NEUROSYPHILIS IN PEDIATRIC POPULATION: A REVIEW OF CASES

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ABSTRACT: Background: Neurosyphilis is the most severe presentation of acquired and congenital syphilis, it occurs when Treponema pallidum penetrates the central nervous system. This development can occur at any time during the evolution of the disease phases. In Brazil in 2021, 2,343 children born with congenital syphilis were diagnosed with neurosyphilis, representing 9.3% of the total. The objective of this study was to analyze the scientific evidence on the medical manifestations presented by pediatric patients affected by neurosyphilis. Methods: In February 2023, PubMed, VHL, Scopus, Lilacs and Bdenf databases were researched for published case reports of patients aged zero to less than 18 years with T. pallidum infection. The data analysis period covered 55 years. Results: Nine articles were found in the period of publication from 1967 to 2022. There were two cases in females and only one with manifestation in an adolescent of acquired neurosyphilis. The adolescent's case was the only one with a favorable outcome after adequate treatment. Other cases resulted in impaired quality of life for patients and family members involved in child care. Conclusion: The reported cases of neurosyphilis were mostly related to late diagnosis. Evidencing the fragility of prenatal care, which is crucial for prevention and intervention by T. pallidum infection causes serious consequences for child development. Therefore, control measures should focus on mandatory prenatal screening during the first trimester of pregnancy, partner notification, prompt treatment and postnatal follow-up of the newborn.

KEYWORDS: Treponemal infections; Neurosyphilis; Syphilis; Congenital; Juvenile neurosyphilis; Syphilis.

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NEUROSSÍFILIS NA POPULAÇÃO PEDIÁTRICA: REVISÃO DE CASOS


PALAVRAS-CHAVE: Infecções por Treponema; Neurossífilis; Sífilis Congênita; neurossífilis juvenil; Sífilis.

NEUROSÍFILIS EN POBLACIÓN PEDIÁTRICA: REVISIÓN DE CASOS

RESUMEN: Introducción: La neurosífilis es la presentación más grave de la sífilis adquirida y congénita, se presenta cuando Treponema pallidum penetra al sistema nervioso central. Este desarrollo puede ocurrir en cualquier momento durante la evolución de las fases de la enfermedad. En Brasil, en 2021, 2.343 niños nacidos con sífilis congénita fueron diagnosticados con neurosífilis, lo que representa el 9,3% del total. El objetivo de este estudio fue analizar la evidencia científica sobre las manifestaciones médicas que presentan los pacientes pediátricos afectados por neurosífilis. Métodos: en febrero de 2023, se investigaron las bases de datos PubMed, VHL, Scopus, Lilacs y Bdehf para obtener informes de casos publicados de pacientes de cero a menos de 18 años con infección por T. pallidum. El período de análisis de los datos abarcó 55 años. Resultados: Se encontraron nueve artículos en el período de publicación de 1967 a 2022. Hubo dos casos en el sexo femenino y solo uno con manifestación en un adolescente de neurosífilis adquirida. El caso de la adolescente fue el único con evolución favorable luego de un tratamiento adecuado. Otros casos resultaron en deterioro de la calidad de vida de los pacientes y familiares involucrados en el cuidado de niños. Conclusión: Los casos notificados de neurosífilis se relacionaron en su mayoría con un diagnóstico tardío. Evidenciando la fragilidad del control prenatal, que es fundamental para la prevención e intervención de la infección por T. pallidum que provoca graves consecuencias para el desarrollo infantil. Por lo tanto, las medidas
de control deben centrarse en el tamizaje prenatal obligatorio durante el primer trimestre del embarazo, la notificación a la pareja, el tratamiento oportuno y el seguimiento posnatal del lactante.

**PALABRAS CLAVE:** Infecciones treponémicas; Neurosífilis; Sífilis congénita; Neurosífilis juvenil; Sífilis.

1. **INTRODUCTION**

Sexually transmitted infections (STIs) are recognized as a significant public health issue, with approximately 1 million people worldwide becoming infected daily. The new report by the World Health Organization (WHO) emphasizes the necessity to intensify efforts in reducing the incidence of STI’s through universal prevention strategies, thereby promoting the “Sustainable Development Goals” (WORLD HEALTH ORGANIZATION, 2022). Among STI’s, syphilis is a notable infection that can also be transmitted vertically during pregnancy. It is caused by the spirochaete *Treponema pallidum* subspecies *pallidum*. This pathogen has a prolonged latent period during which individuals exhibit no signs or symptoms but can remain infectious. This infection is classified into recent syphilis (primary, secondary and recent latent) and late syphilis (late latent and tertiary) (HOOK, 2017).

Brazil serves as a stark reminder of the tenacity of *T. pallidum* as a pathogen. Over the last five years, the country has witnessed a consistent increase in the number of cases of syphilis in pregnant women, congenital syphilis and acquired syphilis. Transmission during pregnancy leads to congenital infection, which has two stages of classification: early congenital syphilis, diagnosed up to two years of age, and late congenital syphilis, with manifestation after this period of life. Several warning signs for the risk of congenital infection are related to the deficit in prenatal care and the insufficient number of consultations or even the total absence of these (GUERRA et al., 2017; MINISTÉRIO DA SAÚDE, 2022).

Neurosyphilis represent the most severe presentation of both acquired and congenital syphilis. *T. pallidum* possesses the capability to penetrate the central nervous system (CNS) (HOOK, 2017). This involvement of the CNS by the spirochete in sexually acquired infection may occur at any time during the evolution of the disease stages (MINISTÉRIO DA SAÚDE, 2022). Congenital neurosyphilis can present two forms, it can be symptomatic or asymptomatic. Late manifestations can occur in over 70% of asymptomatic patients and cause permanent sequelae (CARDOSO et al., 2018).
Neurosyphilis results in enduring sequelae in children. In Brazil in 2021, 2,343 children born with congenital syphilis were diagnosed with neurosyphilis, accounting for 9.3% of the total (MINISTÉRIO DA SAÚDE, 2022). Consequently, it is necessary to understand the characteristics of the disease in the pediatric population, so that prevention strategies are carried out, improvements in care and monitoring of children exposed to syphilis. The objective of this study was to analyze the scientific evidence regarding the clinical manifestations exhibited by pediatric patients affected by neurosyphilis.

2. MATERIALS AND METHODS

This is a integrative review carried out to find data on cases of neurosyphilis in the pediatric population (zero to less than 18 years old). The guiding question was elaborated using the PICOS strategy (an acronym for: P: Population/Patients; I: Intervention; C: comparison/control; O: outcome/outcome), as shown in Chart 1.

A research was carried out in the following databases: PubMed, VHL, Scopus, Lilacs and Bdenf in February 2023. The search terms selected, according to the descriptors in Health Sciences (DECS) and using the Boolean operators “AND” were Neurosyphilis “AND” Reports of cases “AND” in children. Two independent reviewers (CC and MC) screened the search results obtained from databases for inclusion. Full text of the qualified articles was screened by the same two independent reviewers. A third reviewer (SS) was called in to resolve any differences of opinion in order to form a consensus. Inclusion criteria were as follows: a) Case reports with patients from zero to less than 18 years old, with T. pallidum infection and available for a full reading. The exclusion criteria were as follows: a) Studies with people over 18 years of age; b) patients without neurosyphilis and unavailable for complete reading. c) duplicate and unavailable articles.

3. RESULTS

The bibliography search available on the platforms resulted in 42 studies that, after reading and applying the eligibility criteria, nine studies were identified and selected. Figure 1 describes in a flowchart the four stages of study screening as recommended by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (LIBERATI et al., 2009).
Nine studies were eligible, representing seven countries in a period of publication from 1967 to 2022. Two articles reported more than one clinical case (SMITH; ISRAEL, 1967; WOLF; KALANGU, 1993) which only cases involving children and adolescents were considered, totalizing ten clinical cases included in this revision. The cases are ordered according to the year of publication in a summarized table (Table 1 and 2) containing the study description, maternal and obstetric data and clinical evolution followed by its outcome.

**Chart 1: Description of studies included - Cases.**

<table>
<thead>
<tr>
<th>Year of Publication</th>
<th>Clinical Presentation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967</td>
<td><strong>Infant</strong>: Nystagmus; <strong>Preschool</strong>: Retinitis pigmentosa; visual acuity: 4/300; Slow pupillary reactivity; Weak optokinetic responses; Eye discs with blurred margins and finely dotted pigmentation; <strong>School</strong>: Total loss of vision</td>
<td>Blindness due to probable retinitis pigmentosa.</td>
</tr>
<tr>
<td>1979</td>
<td><strong>School</strong>: At 08 years old: Convulsion and myasthenia; At 09 years old: undisciplined behavior; intellectual deterioration; Apomatesia; Social distancing; School dropout; Inappropriate and inappropriate responses to questions; slurred speech; Unpredictable and violent behavior; mood swings. Delay in mental development; Growth retardation; Wide and spastic gait.</td>
<td>Persistence of behavioral symptoms.</td>
</tr>
<tr>
<td>1993</td>
<td><strong>Infant</strong> (03 months): Rapid increase in head circumference; convulsions. <strong>School</strong> (08 years old): Gradual intellectual deterioration; Decreased school performance and unsteady gait; slurred speech; Delay in mental development; Couple social distancing.</td>
<td>Controlled seizures. Head circumference without measurement progression.</td>
</tr>
<tr>
<td>1993</td>
<td><strong>Infant</strong>: Hepatosplenomegaly; Rash; Sneezing. <strong>Preschool</strong>: (no follow-up until 03 years old) at 04 years</td>
<td>Lost to follow up.</td>
</tr>
</tbody>
</table>

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old Onset of non-febrile seizures. School: (08 years old) behavioral disorders.

**Newborn:** Absent respiratory effort; Ascites; hepatosplenomegaly; Petechiae; Gallop rhythm and systolic murmur on cardiovascular auscultation; Anemia (HB 7.7G/L) and thrombocytopenia (Platelets 22,000); Microalbuminuria; Liver function with cholestatic pattern; Tremors of extremities and Myoclonus; Fever; Costochondritis in long bones and.

**Infant:** Stunted growth; tendon hyperreflexia; Increased muscle tone.

**Newborn:** Hypotonia and Seizures. **Infant:** Global developmental delay and spastic diplegic cerebral palsy.


**Newborn:** severe respiratory distress; Pallor; Jaundice; hepatosplenomegaly; convulsion

**Adolescent:** Skin peeling on extremities bilaterally. Brown, verruciform papular rash on the trunk, abdomen, genitals and buttocks. Flat brown spots on palms and soles. Soft, mobile, and enlarged lymph nodes in the neck and bilateral inguinal areas. Perianal warts. Shallow ulcerations on the palate and sparse white lesions on the oral mucosa. Hearing Loss.

Head circumference below the 3rd percentile tremors such as tendon hyperreflexia and a slight increase in muscle tone.

**Global developmental delay and spastic diplegic cerebral palsy.** It showed therapeutic efficacy without description of other alterations.

**Outpatient return after 30 days, stable condition was observed, without seizures and other neurological signs, but with persistence of jaundice.**

**After one year, the audiological reassessment was normalized.**

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**Chart 2: Description of studies included - Description of Studies.**

<table>
<thead>
<tr>
<th>Year of Publication</th>
<th>Country</th>
<th>Age</th>
<th>Infection</th>
<th>Prenatal</th>
<th>Birth History</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967</td>
<td>United States</td>
<td>5 years</td>
<td>Congenital</td>
<td>-</td>
<td>No reports of complications.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Born in a rural area without access to perinatal care.</td>
</tr>
<tr>
<td>1979</td>
<td>South Africa</td>
<td>9 years</td>
<td>Congenital</td>
<td>-</td>
<td>No reports of complications.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Born in a rural area without access to perinatal care.</td>
</tr>
<tr>
<td>1993</td>
<td>Zimbabwe</td>
<td>6 months</td>
<td>Congenital</td>
<td>-</td>
<td>No reports of complications.</td>
</tr>
<tr>
<td>1993</td>
<td>Zimbabwe</td>
<td>9 years</td>
<td>Congenital</td>
<td>-</td>
<td>No reports of complications.</td>
</tr>
<tr>
<td>1998</td>
<td>Argentina</td>
<td>78 days</td>
<td>Congenital</td>
<td>-</td>
<td>No reports of complications.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fetal dropsy; Abnormal cardiotocography; emergency cesarean section; histological of the placenta: villitis with areas of infarction; Apgar 5 and 6 (1' and 5' minutes); Inadequate breathing - Mechanical ventilation; the birth weight of 1550 g.</td>
</tr>
<tr>
<td>2005</td>
<td>Spain</td>
<td>Newborn</td>
<td>Congenital</td>
<td>-</td>
<td>Seroconversion to syphilis during the second trimester with G2P2; Negative first trimester serology for Toxoplasmosis; syphilis, rubella, HIV, Hepatitis B and C. Reported fever and flu-like symptoms in the fourth month of pregnancy.</td>
</tr>
<tr>
<td>2012</td>
<td>Portugal</td>
<td>Newborn</td>
<td>Congenital</td>
<td>-</td>
<td>The baby had an assisted vacuum delivery; Successful</td>
</tr>
</tbody>
</table>
adequate treatment of the pregnant woman and her partner. Immediate resuscitation. Admission exams: non-regent hepatitis B / VDRL / HIV / Rubella. Vaginal delivery with artificial rupture of the membranes showing the presence of meconium-containing fluid; The newborn evolved with fetal and birth bradycardia: weak tone, cyanosis and ineffective respiratory effort. APGAR scores 3 and 8 at (1’ and 5’ minutes). Mechanical ventilation; Administered Surfactant in the first two hours. Normal labor with APGAR scores of 6 and 9 in the 1st and 5th minutes evolving with respiratory effort.

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Age</th>
<th>Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>United States</td>
<td>Newborn</td>
<td>Congenital</td>
<td>No prenatal care. History of precipitated delivery. On admission, maternal ampicillin and acyclovir was administered.</td>
</tr>
<tr>
<td>2022</td>
<td>Indonesia</td>
<td>Newborn</td>
<td>Congenital</td>
<td>Primigravidae with untreated syphilis.</td>
</tr>
<tr>
<td>2022</td>
<td>United States</td>
<td>16 years</td>
<td>Acquired</td>
<td>-</td>
</tr>
</tbody>
</table>

There was a prevalence of males and children younger than one year (CATUENO et al., 2022; LAPUNZINA et al., 1998; SILVA et al., 2012; TAGARRO et al., 2005; WOLF; KALANGU, 1993). Three cases in children aged five to nine years (SMITH; ISRAEL, 1967; WIGGELINKHUIZEN; MASON, 1980; WOLF; KALANGU, 1993) and only one study reported sexually acquired neurosyphilis in an immunosuppressed adolescent with the human immunodeficiency virus (HIV) (HE et al., 2022). Systemic involvement with the digestive and lymphatic system (hepatosplenomegaly), the acute abdomen and skin changes were the findings in common in the newborn group (ISKANDAR et al., 2022; SILVA et al., 2012; SPYDELL, 2018; TAGARRO et al., 2005). However, clinical picture of infants, neurological impairment prevailed.

Irreversible sequelae, such as: visual impairment in a five-year-old child (SMITH; ISRAEL, 1967) and cognitive impairment, memory impairment, social withdrawal, motor impairment was observed in two nine-year-old children (WIGGELINKHUIZEN; MASON, 1980; WOLF; KALANGU, 1993). Immunosuppressed adolescents showed skin manifestations and hearing impairment (HE et al., 2022). In addition, this is the only case that achieved complete reversal of the condition after treatment. In the cases analyzed, the patients had alterations associated with neurosyphilis, such as ventricular abnormalities and high and low density lesions.
(SILVA et al., 2012; TAGARRO et al., 2005), bone changes, cardiac and pulmonary (SPYDELL, 2018; TAGARRO et al., 2005), reinforcing severity and broad systems involvement. Outcomes based on the evaluation performed at the patients' return visit described irreversible sequelae, such as cerebral palsy (SILVA et al., 2012), tendon hyperreflexia and increased tone (TAGARRO et al., 2005). However, two articles did not report clinical changes after treatment (SPYDELL, 2018; WIGGELINKHUIZEN; MASON, 1980), describing only laboratory results with therapeutic response represented by the drop in titers of cell values in CSF.

Diagnoses were based on anamnesis, clinical presentation, treponemal and non-treponemal tests, followed by lumbar puncture. The CSF procedure was performed in all studies. The intravenous crystalline Penicillin G therapeutic regimen was reported in six cases (SILVA et al., 2012; SPYDELL, 2018; TAGARRO et al., 2005; WOLF; KALANGU, 1993), Benzathine Penicillin was applied in three cases (HE et al., 2022; ISKANDAR et al., 2022; SMITH; ISRAEL, 1967) and its route of administration was intramuscular. Only one study mentions the use of Procaine Penicillin with persistently positive serum Venereal Disease Research Laboratory (VDRL) and Treponema Pallidum Hemagglutination (TPHA) tests, but with negative CSF after three months of treatment (WIGGELINKHUIZEN; MASON, 1980). In the congenital cases, maternal and obstetric, patients with late manifestations had little information about pre-and postnatal care. Screening for T. pallidum infection occurred adequately in all cases evaluated. Only one study, whose mother performed prenatal care with identification of the infection and adequate treatment of the pregnant woman and her partner (SILVA et al., 2012). However, the child tested positive after birth and the mother negative at the childbirth. One case of the incomplete prenatal care with intercurrences during pregnancy evolved with an emergency cesarean section was described. In addition, the histological examination of the placenta showed areas of ischemia (TAGARRO et al., 2005).

Three newborns were described whose perinatal data show clinical alterations during and immediately after delivery (ISKANDAR et al., 2022; SILVA et al., 2012; SPYDELL, 2018; TAGARRO et al., 2005), which were described as fetal distress (SILVA et al., 2012; SPYDELL, 2018) and absence of respiratory movements (ISKANDAR et al., 2022; SILVA et al., 2012; SPYDELL, 2018; TAGARRO et al., 2005). The lack of pregnancy follow-up with a previous history of complicated delivery was reported (SPYDELL, 2018) and regarding the other three, it’s not clear that the
follow-up was carried out, but declare the absence of intercurrences in the delivery (LAPUNZINA et al., 1998; SMITH; ISRAEL, 1967; WOLF; KALANGU, 1993). Two cases from rural areas with lack of pre- and postnatal care were described and were diagnosed later (WIGGELINKHUIZEN; MASON, 1980; WOLF; KALANGU, 1993). Within the clinical variability mentioned in hospitalized newborns, there was a predominance of reports with hemodynamic instability, being considered a potential factor in the severity of cases (SPYDELL, 2018; TAGARRO et al., 2005). Neurological, respiratory, dermatological, hematological, muscular, digestive and lymphatic manifestations were frequently described in the table clinical (ISKANDAR et al., 2022; SILVA et al., 2012; SPYDELL, 2018; TAGARRO et al., 2005).

4. DISCUSSION

A study carried with 139 cases of congenital syphilis identified a prevalence of manifestation of neurosyphilis in 23% of children (WOODS, 2005). The involvement of the central nervous system by treponema causes permanent damage (LEITE GASTAL et al., 1999). Developmental delay was present in two cases (SILVA et al., 2012; TAGARRO et al., 2005) diagnosed early in the first year of life. Another study that addressing chronic meningovascular neurosyphilis, which also manifests early, observed symptoms such as cranial nerve palsy and neurodevelopmental regression (WOODS, 2005). An infants, there was a predominance of neurological manifestations, including seizures (LAPUNZINA et al., 1998; WOLF; KALANGU, 1993). During early infancy, ocular alterations with the presence of nystagmus and a negative outcome were described (total absence of visual acuity) (SMITH; ISRAEL, 1967). Convulsive crisis and ocular impairment are commonly related to syphilitic meningitis that is established from early neurosyphilis (MINISTÉRIO DA SAÚDE, 2022; WOODS, 2005).

In early childhood, when there is persistence asymptomatic congenital neurosyphilis that has gone undiagnosed and untreated for years until the appearance of the first signs and symptoms, it is clear that these children have significant definitive psychocognitive alterations such as behavioral changes, gradual intellectual deterioration, reduced school performance, slurred speech and altered gait (WIGGELINKHUIZEN; MASON, 1980; WOLF; KALANGU, 1993). Many of these manifestations are destructive residues of initial lesions and, therefore, are not reversible with antibiotic treatment. It is worth noting that in cases of late manifestations, the
possibility of acquired syphilis should be investigated (DOMINGUES et al., 2021; WOODS, 2005). Although neurosyphilis has a long period of progression before its initial signs, advanced progression is common in immunosuppressed individuals, increasing the risk of developing neurological conditions (GUTIERREZ-GALHARDO et al., 2005).

The CSF procedure was performed in all studies. One investigation (SMITH; ISRAEL, 1967) considered the evaluation of the dark field method to observe the presence of spirochetes in the sample. Another research (TAGARRO et al., 2005) analyzed only the cellular values found in the samples sequentially and periodically, paying attention to the regression of alterations according to the ongoing treatment. On the other hand, six opted for the application of non-treponemal tests (ISKANDAR et al., 2022; LAPUNZINA et al., 1998; SPYDELL, 2018; WIGGELINKHUIZEN; MASON, 1980; WOLF; KALANGU, 1993) and only one case used a treponemal test to confirm the diagnosis (HE et al., 2022). A study conducted based on the measurement of Penicillin in the CSF of patients undergoing treatment demonstrated that Procaine Penicillin resulted in lower concentrations when compared to Crystalline Penicillin levels, justifying the use of Crystalline Penicillin as the first choice in the treatment of patients with congenital neurosyphilis (AZIMI et al., 1994).

When dealing with cases of syphilitic manifestation in pediatric patients, it is necessary to investigate the maternal and gestational history, associating clinical and laboratory evaluation (DOMINGUES et al., 2021). In one case had ischemia in the placenta was observed, and previous studies have indicated that syphilitic infection during pregnancy can lead to lesions in the placenta and umbilical cord veins (SILVA et al., 2012). It is noted that, from an epidemiological perspective, the incidence of neurosyphilis is directly related to the quality of prenatal care (ROEHRS et al., 2020).

A study conducted from July 2017 to December 2017, with parturients admitted to the maternity ward of the University Hospital, in Dourados, Brazil, involving 63 pregnant women diagnosed with syphilis, revealed that 21 of these newborns were born with neurosyphilis (RIBEIRO et al., 2020). According to the 2022 epidemiological bulletin, in Brazil, between 2011 and 2021, only 45.3% of children with congenital syphilis underwent the recommended CSF test for the diagnosis of neurosyphilis (MINISTÉRIO DA SAÚDE, 2022). This indicates an underreporting of neurosyphilis cases in the country, evidenced by the absence of Brazilian publications in this review.
This study had limitations in finding for more robust literature due to the scarcity of publications related to neurosyphilis in the pediatric population. It is encouraged that further research with a high level of evidence is developed to enhance understanding of the complexity of clinical conditions. The scientific theoretical basis is fundamental to stimulate the search for increasingly effective methods in prevention neurosyphilis and reducing the number of undiagnosed and untreated cases during pregnancy. Neurosyphilis, despite being a rare condition, can have serious and irreversible consequences for patients and continues a public health concern. Symptomatic patients at birth exhibited peri- and postnatal complications, as well as neurological manifestations, with significant instability during hospitalization. The majority of children who displayed early neurological signs experienced an unfavorable progression, particularly regarding neuromotor impairment. Late manifestations during school age were predominantly observed within the neurocognitive domain.

The reported cases of neurosyphilis were mostly related to late diagnosis. Evidencing the fragility of prenatal care, which is crucial for prevention and intervention by *T. pallidum* infection causes serious consequences for child development. Therefore, control measures should focus on mandatory prenatal screening during the first trimester of pregnancy, partner notification, prompt treatment and postnatal follow-up of the infant.

5. ACKNOWLEDGMENTS

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Camila Calado Cabral: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing.

Mayara Carolina Cañedo: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing

Luana Rossato: Conceptualization, Data curation, Formal analysis, Writing – review & editing.

Simone Simionatto: Conceptualization, Data curation, Funding acquisition, Project administration, Supervision, Writing – review & editing.