



Review article

A systematic review of pediatric sensorineural hearing loss in congenital syphilis

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ABSTRACT

Introduction: Congenital syphilis is a known cause of progressive sensorineural hearing loss. The prevalence of syphilitic sensorineural hearing loss (SNHL) in childhood is not clearly defined.

Objective: To determine the frequency and characteristics of pediatric SNHL following intrauterine infection with or exposure to *Treponema pallidum* in order to develop evidence-based guidelines for audiologic monitoring.

Data sources: Medline (1950–March 2008), EMBASE (1980–March 2008), CINAHL (1982–March 2008), BIOSIS Previews (1969–March 2008), and Cochrane databases. Manual search of references of identified articles and book chapters.

Study selection: Articles with an inception cohort of children infected with *T. pallidum* during pregnancy, positive serological identification of syphilis infection in the antenatal period or pathognomonic clinical signs of congenital syphilis infection, and longitudinal serial audiologic evaluations to identify the prevalence and progression of SNHL.

Data extraction: Patient information, maternal and infant serologic status, and audiometric data extracted in an independent fashion. Discrepancies resolved through mutual consensus.

Data synthesis: Descriptive statistics.

Results: One prospective cohort study met the inclusion criteria. No cases of SNHL in infants with early congenital syphilis treated with antibiotics in the neonatal period were identified.

Conclusions: There have been no reports of children with confirmed congenital SNHL secondary to *in utero* syphilis infection. Newborns with positive syphilis serology should have hearing screening performed at birth and receive treatment with an appropriate course of penicillin therapy. Longitudinal hearing screening is recommended for all pediatric patients with congenital syphilis, as further studies documenting longitudinal audiometric data for patients previously treated either fully or partly for congenital syphilis are required.

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1. Introduction

Newborn hearing screening programs have been initiated in many countries in an effort to identify hearing loss at an early age [1]. This strategy improves the development of communication skills in the hearing impaired through early intervention. Physicians play a key role in the identification, evaluation and management of these children.

Syphilis exposure in the newborn period is often quoted as a risk indicator for development of sensorineural hearing loss (SNHL). The Joint Committee on Infant Hearing 2007 Position Statement identifies *in utero* syphilis exposure as a risk indicator associated with permanent congenital, delayed-onset, or progressive hearing loss in childhood [2] and review articles on congenital hearing loss quote syphilis as a risk factor for pediatric hearing loss [3–5].

Transplacental vertical transmission of *Treponema pallidum* to the fetus does not appear to occur before the fourth month of pregnancy due to a protective effect of the Langhans' cell layer of the placenta. This cell layer completely atrophies by the sixth month, after which time treponemes in maternal circulation can pass through the placenta and into the fetus [6]. The risk of fetal infection is greatest if the pregnant mother is in the early infectious stages of syphilis infection (primary, secondary, or early latent syphilis stages). Untreated maternal syphilis can lead to spontaneous abortion, stillbirth, premature labour, and intrauterine growth restriction in up to 40% of cases [5]. In the absence of these adverse pregnancy events, there is a 66% transmission rate of syphilis to the fetus in primary, secondary, or early latent maternal syphilis [7,8].

Congenital syphilis has been traditionally divided into early and late stages, based upon the presentation of initial symptoms before or after 2 years of age. An infant with early congenital syphilis may be symptomatic at birth, but more commonly will present in a delayed fashion [6]. The initial symptoms of late congenital syphilis can present anytime from after 2 years of age or into the sixth decade of life. Hutchinson's famous triad linked hearing loss, notched incisors, and interstitial keratitis together as pathognomonic of late congenital syphilis in the 19th century [9]. Two other major clinical signs – mulberry molars and Clutton's joints – are also defined as pathognomonic for infection [10].

The hearing loss seen in late congenital syphilis presenting in childhood is described as a sudden, bilateral, symmetric and profound loss that lacks accompanying vestibular symptoms. In contrast, the hearing loss presentation in adults with late congenital syphilis is also reported as sudden, but typically asymmetric, fluctuating, variable in progression, and often accompanied by tinnitus and vertigo [11]. Differentiation of late congenital syphilis versus acquired syphilis in adults can be difficult to ascertain, as SNHL is also a clinical consequence of acquired syphilis [12].

The incidence of congenital syphilis is increasing in first-world countries [13,14], despite the reality that prevention of congenital syphilis can be achieved in over 98% of cases with penicillin-based regimens [15]. The Center for Disease Control and Prevention recommends that a serologic test for syphilis be performed on all pregnant women at the first prenatal visit, and also at the time of delivery if the mother is at high risk for syphilis [16]. The venereal disease research laboratory (VDRL) and rapid plasma reagin (RPR) tests are nontreponemal tests used for initial screening. These tests typically correlate with disease activity, but are not sufficient for diagnosis alone as false positives can occur with various medical conditions. The fluorescent treponemal antibody absorbed (FTA-Abs), microhemagglutination assay (MHA-TP) and *T. pallidum* particle agglutination assay (TPPA) are treponemal tests specific for syphilis. The treponemal tests tend to remain positive for life

[17]. Infants born to mothers who test positive on nontreponemal and treponemal tests should have a nontreponemal test (VDRL or RPR) performed on infant serum. Umbilical cord blood is not recommended due to the possibility of contamination by maternal blood.

The objectives of this systematic review were to determine the prevalence of immediate and delayed-onset sensorineural hearing loss in pediatric patients diagnosed with congenital syphilis and to determine the characteristics, severity and progression of early congenital syphilitic SNHL if such data existed. The ultimate goal was to develop evidence-based guidelines for audiologic monitoring of children diagnosed with early congenital syphilis infection.

2. Methods

A systematic review of the English literature was performed using an established methodology for systematic reviews [18,19]. Three authors agreed upon a set protocol *a priori* and performed the search independently. The Medline (1950–March 2008), EMBASE (1980–March 2008), CINAHL (1982–March 2008), BIOSIS Previews (1969–March 2008), and Cochrane databases were searched. Cross-references from review articles and book chapters were searched manually.

A set of articles regarding congenital syphilis infections was identified using the combination of the following medical subject heading (MeSH) terms and keywords: syphilis.mp or exp Syphilis, Congenital/or exp Syphilis or Hutchinson's triad.mp or exp Syphilis Serodiagnosis/or VDRL.mp or exp Neurosyphilis/. A second set of articles was retrieved using the terms hearing loss.mp or exp Hearing Loss or sensorineural hearing loss.mp or exp Hearing Loss, Sensorineural or hearing impairment.mp or Hearing disorder\$.mp or exp Hearing disorders or labyrinthitis.mp or exp Labyrinthitis or exp Deafness/or exp Neurosyphilis/or exp Vestibular Diseases/or neuro labyrinthitis.mp or exp Labyrinth Diseases. Relevant studies were identified by combining the two sets of articles, and limiting these to humans and to publications in English.

2.1. Inclusion criteria

1. Prospective longitudinal studies with an inception cohort of children infected with or exposed to *T. pallidum* who were followed over time with serial audiometric evaluation to detect the onset of sensorineural hearing loss, if it developed;
2. adequate audiometric evaluation of all subjects to confirm a sensorineural hearing loss attributable to congenital syphilis, appropriate testing to rule out conductive hearing loss due to nontreponemal etiology, and data supporting efforts taken to exclude other causes of pediatric sensorineural hearing loss;
3. confirmation within the study of congenital syphilis diagnosis based on appropriate serological testing of the cohort of subjects, or the presence of pathognomonic signs of late congenital syphilis infection (Hutchinson's triad). Inclusion of positive serologic results was considered ideal. Clinical signs suggestive of late congenital syphilis was acceptable for inclusion particularly in historical articles, where serologic confirmation may have been incomplete or unavailable.

2.2. Exclusion criteria

1. Editorials, letters, practise guidelines, and consensus development conferences were excluded. Any review articles and book chapters were kept for a review of references. Data was extracted from primary sources only.
2. Any studies with duplicate results presented in multiple publications were excluded. The most recent study with the

longest follow-up was included if study inclusion criteria were met.

3. Studies with incomplete audiometric evaluation from which a frequency thresholds and speech discrimination score could not be determined.
4. Studies with inadequate confirmation of congenital syphilis infection in the neonate or child.

A review of the articles was performed independently by three researchers (JC, SA, EC) instructed or experienced in performance of systematic reviews. Journal titles were reviewed, and articles were included if any researcher felt they were relevant or if it could not be determined if it was irrelevant. Next, the selected abstracts were reviewed using the predetermined inclusion and exclusion criteria. Articles that were considered relevant or of uncertain relevance were then retrieved as full text articles. The full text papers were reviewed independently and studies were either included in the statistical analysis or as articles for discussion. Any discrepancies between researchers were resolved by mutual consensus. As the information available was limited in nature, the data were analyzed using descriptive statistics only.

3. Results

A medical database search identified 86 titles of which 42 abstracts were retrieved, and 30 articles were selected for detailed review. Another 25 articles were identified on cross-reference of

Table 1
Summary of study meeting inclusion criteria.

Author and date	Gleich et al. (1994)
Subjects in study	75
Age at testing	Newborn
Cases with positive serology	100% ^a
Audiometric evaluation	ABR ^b
Percent with hearing loss	0% (0/75) ^c

^a All 75 neonates had a positive FTA-Abs or MHA-TP. 61 of the 75 neonates had a reactive VDRL or RPR.

^b Testing was performed with the subjects in natural sleep. Test stimulus was 0.1 ms rarefaction clicks delivered to a TDH-49 earphone.

^c All ABR's demonstrated symmetric waveforms with normal amplitudes and latencies.

selected full text articles and book chapters, bringing the total number of full text articles reviewed to 55 (Fig. 1). The majority of the additional latter articles did not strictly meet inclusion criteria but were very commonly referenced so were reviewed for information relevant to this review. Preliminary or interim reports of data from subjects included in later studies were excluded to avoid duplication. A full list of reviewed articles is available from the authors upon request.

One study met the inclusion criteria [20]. Seventy-five neonates were born with serologic evidence of congenital syphilis (Table 1). All 75 neonates had positive FTA-Abs or MHA-TP tests, and 61 of the neonates had positive VDRL or RPR tests. All of the neonates had an APGAR score greater than 9 at 5 min postpartum. All underwent ABR click audiometry in the neonatal period as well as

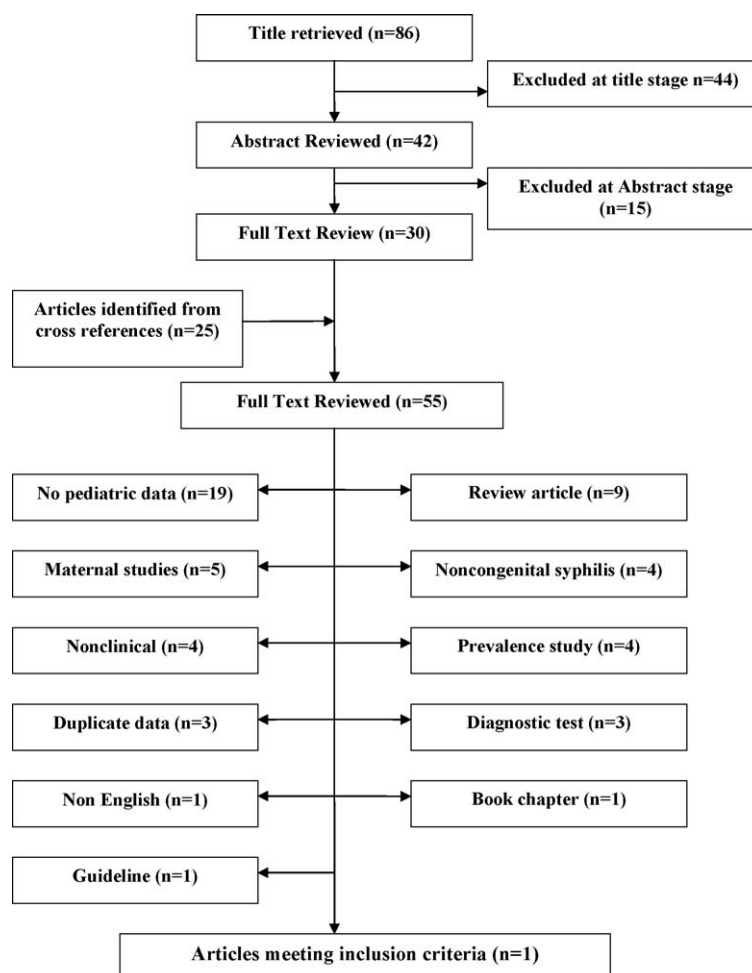


Fig. 1. Summary of systematic literature review.

Table 2
Summary of historical adult late congenital syphilis cohort with pediatric presentation of sensorineural hearing loss.

Study	Publication date	Case series type	Pediatric onset cases ^a	Clinical signs	Serologic tests	Audiometric tests	Prevalence of hearing loss
Tamari	1951	Consecutive	51 of 59	N/A ^b	N/A ^b	PTA, speech, tuning forks	14% (7/50 patients) ^c
Perlman	1952	Selected	5 of 11	Interstitial keratitis, 5/5 pediatric cases	“Serology” ^d	PTA	N/A ^e
Hahn	1962	Selected	4 of 19	Interstitial keratitis, 2/4 pediatric cases	STS, TPI when indicated	PTA, SDT/SDS	N/A ^e
Karmody	1966	Consecutive	15 of 123	N/A ^f	N/A ^f	PTA, SDS	12% (15/123 patients) ^g

^a Tamari’s study identified 59 adult late congenital syphilis patients with a pediatric presentation of hearing loss, defined by 0–10 and 11–20 age range groups. Perlman and Hahn’s studies examined selected adult late congenital syphilis patients with identified ages of noted initial hearing loss. Karmody’s study identified 15 late congenital syphilis patients whose hearing loss started between the ages of 0–10 years.

^b Tamari’s patients presented to otolaryngology with an established diagnosis of syphilis after evaluation by a syphilologist. No patient breakdown on clinical signs or serologic tests used for diagnosis was provided.

^c One pediatric patient was excluded due to a primarily conductive hearing loss.

^d Perlman’s study did not elaborate on what specific serologic tests were performed.

^e Perlman and Hahn’s studies presented selected cases of late congenital syphilis with hearing loss. A pediatric prevalence rate of hearing loss could not be calculated.

^f Karmody’s study did not detail the specific clinical symptoms and signs or serologic testing used to establish the diagnosis of congenital syphilis in their case series.

^g Of the 123 congenital syphilis patients followed, 38% (47 cases) had hearing loss presumably related to infection. Fifteen cases had hearing loss start between the ages of 0–10 years. No data was provided for the 11–24 years age range.

an ophthalmology examination. All of the infants demonstrated symmetric waveforms with normal amplitudes and latencies. No frequency specific audiometric assessments were performed such that some degree of SNHL could have been missed. Ophthalmologic examination revealed no evidence of interstitial keratitis or other abnormalities. All 75 neonates were then treated with procaine penicillin 100,000 units per kg per day for 10 days. No follow-up data for this patient cohort were presented.

A number of studies predating the introduction of the treponeme specific tests in the 1960s were reviewed [21–23,11]. These studies identified congenital syphilis patients whose hearing loss was diagnosed in childhood, but did not provide explicit data regarding the age of onset and characteristics of the pediatric hearing loss. The studies were excluded due to incomplete audiometric, clinical, or serologic data (Table 2), but are mentioned because they provide a historical perspective that has influenced modern management of congenital syphilis and warrant further discussion.

Hahn et al. followed 19 patients with congenital syphilis diagnosed by clinical examination, early serologic tests (serologic test for syphilis and *T. pallidum* immobilization tests), and serial audiometric testing to examine the potential benefits of prednisone on neural deafness [21]. Four adult cases with onset of hearing loss during childhood are reported; however, the article failed to provide complete serial audiometric data, serologic confirmation of syphilis infection, or clinical evidence of infection during the pediatric time period.

Perlman and Leek described a case series of patients with suspected late congenital syphilis [22]. Eleven cases are briefly discussed, with five of the cases reporting onset of hearing loss during childhood. The five cases were all evaluated in adulthood; none of the audiometric, clinical, and serologic data presented assessed these patients during childhood or adolescence.

Tamari and Itkin examined 310 patients with a confirmed syphilis diagnosis that were referred to an otolaryngology clinic for audiologic evaluation [23]. After identifying demographic data and stage of clinical presentation, the prevalence of hearing loss distributed by decade was detailed. The article established a prevalence of 14% for patients with late congenital syphilis presenting with hearing loss between the ages of birth to 20 years. The study did not comment as to whether or not other causes of SNHL were excluded in their study population.

A study by Karmody and Schuknecht is often quoted in the literature in regards to the prevalence of hearing loss in congenital syphilis and the characteristic patterns of pediatric and adult

hearing loss [11]. The article did not provide specific serologic or clinical criteria regarding how the diagnosis of congenital syphilis was established. Of 123 congenital “luetic” cases documented by the authors over a 22-year period, 47 adult syphilis patients were found to have SNHL, identifying a prevalence of 38%. Fifteen patients (12%) with hearing loss developed symptoms of their hearing loss in childhood before the age of 10. Only partial audiometric results were presented, including a total of eight audiograms as well as both speech discrimination and caloric measurements for one patient. Complete audiometric data on the 15 patients who developed hearing loss in childhood was not provided.

4. Discussion

The natural history of syphilitic hearing loss in the pediatric age group is not well established. A number of articles identified patients with late syphilitic hearing loss that originated in childhood; only one article provided meaningful data. Our significant number of cross-referenced studies reflected a number of frequently cited articles identified during the full text article reviews. None of the cross-referenced articles provided meaningful audiometric data, but were beneficial in determining the history of syphilis in pregnancy and its current management strategies.

The only study that performed audiometric testing on a cohort of serologically confirmed infants with congenital syphilis reported that none of the 75 children had evidence of hearing abnormalities during the neonatal period [20], nor did they have evidence of ophthalmologic abnormalities suggestive of interstitial keratitis. All were treated with a penicillin regimen in keeping with the recommended therapeutic guidelines established by the Center for Disease Control and Prevention [16]. Unfortunately, no further longitudinal audiologic testing data were presented on this cohort, data that would have served to estimate the prevalence of delayed-onset hearing loss in children treated for congenital syphilis.

The introduction of penicillin had a profound impact on the morbidity caused by syphilis infection. The positive effects of antibiotic treatment for syphilis were so significant that a marked change in disease management occurred without evidence from controlled trials that are common in current medical research. Historical literature documenting the clinical course of patients with congenital syphilis from the pre-antibiotic era aids our understanding of the otologic sequelae from untreated late

congenital syphilis. However, these data offer little towards furthering our understanding of the clinical course of children with congenital syphilis treated with recommended antibiotics. With effective and appropriate screening programs, maternal and neonatal syphilis infections can be identified and treated early, avoiding significant future morbidity.

Hutchinson's original 19th century study identified the triad of interstitial keratitis, notched incisors, and hearing loss as the three most common clinical signs of late congenital syphilis [9]. The identification of one or more signs of Hutchinson's triad was considered to be pathognomonic for congenital syphilis infection for many decades. Fiumara and Lessell performed a prevalence study examining the presenting clinical signs of 271 patients with congenital syphilis [10], which identified Clutton's joint and mulberry molars as additional pathognomonic signs of congenital syphilis; sensorineural hearing loss was always present with other stigmata of syphilis infection. The establishment of serologic tests for syphilis decreased the reliance on clinical signs for the diagnosis of syphilis. The FTA-Abs test has a reported sensitivity and specificity of 100% and 98%, and has been found to have a positive predictive value 11 times higher than in the general population when applied to a patient with suspected syphilis and otologic symptoms [24]. No studies have correlated clinical signs and serologic testing in the diagnosis of congenital syphilis, impeding the interpretation of earlier reports.

The prevalence of SNHL in late congenital syphilis has been reported over a wide age range. This makes a recommendation for pediatric hearing screening at or up to a specific age difficult. Karmody's study reported 12% of children developed hearing loss from birth to 10 years of age secondary to late congenital syphilis, but did not report any pediatric audiometric data [11]. Fiumara's study reported hearing loss in only 3.3% of 271 adult patients with late congenital syphilis, but lacked data regarding onset, severity, and progression of hearing loss in a pediatric age range [10]. Tamari's study identified a childhood and adolescent prevalence of 14% for late congenital syphilitic hearing loss [23]. Despite the varying ranges of reported pediatric hearing loss, the majority of these patients had evidence of pre-existing symptoms of late congenital syphilis and will not have been treated with recommended antibiotics. Further research should focus on prospective, serial, longitudinal surveys of children with congenital syphilis with documentation of clinical signs, serologic findings, treatment received and audiometric data over time.

Congenital syphilis is a preventable and treatable disease entity. Established cases of syphilitic hearing loss have proven to be negatively responsive to therapeutic intervention [12,25]. Thus, early management of suspected cases of congenital syphilis should be aggressively pursued. Routine maternal prenatal screening and treatment for pregnant women with serologic confirmation or with overt clinical signs of infection has a significant chance of preventing maternal–fetal transmission [15]. Prompt investigation of infants born to high-risk mothers or with suspicious clinical signs suggestive of syphilis infection is recommended. Recommended treatment regimens with penicillin G are influenced by presenting clinical signs, serologic status, and maternal treatment status [16]. Failure of maternal treatment for syphilis in pregnancy has been documented in the literature [26,27] so continued follow-up, investigation, and therapeutic intervention for both the mother and child should be pursued as clinically indicated.

The JCIH 2007 Position Statement recommends repeat audiologic testing between the ages of 24–30 months for any infant with a risk factor for hearing loss [2]. Thus, using this recommendation and the limited data available in the literature, some evidence-

based guidelines for audiometric monitoring of children with early congenital syphilis can be developed:

1. All infants born with congenital syphilis should have hearing screening performed at birth if not performed under a neonatal hearing screening program. There is no data that would suggest they be screened using a different protocol than other well babies. This recommendation should be re-evaluated if further longitudinal data from other studies becomes available. All neonates should receive a full course of penicillin G based upon current recommended treatment guidelines.
2. All children with confirmed syphilis serology at birth who have received appropriate neonatal antibiotic treatment should have a repeat hearing screening performed at least once further by 24–30 months of age. Acquisition of further data in support of lack of development of delayed-onset SNHL in this patient group may ultimately make this further testing unnecessary.
3. All children with confirmed syphilis on serological testing who did not receive appropriate neonatal antibiotic treatment should have on going audiological monitoring at least on an annual basis. The influence of partial and/or late antibiotic treatment on the subsequent development of SNHL is unknown.
4. No cases of progressive or delayed-onset hearing loss in children with previously normal testing have yet been conclusively identified. The development of delayed-onset or progressive hearing loss in children with congenital syphilis should be reported, including age of onset, severity of hearing loss, presence of other clinical signs, treatment regimen, and exclusion of other causes of hearing loss.

5. Conclusions

There have been no reports of children with confirmed congenital SNHL secondary to *in utero* syphilis infection. Newborns with positive syphilis serology should have hearing screening performed at birth and receive treatment with an appropriate course of penicillin therapy. Longitudinal hearing screening is recommended for all pediatric patients, with congenital syphilis, as further studies documenting longitudinal audiometric data for patients with either full or partial previous treatment for congenital syphilis are required.

Conflict of interest

All authors disclose they have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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