebellar hemisphere.



**Figure 10** MRI- atrophic left cerebellar hemisphere with subacute blood products noted in the residual parenchyma.



**Figure 11** Brain MRI at 9 years of age demonstrating residual volume loss of the left inferior cerebellum.

## DISCUSSION

Symptomatic CNS involvement may develop in about 50% of the infants with clinical, laboratory, or radiographic signs of congenital syphilis, although rare in the era of penicillin therapy [3]. The clinical manifestations of neurosyphilis depend on the degree of involvement of the meninges, cerebral blood vessels and brain parenchyma. Distinction between the early meningeal and meningovascular forms and late parenchymatous form is not always possible and has not been described in newborns.

The diagnosis of neurosyphilis is primarily based on the clinical findings and supportive serological investigations. There is lack of a “gold standard” for the diagnosis of neurosyphilis. CSF VDRL is a very specific but insensitive indicator of neurosyphilis; thus, neurosyphilis should still be strongly considered if there are clinical indicators of neurologic disease and reactive serology even if the CSF VDRL is negative [4]. The reactive serological tests for syphilis in serum and clinical findings of hepatosplenomegaly and radiographic findings in all three neonates fulfill the criteria for the diagnosis of congenital syphilis. Although the CUS and MRI abnormalities are not specific, they can provide additional support for the diagnosis in the appropriate clinical setting. The cerebellar hemorrhage and subsequent atrophy of the cerebellum seen on the MRI of our patients cannot, in our view, completely rule out an early vascular involvement. CNS infection is usually due to hematogenous spread in the early stages of syphilis [5].

Although prenatal US done before maternal treatment demonstrated abnormalities including hepatomegaly, placentomegaly, polyhydramnios, ascites, and elevated middle cerebral artery velocimetry [6-9], no CNS ultrasonographic diagnostic pattern of neurosyphilis has been described in the scientific literature and thus CUS is not routinely recommended for the assessment of congenital neurosyphilis. Two of our patients had abnormal antenatal US findings.

The mother of the infant with more severe findings on CUS also had concomitant HIV infection. Data on concomitant syphilis and HIV infection in pregnancy are limited. HIV infected women are more likely to have spontaneous preterm birth when they have concomitant sexually transmitted infection during

**Table 1:** Serologic Tests and Imaging Results of Mothers and Infants.

Case	Maternal Serology RPR/HIV	Maternal Substance of abuse	Infant Serology Serum/CSF	Radiographs	Abdominal Ultrasound	Head US	MRI
1	1:64 -> 1:256/ +	Methamphetamines	1:4/ not done	Metaphyseal lucency and irregularity at distal femur bilaterally	Hepatosplenomegaly	Multiple cystic structures within the midline posterior fossa slightly superior to cerebellar vermis. Possible grade 1 IVH of the left caudothalamic groove. Heterogeneous lesion in right cerebellar hemisphere.	Large right cerebellar hemorrhage, mass effect on the 4 <sup>th</sup> ventricle, no abnormal dilation of the lateral ventricle or 3 <sup>rd</sup> ventricle, basal cisterns and foramen magnus patent.
2	1:64/Neg	Cannabis and Cocaine	1:64/Reactive	Radiographs of the long bones showed the typical lesions of congenital syphilis.	Abdominal US liver within normal limits, increased echogenicity of blood in portal vein, hepatic vein and SVC.	Initial head US right small grade 2 IVH, left cerebellar hemorrhage and subsequent head US showed right grade 2 IVH and right cerebellar echogenic focus with cystic changes.	Brain MRI demonstrated decreased volume of the right cerebellar hemisphere with residual blood product
3	1:64/Neg	Cannabis and Cocaine	1:8/Negative	Radiolucency in femur and humerus bilaterally	Small ascites near liver and possible sludge in gallbladder	Hypoechoic lesion in the left cerebellar hemisphere	Brain MRI showed an atrophic left cerebellar hemisphere with old blood products, most likely due to vascular event leading to infarction caused by in utero infection. Also noted was an abnormal myelination pattern of the posterior limbs of internal capsules and leptomenigeal enhancement surrounding the medulla.

RPR: Rapid plasma regain; HIV: Human Immunodeficiency Virus; CSF: Cerebrospinal fluid; US: ultrasound; MRI: magnetic resonance imaging; IVH: intraventricular hemorrhage; SVC: Superior Vena Cava

pregnancy(10). Also, HIV positive women are likely to have treatment failure of syphilitic infection [6], and hence a longer course of treatment has been recommended for these patients [11]. All of our three newborns were treated for 14 days with penicillin.

Early neurosyphilis becomes clinically apparent after 3 months of life [7,12]. There are a few reports of neuroimaging in infants less than one year displaying ventriculomegaly [13,14].

Cerebral infarction from syphilitic endarteritis has been mostly described in the second year of life [15,16], although it was seen in one of our patients on antenatal ultrasound. However, manifestations such as bulging fontanelle, leptomeningitis, cranial nerve palsies, hydrocephalus and seizures have been described in the neonatal period.

Two of our 3 patients had abnormal intracranial findings on

antenatal ultrasound. Neuroradiological findings in patients with neurosyphilis are nonspecific and may mimic herpes simplex virus infection and/or paraneoplastic limbic encephalitis [12]. Brain MRI may reveal cerebral hypertrophy and hyperintensity in the temporal lobes [13].

Neurologic symptoms due to congenital syphilis in the neonatal period are rare. Only a few patients may present with meningitis, choroiditis, hydrocephalus, or seizures. Severe ischemic-hemorrhagic lesions involving predominantly unilateral periventricular white matter, which are thought to be a result of endarteritis, have been reported in neonates [14]. Meningovascular and parenchymatous forms of neonatal neurosyphilis are usually described in late congenital syphilis [15]. Parenchymal disease can lead to diffuse cerebral and cerebellar degeneration with microglial proliferation and inflammatory infiltrates [15]. In the meningovascular form of

congenital syphilis, perivascular inflammatory exudates and intimal proliferation and leptomenigeal spirochete masses have been described ([15]. Hydrocephalous from meningitis, superficial cortical infiltrates and necrosis can also be part of the brain involvement in congenital syphilis ([15]. In addition, pituitary gland involvement may manifest with persistent hypoglycemia or diabetes insipidus [7-9,16-18].

## CONCLUSIONS AND FINAL REMARKS

Congenital syphilis is a preventable disease of the newborn and all medical staff taking care of pregnant women and newborns should be aware of screening times, concomitant disease and early treatment.

Besides the typical manifestations of congenital syphilis all three of our patients had some abnormal findings on CUS and MRI. Two of our cases had abnormal antenatal US findings as well. It is important to keep in mind that infants with congenital syphilis born to mothers with concomitant HIV be treated for longer duration with penicillin. It is important to keep in mind that there can be CNS involvement and these infants need appropriate follow up. Ideally, newborns should not be discharged from the hospital until serologic status of the mother is confirmed and all appropriate investigations are performed if the mother is seropositive for syphilis.

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### Cite this article

Dominguez Garcia MG, Sardesai S, Vachon LA (2020) Brain Involvement in Congenital Syphilis: Case Series and Brief Literature Review. *Ann Pediatr Child Health* 8(4): 1189.