Syphilis and Hearing Loss

43

Tarik Yagci, Rıza Dündar, and Chae-Seo Rhee

43.1 Introduction

The nineteenth century physician, Hutchinson, was the first to describe the conjunction of three congenital abnormalities frequently found in cases of congenital syphilis. This so-called Hutchinson's triad consists of interstitial keratitis, notching of the incisor teeth and deafness [1]. Congenital syphilis was diagnosed by the presence of one or more elements of the triad for many years. A study involving 271 cases of congenital syphilis undertaken by Fiumara and Lessell identified the other highly significant clinical manifestations of the disorder. Symmetrical hydrarthrosis of the knee joints and mulberry molars were noted to be further features of pathognomonic significance [2]. Where the other manifestations of the condition were present, sensorineural auditory impairment was invariable. More recently, serological screening for syphilis has meant clinical signs are less essential in establishing the diagnosis. It has been reported that the fluorescent treponemal antibody test (FTA-Abs) is 100% sensitive and 98% specific. In cases where there is already known to be auditory impairment and a clinical suspicion of syphilis exists, this test has an 11-fold increase in the ability to predict congenital syphilis, compared to its use in the general population [3]. However, no study has so far examined the relationship between the stigmata of congenital syphilis and serological status, which makes assessment of the findings of older studies challenging [4].

T. Yagci (✉) · R. Dündar
Department of Otorhinolaryngology, Faculty of Medicine, Bilecik Şeyh Edebali University, Bilecik, Türkiye
e-mail: tarikyagci43@gmail.com; dundarkbb2@gmail.com

C.-S. Rhee
Department of Otorhinolaryngology, Head and Neck Surgery, College of Medicine, Seoul National University, Seoul, South Korea
e-mail: csrhee@snu.ac.kr

A. E. Arısoy et al. (eds.), *Hearing Loss in Congenital, Neonatal and Childhood Infections*, Comprehensive ENT, https://doi.org/10.1007/978-3-031-38495-0_43

43.2 Pathophysiological Features

Syphilis is the term used to describe infection by the spirochaetic bacterial organism known as *Treponema pallidum*. The name for this genus, i.e. *Treponema*, is derived from Greek τρέπω (trépō = turn) and νῆμα (nēma = thread), and translates as "turning thread". Some other members of the *Treponema* genus are also capable of causing disease, namely *T. pertenue* and *T. carateum* [5].

T. pallidum as the pathogen responsible for syphilis was identified in 1905 by Schaudinn and Hoffman. Then, in 1906, Wassermann introduced a laboratory diagnostic test to confirm cases of symphilis.

The pathogenic members of the *Treponema* genus cause four specific diseases, as follows [5]:

- The sexually transmitted form of syphilis, due to infection by *T. pallidum pallidum*
- Yaws, resulting from infection with *T. pertenue*
- Bejel, a non-sexually transmitted, endemic form of syphilis resulting from infection by *T. pallidum endemicum*
- Pinta, an infection with *T. carateum*

The natural history of untreated syphilis involves three characteristic phases or stages. Once infected, the individual remains infected for life unless successfully treated. The spirochaete invades across mucous membranes or the skin, after which it divides rapidly and is able to disseminate around the body. Spread occurs via the perivascular lymphatic vessels, followed by the bloodstream, prior to manifestation of the clinical features of the primary lesion. The primary lesion is apparent some hours after transmission and is present in the first and second stages of the disorder. Within the lesion, there are numerous infective spirochaetes [5].

The secondary lesion occurs as a result of the immune system's response to the presence of the bacterium in tissues derived from the embryonic ectoderm. These tissues include the central nervous system, mucosae, and skin. The point at which this occurs is between 6 and 12 weeks after inoculation. During this phase of the disease, the bacteria rapidly divide and may become disseminated throughout the whole body. Accordingly, the final, tertiary, stage of syphilis may be observed in any of the organs of the body [5].

Between 1 and 2 months after the secondary lesion appears, it enters a latent stage. For the first year after this occurs (termed the first year of latency), the lesions may become symptomatic again. This recurrence of secondary lesions can only be seen in the first year of latency. Beyond this point, the disease may take two forms: late latent, in which no symptoms are apparent, or tertiary syphilis, in which symptoms do appear. In cases of late latent syphilis, reinfection or relapse are both uncommon [5].

There are a number of different presentations associated with tertiary syphilis. Meningeal syphilis is an uncommon presentation, which may be seen some years after the initial inoculation. A focus of ischaemic damage or a cerebrovascular

accident may result from neurosyphilis at the late stage, since it causes endarteritis in the small calibre cerebral blood vessels. In meningovascular syphilis, any portion of the brain and spinal cord may be involved. Loss of cortical neurones presents as various mental disorders and abnormal neurological findings [5].

For congenital syphilis to occur, the spirochaete must cross the placental barrier. In mothers who have primary or secondary syphilis and remain untreated, there is a 90% risk of this occurring. The foetus may become infected at any point in the pregnancy. Early presenting congenital syphilis presents up to the age of 2 years. Thereafter, if congenital syphilis presents, it is considered late-presenting. The US Centres for Disease Control and Prevention state that syphilis which remains without treatment in pregnant women, particularly first stage syphilis, may cause auditory impairment, neurological abnormalities, abnormal development of osseous tissues, stillbirth, or death of the newborn child [6]. Congenital neurosyphilis may mimic non-accidental injury in its features, causing diagnostic confusion [7].

Infection with *T. pallidum* does not cause abnormalities in organogenesis, since foetal inflammatory responses are not seen before the second trimester, by which point the organs have already formed. However, syphilis can affect any organ or system in the foetus. In cases where infection occurs at an early stage, the presentation is similar to that seen in the second stage of acquired syphilis, since the foetus is reacting to the dissemination of the bacterium across the placental barrier. There is no primary stage defined for congenital syphilis. If congenital syphilis presents in a child above the age of 2 years, it is classified as late-onset. These patients cannot transmit the disease, usually [5].

43.3 Aetiology

Syphilis occurs secondary to infection by the spirochaetic organism, *T. pallidum*. There are two usual modes of transmission, either via the placenta in an infected mother or through sexual contact, but the infection may also occur through contaminated blood or tissues [5].

There are two possibilities for syphilis to occur in a child patient, i.e. congenitally by the bacterium crossing the placental barrier, or as an acquired infection through sexual contact. There is a risk of 50–80% or more of vertical transmission of infection if early syphilis occurs during pregnancy [5].

43.4 Prognosis

Provided treatment occurs early enough and is correctly administered, the majority of cases have an excellent prognosis. Nonetheless, in HIV+ individuals, there is a high risk that syphilis will resist treatment, as indicated by serology. Indeed, the majority of HIV+ patients either do not respond at all or respond insufficiently to treatment of syphilis [5].

43.5 Diagnosis

43.5.1 Serological Investigations

Since the way syphilis presents clinically varies widely, serological investigations play a key part in establishing the correct diagnosis. *T. pallidum* fails to grow on artificial culture media and is not demonstrable by staining with the usual laboratory methods, hence serology plays a major role in confirming the diagnosis and assessing the extent to which the patient responds to antibiotics [5].

There are two kinds of serological investigation suitable for investigating syphilis—the non-treponemal reaginic tests and tests which are specific to treponemal organisms. A positive outcome to the first type calls for verification by the second. The patient may, if clinically necessary, begin treatment prior to confirmatory testing [5].

43.5.2 Non-treponemal Reaginic Serological Testing

The two most common non-treponemal reaginic tests used in routine screening are the rapid plasma reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) tests. They benefit from comparable sensitivity, have low associated cost, are straightforward to undertake, and give a quick answer. This type of test is also valuable in assessing how the patient responds to treatment or to see if reinfection has occurred [5].

Non-treponemal reaginic tests quantify immunoglobulins which target either a lipid-containing antigen that is formed as a result of infection or the bacterial antigens themselves. The immunoglobulins of non-specific type are present between 1 and 2 months after inoculation occurs [5].

In 70% of cases, there are immunoglobulins against the pathogen formed under a fortnight after a chance appears and in all cases of secondary or latent syphilis, the serum contains anti-treponemal antibodies. Testing may be falsely negative if undertaken too soon in primary syphilis, during latent acquired syphilis that has lasted a long time, or in the late congenital form of the disease [5].

The titres obtained in serological testing closely match how actively syphilis is progressing, hence they are especially useful for screening purposes. As early syphilis develops, there is an accompanying quadruple or greater elevation in titre. There is invariable positivity in cases of secondary syphilis and the titre is frequently markedly raised, such as 1:32, or higher [5].

There is a 2% risk of false negativity, particularly in cases of secondary syphilis or in pregnant women, due to a prozone phenomenon, whereby a very elevated immunoglobulin concentration in non-diluted test serum can prevent visualisation of a positive test reaction. If there is a clear clinical suspicion of syphilis, such as an infant bearing the stigmata of congenital syphilis, even though serological testing of the mother was apparently negative, the sample will need to be diluted before re-performing the test, in order to exclude the occurrence of the prozone effect [5].

The results of the quantitative serological tests, RPR and VDRL, are generally negative a year after successful eradication of primary syphilis, 2 years after eradication of the infection in secondary or congenital syphilis, and 5 years after adequate treatment of late syphilis. Before negative serology occurs, an ongoing reduction in titre of 75% is evidence of successful treatment. Likewise, if the titre again rises fourfold, the explanation is likely to be either relapse or re-infection, in which case the clinical management will require revision [5].

False positivity of non-treponemal serology may occur when the antigen to which the test responds is present in other tissues. Serological negative occurring under 6 months indicates an acute case, while if seronegativity does not occur within this window, the case is considered chronic. In acute cases, false-positivity potentially arises from other acute events involving the immune system, such as an acute infection with a different bacterium or virus, vaccination, or the early stages of infection with human immunodeficiency virus [5].

False positivity may also occur in chronic syphilitic infections. In such cases, the cause may be intravenous drug administration, autoimmune and connective tissue disorders (in particular, systemic lupus erythematosus), the effects of old age, or hypergammaglobulinaemia. The employment of tests specific for treponemal antigens is generally sufficient to discover whether false positivity has actually occurred [5].

43.5.3 Specific Anti-Treponemal Testing

Specific anti-treponemal tests quantify immunoglobulins targeting *T. pallidum* directly, such as *T. pallidum* immobilisation (TPI), fluorescent treponemal antibody absorption (FTA-Abs), or *T. pallidum* particle agglutination (TPPA). Whenever a non-treponemal reaginic test returns positive, a specific anti-treponemal test should be performed to exclude false positivity [5].

Specific anti-treponemal testing is positive not only in syphilis, but also in other conditions where spirochaetes are involved, namely yaws, pinta, leptospirosis, rat-bite fever, relapsing fever, and Lyme disease. In the latter case, VDRL should have been negative [8].

Seroreactivity on these tests can be demonstrated shortly after infection occurs and, generally speaking, the tests will remain positive for the patient's whole life, even where the spirochaete has been successfully eradicated. There is no relation between this type of serological positivity and how active syphilis is, and the results are not given quantitatively [5].

Immunoglobulin M specific to *T. pallidum* can be measured. At present, polymerase chain reaction amplification of the bacterial DNA is not offered by many laboratories [5].

43.6 Congenital Syphilis

Neonatal exposure to syphilis has frequently been cited as a potential aetiology for deafness of sensorineural type. The Joint Committee on Infant Hearing 2007 Position Statement considers vertically transmitted syphilis to be a risk factor for irreversible congenital, late-onset, or progressive auditory impairment in children [9]. Several review articles focusing on congenital auditory impairment identify syphilis as an aetiological factor in deafness in children [10–12].

It seems that the foetus cannot contract syphilis until the beginning of the second trimester, as the cytotrophoblastic cells form an impenetrable barrier to invasion by *T. pallidum* up to that point. By the sixth month of the pregnancy, the cytotrophoblastic cells are atrophic and no longer prevent the spirochaete from crossing the placental barrier [13]. There is a correlation between the stage of maternal syphilis and the risk of vertical transmission, with the earlier stages (i.e. primary, secondary, or early latent) presenting the greatest danger to the foetus. If the mother is not treated for syphilis, there is an up to 40% risk of miscarriage, stillbirth, premature delivery, or intrauterine growth restriction [12]. In cases where these adverse outcomes do not occur, the rate of vertical transmission in maternal early stage syphilis is 66% [4, 14, 15].

By tradition, the second birthday has been chosen as the point dividing cases of congenital syphilis into early or late-presenting. Neonates with early congenital syphilis may exhibit the stigmata of disease at birth, but the clinical manifestations usually appear somewhat later [13]. The first manifestations of the late-presenting variant of syphilis may appear at any point after the second birthday, right up to when the patient is in his or her 50s. In the 1800s, diagnosis of late congenital syphilis depends on the presence of Hutchinson's triad, namely deafness, notching of the incisors, and interstitial keratitis. The conjunction of these three features is pathognomonic [1]. There are a further two major clinical findings which have a similar pathognomonic status, i.e. the presence of mulberry molars and symmetrical hydroarthrosis [2, 4].

43.7 Pathogenesis

From the beginning of congenital syphilis, the spirochaetic bacterium, *T. pallidum*, is already present in the foetal bloodstream, which means that it can be disseminated into virtually every organ of the foetus. The clinical features arise due to the immune response to this event. Damage to the following organs is the most common and of the highest severity: osseous tissues, liver, pancreas, gut, kidneys, and spleen. The degree of abnormality induced by the disease in different organs may vary considerably, from cases where organ injury is evident only on laboratory or radiological investigations, to fulminant cases with multi-organ damage. Overt indications that the child is infected may be noted in utero, neonatally, or, if treatment has not been administered, at a later stage in childhood [8, 16].

43.8 Clinical Findings

By convention, early congenital syphilis is applied to cases where the stigmata of disease are apparent before the child's second birthday [17]. In the absence of treatment, the clinical features are usually apparent before the age of 3 months, with the peak incidence being before the age of 5 weeks [17, 18].

Between around 60% and 90% of live newborn infants who are affected by congenital syphilis exhibit no signs of the disease at the time they are born [19, 20]. The degree to which physical findings are apparent at birth is influenced by when in the pregnancy the infection was transmitted and what treatment was administered [21]. For infants who do manifest signs, the most frequently occurring findings are the following [16, 19, 22]:

- Hepatomegaly
- Icterus
- Rhinorrhoea (referred to as "snuffles")
- Exanthem
- Tender, enlarged lymph nodes at multiple body sites
- Anomalous development of the skeleton

43.9 Congenital Syphilis and Deafness

The auditory impairment associated with late congenital syphilis, when it presents during childhood, has the following characteristics: acute onset; affects both ears equally; and is profound. There are no associated symptoms of vestibular involvement. This presentation differs from when the condition presents in adulthood, when the associated characteristics are an acute onset (as in children) but usually asymmetrical, of varying intensity, progressing variably, and with frequent symptoms of tinnitus and vertigo [23]. It may be challenging to distinguish between cases where the infection was acquired after birth or before birth, since sensorineural-type auditory impairment is a feature of both types of syphilis [24].

There are data available on how common sensorineural auditory impairment is, but the age ranges involved are sufficiently wide that specific recommendations for when auditory screening should be performed are challenging to make. In a study by Karmody [23], a prevalence for deafness of 12% was reported. The group studied included children with late congenital syphilis and covered the range from birth up to the tenth birthday. According to a study authored by Fiumara, among 271 adults affected by late congenital syphilis, the prevalence of auditory impairment was no higher than 3.3%. However, the study did not report when deafness began, how severe it was, or how it progressed while the patients were still children [2]. According to Tamari [25], the frequency of auditory impairment secondary to late congenital syphilis is 14% in childhood and adolescence. Although the reported data categorised cases using different age ranges, which complicates interpretation, what is clear is that most of the cases of late congenital syphilis reported already had

stigmata of the disease and appropriate treatment had not been undertaken. In the future, studies that employ a prospective design, using serial observations and thus obtaining a longitudinal perspective, will be called for. Besides the diagnosis of congenital syphilis, other data needed for a fuller understanding of the condition will include clinical findings, any serological results, details of pharmacotherapy, and serial audiometric observations.

43.10 Pharmacotherapy

43.10.1 Treating Syphilis in Pregnant Women

Penicillin may be used in any case of syphilis occurring during pregnancy, during all three trimesters [26, 27]. The antibiotic is administered intramuscularly once every week for 3 weeks. The form used is benzathine penicillin at a dose of 2.4 million U each time. A meta-analysis which examined outcomes in pregnant women administered penicillin found that this dosage caused a 97% fall in cases of clinically detectable congenital syphilis, 82% fewer stillbirths, 64% less premature delivery, and 80% reduction in fatal outcomes during the newborn period [5].

There is, unfortunately, no treatment of equal proven efficacy to penicillin for use in patients with an allergy to penicillin. Erythromycin does not consistently prevent congenital syphilis in the same way as penicillin [5].

The penicillin allergy should be confirmed as genuine by demonstrating a wheal and flare on the skin in response to exposure to penicilloyl-polylysine or penicillin G minor determinant mixture. If the allergy is confirmed, the patient will need to be admitted to hospital for a course of desensitisation, so that penicillin treatment of syphilis can go ahead. The Centres for Disease Control and Prevention have issued specific recommendations for this situation [5].

43.10.2 Congenital Syphilis in Neonates

Penicillin G (aqueous or procaine) should be administered for between 10 and 14 days in all cases of congenitally acquired syphilis in neonates, regardless of whether diagnostically confirmed or not. If there is a high degree of clinical suspicion of the disorder or the diagnosis has been confirmed by testing, the use of aqueous crystalline penicillin G is advised. The dose to use is based on chronological age, without factoring in gestational age [5].

The recommendation is for a total daily dose of between 100,000 and 150,000 U/kg, divided into twice or three times daily and lasting 10–14 days. Although some experts advocate the use of procaine penicillin G at a dose of 50,000 U/kg administered intramuscularly, this agent suffers from the major disadvantage that the concentration in cerebrospinal fluid is inconsistent and may be too low for eradication of the spirochaete.

The following points provide evidence to support the diagnosis of congenital syphilis [5]:

- The physical examination or imaging investigations indicate activity of the infection
- On serological testing on non-treponemal type, the titre is a minimum fourfold above that recorded in the mother
- The VDRL test on cerebrospinal fluid is positive; there is leucocytosis or the protein content is abnormally elevated
- There is positivity of immunofluorescence tests for anti-treponemal IgM or of FTA-Abs
- Darkfield microscopy reveals spirochaetes, or treponemal organisms can be demonstrated by staining in placental or umbilical tissues

43.10.3 Congenital Syphilis in Older Infants and Children

For infants above the age of 4 weeks with a diagnosis of congenital syphilis, the treatment consists of aqueous crystalline penicillin (200,000–300,000 U/kg/day, administered intravenously q.d.s as a divided dose, with the course lasting between 10 and 14 days) [5].

References

1. Hutchinson J. A clinical memoir on certain diseases of the eye and the ear consequent to inherited syphilis. London: John Churchill; 1863. p. 174–83.
2. Fiumara NJ, Lessell S. Manifestations of late congenital syphilis. An analysis of 271 patients. Arch Dermatol. 1970;102:78–83.
3. Hughes GB, Rutherford I. Predictive value of serologic tests for syphilis in otology. Ann Otol Rhinol Laryngol. 1986;95:250–9.
4. Chau J, Atashband S, Chang E, Westerberg BD, Kozak FK. A systematic review of pediatric sensorineural hearing loss in congenital syphilis. Int J Pediatr Otorhinolaryngol. 2009;73(6):787–92.
5. Waseem M. Pediatric syphilis. In: Steele RW, editor. Medscape; 2018. Updated: Apr 18, 2018. https://emedicine.medscape.com/article/969023-overview. Accessed online 26 Sept 2022.
6. Triemstra J, Reno K, Chohlas-Wood R, Nash C. A brief resolved unexplained event and congenital neurosyphilis. Pediatr Ann. 2017;46(2):e61–4.
7. Hérissé AL, Chiaverini C, Hubiche T, Tran A, Rondel J, Rosello O, et al. Non-accidental injury or congenital infection? Arch Dis Child. 2017;102(9):852.
8. Christian CW, Lavelle J, Bell LM. Preschoolers with syphilis. Pediatrics. 1999;103:E4.
9. Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention. Pediatrics. 2007;120:898–921.
10. Roizen NJ. Nongenetic causes of hearing loss. Ment Retard Dev Disabil Res Rev. 2003;9:120–7.
11. Brookhouser PE. Sensorineural hearing loss in children. Pediatr Clin N Am. 1996;43:1195–216.
12. Bale JF Jr. Congenital infections. Neurol Clin. 2002;20:1039–60.
13. Ingall D, Dobson SRM, Musher D. Syphilis. In: Remington JS, Klein JO, editors. Infectious diseases of the fetus and newborn infant. 3rd ed. Philadelphia: WB Saunders Co.; 1990. p. 367–94.

14. Hollier LM, Harstad TW, Sanchez PJ, Twickler DM, Wendel GD Jr. Fetal syphilis: clinical and laboratory characteristics. Obstet Gynecol. 2001;97(6):947–53.
15. Mascola L, Pelosi R, Alexander CE. Inadequate treatment of syphilis in pregnancy. Am J Obstet Gynecol. 1984;150:945–7.
16. Dobson SR. Congenital syphilis: clinical features and diagnosis. In: Kaplan SL, Weisman LE, Armsby C, editors. UpToDate. Last updated: Mar 26; 2021.
17. Dobson SR, Sanchez PJ. Syphilis. In: Cherry JD, Harrison GJ, Kaplan SL, et al., editors. Feigin and Cherry's textbook of pediatric infectious diseases. 8th ed. Philadelphia: Elsevier Saunders; 2019. p. 1268.
18. Herremans T, Kortbeek L, Notermans DW. A review of diagnostic tests for congenital syphilis in newborns. Eur J Clin Microbiol Infect Dis. 2010;29:495.
19. Bowen V, Su J, Torrone E, et al. Increase in incidence of congenital syphilis - United States, 2012–2014. MMWR Morb Mortal Wkly Rep. 2015;64:1241.
20. Ortiz-Lopez N, Diez M, Diaz O, et al. Epidemiological surveillance of congenital syphilis in Spain, 2000–2010. Pediatr Infect Dis J. 2012;31:988.
21. Woods CR. Syphilis in children: congenital and acquired. Semin Pediatr Infect Dis. 2005;16:245.
22. Rawstron SA, Hawkes SJ. Treponema pallidum (Syphilis). In: Long SS, Pickering LK, Prober CG, editors. Principles and practice of pediatric infectious diseases. 4th ed. Edinburgh: Elsevier Saunders; 2012. p. 941.
23. Karmody CS, Schuknecht HF. Deafness in congenital syphilis. Arch Otolaryngol. 1966;83:18–27.
24. Becker GD. Late syphilitic hearing loss: a diagnostic and therapeutic dilemma. Laryngoscope. 1979;89:1273–88.
25. Tamari MJ, Itkin P. Penicillin and syphilis of the ear. Part I. Eye Ear Nose Throat Mon. 1951;30:252–61.
26. Rac MW, Bryant SN, McIntire DD, Cantey JB, Twickler DM, Wendel GD Jr, et al. Progression of ultrasound findings of fetal syphilis after maternal treatment. Am J Obstet Gynecol. 2014;211(4):426.e1–6.
27. Kahn JG, Jiwani A, Gomez GB, Hawkes SJ, Chesson HW, Broutet N, et al. The cost and cost-effectiveness of scaling up screening and treatment of syphilis in pregnancy: a model. PLoS One. 2014;9(1):e87510.