

Original articles

Development of infants presented with congenital syphilis in their first months of life

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ABSTRACT

Purpose: to evaluate the cognitive, language, and motor development of infants with congenital syphilis in their first months of life.

Methods: a sample of 52 infants, from 21 to 112 days of age, born in public maternity hospitals, divided into a study group of 28 infants with congenital syphilis and a control group 24 infants without risk indicators for hearing loss. They underwent the Neonatal Hearing Screening Protocol with automated Brainstem Auditory Evoked Potential. The research instrument was the Bayley-III Scale, consisting of the cognitive, language (receptive and expressive), and motor (fine and gross) subscales. The raw scores were entered into the software that accompanies the Bayley-III scale kit to calculate the scores (scaled and composite) and perform qualitative analysis. The Mann-Whitney test and the Wilcoxon test was applied and used a 5% significance level.

Results: a similarity between groups for the demographic parameters, maternal education level, and socioeconomic level, was seen. There was no statistically significant difference between groups when comparing the cognitive, receptive language, expressive language, fine motor, and gross motor subscales.

Conclusion: infants with congenital syphilis treated at birth have a cognitive, language, and motor development within that expected for their age group in their first months of life.

Keywords: Syphilis, Congenital; Infant; Infant Development; Cognition; Child Language; Psychomotor Performance

INTRODUCTION

According to the World Health Organization (WHO), syphilis is one of the most common sexually transmitted infections in the world and deserves attention due to an annual increase of about six million cases¹. In addition to sexual contact, the transmission of syphilis may occur from the mother to the fetus if she is not treated or receives inadequate prenatal care. The disease is then called, congenital syphilis (CS)^{2,3}.

In Brazil, the incidence of congenital syphilis in 2018 was 9.0/1,000 live births, and 9.6/1,000 live births in the Northeast Region⁴. Congenital syphilis may have fatal consequences, such as abortion, stillbirth, newborn death, low birth weight, prematurity, and late congenital manifestations such as sensorineural hearing loss and learning difficulties^{1,3}.

Neurological clinical manifestations may appear in the first year of life in an acute form with characteristics of bacterial meningitis or as changes related to chronic syphilis, such as the presence of hydrocephalus, cranial nerve palsy, deterioration of intellectual/neuropsychomotor development, or cerebral infarction^{3,4}. Developmental delays have been reported in children diagnosed with congenital syphilis followed up to 60 months of life. However, when mothers are treated properly during prenatal care, there is a decrease in developmental complications⁵. A study⁴ evaluated the neurodevelopment of children with congenital syphilis and reported diagnoses of neurodevelopment deficiency, including cerebral palsy, visual impairment, sensorineural hearing loss, mental retardation, seizure disorder, microcephaly, and language delay.

Despite reports of neurological impairment in congenital syphilis, studies^{5,6} have not presented data on functional developmental assessments involving motor, cognitive, and language aspects after performing a longitudinal monitoring. The early detection of these neurodevelopmental changes may allow a rapid start of intervention, benefiting this population with a rehabilitation process^{7,8}.

Evaluation scales have been used to monitor neurodevelopment,^{8,9} as they are a viable, reliable, and standardized way of assessing domains and skills⁸. The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), is an internationally tool used to assess infant development in different aspects: cognition, receptive and expressive language, fine and gross motor skills, and socioemotional and adaptive behavior¹⁰.

This scale has proven to be a useful tool to be applied to infants without indications of risks or associated pathologies in South America,^{11,12} as well as premature infants¹³ and children at risk of delayed motor development¹⁴. It is a tool used for the identification of developmental delays, description of the development profile, and analysis of risk factors in relation to development aspects⁹.

In view of the possible late implications caused by congenital syphilis, monitoring development, especially regarding cognitive, language and motor aspects, is a means of observing possible changes and referring the infant to an early intervention. Therefore, this study aims to evaluate the cognitive, language, and motor development of infants with congenital syphilis in their first months of life using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)¹⁰.

METHODS

This transversal, observational and prospective study was approved by the Committee of Research Ethics of the Onofre Lopes University Hospital (number 3.360.991), Brazil. All the parents and/or guardians of the infant signed an informed consent (IC) after reading and understanding the research objectives and procedures.

The convenience sample consisted of 52 infants, aged 21 days to three months and 22 days (112 days) of age, born in public maternity hospitals. The infants were divided into two groups. The study group (SG) was composed of 28 infants with congenital syphilis³ and the control group (CG) consisted of 24 infants without congenital syphilis and without the presence of other risk indicators for hearing loss (RIHL)¹⁵.

To define and characterize infants with congenital syphilis, the infant must be the child of a symptomatic or not mother and present at least one reagent test – treponemal and/or non-treponemal with any titration, regardless of the results of the clinical evaluation or complementary exams of the infant, following the guidelines of the Ministry of Health³. The infants in the control group were children of mothers with a non-reactive test and asymptomatic for syphilis, as well as infants with a normal test for detection of syphilis at the time of birth.

All infants passed the Neonatal Hearing Screening Protocol with Automated Brainstem Auditory Evoked Potential (A-BAEP). Information about the infant and its mother were collected, in part, from the maternity records (X-Ray of long bones, cerebrospinal fluid, hematocrit, platelets, mother's and newborn's venereal

disease research laboratory) and from discharge summaries (date of birth, gestational age, cephalic perimeter, apgar and birth weight). Subsequently, mothers also answered a questionnaire containing information on the history of prenatal care and on the birth and first month of the infant, in addition to the application of the Brazilian Economic Classification Criterion questionnaire (CCEB)¹⁶ for the socioeconomic characterization of families. A researcher, when interviewing parents or guardians during the anamnesis, also applied the questions contained in the CCEB, and then the items were summed according to the pre-established score for the number of items reported. The original classification proposed by the CCEB¹⁶ groups into A1, A2, B1, and B2 a high socioeconomic level, into C1 and C2 an average socioeconomic level, and into D and E a low socioeconomic level. Information was also collected about the educational level of the infants' mothers. It is classified as high when the mother has higher education (complete or incomplete), medium, if the mother has attended high school, and low if the mother has a complete or incomplete elementary schooling or less.

The research instrument was the Bayley-III Development Scale, which consists of the subscales cognitive, language (receptive and expressive), and motor (fine and gross). The application of the scale was based on the observation of the infants' reactions to different stimuli and on artificial situations, standardized and organized by the researchers.

The starting point of the evaluation corresponded to the infant's chronological age on the day of the evaluation. For infants with a history of prematurity (five infants with gestational age over 35 weeks were included), the baseline to start the test followed the corrected age of the child according to the methodology proposed in the test¹⁰.

The application of the test lasted an average of 45 minutes. It was always carried out by the same researcher, who took a course and trained on the scale. The sequence of application of the subscales was random for both groups, but the application of the receptive language subscale was always prior to the expressive language subscale. At the end, the points of each scale were summed to generate the respective raw scores and entered into the software

that accompanies the Bayley-III scale kit, together with the infant's identification data, gestational age, and birth age in order to calculate scaled and composite scores. The mean normality of the scaled score is 10 and the standard deviation is 3. Values between 5 and 6 represent a mild developmental delay, and below that the values represent a moderate to severe delay. The normality range of the composite score is 85 to 115 points. Values between 84 and 70 represent a mild developmental delay, and below 70 the values represent a moderate to severe delay¹⁰.

The qualitative analysis carried out by the software showed, for each infant, in each scale, the following categorizations: higher, high average, average, borderline, low average, and extremely low average¹⁰.

Initially, the Shapiro-Wilk test was applied when there was no normal data distribution. Thus, the nonparametric Mann-Whitney test was used for inter-group comparative analyses (congenital syphilis vs. control) of each subscale (receptive and expressive language, cognitive, fine and gross motor) and the Wilcoxon test for intragroup analyses (the same infants on each subscale). The significance level was 5%.

RESULTS

Table 1 shows the characterization of infants in each group, with similarities between them regarding age, sex, gestational age, cephalic perimeter, Apgar scores at 1 and 5 minutes, birth weight, maternal education level, and socioeconomic level. There was no statistically significant difference in the analysis of these parameters between groups.

Most infants in the sample were at term (86.54%), with no groups having premature infants with a gestational age less than 32 weeks. The average cephalic perimeter in both groups was within the normal range, and the average of the Apgar at 1 and 5 minutes varied between 8 and 9. Approximately 65% of the mothers of the evaluated infants had a medium educational level. The predominant education level was elementary school and/or complete high school. There was an even greater concentration of mothers in the medium and low socioeconomic levels, comprising 50% and 40.4% of the sample, respectively.

Table 1. Demographic data of the studied sample by group

| | Total sample (n=52) | Study Group (n=28) | Control Group (n=24) | P value |
|-------------------------------------|---------------------|--------------------|----------------------|---------|
| Test age (days) | | | | |
| Mean ± SD | 49.1 ± 20.3 | 49.8 ± 21.6 | 48.4 ± 19.1 | 0.8 |
| Minimum-maximum | 21-112 | 21-112 | 22-82 | |
| Sex | | | | |
| Males | 25 (48.0%) | 16 (57.1%) | 9 (37.5%) | 0.1 |
| Females | 27(51.9%) | 12 (42.8%) | 15 (62.5%) | |
| Gestational age | | | | |
| 32w – 36w6d | 4 (7.6%) | 0 (0%) | 4 (100%) | |
| 37w – 40w6d | 45 (86.5%) | 26 (57.7%) | 19 (42.2%) | |
| >41w | 3 (5.7%) | 2 (66.6%) | 1 (33.3%) | |
| Cephalic perimeter | | | | |
| Mean ± SD | 34.1 ± 1.7 | 34.2 ± 1.8 | 33.8 ± 1.9 | 0.6 |
| 1-minute Apgar score | 8.3 ± 0.9 | 8.3 ± 1.1 | 8.4 ± 0.6 | 0.8 |
| Mean ± SD | | | | |
| 5-minute Apgar score | | | | |
| Mean ± SD | 8.9 ± 0.4 | 9.0 ± 0.5 | 8.9 ± 0.3 | 0.4 |
| Birth weight | | | | |
| 1500 – 2500 g | 6 (11.5%) | 4 (66.6%) | 2 (33.3%) | 0.7 |
| | 2148.8 ± 160.4 | 2074.5 ± 231.9 | 2297.5 ± 53.0 | |
| > 2500 g | 46 (88.5%) | 24 (52.2%) | 22 (47.8%) | |
| | 3372.6 ± 429.3 | 3388.9 ± 1320.9 | 3354.9 ± 292.4 | |
| Maternal instructional level | | | | |
| High | 5 (9.6%) | 2 (7.1%) | 3 (12.5%) | |
| Medium | 34 (65.4%) | 18 (64.3%) | 16 (66.6%) | 0.8 |
| Low | 13 (25%) | 8 (28.6%) | 5 (20.8%) | |
| Socioeconomic level | | | | |
| Low | 5 (9.6%) | 1 (3.5%) | 4 (16.8%) | 0.7 |
| Medium | 26 (50%) | 15 (53.6%) | 11 (45.8%) | |
| High | 21 (40.4%) | 12 (42.8%) | 9 (37.5%) | |

Captions: SD – standard deviation; w – weeks; d – days; g – gram.

*p value < 0.05 Mann-Whitney U test.

All subjects in the study group presented the Venereal Disease Research Laboratory (VDRL) reagent test. However, most had a low titration, and 53.6% of mothers had a VDRL lower than 1:8 on the delivery

day, as Table 2 shows. There were no clinical findings regarding signs and symptoms in the medical records of maternity hospitals. In anamnesis, the mothers did not report any specific complaints at birth.

Table 2. Objective clinical data at birth of babies with congenital syphilis

| Experimental Group n = 28 | ≥ 1:8 | < 1:8 | Unregistered information |
|---------------------------|------------|------------|--------------------------|
| Mother's VDRL | 12 (42.9%) | 15 (53.6%) | 1 (3.6%) |
| Newborn's VDRL | 5 (17.9%) | 23 (82.1%) | - |
| | Abnormal | Adequate | Unaccomplished |
| XR of Long Bones | 1 (3.6%) | 16 (57.1%) | 11 (39.3%) |
| CSF | - | 1 (3.2%) | 27 (96.4%) |
| Hematocrit | - | 27 (96.4) | 1 (3.5%) |
| Platelets | - | 27 (96.4%) | 1 (3.6%) |

Captions: VDRL – Venereal Disease Research Laboratory; XR – X-Ray; CSF – Cerebrospinal Fluid.

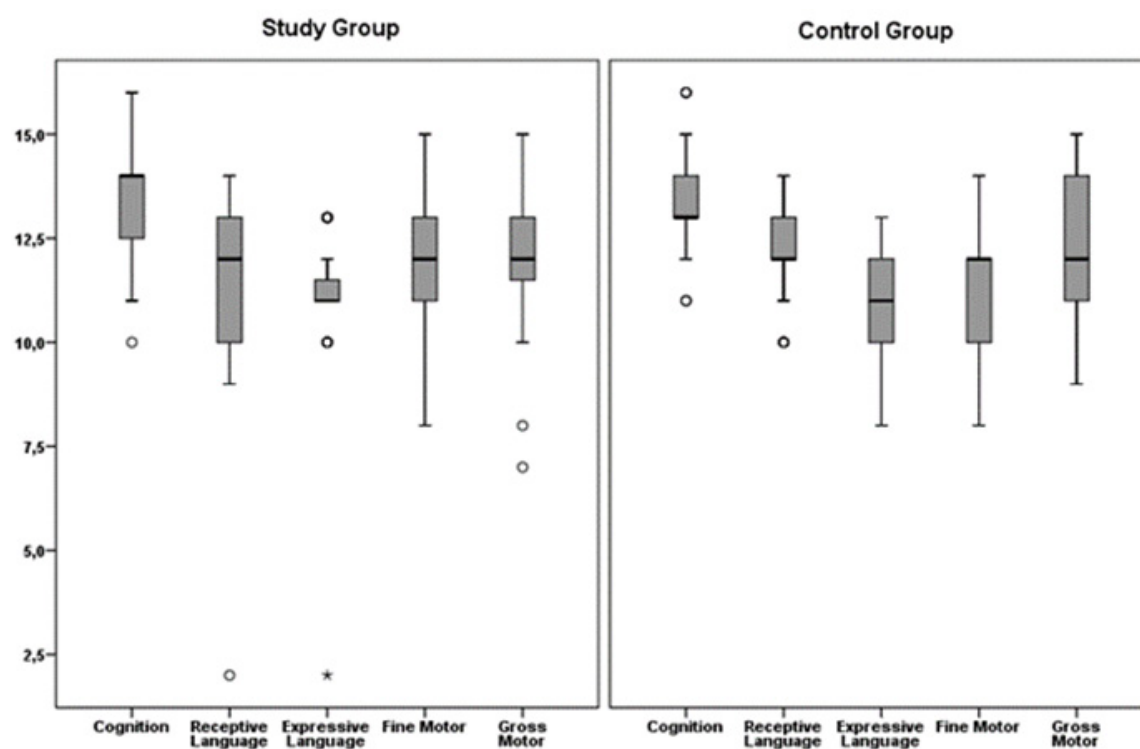
Table 3 shows that there was no statistically significant difference between SG and CG when comparing the means of cognitive, receptive and expressive language, and fine and gross motor subscales.

Figure 1 shows that most subjects in both groups had values higher than the average expected in the Bayley-III Scale.

Table 3. Descriptive and inferential statistics by group of scaled score's performance in Bayley-III scale

| | Study Group | | | | Control Group | | | | p |
|---------------------------|-------------|----|----|----|---------------|----|----|----|-----|
| | (Mean ± SD) | Q1 | Q2 | Q3 | (Mean ± SD) | Q1 | Q2 | Q3 | |
| Cognition Scale | 13.4 (±1.5) | 13 | 14 | 14 | 13.5 (±1.4) | 13 | 13 | 14 | 0.9 |
| Receptive Language Scale | 11.4 (±2.3) | 10 | 12 | 13 | 12.1 (±1.2) | 12 | 12 | 13 | 0.3 |
| Expressive Language Scale | 11 (±2.0) | 11 | 11 | 12 | 11.2 (±1.3) | 10 | 11 | 12 | 0.9 |
| Fine Motor Scale | 12.0 (±1.5) | 11 | 12 | 13 | 11.3 (±1.6) | 10 | 12 | 12 | 0.1 |
| Gross Motor Scale | 12.0 (±1.8) | 12 | 12 | 13 | 12.0 (±1.7) | 11 | 12 | 14 | 0.8 |

Captions: SD – standard deviation; *p value < 0.05; Mann-Whitney U test; Q1–25th percentile; Q2 – 50th percentile (median); Q3 – 75th percentile.

**Figure 1.** Box-plots of scaled scores in the subscales evaluation, according to the group

The qualitative analysis (Table 4) showed that most subjects presented evaluation results within or above the average. Only one subject in the CG had an

extremely low qualitative score on the language scale and one subject in the SG was classified below the average on the motor scale.

Table 4. Percentage of babies in subscale by group in qualitative analysis

| Subscale | SG (n=28) | CG (n=24) |
|-----------------------|-----------|------------|
| Cognition | | |
| Higher / High average | 22 (79%) | 22 (92%) |
| Average | 6 (21%) | 2 (8%) |
| Language | | |
| Higher / High average | 8 (29%) | 8 (33.3%) |
| Average | 20 (71%) | 15 (62.5%) |
| Extremely low average | 0 (0%) | 1 (4.8%) |
| Motor | | |
| Higher / High average | 12 (43%) | 14 (58%) |
| Average | 15 (54%) | 10 (42%) |
| Low average | 1 (3%) | 0 (0%) |

DISCUSSION

The mothers and infants who composed the SG received a ten-day treatment with crystalline benzylpenicillin, procaine, or benzathine before hospital discharge, as recommended by the Ministry of Health³. This study shows that infants with congenital syphilis who received treatment have a cognitive, language, and motor development as expected for their age group in the first months of life, similar as infants who did not present risk indicators for child development.

According to the Joint Committee on Infant Hearing¹⁵, intrauterine syphilitic infection is one of the risk indicators for hearing loss (RIHL). This is the main differentiating factor among infants that comprised the sample, since there were no other risk indicators for hearing loss in the clinical history of infants.

The vertical transmission of congenital syphilis may occur at any gestational stage and cover a wide spectrum of clinical manifestations, with repercussions proportional to the seriousness of the case. When the infant is born, it must undergo thorough a clinical examination and laboratory tests to investigate the congenital infection. Initially, the infant undergoes the non-treponemal test (the VDRL is the most common), in addition to tests such as complete blood count, Cerebrospinal Fluid (CSF) analysis, radiography of long bones and chest, imaging exams, and other exams according to the manifestations of the newborn. According to maternal treatment during pregnancy

or through clinical examinations and/or titration of the non-treponemal test, the infant is treated with benzylpenicillin (potassium/crystalline, procaine, or benzathine), following the protocol of the Ministry of Health. Despite receiving treatment with penicillin in the maternity hospital, it is extremely important to maintain an intensive clinical monitoring of the infant for at least two years³.

The absence of adequate treatment during pregnancy increases the risk of symptoms associated with congenital syphilis^{5,17}. When performed properly within the first three months of the infant's life, the treatment of congenital syphilis can prevent most clinical manifestations of the disease, with the exception of interstitial keratitis and bone deformities³. It is noteworthy that all infants evaluated in this study were asymptomatic at birth and during outpatient follow-up, which may explain the normal development in the first months of life, according to the Bayley Scale. Another important finding is that most mothers and newborns had VDRL titration lower than 1:8 at the time of delivery. This means a low titration, which may reflect a serological response after treatment during pregnancy. These facts could, therefore, explain the absence of repercussions on development and the absence of differences between groups when comparing the means of the subscales of the Bayley-III scale.

The literature reports that two thirds of infants affected by congenital syphilis are asymptomatic¹⁷ and

that fatal cases or changes in development may occur in the absence or inadequate maternal treatment during the prenatal care, or in a late treatment of the infant^{5,18}. Manifestations can be early, even during pregnancy and childbirth, such as abortion or stillbirth, prematurity and low birth weight,³ the latter two being important factors of risk for development of chronic and functional changes, in addition to leading to consequences on the individual's quality of life until adulthood¹⁹.

Children whose mothers received adequate treatment for syphilis during pregnancy and at birth showed no clinical changes and the laboratory tests resulted normal for syphilis, with a satisfactory evolution of development. In view of this, it is possible to state that the presence of congenital syphilis and its adequate treatment may not be a risk factor for child development.

The expansion of access to testing, diagnosis, and treatment with benzathine penicillin in primary care may be related to the reduction of vertical transmission of syphilis. However, current actions are still not enough to eradicate the incidence of acquired, gestational, and congenital syphilis, which is increasing in Brazil²⁰.

In addition, it is essential for the health system to record maternal treatment in health documents, such as the pregnant woman's handbook, so that maternity hospitals ensure a proper treatment of the mother-fetus binomial and avoid treatment of newborns due to lack of information on the treatment of pregnant women. Such a situation may have occurred with some of our subjects, who received treatment after birth, despite an adequate treatment during pregnancy, which was unknown to the maternity and outpatient care teams.

This study stresses, therefore, the importance of the Unified Health System Network and the policies of Health of Women and Pregnant Women for the prevention of syphilis, as well as the strengthening of health surveillance policies for the reduction of acquired, gestational, and congenital syphilis in Brazil. This involves efficiency in the processes of testing, diagnosis, notification, treatment, monitoring, and prevention of this infection in the integrated care flow of Health Care Networks (primary, secondary, and tertiary).

In view of the pandemic scenario caused by the new Coronavirus (SARS-CoV-2), the protective measure of social isolation resulted in the cessation of data collection activities. Thus, the impossibility of increasing the sample size and the cross-sectional design, which made unfeasible to assess and monitor

the development of infants at 12 and 24 months, is a limitation of this study. Therefore, it is suggested that future studies analyze, characterize, and compare the development of infants with congenital syphilis, or even of those exposed to syphilis, in a longitudinal way.

CONCLUSION

Infants presented with congenital syphilis treated at birth have a cognitive, language, and motor development within the expected range for their age group in the first months of life. Cohort studies are needed to see if there will be any delay in the development of these babies over the first and second years of life.

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