NEUROSYPHILIS IN THE NETHERLANDS THEN AND NOW

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Neurosyfilis in Nederland: toen en nu

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CHAPTER 1

GENERAL INTRODUCTION

A woodcutting attributed to Albrecht Dürer (1495). This woodcutting depicts a mercenary whose face and body are covered with multiple pustules due to syphilis.
Source: https://i.redd.it/harxv7q34ef01.jpg

HISTORICAL CONSIDERATIONS

Syphilis

The first descriptions in Europe of a disease that we now mention syphilis date back to the late 15th century, a period when this infectious process became epidemic (Pérez-Trullén et al., 2015). Several theories have been proposed to explain this epidemic (Tampa et al., 2014; Pérez-Trullén et al., 2015). The Columbian hypothesis states that syphilis was carried from America to Europe by Columbus' crew, and subsequently to Naples by both sailors and mercenaries. From there, syphilis spread across Europe (Berger and Dean, 2014; Pérez-Trullén et al., 2015). The pre-Columbian hypothesis proposes evolution of the causative agent of syphilitic diseases, *Treponema pallidum (T. pallidum)*, from the non-venereal treponematoses (yaws and bejel) already existing in Europe (Crosby, 1969; Tampa et al., 2014; Pérez-Trullén et al., 2015). The unitarian hypothesis advocates that the treponemal diseases have always had a global distribution (Tampa et al., 2014).

The first recorded European outbreak of the disease, occurred in 1494 or 1495 in Naples, Italy, during a French invasion (Crosby, 1969). Initially, the people of Naples called it the "French disease", since French troops were considered to have caused the spread of the disease (Crosby, 1969). At the time, the early stages of the disease were associated with mortality rates of 25% and more (Berger and Dean, 2014). Of all the miseries visiting Europe in his lifetime, philosopher/humanist Desiderius Erasmus (1466, 1467 or 1469 –1536) judged few more horrible than the "French disease" (Crosby, 1969). Engelbrecht II (1451-1504), a great-uncle of William of Orange, died shortly after the outset of the syphilis epidemic and probably was one of the first victims in the area that is now known as the Netherlands. The extensive deviations of his bones were typical of the treponematoses and characteristic of tertiary stage syphilis (Maat et al., 1997).

Francisco Lopez de Villalobos (1473-1549) published the first book on the illness, *El Sumario de la Medicina con un Tratado sobre las pestiferas Bubas*, in 1498 (Berger and Dean, 2014). In 1530 the Veronese physician and author Girolamo Fracastoro (1483-1553) published a Latin poem entitled "Syphilis, sive Morbus Gallicus" ("Syphilis, or the French disease"), describing the ravages of the disease in Italy (Berger and Dean, 2014). The name Syphilis is a Latinized form of ancient Greek Σύφιλος (Sýphilos), which can be translated as (σῦς (sŷs) pigs φιλεῖν (philéin) lover. Fracastoro used the term "syphilis" again in his medical treatise *De Contagione*, published in 1546. William Cullen (1710-1790) used the term "syphilis" to identify the disease as the major venereal disease, differentiating it from the minor venereal disease, known as gonorrhoea (Cullen, 1827). More than 100 different names have been used for syphilis, among which those referring to the alleged country of origin. Each country whose population was affected by the infection blamed the neighbouring (and sometimes enemy) countries for the outbreak (Tampa et al., 2014). The Dutch, for example, had a colonial war with the Spanish and referred to the disease as the "Spanish disease" (Tampa et al., 2014). Other names referred to the external appearance of the disease (for example "Great Pox", "Evil Pox" and "Morbus pustulatus"), the affected body parts or the probable cause. As early

as at the end of the 15th century sexual transmission of the disease was suspected, hence the 16th century designation "Lues venera" (meaning "venereal pest") (Tampa et al., 2014).

The oldest known European representation of syphilis is a woodcutting attributed to Albrecht Dürer (1495) (Tampa et al., 2014). The woodcutting depicts a mercenary whose face and body are covered with multiple pustules (figure 1).

Neurosyphilis

General Paralysis of the Insane

The Parisian physician Antoine Laurent Jessé Bayle (1799-1858) is honoured as the "discoverer" of General Paralysis of the Insane (GPI), because of his observations in 1822, that a certain constellation of psychological, physical and neuropathological manifestations constituted one disease entity (Artvinli, 2014). He termed this disease "arachnitis chronique" and gave a detailed description in his medical thesis "*Recherches sur l'arachnitis chronique, la gastrite et la gastro-entérite chroniques, et la goutte, considérées comme causes de l'aliénation mentale*." As described extensively by Hare (Hare, 1959) and Pérez-Trullén and colleagues (Pérez-Trullén et al., 2015), the disease recognized by English-speaking physicians as GPI, has, like syphilis, "suffered from a plurality of names" (Hare, 1959). Most terms refer to the 19th century observation that the disease progressed from psychiatric symptoms (such as cognitive decline, mania and psychosis) to neurological symptoms (such as motor alterations (paralysis)) (Pérez-Trullén et al., 2015). At the end of the nineteenth century many English and French synonyms existed, while the American writers favoured the term "general paresis" and the German writers "dementia paralytica" (Hare, 1959).

Although as early as 1857 the Danish Esmarch and Jessen had statistically linked syphilis to the later appearance of GPI, at the end of the 19th century, the causes of GPI were still believed to be hereditary, head trauma, excessive cold, fright, alcoholism, venery or exhaustion (Pearce, 2012). Austrian psychiatrist Richard von Krafft-Ebing (1840-1902), summing up the aetiology of dementia paralytica, coined the motto: "syphilisation and civilisation" (Hauser, 1992). He regarded syphilis, rachitis and alcohol abuse as predisposing factors of dementia paralytica. He postulated that syphilitic infection led to premature ageing, an excessive use of the brain, which then, in turn, was more susceptible to the development of dementia paralytica when hit by a psychological or mechanical trauma (Hauser, 1992).

Jean-Alfred Fournier (1832-1914), Professor of Dermatology at the University of Paris and Director of the internationally renowned venereal clinic at the Hospital of St Louis, introduced the concept of "parasyphilis" (tabes dorsalis (TD) and GPI) (Haas, 1998). In the *Annales de Dermatologie et de Syphiligraphie* of 1875-1876, Fournier put forward in two articles the idea of a syphilitic origin for TD (Waugh, 1974). He proposed that syphilis was the cause of the symptoms of paralysis, motor incoordination and locomotor ataxia (Waugh, 1974).

Only in the first few decades of the 20th century, serological and pathological confirmation of the syphilitic origin of GPI was definitely established (Pearce, 2012).

Tabes dorsalis

In the pre-antibiotic era, the most common form of neurosyphilis was tabes dorsalis (TD), or locomotor ataxia. The Latin term "tabes" means wasting, consumption and "disease which rots the blood" (Olry and Haines, 2018). The English writer Edward Phillips (1630 – ca. 1696), a nephew of the famous poet John Milton (1608-1674), already gave a definition of TD in the 1706 sixth edition of his dictionary: "Tabes Dorsalis, a Consumption in the Marrow of the Back-bone, which happens to those that are too much given to Venery" (Olry and Haines, 2018).

TD typically manifested several decades after primary syphilitic infection. Moritz Heinrich Romberg (1795-1873) was the first to describe the classic manifestations of TD: progressive ataxia, lightning pains, paraesthesias, bladder dysfunction and failing vision (optic atrophy) (Romberg, 1839). Romberg included excessive drinking and sexual activity among the possible causes of the condition, but did not mention syphilis (Nitrini, 2000). It was in these patients in particular that he described the sign that now carries his name. The Romberg sign refers to the typical sway of a patient standing in upright position with eyes closed. (Keppel-Hesselink and Koehler, 2000). A few years later, in 1858, Guillaume Duchenne (1806-1875) gave an almost complete clinical description of TD, which he named "progressive locomotor ataxia". Duchenne mentioned syphilis as the only reasonable or apparent cause, but considered a causal relation uncertain (Nitrini, 2000). In 1869, Douglas Argyll Robertson (1837-1909) described patients who lost pupillary reaction to bright light, but preserved accommodation, although he did not associate this with syphilis (Berger and Dean, 2014). The classic visceral crises of TD may result in severe gastrointestinal pains or laryngeal pains and hoarseness (Read and Donovan, 2012) and Charcot arthropathy, a neuropathic slowly progressive, chronic, destructive form of joint degeneration named after the famous French neurologist Jean Martin Charcot (1825-1893). TD is histologically characterized by demyelination of the posterior columns, posterior roots and posterior root ganglia.

Treatment in the pre-antibiotic era

Heavy metal chemotherapy

"For one night with Venus, a lifetime with Mercury" (Morton, 1990)

Mercury is the earliest known chemotherapy for syphilis. It was used in Arabic medicine in the treatment of several dermatological diseases as well as leprosy and succeeded to rapidly gain an important role in medical field at that time (Tampa et al., 2014). Mercury is easily absorbed through the skin, respiratory and gastrointestinal tract. As early as the late-15th century, mercury was administered both topically and orally, and remained the mainstay of antiluetic chemotherapy for nearly 500 years until the advent of penicillin in the 1940s (O'Shea, 1990). The attraction of mercury was based on two premises. The first and correct premise was the theory that syphilis was caused by invisible particles transmitted from one host to another. The second, incorrect, premise was based on the pharmacological properties of mercury salts. In harmony with the ancient humoral pathophysiology, it was thought that by inducing

diuresis and salivation the syphilitic "agent" would be excreted, aborting the illness. However, diuresis is merely an unpleasant side effect of medication and salivation indicates toxicity (O'Shea, 1990). Although bismuth, less toxic and more spirochetocidal than mercury, was introduced in 1884, it was not widely used until after the First World War (O'Shea, 1990).

In 1910, Paul Ehrlich (1854-1915) introduced the first scientifically designed drug against microbes: salvarsan (3-amino-4-hydroxyphenylarsenic), or arsphenamine, also known as "compound 606". His methodical search for a specific curative for an identified disease can be regarded as the introduction of targeted chemotherapy (Loyd et al., 2005). In 1908, Paul Ehrlich won the Nobel Prize for his work on salvarsan, nicknamed by Ehrlich "The Magic Bullet", and neosalvarsan that became available in 1912 and superseded the more toxic and less water-soluble salvarsan). Arsenicals were highly effective, less toxic compounds than mercury and, although difficult to administer during a lengthy and unpleasant treatment, arsenicals became the most widely prescribed drug in the world until penicillin came into use in the 1940's. "Heavy metal chemotherapy" (including the use of bismuth and arsenicals) was undoubtedly of use in the treatment of cutaneous lesions of syphilis (O'Shea, 1990). However, these heavy metals did not cross the blood-brain barrier well and were less effective against late stage neurosyphilis.

Malaria Fever Therapy
The healing effect of fever has been mentioned in antiquity: in the works of Hippocrates ("Quartana epilepsiae vindex appellator", on the beneficial influence of a malaria infection on epilepsy) and Galenus (129-199), who cited a case of melancholy cured as a result of an attack of quartan fever (Whitrow, 1990). On June 14, 1917, Julius Wagner-Jauregg (1857–1940) performed his first experiment on intentionally induced malaria for the treatment of patients with GPI in Vienna (Whitrow, 1990). The resulting spiking malarial fevers were supposed to kill the heat-sensitive treponemes. Fever spikes were managed and terminated after 10-12 epochs by quinine and then followed either by salvarsan, neosalvarsan or bismuth as adjuvant therapy. In 1921 Wagner-Jauregg reported an impressive therapeutic success and malaria fever therapy became standard treatment for GPI worldwide. In 1927 Wagner-Jauregg was the first psychiatrist to be awarded the Nobel Prize in Physiology or Medicine "for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica" (Whitrow, 1990). Despite the reported beneficial effect of malaria fever therapy its risks were considerable. Treatment mortality rates varied from 4% (Gambino, 2015) to 20% (Nicol, 1933; Winckel, 1938; Albert, 1999; Davis, 2008; Kragh, 2010). In 1921 malaria fever therapy was introduced in the Netherlands (Winckel, 1938).

The final therapeutic breakthrough in the treatment of syphilis was the introduction of penicillin by John Mahoney and colleagues in the 1940s (Mahoney et al., 1943). Penicillin aims to bring about the in vivo destruction of *T. pallidum* subsp. pallidum and this antibiotic remains the drug of choice for treatment of syphilis.

PATHOGENESIS AND TRANSMISSION OF SYPHILIS

Syphilis, also known as "Lues venera" ("the scourge of Venus" (named after the Roman goddess of love)), or "Lues", is caused by infection with *T. pallidum* subspecies pallidum (beyond simply referred to as *T. pallidum*). *T. pallidum* is a spiral-shaped bacterium that cannot be continuously cultivated *in vitro* and that is usually transmitted by direct contact with an infectious lesion or by an infected pregnant woman to her fetus (Janier et al., 2014). In the 20th century, Schaudinn and Hoffmann identified the causative agent of syphilis: a spiral-shaped, Gram-negative, highly mobile bacterium that they initially labelled as *Spirochaeta Pallida*, and later renamed *T. pallidum*. This micro-organism measures 6-15 μm in length, but only 0.15 μm in width, a dimension below the resolution of light microscopy (Berger and Dean, 2014).

Four different *Treponema* spp. are human pathogens, including 3 subspecies of *T. pallidum* (*T. pallidum* subsp. pallidum [syphilis], subsp. pertenue [yaws], and subsp. endemicum [non-venereal epidemic syphilis]) and the pinta agent T. carateum. None of these pathogens has yet been successfully cultivated in axenic medium and isolation in pure culture is not a diagnostic option (Lagier et al., 2015). *T. pallidum* can be propagated only in laboratory animals (rabbits) by intratesticular, intradermal, intravenous, or intracisternal inoculation (Lagier et al., 2015). *T. pallidum* grows slowly, with a doubling time of 30 to 33 h, and a mean of 1010 bacteria has been harvested from the testis of a rabbit (Lagier et al., 2015).

The infectivity of *T. pallidum* is exemplified by the fact that an individual inoculated with only 57 organisms has a 50% chance of being infected (Eccleston et al., 2008). Syphilis will develop in approximately 30% to 60% of those exposed to primary or secondary syphilis (Bhatti, 2007). *T. pallidum* is able to pass through intact mucous membranes or compromised skin (Kent and Romanelli, 2008; Stamm, 2010) and can be found intracellularly. The organisms invade interstitial spaces and chiefly proliferate there, with a doubling time of only 30-33 hours (Berger and Dean, 2014). Shortly after infection, spirochetemia results in hematogenous dissemination of *T. pallidum* to virtually any organ, including the central nervous system (CNS) (Berger and Dean, 2014).

Syphilis is transmissible during the primary and secondary stages. Transmission mainly occurs via sexual activities (Kent and Romanelli, 2008), however, maternal transmission during pregnancy and birth does occur, resulting in congenital syphilis (Woods, 2009; Janier et al., 2014). Transmission of the disease to infants breast fed by affected wet nurses was already commented on in the early literature (Berger and Dean, 2014). Rarely syphilis can be transmitted by direct non-sexual contact with an infectious lesion or by (donated) infectious blood. *T. pallidum* is heat-sensitive and unable to survive more than a few days without a host. Humans are the only known natural reservoir (Berger and Dean, 2014).

Clinical manifest neurosyphilis is the occurrence of neurological complications of syphilis and may occur during all stages of this disease (Berger, 2011).

EPIDEMIOLOGICAL ASPECTS OF SYPHILIS

Although curative modern antibiotics and public health measures were responsible for the dramatic decline in the prevalence of syphilis from the middle of the last century (Berger, 2011), a worldwide increase in the incidence of syphilitic infections is reported since the turn of the millennium (Fenton et al. 2008). Although syphilis was nearly eliminated in China in the early 1960s, the incidence began to rise in the 1980s. An almost 16-fold increase occurred in the period 1991- 2005. In 2013, 444,952 cases of syphilis were reported with a rate of almost 33 cases per 100,000 (Stamm, 2016).The annual incidence of syphilis in the United States was 14.7 per 100,000 in 2009, after a 18-fold decline of the annual incidence rate from a peak of 72 cases per 100,000 in 1943 to 4 per 100,000 in 1956 (Berger, 2011).

Between 2010 and 2015, many European countries observed a sharp increase up to 50% in the rates of reported syphilis infections (ECDC, 2017). In the European Union and European Economic Areas, 28,701 syphilis cases (6.0 per 100,000) were reported in 2015, mostly in patients older than 25 years of age (ECDC, 2017). Host-associated factors that drive the re-emergence and spread of syphilis include high-risk sexual activity, migration and travel, economic and social changes that limit access to health care (Fenton et al., 2008; Stamm, 2016) and substance abuse (Fenton et al., 2008).

Men are diagnosed with syphilis more often than women, especially men who have sex with men (MSM) (Bhai and Lyons, 2015; ECDC, 2017), probably related to changing sexual and social norms and to interactions with increasingly prevalent Human Immunodeficiency Virus (HIV) infection (Fenton et al., 2008). HIV and syphilis are often present as co-infections (Karp et al., 2009; Marra, 2009). Patients with HIV may be predisposed to neurosyphilis due to an inability to clear the initial neuroinvasion (Marra, 2009). The epidemiology of modern neurosyphilis is not well defined due to the paucity of population-based data (Ghanem, 2010). However, the majority of cases are reported in HIV-infected patients (Marra, 2009). Decreasing reports of late neurosyphilis have been encountered with increasing reports of early neurologic involvement (Ghanem, 2010).

CURRENT CLINICAL PRESENTATION AND CLASSIFICATION OF SYPHILIS

"There was a young man of Back Bay,
Who thought syphilis just went away,
And felt that a chancre,
Was merely a canker,
That went away in a week and a day.

Now at first he got acne vulgaris,
The kind that is rampant in Paris,
It covered his skin,
From forehead to shin,

And his friends all ask where his hair is.

With symptoms increasing in number,
His aorta's in need of a plumber,
His heart is cavorting,
His wife is aborting,
And now he's acquired a gumma.

Consider his terrible plight,
His eyes won't react to the light,
His hands are apraxic,
His gait is ataxic,
And he's developing gun-barrel sight.

His passions are strong, as before,
But his penis is flaccid, and sore,
His wife now has tabes
And sabre-shinned babies,
She's really worse off than a whore.

There are pains in his belly and knees,
His sphincters have gone by degrees,
Paroxysmal incontinence,
With all its concomitants,
Brings on quite unpredictable pees.

Though treated in every known way,
His spirochetes grow day by day,
He's developed paresis,
Converses with Jesus,
And thinks he's the Queen of the May."

(Asimov, 1975)

Sir William Osler (1849-1919) referred to syphilis as "the great imitator", due to its varied clinical presentations, mimicking in its various stages a wide variety of dermatological, internal, neurological and psychiatric disorders (Fitzgerald, 1951).

The terminology surrounding different stages of syphilis and neurosyphilis can be confusing (Kulkarni and Serpa, 2018). Definitions for terms related to clinical stages of syphilis as presented by Kulkarni and Serpa are represented in table 1 (Kulkarni and Serpa, 2018).

Table 1: Definitions for terms related to clinical stages of syphilis as presented by Kulkarni PA and Serpa JA, 2018.

Term	Definition
Syphilis	Generic term that refers to infection with the organism *T. pallidum* at any stage with or without the presence of any clinical signs or symptoms
Early syphilis	Generally thought to encompass primary syphilis, secondary syphilis and early latent syphilis
Late syphilis	Thought to represent late latent syphilis and tertiary syphilis
Primary syphilis	Initial stage of syphilis consisting of a genital chancre that appears at the site of inoculation approximately 10-90 days after acquisition of the infection
Secondary syphilis	Second stage of syphilis resulting in a wide spectrum of symptoms, including fevers, malaise, lymphadenopathy and rash (among myriad other possibilities)
Early latent syphilis	Evidence of infection due to *T. pallidum* as determined by serological testing but absence of signs or symptoms of clinical disease with infection having occurred within the prior 12 months
Late latent syphilis	Evidence of infection due to *T. pallidum* as determined by serological testing but absence of signs or symptoms of clinical disease with infection having occurred more than 12 months prior
Tertiary syphilis	Last stage of syphilis thought to occur approximately 5-30 years after initial infection with major forms being cardiovascular syphilis and non-central nervous system gummatous syphilis
Neurosyphilis	Infection of the central nervous system due to *T. pallidum* that can occur at any stage of syphilis
Early neurosyphilis	Neurosyphilis that occurs in the initial months to years after infection; thought to affect cerebrospinal fluid, meninges, and vasculature more often and comprise the syndromes syphilis meningitis and meningovascular syphilis
Late neurosyphilis	Neurosyphilis that occurs years to decades after initial infection; affects brain and spinal cord parenchyma more often; comprises the clinical syndromes general paresis (also known as syphilitic dementia or dementia paralytica) and tabes dorsalis

Primary syphilis

Primary syphilis is typically acquired by direct, mostly sexual contact with the infectious lesions of another person (Janier et al., 2014). Classically, a single, firm, painless, non-itchy skin ulceration, called a chancre, appears at the site of infection, between 3 to 90 days after infection. Occasionally, more common in patients co-infected with HIV, multiple lesions may be present (40%) (Kent and Romanelli, 2008).

Secondary syphilis

"Know syphilis in all its manifestations and relations,
and all other things clinical will be added to you." Sir William Osler (Bean, 1950)

Secondary syphilis develops in 60-90% of untreated patients approximately four to ten weeks after primary infection (Kent and Romanelli, 2008) and is known for its many different clinical presentations. Classically, secondary disease manifests with skin rash, mucosal ulceration and lymphadenopathy. Condylomata lata, pearl-gray raised horny (hyperkeratotic) lesions on the

genitals and anus, may also occur. All lesions contain spirochetes and are therefore infectious. Inflammation of the optic nerve, uveitis luetica, interstitial keratitis and otitis luetica are the most common complications at this stage of infection. Syphilitic meningitis, meningovascular syphilis, hepatitis, nephritis, gastritis and joint inflammation may also occur (Kent and Romanelli, 2008).

Latent syphilis

Even in untreated individuals signs of secondary syphilis often resolve spontaneously and patients become symptomless. This latent syphilis can last for several years until new manifestations of the disease develop.

Tertiary syphilis

Tertiary, non-transmissible, syphilis may occur approximately 3 to 15 years after the initial infection in a third of infected patients without treatment and may be divided into three categories: gummatous syphilis (15%), cardiovascular syphilis (10%) and late, parenchymatous neurosyphilis (6.5%) (Bhatti, 2007; Kent and Romanelli, 2008;). Gummatous syphilis is characterized by the formation of chronic gummatas that typically affect the skin, bone, and liver, but can occur anywhere (Kent and Romanelli, 2008). The most common complication of cardiovascular syphilis is syphilitic aortitis which may result in aneurysm formation (Kent and Romanelli, 2008).

Asymptomatic neurosyphilis

The most common form of neurosyphilis currently diagnosed is asymptomatic neurosyphilis (Berger and Dean, 2014), a stage of disease with cellular, biochemical and serological evidence of infection in the cerebrospinal fluid in the absence of neurological signs and symptoms. Cerebrospinal fluid abnormalities occur with a reported frequency of 16 - 48% in association with early (primary or secondary) syphilis (Berger and Dean, 2014). Although the presence of cerebrospinal fluid abnormalities does not necessarily predict the development of symptomatic neurosyphilis, the absence of cerebrospinal fluid abnormalities two years after initial infection has been considered to preclude the subsequent development of neurosyphilis (Berger and Dean, 2014).

Asymptomatic (latent) neurosyphilis can reactivate at a later stage, probably related to decreased immunity of the host. Two infamous studies of untreated syphilis have provided data on the frequency with which neurosyphilis develops in untreated syphilis patients. In the Oslo study, 9.4% of the men and 5.0% of the women ultimately developed neurosyphilis in 30 years (Clark and Danbolt, 1955). In the 40-year Tuskegee study, 6.5% developed neurosyphilis (Berger, 2011). Since then, the widespread use of of antibiotics, with beta-lactamase dominating usage (Bhai and Lyons, 2015), HIV co-infection (Bhai and Lyons, 2015), and variation in the incidence of different strains of *T. pallidum* (Marra, 2010) may have altered the course of the disease. However, there is only limited recent data on the natural course of syphilis.

Symptomatic neurosyphilis

The specific neurological manifestations of syphilis are, in some respects, a function of the time from infection, and classically neurosyphilis is divided in asymptomatic, early and late neurosyphilis (Flood et al., 1998). However, several forms of neurosyphilis may coexist in any patient (Berger, 2011).

Early neurosyphilis

Early neurosyphilis may be asymptomatic or manifest within months to several years after the initial infection. The pathophysiology involves an acute meningovascular and ocular inflammation resembling other infectious, inflammatory or autoimmune processes of the CNS. Clinical manifestations include meningitis, stroke, vertigo, optic neuritis or uveitis.

Meningeal neurosyphilis

Within a year of initial infection involvement of the meninges may result in meningitis with headache, and / or cranial nerve palsies, in particular VII, VIII, VI and II, with or without meningeal signs (photophobia, nausea, vomiting) or meningismus (Flood et al., 1998; Ghanem, 2010).

Meningovascular neurosyphilis

Meningovascular disease typically occurs after six to seven years and consists of endarteritis of vessels anywhere in the CNS, resulting in thrombosis and infarction (Ghanem, 2010) About 10% of patients with neurosyphilis and almost 3% of all syphilis patients present with a stroke. In one study up to 74% of this category of patients were below the age of 50 (Abkur et al., 2015).

Syphilitic uveitis

Syphilitic uveitis is defined by symptoms of decreased vision, eye pain or photophobia with diagnosis confirmed by slit-lamp examination (Flood et al., 1998).

Late neurosyphilis

"Walking on air
Never a care
When you've met Lues...
Get her on the brain and she'll drive you insane,
She'll touch your heart with her own special art,
A light in your eyes,
And we realize,
You've met our Lues."

(Heathfield, 1976)

Late neurosyphilis primarily affects the CNS parenchyma and occurs 15-30 years after initial infection and results most commonly in the clinical syndromes of General Paralysis of the Insane and tabes dorsalis (Berger and Dean, 2014).

General Paralysis of the Insane

"Know paretic neurosyphilis in all its aspects and you know all of psychiatry"
Hiram Houston Merritt, Jr (Merrit et al., 1946)

General Paralysis of the Insane (GPI) usually presents with a wide array of progressive neuropsychiatric symptoms, ranging from cognitive dysfunction to psychoses and mood disorders. Merritt paraphrased Osler's dictum on syphilis to "Know paretic neurosyphilis in all its aspects and you know all of psychiatry" (Merrit et al., 1946).

Tabes dorsalis
Pupillary abnormalities, including Argyll-Robertson pupils (pupils that are small, asymmetric, irregular, and poorly responsive to direct light with maintained appropriate constriction on accommodation) were once a hallmark symptom of TD. Other signs include diminished reflexes, impaired vibratory sense and proprioception, ocular palsies and Charcot's joints.

Congenital syphilis
Congenital syphilis, transmitted during pregnancy or birth, is a preventable disease, easily diagnosed in laboratory and treatable with a high probability of arresting infection. Nevertheless it remains a major problem in developing countries and globally 0.7 million to 1.5 million cases occur annually. The majority of cases result in stillbirth or perinatal death (Douglas, 2009). Deficiency in health education and prenatal care, poor diagnosis, inappropriate treatment of pregnant women and their sex partners, disadvantaged socioeconomic conditions, difficult access to health services and poor guidelines might contribute to the incidence of congenital syphilis (Teixeira et al., 2017). In the Netherlands, the number of congenital syphilis infections found in neonates and young infants (<1 year) ranged from 0 or 1 per year from 2008 to 2017, but increased to 3 in 2017 (Visser et al., 2018). The number of congenital syphilis in non-neonates in the Netherlands is unknown. More than half of syphilitic infants are born without symptoms. Therefore patients may remain undiagnosed. In 20% of cases, neurosyphilis develops. Other symptoms that develop during the first couple of years of life include enlargement of the liver and spleen (70%), rash (70%), fever (40%) and lung inflammation (20%) (Woods, 2009).

DIAGNOSTIC TESTS

The diagnosis "neurosyphilis" is based on a combination of clinical features and laboratory findings. However, at present there are no uniform clinical diagnostic criteria and a perfect "gold standard" diagnostic test is not available (Marra, 2009). Moreover, the diagnostic tests are unable to distinguish between the various stages of the disease.

Therefore, serological tests of the cerebrospinal fluid are the most specific tests to confirm a diagnosis of neurosyphilis. Currently, in the Netherlands, *Treponemal* tests (TT), for example the *Treponemal pallidum* hemagglutination (TPHA) test, *Treponemal pallidum* particle agglutination (TPPA) test and enzyme-linked immunosorbent assays (ELISA) based on specific recombinant *T. pallidum* membrane proteins, are used to screen for syphilitic infection. Since these tests remain reactive for years, even after successful treatment, non-*Treponemal* tests (nTT) test are often applied to confirm active syphilitic infection and to evaluate treatment outcome (Peeling, 2006). Although a diagnosis of neurosyphilis is confirmed with a positive VDRL (Venereal Disease Research Laboratory test) in cerebrospinal fluid (CSF), this finding is observed in only about one third of neurosyphilis cases. Nevertheless a positive test can be considered as indicative of neurosyphilis in late syphilis in the absence of substantial blood contamination. However, in early syphilis the significance of a positive CSF VDRL test is less clear (Janier et al., 2014). A positive CSF TT does not confirm the diagnosis of neurosyphilis but a negative CSF TT result is highly unlikely in neurosyphilis.

Peripheral treponemal antibodies can result in measurable CSF levels due to passive passage through an intact blood-brain barrier. Antibody leakage from blood to CSF can be distinguished from intrathecal antibody production by calculating an IgG serum / CSF index: the Reiber or TPPA index (Reiber, 1994a; Reiber, 1994b; Luger et al., 2000). In neurosyphilis these indexes are elevated. Several authors have proposed the use of pleiocytosis with predominantly mononuclear cells or an elevated protein level. However these abnormalities are nonspecific (Kulkarni and Serpa, 2018). Moreover, protein level as well and number of mononuclear cells in CSF can be normal in neurosyphilis, especially in parenchymatous neurosyphilis (tabes dorsalis, general paresis of the insane) (Janier et al., 2014).

As mentioned before, in the Oslo study, 9.4% of men and 5.0% of women eventually developed neurosyphilis after syphilitic infection (Clark and Danbolt, 1955). No symptoms developed in the remaining patients; thus the presence of CSF abnormalities does not necessarily predict the development of clinically manifest neurosyphilis. Conversely, the development of neurosyphilis is not to be expected if CSF abnormalities are lacking (Berger and Dean, 2014).

Although neuroimaging is not specifically required for the diagnosis of neurosyphilis, radiologic studies can provide adjunctive information in different circumstances and are helpful in excluding other pathologies (Berger and Dean, 2014; Kulkarni and Serpa, 2018). Cranial magnetic resonance imaging (MRI) manifestations of neurosyphilis include meningeal enhancement or CSF enhancement in the case of syphilitic meningitis and ischaemia and infarction in meningovascular syphilis (Berger and Dean, 2014; Kulkarni and Serpa, 2018).

Central nervous system gummatous syphilis can be seen in neuroimaging in the form of space occupying lesions (Kulkarni and Serpa, 2018). Rarely, the radiographic appearance of neurosyphilis may mimic the appearance of normal pressure hydrocephalus or herpes encephalitis (Berger and Dean, 2014). Cranial MRI of patients with GPI has demonstrated frontal and temporal atrophy, subcortical gliosis and increased ferritin in the basal ganglia (Berger and Dean, 2014). Lesions on T2-weighted and fluid attenuated inversion recovery (FLAIR) MRI in the temporal lobes, particularly the mesial region, are also reported in patients with neurosyphilis (Leypoldt et al., 2015), necessitating exclusion of autoimmune antibody encephalitis in cases suspected of neurosyphilis and vice versa. In TD, spinal imaging can show increased signal intensity in the spinal cord (Kulkarni and Serpa, 2018).

PENICILLIN TREATMENT OF NEUROSYPHILIS

Since controlled, randomized, prospective studies for optimal dose and duration of therapy are lacking, as yet no uniform worldwide recommended treatment regimen for neurosyphilis is available (Berger and Dean, 2014). The European guidelines recommend inpatient management and daily administration of benzylpenicillin 18–24 million units intravenously, divided over 3–4 million units dosages every four hours for 10–14 days, as first line therapy (Janier et al., 2014). Second line therapy options are ceftriaxone 1–2 g intravenously daily for 10–14 days and, if hospitalization and / or intravenous administration of antibiotics is impossible, procaine penicillin 1.2–2.4 million units intramuscular once daily combined with probenecid 500 mg four times daily, both during 10–14 days (Janier et al., 2014).

Follow-up examination of cerebrospinal fluid should be performed six weeks – to six months after treatment of neurosyphilis (Janier et al., 2014). In general, the clinical prognosis after completion of treatment with intravenous aqueous crystalline penicillin G depends on the clinical manifestation of neurosyphilis (Kulkarni and Serpa, 2018). Patients with GPI and TD will most likely experience residual cognitive and sensory disturbances respectively, while patients with a syphilitic meningitis or gummata have a good prognosis (Kulkarni and Serpa, 2018).

AIM AND OUTLINE OF THE THESIS

The aim of this thesis threefold. First, to describe the clinical presentation of General Paralysis of the Insane (GPI) in the first half of the 20th century. Second, to investigate malaria fever therapy, the only therapy considered effective in neurosyphilis in that era in patients with GPI. And last, to examine the epidemiology and clinical presentation of neurosyphilis in the current era.

In **Chapter 2** the clinical presentation of 105 patients with GPI admitted to a Dutch psychiatric hospital in the period 1924-1954 is described. In **Chapter 3**, malaria fever therapy for GPI is investigated in the same cohort of patients. In **Chapters 4 and 5** current epidemiological and clinical aspects of neurosyphilis are presented. In **Chapter 4** the epidemiology of neurosyphilis in Dutch general hospitals in the period 1999-2010 is

investigated in a nationwide study. The clinical data of a series of patients with laboratory confirmed neurosyphilis are analysed in **Chapter 5.** In **Chapter 6** a case of neurosyphilis mimicking autoimmune encephalitis is presented. A general discussion and conclusions, including future perspectives, are presented in **Chapter 7** and **Chapter 8** respectively. Finally, in **Chapter 9** and **Chapter 10** the findings of this thesis are summarized.

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CLINICAL PRESENTATION OF GENERAL PARALYSIS OF THE INSANE

IN A DUTCH PSYCHIATRIC HOSPITAL, 1924–1954

Sint Anna hospital Venray, 2010

ABSTRACT

General paralysis of the insane (GPI) or dementia paralytica was once a fatal complication of syphilitic infection and a major reason for psychiatric hospitalization. Nowadays, physicians consider GPI to be exceptional. It should be noted, however, that syphilis re-emerged worldwide at the turn of the 20th to 21st century and a revival of GPI can, therefore, be expected. Advanced diagnosis is crucial in that treatment in the early, inflammatory phase is warranted before irreversible tissue damage occurs. Therefore, a renewed clinical awareness of the broad spectrum of psychiatric and neurologic signs and symptoms of GPI is needed. In this historical cohort study, comprising 105 patients with GPI admitted to the Dutch Vincent van Gogh Psychiatric Hospital in the period 1924–1954, the clinical presentation of this invalidating disorder is investigated and described in detail.

INTRODUCTION

Given the dramatic decline of the incidence of syphilis after the introduction of antibiotic treatment, general paralysis of the insane (GPI), also termed dementia paralytica, a late complication of untreated syphilis, was expected to become 'something of a neuropsychiatric rarity' [1, 2]. However, GPI has not yet disappeared and should, therefore, still be considered in the diagnostic workup of psychiatric and neurological patients [3].

In the 19th century, GPI was described by Clouston, a Scottish 'alienist' (as physicians specialized in the treatment of mental illness were referred to at that time [4]) and superintendent of the Royal Edinburgh Asylum between 1873 and 1908, as the 'most terrible of all brain diseases' [5, 6]. About 2 decades after an untreated syphilitic infection, GPI presented with progressive mental and physical decline in 3–5% of the patients. In the first phase of the disease, the so-called medico-legal period, ill-judged actions due to neurocognitive dysfunctions could result in serious social and legal repercussions. No cure was known as yet, and most patients with GPI deteriorated and died within 6 years after diagnosis, albeit that remissions did occur [7].

Although in the first half of the 19th century, the clinical and pathological features of GPI as well as its syphilitic origin were described, at the end of the 19th century, GPI was considered 'parasyphilitic', that is, syphilis was not the exclusive causative factor [8, 9]. The Austrian psychiatrist von Krafft-Ebing referred to 'civilization and syphilization' as the most important factors in the development of GPI [10]. He postulated that environmental and psychological factors associated with urban life, the 'civilization' (e.g. stress, hard work, tobacco and 'excesses in Baccho et Venere'), in combination with syphilitic infection led to premature aging. The latter resulted in increased susceptibility to the development of GPI in case of a psychological or mechanical trauma [11]. Subsequent to the hypothesis of von Krafft-Ebing, during the first few decades of the past century, the syphilitic origin of GPI could be established definitely and serologically confirmed [9].

At the turn of the 19th to 20th century, GPI was a worldwide problem with considerable social and economic impact and had become a heavy burden on the health-care system [12]. Although exact figures are unknown, asylums throughout the world reported, in the first decades of the 20th century, an increase in admission rates up to 20% [2, 13]. At the Royal Edinburgh Asylum, Scotland's largest asylum, up to 17% of admissions and 34% of deaths concerned the patients with GPI [6]. Death from GPI in all Scottish asylums increased from 8.9 to 12.5 per 1,000 resident patients [5]. In the period from 1875 to 1915, the proportion of GPI patients in the total asylum population in The Netherlands increased from over 2 to nearly 7% [14].

In order to understand the longitudinal development of GPI in the late pre-antibiotic era, here, the clinical presentation at asylum admittance as described in the historic patient records of the Vincent van Gogh Institute for Psychiatry (VvGI) in Venray, The Netherlands, is investigated.

METHODS

Patients were included if they had died while being hospitalized at the VvGI in the period 1924–1954 and had an established diagnosis of GPI. Identification was performed by using annual hospital reports and the corresponding individual patient's records, as stored at the Social Historical Centre of Limburg in Maastricht. Data were anonymized before evaluation. Since megalomania and dementia are symptoms of what is usually called 'classical GPI' [15], special attention was given to the mentioning of dementia and/or delusions of grandeur, that is, grossly exaggerated belief of self-worth, power, knowledge or identity or of an exceptional relationship with a divinity or famous person [16]. The protocol was approved by the Vincent van Gogh Institutional Review Board (number: 13.034).

The typical clinical presentation of GPI will be illustrated by 2 detailed case descriptions.

RESULTS

A total of 2,731 patients (1,460 men and 1,271 women) died while being hospitalized in the VvGI. From this cohort, 180 patients (6.6%; 137 men and 43 women) had been diagnosed with GPI. The individual clinical records of 105 patients (58.3%; 91 men and 14 women) out of the total of 180 GPI patients were available for evaluation. From the total of 105 patients, 9 (8 men and 1 woman) had previously been admitted to the VvGI. Only data concerning last admissions were used for analysis.

Demographic Data

Mean age at admission was 50.6 years, which was significantly lower in females than in males (45.0 vs. 51.4; $p = 0.03$; Student's t test) with a median age for men and women of 50.4 and 43.2 years, respectively. Information on education was available for 84 patients of whom 95% had completed elementary school only. Women were mainly housewives, and all but 1 male patient belonged to lower working class. In 4 patients, the spouse also had a diagnosis of syphilis. Details are presented in table 1.

Table 1. Demographics of the patients (n = 105; 91 men and 14 women)

Mean age at admission, years (median)	50.6 (49.7)
Range	31.5-82.1*
Median duration of disease at admission (known for n = 84), years	1.1
Range	0.02-12
Marital status, n	
Married	75
Widowed	13
Divorced	4
Single	13
Residence before admission, n	
General hospital ward	52
Own home	35
Another asylum	5
Other institutes	11
Unknown	2
*Mean age females (n = 14): 45 years; males (n = 91): 51.3 years	

Diagnosis

In 96 out of 105 patients, a diagnosis at admission was available (table 2). A history of treatment for syphilis or neurosyphilis was known for 14 and 36 patients, respectively. Data on the positive results of the Wassermann test in serum and/ or cerebrospinal fluid could be retrieved in 68 patients (55 men and 13 women). In two male patients, a negative result of the Wassermann test in serum was documented, but both had a known history of neurosyphilis and had probably received anti-syphilitic treatment in a general hospital prior to admission to the VvGI. In 33 patients, a diagnosis of GPI had been made in a general hospital in an earlier phase of their disease. In two patients, no results of serological tests were present in their clinical records; however, they were reported to be diagnosed with GPI. Both patients resided at home before admittance and displayed aggressive behaviours.

Table 2. Diagnosis at admission known for 96 patients (84 men and 12 women)

	All patients	Male	Female
Dementia paralytica	67	60	7
Taboparalysis	8	6	2
Other forms of dementia	7	7	0
Schizophrenia	5	4	1
Paranoia	2	2	0
Mania	2	0	2
Religious delusion	1	1	0
Manic depressive psychosis	1	1	0
Acute hallucinosis	1	1	0
Epilepsia	1	1	0
Imbecillitas	1	1	0

Symptoms and Signs

Concerning the neuropsychiatric syndrome, the most frequently observed symptoms at admission were lack of judgment and insight, dementia and hyperactivity (table 3).

Table 3. Psychiatric symptoms reported at admission in 105 patients (91 men and 14 women)

	Total			Males			Females		
	Missing*	Present	%present	Missing*	Present	%present	Missing*	Present	%present
Lack of judgment and insight	3	94	90	2	82	90	1	12	86
Dementia	5	86	82	5	77	85		9	64
Hyperactivity	4	80	76	4	69	76		11	79
Mania	5	74	70	5	64	70		10	71
Confusion	14	71	68	11	63	69	3	8	57
Delusions	9	66	63	9	54	59		12	86
Irritability	12	63	60	10	58	64	2	5	36
Aggression	9	61	58	8	55	60	1	6	43
Restlessness at night	21	47	45	21	40	44		7	50
Hallucinations	21	42	40	19	32	35	2	10	71
Depression	10	42	40	10	34	37		8	57
Euphoria	10	38	36	10	29	32		9	64
Memory problems	37	33	31	34	26	29	3	7	50
Emotional lability	12	23	22	11	16	18	1	7	50
*Number of patients with insufficient information in the patient's record.									

Delusions of grandeur were documented in 46 patients (table 4). About half of the patients (n = 52) were referred to the VvGI because of their challenging behaviours in the general hospital ward. In 11 patients living at home, prior to admission, behavioural problems had resulted in judicial contacts.

As to neurological manifestations, key symptoms were disordered speech (including dysarthria, mutism and stuttering), pupillary abnormalities and micturition disorders (table 5). In 43 patients, information on examination of pupils was available. In six patients, a complete description of Argyll Robertson pupils was given. Anisocoria and small pupils that reacted very poorly to light were the main abnormalities in the other patients.

Table 4. Delusions reported at admission in 105 patients (91 men and 14 women), classified according to Wing et al., 1980

	Total	Males	Females
Delusions of grandiose ability and/or identity	44	36	8
Delusions of persecution	5	3	2
Nihilistic delusions	1	1	0
Hypochondriacal delusions	7	7	0
Delusions of guilt	3	2	1
Delusions of reference	1	1	0
Religious delusions	1	1	0
Delusions of pregnancy	1	0	1
Unspecified delusions	7	6	1
Some patients presented with several kinds of delusions.			

Table 5. Neurological symptoms reported at admission in 105 patients (91 men and 14 women)

	Total			Males			Females		
	Missing*	Present	%present	Missing*	Present	%present	Missing*	Present	%present
Speech disorders: Sylbenstolpern, dysarthria, mutism	4	82	78	4	71	78		11	79
Pupillary abnormalities in shape, size and/or response to light	47	50	48	44	38	42	3	12	86
Micturition disorders	24	46	44	24	37	41		9	64
Cranial nerve involvement	69	25	24	66	17	19	3	8	57
Tremors	66	20	19	60	17	19	6	3	21
Cerebrovascular accidents	73	8	8	69	6	7	4	2	14
*Number of patients with insufficient information in the patient's record to conclude whether a symptom was present or not									

Case Descriptions

Patient 1 is a 42-year-old married woman, referred to the VvGI in August 1931. She had a 1-year history of epileptic seizures followed by short periods with difficulties in speaking and swallowing. For several weeks, she believed herself to be related to the royal family and thought the queen would visit her for dinner. She bought very expensive clothes and distributed several of these to workmen in the street. In addition, she complained about 'hearing voices' and she felt 'manipulated by electricity'.

At admission, psychiatric examination disclosed memory deficits with marked disorientation and impaired imprinting and judgment. There were persistent paranoid delusions and delusions of grandeur. Euphoria alternated with episodes of depression. Speech was strongly disturbed by so-called 'Sylbenstolpern', that is, the omission and transposition of syllables. Neurological examination showed mildly miotic, angular, even-sized pupils with decreased pupillary light and accommodation reflexes. Tendon reflexes on the lower extremities were brisk. Wassermann tests performed in blood and cerebrospinal fluid confirmed the diagnosis of GPI.

Following treatment with malarial fever, mood swings became less prominent but the delusions of grandeur persisted. The patient showed rapid physical decline, became bedridden, developed urinary incontinence and pressure ulcers and died 13 months after admission.

Patient 2 is a 44-year-old male construction worker, re-admitted to the VvGI in February 1940. As stated in a letter written by his sister, his behaviour had changed in the previous 3 weeks. Shortly after the death of his wife, he had become increasingly anxious and violent, verbalizing 'strange language'. He was known to suffer from GPI and had been admitted two years earlier for malaria fever therapy. Upon the request by his family, he was discharged one year later as 'sufficiently recovered' and subsequently functioned adequately at home.

On re-admittance, the patient was very confused, irritable, restless and aggressive. He experienced vivid visual hallucinations and feelings of depression with suicidal ideation. Neurological examination showed unspecified pupillary abnormalities and brisk knee tendon reflexes. He died from total exhaustion within one month.

DISCUSSION

In the present study, the clinical presentation of GPI at asylum admission is described in a group of 105 patients, who died while they were hospitalized in the VvGI over a period of three decades in the first half of the past century. In this late pre-antibiotic era, fever therapy induced by malaria was used as a treatment for GPI [8]. Based on the observation that psychotic patients occasionally showed great improvement after an intercurrent feverish illness, patients were treated with intentionally induced malaria, a method developed by Wagner - Jauregg, who was awarded with the Nobel Prize in Physiology or Medicine in 1927 for his work on the treatment of GPI by malaria inoculation. As early as in 1921, treatment for malarial fever was introduced in The Netherlands [8] and soon afterwards was also implemented in the VvGI, as is reflected in the two case descriptions above.

Although case notes of the Dutch GPI patients have been evaluated from the social and historical perspective [14, 17], this is the first retrospective study aimed at evaluating the signs and symptoms on asylum admittance systematically. Most patients were referred to the VvGI because of behavioural problems that were too difficult to manage at home or at a

general hospital ward, that is, aggression and challenging behaviour. The majority of patients were middle-aged men, an observation also made by other investigators [5, 6, 14, 17, 18]. The finding that all patients were from the lower working class is in accordance with the results of the study by Slijkhuis and Oosterhuis [14] on GPI patients in Dutch psychiatric hospitals in the period 1870–1920. These observations suggest that in The Netherlands, patients from higher socioeconomic classes were treated in private institutes or received nursing care at home. Therefore, the finding that syphilis was less likely to be diagnosed in wealthy female patients [5] could not be examined in this study.

Like in other studies, an under-representation of farmers is observed, which has been interpreted previously as a consequence of life and work in rural areas far from the turbulent city life [3, 5, 7, 18]. In general, records retrieved in this historical series were rather short and not always complete regarding the description of symptomatology. The best documented were those on female patients. As stressed by other investigators, this brevity was most probably related to the legal rules in that era [19]. In accordance with the 1884 Dutch insanity law, medical records also served a legal purpose and, in fact, diagnostic justification for (forced) admission and/or prolonged hospitalization was considered superior to detailed description of symptoms and disease course. From the juridical viewpoint, the medical diagnosis of dementia referred to a state of intellectual failure, causing psychosocial incompetence and, therefore, legalized forced psychiatric hospitalization [19, 20]. However, brevity of patient records may also have resulted in incompleteness of clinical data leading to the under-rating of the incidence of symptoms and signs. Nonetheless, an array of psychiatric and neurologic symptoms could be established.

As can be inferred from table 3, female patients presented mainly with a variety of psychotic symptoms (predominantly an array of delusions of grandeur), whereas dementia was more prevalent in male patients. In both male and female patients, fleeting ideas of grandiosity were common (table 4). In many patients, abrupt alteration of emotions was noticed, a feature considered as a core symptom by Kraepelin.

According to Kraepelin's taxonomy, the majority of patients can be classified as the 'demented type of GPI' [21]. He observed that this type of GPI patient 'usually ceases to concern himself regarding his obligations' and 'often (he) comes into conflict with the public regulations or with the law'.

Although 'the demented type of psychosis' has been reported as the most frequent presentation of GPI in clinical patients [1], the preponderance of dementia in the total patient group should be interpreted with caution. In the records, the term 'dementia' was probably used in its 19th century meaning, that is, terminal states of a wide variety of mental disorders [22]. Deterioration of intellectual functioning and personality in GPI patients may also have been the result of other long lasting and untreatable psychiatric disorders that would nowadays be diagnosed as delirium or psychotic depression.

As of neurological symptoms, speech disorders, pupillary abnormalities, and tremors were among the most common signs, in accordance with the clinical description of GPI in the pre-antibiotic era [7, 23]. The speech disorders documented here comprised problems with

articulation and phasic disturbances. In some patients, tremor of the lips and tongue and a 'facies paralytica' (i.e. facial muscle hypotonia with flattening and smoothing out of the facial lines caused by disappearance of motor nerve cells of the cerebral cortex) contributed to dysarthria. In about half the patients, pupillary abnormalities were recorded, most often anisocoria and the absence of reaction of the pupils to bright light. In 6 patients, a full description of the Argyll Robertson pupil was recorded: a miotic pupil with defective reaction to light and preserved contraction on accommodation [24]. Since most patients showed restlessness and/or aggressive behaviour on admittance, they were most probably unable to cooperate on a complete pupillary assessment.

Although disturbance of the sphincters is not an integral part of GPI except in the terminal stages, micturition disorders were noted in about half of the patients [7]. These dysfunctions may have been related to tabes dorsalis and dementia.

At admission, nine patients had a history of epileptic seizures and ten patients of cerebrovascular disease (table 3), the latter probably caused by syphilitic vascular disease. Cranial nerve abnormalities, as observed in several patients (table 5), may have been the sequelae of syphilitic meningitis.

Summarizing, the clinical presentation of GPI in patients, in the first half of the past century, includes a wide range of psychotic and mood disorders accompanied by impaired judgment. Prevailing neurological symptoms comprised impaired speech, pupillary abnormalities and cranial nerve dysfunction. Since at present, unfamiliarity with GPI is proverbial and screening for (neuro)syphilis is no longer obligatory, physicians from various disciplines should be aware of this disorder that presents with a marked heterogeneity. This holds especially since the prevalence of syphilis has increased over the past decades.
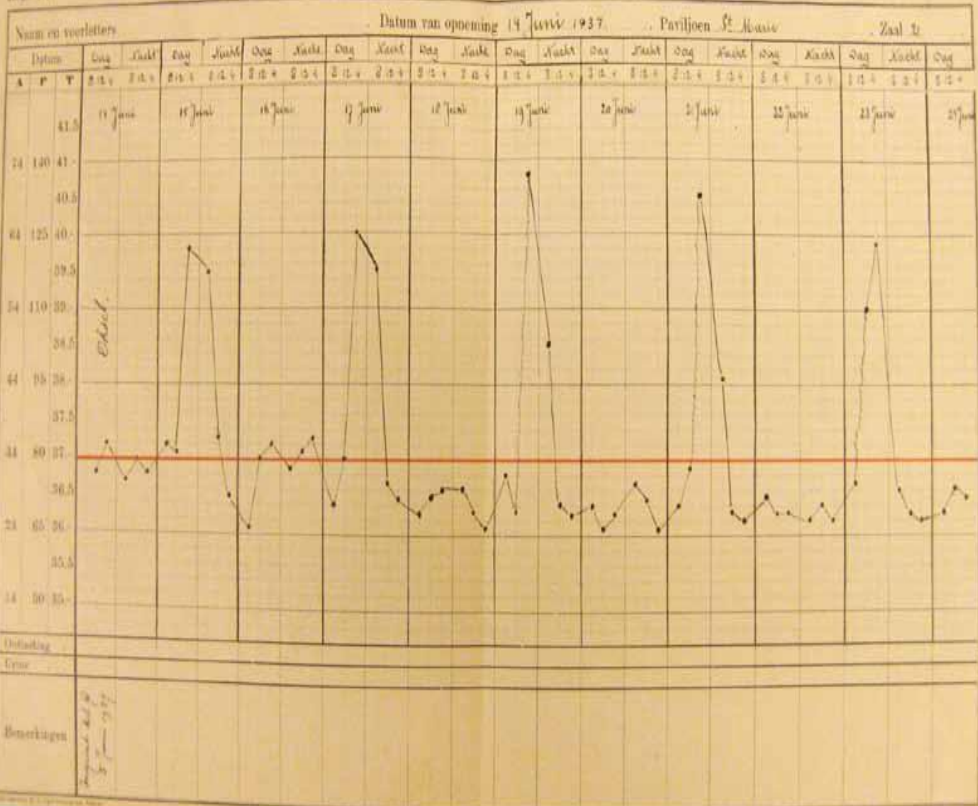
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ST SERVATIUSGESTICHT TE VENRAY

Reg. Nr

Naam en voorletters _____ Datum van opneming 14 Junii 1937 _____ Paviljoen St Maria _____ Zaal 2

MALARIA FEVER THERAPY FOR GENERAL PARALYSIS OF THE INSANE:

A HISTORICAL COHORT STUDY

A body temperature chart dated 1937 of a patient with General Pareses of the Insane during Malaria Fever Treatment.

ABSTRACT

Background / Aims: This year* marks the 100th anniversary of the first malaria fever treatment (MFT) given to patients with general paralysis of the insane (GPI) by the Austrian psychiatrist and later Nobel laureate, Julius Wagner-Jauregg. In 1921 Wagner-Jauregg reported an impressive therapeutic success of MFT and it became the standard treatment for GPI worldwide. In this study, MFT practice in the Dutch Vincent van Gogh psychiatric hospital in GPI patients who had been admitted in the period 1924–1954 is explored.

Methods: To identify patients with GPI, cause-of-death statistics was used. Data on MFT were retrieved from annual hospital reports and individual patient records.

Results: Data on MFT were mentioned in the records of 43 out of 105 GPI patients. MFT was practiced in a wide range of patients with GPI, including those with disease duration of more than one year, up to 70 years of age, and those with a broad array of symptoms and comorbidities, such as (syphilitic) cardiac disease. Inoculation with malaria was done by patient-to-patient transmission of infected blood.

Conclusions: MFT practice and mortality rates in MFT-treated patients correspond to similar findings worldwide. MFT was well tolerated and MFT-treated patients had a significantly longer survival.
* 2017

INTRODUCTION

General paralysis of the insane (GPI), also designated as "general paralysis" and "dementia paralytica", is a chronic syphilitic meningoencephalitis that causes the progressive degeneration of the central nervous system and a general dissolution of mental and physical capacities. Isolated reports of this previously undescribed and uniformly fatal form of insanity first arose in the late 18th century [1].

On June 14, 1917, Julius Wagner-Jauregg (1857–1940) performed his first experiment on intentionally induced malaria for the treatment of patients with GPI in Vienna [2]. In 1921, he reported an impressive therapeutic success and thereafter this became the standard treatment for GPI worldwide. In 1927, Wagner-Jauregg was the first psychiatrist to be awarded the Nobel Prize in Physiology or Medicine "for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica" [2]. Despite the reported beneficial effect of malaria fever treatment (MFT), its risks were considerable. Treatment mortality rates varied from 4, 3% [3] to 20% [4–8].

While in Denmark introduction of MFT was hampered by the risk of reintroducing an extinct disease [7], Plasmodium vivax tertian malaria was still endemic in the Netherlands [9]. Already in 1921, K.H. Bouman (Dutch neuropsychiatrist) was the first to treat neurosyphilitic patients with MFT in the Netherlands [8]. In 1922, promising results were reported [10] and soon afterwards, MFT was introduced in the treatment of psychiatric patients in Venray, the Netherlands.

Although research on the history of MFT in GPI patients has been performed in the United States [11– 13], Britain [14], Scotland [6], and Denmark [7], no historic study on MFT in GPI patients in a psychiatric hospital in the Netherlands has as yet been reported. Therefore, in this retrospective cohort study, we investigated MFT-practice in GPI patients who were admitted during the period 1924–1954 and died while hospitalized in a psychiatric hospital in the Netherlands.

METHODS

For this study, the practice of MFT was investigated in patients with an established diagnosis of GPI, who had been admitted during the period 1924–1954 and died while hospitalized in either the psychiatric hospital for male or for female patients in Venray, the Netherlands, at present together known as Vincent van Gogh Institute for Psychiatry (VvGI).

To identify patients with GPI, cause-of-death statistics collected over the period 1924–1954, as stored in the institute's historical archive, located at the Social Historical Centre of Limburg in Maastricht, was used. Individual medical case records of GPI patients, collected at the same archive, were scrutinized.

Data on MFT were retrieved from annual hospital reports and individual patient records. The admission age of first hospitalization was used. For each patient, data on the first application of MFT were analysed. In case the date of inoculation was not mentioned in the

medical record, it was set at 14 days before the first fever spike was recorded. Epidemiological data and clinical course of all patients were collected to analyse selection criteria and treatment results. Influence of MFT on survival was analysed with a Kaplan-Meier survival curve. Data were anonymized before evaluation. Study approval was obtained by the Vincent van Gogh Institutional Review Board (Number: 13.034).

To illustrate the MFT procedure in GPI, two case descriptions are presented.

RESULTS

Data from the Annual Hospital Reports
Annual reports for the years 1929–1954, except those from 1936 to 1950, were available for evaluation. In those years, approximately 750 male and 750 female patients resided in the psychiatric hospital and each year approximately 140 male and 130 female patients were admitted.

Data from the Cause-of-Death Registers
During the period 1924–1957, 180 patients (137 men, 43 women) with an established diagnosis of GPI died while in the hospital.
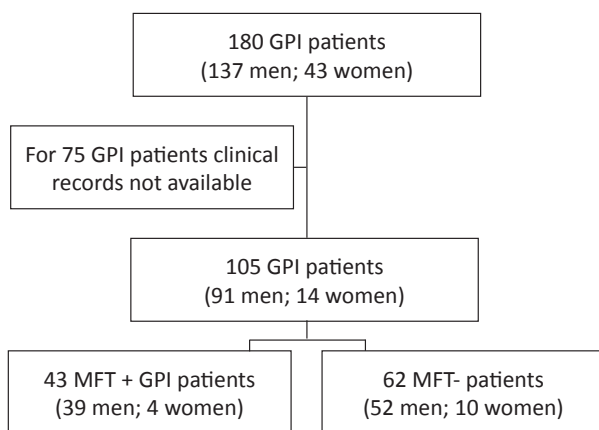
Patient Records

Fig. 1. Number of general paralysis of the insane (GPI) patients deceased during 1924–1957 based on cause-of-death statistics, number of patients whose clinical record was available, and number of patients with malaria fever therapy (MFT+) and without (MFT–).

The clinical records of 105 (58%) (91 men and 14 women) of the total of 180 GPI patients were available for analysis. Of these 105 patients, 10 (9.5%) had been admitted more than once (9 men, 1 woman). Data on MFT were mentioned in the records of 43 out of 105 patients (41%: 39 men; 4 women; figure 1). Two patients received MFT twice. In this study, only data on the first MFT were analysed.

MFT Procedure

No differences were found with respect to disease duration before admission, earlier MFT, and other antineurosyphilitic treatments in patients with and without MFT. Details on patient characteristics are presented in table 1.

Age of MFT-treated patients varied from 31.5 to 69.0 years (n = 43; mean 48.0 years) vs. 32.9–82.1 years (n = 62; mean 51.9 years) of untreated patients. Pre-treatment screening comprised a thorough clinical examination, laboratory tests, and X-ray of the chest. In five of these patients, an enlarged configuration of the ascending aorta was noticed, suggestive of a syphilitic aortic aneurysm. One additional MFT-treated patient had a medical history of a syphilitic aortic aneurysm, but the data on the chest X-ray of this patient are unknown.

Table 1. Characteristics of patients with general paralysis of the insane treated with malaria fever therapy (MFT+) or without (MFT-)

	MFT+ (*n* = 43)	MFT– (*n* = 62)
Gender, female, *n* (%)	4 (9.3)	10 (16.1)
Age at admission, mean (range)	48.0 (31.5–69.0)	51.9 (32.9–82.1)
With known duration of disease before admission, *n* (%)	34 (79)	49 (79)
Duration of disease before admission, years, mean (range); median	1.6 (0.1–8.0); 1.0	2.0 (0.1–9.0); 1.0
Treated for (neuro) syphilis before current admission, n (%)	16 (37)	25 (40)
None or unknown earlier treatments, n (%)	27 (63)	37 (60)
Earlier MFT treatment, *n* (%)	4 (9)	7 (11)
Symptoms, *n* (%)		
Abnormal mood fluctuations	17 (40)	21 (34)
Depression	9 (21)	16 (26)
Mania	33 (77)	40 (65)
Dementia	33 (77)	52 (84)
Speech disorders	38 (88)	43 (69)
Tremors	7 (16)	13 (21)
Abnormal pupil (reflexes)	19 (44)	30 (48)
Age at death, mean (range)	52.4 (33.8–70.5)	54.1 (33.1–82.1)
Survival from admission to death, years, mean (range); median	4.3 (0.0–25.4); 1.8	2.1 (0.0–20.6); 0.9
Duration of disease until death, years, mean (range); median	6.5 (0.2–25.6); 4.4	3.8 (0.2–21.2); 3.0

The interval between admission and the start of MFT (known for 42 patients) ranged from two days to six months. Thirty patients were treated with MFT within one month after admission. Patients were inoculated by subcutaneous injection between the shoulder blades with 1–3 cm^3 blood containing malaria parasites. Infected blood was usually obtained from another patient who underwent MFT. In none of the medical records, transmission of malaria by infected mosquitoes was noted. For nine patients, the Plasmodium species was recorded: seven were treated with *P. malariae* and two with *P. vivax*.

Typically, the first febrile attack occurred after an incubation period of about two weeks. After 8–12 paroxysms of high fever (39–40°C = 102–104°F) in a period of 10–14 days, patients were treated with quinine sulphate to terminate the malaria infection. In two patients, MFT fever spikes discontinued spontaneously. Following malaria treatment with

quinine, patients received additional anti-syphilitic treatment with metals like arsenic and bismuth.

MFT Complications

In 14 patients, premature termination of MFT was recorded and four of those died within one month of malaria inoculation. In 13 cases, one or more reasons for premature termination were mentioned: occurrence of daily fever spikes without fever-free, restorative days (n = 5), diarrhea (n = 3), anemia (n = 2), exhaustion (n = 2), pneumonia (n = 1), jaundice (n = 1), and/or pyelocystitis (n = 1).

Survival and Cause of Death

Patients treated with MFT had a significantly longer survival after admission (p = 0.02; log-rank test; figure 2).

Fig. 2. Survival after admission (Kaplan-Meier) per treatment category. Curves shown till 8 years follow-up. Malaria fever therapy (MFT+) and MFT– survival differ significantly (p = 0.02; log-rank test).
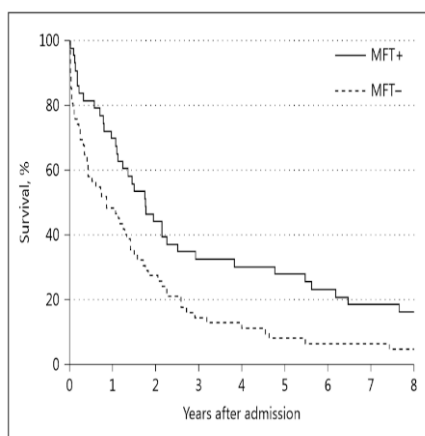
Cause of death was recorded in 24 (56%) MFT-treated patients and in 33 (53%) non-MFT-treated patients. In both groups, pneumonia, epileptic seizures and pressure ulcers were contributing factors to the cause of most deaths. One non-MFT-treated patient died from malaria. It is not known whether malaria in this case was a relapse of a prior spontaneous infection or due to earlier undocumented MFT. Details are presented in table 2.

Table 2. Causes of death of patients with general paralysis of the insane treated with malaria fever therapy (MFT+) or without (MFT−)

	MFT+	MFT-	Total
Number with cause of death mentioned in files	24	33	57
Epileptic insults, *n* (%)	7 (29)	10 (30)	17 (25)
Pneumonia, *n* (%)	7 (29)	9 (27)	16 (28)
Other infections, *n* (%)	2 (8)	6 (18)	8 (14)
Decubital lesions, *n* (%)	3 (13)	4 (12)	7 (12)
Heart failure, *n* (%)	2 (8)	5 (15)	7 (12)
MFT, *n* (%)	3 (13)		3 (5)
Haematemesis, *n* (%)	1 (4)	1 (3)	2 (4)
Jaundice, *n* (%)	2 (8)		2 (4)
Nephritis, *n* (%)	1 (4)	1 (3)	2 (4)
Cerebro vascular accident, *n* (%)		2 (6)	2 (4)
Gastric cancer, *n* (%)	1 (4)		1 (2)
Malaria, *n* (%)		1 (3)	1 (2)

Case Descriptions

Case A

A 43-year-old married man was admitted to the hospital in June 1938 because of progressive confusion and aggressive impulsive behaviour. His medical history revealed a short episode of confusion two years earlier.

On admission, he showed confused, agitated, and destructive behaviours with frequent shouting, singing and spitting. He had a reduced need for sleep and persistently refused food and medical examination. Neurological observation demonstrated gait disturbances, but no obvious motor or sensory deficits.

Routine laboratory testing revealed a positive Wassermann test in blood and cerebrospinal fluid and the diagnosis of GPI was made. Subsequently, the patient was inoculated with malaria parasites and he developed daily fever spikes. After nine fever spikes, the malaria infection was treated with quinine. Following MFT, salvarsan and bismogenol were prescribed. His physical condition recovered rapidly and, although he occasionally showed aggressiveness toward his wife, gradually some improvement of his mental condition was noted too. Since his mental and neurological states were sufficiently improved, he was discharged nine months after admission.

One year later, the patient was readmitted. His sister wrote in a letter to his physician that he had been functioning rather well until the unexpected death of his wife. Thereafter, he became frightened and depressed. Psychiatric examination at readmittance revealed a depression with suicidal ideations and visual hallucinations. He was confused, restless and unable to communicate and died within four weeks after readmission, due to physical and mental exhaustion.

Case B

In August 1938, a 58-year-old barkeeper, who had been a widower for nearly ten years, was admitted to the hospital. For over one year, he progressively developed depressive symptoms and became introverted, often mumbling to himself. Occasionally, there were aggressive outbursts during which he chased his customers out of his bar. Mental status examination on admission revealed a depressed man with suicidal ideations and a gloomy appearance. He frequently showed episodes with intensive crying and fears of financial ruin. Mild psychomotor retardation was noticed, but memory and intellectual function were intact. His behaviour was characterized by paranoia without reporting hallucinatory experiences. At medical examination his pupils were regular, equal and slowly reacting to light. Achilles tendon reflexes were absent bilaterally. Laboratory tests demonstrated a positive Wassermann reaction in blood (+7 on a scale from 0 to 10) and cerebrospinal fluid (+8 on a scale from 0 to 10). A diagnosis of GPI was made and MFT was started within one month of admission. The patient developed several spikes of high fever. Due to severe anemia and decubital lesions, MFT had to be discontinued prematurely. For several months, he remained depressive and severely restricted in performing the activities of daily living. Four months after MFT, however, his mood changed and he became manic with delusions of grandeur. In the following months, he showed several mood swings. In April 1940, he was discharged on parole on request of his family.

Two years later, the patient became confused and agitated. He quarrelled with his children and customers at daytime and wandered the streets at night. His general physician requested readmission and suggested retreatment with MFT because of the partial success ascribed to the first treatment. On readmission, the patient was very confused and disoriented. Although his speech was severely dysarthric, he was able to express his delusional belief that all close to him had deceased. His mood changed rapidly from euphoric to depressive and periodically he was very anxious. Within two weeks of admission, MFT was started and the patient was subcutaneously injected with 3 mL blood containing *P. malariae* (quartan malaria). Fourteen days later, regular spikes of fever started. Severe anemia and heart failure necessitated treatment with digitalis. After six fever spikes within two weeks, the patient became exhausted. MFT was terminated with quinine and he received neo-salvarsan and bismogenol. His clinical condition remained unchanged until his death one year later. No specific cause of death was recorded in the case notes.

DISCUSSION

To the best of our knowledge, this paper is the first historical study on MFT in GPI in a psychiatric hospital in the Netherlands. In this cohort study focusing on MFT in the period 1924–1957, MFT practice was analysed in 43 patients with GPI. Although MFT has been used for thousands of patients across the world and has greatly contributed to the knowledge of malariology [8], its value for treatment of GPI remains doubtful. The reported magnitude of

success of MFT was highly variable and the rapid and widespread acceptance of this therapy probably reflects the absence of an effective treatment for this disease at the time [5].

Comparative, well-controlled, trials of MFT versus standard therapy, or MFT versus other types of fever have not been reported. Only observational studies are available with many differences in often poorly described patient characteristics, criteria of diagnosis, response to therapy, and follow-up. Although many cases were treated in general hospitals, complex behavioural problems, probably related to more advanced stages of the disease, often necessitated referral to a psychiatric hospital [6, 15]. Therefore, patient characteristics of those treated in a psychiatric hospital may differ from those treated in a general hospital.

Differences in malarial strains used, number of fever spikes and pharmacological treatments preceding or following MFT, particularly tryparsamide or bismuth, may also have influenced the results [16]. Moreover, detailed evaluation of treatment outcome and differentiation between treatment outcome and spontaneous remission requires a long follow-up period. Factors influencing clinical decision for initiating MFT are rarely noted in the medical records. However, perceived favourable results may have influenced this decision.

MFT-Procedure

The typical MFT practice is described in case A.

No patient aged over 69 received MFT, which is in concordance with MFT practice in Amsterdam [8] and Scotland [6].

Prior to MFT, all patients underwent a detailed examination, since high spikes of malarial fever could be exhausting, especially in conditions like (syphilitic) heart disease, cachexia, diabetes mellitus, obesity and tuberculosis [5, 6]. Noteworthy, in 8 of 43 cases treated with MFT, an indication of syphilitic aortic heart disease existed. This illustrates that these comorbid diseases were not always considered contraindications. Bed rest, nursing care and nourishing diet were often applied to improve health status prior to MFT [8]. This may explain why MFT sometimes started more than two months after admission.

Disease duration exceeded one year in half of the MFT treated patients, while in other Dutch hospitals and Scottish asylums, specific therapy was rarely used in patients who had been insane for over a year prior to admission [10, 17]. Due to irreversible tissue damage, complete remission of symptoms was not to be expected in these cases. Nevertheless, partial recovery of neurological and psychiatric symptoms was described [4] and this may explain the application in a rather heterogeneous group of patients.

Patients with all kinds of neuropsychiatric symptoms at admission received MFT, including almost half of the patients with manic symptoms. Studies from this period reported contradictory observations on the relationship between clinical presentation and treatment outcome [4, 6].

Inoculation with malaria was done by patient-to-patient transmission of infected blood, as was the most common method worldwide [3, 6, 7]. In the Netherlands, the malarial species *P. vivax*, Madagascar strain (malaria tertiana), and since 1933 even *P. malariae* (quartan malaria) were most often used [8]. In general, *P. vivax* , due to its supposed benign

characteristics, high and regular cycles of fever and quinine sensitivity, was considered the most suitable species. *P. malariae* was reserved for GPI patients who were not susceptible to *P. vivax* (probably due to immunity acquired by an earlier infection [8]), for those requiring re-inoculation, such as in the above described case B, and for older and more debilitated patients [5].

Complications and Survival

The complications of MFT reported in this study, that is, severe headache, malaise, anaemia, cardiovascular collapse, jaundice and renal disease, were in part related to the malaria infection. MFT could provoke a daily recurrence of high fevers instead of the aimed recurrence every third or fourth day. In this study, MFT was prematurely terminated in 10 patients, predominantly because of such protracted, daily fevers.

Since no register of diagnosis on admission was available, death statistics was used to identify GPI patients, which may have biased the study to some extent. Patients who improved sufficiently to be discharged could not be included except for those who were readmitted to VvGI and died while hospitalized. Since survival in all GPI patients (MFT- and non-MFT-treated) was longer than in the pre-MFT era, improved medical care may have contributed to prolonged survival. Nevertheless, patients treated with MFT had a significantly longer survival after admission and a prolonged total survival after onset of disease, both one year (70 vs. 48%) and five years (28 vs. 8%) after admission. This effect of therapy on survival still exists after excluding patients who died within three weeks after admission.

It should be kept in mind that on admission the group of MFT-treated patients was possibly in a better medical condition than the group of non-treated patients and it is likely that this has affected the survival time. However, this is not reflected by differences in baseline conditions that may be associated with higher risk of death (table 1).

The most important cause of death in MFT and non MFT-treated patients was progression of the syphilitic disease process, resulting in epileptic seizures, confinement to bed, pressure lesions and increased risk of pneumonia.

Since only clinical records of deceased patients were examined, the finding of a death rate of 16% within two months of MFT could be an overestimation of the actual risks. It has to be emphasized here that several factors contributed to the broad range of reported mortality, such as different criteria for MFT-related mortality, great variation in patient populations, as well as selection criteria for therapy, malarial species and strains used, number and height of fever spikes. Nicol, for instance, reported a mortality rate varying from 10 to 15%, depending on the stage of disease and plasmodium strain used [4]. Moreover, MFT-related mortality may have decreased over time due to accumulated experience or increased due to expansion of inclusion criteria as a result of presumed effectiveness [7].

MFT remained the standard therapy for GPI until the discovery of penicillin in the mid-1940s as an effective and safer treatment for syphilis in all stages [6]. However, penicillin therapy was not immediately widely accepted and often applied in combination with MFT to

ensure bactericidal antibiotic levels in the central nervous system in the United States and in the Netherlands up to the mid1960s [1, 5] and in the United Kingdom until the 1970s [5, 6].

CONCLUSIONS

MFT was practiced in a wide range of patients with GPI, including those with disease duration of more than one year, up to 70 years of age, with a broad array of symptoms and comorbidities, such as (syphilitic) cardiac disease. Notwithstanding these broad inclusion criteria, practice and mortality rates in MFT-treated patients correspond to findings worldwide. MFT was well tolerated and MFT-treated patients had a significantly longer survival. Main causes of death in patients with GPI were epileptic seizures and infectious diseases, irrespective of MFT.

ACKNOWLEDGMENTS

DISCLOSURE STATEMENT

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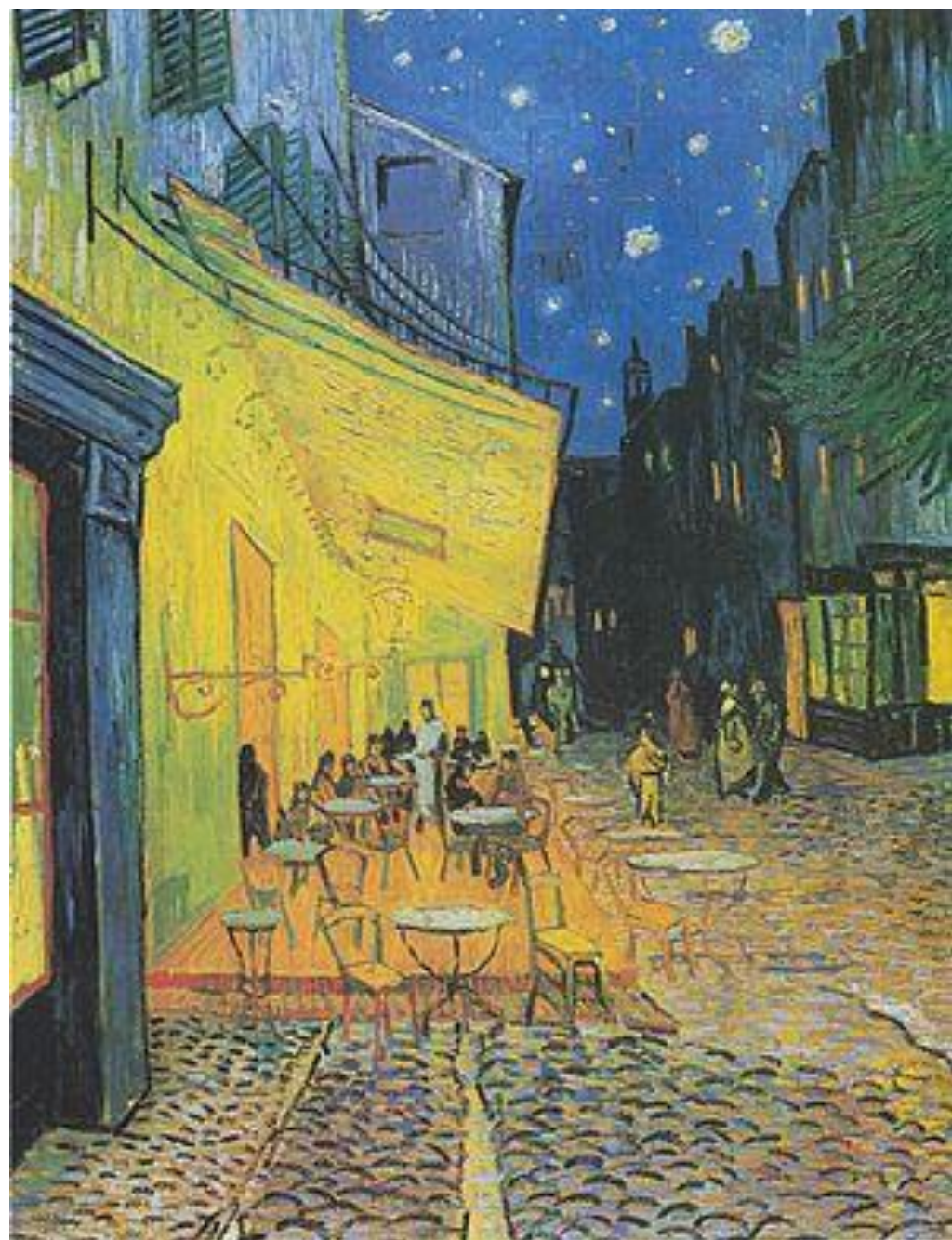
CHAPTER 4

NEUROSYPHILIS
IN THE MIXED URBAN-RURAL COMMUNITY OF THE NETHERLANDS

ABSTRACT

Objective: Neurosyphilis is caused by dissemination into the central nervous system of *Treponema pallidum*. Although the incidence of syphilis in the Netherlands has declined since the mid-1980s, syphilis has re-emerged, mainly in the urban centres. It is not known whether this also holds true for neurosyphilis.

Methods: The epidemiology of neurosyphilis in Dutch general hospitals in the period 1999–2010 was studied in a retrospective cohort study. Data from the Dutch sexually transmitted infection (STI) clinics were used to analyse the number of patients diagnosed with syphilis in this period.

Results: An incidence of neurosyphilis of 0.47 per 100,000 adults was calculated, corresponding with about 60 new cases per year. This incidence was higher in the western (urbanised) part of the Netherlands, as compared with the more rural areas (0.6 and 0.4, respectively). The number of patients diagnosed with syphilis in STI clinics increased from 150 to 700 cases in 2004 and decreased to 500 new cases in 2010. The sex ratio was in favour of men, yielding a percentage of 90% of the syphilis cases and of 75% of the neurosyphilitic cases. The incidence of neurosyphilis was highest in men aged 35–65 years, and in women aged 75 years and above. The most frequently reported clinical manifestation of neurosyphilis was tabes dorsalis. In this study, 15% of the patients were HIV-seropositive.

Conclusion: The incidence of neurosyphilis in a mixed urban–rural community such as the Netherlands is comparable to that in other European countries. Most patients are young, urban and men, and given the frequent atypical manifestations of the disease reintroduction of screening for neurosyphilis has to be considered.

SIGNIFICANT OUTCOMES

- In this first nationwide study on neurosyphilis in the Netherlands, a mean annual incidence of 0.47 per 100,000 adults was found, with predominantly male subjects.
- The highest incidence of neurosyphilis was found in the most urbanised part of the Netherlands (0.6 per 100,000 adults).
- Tabes dorsalis is the most frequently registered subclassification of neurosyphilis, comparable to observations in the pre-antibiotic era.

LIMITATIONS

- Given the sometimes very long latent period, the increased incidence of syphilis could still be followed by an enhanced incidence of neurosyphilis in the near future.
- Underdiagnosis and underrepresentation of neurosyphilis and HIV should still be taken into account.

INTRODUCTION

Neurosyphilis is defined as any involvement of the central nervous system (CNS) at any stage of syphilitic infection, caused by *Treponema pallidum* subspecies pallidum (1). On the basis of clinical manifestations, it is classified in early, late and asymptomatic neurosyphilis. Early neurosyphilis is characterised by meningitis, cranial nerve abnormalities and cerebrospinal accidents. The most common clinical syndromes of late neurosyphilis are tabes dorsalis and general paralysis of the insane, of which the former was the most prevalent form in the pre-antibiotic era (2).

After the introduction of penicillin therapy in the 1940s and the expansion of screening, treatment and prevention programmes, the incidence of both syphilis and neurosyphilis decreased significantly in high-income countries (3,4). Given the subsequently rapid decrease of syphilis-associated dementia, the American Academy of Neurology omitted standard screening for syphilis in the diagnostic workup of dementia, except for the high-incidence regions (5).

It should be stressed, however, that, despite the post-antibiotic reduction of syphilis incidence, re-emergence of the disease occurred at several time points in the United States, Australia and many European countries (4,6). In the latter, such as the Netherlands, the increase of syphilis incidence was most pronounced in major urban centres, particularly in populations of men who have sex with men (4,7,8). Other factors contributing to this increase are HIV infection, intravenous use of illegal drugs and immigration into western European countries of people from countries with endemic syphilis (9–11). The number of hospitalisations because of syphilis increased in large urban areas in Spain between 1997 and 2006 (12), whereas in the United Kingdom resurgence was initially observed in the larger cities but later progressed to the suburban and rural settings (13).

In the western European countries, there is an ongoing debate about the utility of routine serological screening for syphilis in the workup of neurological and psychiatric conditions (14–16). Consequently, clinicians are increasingly unaware of syphilis – a disease referred to as 'the great imitator' by Sir William Osler (1849–1919) because of its varied presentations – and less experienced in the interpretation of serological values. This relative unfamiliarity with neurosyphilis may lead to a marked delay in case detection, as had happened with other infectious diseases that were assumed to be under control (17). In the Netherlands, 11 cases of neurosyphilis with neurological and/or psychiatric phenomena have been recently published (table 1). Analysis of these reports showed that neurosyphilis was often not included in the differential diagnosis but incidentally detected by routine blood screening, followed by examination of the cerebrospinal fluid.

Table 1. Case reports on neurosyphilis in the Netherlands over the last decade

	Sex and age (years)	HIV-seropositive	Duration of illness	Neurosyphilitic syndrome
Hilderink and Eerenberg (18)	F, 50	?	> 1 year	Dementia paralytica
Overbeek et al. (19)	M, 34	?	> 1 year	Dementia paralytica
	F, 24	-	Several days	Dementia paralytica
	M, 46	+	?	Dementia paralytica
Van Coevorden et al. (20)	M, 44	-	4 months	Tabes dorsalis and uveitis luetica
Blok et al. (21)	M, 39	-	1 month	Meningitis with cranial nerve involvement
	M, 38	+	Several days	Meningitis with cranial nerve involvement
Niermeijer et al (22)	M, 69	?	Several months	Dementia paralytica and ocular syphilis
Zoons and van de Beek (23)	M, 45	?	> 1 year	Meningovascular neurosyphilis
Lens-Daey Ouwens et al. (24)	M, 45	-	Several months	Meningovascular neurosyphilis
Segers-van Rijn and Blom (25)	M, about 50	+	> 1 year	Dementia paralytica

F, female; M, male; ?, unknown

As the efficacy of antibiotic treatment depends on the stage of neurosyphilis, early diagnosis is highly important (1). In general, all symptoms completely resolve after antibiotic treatment in patients with early, meningeal neurosyphilis, with the exception of HIV-infected patients who may have persistent signs and symptoms for more than a year after such a therapy (26,27). However, owing to parenchymal brain damage, complete remission of symptoms does not always occur in patients with late neurosyphilis, albeit that disease progression may be prevented (28–30).

In Europe, a yearly neurosyphilis incidence varying from 0.16 to 2.1 per 100,000 inhabitants is documented (31–33). As the incidence of syphilis is probably related to demographic parameters such as the urban–rural balance, a small country with a high population density such as the Netherlands is suitable for investigating the epidemiology of syphilis and neurosyphilis.

AIMS OF THE STUDY

In the absence of a nationwide surveillance programme for neurosyphilis, data on syphilis and neurosyphilis in the Netherlands over a 12-year period (1999–2010) were analysed in the present study, by their epidemiological and clinical characteristics.

MATERIALS AND METHODS

Hospital data

In this retrospective cohort study, hospital data of neurosyphilis cases admitted to general hospitals were collected from the Dutch National Medical Registration over a 12-year period. In 1999–2004, this register had a coverage of 99%, whereas in the period 2005–2010 this figure was about 80–90% (population 16 million). All the patients included were aged 20 years or above, with a primary or secondary discharge diagnosis of neurosyphilis.

Neurosyphilis was defined according to the International Classification of Diseases, ninth revision Clinical Modification (ICD9-CM) using the ICD9-CM code 094 and subcategory codes for all manifestations of neurosyphilis and 91.81 for acute syphilitic meningitis. The hospital data comprised age, gender, date of discharge and a four-digit zip code. These data combined with patient identifiers were used to exclude duplicate hospitalisations. Incidence was defined as the number of cases with a discharge diagnosis (primary or secondary) of neurosyphilis per 100,000 of the Dutch population, aged 20 years or above in the period from 1999 to 2010. Demographic parameters were analysed for all neurosyphilitic patients. Comorbidity with HIV infection was recorded according to ICD9-CM codes for HIV-seropositivity (042 to 044 and 795.8). Zip codes were used for geographic classification.

Data from centres for sexually transmitted infections (STI)

Data from the Dutch STI centres were used to analyse the number of syphilis cases diagnosed between 1999 and 2010. Until 2002, STI surveillance was based on voluntary registration by these centres. In 2003, a surveillance system comprising the most important centres became operational, yielding an 80% coverage. One year later, all existing STI centres were connected, providing national coverage. These clinics offer STI and HIV testing and treatment, free of charge, for high-risk groups and people who want to be tested anonymously. All new STI consultations and corresponding diagnoses are reported anonymously to the Centre for Infectious Disease Control for surveillance purposes. Attendees of a STI clinic are offered standard testing for chlamydia, gonorrhoea, syphilis and HIV. Other STI tests are conducted if necessary.

Data analysis

All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Although the number of syphilis cases diagnosed in the STI clinics increased to 700 cases in 2004, followed by a decrease to 500 new cases in 2010 (figure 1), no time trend for incidence of neurosyphilis could be found. In the period from January 1999 to December 2010, 695 discharge diagnoses of neurosyphilis were registered in the Dutch National Medical

Registration, varying from 41 to 72 cases per year. A primary discharge diagnosis of neurosyphilis was recorded in 560 cases (81%) and a secondary in 135 cases (19%).
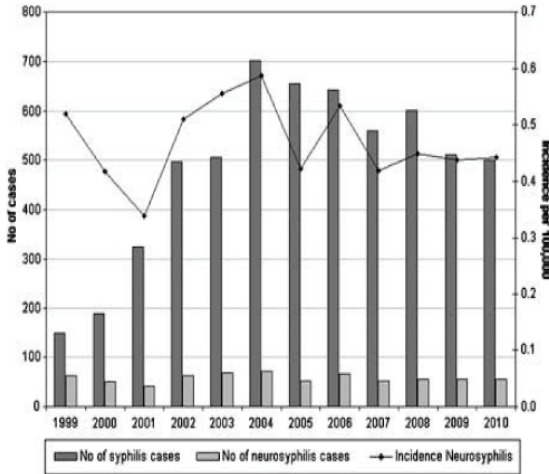

Figure 1. Number of syphilis diagnoses, number of hospitalisations because of neurosyphilis (left axis) and incidence of neurosyphilis (right axis) in the Netherlands (1999–2010).

The annual incidence of neurosyphilis varied from 0.34 to 0.59 per 100,000 of the population aged 20 years or above. Of all the patients recorded with syphilis (n = 5311) in the STI clinics or neurosyphilis () in the Dutch National Medical Registration (n = 695), the majority were men (91% and 76%, respectively). With respect to neurosyphilis, the mean annual incidence per 100,000 was 0.7 in men and 0.2 in women. Median age for men was 47 years (oldest 86 years) and 54 years for women (oldest 92 years) (figure 2).
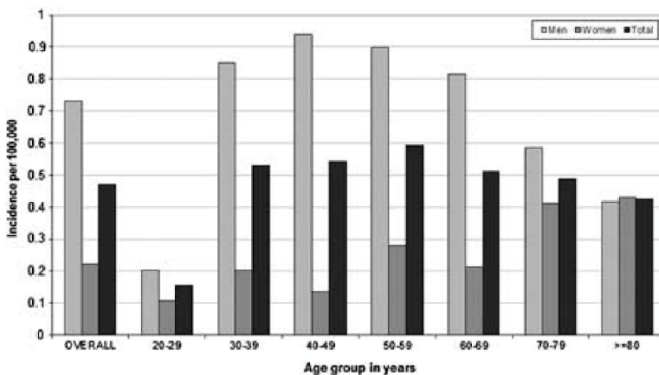

Figure 2: Mean incidence of hospitalisations because of neurosyphilis in the Netherlands by age group and sex (1999–2010).

As presented in table 2, the incidence of neurosyphilis differed per age group and gender, with the highest incidence for men in the age range of 30–50 years, and for women in the age range of 70 years and above. The mean annual incidence of hospitalisation for neurosyphilis was significantly higher in the western, most urbanised part of the Netherlands (0.6 per 100,000 of the population). In the rest of the Netherlands, the incidence was 0.4 per 100,000 of the population.

Table 2. Overall data on syphilis and neurosyphilis in the Netherlands (1999–2010)

	Total (*n*)	% of all neurosyphilis cases	M:F ratio	% HIV-seropositive	Age range	Median age
Syphilis	5836	-	10.1/1	Unknown	Unknown	Unknown
Neurosyphilis	695	-	4.2/1	15	21-92	49
Asymptomatic	38	5	2.8/1	13	22-78	40
Early	11	2	10/1	18	26-86	42
Late	204	29	2.3/1	1	20-92	59.2
NOS/ NEC	427	61	4.6/1	21	20-84	46
Others	15	2	4.0/1	20	26-75	48

Hospital data of all patients revealed a diagnosis of late neurosyphilis in 204 cases (29%), asymptomatic neurosyphilis in 38 (5%), early neurosyphilis in 11 (2%) and other forms of neurosyphilis in 15 (2%) cases. Clinical characteristics are summarised in table 2.

Clinical manifestation was not specified (neurosyphilis NEC or NOS) in 427 cases (61%). Tabes dorsalis (170 cases) was the most frequent registered form of neurosyphilis.

Median age did not differ significantly between patients with general paresis of the insane (59.5 years) and patients with tabes dorsalis (59.0 years). Patients with early neurosyphilis were significantly younger (median age 42 years) than those with late neurosyphilis (median age 59 years). Gender was not correlated with any clinical manifestation. An additional HIV-positive status was reported in 101 patients (15%) who had a median age of 40 years (range 27–70) and were mostly men (93%).

DISCUSSION

This is the first nationwide study on neurosyphilis in the Netherlands, covering a recent period of 12 years, in which a mean annual incidence of 0.47 per 100,000 adults was found from a retrospective analysis of hospital data, with predominantly male subjects. The mean annual incidence of hospitalisation for neurosyphilis was significantly higher in the western, most urbanised part of the Netherlands (0.6 per 100,000 of the population). In the rest of the Netherlands, the incidence was 0.4 per 100,000 of the population.

The yearly incidence found in this study is higher than that observed in the 1970s in Leicester (0.18 per 100,000 inhabitants) (32) and in the 1980s in Greater Copenhagen (0.16–0.46) (31), but lower than in the northern area of the island of Gran Canaria and the whole island of Lanzarote in the 1990s (0.2–2.1 per 100,000) (33). As for the sex ratio, it was found that the higher syphilis infection rate in men is comparable to that reported in most European countries (8). This also holds true for neurosyphilis (31–36). Similarly, neurosyphilis affected men twice as often as women (10% and 5%, respectively) in the pre-antibiotic era (37). However, comparison of the incidence rates of neurosyphilis in the various European countries is difficult because of the considerable variability in case definitions.

Interestingly, although a marked increase in syphilis is documented nationwide in STI clinics in the Netherlands up to 2004, no change in neurosyphilis incidence is observed over the past 12 years. This might be the result of continued efforts towards earlier and improved syphilis screening and treatment in STI clinics, and routine screening of pregnant women and blood donors (38,39). As standard screening for syphilis in psychiatric and neurological patients is no longer routinely included in laboratory testing, there is a risk for underdiagnosis and subsequent underregistration of neurosyphilis. It should be stressed, however, that because of the long latency between syphilis and neurosyphilis, a rise in the documented incidence of neurosyphilis may still occur in the decades to come.

Although tabes dorsalis is the most frequently registered subclassification of neurosyphilis in the present study, comparable to observations in the pre-antibiotic era, a correct interpretation of this finding cannot be given as 54% of cases was classified as neurosyphilis NOS. In contrast, other studies have reported that tabes dorsalis has become increasingly rare in the antibiotic era (31,35,40). In an earlier Dutch clinical cohort study, the overall figures of early and late neurosyphilitic syndromes were more or less the same in the pre- and post-antibiotic eras, with the exception of an increased incidence of asymptomatic neurosyphilis (1930–1940: n = 518; 1970–1984: n = 121). The rise in incidence of tabo paralysis and decline in tabes dorsalis in the post-antibiotic era group was interpreted as the result of a more accurate neuropsychological patient investigation (35). As can be inferred from this study on a relatively large group of patients, neurosyphilis in the Netherlands is not restricted to HIV-positive patients, a finding that corroborates results from a smaller sample Danish study (36). In some studies, HIV-positive patients are reported to not only have a higher incidence of early rather than late neurosyphilis, but also a shorter period before the manifestation of late forms of neurosyphilis (27,41,42). This may be explained by their compromised immune system. In the pre antibiotic era, the majority of cases with acute syphilitic meningitis occurred after an unsuccessful therapy for early syphilis. It was hypothesised that exposure to drugs that did not reach treponemocidal levels in the CNS resulted in diminished immune response and clinically manifest neurosyphilis (1).

In line with these observations, the median age of HIV-seropositive neurosyphilitic patients in the present study was significantly lower than the overall median age. As subclassification of neurosyphilis was registered in only 24% of the HIV-positive neurosyphilitic patients, the relationship between early versus late neurosyphilis and HIV-seropositivity

cannot be fully elucidated. The high number of cases with an ICD9-CM neurosyphilis NOS/NEC code may result from atypical clinical manifestations of the disease. In contrast, in a recent Danish study, only 13% of the cases were reported with the classification of neurosyphilis NOS (36).

In the present study, cases with early neurosyphilis were significantly younger than those with late forms of the disease as could have been expected, assuming that manifestations of neurosyphilis occur in a consecutive order. In contrast, however, no significant difference in median age in patients with tabes dorsalis and general paralysis of the insane (considered the last stage of neurosyphilis) was found in the present study. Moreover, previous studies in the Netherlands and Denmark did not disclose any differences in age between cases classified with 'early' and 'late' neurosyphilis (35,36). Although the traditional classification is based on the idea that syphilitic meningitis, meningovascular syphilis, tabes dorsalis and general paresis of the insane occur in a sequential order, these forms rarely exist in pure form at autopsy (43). Classifying the clinical manifestations of neurosyphilis might be complicated by the overlap between the clinical syndromes (44), thus explaining the high rate of cases without clinical classification (neurosyphilis NOS and NEC) in this study.

Although it seems unlikely that new cases of neurosyphilis are missed out as all patients with a new diagnosis of neurosyphilis are treated with intravenous antibiotics in a general hospital, underdiagnosis and therefore underregistration of neurosyphilis and HIV should still be taken into account. As stated before, the low incidence of neurosyphilis co-occurs with less familiarity of clinicians with the asymptomatic and atypical manifestations of the disease. Reintroduction of screening for neurosyphilis should therefore be considered seriously (45). Further research on the frequent atypical clinical symptomatology is needed to improve both diagnosis and management of patients with neurosyphilis.

Summarising, over the past 12 years, neurosyphilis was diagnosed in about 60 Dutch hospitalised adult patients per year, indicating that neurosyphilis is yet to be considered in the differential diagnosis. The incidence of neurosyphilis is highest in young, urban men, although tabes dorsalis is the most frequently reported clinical manifestation.

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AUTHORS' CONTRIBUTIONS

I.M. Daey Ouwens contributed substantially to the conception and design of the study and the interpretation of the data and the draft of the article. F.D.H. Koedijk contributed substantially to the acquisition, analysis and interpretation of data and the draft of the article. A.T.L. Fiolet contributed substantially to the design of the study, the interpretation of the data and the draft of the article. M.G. Van Veen and C.C. Van den Wijngaard contributed substantially to

the conception and design of the study, the acquisition, analysis and interpretation of the data. W.M.A. Verhoeven, J.I.M. Egger and M.A.B. van der Sande contributed substantially to the conception and design of the study and the interpretation of the data and revised the manuscript critically for intellectual content. All authors have seen and approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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CHAPTER 5

CLINICAL PRESENTATION OF LABORATORY CONFIRMED NEUROSYPHILIS IN A RECENT CASES SERIES

ABSTRACT

Objectives: The worldwide increase in the incidence of syphilis necessitates alertness to the occurrence of neurosyphilis. Early recognition of neurosyphilis allows for timely treatment, leading to a better treatment outcome. This retrospective study aims to describe the clinical presentation of neurosyphilis in a recent series of neurosyphilis patients.

Methods: All patients were included with a new, laboratory confirmed, diagnosis of neurosyphilis in the period 2004-2018. The clinical data were analysed.

Results: 34 neurosyphilis patients (1 woman and 33 men) were identified. Age varied from 31-84 years (median age: 44 years). A history of syphilis infection was known for 11 (32%) patients; 12 (35%) patients were HIV seropositive. The distribution of the clinical syndromes was as follows: 16 patients with early neurosyphilis (acute meningitis, meningovasculitis and / or uveitis), 9 patients with late neurosyphilis (General Paralysis of the Insane and / or Tabes Dorsalis), 2 patients with symptoms of both early and late neurosyphilis, 6 patients with asymptomatic neurosyphilis and in 1 patient insufficient data were available to determine a clinical syndrome. Early neurosyphilis was seen in all age categories, late neurosyphilis only occurred in patients > 40 years.

Conclusion: Neurosyphilis occurs in adults in all age groups, in men more frequent than in women, often in HIV-infected patients, and can present with a wide range of clinical syndromes. Usually no previous infection with syphilis is known.

INTRODUCTION

A worldwide increase in the incidence of syphilitic infections is reported since the turn of the 21st century (Fenton et al. 2008). In 2008, the World Health Organization estimated 10.6 million cases among adults worldwide. In the European Union and European Economic Areas, 28,701 syphilis cases (6.0 per 100,000 population) were reported in 2015, mostly in patients older than 25 years of age (ECDC 2017). Between 2010 and 2015, many countries observed a sharp increase of over 50% in the rates of reported syphilis infections, mainly in man having sex with men (MSM) (ECDC 2017), probably related to changing sexual and social norms and to interactions with increasingly prevalent Human Immunodeficiency Virus (HIV) infection (Fenton et al. 2008). Syphilis seems to occur more frequently in the context of substance abuse, migration and underinvestment in public-health services (Fenton et al. 2008).

The causative bacterium of syphilitic infection, the neurotropic *Treponema pallidum* subspecies pallidum, probably enters the central nervous system (CNS) shortly after infection in up to one-quarter of patients with early syphilis (Marra 2004). In 16-48% of cases with early (primary or secondary) syphilis, abnormalities in the cerebrospinal fluid (CSF) have been detected (Berger and Dean 2014). In a minority of the cases, those unable to spontaneously eradicate the infection from the CSF, asymptomatic or symptomatic neurosyphilis will develop within months or decades (Berger and Dean 2014). In the pre antibiotic era, the Oslo study on the natural history of untreated syphilis demonstrated that 9.4% of the men and 5.0% of the women ultimately developed neurosyphilis (Clark and Danbolt 1955). Since then, early treatment of syphilitic infection with penicillin, antibiotic treatment for intercurrent infections, variation in the incidence of different strains of syphilis, and HIV co-infection, may have changed the course of the disease. However, recent data on the natural history of syphilis are unavailable as yet.

The clinical manifestations of neurosyphilis are traditionally divided into 'early' and 'late' neurosyphilis. Early neurosyphilis, presenting as meningitis or meningovascular disease, typically manifests within months to several years after the initial infection. Within a year of initial infection involvement of the meninges may result in meningitis with headache, meningismus and cranial nerve palsies, in particular VII, VIII, VI and II. Meningovascular disease typically occurs after 6-7 years. About 10% of patients with neurosyphilis and almost 3% of all syphilis patients present with a stroke. In one study, up to 74% of this category of patients were under the age of 50 (Abkur et al. 2015).

Late neurosyphilis primarily affects the CNS parenchyma and occurs 15-30 years after initial infection and results most commonly in the clinical syndromes of General Paralysis of the Insane (GPI) (also termed General Paralysis or Dementia Paralytica) and Tabes Dorsalis (TD) (also known as syphilitic myelopathy) (Berger and Dean 2014). GPI presents with progressive neuropsychiatric symptoms. TD, which affects the dorsal roots, posterior column of the spinal cord, and optic nerves, presents as sensory ataxia with incontinence, pain, and optic atrophy (Marra 2004). Pupillary abnormalities, including Argyll-Robertson pupils (pupils

that are small, asymmetric, irregular, and poorly responsive to direct light with maintained appropriate constriction on accommodation) were once a hallmark symptom of TD.

The clinical diagnosis of neurosyphilis is challenging, since neurosyphilis can affect every part of the CNS and may mimic a wide variety of neurological and mental disorders. Moreover, at present no uniform clinical diagnostic criteria have been established. Therefore, CSF analysis is considered crucial for a diagnosis of neurosyphilis. However, a perfect "gold standard" diagnostic test is not available. Treponemal tests, for example the *Treponemal pallidum* hemagglutination (TPHA) and *Treponemal pallidum* particle agglutination (TPPA) tests, are used to screen for syphilitic infection. Since these tests may remain reactive for years, even after successful treatment, non-treponemal tests as the Veneral Disease Research Laboratory (VDRL) and the Rapid Plasma Reagin (RPR) test are often used to confirm active syphilitic infection (Peeling 2006). As treponemal antibodies can passively pass an intact blood-brain barrier, higher IgG levels in serum results into higher CSF levels. This leakage of antibodies through the serum-CSF barrier can be distinguished from additional intrathecal production of antibodies by the IgG-serum/CSF index, using the Reiber or TPPA index (Reiber 1994a; Reiber 1994b; Luger et al. 2000).

The present study aims to investigate the clinical characteristics of patients in whom cerebrospinal fluid tested positive for neurosyphilis in the period 2004-2018 in a country with a relatively low syphilis incidence.

MATERIAL AND METHODS

In this retrospective case series, all patients with a clinical diagnosis of neurosyphilis, confirmed with a CSF VDRL or PRP ≥ 4, a CSF TPHA ≥ 500, and/or a TPHA CSF-serum index ≥ 70 during the period 2004 to 2018 were examined.

The study protocol was reviewed and approved by the Medical Ethics Committee of the University Medical Centre Groningen, the Netherlands (Number: 2009/333).

CSF serological tests to confirm neurosyphilis were performed by the department of medical microbiology of Certe. Certe is a reference laboratory for syphilis serology, covering a catchment population of 1.1 million inhabitants and nine hospitals in the northeast part of the Netherlands, including the University Medical Centre Groningen. In results and tables of this paper titres, such as 1:250, will be represented as dilutions only, e.g. 250, and the term VDRL will be used instead of VDRL/RPR. In the Certe laboratory the CSF VDRL was completely replaced by the RPR test in 2014 after a lengthy comparison of both methods showed essentially similar results. The TPPA serum-CSF index was calculated as follows: (TPPA cerebrospinal fluid/1000)*(albumin serum/albumin cerebrospinal fluid) (Luger et al. 2000). A TPPA CSF-serum index of ≥ 70 was considered to demonstrate laboratory evidence for a diagnosis of neurosyphilis (Luger et al. 2000). Patients with a history of prior neurosyphilis were excluded.

The medical record of each patient was extensively reviewed for demographic, clinical and laboratory data. Duration of syphilitic disease was pragmatically determined as the

interval between positive syphilis serology in the serum and the CSF. Date of onset of neurosyphilis was determined as start of the first neurosyphilitic symptoms as documented in the records. Disease duration of neurosyphilis prior to diagnosis was determined as the interval between the date of reported onset of complaints compatible with neurosyphilis and that of serological confirmation of neurosyphilis. Patients with neurosyphilis were classified according to the criteria as described by Flood et al. (Flood et al.1998; see: Appendix 1). Asymptomatic neurosyphilis was defined as laboratory confirmed neurosyphilis without neurological signs or symptoms.

For normally distributed data mean and standard deviation were calculated. Non-normally distributed data were described with median, minimum and maximum values. The non-parametric Wilcoxon rank-sum test was used to test for differences in age distribution in relation to HIV status using an alpha of 0.05 as significant.

To illustrate the clinical presentation of neurosyphilis, a case description is presented.

RESULTS

Patient characteristics

A total of 34 patients (33 men and 1 woman) were identified with neurosyphilis confirmed with CSF serology. Median age was 44.1 (range 31.3 - 84.0) years. For 30 patients the referring medical speciality was known. Most patients were referred to the neurologist by internist (n=8; 27 %), general practitioner (n=7; 23%), psychiatrist (n=5; 17%) or ophthalmologist (n=4; 13%). In more than half of the male patients (n=19; 58%), the medical record mentioned that they had sex with men.

A history of syphilis was documented for 11 (32%) patients. In 10 (29 %) a history of psychiatric disease was present including substance abuse (n=6), depression (n=4) and /or psychosis (n=2). No patient had a history of dementia. For twelve (35 %) patients a positive HIV serology was documented. The median interval between the diagnoses of HIV infection and neurosyphilis was 2,5 years. The median age of neurosyphilis patients with a documented HIV-infection was significantly lower as compared to those without a documented HIV infection (41.1 years versus 45.1 years; p=0.03).

Presenting symptoms and signs

Information on presenting symptoms was available in 32 (94%) of the patients (table 1).

Several patients presented with more than one symptom. Most common symptoms were memory or cognitive complaints (n=8; 25%) and visual complaints (n=6; 19%). Three (9%) patients were asymptomatic. Table 2 shows the clinical findings on neurological examination at presentation.

Table 1: Presenting symptoms in patients with laboratory confirmed neurosyphilis (n=34).
*fatigue, dysphagia, headache, myalgia.

Symptoms	n (%)
Memory or cognitive complaints	8 (25%)
Visual complaints	6 (18%)
Psychiatric complaints	6 (19%)
Hemiparesis	5 (16%)
Gait disturbances	5 (16%)
Dizziness	4 (13%)
Non-specific symptoms*	10 (31%)
None	3 (9%)

Table 2: Neurological signs in patients with laboratory confirmed neurosyphilis (n=34).

Neurological signs	n (%)	Missing
Cognitive dysfunction	12 (39%)	3
Cranial nerve abnormalities	6 (20%)	4
Abnormal reflexes	5 (17%)	5
Motor abnormalities	5 (17%)	4
Sensory abnormalities	5 (17%)	5
Gait disturbances	4 (14%)	6
Pupillary abnormalities	3 (10%)	5
Epilepsy not otherwise explained	1 (3%)	5

Cognitive dysfunction or psychiatric signs at the time of neurosyphilis diagnosis were present in 12 (39%) and 8 (24%) patients, respectively. Delirium was the most common psychiatric disorder at presentation (n=4). Three patients had pupillary abnormalities.

Classification of symptoms
As depicted in table 3, clinical manifestations were categorized in 33 patients.

Table 3: Age, HIV status and interval between positive syphilis serology in serum and CSF per classification in patients with laboratory confirmed neurosyphilis (n=34).

	N	Median age in years (range)	Number of known HIV+ patients	Interval between positive syphilis serology in the serum and the CSF in days (range)
Early neurosyphilis	16	**41 (31-84)**		**97 (4-1642)**
Acute syphilitic meningitis	5		3	
Meningovascular syphilis	5		1	
Uveitis	5		3	
Acute syphilitic meningitis and uveitis	1		1	
Late neurosyphilis	9	**61 (43-70)**		**214 (28-601)**
General Paralysis of the Insane	6		1	
Tabes Dorsalis	2		0	
General Paralysis of the Insane and Tabes Dorsalis	1		0	
Combined early and late neurosyphilis	**2**	**44 (43-46)**		Not available
General Paralysis of the Insane and acute syphilitic meningitis	2		0	
Asymptomatic	6	**43 (34-45)**	2	Not applicable
Unclassifiable due to incomplete data	1		1	

Due to incomplete data classification was not possible for one patient. Age at diagnosis per clinical syndrome is presented in figure 1.
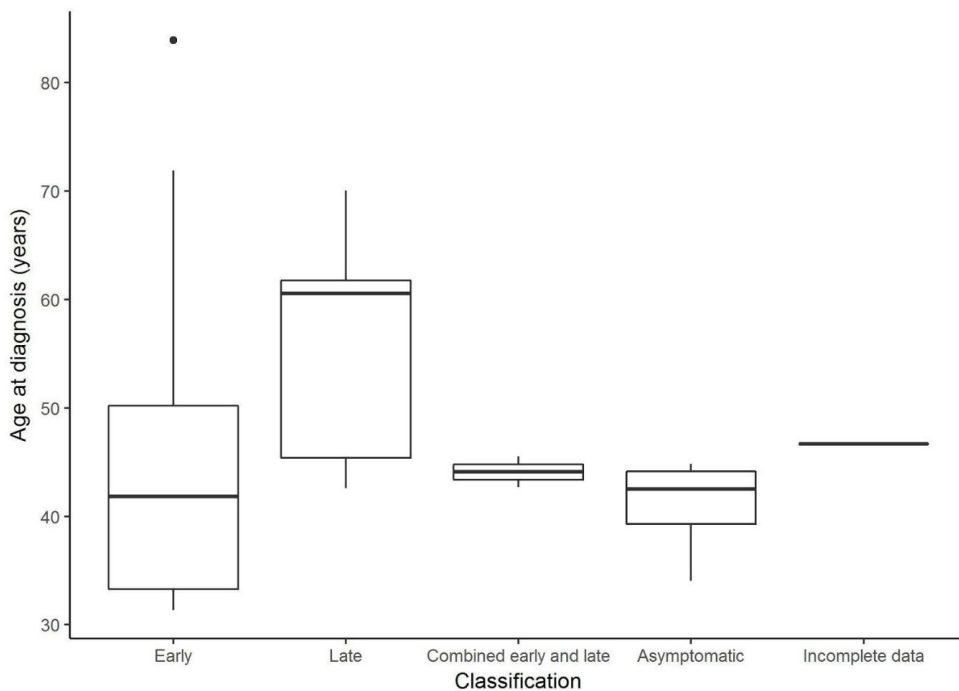
Figure 1: Average age (years) at diagnosis per classification (n=34).

GPI was the most frequent syndrome (n=9, 27%), followed by acute syphilitic meningitis (n=6; 18%). Early neurosyphilis was noticed in all age categories. Late neurosyphilis was not present in patients below 40 years of age (see figure 2).
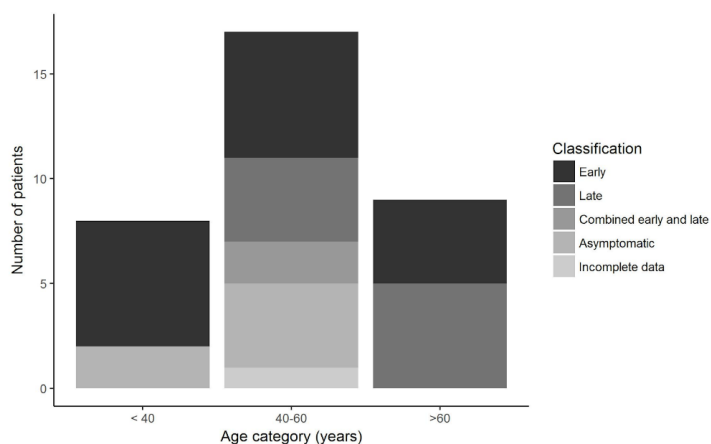

Figure 2: Classification of neurosyphilis per age category (n=34)

Duration of syphilitic disease

The interval between positive syphilis serology in the serum and the CSF was less than one year in 24 patients. Of those, ten presented with early neurosyphilis, seven with late neurosyphilis, four were asymptomatic and two patients presented with combined early and late neurosyphilis. In 10 patients, the interval between positive syphilis serology in the serum and the CSF was more than one year, in that six presented with early neurosyphilis, two with late neurosyphilis whereas two were asymptomatic.

Median interval between positive syphilis serology in the serum and the CSF was 138 days (ranging from 4 days to 4.5 years). Date of first symptoms of neurosyphilis was reported for 17 (61%) out of 28 patients with symptomatic neurosyphilis. As presented in figure 3, disease duration of neurosyphilis prior to diagnosis differed between age categories (43 days for patients aged < 40 year, 269 days for those aged from 40-60 year and 383 days for those > 60 years).
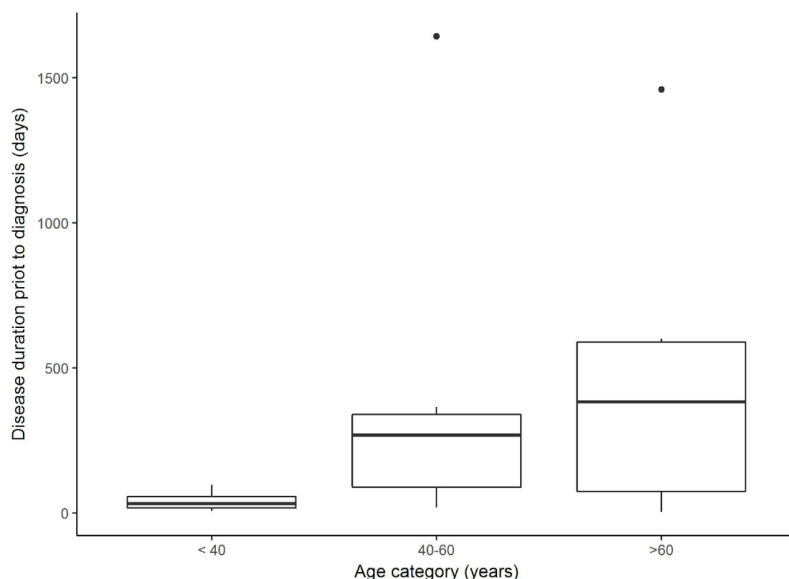

Figure 3: Disease duration of neurosyphilis prior to diagnosis per age category in days (n=34)

All patients had a TPPA CSF-serum index of ≥ 70. Additional laboratory results are presented in table 4.

Table 4: Laboratory data in patients with a clinical diagnosis and laboratory confirmed neurosyphilis (n=34)
CSF = cerebrospinal fluid; TPHA = *Treponema Pallidum* Haemagglutination Test; VDRL = Venereal Disease Research Laboratory

	Median (interquartile range)	Missing
Total CSF protein	0.52 (0.38-0.98) g/l	10
Number of mononuclear cells in CSF	21 (4-48)	11
VDRL in CSF	2 (0-4)	9
TPHA index	345 (163-1292)	0

Treatment

Information on antibiotic treatment was available for 28 (82%) patients. All but one patient were initially treated with penicillin; one received doxyxycline. Information on dosing was available for 17 patients. Three patients were treated with less than 18 million units per day. Information on duration of penicillin treatment was available in 23 patients in that 21 received antibiotic   days, one for 10 days and one for six days. Additional treatment with steroids was known for three patients of whom two had uveitis and one GPI.

Case description

A 40-year-old Caucasian man, married and working full time as a circus employee, was admitted to a psychiatric hospital with acute onset of confusion. His medical history was characterized by chronic episodic alcohol abuse and sporadic epileptic seizures. Recently, the patient had been diagnosed with cerebral infarction in the left parieto-occipital region. Apart from alcohol misuse, no specific etiology of a suspected stroke could be identified. His EEG recording showed epileptiform discharges and since the patient was known to have had several epileptic seizures, alcohol withdrawal epileptic seizures were suspected. Treatment with antiepileptic drugs and secondary stroke prevention measures were initiated.

One day prior to admission to the psychiatric hospital, the patient was referred to the emergency department of a general hospital because of tonic-clonic epileptic seizures within the past 24 hours. Against medical advice, he left the hospital after one day. However, later that day he was admitted to a psychiatric hospital with acute onset of confusion, hypermotility, altered behavior, and irritability.

At psychiatric admission, a poorly groomed, right-handed man was seen with a blood pressure of 127/74 mmHg at a pulse rate of 94 / min. The patient was without fever and systemic examination was unremarkable. Albeit that he was alert and attended to the examiner when his name was called, there was disorientation in time and place. He did not understand all the questions and did not follow commands. He showed paucity of speech, often answered monosyllabically, was unable to concentrate and was not able to recall anything from the days prior to admission. In addition, there were gaps in his long-term memory. There were no indications of delusions or hallucinations. His mood was neutral, with

no indication of suicidal ideation or ideas of self-harm. The fingertip nose test and the knee heel test were performed correctly. The tendon reflexes on the arms were low and on the legs lively. His walking pattern was slow and broad-based. He was incontinent for urine and feces. Initially, the patient was cooperative, later he became irritable and refused further physical examination. On the second day of admission, the patient developed a delirium with vivid visual hallucinations.

Laboratory investigations revealed positive serological blood tests for syphilis in serum (TPPA 5000,000; VDRL 32) and CSF (TPPA 500,000; VDRL 16) without any hematological, renal, hepatic, thyroid, or metabolic dysfunctions. HIV tests were negative. Subsequently, a diagnosis of meningovascular neurosyphilis was made and, in accordance with the European Guidelines (Janier et al. 2014) treatment was started with intravenous benzylpenicillin (24 million units daily in six divided doses). Because the patient repeatedly removed his infusion, after two days penicillin was replaced with doxycycline in an oral dose of twice daily 200 mg. Six days later he refused oral medication, and treatment was therefore continued with ceftriaxone 2000 mg 1 dd intramuscularly for 11 days. The comorbid psychotic symptoms were treated according to hospital standard.

In the first month after initiation of antibiotic treatment, there was a slow improvement in the patient's functional and cognitive status. He displayed more initiative, his gait pattern improved and the incontinence disappeared. Short-term memory and orientation capacity slowly recovered over time. After four months the patient was discharged.

DISCUSSION

This retrospective study, covering a period of 14 years, provides information on the clinical presentation and treatment of 34 patients with laboratory confirmed neurosyphilis in a geographically defined area in a country with low syphilis incidence.

Patient characteristics

Age at symptomatic presentation ranged from 31 - 84 years (median age: 44 years), which is in accordance with the data reported by other investigators (Zhang et al. 2013, Daey Ouwens et al. 2014, Drago et al. 2016). A lower age at presentation was reported by studies in populations with high rates of syphilis and HIV-co-infection from San Francisco (range 22-88 years; median age 39 years) (Flood et al. 1998) and South Africa (range 17 - 67 years; average 39 years) (Timmermans and Car 2004).

In the present study, the proportion of female patients was lower than that of males, whereas the reported data on the percentage of female patients varies from 9 to 25% (Flood et al. 1998, Mitsonis et al. 2008, Zhang et al. 2013, Daey Ouwens et al. 2014, Drago et al. 2016). Male predominance has previously been observed in studies on neurosyphilis, especially in studies with a high number of HIV-infected cases (Flood et al. 1998). In the present study, HIV-seropositivity was documented for 35% of patients, which is a higher percentage as reported in other studies (Daey Ouwens et al. 2014, Drago et al. 2016). The here

reported relative absence of female patients may be related to either the high male-to-female ratio of syphilis patients in the Netherlands (ECDC 2017) or the low number of patients included.

Presenting symptoms and signs

At admission, in one third of the patients, psychiatric and / or cognitive complaints were present which is in concordance with data reported by other investigators (Mitsonis et al. 2008, Zhang et al. 2013, Lin et al. 2014). Most probably, cognitive function was not extensively assessed in all included patients, so that the current number may be an underestimation. In the pre-penicillin era, isolated neuropsychiatric symptoms often preceded the full blown clinical manifestation of GPI (Kraepelin 1913). The results of our study advocate that psychiatrists should consider neurosyphilis in the differential diagnosis of all patients with a positive syphilis serology in the blood in the presence of unexplained (progressive) changes in cognition and behaviour, especially when focal neurological signs are lacking.

In the present study, only three patients presented with TD, which is in accordance with the general observation that the incidence of TD has decreased since the beginning of the pre-antibiotic era (Wolters 1987, Carr 2003). Interestingly, speech and micturition disorders, frequently concomitant with late neurosyphilis in the past (Kraepelin 1913, Daey Ouwens et al. 2015), were not observed in the present study.

Although cognitive dysfunction as well as psychotic and depressive symptoms classically belong to GPI, these can also result from meningeal involvement (Drago et al. 2016). This may explain our finding of the coexistence of symptoms of meningitis and GPI in two patients.

Classification

Although the terms "early" and "late" suggest a correlation between duration of syphilitic disease and clinical presentation of neurosyphilis, data on the initial syphilitic infection are rarely reported. Moreover, precise definitions and consensus of the clinical characteristics that accompany these terms are lacking, in that e.g. the reported interval between initial syphilitic infection and vascular syphilis as a presenting syndrome of neurosyphilis varies from less than one year to 4 - 7 years (Carr 2003). Since detailed information about time of occurrence, duration and nature of prior syphilitic symptoms is seldom reported by patients, the interval between syphilitic infection and clinical manifest neurosyphilis is often difficult to establish. Also in this study, in the majority of patients the first known positive blood test of syphilis was performed within 90 days of CSF test of neurosyphilis, suggesting that for most patients the diagnosis of syphilis and neurosyphilis were simultaneously established. Possibly, prior syphilitic infection is not reported by patients with a low number of (unnoticed) syphilitic skin lesions. A low number of skin lesions might be related to a lower concentration of treponemas. Exposure to lower concentrations of treponemas could also attenuate the host immune response causing impaired ability to clear those that managed to invade the CNS.

Consequently, this may result in a greater likelihood to develop symptomatic neurosyphilis (Zhang et al. 2013).

Treatment

Since controlled, randomized, prospective studies for optimal dose and duration of therapy are lacking no uniform worldwide recommended treatment regimen for neurosyphilis is available as yet (Berger and Dean 2014). The European guidelines recommend daily administration of benzylpenicillin 18–24 million units intravenously, divided over 3–4 million units dosages every 4 hours for 10–14 days as first line therapy (Janier et al. 2014). Second line therapy options are ceftriaxone 1–2 g intravenously daily for 10–14 days and, if hospitalization and / or intravenously administration of antibiotics is impossible, procaine penicillin 1.2–2.4 million units intramuscular daily combined with probenecid 500 mg four times daily, both during 10–14 days.

In the present study, cognitive dysfunction and psychiatric symptoms may have hampered intravenous administration of antibiotics which probably explains intravenous treatment for less than 14 days in some patients.

In the literature, the Jarisch-Herxheimer reaction (J-HR), a clinical syndrome composed of abrupt onset of fever, chills, myalgias, tachycardia, vasodilatation with flushing, exacerbated skin rash, and / or mild hypotension, that can occur in patients after the first adequate dose of an antimicrobial drug to treat infectious diseases, is reported in a substantial proportion of syphilis patients. In addition, HIV seropositivity (Yang et al. 2010) and several clinical manifestations of neurosyphilis, such as syphilitic optic neuritis and involvement of the auditory nerve, have been described as a potential risk factor for a dramatic course of J-HR (Zifko et al. 1994, Kojan et al. 2000, Fathilah and Choo 2003, Tucker et al. 2011). Therefore, the European guidelines recommend inpatient management in cases with cardiovascular or neurological involvement and prevention of Jarisch Herxheimer reaction by treatment with Prednisolone 20–60 mg daily for 3 days, starting anti-treponemal treatment after 24 h of commencing prednisolone (Janier et al. 2014).

The present case report illustrates that meningovascular neurosyphilis is a severe condition but reversible with appropriate therapy and stresses that neurosyphilis should be included in the differential diagnosis of a young patient with a cryptogenic stroke and in any patient in an acute confusional state.

In sum, main findings of the present study concerning presentation of neurosyphilis are male predominance, regular cognitive, memory and visual complaints and a broad age range. In addition, HIV- seropositivity and prior psychiatric disease were frequently reported. Since most patients were not able to mention any previous syphilitic infection, the interval between first signs and diagnosis was generally long. The results may be biased since only those patients were included in whom CSF analysis was performed by a certificated reference laboratory. Cognitive and memory complaints were probably not systematically assessed, which may have resulted in underestimation of the presence of these symptoms.

DISCLOSURE

The authors declare no potential conflict of interest.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Appendix 1: Clinico-pathological classification of neurosyphilitic symptoms based on Flood et al. 1998.

1. Early neurosyphilis
    1. Syphilitic meningitis: acute syphilitic meningitis, defined by symptoms or findings of acute headache, and/or cranial nerve deficits, with or without meningeal signs (photophobia or meningismus)
    2. Syphilitic meningovascular disease: defined by findings of stroke or other upper motor neuron deficits on exam with characteristic lesions on computed tomography or magnetic resonance imaging of the brain and/or changes consistent with medium-sized vessel vasculitis on angiogram; and
    3. Uveitis, defined by symptoms of decreased vision, eye pain, or photophobia with diagnosis confirmed by slit-lamp examination

1. Late neurosyphilis
    1. General Paralysis of the Insane: defined by a dementia syndrome or subacute psychosis not clearly explained by another process
    2. Tabes Dorsalis: defined by posterior column deficits such as sensory ataxia, Argyll-Robertson pupil, and/or lightning pains

CHAPTER 6

A CASE OF NEUROSYPHILIS
MIMICKING AUTOIMMUNE ENCEPHALITIS

Submitted as:

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INTRODUCTION

Neurosyphilis can imitate a wide range of neurological and psychiatric diseases. To illustrate that neurosyphilis should be considered in cases suspected of autoimmune encephalitis (AE) and vice versa, here, a case of neurosyphilis is reported who presented with new onset focal epilepsy, swelling of the left amygdala and temporal slowing of the electro-encephalogram (EEG) suggestive of a diagnosis of AE. Early recognition and treatment are crucial to prevent further cognitive decline in both neurosyphilis and autoimmune encephalitis.

CASE REPORT

A 62-year-old right handed man was referred to a neurology department because of transient loss of consciousness for one year. His wife reported that attacks typically started with a moaning sound "resembling a baby's crying", followed by stiffening of the right arm, unresponsiveness, stiffening all over and shaking during several minutes. Afterwards he spoke in his mother tongue, a language not familiar to his wife. Generally, full recovery took fifteen minutes. These episodes were often preceded by anger, followed by a slightly euphoric feeling. The patient's medical history was significant for severe heart failure, a dilated left cardiac ventricle, severe mitral and aortic valve insufficiency, current treatment with warfarin, approximately 40 packyears of cigarette smoking and therapy for gambling addiction. The patient reported prior antibiotic treatment for syphilis, however he could not provide details on these issues. His personal and family history were negative with regard to seizures and febrile convulsions. Clinical and neurological examination were unremarkable.

Interictal EEGs showed intermittent temporal slowing, more on the left than on the right side, but no specific epileptic discharges. FLAIR and T2WI cranial MRI sequences demonstrated an increased volume of the left amygdala as well as a marked atrophy in the parietal regions. A specific focus of temporal lobe epilepsy was not found. Anti-neuronal antibodies, including NMDA-R, VGKC-complex, Hu, Yo, Ri, Tr, ampfifysine, CV2, Ma1/2 were not detected; syphilis screening test was positive and the Venereal Disease Research Laboratory test (VDRL) was 16, demonstrating active syphilis infection. No HIV-test was performed. Cerebrospinal fluid (CSF) analysis revealed normal cell count, protein and glucose concentration; Treponema blot: positive; *Treponema pallidum* haemagglutination: positive (1:1024) and rapid plasma reagine: positive (< 1.1).

A diagnosis was made of parenchymatous neurosyphilis presenting with subacute mesial encephalitis and focal epilepsy originating in the language dominant hemisphere with focal to bilateral tonic-clonic seizures. Treatment with lamotrigine 75 mg bid and intravenous penicillin at a dose of 12 million units/d for 10 days was initiated. Two months after initiation of antibiotic and anti-epileptic treatment the patient was seizure free and at that time a second MRI revealed that the left amygdala was still hyper-voluminous. Two years later the patient was still seizure free and lamotrigine was tapered off.

The patient was lost for follow-up serological examination.

DISCUSSION

In our case, a history of new onset focal epilepsy, swelling of the left amygdala and intermittent temporal slowing on interictal EEG suggested a diagnosis of AE. Seizures in AE are most often associated with Anti-NMDA-R, LGI1, GABAbR, GABAaR and DPPX antibodies, whereas LGI1 is particularly associated with faciobrachial dystonic seizures (Van Sonderen et al., 2016). However, antibody testing is not always readily accessible, test results can take several weeks and cannot serve as a gold standard since absence of antibodies does not exclude AE and positive tests do not always imply an accurate diagnosis. Therefore, in the initial assessment of suspected AE thorough neurological evaluation and standard diagnostic tests (EEG, MRI and CSF studies) should prevail as early initiation of immunotherapy in AE may improve prognosis. MRI images with increased FLAIR/T2WI signal with highly selective medial temporal lobe involvement, without contrast enhancement, are associated with AE, neurosyphilis, Sjögren's syndrome, Human Herpes Virus 6 infection and rare cases of lupus (Leypoldt et al., 2015).

Most patients with neurosyphilis mimicking AE are men, with a median age of 54 years (Serrano-Cardenas et al., 2018). The most common clinical manifestations at admission were cognitive impairment, seizures and psychiatric disorders. Typical findings on EEG are focal slow waves and periodic lateralized epileptiform discharges.

AE and neurosyphilis might partially overlap as illustrated by the report of two patients with serological confirmed neurosyphilis accompanied with positive NMDA-R antibody tests in serum and CSF (Qin et al., 2017). In these cases, neurosyphilis and anti-NMDAR encephalitis may have occurred simultaneously. However, it could be hypothesized that neurosyphilis caused a secondary immunological response of anti-NMDAR-Ab production, analogous to AE following Herpes Simplex encephalitis (Qin et al., 2017). In our patient no serum NMDA-R antibodies were detected and CSF antibody tests were, unfortunately, not performed.

As illustrated by our case, a diagnosis of neurosyphilis should not be excluded in those with a history of antibiotic treatment for syphilis. Late complications of syphilis and progression to neurosyphilis can develop, also in immunocompetent patients, despite standard antibiotic therapy for syphilis. It is not known, whether syphilitic infection contributed to cardiac disease in our patient.

IN CONCLUSION

Neurosyphilis presenting with focal seizures and MRI abnormalities of the amygdala can mimic AE and neurosyphilis should be excluded prior to initiation of immunotherapy in patients suspected of AE, even in those who were considered adequately treated for syphilis in the past. Further studies are required to determine whether immunologic mechanisms contribute to this atypical presentation of neurosyphilis.

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CHAPTER 7

GENERAL DISCUSSION

In this section the work of this thesis will be reviewed from a broader perspective. Specific attention will be given to General Paralysis of the Insane (GPI) and the treatment of neurosyphilis.

EPIDEMIOLOGICAL ASPECTS OF NEUROSYPHILIS

Syphilology, a medical discipline studying the diagnosis and treatment of syphilis, arose as a new medical speciality at the end of the 19th century due to the high prevalence of syphilitic disease and other venereal diseases (Albert, 1999). Nowadays, in higher-income parts of the world, physicians often classify syphilis among the extraordinary diseases. However, despite considerable advances in diagnosis, knowledge of pathophysiological aspects and treatment as well as the high rates of cure since the widespread use of antibiotic therapy for syphilis after the Second World War and extension of screening, treatment and prevention programs, syphilis persisted as a worldwide challenge in health care (Tuddenham and Ghanem, 2018). Estimates suggest a global prevalence of 12 million people in 1995 (Gerbase et al., 1998). The rates of primary and secondary syphilis have increased in the past decade both in the developing and developed countries (Tuddenham and Ghanem, 2015). In Russia and the now independent states of the former Union of Soviet Socialist Republics, after achieving a notification rate of 4.2 cases per 100,000 in 1988, the rate of syphilis cases rose to 263 per 100,000 in 1996 (Kent and Romanelli, 2008). In the United States, higher rates of sexually transmitted infections, particularly syphilis, are reported more often in men who have sex with men (MSM) than in other risk groups (Gianella et al., 2015) and a similar trend was noticed in the Netherlands (Visser et al., 2018) and other developed countries (Ho and Spudich, 2015). In MSM, immunomodulatory mechanisms secondary to the presence of other infections might be involved. Particularly Human Immunodeficiency Virus (HIV)-infected individuals seem susceptible to acquisition of syphilis (Gianella et al., 2015). Use of methamphetamine and other drugs, participation in specific sexual networks and a higher number of sexual partners appear to be associated with this increased susceptibility (Gianella et al., 2015).

In the Netherlands, syphilis is not a notifiable disease and therefore exact data on the incidence of syphilis are lacking. Instead, data derived from Sexual Health Clinics and General Practitioners is used for surveillance. In 2017, 1,228 clients (95.3% MSM, 2.4% heterosexual men, 2.3% women) received a new diagnosis of syphilis at Sexual Health Clinics (Visser et al., 2018). The estimated disease burden of syphilis in the Netherlands in 2015 was 15 DALY (disability adjusted life years), with a 95% uncertainty interval of 12-17 (Gier de et al., 2017). However, the typically painless chancre of primary syphilis often develops unnoticed by patients, especially when located in a less visible body area (e.g., vagina, cervix, anus, rectum) and therefore many patients present only after this first stage of syphilis has passed.

Presently, robust estimates of the prevalence of neurosyphilis worldwide are lacking and much of the knowledge comes from the pre-antibiotic era (Tuddenham and Ghanem, 2018). In Europe, a yearly neurosyphilis incidence varying from 0.16 to 2.1 per 100,000

inhabitants is estimated (Nordenbo and Sorensen, 1981; Alani and Millac, 1982; Conde-Sendin et al., 2004). In line with this finding, an incidence of 0.47 per 100,000 adults was calculated in the study in the Netherlands, presented in **Chapter 4**, which examined countrywide hospital discharge diagnoses of neurosyphilis between 1999 and 2010 from a national registry. However, comparison of incidence rates of neurosyphilis in the various European countries is difficult, because of considerable differences in case definitions.

As for the sex ratio, the higher neurosyphilis rate in men as documented in the Netherlands (**Chapter 4**), is comparable to that reported in other European countries. It is unknown whether male predominance in syphilis and neurosyphilis patients is related to social-cultural and behavioural factors, or underlying biological characteristics that influence the susceptibility to protract syphilis or to develop neurosyphilis after syphilitic infection. Nevertheless, MSM constitute an important subpopulation in syphilis epidemiology, with the use of sex enhancing and other recreational drugs (e.g., the combined use of sildenafil and methamphetamines) promoting concurrent sexual partnerships, increased rates of new partner acquisition, and short intervals between new sex partners, all of which enhance sexual spread of infections (Fenton et al., 2008).

HIV seropositivity was reported in 15% of neurosyphilis patients hospitalized in the Netherlands (**Chapter 4**). However, this percentage was based on hospital discharge diagnoses rather than documented clinical examination or laboratory criteria and, therefore, HIV seropositivity might have been underreported. In the study on the clinical presentation of neurosyphilis patients (**Chapter 4**) laboratory data demonstrated that 12 out of 34 neurosyphilis patients were known to have positive HIV tests at the time neurosyphilis was diagnosed. In this study, most HIV seropositive patients presented with early neurosyphilis. The natural history of neurosyphilis may be significantly altered by concomitant HIV infection (Berger and Dean, 2014). Whether increasing numbers of reported neurosyphilis - particularly early neurosyphilis - cases in HIV infected persons is a result of biological susceptibility, as a consequence of immunosuppression or increased detection as a result of enhanced follow-up is not known as yet (Tuddenham and Ghanem, 2018).

CLINICAL PRESENTATION OF NEUROSYPHILIS

General Paralysis of the Insane (GPI) was a common cause of psychosis and psychiatric hospitalization in the nineteenth century (Frankenburg and Baldessarini, 2008). Even as recently as in the mid-twentieth century, GPI accounted for 10% of all first admissions to psychiatric hospitals and for more than 20% of all patients residing in psychiatric hospitals in the United States (Frankenburg and Baldessarini, 2008). Like most research into the historical aspects of GPI (Thompson, 1984; Braslow, 1997; Hurn, 1998; Davis, 2008; Slijkhuis and Oosterhuis, 2012), the studies presented in **Chapter 2** and **Chapter 3** focus on patients with this condition in a psychiatric hospital in the first half of the 20th century. At that time, GPI patients without serious behavioural problems were probably mostly treated in general hospitals, as is indicated by the referral of several patients to Vincent van Gogh Institute for

psychiatry (VvGI) due to challenging behaviours that first appeared during their stay on a general hospital ward and the high number of patients with a history of anti-syphilitic therapy elsewhere prior to admission to VvGI. Therefore, the findings presented in **Chapter 2** and **Chapter 3** are probably mainly representative of patients in a late stage of neurosyphilis. In agreement with the findings of other investigators, the majority of GPI patients hospitalized in VvGI were middle-aged. This results from the sexual transmissibility of syphilis and the fact that GPI manifests at a late stage of syphilis, usually at least 10 years after infection. Since the beginning of the 19th century, GPI is predominantly reported in men (Hare, 1959). The underlying biological, cultural and individual behavioural mechanisms are unknown. Torres suggests that the greater sexual freedom allowed to men as compared to women in the 20th century could explain that GPI was found much more often in men than in women (Torres, 2014). However, sexual freedom for women has increased in the western world in the 21st century and GPI is still more often diagnosed in men than in women (see **Chapter 4** and **Chapter 5**), therefore this sociological explanation is probably not sufficient to explain the differences in incidence of GPI.

The total group of GPI patients in VvGI as described in **Chapter 2** presented at admission with a broad array of neuropsychiatric and neurological manifestations, which is in accordance with Kraepelins description of a wide range of initial symptoms and a large variety in the course of GPI (Kraepelin, 1903). Lack of insight and judgement, "dementia" and hyperactivity were most often reported. This lack of insight and judgment in combination with delusions, especially when persecutory in nature, probably contributed to the frequently reported challenging behaviours of patients prior to admission to VvGI. About half of the patients with GPI were referred to VvGI, because of provocative behaviour in a general hospital ward, while in about 20% of those living at home, prior to admission, severe behavioural problems had resulted in judicial contacts. These findings suggest that GPI patients were referred to a psychiatric hospital only when their behaviour caused serious problems for their environment and justified forced hospitalization.

Delusion of grandeur or "megalomania" was reported in almost half of the patients presented in **Chapter 2**. Patients suffering from such "delusions of grandeur" demonstrated a grossly exaggerated belief of self-worth, power, knowledge or identity or of an exceptional relationship with a divinity or famous person (Wing et al., 1980). This type of delusion is not pathognomonic for neurosyphilis, as megalomania may also occur in other diseases, including bipolar disorder and schizophrenia. In patients with GPI, delusions of grandeur may have particularly impressed physicians due to the contrast between the content of the delusions and the often deplorable conditions of the patients. Megalomia probably reflected the lack of insight of these patients into their condition (Davis, 2012 p.87). A recent survey of the literature of the period 2010-2015 demonstrated that GPI was the commonest reported form of neurosyphilis (49%), often manifesting with cognitive impairment and psychiatric symptoms (Drago et al., 2016b). Many of the patients of this review were admitted to a psychiatric unit rather than to a medical or neurological one (Drago et al, 2016b). The results of a study on the current clinical presentation of neurosyphilis presented in **Chapter 5** are in

accordance with these findings. In this study, syphilitic disease was first diagnosed during routine serological screening for syphilis in a psychiatric hospital in several patients. These data suggest that, given the increasing incidence of syphilis and the decreasing familiarity of clinicians with the multisystemic and multiphasic nature of syphilis, reintroduction of screening for syphilis at psychiatric, neurological and geriatric departments should seriously be considered.

At admission to VvGI cardiovascular disease was reported in 14 (7,5%) GPI patients, as described in **Chapter 2**. In six patients an aortic aneurysm was described and 8 patients had a history of cerebrovascular accident. Heart failure and cerebrovascular accident were documented as cause of death in 7 and 2 patients respectively. Cardiovascular syphilis was a common late manifestation of syphilis prior to the introduction of penicillin as the standard therapy for syphilis. In 1956, Macfarlane and colleagues reported a diagnosis of cardiovascular syphilis in 15% (202 patients) of 1,330 syphilitic patients referred for cardiovascular investigation in the period 1945-1951 (Macfarlane et al., 1956). Although cardiovascular syphilis is still present today (Roberts et al., 2009), no cardiovascular disease was noted in the records of the cases described in **Chapter 5**.

In the pre-antibiotic era, Tabes Dorsalis (TD) affected 3-9% of persons infected with syphilis (Merritt at al., 1946) and TD was the most frequently reported manifestation of neurosyphilis in the study presented in **Chapter 2**. However, in the antibiotic era, a shift in clinical patterns of patients diagnosed with neurosyphilis is noted, with a decreasing rate of late neurosyphilis, in particular of TD (Hooshmand et al., 1972; Wolters, 1987) and TD is rarely diagnosed today (Kulkarni and Serpa, 2018). The cause of this change in clinical presentation is unknown as yet (Zhang et al., 2015). However, as mentioned before, exact data of the incidence of TD and precise diagnostic criteria are lacking. A possible explanation for this phenomenon might include changes in diagnostic methods. Currently, examination of the cerebrospinal fluid (CSF), including syphilis serology, in patients with pain in the distal extremities with or without bladder dysfunction, is less often performed than in the pre-antibiotic era, due to the increased availability and accuracy of imaging techniques and a decreased a priori probability of syphilis. Micturition disturbances related to neurosyphilis had a high prevalence in the pre-penicillin era, as demonstrated in patients with GPI in **Chapter 2**. Neurogenic bladder dysfunctions due to syphilis still occurs, particularly in immunodeficient patients (Prydacz et al., 2018). These patients most often present with urine retention resulting from neurogenic detrusor underactivity (Prydacz et al., 2018).

The clinical importance of diagnosing asymptomatic neurosyphilis (ANS) was evident in the pre-antibiotic era. Syphilis patients with demonstrated ANS had a significantly higher chance of developing late neurological complications than syphilis patients, whose CSF tests were normal (Ghanem, 2010). Diagnosing ANS lost relevance after the introduction of penicillin in the 1940s and the subsequent decrease in the incidence of neurosyphilis. The clinical significance of detecting ANS in the penicillin era is unknown, because no studies have been reported comparing the long-term results of treatment with one of the recommended antibiotic regimens in patients with and without asymptomatic CSF abnormalities (Ghanem,

2010). The increasing number of patients suffering from neurological complications in HIV-infected patients (Ghanem, 2010) and case reports on the unmasking of syphilitic infection and rapid development of neurosyphilis in patients treated with immunomodulating therapy (Bories-Haffner et al., 2010; Bettenworth et al., 2012; Kase et al., 2015) have updated this dilemma. These findings stress the importance of screening for syphilis also in these patients prior to initiate immunomodulating therapy.

THOUGHTS ABOUT THE PATHOGENESIS OF NEUROSYPHILIS

The pathology of neurosyphilis results from the invasion of the central nervous system by *T. pallidum* and the associated immunological response (Berger and Dean, 2014). In the pre-antibiotic era, early neurosyphilis was rarely diagnosed among persons who were not treated for syphilis (0.3%), but the incidence increased nearly ten-fold in those, who were inadequately treated (2–3%). The latter suggests that inadequate or incomplete treatment may alter the immune response, resulting in an increased risk to develop early neurosyphilis (termed "neurorecurrence") (Tuddenham and Ghanem, 2018). A similar alteration of the host's immune response may be involved in the pathogenesis of neurosyphilis in human immunodeficiency virus (HIV) infected patients. In syphilis patients with concomitant HIV infection, symptomatic neurosyphilitic meningitis during secondary syphilis is not uncommon and suggests a more aggressive course of disease (Berger and Dean, 2014). However, a randomized controlled trial of enhanced therapy for early syphilis in patients with and without HIV infection in the 1990s could not substantiate this hypothesis (Rolfs et al., 1997).

Several studies have demonstrated that long-term complications of syphilis such as neurosyphilis can develop, also in immunocompetent patients, despite adequate penicillin treatment for early manifestations of syphilis (Zhou et al., 2012; Drago et al., 2016b; Rebora et al., 2018). This finding may refer to particularly neuroinvasive *T. pallidum* strains or to the incapacity of penicillin to pass effectively through the hemato-encephalic barrier, achieve treponemicidal concentrations in the central nervous system (CNS) and/or destroy *T. pallidum* present in the CNS (Drago et al., 2016a). However, other hypotheses that involve autoimmune or autoinflammatory mechanisms, can be put forward. Recent findings suggest that in neurosyphilis patients down regulation of the systemic immune response may promote disease progression towards neurological involvement and, conversely, the CNS damage may be due to an uncontrolled local host immune response (Drago et al., 2016a). The development of chronic neurosyphilis may be the result of an uncontrolled local production of antibodies by persistent antigenic stimulation due to survival of spirochetes or, most likely, from residues of bacteria in the form of protein (Drago et al., 2016a).

Production of auto-immune antibodies may also play a role in the rare neurosyphilis cases that mimic autoimmune encephalitis (AE), as in the patient described in **Chapter 6**. In these cases, neurosyphilis presents with progressive cognitive impairment, new onset epilepsy and psychiatric disorder in combination with predominant mesiotemporal or frontobasal hyperintensities hyperintense on Fluid Attenuation Inversion Recovery (FLAIR)

and T2 weighted (T2WI) sequences on magnetic resonance imaging (MRI) and intermittent temporal slowing on electroencephalogram (EEG) (Hama et al., 2008; Budhram, 2017; Serrano-Cardenas et al., 2018). Recently, Qin and colleagues reported two patients with serological confirmed neurosyphilis accompanied with positive anti-N-methyl-d-aspartate Receptor (NMDAR) antibody tests in serum and CSF (Qin et al., 2017). Neurosyphilis and anti-NMDAR encephalitis might have occurred simultaneously, however, neurosyphilis may have caused a secondary immunological response of anti-NMDAR-antibody production (Qin et al., 2017). It could be hypothesized that not only both bacterial and autoimmune pathophysiological mechanism are involved in neurosyphilis, but also that different clinical presentations of neurosyphilis are linked with different autoimmune antibodies and different neuroinflammatory profiles.

TREATMENT OF NEUROSYPHILIS

Fever therapy

The notion that fever can have a healing effect in patients with a brain disease has been described since ancient times (Bierman, 1942). Samuel Alexander Kinnier Wilson (1878-1937) suggested involvement of the immune system in the effect of fever in epilepsy patients (Wilson, 1935). He mentioned the observation ascribed to Hippocrates that "intermittent fever", a disease known today as malaria, replaced or mitigated epilepsy ("quartana epilepsia vindex appellatur") and the beneficial effects of "exanthems and other fevers of childhood, especially perhaps measles, chicken-pox, typhoid and scarlatina" (Wilson, 1935). Galenus (129-199) reported a healing effect of fever in a patient suffering from melancholy (Whitrow, 1990; Albert, 1999). Reports from the Middle ages describe improvement of psychiatric symptoms in patients in asylums suffering from cholera (Albert, 1999). A 17th century engraving by Jacques Lainet (Paris, 1659) represented treatment of syphilis through fumigation with mercury, carried out in an oven. The resulting intense sweating along with salivation was thought to rid the body of disease poisons (Bierman, 1942). Herman Boerhaave (1668-1738), who was the first physician to introduce thermometer measurements in clinical practice, wished that he could produce the febrile curing action by artificial means and is quoted to have remarked "I would be the greatest physician if I could produce intermittent fever as easily as suppress it" (Bierman, 1942).

In the late 19th century many investigators reported on the effect of spontaneous fever on mental disease and in 1887 Julius Wagner-Jauregg (1857-1940), an Austrian psychiatrist, published an extensive review on this topic, including descriptions of his own cases (Wagner-Jauregg, 1887). In the same period the "germ theory", the hypothesis that some infectious diseases, such as malaria and typhoid, were caused by microorganisms evolved. These developments merged into the idea to induce fever to alleviate psychiatric symptoms rather than to wait for an outbreak or epidemic to occur (De Young, 2015 p.120). Wagner-Jauregg's first attempts to apply pyrotherapy involved inoculating several psychiatric patients with streptococci derived from wounds of patients with erysipelas, injections of

tuberculin and typhus vaccine, all intended to produce fever in patients with psychoses (Tsay, 2013). The results of these treatments, however, were not satisfying. In 1917, he continued this line of research by inoculating GPI patients with blood from patients, who were suffering from tertian malaria. Soon thereafter he reported favourable results of this treatment (Whitrow, 1990; Gartlehner and Stepper, 2012). The availability of quinine as an effective cure of malaria and the absence, at the time, of an effective treatment for GPI, probably contributed to the rapid international adoption of this technique, known as malariotherapy or malaria fever therapy (MFT) (Whitrow, 1990; Albert, 1999; Gartlehner and Stepper, 2012; Tsay, 2013), as described in **Chapter 3.**

In 1927, Wagner-Jauregg was awarded the Nobel Prize of Medicine or Physiology "for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica''. It should be noted, however, that the idea that fever was beneficial in syphilis was first noted more than three centuries previously by Spanish physician Ruy Diaz de Isla (1462-1542) (Albert, 1999). Moreover, not Wagner-Jauregg, but the Ukrainian psychiatrist Alexander Samoilovich Rosenblum (1826-1903) was the first to report a therapeutic effect of intentionally induced malaria in patients with GPI in 1876 (Tsay, 2013). The controversial nature of inducing fever in patients, especially with the rise of conservatism in Russia, might have prompted Rosenblum to omit this fact in his article (Tsay, 2013).

In 1924, when Wagner-Jauregg was first nominated for the Nobel Prize in Physiology or Medicine, B. Gadelius, a Swedish professor of psychiatry, was the referee for awarding the Nobel Prize. Gadelius did not agree with the nomination, because, in his eyes, a doctor who administered malaria to a patient with GPI was a criminal (Whitrow, 1990). MFT raised a large number of ethical questions, all the more complicated by attempts to understand them in the context of the early 20th century, when neurosyphilis was a devastating and almost invariable mortal disease with little help from conventional medical therapy (including mercury, arsenic and bismuth compounds) (Gambino, 2015). What should be considered as "acceptable risks" in the treatment of this devastating disease? "Consent" was an evolving concept at the time and the interpretation, especially with regard to patients with a disease that impaired their ability for effective reasoning was another matter of debate (Gambino, 2015). Since most hospitals did not have a research centre that cultivated colonies of mosquitoes to preserve a malarial strain, treatment of GPI patients with MFT needed to be suspended if physicians could not locate a patient with malaria willing to serve as a donor. As early as 1923 an editorial in the *American Journal of Psychiatry* urged that "... every large hospital for mental disorders may have to maintain one or more malarial patients as source of infectious material" (Whitrow, 1990). Therefore, often a psychiatric patient with (induced) malaria served as a reservoir and this might have caused suspension of his or her own treatment of malaria with quinine.

Since the end of the Second World War the important medical achievements of Wagner-Jauregg were overshadowed by his antisemitism, his close tie with the Nazi Party and his support for the concept of "racial hygiene" (Whitrow, 1990; Tsay, 2013). In the interbellum, "racial hygiene" was a popular ideology throughout Europe and Wagner-Jauregg argued for

the forced sterilization of people who were mentally ill, criminal or considered genetically inferior (Gartlehner and Stepper, 2012).

For a number of years, MFT was accepted as a truly specific treatment of neurosyphilis. The data from clinical and experimental evidence suggested that increased body heat was the effective therapeutic agent, which stopped active neurosyphilis (Bennett et al., 1941). A variety of biologic, infectious and physical agents (e.g. hot baths and diathermy) were investigated and reported to have equal or superior results to MFT (Bennett et al., 1941; Bierman, 1942).

Penicillin treatment

In the 1940s, syphilis still presented an important problem for health care worldwide as a considerable cause of neurological, cardiovascular and perinatal morbidity and mortality. The estimated prevalence rate of syphilis in the United States was 5% - 10%, with rates as high as 25% in lower socioeconomic classes (Douglas, 2009). A major therapeutic breakthrough followed in 1943 when Mahoney and colleagues (Mahoney et al., 1943) reported a favourable effect of penicillin for the treatment of syphilis and soon penicillin treatment became the standard of care for all syphilitic infections. Penicillin treatment for syphilitic infections was further optimized with regard to dose, duration and serological follow-up based on case series and expert opinion, rather than on large, well-controlled clinical trials. Within a year, widespread use of penicillin for the treatment of all stages of syphilis (primary, secondary, tertiary, latent) resulted in dramatic decreases in the incidence of syphilis and related mortality (Douglas, 2009).

Current European guidelines for the management of syphilis recommend treatment of early syphilis (primary, secondary and early latent, i.e. acquired ≤1 year previously) as first line therapy option with benzathine penicillin G (BPG) 2.4 million units intramuscularly (IM) (one injection of 2.4 million units or 1.2 million units in each buttock) on day 1 (Janier et al., 2014).

Since cardiovascular syphilis and neurosyphilis still exist and are reported to occur also after treatment of early syphilis according to the current guidelines, enhanced treatment for early syphilis might be considered (Zhou et al., 2012). In a recent study, addition of doxycycline and ceftriaxone to the conventional BPG treatment was found to result in a higher and faster cure rate of early syphilis (Drago et al., 2016c). Moreover, this enhanced treatment provided treponemicidal antibiotic levels in the cerebrospinal fluid, and therefore it might prevent late complications (Drago et al., 2016c). For late latent (i.e. acquired >1 year previously or of unknown duration), cardiovascular and gummatous syphilis BPG 2.4 million units IM (one injection 2.4 million units single dose or 1.2 million units in each buttock) weekly on day 1, 8 and 15 is recommended as first line therapy option (Janier et al., 2014).

The optimal management of neurosyphilis, ocular and auricular syphilis continues to be inpatient treatment with benzylpenicillin 18–24 million units intravenous daily, as 3–4 million units every 4 h during 10–14 days. Follow-up examination of cerebrospinal fluid should be performed 6 weeks–6 months after treatment of neurosyphilis (Janier et al., 2014).

Within 24 hours after antibiotic treatment patients might experience an array of symptoms like fever, chills, headache, myalgias, and exacerbation of existing cutaneous lesions with symptoms resolving a few hours later, known as the Jarisch–Herxheimer reaction (JHR) (Read and Donovan, 2012; Buitrago et al., 2014; Butler, 2017). JHR was named after two dermatologist-syphilologists, the Austrian Adolf Jarisch (1850-1902) (Jarisch, 1895) and the German Karl Herxheimer (1861 –1942) (Herxheimer and Martin, 1902), who independently reported the phenomenon in patients with syphilis who developed exacerbations of their skin lesions after treatment with mercurial compounds, in 1895 and 1902 respectively (Belum et al., 2013; Butler, 2017).

Although classically, JHR was observed during treatment of syphilis, it is now well documented in louse-borne relapsing fever, leptospirosis, tick-borne relapsing fever and lyme disease, while case reports mention JHR in a range of other infectious diseases including meningococcal meningitis (Belum et al., 2013; Butler, 2017). Clinical observations of patients with the JHR suggest a role for endotoxin, while experimental evidence indicates involvement of non-endotoxin pyrogen and spirochetal lipoproteins (Butler, 2017). However, the exact pathogenesis remains to be elucidated (Butler, 2017). In prospective studies, randomized trials of antimicrobial drugs, surveys and meta-analysis, JHR is reported not only in primary and secondary syphilis (40% of the cases), but also in neurosyphilis (Butler, 2017). The reported frequency rate in neurosyphilis varies from 8-75%, indicating large variations in patients' susceptibilities as well as varying criteria used by observers of the reaction (Butler, 2017).

The transient worsening of syphilitic lesions may have serious consequences in important small arteries, such as those surrounding the coronary ostium or the optic nerve, as reported in several cases (Marra, 2009). Many experts recommend a combined treatment of antibiotics and topical, periocular and systemic (oral or intravenous) corticosteroids in patients with ocular syphilis (Marra, 2009). The British guidelines of 2008 (Kingston et al., 2008; Kinston et al., 2016) and the 2014 European guidelines on the management of syphilis (Janier et al., 2014) state that prednisolone can prevent the febrile episode and that, although steroids are not proven to ameliorate local infection, biological plausibility suggests that steroids may help preventing JHR in early syphilis with optic neuritis and uveitis. Therefore, in these cases, administration of prednisolone 20–60 mg daily for 3 days is recommended, starting antitreponemal treatment after 24 h of commencing prednisolone. Since the efficacy of this strategy is not proven (Read and Donovan, 2012), this advice is not included in the US guidelines (Workowski and Bolan, 2015).

Other therapeutic options
Neurosyphilis commonly presents with neuropsychiatric symptoms (see also **Chapter 5**). Early cohort studies demonstrated that cognitive deficits in neurosyphilis patients were least likely to respond to treatment, while re-emergence of gross neurological signs after treatment was common over prolonged time. It is not known whether this was paralleled by a decline in cognitive function (Chen et al., 2017). However, epidemiological studies with long-term

follow-up conducted in the pre-penicillin era included patients who were treated with regimens of varying effectiveness and their outcomes may not necessarily apply to patients treated with penicillin (Ghanem, 2010). Despite evidence of short-term improvement, there are insufficient data to support long-term benefit of penicillin therapy on cognitive function (Moulton and Koychev, 2015) and psychiatric disease in neurosyphilis. Case reports mention persisting psychiatric symptoms after penicillin therapy for neurosyphilis (Ni et al., 2016), even years after antibiotic treatment (Roy et al., 2016), also after remittance of neurologic symptoms (Allen et al., 2014; Othman and Nordin, 2018). Refractory psychiatric symptoms may result from nonadherence to psychotropic medication as well as from an ongoing infectious or inflammatory irreversible brain damage, as evidenced by cerebral atrophy (Allen at al., 2014). Recently, augmentation of clozapine with electroconvulsive therapy has been suggested as a possible strategy in pharmacotherapy resistant psychiatric conditions, such as depression and psychosis, in neurosyphilis patients (Othman and Nordin, 2018). Future studies should address the hypothesis of local production of antibodies in the CNS resulting in ongoing neuroinflammation and associated therapeutic implications that may include immunomodulatory therapy in (a subsection of) patients with neurosyphilis.

Outcome measures

Objective outcome measures of therapy for neurosyphilis are confined to normalization of CSF abnormalities. Success of antimicrobial therapy is marked by decline in CSF leukocyte count at six months and resolution of all CSF abnormalities at two years and clinical improvement or stabilization (Marra, 2017). CSF abnormalities may resolve more slowly in HIV-infected persons than in those not infected with HIV and clinical abnormalities may persist after resolution of all CSF abnormalities (Marra, 2009).

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CHAPTER 8

CONCLUSIONS AND THOUGHTS ABOUT FUTURE DIRECTIONS

This chapter offers some concluding remarks and identifies future directions to expand our conceptualization and treatment of neurosyphilis.

This study reminds clinicians that syphilis is a multisystemic and multiphasic disease. Since the beginning of the 20th century, significant progress has been made in the diagnosis and treatment of the various manifestations of syphilis. However, despite the efficacy of penicillin in most cases of syphilis, neurosyphilis is still present and should be considered in the diagnostic workup of various neurological and psychiatric disorders. Moreover, in developed countries, many clinicians are unfamiliar with syphilis, due to the low incidence of syphilis over the last two decades of the 20th century, while early recognition of neurosyphilis is imperative since early institution of antibiotic treatment is associated with better outcome.

In the absence of reliable data, it is difficult to know the extent to which neurosyphilis is overlooked in clinical practice. Given the results of the investigations presented in this thesis, further large-scale studies are warranted to elucidate the more exact prevalence of (neuro)syphilis especially in patients with psychiatric diseases. It is therefore recommended to re-introduce the obligatory screening for syphilis in order to initiate appropriate treatment as soon as possible. Patients with late neurosyphilis may have non-reactive serum nontreponemal tests (such as the Venereal Disease Research Laboratory (VDRL) and the Rapid Plasma Reagin (RPR)). Therefore, serum treponemal tests should be used for screening for neurosyphilis, for example, in the Netherlands, the *Treponemal pallidum* hemagglutination (TPHA) test, *Treponemal pallidum* particle agglutination (TPPA) test or enzyme-linked immunosorbent assays (ELISA). If serologic testing for syphilis is positive, lumbar puncture is essential to assess for cerebrospinal fluid abnormalities that demonstrate neuro-invasive disease (leukocyte count $\geq 5 \times 10^6$ /L, positive VDRL).

Unfortunately, many questions about the pathogenesis, diagnosis and management of neurosyphilis still persist. Recent findings suggest that down regulation of the systemic immune response may promote disease progression towards neurological involvement and, conversely, the damage in the central nervous system may be due to an uncontrolled local host immune response. *T. pallidum* may initiate and maintain chronic inflammation and tissue damage in neurosyphilis, independent of active infection. It could be hypothesized that not only both infectious and (auto)immune pathophysiological mechanism are involved in the pathogenesis of neurosyphilis, but also that different clinical presentations of neurosyphilis are linked with specific (as yet undiscovered) autoimmune antibodies and distinct neuroinflammatory profiles.

Future research into the pathogenesis of neurosyphilis may address these hypotheses and, if correct, investigate related therapeutic implications: is there a role for immunotherapy in (a subsection of) patients with neurosyphilis?

The diagnosis of neurosyphilis is a challenging medical issue as neurosyphilis presents in many guises, Human Immunodeficiency Virus infection can change the course of syphilis and, due to the inability to culture *T. pallidum*, only indirect measurement of syphilitic disease activity is possible. Since syphilis screening in neurological, psychiatric and geriatric patients is

no longer standard practice in the Netherlands, a high à priori index of suspicion is needed to consider a diagnosis of neurosyphilis. Therefore, a detailed history of sexually transmitted disease and subsequent treatment is required and a diagnosis of neurosyphilis should not be excluded based on a history of currently considered "adequate" antibiotic treatment for primary of secondary syphilis.

Careful description of neurological and psychiatric symptomatology and validated bedside cognitive tests should be performed in neurosyphilis patients and are valuable tools for the clinical assessment of illness severity and can be used to evaluate clinical response to treatment.

Hopefully, in the near future, we will reconceptualise neurosyphilis as a syndrome that constitutes of specific **neurological and psychiatric manifestations** following infection with a specific **strain of *T. pallidum*** (resistant or not resistant to penicillin), due or not due to maternal, sexual or other **mode of transmission**, in a person with a specific **genetic profile**, with or without a **competent immune system**, and with or without **specific (active) (autoimmune) antibodies** in serum and/or cerebrospinal fluid. Such a descriptive diagnosis might eventually substantiate a personalized prognosis and an individualized treatment proposal, including, if indicated, vascular preventive measures, anti-epileptic drugs, immunotherapy, psychoactive medication, cognitive rehabilitation therapy and psychosocial interventions.

De Spaanse Pokmeester
Beschrijvende
Den Oorsprong oorsaak en Regte
genesing der
POKKEN.

CHAPTER 9

SUMMARY

ZUSAMMENFASSUNG

RESUMÉ

In the foreground a patient suffering from the "Spanish pox" is treated with mercury in an "oven".
Source: http://www.beroepenvantoen.nl/Oude-beroepen-P.html

SUMMARY

Syphilis is a mainly sexually transmitted multistage infectious disease with a long and variable course. Neurosyphilis may present with meningitis, meningovascular or parenchymatous disease. The clinical syndromes of parenchymatous neurosyphilis comprise General Paresis of the Insane (GPI, also known as syphilitic dementia or dementia paralytica) and Tabes dorsalis. In the beginning of the 20th century, patients with neurosyphilis were treated with heavy metals and malaria fever therapy (MFT). At that time, GPI was a major reason for psychiatric hospitalisation. Most patients with GPI died within three years of admission, irrespective of treatment. The incidence of syphilis and neurosyphilis declined after the introduction of antibiotic therapy. Nevertheless, in the last decades, the incidence of syphilis has worldwide sharply increased, and, therefore, a revival of GPI can be expected. Research on the current clinical presentation of neurosyphilis is warranted since early recognition and treatment improve outcome.

In the first part of this thesis, the clinical presentation of patients with GPI and treatment of GPI with MFT are examined. In the second part of the present thesis the epidemiology and clinical presentation of neurosyphilis in the 21st century are investigated.

In **Chapter 2**, the clinical presentation of 105 patients with GPI admitted to a Dutch psychiatric hospital in the period 1924-1954 is described. At admittance, patients presented with a wide range of psychotic and mood disorders accompanied by impaired judgment. Prevailing neurological symptoms comprised impaired speech, pupillary abnormalities and cranial nerve dysfunction. The result of MFT was investigated in the same cohort of patients and described in **Chapter 3**. MFT was practiced in a wide range of patients with GPI up to 70 years of age, including those with a disease duration of more than 1 year and those with a broad array of symptoms and co-morbidities, such as (syphilitic) cardiac disease. Notwithstanding these broad inclusion criteria, practice and mortality rates in MFT-treated patients corresponded to findings worldwide. MFT was well tolerated and MFT-treated patients had a significantly longer survival. It should be kept in mind that on admission, the group of MFT-treated patients was possibly in a better medical condition than the group of non-treated patients and it is likely that this has affected the survival time. However, this is not reflected by differences in baseline conditions that may be associated with higher risk of death. Main causes of death in patients with GPI were epileptic seizures and infectious diseases, irrespective of MFT.

In **Chapter 4** the epidemiology of neurosyphilis in Dutch general hospitals in the period 1999-2010 is investigated in a nationwide study. In this study neurosyphilis was diagnosed in about 60 Dutch hospitalised adult patients per year, indicating that neurosyphilis is yet to be considered in the differential diagnosis. The incidence of neurosyphilis was highest in young, urban men, although Tabes dorsalis was the most frequently reported clinical manifestation. The low incidence of diagnosis of neurosyphilis co-occurs with less familiarity of clinicians with the asymptomatic and atypical manifestations of the disease. Since further research on the frequent atypical clinical symptomatology is needed to improve both diagnosis and management of patients with neurosyphilis, in **Chapter 5** the clinical data of a series of

patients with laboratory confirmed neurosyphilis are analysed. Main findings are male predominance, regular cognitive, memory and visual complaints as well as a broad age range. In addition, HIV- seropositivity and previous psychiatric disease were frequently reported. Since most patients were not able to mention any earlier syphilitic infection, the interval between first signs and diagnosis was generally long. The results of this study may be biased since only those patients were included in whom CSF analysis was performed by a certificated reference laboratory. Cognitive and memory complaints were probably not systematically assessed in all patients, which may have resulted in underestimation of the presence of these symptoms. The number of patients diagnosed with GPI was too low to enable comparison with the clinical presentation of GPI in the study as described in **Chapter 2**. In **Chapter 6** a case of neurosyphilis mimicking autoimmune encephalitis is presented, indicating that exclusion of neurosyphilis should be considered in patients presenting with focal seizures and MRI abnormalities of the amygdala.

A general discussion and conclusions, including future perspectives, are presented in **Chapter 7** and **Chapter 8** respectively. Finally, in **Chapter 9** and **Chapter 10** the findings of this thesis are summarized.

ZUSAMMENFASSUNG

Syphilis ist eine Infektionskrankheit die überwiegend sexuell übertragen wird und einen langen und variablen Krankheitsverlauf hat. Die klinischen Manifestionen der Neurosyphilis können in eine meningeale, meningovaskuläre und ein parenchymatöse Subform unterteilt werden. Ein Befall des Zentralnervensystems mit Gummen ist ebenfalls möglich, aber selten.

Bei der Neurosyphilis ist das Parenchym von Gehirn und Rückenmark betroffen. Die klinischen Syndrome der parenchymatösen Neurosyphilis umfassen die progressive Paralyse (auch bekannt als Dementia Paralytica) und die Tabes dorsalis. Zu Beginn des 20. Jahrhunderts wurden Patienten mit Neurosyphilis mit Schwermetallen und Malaria-Fieber-Therapie (MFT) behandelt. Zu dieser Zeit war die progressive Paralyse ein Hauptgrund für psychiatrische Krankenhausaufenthalte. Die meisten Patienten mit progressiver Paralyse starben innerhalb von drei Jahren nach der Aufnahme, unabhängig von der Behandlung. Die Inzidenz von Syphilis und Neurosyphilis nahm nach Einführung der Antibiotikatherapie ab. Dennoch hat in den letzten Jahrzehnten die Inzidenz von Syphilis weltweit stark zugenommen, und daher ist mit einer Wiederbelebung des progressive Paralyse zu rechnen. Die Erforschung des gegenwärtigen klinischen Erscheinungsbilds der Neurosyphilis ist gerechtfertigt, da die Früherkennung und Behandlung das Ergebnis verbessern kann.

In der vorliegenden Dissertation werden die Epidemiologie und das klinische Erscheinungsbild der Neurosyphilis im 21. Jahrhundert untersucht. Im historischen Teil dieser Arbeit, der sich auf die erste Hälfte des 20. Jahrhunderts bezieht, werden die klinische Präsentation und Behandlung von MFT bei Patienten mit progressive Paralyse untersucht.

In **Kapitel 2** wird die klinische Darstellung von 105 Patienten mit progressiver Paralyse beschrieben, die zwischen 1924 und 1954 in eine niederländische psychiatrische Klinik eingewiesen wurden. Bei der Aufnahme hatten die Patienten ein breites Spektrum an psychotischen Symptomen und Stimmungsstörungen, die mit einer Beeinträchtigung des Urteilsvermögens einhergingen. Vorherrschende neurologische Symptome umfassen Sprachstörungen, Pupillenanomalien und Hirnnervenstörungen. Das Ergebnis der MFT wurde in der gleichen Kohorte von Patienten untersucht und in **Kapitel 3** beschrieben. Die MFT wurde bei einer Vielzahl von Patienten mit progressive Paralyse durchgeführt, auch bei Patienten mit einer Krankheitsdauer von mehr als 1 Jahr, sogar bis zu einem Alter von 70 Jahren sowie bei Patienten mit einer breiten Palette von Symptomen und Begleiterkrankungen, wie (syphilitische) Herzerkrankungen. Ungeachtet dieser umfassenden Einschlusskriterien entsprachen die Praxis- und Sterblichkeitsraten bei MFT-behandelten Patienten den weltweiten Ergebnissen. MFT wurde gut vertragen und mit MFT behandelte Patienten hatten ein signifikant längeres Überleben. Haupttodesursachen bei Patienten mit progressive Paralyse waren epileptische Anfälle und Infektionskrankheiten, unabhängig ob eine Behandlung mit MFT stattgefunden hat oder nicht.

In **Kapitel 4** wird die Epidemiologie der Neurosyphilis in niederländischen Allgemeinkrankenhäusern im Zeitraum 1999-2010 in einer nationalen Studie untersucht. In dieser Studie wurde Neurosyphilis bei etwa 60 Erwachsenen pro Jahr diagnostiziert, was

darauf hinweist, dass Neurosyphilis in der Differentialdiagnose noch zu berücksichtigen ist. Die Inzidenz von Neurosyphilis war bei jungen Männern in der Stadt am höchsten, obwohl Tabes dorsalis die am häufigsten berichtete klinische Manifestation war. Die geringste Inzidenz der Diagnose von Neurosyphilis tritt bei Ärzten auf, die wenig vertraut mit den asymptomatischen und atypischen Manifestationen der Krankheit sind.

Da weitere Untersuchungen zur häufigen atypischen klinischen Symptomatik erforderlich sind, um sowohl Diagnose und Behandlung von Patienten mit Neurosyphilis zu verbessern, werden in **Kapitel 5** die klinischen Daten einer Reihe von Patienten mit vom Liquordiagnostik bestätigter Neurosyphilis analysiert. Hauptbefunde sind männliche Prädominanz, regelmäßige Beschwerden kognitiver, mnestischer und visueller Art sowie ein breites Altersspektrum. Darüber hinaus wurde häufig über HIV-Seropositivität und frühere psychiatrische Erkrankungen berichtet. Da die meisten Patienten keine frühere syphilitische Infektion erwähnen konnten, war die Zeitspanne zwischen den ersten Anzeichen und der Diagnose im Allgemeinen lang.

Die Ergebnisse dieser Studie könnten verzerrt sein, da nur Patienten eingeschlossen wurden, bei denen die CSF-Analyse von einem zertifizierten Referenzlabor durchgeführt wurde. Kognitive und Gedächtnisbeschwerden wurden wahrscheinlich nicht bei allen Patienten systematisch bewertet, was möglicherweise zu einer Unterschätzung des Auftretens dieser Symptome geführt hat. Die Anzahl der mit progressiver Paralyse diagnostizierten Patienten war zu gering, um einen Vergleich mit der klinischen Darstellung von progressiver Paralyse in der Studie gemäß **Kapitel 2** zu ermöglichen. In **Kapitel 6** wird ein Fall von Neurosyphilis vorgestellt, der eine Autoimmunenzephalitis imitiert, was darauf hinweist, dass der Ausschluss von Neurosyphilis bei Patienten mit fokalen epileptischen Anfällen und magnetresonanztomographischen Anomalien der Amygdala differentialdiagnostisch in Betracht gezogen werden sollte.

Eine allgemeine Diskussion und Schlussfolgerungen einschließlich zukünftiger Perspektiven werden in **Kapitel 7** und **Kapitel 8** vorgestellt. Abschließend werden in **Kapitel 9** und **Kapitel 10** die Ergebnisse dieser Arbeit zusammengefasst.

RÉSUMÉ

La syphilis est une maladie infectieuse à transmission sexuelle prédominante qui connaît une évolution longue et variable de la maladie. La neurosyphilis peut être associée à une méningite, une maladie méningovasculaire ou parenchymateuse. L'infestation du système nerveux central par des gencives est également possible, mais rare. Dans la neurosyphilis parenchymateux le parenchyme est affecté par le cerveau et la moelle épinière. Les syndromes cliniques de neurosyphilis parenchymateux incluent la paralysie générale et la tabès (dorsale). Au début du 20ème siècle, les patients atteints de neurosyphilis étaient traités avec un traitement aux métaux lourds et avec la malaria-thérapie. A cette époque, la paralysie générale était une cause majeure d'hospitalisation psychiatrique. La plupart des patients atteints de cette maladie sont décédés dans les trois ans suivant leur admission, quel que soit le traitement. L'incidence de la syphilis et de la neurosyphilis a diminué après l'introduction de la thérapie antibiotique. Néanmoins, au cours des dernières décennies, l'incidence de la syphilis a considérablement augmenté dans le monde et on peut donc s'attendre à une recrudescence de la neurosyphilis. La recherche sur la présentation clinique actuelle de la neurosyphilis est justifiée dans la mesure où la reconnaissance précoce et le traitement améliorent les résultats.

Dans la première partie de cette thèse, concernant la première moitié du 20e siècle, la présentation clinique et la malaria-thérapie chez les patients atteints de la paralysie générale sont examinés. Dans la deuxième partie de ce travail l'épidémiologie et l'apparence clinique de la neurosyphilis au XXIe siècle sont examinées.

Le **Chapitre 2** décrit la présentation clinique de 105 patients atteints de paralysie générale admis dans un hôpital psychiatrique néerlandais au cours de la période 1924-1954. À l'admission, les patients présentaient un large éventail de troubles psychotiques et d'humeur accompagnés d'une altération du jugement et du raisonnement. Les principaux symptômes neurologiques comprenaient une altération de la parole, des anomalies (l'anisocorie) de la pupille et un dysfonctionnement des nerfs crâniens. Le résultat de la malaria-thérapie a été étudié dans la même cohorte de patients et décrit au **Chapitre 3**. La malaria-thérapie a été pratiquée sur un large éventail de patients atteints de la paralysie générale, y compris ceux présentant la maladie d'une durée de plus d'un an, même jusqu'à 70 ans et ceux qui présentent un large éventail de symptômes et de comorbidités, tels que la maladie cardiaque (syphilitique). Malgré ces critères d'inclusion généraux, les taux de pratique et de mortalité chez les patients traités avec malaria-thérapie correspondaient aux résultats obtenus dans le monde entier. La malaria-thérapie était bien toléré et les patients traités ainsi avaient une survie significativement plus longue. Les principales causes de décès chez les patients atteints de la paralysie générale étaient les crises d'épilepsie et les maladies infectieuses, indépendamment de la malaria-thérapie.

Le **Chapitre 4** examine l'épidémiologie de la neurosyphilis dans les hôpitaux généraux néerlandais de 1999 à 2010 dans le cadre d'une étude nationale. Dans cette étude, la neurosyphilis a été diagnostiquée chez environ 60 patients adultes hollandais hospitalisés

chaque année, ce qui indique que la neurosyphilis doit encore être prise en compte dans le diagnostic différentiel.

L'incidence de la neurosyphilis était la plus élevée chez les hommes jeunes et urbains, bien que la manifestation clinique la plus fréquemment rapportée ait été tabès. La faible incidence du diagnostic de neurosyphilis est concomitante de la familiarité des cliniciens avec les manifestations asymptomatiques et atypiques de la maladie.

Etant donné que des recherches complémentaires sur la symptomatologie clinique atypique fréquente sont nécessaires pour améliorer à la fois le diagnostic et la gestion des patients atteints de neurosyphilis, le **Chapitre 5** analyse les données cliniques d'une série de patients présentant une neurosyphilis confirmée en laboratoire. Les principales conclusions sont la prédominance masculine, des plaintes régulières sur le plan cognitif, de la mémoire et de la vue, et cela sur une vaste tranche d'âge. De plus, une séropositivité au Virus de l'immunodéficience humaine et une maladie psychiatrique antérieure ont été fréquemment rapportées. La plupart des patients n'ayant pu mentionner aucune infection syphilitique antérieure. Cela peut avoir entraîné un intervalle prolongé entre les premiers signes et le diagnostic. Les résultats de cette étude peuvent être biaisés, car seuls les patients pour lesquels une analyse du Liquide Cephalo-Rachidien a été réalisée par un laboratoire de référence certifié ont été inclus. Les problèmes de mémoire et de vue n'ont probablement pas été systématiquement évalués chez tous les patients, ce qui peut avoir entraîné une sous-estimation de la présence de ces symptômes. Le nombre de patients diagnostiqués avec paralysie générales était trop faible pour permettre une comparaison avec le tableau clinique de cette maladie dans l'étude décrite au **Chapitre 2**. Au **Chapitre 6**, un cas de neurosyphilis imitant l'encéphalite auto-immune est présenté, ce qui indique qu'une exclusion de la neurosyphilis doit être envisagée, chez des patients présentant des convulsions focales et des anomalies d'imagerie par résonance magnétique du corps amygdaloïde.

La discussion générale et des conclusions, y compris les perspectives futures, sont respectivement présentées aux **Chapitres 7 et 8**.

Enfin, les **Chapitres 9 et 10** résument les résultats de cette thèse.

'Ick vont lest eenen vrient, die in syn groene jaren
Met ons was uytgereyst, en over zee gevaren;
hy scheen in geenen deel gelyck hij eertijts plagh;
Nadien hy byster vreemt,en wonder deerlick sagh
Syn hooft meest sonder hair syn neuse was gesoncken,
Syn lippen sonder verf, syn holle tanden stonken,
Syn handen blaeu gepleckt, syn beenen sonder kuyt,
En dan een lelick vocht, quam hem ten oogen uyt'.

'Me gaet by Meester Jan, die tijdt gezwind aen 't stoven;
Die douwt den vuylen Romp in een berookten Oven;
Een schadelijken domp om-vangt zijn naekte le'en,
Die, machteloos door 't zweet, nu tuymelen daer he'en;
Die gaet in 't stinckend Rift bereydt Quik-zilver gietten;
Dat doet een vuylen vloed na zijne lippen vlietten;
Me quijlt er nacht, en dag; tot dat het tanden-rek,
Door 't giftig zever-zap, hem rammelt in den bek.
't Viel licht, indien hierme'e het guijlen op wou kouwen,
Maer neen, hij moet van nieus aan Deel Ducaten spouwen;
Het lijf moet van 't Vergif, voor 't lest, gezuyvert zijn:
Daartoe houd Jan het Goud de beste medicijn.

Na lange tijd-verloop zie ik den Gast verrijzen:
Zijn dood-gelijk Gelaet doet zijn Aenschouwers yzen:
't Geheuvelt kakebeen dat wijzt genogzaem uyt
Dat zelde zijn banquet viel boven droog bisquyt'.

NEDERLANDSE SAMENVATTING / SUMMARY IN DUTCH

ACHTERGROND

General Paralysis of the Insane (GPI), in Nederland ook wel "dementia paralytica" genoemd, was in het verleden een fatale vorm van neurosyfilis die zeer frequent een, al dan niet gedwongen, opname in een psychiatrische ziekenhuis noodzakelijk maakte. Tegenwoordig veronderstellen artsen vaak dat syfilis en neurosyfilis zeldzame aandoeningen zijn. Maar sinds het begin van de 21ste eeuw is de incidentie van syfilis wereldwijd gestegen en een toename van het aantal gevallen van neurosyfilis is te verwachten. Vroege diagnose en snelle start van behandeling zijn van groot belang bij neurosyfilis om te voorkomen dat schade aan zenuwcellen tot onherstelbaar verlies van functie leidt. Derhalve is een hernieuwde bewustwording van het brede spectrum van psychiatrische en neurologische verschijnselen van deze aandoening noodzakelijk.

DOELSTELLING

Het doel van dit onderzoek is ten eerste het beschrijven van de epidemiologie en klinische presentatie van neurosyfilis in de 21^e eeuw en ten tweede het vergelijken van de klinische presentatie van GPI in de eerste helft van de 20ste eeuw met die in de 21ste eeuw.

VERLEDEN

In **hoofdstuk 2** wordt de klinische presentatie van GPI bij opname in het psychiatrisch ziekenhuis in Venray in de eerste helft van de 20^e eeuw beschreven aan de hand van de oorspronkelijke patiëntendossiers van 105 patiënten (91 mannen en 14 vrouwen). De meest gerapporteerde psychiatrische verschijnselen waren oordeels– en kritiekstoornissen, psychotische stoornissen en stemmingsstoornissen. Grootheidswanen werden bij bijna de helft van de patiënten gerapporteerd. Opvallend was dat veel patiënten zeer snelle stemmingswisselingen doormaakten. Spraakstoornissen in de zin van "Sylbenstolpern" (het weglaten of verplaatsen van lettergrepen in een woord), uitspraakstoornissen en onvermogen om te spreken vormden de meest frequent vermelde neurologische symptomen, gevolgd door pupilafwijkingen (zoals de Argyll-Robertson pupil: een nauwe pupil met afgenomen reactie op licht bij behouden reactie op convergentie) en problemen bij plassen.

In 1921 vond in Nederland de introductie van malariakoortstherapie bij patiënten met GPI plaats en al snel werd deze behandeling toegepast in het psychiatrisch ziekenhuis in Venray. Men injecteerde met malaria geïnfecteerd bloed onder de huid tussen de schouderbladen. Ongeveer 10 dagen later trad een eerste koortspiek op en na circa 10 episodes van hoge koorts volgde eerst behandeling van de malaria met kinine, gevolgd door behandeling met een combinatie van arsenicum, bismut en kwik gericht tegen de *Treponema pallidum*, de bacterie die syfilis veroorzaakt. Uit onderzoek naar het effect van malariakoortstherapie bij de patiënten met GPI beschreven in **hoofdstuk 2**, bleek dat met malariakoortstherapie behandelde patiënten (*n* = 43) een langere overlevingsduur na opname

hadden dan niet met malariakoortstherapie behandelde patiënten (*n* = 62), zie **hoofdstuk 3**. Het is echter niet duidelijk of de langere overlevingsduur (geheel) is toe te schrijven aan de effectiviteit van malariakoortstherapie of dat selectiecriteria voorafgaand aan de therapie een rol speelden. Want malariakoortstherapie vormde een zeer sterke fysieke belasting en patiënten met een matige tot slechte lichamelijke conditie (bijvoorbeeld met ernstig hartfalen door syfilitische infectie van het hart) kwamen niet voor malariakoortstherapie in aanmerking. Desalniettemin werd malariakoortstherapie toegepast bij patiënten tot de leeftijd van 71 jaar en bij patiënten met een breed scala aan klinische verschijnselen, ook bij een ziekteduur langer dan één jaar. De wijze van uitvoering van de malariakoortstherapie behandeling en de mortaliteitscijfers bij met malariakoortstherapie behandelde patiënten stemden overeen met de bevindingen in de rest van de Europa en de Verenigde Staten. Epileptische aanvallen en infectieziekten waren de meest voorkomende doodsoorzaken, zowel bij patiënten mét als bij patiënten zonder malariakoortstherapie.

HEDEN

Na de tweede wereldoorlog kwam penicilline beschikbaar voor de behandeling van syfilis. Uitbreiding van programma's gericht op screening, behandeling en preventie leidden tot een sterke daling van de incidentie van syfilis in Nederland en andere economisch welvarende landen. In Nederland werd de meldplicht voor syfilis opgeheven en later ook de standaard screening op syfilis bij neurologische patiënten. Hoewel syfilis vrijwel verdween uit het gezichtsveld van de neuroloog, hield de ziekte niet op te bestaan. De epidemiologische studie beschreven in **hoofdstuk 4** maakte gebruik van data van SOA-poliklinieken en ontslagdiagnoses, zoals vermeld in de Landelijke Medische Registratie, in de periode 1999-2010. In deze periode werd in totaal bij 60 patiënten per jaar voor de eerste keer de diagnose neurosyfilis gesteld. Deze studie toonde aan dat de incidentie van neurosyfilis in Nederland significant hoger was in het meer verstedelijkte deel van Nederland (0.6) dan in de rest van Nederland (0.4). Zowel de diagnose syfilis als neurosyfilis werd vaker bij mannen gesteld dan bij vrouwen, namelijk in 90% van de gevallen van syfilis en 75% van de gevallen van neurosyfilis. Bij mannen werd de hoogste incidentie van neurosyfilis vastgesteld in de leeftijdscategorie 35-65 jaar, bij vrouwen in de leeftijdscategorie van 75 jaar en ouder. Opvallend is dat tabes dorsalis de meest gerapporteerde klinische verschijningsvorm van neurosyfilis was.

De retrospectieve studie beschreven in **hoofdstuk 5** was gericht op een gedetailleerde inventarisatie van de klinische presentatie van neurosyfilis bij patiënten met een positieve syfilisserologie in het hersenvocht, vastgesteld in Certe, in de periode 2004-2018. Certe is een organisatie voor integrale medische diagnostiek en advies voor de eerste- en tweedelijnsgezondheidszorg en fungeert als referentielaboratorium voor syfilisserologie. In deze periode werd de diagnose neurosyfilis vastgesteld bij 34 patiënten (1 vrouw en 33 mannen), met een leeftijdsspreiding van 31 tot 84 jaar (mediane leeftijd: 44 jaar). Ten tijde van het stellen van de diagnose neurosyfilis was bij 12 (35%) patiënten bekend dat zij besmet

waren met het **Human immunodeficiency virus** (HIV). Cognitieve dysfunctie en psychiatrische verschijnselen werden bij een derde van de patiënten gerapporteerd. Aangezien gestandaardiseerd psychiatrisch en neuropsychologisch onderzoek geen onderdeel van de diagnostische work-up vormden, kan hier sprake zijn van onderrapportage. De verdeling van de klinische syndromen was als volgt: 16 patiënten met vroege neurosyfilis (acute meningitis, meningovasculitis en/of uveitis), 9 patiënten met late neurosyfilis (GPI of tabes dorsalis), 2 patiënten met zowel symptomen passend bij vroege als bij late neurosyfilis, en 6 patiënten met asymptomatische neurosyfilis. Bij één patiënt waren onvoldoende gegevens beschikbaar om het klinische syndroom te kunnen vaststellen. Vroege neurosyfilis trad in alle leeftijdscategorieën op, late neurosyfilis werd alleen gezien bij patiënten ouder dan 40 jaar.

In **hoofdstuk 6** wordt een 62 jarige man beschreven met sinds 1 jaar bestaande focale epilepsie. De Magnetic Resonance Imaging (MRI) scan van de hersenen liet aanwijzingen zien voor een zwelling van de amygdala, een amandelvormige structuur diep in de slaapkwab. Het EEG toonde intermitterende trage activiteit ter plaatse van de slaapkwabben, links meer dan rechts Op grond van deze combinatie van gegevens werd aanvankelijk de diagnose autoimmuun ontsteking van de hersenen overwogen. In het bloed werden geen anti-neuronale antistoffen aangetoond en derhalve kon de diagnose autoimmuun hersenontsteking niet worden bevestigd. Maar er werden wel antistoffen tegen *Treponema pallidum*, de veroorzaker van syfilis, in het bloed en in het hersenvocht van deze patiënt gevonden en daarmee was de diagnose neurosyfilis bewezen. Zowel bij neurosyfilis als bij autoimmuun hersenontsteking is het tijdig stellen van de diagnose en starten van adequate behandeling van groot belang om een optimaal behandelresultaat te kunnen bereiken. Deze patientenbeschrijving illustreert dat het spectrum aan uitingsvormen van neurosyfilis zeer breed is en onderstreept het belang van het uitsluiten van neurosyfilis alvorens immunotherapie te starten bij patiënten met een klinische verdenking op autoimmuun hersenontsteking.

Het aantal patiënten met GPI in de 21ste eeuw beschreven in **hoofdstuk 5** is te gering om het klinische beeld van deze aandoening betrouwbaar te vergelijken met dat van GPI patiënten in het begin van de 20ste eeuw. Desalniettemin is het opvallend dat bij 4 patiënten beschreven in **hoofdstuk 5** de diagnose neurosyfilis door routinematige screening op syfilis bij opname in een psychiatrisch ziekenhuis aan het licht kwam, hetgeen het belang van deze screening onderstreept.

EN VERDER

Deze studie helpt eraan herinneren dat syfilis een multisysteem aandoening is met een multifasisch beloop. Ondanks alle verbeteringen in diagnostiek en de effectiviteit van penicilline, met name voor de behandeling van de huidmanifestaties van syfilis, komt neurosyfilis nog steeds voor, ook na thans adequaat geachte behandeling van de vroege stadia

van syfilis. Derhalve hoort neurosyfilis thuis in de differentiaaldiagnose van uiteenlopende psychiatrische en neurologische ziektebeelden.

Als gevolg van de lage incidentie van syfilis in de laatste decades van de 20ste eeuw, zijn veel hedendaagse clinici niet vertrouwd met de uiteenlopende verschijningsvormen van neurosyfilis. Bij afwezigheid van betrouwbare cijfers aangaande de incidentie van deze aandoening is het niet vast te stellen hoe vaak en bij welke patiënten deze diagnose wordt "gemist". De resultaten van dit onderzoek ondersteunen de noodzaak om screening op syfilis opnieuw in te voeren bij psychiatrische en neurologische patiënten. Ten eerste kan zo tijdig adequate therapie kan worden gestart en ten tweede kan zo in de toekomst de incidentie en presentatie van neurosyfilis volledig in kaart worden gebracht. Alleen treponemale testen (zoals de *Treponema pallidum* hemagglutinatie test, *Treponema pallidum* particle agglutinatietest of de Enzyme Linked Immunosorbent Assays test) zijn geschikt voor screening, aangezien met name bij late neurosyfilis non-treponemale testen (zoals de Venereal Disease Research Laboratory test en de Rapid Plasma Reagin test) vals negatief kunnen zijn. Bij positieve syfilisserologie in bloed dient altijd onderzoek van hersenvocht te volgen.

Nog veel vragen aangaande de ontstaanswijze, diagnostiek en behandeling van neurosyfilis zijn onbeantwoord. Zo is nog altijd niet duidelijk hoe de *Treponema pallidum*, die al korte tijd na infectie in het centraal zenuwstelsel kunnen bevinden, jarenlang asymptomatisch aanwezig kunnen blijven, schijnbaar onopgemerkt door het afweersysteem. Evenmin is bekend welke factoren de omslag van asymptomatische naar symptomatische neurosyfilis veroorzaken. Recent onderzoek suggereert dat zowel infectie als (auto)immuun gerelateerde mechanismen hierbij betrokken zijn. Mogelijk kunnen de verschillende klinische verschijningsvormen van neurosyfilis in de toekomst gerelateerd worden aan een specifiek "ontstekingsprofiel" en (nu nog onontdekte) auto-immuun-antistoffen. Toekomstig onderzoek kan hopelijk duidelijkheid verschaffen ten aanzien van de rol van auto-immuun-antistoffen bij het ziekteproces en de eventueel hieraan gekoppelde therapeutische consequenties.

Zowel gedetailleerde beschrijving van neuropsychiatrische klachten en verschijnselen als gestandaardiseerd en gevalideerd neuropsychologisch onderzoek van patiënten met neurosyfilis zijn waardevolle methoden om de ernst van deze manifestaties in kaart te brengen en de effectiviteit van ingestelde behandeling te evalueren.

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loop der jaren veel lief en leed gedeeld en gelukkig ook vaak gelachen. Ik wens jou heel veel succes met je eigen promotie-onderzoek. Maar het blijft jammer dat jouw hart meer bij de cardiologie dan de neurologie ligt…..

Lieve Elisabeth, dankzij jouw bijzondere interesse in de opkomst van de natuurwetenschappen, de industrialisatie en de verstedelijking, hebben we met veel plezier gelezen en gediscussieerd over "het leven in de stad" als bijdragende factor aan het ontstaan van ziektebeelden, de opkomst van de genetica en de latere ontsporing van de eugenetica. Aan de hand van "temperatuurstaten" trachtten wij de exacte samenhang tussen grootheidswanen, malaria en arsenicum te doorgronden. Jij groeide uit van geïnteresseerde dochter tot volwaardig mede-onderzoeker bij het historische deel van dit onderzoek, met eigen posterpresentaties en voordrachten. Het is een voorrecht om fascinatie voor dergelijk onderzoek met je dochter te kunnen delen. Heel hartelijk dank hiervoor en voor jouw inzet bij de totstandkoming van dit proefschrift.

Ik dank alle betrokken collega's voor zinvolle discussies, alle co-auteurs voor de prettige samenwerking, en natuurlijk Annie en Henny, voormalig medewerkers van de bibliotheek van Vincent van Gogh, die zo succesvol bergen literatuur voor mij verzamelden. Aan Lod en alle stafleden van het museum voor de geschiedenis van Vincent van Gogh ben ik dank verschuldigd voor het speuren in de uitgebreide archieven en het samenstellen van lijsten waar ik mee aan de slag kon.

Lieve Ellen, ik mis de momenten van samen filosoferen over de relatie tussen hersenen en gedrag, al dan niet in combinatie met een praktische toepassing bij "onze" patiënten. Gelukkig, met dank ook aan Jos, hebben we nog ons jaarlijkse onderwijsmoment bij het RINO.

De medewerkers van het bureau van de pedel bedank ik graag hartelijk voor hun inspanningen om in de overgangsfase van "Hora Est" naar "Hora Finita" mij met raad en daad bij te staan om de administratieve kant van het promotietraject op de juiste wijze vorm te geven. Zonder jullie hulp was ik ongetwijfeld "Definitief Digitaal Verdwaald".

Gedurende dit onderzoek heb ik met zeer veel mensen uit uiteenlopende disciplines en diverse organisaties samengewerkt en ik ben ervan overtuigd dat een dergelijke interdisciplinaire samenwerking de meest effectieve en de meest inspirerende werkwijze is bij het oplossen van complexe vraagstukken. Dank aan een ieder die op één of andere manier heeft bijgedragen aan het tot stand komen van dit proefschrift, helaas is het niet mogelijk om alle namen te noemen, maar ik maak graag nog één uitzondering...

Lieve Henriëtte, als geen ander bezorgde jij mij, en Falco!, en mijn gezin een tweede thuis in Limburg, een plek waar ik vele uren aan dit proefschrift heb gewerkt. Bovendien stond je altijd klaar om mij te ondersteunen: om het even of het ging om bellen, typen, faxen, zoeken naar gaatjes in agenda's of uitblazen onder het genot van heerlijke "home-made" aspergesoep! Hartelijk dank!

Alle patiënten die ik tijdens mijn werkzaamheden heb ontmoet, ben ik dankbaar voor het in mij gestelde vertrouwen en voor de inspiratie die zij mij schonken om te blijven leren.

Lieve Daniël, bij jou kan ik altijd terecht om te filosoferen over rechtvaardigheid, ethiek, het belang van politieke keuzes en onze maatschappelijke verantwoordelijkheid voor mensen voor wie onze wereld te complex is. Dankzij jou weet ik nu tenminste iets over Plato, Nietzsche en Dworkin, maar het meeste houd ik toch van de wereldvisie van Franciscus van Assisi!

Lieve Julia, tijdens onze wandelingen met Falco over de North Sea Trail hebben we veel gepraat over "onze benen" en "het leven", malle avonturen meegemaakt en heel veel plezier gehad. De mooiste herinneringen bewaar ik aan het samen kijken naar de zonsondergang boven de Noordzee, een "magisch" beeld dat alles in een ander perspectief plaatst. Ik hoop op nog veel van zulke momenten.

Liefste Peter, mijn "Rots" in de branding, al 40 jaar ben jij er altijd, en mijn allergrootste dank gaat uit naar jou. We delen een passie voor de geneeskunde, in het bijzonder voor de neuropsychiatrie. Als trouwe metgezel heb je meegeleefd met alle "ups" en "downs" die bij een promotietraject horen. Maar bovenal heb je mijn vertrouwen gesterkt en mij onvoorwaardelijk gesteund bij het uitvoeren van mijn plannen. Jouw fantastische zorgen voor onze kinderen, onze huisdieren en voor mij (compleet met de onmisbare cappuccino bij het ontwaken en Tony Chocolonely na de avondmaaltijd) hebben het mogelijk gemaakt om dit onderzoek te verrichten en te voltooien.

En nu: op de fiets! Op naar Rome!

CURRICULUM VITAE

Ingrid Marianne Daey Ouwens was born in The Hague on March 19, 1957. In 1976 she obtained her "gymnasium" diploma at the "Stedelijk Gymnasium" in Leiden. Afterwards, she studied Medicine in Leiden at Leiden University. In 1983 she obtained her medical degree and in the same year commenced her residency in Neurology at Leyenburg Hospital (Dr. L.J. Endtz) and Psychiatric Hospital Rosenburg in The Hague (Dr. P.J. Stolk). In 1987 she received her certificate in Neurology and started as a neurologist in Psychiatric Hospital Bloemendaal in The Hague. In 1990 she trained in Clinical Neurophysiology at the Neurophysiology department of the University Medical Centre of Utrecht.

She practised as a neurologist at Lorentz Hospital in Zeist, GGZ Drenthe in Assen and at the Centre of Excellence for Neuropsychiatry at Vincent van Gogh institute for Psychiatry in Venray. In 2009 she started this PhD research project (Em. Prof. dr. W.M.A. Verhoeven). Since 2016 she practises as a neurologist at Stichting Epilepsie Instellingen Nederland, in the epilepsy clinic in Heemstede, the Netherlands.

LIST OF PUBLICATIONS

This thesis

Daey Ouwens IM, Thijs RD, Koehler PJ, Fiolet ATL, Verhoeven WMA. A case of neurosyphilis mimicking autoimmune encephalitis. 2019; submitted.

Daey Ouwens IM, Ott A, Fiolet ATL, Koehler PJ, Vos M, Oldhoff JM, Verhoeven WMA. Clinical presentation of laboratory confirmed neurosyphilis in a recent cases series. Clin Neuropsychiatry 2019;16:17-24.

Daey Ouwens IM, Lens CE, Fiolet ATL, Ott A, Koehler PJ, Kager PA, Verhoeven WMA. Malaria Fever Therapy for General Paralysis of the Insane: A Historical Cohort Study. Eur Neurol. 2017;78:56-62.

Daey Ouwens IM, Lens CE, Fiolet ATL, Ott A, Koehler PJ, Verhoeven WMA. Clinical presentation of General Paralysis of the Insane in a Dutch psychiatric hospital, 1924-1954. Eur Neurol. 2015;74:54-9.

Daey Ouwens IM, Koedijk FDH, Fiolet ATL, Van Veen MG, Van den Wijngaard CC, Verhoeven WMA, Egger JIM, Van der Sande MAB. Neurosyphilis in the mixed urban-rural community of the Netherlands. Acta Neuropsychiatr. 2014;26:186-92.

Other peer-reviewed publications

Penders GEM, Daey Ouwens IM, van der Heijden FMM. Wernicke - encefalopathie en droge beriberi als late complicaties van bariatrische chirurgie bij patiënte met psychiatrisch belast verleden (Wernicke encephalopathy and dry beriberi: late complications after bariatric surgery performed on a patient with a psychiatric history). Tijdschrift voor Psychiatrie 2017:59;116-20.

Lens - Daey Ouwens IM, Heijstra MP, Timmerman L. Neurosyfilis: onverwacht weerzien met een oude bekende. (Neurosyphilis: unexpected reunion with an old acquaintance). Tijdschrift voor Psychiatrie 2011;53:125-9.

Other publications

Lens - Daey Ouwens IM, Ott A. Neurosyfilis: een diagnose om niet te vergeten. Infectiebericht 2009;4:24-28.

Daey Ouwens IM, Lens PF. Het gevoel van vermoeidheid; een onderzoek naar de kenmerken van het gevoel van vermoeidheid bij gezonde volwassenen. Soma en Psyche 1992;18;7-12.

Daey Ouwens IM, Lens PF. Leidt invaliditeit tot depressiviteit? De oorzaak van depressieve verschijnselen bij multiple sclerose. [Does disability cause depression? The cause of depressive symptoms in multiple sclerosis]. Soma and Psyche 1991;15:6-9.

Daey Ouwens IM, Lens PF. Vermoeidheid en Multiple Sclerose. Soma en Psyche 1990;16:6-10.

Bruinen TCM, Daey Ouwens IM. Het arylsulfatase-A enzym en schizofrenie. COBO-bulletin 1987;87:34-40.

Daey Ouwens IM. Psychiatrische verschijnselen en Multiple Sclerose: erbij of erdoor? Soma en Psyche 1987;13-16.

Publications in books

Daey Ouwens IM: Depressie en geheugenstoornissen bij MS. In: Zelfzorgboek Multiple Sclerose. Amsterdam, Stichting September, 2001. pp 2003-7.

Lens PF, Daey Ouwens IM. Capai atau kesal – een inventarisatie van het gevoel van vermoeidheid bij Indische kampkinderen. In: De Jong AJ en Verwoerd W (red): Facetten van traumabehandeling. Assen, 1996. pp 83-91.

Abstracts

Ott A, Daey Ouwens IM, Fiolet A, Koehler PJ, Vos M, Oldhoff JM, Verhoeven WMA. Serology and clinical classification in a recent case series of neurosyphilis patients. ESCMID congres 2019, in press.

Daey Ouwens I, Thijs R. Adult onset epilepsy as the presenting symptom of Fetal Alcohol Spectrum Disorder: A Case Report. Epilepsia 2018;59:p.S82.

Lens CE, Daey Ouwens IM, Fiolet ATL, Ott A, Koehler PJ, Verhoeven WMA. The clinical spectrum of General Paralysis of the Insane: a historical cohort study. Eur. Psychiatry 2015;30:S1247.

Boersema C, Daey Ouwens IM, Ruys TA, Gerrits MCF, Vlasveld LT, Verhoeven WMA. Acute intermittent porphyria and cycloid psychosis. Eur. Psychiatry 2013; 28:S1.

Daey Ouwens IM, Lens CE, Ott A, Koehler PJ, Verhoeven WMA. Megalomania in dementia paralytica. Eur Arch Psychiatry Clin Neurosci 2013;263:S75-S76.

Daey Ouwens IM, Fiolet ATL, Ott A, Koehler PJ, Verhoeven WMA. The clinical spectrum of neurosyphilis today. J Neurol. 2013;260: S19-S20.

Daey Ouwens IM, Fiolet ATL, Ott A, Koehler PJ, Koedijk FDH, Van den Wijngaard CC, Van der Sande MAB, Verhoeven WMA. Dementia paralytica and HIV infection. J Neurol. 2013;260:S41.

Daey Ouwens IM, Fiolet ATL, Ott A, Koehler PJ, Verhoeven WMA. The clinical spectrum of neurosyphilis today. Eur. Psychiatry 2013;28;S1-S1.

Daey Ouwens IM, Fiolet ATL, Koehler PJ, Verhoeven WMA. Prognostic factors regarding the treatment of Dementia Paralytica with malaria fever therapy: a historical cohort study. Eur. Psychiatry 2012;27:S1.

Lens-Daey Ouwens IM, Verhoeven WMA, Ott A, Koehler PJ. Malaria-Fever Therapy for a 19-Year-Old Boy with Dementia Paralytica. J Hist Neurosci. 2012;21;54-5.

Lens-Daey Ouwens IM, Van Veen MG, Van den Wijngaard CC, Notermans DW, De Vries HJC, Van der Sande M. Neurosyphilis with psychiatric co-morbidity in general hospitals in the Netherlands, 1999-2007. Eur. Psychiatry 2010;25:S1527.

Daey Ouwens IM, Franssen H, Abels MMEF. In Search of the Negative Side of the Radial Generator of Median nerve Somatosensory Evoked Potential (SEP). Brain Topography 1993;5:S435.

Conference papers in proceedings

Daey Ouwens IM: Malaria Fever Therapy: a centennial. International Society of the History of the Neurosciences meeting 2017 program and abstract book, p. 55 http://www.ishn.org/

Daey Ouwens IM, Lens CE, Ott A, Koehler PJ, Kager PA, Verhoeven WMA. Treatment of general paralysis of the insane by malaria. International Society of the History of the Neurosciences meeting 2016 program and abstract book, p 9. http://www.ishn.org/

PhD PORTFOLIO

Summary of PhD training and teaching

Name PhD student:	Ingrid Marianne Lens – Daey Ouwens	
Erasmus MC Department:	Psychiatry	
PhD period:	2009 - 2019	
Promotors:	Em. Prof. dr. W.M.A. Verhoeven and Prof. dr. W. Hoogendijk	
Supervisor:	Dr. P.J. Koehler	

	Date, location	Workload in ECTS
General courses		
CPO Methodologie van Patiëntgebonden Onderzoek en Voorbereiding Subsidieaanvragen	16-02-2010; Rotterdam, NL	0,3
Biomedical English Writing and Communication	2011; Rotterdam, NL	0,3
Schrijf een artikel! (pe-online ID nr: 3655)	06/10/2009 + 24/11/2009; Zeist, NL	0,6
Verantwoord omgaan met medische statistiek (pe-online ID nr: 3219)	04-11-2009; Zeist, NL	0,3
Journal Club SEIN Heemstede (June 2016- June 2019) 60 x 1h	June 2016-June 2019	2,0

Didactic skills	Date, location	Workload in ECTS
Teach the teachers plus: Leerzame overdracht (pe-online ID No: 319099)	20/11/2018; Heemstede, NL	0,15
Teach The Teachers Triversum/Sein (pe-online ID No: 181735)	17/06/2016; Heemstede, NL	0,15
Werken met tutorgroepen (pe-online ID No: 213666)	14/09/2015: Tilburg, NL	0,15
Landelijke training tutoren (pe-online ID No: 157555)	15/09/2014; Tilburg, NL	0,15
Werken met tutorgroepen (pe-online ID No: 156261)	24/03/2014: Tilburg, NL	0,15
Training toetsvragen maken (pe-online ID No: 163285)	20/11/2013: Utrecht, NL	0,3
Opleiden in de klinische praktijk (pe-online ID No: 102965)	16/05/2013; Tilburg, NL	0,3
Opleiden in de klinische praktijk (pe-online ID No: 102958)	12/02/2013; Tilburg, NL	0,3
Teach the Teacher 3: Begeleiden, toetsen en beoordelen (pe-online ID No: 43975)	28-29/09/2009 Groningen, NL	0,6

Oral Presentations / lectures	Date, location	Workload in ECTS
Neurosyfilis: de terugkeer van een oude bekende? Regionale nascholing: Neurologisch Noord-Holland	29/11/2018, Zaandam, NL	0,5
Following the footsteps of Jack the Ripper. 8th Hammersmith course, Londen, 2018	2/11/2018; London, UK	0,5
Malaria Fever Therapy: a centennial. 22nd Meeting Internat Society of the History of the Neurosci	2017, Besancon, France	0,5
Amokmakers: psychiatrische patienten of politieke activisten? 23[e] Wetenschappelijke vergadering van de werkgroep Geschiedenis van de Neurowetenschappen, Amsterdam	18/11/2016; Amsterdam, NL	0,5
Waar is de man gebleven die denkt dat hij Napoleon is? Regionaal Microbiologisch-Infectiologisch Symposium van het Infectiepreventienetwerk Noord-Nederland	14/11/2016; UMCG, Groningen, NL	0,5
Treatment of general paralysis of the insane by malaria. 21st Meeting Internat Society of the History of the Neurosci	11/07/2016; Maastricht, NL	0,5
The intimate link between syphilis and psychiatry. Department of Psychiatry Erasmus MC, Rotterdam	2014; Rotterdam, NL	0,5
Dementia paralytica and HIV infection. 23th Meeting of the European Neurological Society	8-11 June, 2013; Barcelona, Spain	0,5
The clinical spectrum of neurosyphilis today. 23th Meeting of the European Neurological Society	8-11 June, 2013; Barcelona, Spain	0,5
Acute intermittent porphyria and cycloid psychosis. Voorjaarscongres Ned Ver v Psych, Maastricht, 2012	2012, April; Maastricht, NL	0,5
Malaria-Fever Therapy fo a 19-Year-Old Boy with Dementia Paralytica. 16th Meeting Internat Society of the History of the Neurosci	16-23/06/2011, July; Calgary, Alberta, Canada	0,5
"Neurosyfilis anno 2010: wat zien we?" geaccrediteerde nascholings-bijeenkomst psychiatrie Vincent van Gogh Institute voor GGZ	2010, April; Venray, NL	0,5
"Een acuut verwarde man van 45 jaar". geaccrediteerde neuropsychiatrische nascholing: "Het brein in beweging".	2010, January; Wengen, Switzerland	0,5
"Neurosyphilis: Back to the Future?" OOR nascholingsavond psychiatrie	2009, May; Groningen, NL	0,5

Teaching		
Teaching neurology of residents in psychiatry GGZ Drenthe 2008-2010: 20 lectures	2008-2010	2,0
Teaching neurology of residents in psychiatry and supervision of their presentations on neurology, Vincent van Gogh Instituut voor GGZ: 50 lectures	2010-2016	5,0
Expert at expertmeetings regional onderwijs psychiatrie Vught: 10 lectures	2010-2016	3,0
Supervising expertpresentation 2 psychiatry residents	2014-2015	2,0

Posterpresentations	Date, location	Workload in ECTS
Daey Ouwens IM, Lens CE, Ott A, Koehler PJ, Verhoeven WMA. De klinische presentatie van neurosyfilis in een recent cohort patiënten met laboratorium bevestigde neurosyfilis. Wetenschappelijke vergadering Ned Ver v Neurologie	08-09/11/2018; Nunspeet, NL	0,5
Lens CE, Daey Ouwens IM, Fiolet ATL, Ott A, Koehler PJ, Verhoeven WMA. The clinical spectrum of General Paralysis of the Insane: a historical cohort study. 5th European Conference on Schizophrenia Research	24-26/09/2015; Berlin, Germany	0,5
Daey Ouwens, I.M., Fiolet, A.T.L., Ott, A., Koehler, P.J., Verhoeven, W.M.A. Het klinische spectrum van neurosyfilis anno 2012. 41e Voorjaarscongres Ned Ver v Psychiatrie	12-13/04/2013; Maastricht, NL	0,5
Daey Ouwens IM, Fiolet ATL, Ott A, Koehler PJ, Verhoeven WMA. Dementia paralytica en malariakoortstherapie. 41e Voorjaarscongres Ned Ver v Psychiatrie	12-13/04/2013; Maastricht, NL	0,5
Daey Ouwens IM, Fiolet ATL, Ott A, Koehler PJ, Verhoeven WMA. Dementia paralytica en Malaria-koorts-therapie. Wetenschapsdagen Ned Ver v Neurologie	1-2/11/2012; Nunspeet, NL	0,5
Daey Ouwens IM, Fiolet ATL, Ott A, Koehler PJ, Verhoeven WAM. Malaria Fever Therapy and Dementia Paralytica: a historical cohort study. 20th European Congress of Psychiatry	3-6/3/2012, Praque, Czech Republic	0,5
Lens-Daey Ouwens IM, Van Veen MG, Van den Wijngaard CC, Notermans DW, De Vries HJC, Van der Sande M. Neurosyphilis with psychiatric co-morbidity in general hospitals in the Netherlands, 1999-2007. 18th European Congress of Psychiatry	27/2-2/3 2010; Munchen, Germany	0,5

Specific courses (e.g. Research school, Medical Training)	Date, location	Workload in ECTS
Wetenschapsdagen Ned Ver v Neurologie 2018 (pe-online ID No: 336037)	08-09/11/2018	0,6
8 Hammersmith Course London (pe-online ID No: 322818)	02-03/11/2018	0,6
Regionale nascholing: Neurologisch Noord-Holland	29/11/2018, Zaandam, NL	0,15
22nd Meeting Internat Society of the History of the Neurosci	19-23/06/2017, Besancon, France	1,8
3 jarige cursus "Reading Freud" (pe-online ID No: 281512) 12 bijeenkomsten x 0,3	2015-2017, Venray, NL	3,6
21st Meeting Internat Society of the History of the Neurosci	11-16/07/2016; Maastricht, NL	1,8
23e Wetenschappelijke vergadering van de werkgroep Geschiedenis van de Neurowetenschappen, Amsterdam	18/11/2016; Amsterdam, NL	0,15
Regionaal Microbiologisch-Infectiologisch Symposium van het Infectiepreventienetwerk Noord-Nederland	14/11/2016; UMCG, Groningen, NL	0,15
5th European Conference on Schizophrenia Research	24-26/09/2015; Berlin, Germany	0,9
Nascholing ronde de documentaire "Dwaas en Deskundig" (pe-online ID No: 158383)	27/05/2014	0,15
Nascholingsbijeenkomst "DSM-5: kansen en dilemma's" (pe-online ID No: 162131)	10/10/2013	0,3

23th Meeting of the European Neurological Society	8-11 June, 2013; Barcelona, Spain	1,2
Workshop BOPZ (pe-online ID No: 149001)	03/06/2013; Venray, NL	0,15
41st Voorjaarscongres Ned Ver v Psychiatrie	10-12/04/2013; Maastricht, NL	0,9
40th Voorjaarscongres Ned Ver v Psychiatry	3-5/04/2012, April; Maastricht, NL	0,9
Wetenschapsdagen Ned Ver v Neurologie	1-2/11/2012; Nunspeet, NL	0,6
16th Annual Meeting of the Internat Society of the History of the Neurosci	16-23/06/2011, July; Calgary, Alberta, Canada	2,4
18th European Congress of Psychiatry	27/2-2/3 2010; Munchen, Germany	1,2
Het brein in beweging (pe-online ID No: 64372)	11-16/01/2010; Wengen, Switserland	1,8
OOR Geaccrediteerde nascholingsavond psychiatrie	2009, May; Groningen, NL	0,15
	Total	53,15