นิพนธ์ต้นฉบับ

Late syphilis patients admitted to King Chulalongkorn Memorial Hospital

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Objective : *To investigate the prevalence, the clinical manifestations and the treatment of late syphilitic infection among patients admitted to King Chulalongkorn Memorial Hospital during 1987-1998.*

Design : *A retrospective study.*

Setting : *A university hospital.*

Subjects : *61 patients with a diagnosis of late syphilis and a positive result from an FTA - ABS/TPHA test in serum and/or cerebrospinal fluid.*

Methods : *The syphilitic patients were classified into two groups, early and late syphilitic infections. Early syphilis includes primary, secondary and early latent infections, and late syphilis corresponds to late latent and tertiary infections. Tertiary syphilis is further classified into neurologic, cardiovascular and gummatous syphilis. Age, sex, clinical manifestations, associated HIV infections, serologic findings, CSF profiles and treatment of the syphilis were examined. Apart from a descriptive analysis, the SPSS-PC program was used to perform chi-square and unpaired t-tests for calculation of the statistical differences between the two compared groups.*

Results : *The diagnosis of syphilis was made in 126 patients, accounting to 0.03% (126 from 396,452 patients) of total admission. However, only 70 patients*

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had a positive serologic confirmation for the reported syphilitic infection. There were 9 and 61 patients who were documented with early and late syphilis, respectively. Among the patients with late syphilis, 32 (52.5 %) and 29 (47.5 %) patients were diagnosed late latent and tertiary syphilis, respectively. Among the patients with tertiary syphilis, 12 (41.4%), 9 (31%) and 8 (27.6 %) patients had asymptomatic neurosyphilis, symptomatic neurosyphilis and otosyphilis, respectively. Surprisingly, in contrast to other reports, no cardiovascular syphilis was present. Six of 46 patients (13%) who had a serologic test for HIV were positive. The significant titer of serum VDRL (≥ 1:8) was observed only in 19 patients (31.1 %) who were documented with late infection compared to 9 patients (100 %) with early infection, respectively. The overall rate of improper management was 38.6 % in this study.

Conclusions : *Even though syphilis is an uncommon disease, the progression to late serious complications may occur if patients do not receive adequate treatment. This study shows a high rate of inappropriate treatment among the syphilitic patients with late complications, hence an urgent need for improvement of knowledge about the natural course and proper management of late syphilitic infection is indicated.*

Key words : *Late syphilis, Prevalence, Clinical characteristics.*

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ธีรพล สุขมาก, ชุษณา สวนกระต่าย, อรวดี หาญวิวัฒน์วงศ์, สุทธิชัย จิตะพันธ์กุล. การศึกษาโรคซิฟิลิสระยะหลัง (late syphilis) ของผู้ป่วยในที่โรงพยาบาลจุฬาลงกรณ์. จุฬาลงกรณ์เวชสาร 2543 ม.ค; 44(1): 19 - 30

วัตถุประสงค์ : *เพื่อศึกษาถึงความชุก อาการแสดงทางคลินิก และการรักษาของผู้ป่วยโรคซิฟิลิสระยะหลัง (late syphilis) แผนกผู้ป่วยในที่โรงพยาบาลจุฬาลงกรณ์*

รูปแบบการวิจัย : *การศึกษาแบบย้อนหลัง*

สถานที่ทำการศึกษา : *โรงพยาบาลจุฬาลงกรณ์*

ประชากรศึกษา : *ผู้ป่วยในที่ได้รับการวินิจฉัยว่าเป็นโรคซิฟิลิสและมีผลบวกในการทดสอบ FTA- ABS/TPHA ในซีรั่ม (serum) หรือน้ำหล่อสมองและไขสันหลัง (CSF)*

วิธีการศึกษา-วัดผล : *แบ่งผู้ป่วยโรคซิฟิลิสออกเป็นระยะแรก (early syphilis) และระยะหลัง (late syphilis) โดยซิฟิลิสระยะแรกหมายถึงระยะที่หนึ่ง (primary syphilis) ระยะที่สอง (secondary syphilis) และระยะ early latent ส่วนซิฟิลิสระยะหลังหมายถึงระยะ late latent และซิฟิลิสระยะที่สาม (tertiary syphilis) โดยที่ซิฟิลิสระยะที่สามยังแบ่งออกเป็นซิฟิลิสทางระบบประสาท (neurologic syphitis) ซิฟิลิสทางระบบหัวใจและหลอดเลือด (cardiovascular syphilis) และ gummatous syphilis โดยใช้อายุ เพศ อาการแสดงทางคลินิกการมีหรือไม่มีการติดเชื้อ HIV ร่วมด้วย ผลการตรวจทางห้องปฏิบัติการจากซีรั่มและน้ำหล่อสมองและไขสันหลังแล้ววิเคราะห์ข้อมูลโดยใช้ chi - square และ unpaired t - test จากโปรแกรม SPSS-C*

ผลการศึกษา : *มีผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นโรคซิฟิลิส 126 ราย คิดเป็น 0.03 % ของผู้ป่วยใน (126 จาก 396,452 ราย) ในจำนวนนี้มีเพียง 70 รายที่มีผลทางห้องปฏิบัติการยืนยันว่าเป็นซิฟิลิสจริง โดยพบว่า 9 รายเป็นซิฟิลิสระยะแรก และ 61 รายเป็นซิฟิลิสระยะหลัง โดยในผู้ป่วยซิฟิลิสระยะหลังนี้ 32 ราย (52.5 %) อยู่ในระยะ late latent และ 29 ราย (47.5 %) อยู่ในระยะที่สาม (tertiary syphilis) ผู้ป่วยระยะที่สามนี้ 12 ราย (41.4 %) เป็นซิฟิลิสทางระบบประสาทที่มีอาการ (Asymptomatic neurosyphilis) 8 ราย (27.6 %) เป็น otosyphilis แต่ไม่พบซิฟิลิสทางระบบหัวใจและหลอดเลือดเลย ยังพบว่า 6 ใน 46 ราย (13 %) มีการติดเชื้อ HIV ร่วมด้วย ผู้ป่วย*

ซิฟิลิสระยะหลังนั้นมีระดับ VDRL ≥ 1:8 19 รายจาก 61 รายคิดเป็น 31.1 % ต่างจากซิฟิลิสระยะแรกที่มี VDRL ≥ 1:8 ทั้ง 9 ราย (100 %) ในผู้ป่วยที่ทำการศึกษาทั้ง 70 รายพบว่าได้รับการรักษาโรคซิฟิลิสไม่ถูกต้อง 38.6 %

วิจารณ์และสรุป : ถึงแม้ว่าโรคซิฟิลิสเป็นโรคที่พบไม่บ่อย แต่ถ้าได้รับการรักษาที่ไม่ถูกต้องจะมีผลแทรกซ้อนตามมาได้ จากการศึกษานี้พบว่ามีการให้การรักษาที่ไม่ถูกต้องจำนวนมาก จึงจำเป็นที่จะต้องได้รับการแก้ไขโดยเร่งด่วน

Syphilis is a complex systemic infection caused by the spirochete *Treponema pallidum* subspecies pallidum. It is usually acquired by sexual contact with an infected lesion including chancre or mucous patch, but nonsexual personal contact mostly by blood transfusion, and vertical infection are also documented. After an average incubation period of four weeks (10 days – 100 days), a primary lesion appears and is often associated with regional lymphadenopathy.[1] Then there is a secondary bacteremic stage which usually manifests as generalized mucocutaneous lesions,[2] followed by a latent period of subclinical infection persisting for several years.[3] In some untreated cases, the tertiary stage, which is characterized by progressively destructive mucocutaneous,[4,5] musculoskeletal [6,7] lesions, aortitis,[8,9] or central nervous system disease[10,11,12] eventually develops. The course and clinical characteristics of syphilis have been studied both in retrospective and prospective fashions.[8,13-21] Only three studies involving a large number of patients have been well documented.[22-24] However, all of them were conducted more than 30 years ago in the pre-AIDS era. Those populations at high risk for syphilitic acquisition are also at high risk for contacting HIV.[10,25-27] The clinical manifestations, the response to therapy and the duration of the stages of syphilis may be greatly altered by the immunosuppression state from HIV coinfection.[28,29-36] Thus, we retrospectively reviewed the database of patients admitted during 1987-1998 from the Statistical Department of King Chulalongkorn Memorial Hospital.

Subjects and Methods

Based on the database of the Statistical Department of King Chulalongkorn Memorial Hospital during 1987-1998, 126 patients with a diagnosis of syphilis were listed. Of these, 109 records were obtained and reviewed. However, only 70 patients had a positive serologic confirmation for the syphilitic infection (a positive result of FTA-ABS/TPHA test in serum and/or cerebrospinal fluid).[37-39] The syphilitic patients were classified into two groups, early and late syphilitic infections. Early syphilis includes primary, secondary and early latent infections, (within 2 years) and late syphilis corresponds to late latent and tertiary infections. Tertiary syphilis is further classified into neurologic, cardiovascular and gummatous syphilis. Primary syphilis is diagnosed based on the presence of a primary chancre during admission. Secondary syphilis is diagnosed based on the clinical symptoms and a history of primary chancre two to eight weeks prior to admission.[1] Latent syphilis is diagnosed when the patients are seropositive, but there is no demonstration of other evidence of active disease. Patients who have latent syphilis and who acquired syphilis within the preceding year are classified as having early latent syphilis.[40] Patients can be demonstrated as having early latent syphilis if, within the year preceding the evaluation, they had a) a documented seroconversion, b) unequivocal symptoms of primary or secondary syphilis or c) a sex partner who had primary, secondary, or early latent syphilis.[40] All other patients of latent syphilis of unknown duration are classified as late latent syphilis. Neurosyphilis are defined by one of the following criteria: a) a definite criteria, the presence of seropositive VDRL in cerebrospinal fluid (CSF), b) a probable criteria, a seropositive FTA-ABS/TPHA test and an elevation of protein or pleocytosis (WBC> 5 cells/μl) in a CSF

and c) a possible criteria, the presence of abnormal profiles in a CSF but a missing or unknown CSF serology. Nine and 61 patients were diagnosed with early and late syphilis, respectively, but only late syphilis was further investigated in detail.

Age, sex, clinical manifestations, associated HIV infection, serologic findings, CSF profiles and treatment of syphilis were examined. Apart from a descriptive analysis, the SPSS-PC program was used to perform chi-square and unpaired t-tests for calculation of the statistical difference between the two compared groups.

Results

The prevalence of syphilitic infection among patients admitted between 1987-1998 was 126 of 396,452 patients (0.03 %). The mean age (SD) of the 61 and nine patients who were diagnosed with late and early syphilis were 49.6 (20.2) and 29.6 (7.8) years, respectively ($p = 0.005$). Of the late syphilis group, the age range was 18-90 years, and 37 (60.7 %) patients were male. Thirty two (52.5 %) and 29 (47.5 %) patients were categorized as having late latent and tertiary syphilis, respectively. The mean ages (SD) of the patients with late latent and tertiary syphilis were 45.3 (20.0) and 54.3 (19.6) years, respectively ($p = 0.08$) (Table 1). Among those with tertiary syphilis, 12 (41.4 %) patients had asymptomatic neurosyphilis, nine (31 %) patients had symptomatic neurosyphilis, and eight (27.6 %) patients had otosyphilis. Among those with symptomatic neurosyphilis (otosyphilis not included), two (22.2 %) patients presented with stroke syndrome, four (44.4 %) with dementia syndrome, two (22.2 %) with tabes dorsalis, and one (11 %) with optic neuritis (Table 2). There was no statistical difference of mean age between the patients with otosyphilis, other neurosyphilis and late latent syphilis. Six of 46 patients (13%) had an associated HIV infection.

All cases had a positive FTA-ABS/TPHA test in serum and/or cerebrospinal fluid. However, the significant titer of VDRL in serum ($\geq$1:8) was found in only 19 patients (31.1 %), compared to nine patients (100 %) with early infection (data not shown) (Table 3). A definite, probable or possible diagnosis of the patients with asymptomatic neurosyphilis was documented in three, five, and four patients, respectively (Table 4). Of the patients with symptomatic neurosyphilis, a definite, probable or possible diagnosis was documented in five, three and one patients respectively. The result of CSF examinations of the patients with late latent, neurosyphilis and otosyphilis was obtained in 14 (43.8 %), 20 (95.2 %), three (37.5 %) patients, respectively. Among those with late latent syphilis, two (14.3 %) and three (21.4 %) patients had an abnormal CSF profile (a pleocytosis or an elevation of protein) and a positive test for syphilis, respectively (Table 5). A CSF examination was done in 11 (91.7 %) patients and 9 (100 %) with asymptomatic and symptomatic neurosyphilis, respectively.Among those with asymptomatic neurosyphilis, seven (63.6 %) and one (9 %) had abnormal CSF profiles and a positive test for syphilis, respectively. Among those with symptomatic neurosyphilis, six (66.7 %) and three (33.3 %) had an abnormal CSF profile and a positive test for syphilis, respectively. Among those with otosyphilis only one (33.3 %) patient had abnormal CSF profiles (missing data for five cases). Only 14 patients (43.8 %) with late latent syphilis were given a lumbar puncture for a CSF examination.

The results of a CSF examination of 19 patients with neurosyphilis was obtained. All patients with otosyphilis were given a lumbar puncture for a CSF examination, but the results of only three patients (37.5 %) were obtained. Two patients with late latent syphilis, 13 patients with neurosyphilis and one with otosyphilis had an abnormal CSF, profile either a pleocytosis or an elevation of protein level. Of those, five had a pleocytosis in their CSF (mononuclear cells > 5 cells/μl) which ranged from 8 - 80 cells/μl (data not shown). All 16 cases had an elevation of CSF protein (CSF protein > 50 mg/dl) which ranged from 51-230 mg/dl (53.8 % and had a CSF protein above 100 mg/dl). Positive rates of serological tests for syphilis in CSF were low (Table 5). Only eight of 20 (33.3 %) patients with neurosyphilis had a documented CSF reactive VDRL test.

For penicillin nonallergic patients, intramuscular benzathine penicillin, 2.4 million unit (mU) weekly for three weeks and intravenous penicillin G sodium 18-24 mU for 10-14 days are the treatments of choice for patients with late latent and otosyphilis as well as neurosyphilis, respectively. Therefore, 12 of 29 (41.4 %), 15 of 20 (75 %) and eight of eight (100 %) patients who were diagnosed late latent syphilis, neurosyphilis and otosyphilis, respectively, received an appropriate treatment (Table 6). Thus, the overall rate of improper management was 38.6 %.

Table 1. The characteristics of the patients with late syphilis. The percentage in each group of the patients examined is represented in the parenthesis.

	Late latent syphilis	Tertiary syphilis		
		Asymptomatic neurosyphilis	Symptomatic neurosyphilis	Otosyphilis
Total number	32	12	9	8
Mean age (SD)	45.3 (20.0)	50.8 (19.9)	54.3 (20.1)	58.9 (19.3)
Male patients	19 (59.4)	9 (75)	6 (66.7)	3 (37.5)

Table 2. The manifestations of late syphilis among 61 patients recruited in this study.

	Late latent syphilis	Tertiary syphilis					
		Otosyphilis	Neurosyphilis				
			Asymptomatic	Symptomatic			
				Stroke	Dementia	Tabes dorsalis	Optic neuritis
Number	32	8	12	2	4	2	1
Percentage	52.5	13.1	19.7	3.3	6.6	3.3	1.6

Table 3. The serologic findings of serum of the patients with late syphilis. The percentage in each group of the patients examined is represented in the parenthesis.

	Late latent syphilis	Tertiary syphilis		
		Asymptomatic neurosyphilis	Symptomatic neurosyphilis	Otosyphilis
Number of patients	32 (100)	11 (91.7)	7 (77.8)	8 (100)
Positive FTA-ABS/TPHA	32 (100)	11 (100)	7 (100)	8 (100)
VDRL titer over 1:8	12 (37.5)	5 (45.5)	2 (28.6)	-

Table 4. The level of diagnosis in 21 patients with neurosyphilis (otosyphilis not included). A definite diagnosis represents a seropositive VDRL test in a CSF. A probable diagnosis represents a seropositive FTA-ABS/TPHA test and a pleocytosis or an elevation of protein in a CSF. A possible diagnosis represents a missing or unknown serology and represented in the parenthesis.

Level of diagnosis	Neurosyphilis	
	Asymptomatic	Symptomatic
Definite	3 (25)	5 (55.6)
Probable	5 (41.7)	3 (33.3)
Possible	4 (33.3)	1 (11.1)
Total	12	9

Table 5. The profile and serologic findings of cerebrospinal fluid (CSF) of the patients with late syphilis. Percentage in each group of the patients examined is represented in the parenthesis.

	Late latent syphilis	Tertiary syphilis		
		Asymptomatic neurosyphilis	Symptomatic neurosyphilis	Otosyphilis
Number of patients	14 (43.8)	11 (91.7)*	9 (100)	3 (37.5)**
Abnormal CSF profile	2 (14.3)	7 (63.6)	6 (66.7)	1 (33.3)
Positive FTA-ABS/TPHA	3 (21.4)	1 (9)	3 (33.3)	-
Reactive VDRL	0	3 (27.3)	5 (55.6)	-

* missing data for 1 case.

**missing data for 5 cases.

Table 6. The treatment of syphilis in 61 patients with late syphilis. The percentage in each group of the patients examined is represented in the parenthesis.

	Late latent syphilis	Tertiary syphilis		
		Asymptomatic neurosyphilis	Symptomatic neurosyphilis	Otosyphilis
Number of patients with available data of treatment.	29*	11**	9	8
• Penicillin G sodium 18-24 mU IV for 10 -14 days.	11 (37.9)	7 (63.6)	8 (88.9)	-
• Penicillin G sodium 6-12 mU IV for 10 days.	-	3 (27.3)	-	-
• Benzathine penicillin 2.4 mU weekly for 3 times.	12 (41.4)	-	1 (11.1)	8 (100)
• Benzathine penicillin 2.4 mU once.	4 (13.8)	-	-	-
• Tetracycline 2 g/day or doxycycline 200 mg/day for 10 days.	2 (6.9)	1 (9)	-	-

* Death for 1 case and missing data for 2 cases.

**Missing data for 1 case.

Discussion

The three large well-documented studies[22-24] of syphilitic infection were reported more than 30 years ago, in the pre-AIDS era. At present, the incidence of HIV infection is increasing particularly in the developing countries, hence this may influence the infection rate, the clinical manifestations, the natural course and the response to therapy of syphilis. Apart from this , the study of syphilitic infection in Thailand has not been well documented before. To our knowledge, the present study is the first one which investigates the occurrence and characteristics of syphilitic infection in Thailand. The study was performed in a retrospective fashion since the incidence of the late syphilitic infection is very low, accounting to only 0.03% of admissions. The age groups for late and early syphilis were compared and the result was similar to previous reports[22-23] which showed that patients with early syphilis had mean ages in the third decade, about 20 years younger than those with late syphilis. No statistical difference of mean age among patients with late latent, neurosyphilis and otosyphilis was observed. HIV coinfection was observed in 13% of the patients who had a serologic test for HIV infection. Asymptomatic neurosyphilis and otosyphilis were common among those patients with tertiary syphilis. Among the patients with symptomatic neurosyphilis, parenchymatous neurosyphilis was more common than meningovascular neurosyphilis. The disproportion probably implies that most of the syphilitic patients with meningitis are asymptomatic. Based on these results, it would be indicated that every patient who

is diagnosed with late latent infection should have a lumbar puncture for a CSF examination to exclude asymptomatic meningovascular neurosyphilis. About 60% of the patients with late latent syphilis were not evaluated for neurosyphilis. Therefore, it would appear that some patients with asymptomatic neurosyphilis might be unrecognized and undertreated. Surprisingly, the occurrence of cardiovascular syphilis was not observed in this study, in contrast to others.[22-24] The development of late complications was shown to occur twice as often in men as in women, and in blacks more than in whites,[3] hence one possible explanation is in part due to a racial difference. The underdiagnosis of cardiovascular syphilis may be another possibility on the basis of both an inexperienced clinician and a difficulty of definite diagnosis. Since the clinical manifestations of cardiovascular syphilis can mimic other several conditions, including atherosclerotic heart and rheumatic heart diseases, the clinician who does not have experience with this disease may not recognize it. Furthermore, a definite diagnosis of syphilis needs a pathological confirmation, hence it is impossible to obtain a biopsy specimen from every patient. Five neurosyphilitic patients had a seropositive VDRL test in spite of a seronegative FTA-ABS/TPHA test in their cerebrospinal fluid. This result is in contrast to most other reports[1,3,39,40] which showed that an FTA-ABS/TPHA test is more sensitive, but less specific than a VDRL test to diagnose neurosyphilis. The reason for this conflicting data remains unknown, and further evaluation is required. A high rate of inappropriate treatment, either under or over treatment, in syphilitic patients with late infections was observed, hence there is an urgent need for providing knowledge of the natural course and proper management of late syphilis.

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