Article

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Abstract: Background: Congenital syphilis (CS) is a transplacental infection that an lead to many long-term sequelae when not adequately treated; however, knowledge about the motor and neurological signs that newborns (NB) with CS may present is scarce. **Objective:** To describe the results of neurological assessment scales and general movements in NB with CS in the first days of life. **Methods:** Cross-sectional study. The Hammersmith Neonatal Neurological Examination (HNNE) and General Movements Assessment (GMA) scales were used to evaluate NB under treatment for CS in a public Brazilian hospital in the first days of life. **Results:** Sample consisted of 11 NB, with a mean birth weight of 3140.5g, and Apgar score at 5 minutes of 8.3. Among the 11 mothers, 4 (36.4%) had fewer than 6 prenatal visits and 5 (45.5%) did not receive any syphilis treatment. All NB (100%) were asymptomatic, with normal long bone X-rays and cerebrospinal fluid analysis. The mean score on the HNNE was 22 (suboptimal/abnormal). Eight NB (72.7%) showed abnormalities on GMA scale (6 [54.5%] being mildly abnormal and 2 [18%] definitely abnormal. Only 3 NB (27.3%) returned for outpatient follow-up. **Conclusions:** A high prevalence of abnormalities in neurological and GMA scales was observed in NB with asymptomatic CS in the first days of life. Most mothers did not receive adequate treatment for syphilis during pregnancy, and there were important deficiencies in post-discharge follow-up. Further studies are needed to confirm these findings and investigate whether the observed abnormalities are linked to biological or environmental factors during pregnancy.

Keywords: Congenital syphilis; newborns; neurological examination

1. Introduction

Congenital syphilis (CS) is part of the ZSTORCH group of infections (syphilis, toxoplasmosis, rubella, human immunodeficiency virus, hepatitis B and C, cytomegalovirus, herpes virus, and zika virus), most of them associated with an increased risk of neonatal morbidity and mortality, as well as neurological sequelae [1,2]. The incidence of CS in Brazil was 9.9 / 1.000 live births in 2022 [3]. When untreated at birth or within the first 3 months of life, CS can lead to systemic, cutaneous, hematological, musculoskeletal, kidney, respiratory manifestations and sequelae, neurological impairment and developmental delay [4]. However, the literature is scarce regarding motor and developmental delay in this population, especially at a young age. Early detection of potential problems allows for early beginning of medical and physiotherapeutic intervention, using the neuroplasticity window and promoting better recovery [5].

Simple, low-cost tests with high sensitivity can indicate the motor and neurological profile of newborns (NB). Screening scales are ideal for patients with CS. The Hammersmith Neonatal Neurological Examination (HNNE) is a rapid test that can be completed in 10 to 15 minutes and allows for early identification of neurological developmental delays [6]. The General Movements Assessment (GMA) identifies neurological abnormalities by evaluating the spontaneous movements of the infant up to five months of corrected age [7].

The study by Padilha et al. [8] evaluated General Movements (GM) in high-risk NB at a Neonatology Unit (NU) in a specialized hospital for maternal and child care. They observed that CS was the second leading cause of hospitalization, with prematurity being the first. In the assessment tests, NB with CS were predominantly classified as pre-pathological/pathological in GM evaluation. These tests are compatible with the reality of public health in Brazil, where simple, low-cost tests with high sensitivity are needed to identify motor and neurological profile of NB with CS [9].

The aim of this study was to describe the results of neurological assessment scales and GM in NB with CS hospitalized in the NU of a tertiary hospital in Brazil.

2. Materials and Methods

Cross-sectional study design. The sample consisted of NB with CS hospitalized in the NU of a tertiary reference public hospital in Porto Alegre, a state capital in southern Brazil. This city has the highest rates of syphilis detection in pregnant women and CS in the country, which are up to three times higher than the national average in the country [3]. The sample was recruited sequentially, including all live births with CS admitted for treatment between August and December 2023.

The research excluded NB with other coexisting congenital ZSTORCH infections that could lead to early neurologic problems (congenital zika virus, toxoplasmosis, rubella, cytomegalovirus and herpes virus infections), major congenital anomalies or genetic syndromes, which could present motor or neurological delays as their main characteristics. Additionally, preterm NB less than 34 weeks were excluded due to the increased risk of clinical complications and neurological deficits [10].

The instruments used were: (1) HNNE, a neurological assessment used as a diagnostic method for cerebral palsy [6]. The scoring on this scale is based on the gestational age of the NB and the classification is determined by the sum of points. Scores equal to or above 30.5 for full-term NB and above 26 for preterm NB are considered "optimal". Scores below these thresholds are classified as "suboptimal" or "abnormal"[11] and (2) GMA, which evaluates the Central Nervous System (CNS) through observation of the NB's spontaneous movements [12]. These GM change according to the NB's maturation, thus varying based on gestational age [7]. The classification of GM varies between "normal optimal," "normal suboptimal," "mildly abnormal," and "definitely abnormal," based on the complexity, variability, and fluency of the NB's spontaneous movements observed for 1 (one) minute.

The ABEP (Brazilian Association of Research Companies) classification was also used. This is a questionnaire for assessing Brazil's economic classification, which ranges from 'A' to 'E', where 'A' represents a higher socioeconomic condition, down to 'E', which corresponds to the lowest socioeconomic condition [13].

Maternal syphilis treatment during pregnancy was considered adequate according to the Brazilian Ministry of Health protocol of 20224, which includes: mandatory use of Benzathine Penicillin, initiated up to 30 days before delivery; completion of the therapeutic regimen according to the clinical stage of the infection; and adherence to the recommended interval between doses. Additionally, there should be a decrease in seric maternal nontreponemal titers by at least two dilutions within three months, or four dilutions within six months after the end of treatment [4]. The nontreponemal test used for this purpose in our setting is the VDRL (Venereal Disease Research Laboratory) test.

Regarding the NB, in addition to the seric VDRL test, the diagnosis of CS is based on the maternal treatment history (adequate or not), presence of abnormalities in physical examination (systemic, neurological, cutaneous, hematological, pulmonary, renal, musculoskeletal, among others), abnormalities in long bone X-rays, and analysis of cerebrospinal fluid (to assess for neurosyphilis). Upon diagnosis of CS, the NB is referred to the NU for treatment with Crystalline Penicillin for 10 days.

The mother's and NB's medical records were analyzed to collect demographic, gestational, maternal, and neonatal data. The ABEP questionnaire was administered to the NB's caregiver to assess the family's socioeconomic status and the educational level of the household head. Evaluations using the HNNE and GMA scales were then conducted during the NB's hospitalization.

Regarding the HNNE scale, a score equal to or above 30.5 for full-term NB or 26 for preterm NB was considered "optimal." Scores below these values were classified as "suboptimal" or "abnormal.". For the GMA scale, results were categorized as follows: "normal optimal" (corresponding to "three plus" in complexity and variability and "one plus" in fluency), "normal suboptimal" ("two plus" in complexity and variability and "one minus" in fluency), "mildly abnormal" ("one plus" in complexity and variability and "one minus" in fluency"), and "definitely abnormal" ("one minus" in all three criteria). We considered "mildly abnormal" and "definitely abnormal" as abnormal classifications. Extreme alert must be carried out when "cramped synchronized movements" (CSM) are observed. These movements are defined as stiffness, lack of fluency and gracefulness in movements, including simultaneous contraction and relaxation of muscles, with a high predictive value for cerebral palsy.

Data were analyzed using the Statistical Package for Social Science (SPSS 20.0). Quantitative variables were described using means and standard deviations, and qualitative variables were described using frequencies and percentages. "p" values were considered statistically significant if < 0,05.

The research project was approved by the Institutional Research Ethics Committee. All parents and/or legal guardians of the participants signed an Informed Consent Form.

3. Results

3.1. The Sample

The sample consisted of 11 NB who were admitted to the UN for the treatment of CS during the study period. There was a significant decrease in admissions from September to October due to technical/administrative reasons in the UN, which consequently led to a much smaller number of admissions for all reasons, including CS, compared to usual periods.

Maternal and neonatal demographic data can be observed in Table 1.

Table 1. Maternal and neonatal demographic data (n=11).

	Mean ± SD	Min - Max
Nº Prenatal appointments	7 ± 5.2	0 – 16
GA (weeks)	39.2 ± 1.3	37 – 41
Birth weight (g)	3140 ± 457	2230 – 3925
Apgar at 5th minute	9.1 ± 0.8	8 - 10

Legend: SD: Standard Deviation - GA: gestational age - g: grams. Min: minimum - Max: maximum.

3.2. Demographic, Maternal and Neonatal Characteristics

All NB were born full-term and with a high Apgar score. Only 1 NB (9%) was classified as small for gestational age (SGA); the others were appropriate for gestational age (AGA). Regarding prenatal care appointments, four mothers (36.4%) did not attend the minimum recommended 6 visits according to the Ministry of Health guidelines, with two of them (18.2% of the total) having no prenatal visits at all.

Regarding maternal treatment, 10 women (90.9%) reported receiving a syphilis diagnosis during this pregnancy. Among them, 5 (45.5%) did not undergo any treatment for the disease during the current pregnancy; 2 (18.2%) received incomplete treatment; and 4 (36.3%) completed all doses but did not achieve a decrease in VDRL titers, leading to the diagnosis of CS in their NB. Only 5 sexual partners (45.5%) also received treatment.

Three pregnant women (27.3%) used psychoactive substances / illicit drugs during pregnancy, and 2 (18.2%) were coinfected with HIV.

All NB included in the study were asymptomatic, had normal blood counts, normal long bone radiographs, and normal cerebrospinal fluid analysis, indicating the absence of neurosyphilis. No infants were excluded during the period due to prematurity, genetic syndromes, or major malformations.

Regarding socioeconomic evaluation, 6 families (54.5%) fit into category C2 (lower middle class); the remaining categories can be observed in Table 2.

Table 2. Socioeconomic Evaluation (n=11) .

ABEP Categories	Frequency	Percentage (%)
B2 (upper middle class)	1	9.1
C1 (middle class)	2	18.2
C2 (lower middle class)	6	54.5
D/E (lower classes)	2	18.2

Legend: ABEP: Brazilian Association of Research Companies.

3.3. Neurologic Assessment Scale (HNNE)

All 11 NB (100%) showed abnormal neurological assessment using the HNNE scale. The mean score was 22, considered "suboptimal/abnormal'. Table 3 shows the scale scores for the evaluated NB. Table 4 demonstrates the most frequently abnormal items in the scale application (out of a total of 34 items).

Table 3. Results of the HNNE Scale (n=11).

	Max Score of the Scale	Mean ± SD	Min-Max
Total HNNE Score	34	22 ± 2.4	19 – 26
Posture and tone	10	4.3 ± 1.6	2 – 7
Tone patterns	5	4.5 ± 0.5	4 – 5
Reflexes	6	4.6 ± 0.8	4 – 6
Movements	3	1.4 ± 0.9	0 – 3
Abnormal signs	3	2.4 ± 0.5	2 – 3
Behavior	7	4.8 ± 1.3	3 - 7

Legend: SD: Standard Deviation - Min: minimum - Max: maximum.

Table 4. Most frequently abnormal items of HNNE scale (n=11).

	N (%) abnormal
Posture 1	11 (100)
Spontaneous Movements 1 (Quantitative)	8 (72.7)
Spontaneous Movements 2 (Qualitative)	9 (81.8)
Ventral suspension	9 (81.8)
Tremors	3 (27.3)
Cramped synchronized movements	1 (9.1)

3.4. General Movements Scale

Regarding the GMA scale, 8 NB (72.7%) showed abnormalities, with 6 (54.5%) classified as "mildly abnormal" and 2 (18.2%) as "definitely abnormal". Among the 6 cases classified as "mildly abnormal", 3 of these mothers (50%) used psychoactive substances or illicit drugs during pregnancy (marijuana, cocaine, crack, or alcohol), and 1 (16.7%) was seropositive for HIV.

Three out of the 11 NB (27.3%) were referred for institutionalization through judicial proceedings due to termination of parental rights, being discharged from the hospital directly to the shelter.

3.5. After-Discharge Follow-Up

After hospital discharge, among the 11 evaluated patients, only 3 (27.3%) returned for outpatient follow-up at the routine CS outpatient clinic after 3 months. These 3 patients were the NB who were

institutionalized after hospitalization; therefore, they were brought to the appointment by the shelter caregivers.

Among the 2 NB who had the lowest scores in the assessment of GM, classified as "definitely abnormal", one did not return for follow-up at the outpatient clinic, and the other was referred to an institution due to a mother who was homeless, user of psychoactive substances, and seropositive for HIV without treatment. This NB was the only SGA in the study. When he attended the clinic, the caregivers were forwarded to undergo physiotherapy for the developmental issues.

Among the 6 neonates with "mildly abnormal" GMA scores, only 2 attended the outpatient clinic for follow-up, both of whom came from institutions. One of them was already in an adoptive family.

4. Discussion

This study found a high prevalence of neurological abnormalities assessed through specific scales in NB with CS within the first days of life. This was observed despite all neonates being full-term, having good birth weights, high Apgar scores, asymptomatic CS, and no neurosyphilis.

Both scales used are sensitive and validated for the target population. According to Hadders-Algra [5], "neurodevelopment peaks in the second half of gestation and at three months of postnatal age, but remains high until the first year of life." Therefore, early detection of developmental disorders allows for early intervention, leading to more successful outcomes due to high neuroplasticity during this period.

There are few studies involving simultaneous testing of both scales in NB with CS. The HNNE scale is used to classify the risk of cerebral palsy, with an inter-rater reliability of 96%. All NB in this study showed abnormalities in the scores of this scale. Chaves et al also found "suboptimal/abnormal" scores in a small group of neonates with CS and observed, using the Hammersmith Infant Neurological Examination (HINE), that these abnormalities were maintained up to 52 weeks of age in these infants, suggesting that neurological changes may persist at least until the end of the first year of life.

The GMA scale evaluates the CNS through observation of the NB's spontaneous movements [12]. The study by Padilha et al[8] evaluated the GM of NB hospitalized in a NU and found that half of the ones with CS had abnormal results in these tests. In the present study, 72.7% of the NB showed abnormalities, even mild ones, in the GMA, with two of them (18.2%) considered as "definitively abnormal". Additionally, one NB presented with CSM, which are sudden block-like movements where the limbs move in synchronous rigidity. These movements indicate loss of supraspinal control and are considered pathological, with a high association with cerebral palsy when they occur frequently,[7] and may also be associated with abnormalities in cerebral magnetic resonance imaging [26].

According to data from the Department of Chronic Conditions and Sexually Transmitted Infections of the Syphilis in Brazilian Municipalities in 2022, inadequate treatment [3] during pregnancy was reported in 81% of NB who needed treatment for CS. In the present study, although 63.6% of mothers had adequate prenatal care with 6 or more visits, as recommended by the Brazilian Ministry of Health, 45.5% did not receive any treatment for syphilis during the current pregnancy. These findings are consistent with the study by Rocha et al [18], where despite prenatal care and testing for syphilis, only 7.9% of mothers were adequately treated during pregnancy. Furthermore, Araújo et al [19] found VDRL titers at delivery greater than 1:8 in 79.8% of cases in mothers and 14.4% in newborns, which was associated with worse outcomes in the neonates [19].

These data suggest the importance of more effective monitoring of pregnant women with syphilis, through more strict prevention, treatment and follow-up actions. It is known that treatment, as well as correct monitoring of these pregnant women and treatment of their sexual partners also, are crucial in reducing pregnancy complications and the prevalence of syphilis in the fetus and NB.

It's important to emphasize that the correct treatment of syphilis in pregnant women involves several criteria. The woman needs to be well-informed that the three doses of Penicillin must be

administered with an interval of 7 to a maximum of 9 days. Untreated sexual partners can increase the risk of reinfection in the pregnant woman by up to 50%. Even with correct treatment, depending on the level of circulating treponemes, gestational age, and other comorbidities (e.g., HIV coinfection or maternal neurosyphilis), the therapeutic failure rate can reach up to 14%, significantly increasing the risk of syphilis in the fetus despite the mother receiving "adequate" treatment. This underscores the importance not only of treatment but also of closely monitoring these pregnant women for the neonatal outcome [4].

Another important issue addressed in this study, which aligns with inadequate treatment of gestational syphilis, is the socioeconomic status of families, which directly influences access to healthcare services [20]. In this study, the vast majority (90.9%) of families were classified in socioeconomic classes C, D, and E, in line to several studies reporting socioeconomic vulnerability and low maternal education as recurring factors associated with cases of CS [20,21]. Regarding motor development, the study by Delgado et al evaluated infants aged 4 to 17 months and found that socioeconomic factors, such as receiving government benefits and low maternal education, are independent risk factors for neurodevelopmental impairment.

The lack of adherence to post-discharge outpatient follow-up, whether due to access or mobility difficulties, or lack of understanding of the prognosis and potential sequelae of CS, had a significant impact in this study. Among the 11 patients studied, the only 3 patients who attended the first follow-up appointment were those referred to and brought by judicial institutions. It is also striking the high prevalence of mothers with substance abuse disorders and coinfection with HIV, factors possibly related to poor adherence to prenatal care, lack of treatment during pregnancy, and inadequate follow-up of the NB after discharge.

The study has some limitations, including a small sample size, which prevented conducting association tests between abnormal test results and other maternal or neonatal risk factors. It was also not possible to demonstrate the relationship between socioeconomic variables and abnormalities in scale results, despite previous studies showing such associations. We also did not include a control group which could confirm that the findings were due to syphilis itself or other in utero environmental issues, what makes the results difficult to interpret. Furthermore, our study was not blinded, as the investigators conducting and scoring the behavioral tests on the babies knew that the babies had congenital syphilis. Therefore, the investigators could be unconsciously biased in the assessments. Follow-up of these patients is being processed at 3 and 6 months of age and the researchers are going to observe if these abnormalities persist during the first year of life.

5. Conclusions

In this study, abnormal results were found in the HNNE and GMA scales in hospitalized NB treating CS, as early as their first days of life. Most of the families belonged to lower socioeconomic classes. There was a high prevalence of mothers who did not receive any treatment for syphilis. Additionally, the majority of families did not attend the post-discharge follow-up for their NBs.

Further studies with a larger number of NB are recommended to confirm these findings and determine whether the observed abnormalities and delays are more closely associated with biological factors or socioeconomic conditions of the families, and if they persist through the first year of life. Despite the limitations of the study, there is a critical need for preventive measures, guidance, and monitoring of pregnant women with syphilis at the public health level in Brazil. Early referral of any NB with suspected neurodevelopmental delay is crucial. Early neurological and motor testing of NB with CS allows for identification of abnormalities before hospital discharge, facilitating early follow-up and intervention. This approach can prevent future expenses related to avoidable complications and capitalize on the period of heightened neuroplasticity.

Author Contributions: Conceptualization of the study: BVRS, CSA. Methodology: BVRS, CSA. Software / Creation of the database of the study: BVRA, CSA, LF. Validation of the tested methods: BVRS, CSA, GFB, RSB,

Abbreviations Used in this Article

CS – Congenital Syphilis

HNNE - Hammersmith Neonatal Neurological Examination

GMA – General Movements Assessment

NB – Newborn

GM – General Movement

NU – Neonatal Unit

ZSTORCH – Group of congenitakl infections (Zikavirus, Toxoplasmosis, Others [mainly hepatitis A, B, C and Human Immunodeficiency Virus], Rubella, Cytomegalovirus, Herpes)

CNS – Central Nervous System

ABEP – Brazilian Association of Research Companies (in English)

VDRL – Veneral Disease Research Laboratory

CSM – Cramped Synchronized Movements

SPSS – Statistical Package os Social Science

HIV – Human Immunodeficiency Virus

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