

## CLINICAL REPORT

# Incidence, Clinical Presentation and Treatment of Neurosyphilis in Denmark 1980–1997

Anne Grethe DANIELSEN<sup>1</sup>, Kaare WEISMANN<sup>1</sup>, Børge B. JØRGENSEN<sup>2</sup>, Michael HEIDENHEIM<sup>1</sup> and Anne Mette FUGLEHOLM<sup>1</sup>

<sup>1</sup>Department of Dermato-venereology, Bispebjerg Hospital, University of Copenhagen and <sup>2</sup>Department of Treponematosis, Statens Serum Institut, Copenhagen, Denmark

**Neurosyphilis is now a rare disease in the developed countries. In Denmark 92 cases of neurosyphilis were identified in the period 1980–1997. We obtained the hospital records for 77 of these patients and studied the clinical presentation, treatment and result of the treatment. Most patients were treated with penicillin by the intramuscular or intravenous route, but the amounts and duration of the antibiotic treatment varied a lot among the patients. All patients treated with intravenous penicillin were cured. Key words: neurosyphilis; treatment; penicillin.**

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Anne G. Danielsen, Department of Dermatology D40, Bispebjerg Hospital, University of Copenhagen, Bispebjerg Bakke 23, DK-2400 Copenhagen NV, Denmark. E-mail: anne.danielsen@dadlnet.dk

Tertiary syphilis is a rare disease in the developed countries, mainly as a result of the high standard of medical care and occasional antibiotic treatment of other infections such as tonsillitis and other common respiratory infections. The low incidence of tertiary syphilis during the last 50 years makes it very difficult to maintain a high level of alertness about the clinical presentation and the diagnosis of the disease. Thus in Denmark most cases of neurosyphilis (NS) are diagnosed by routine blood screening with the cardiolipin Wassermann reaction (CWRM) of patients with neurological or psychiatric symptoms.

Since penicillin was introduced it has remained the drug of choice for all stages of syphilis. Treatment with benzathine penicillin G or procaine penicillin, which is given in primary and secondary syphilis, does not always lead to spirocheticidal penicillin levels in cerebrospinal fluid (CSF) (1). Therefore treatment with penicillin preparations that achieve a high serum concentration of penicillin has been recommended during the last 25 years. We present herein the incidence, clinical presentation and treatment of NS in 92 cases diagnosed in Denmark during 1980–1997.

## MATERIALS AND METHODS

### Patients

Patients with NS were identified from the 'Syphilis Index' at Statens Serum Institute in Copenhagen. All patients with syphilis in Denmark have been registered in this index since 1920. The patients are identified by sex, first letter of surname, exact date of birth, name of physician (or hospital) diagnosing the case, and date of diagnosis (2).

After obtaining permission from the Central Scientific-Ethical Committee of Denmark, clinical records were collected from hospitals and clinics where the patients had been diagnosed and treated for NS. We received records for 77 of the 92 patients diagnosed with NS. Not all of the records contained all the information described in this paper. Records from the remaining 15 patients could not be studied because the records could not be found or permission to study them was not given by the doctors in charge. Fortunately brief information about the symptoms, syphilis category and treatment could be found in the index and is included in the data.

### Serological examinations

From 1980 to 1985 all blood samples were tested by CWRM, Kahn's standard test (KR) and Meinicke's clarification test (MR). After 1985, KR and MR were replaced by the automated reagin test (ART), antitreponemal IgG (AF-G) and IgM (AF-M) and the fluorescent treponemal antibody-absorption test (FTA-ABS).

The CSF was tested by the CWRM, AF-G, AF-M and FTA-ABS. Protein and cell number were determined.

### Criteria for neurosyphilis

In all patients classified as having NS, CWRM and FTA-ABS were positive in both peripheral blood and in CSF. In CSF the amount of protein and the leukocyte number were increased. The patients were divided into four main groups according to the final diagnosis: asymptomatic NS (group A), meningovascular NS (group M), parenchymatous NS (group P) and unclassified NS (group U).

## RESULTS

During the period 1980–1997, a total of 92 patients (72 men and 20 women) were identified with NS. They were living in Denmark, Greenland or the Farø Islands at the time of the diagnosis. The median age at the time of diagnosis was 47 years for men and 52 years for women. Twenty-five of the 92 (27%) cases

were categorized as asymptomatic NS, 9 (10%) as meningovascular NS and 46 (50%) as parenchymatous NS. In 12 (13%) the category of NS could not be classified.

Neurological symptoms were found in 33 (36%) of the patients; these individuals were referred to a department of neurology where the diagnosis of NS was verified (Table I). In only one of 44 patients primarily attending neurology and psychiatry clinics, a tentative diagnosis of NS diagnosis was made prior to routine CWRM testing, which is carried out in most of these departments in Denmark.

In 15 cases (16%) the test was found to be positive during a routine check because the patient suffered from other venereal diseases or was undergoing surgery in the genital region. Dermatological symptoms (rash on the skin or alopecia) was the reason for testing in 11 patients (12%) (Table I).

The patients were treated at different hospitals and clinics with various treatment schedules (Table II). Most patients were treated with penicillin by the intravenous or intramuscular route. A few were allergic to penicillin and alternative antibiotics were given; the patients attended a clinic or hospital until the CWRM test for the blood and CSF had decreased to zero or remained steadily close to zero.

Table I. Symptoms leading to neurosyphilis (NS) and speciality in which the diagnosis was determined

	No. of patients with NS			
	Group A	Group M	Group P	Group U
<i>Reasons for first serological examination</i>				
Neurological symptoms	0	6	25	2
Psychiatric symptoms	0	0	11	0
Other venereal diseases	9	0	1	0
Rash on the skin	7	0	1	2
Found by routine testing	4	1	0	0
Dementia	0	0	5	0
Visual problems	1	0	2	0
Non-characteristic symptoms	1	0	1	0
Alopecia	1	0	0	0
Unknown	2	2	0	8
<i>Speciality making the diagnosis</i>				
Neurology	0	2	26	0
Dermato-Venereology	14	1	2	2
Internal Medicine	1	2	4	2
Psychiatry	0	0	7	0
Family doctor	5	0	2	0
Ophthalmology	1	0	2	0
Neurosurgery	0	1	1	0
Gynaecology	1	0	0	0
Urology	0	0	1	0
Geriatric	0	0	1	0
Audiology	0	1	0	0
Unknown	3	2	0	8

Group A, asymptomatic; group M, meningovascular; group P, parenchymatous; group U, unclassified.

Full recovery after treatment was seen in all patients who had asymptomatic NS except in one patient, who had minor neurological problems (Table II). The patients with severe neurological and psychiatric symptoms improved after treatment with intravenous penicillin, but all had some degree of permanent brain damage. Two patients who were treated with intramuscular injections of penicillin did not respond to the treatment, and CWRM titres remained high in both serum and CSF. Following intravenous treatment with penicillin the CWRM titres decreased.

Most patients could not recall when or where they had been infected with syphilis. Of those that did remember, most thought they were infected in Denmark or Greenland. In 50 (54%) of the patients the sexual preference was mentioned in the records; of these 17 (34%) were homosexuals, 32 (64%) were heterosexuals and one was bisexual.

Prior serological results were available for 47 patients, of whom 12 (26%) had been infected with syphilis previously and the CWRM titres in the blood had decreased to zero after the treatment.

HIV status was known at the time of the NS diagnosis in 33 patients of whom 11 (33%) were HIV-positive.

## DISCUSSION

Since World War II there has been a general decrease in the incidence of early syphilis in the Western part of the world (3). In Denmark, the number of cases declined from 400 cases per year in the 1960s to 40 cases per year in the 1990s (4–8).

There has also been a decrease in the number of patients suffering from late syphilis in Denmark. In the 1960s on average 10.5 patients per year (0.21/100,000) were diagnosed with NS in Denmark (9). In the 1970s the number had declined to 6 patients per year (0.12/100,000) (10). In this report, we show that during 1980–1989, 6.2 patients per year (0.13/100,000) were diagnosed with NS. During 1990–1997 the average number was 3.8 patients per year (0.08/100,000).

The main reason for the decline in the number of patients with NS in the Western world is probably the frequent use of antibiotic therapy for various infections. A diagnosis and correct treatment of early syphilis probably plays a role too.

In a study from the 1970s (10), Danish patients with NS were diagnosed with asymptomatic NS in 31% of cases, similar to the present study, 27%.

In the present study, 50% of patients were diagnosed with parenchymatous NS, which is higher than the 29% in the report by Perdrup et al. (10). This means that most patients diagnosed with NS in 1980–1997 had more severe symptoms than in earlier reports. Many patients were diagnosed with NS because they presented with neurological symptoms (36%), whereas 17%

Table II. Treatment schedule and result for the 92 patients with neurosyphilis (NS)

	No. of patients with NS			
	Group A n=25	Group M n=9	Group P n=46	Group U n=12
<i>Treatment</i>				
Procaine penicillin 0.6 MIU × 1 for 10 days given three times at monthly intervals by intramuscular route	3	0	5	0
Procaine penicillin 1.2 MIU for 3 weeks by intramuscular route	1	0	5	0
Procaine penicillin 1.2 MIU by the intramuscular route and probenecid 500 mg four times a day for 3 weeks	1	2	1	0
Procaine penicillin 0.6 MIU for 3 weeks by the intramuscular route	2	0	2	0
Penilente 2.4 MIU three times at monthly intervals by the intramuscular route	1	0	0	0
Penilente 2.4 MIU four times with 5-day intervals and pondocillin 500 mg for 21 days	2	1	1	0
Penicillin 10 MIU × 2 in 15 days by intravenous route	5	1	11	0
Penicillin 15–21 MIU/day in 10 days by intravenous route	2	0	9	0
Penicillin 10–20 MIU/day in 14 days by intravenous route	0	1	11	0
Penicillin 10 MIU × 4 until a total of 90 MIU given by intravenous route	1	0	0	0
Rocephalin 2 g for 14 days given by intravenous route	1	0	1	1
Tetracycline 500 mg × 4 in 15 days (p.o.)	2	0	0	0
Erythromycin 500 mg × 4 in 30 days plus tetracycline 500 mg × 4 in 30 days (p.o.)	0	0	0	1
Unknown	4	4	0	10
<i>Result</i>				
Full recovery	21	3	10	2
Dementia	0	0	19	0
Vision poor	0	0	1	0
Neurological problems	1	1	5	0
Unknown	3	5	11	10

Group A, asymptomatic; group M, meningovascular; group P, parenchymatous; group U, unclassified.

presented with psychiatric symptoms/dementia and 12% had rash on the skin or alopecia. Only 5% were diagnosed by routine testing before surgery or other invasive procedures (Table I).

Through using the CWRM test as a routine test in departments of neurology several patients were diagnosed with NS; 8% of the patients with NS were diagnosed in a department of psychiatry and all were severely ill (Table I).

Among the patients referred to the departments of neurology and psychiatry the tentative diagnosis of NS was only suspected in one patient, before the result of the CWRM test was known. This emphasizes the importance of maintaining a high level of alertness about the clinical presentation and diagnosis of NS.

Most of the patients diagnosed with NS in Denmark in the period from 1980 to 1997 were men, only 22% of the patients with NS were women. This is in agreement with the figures found by Perdrup et al. in the 1970s (10). It also correlates with the much higher incidence of early syphilis in men in Denmark (4–8).

In the early 1980s patients with NS included in this report were treated with procaine penicillin (intramuscular route) for 10 days. Treatment was repeated two to three times at monthly intervals. Alternatively the treatment was benzathine penicillin 2.4 MIU three times with weekly intervals. During the 1990s penicillin given intravenously in high doses became the standard

treatment in order to achieve a high concentration of penicillin in the CSF. Since the 1970s physicians have been aware of the importance of treating NS with high doses of penicillin given intravenously, which ensures a sufficient spinal fluid concentration of penicillin for 14 days (1, 11). In this study two patients treated with procaine penicillin were not cured. One of the patients was HIV-positive, which could explain the lack of response to therapy (12). The other patient was HIV-negative. In both cases the following intravenously administered penicillin cured the patients. Earlier reports also show failure in treatment when penicillin has not been administered intravenously (11). This emphasizes that penicillin given intravenously is superior to other treatments for NS.

In conclusion there has been a surprisingly great variation in the treatment regimes in Denmark. The follow-up has been strict and has included all of the patients and the result of the treatment of NS has been successful.

We would like to emphasize the importance of screening for syphilis in all venereological clinics and especially among homosexual men. This will reveal syphilis before it enters the last stage of the disease. Screening with CWRM in departments of neurology and psychiatry is of great importance and symptoms such as uncharacteristic rash on the skin and certain kinds of alopecia should lead to screening with the CWRM. Penicillin in high doses given by the intravenous route should be the standard

treatment for NS, especially in cases where the patient might be lost to follow-up.

## REFERENCES

1. Mohr JA, Griffiths W, Jackson R, Saadah H, Bird P, Riddle J. Neurosyphilis and penicillin levels in cerebrospinal fluid. *JAMA* 1976; 236: 2208–2209.
2. Reyn A. The Syphilis index at Statens Seruminstitut, Copenhagen. *Dan Med Bull* 1954; 1: 211–213.
3. Musher DM. Early syphilis. In: Holmes KK et al., eds. *Sexually transmitted diseases*, 3rd edn. New York: McGraw-Hill, 1998: 479–485.
4. Epinyt, Statens Serum Institut, weeks 44–45, 1987.
5. Epinyt, Statens Serum Institut, week 9, 1988.
6. Epinyt, Statens Serum Institut, week 10, 1989.
7. Epinyt, Statens Serum Institut, weeks 26–33, 2002.
8. Epinyt, Statens Serum Institut, week 17, 1998.
9. Fischer A, Kristensen JK, Husfelt V. Tertiary syphilis in Denmark 1961–1970. *Acta Derm Venereol* 1976; 56: 485–488.
10. Perdrup A, Jorgensen BB, Pedersen NS. The profile of neurosyphilis in Denmark. A clinical and serological study of all patients in Denmark with neurosyphilis disclosed in the years 1971–1979 incl. by Wassermann reaction (CWRM) in the cerebrospinal fluid. *Acta Derm Venereol Suppl* 1981; 96: 1–14.
11. Tramont EC. Persistence of *Treponema pallidum* following penicillin G therapy. Report of two cases. *JAMA* 1976; 236: 2206–2207.
12. Gordon SM, Eaton ME, George R, Larsen S, Lukehart SA, Kuypers J, et al. The response of symptomatic neurosyphilis to high-dose intravenous penicillin G in patients with human immunodeficiency virus infection. *N Engl J Med* 1994; 331: 1469–1473.