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LATE COMPLICATIONS OF SYPHILIS*

A Comparative Epidemiological and Serological Study of Cardiovascular Syphilis and Various Forms of Neurosyphilis

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Late complications of syphilis present a serious threat to life and health despite their decreasing incidence. From the point of preventive medicine they have assumed increasing importance after the introduction of penicillin therapy, since their development apparently can be readily prohibited by treatment of syphilis in its early (infectious) phase. Once established, syphilitic cardiovascular disease is difficult to treat and is usually progressive. The prognosis is better in neurosyphilis provided that the treatment is started early after the appearance of symptoms. As soon as irreversible neuron damage has occurred, restoration of function can hardly be expected.

The purpose of the present study was to collect epidemiological data on patients with late complications of syphilis and to study such data in relation to serological findings. This might shed light on the natural history of syphilis and be helpful in the combating its late complications.

Material and Methods

The patients included in the present study had cardiovascular or neurosyphilis diagnosed in hospitals under the care of a specialist during the five-year period 1963–68. All patients showed positive standard lipoidal or treponemal tests for syphilis. Patients with a history of initial syphilitic infection or of previous treatment but having negative serological tests were not included.

The selection of the cases was based on information obtained from a register kept of patients with positive tests found at the State Serum Institute and from request forms for the treponemal tests. In about half of the cases this information was considered to be sufficient, while in the others it was supplemented with data from hospital records. A few cases had to be excluded because this additional information was not obtained.

The clinical criteria for the inclusion of the patients in the study material were as follows:

Aortic aneurysm. Only patients with thoracic aneurysms were included.

Aortic insufficiency. Congestive heart failure was not considered to be a requisite. Patients with simultaneous mitral valve disease were excluded.

Uncomplicated aortitis. Included were patients with roentgenologically observed dilatation of the aorta (without aneurysm) or calcification in the ascending aorta typical of syphilitic mesaortitis and cases in which the diagnosis was made at autopsy.

Meningovascular syphilis. Only symptomatic cases were included. Reliance was placed on the original diagnosis although the diagnostic criteria apparently varied.

General paralysis. Again, the clinical

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diagnosis was decisive although it was felt that some hospitals were reluctant to establish this diagnosis.

Tabes dorsalis. At least two different symptoms or signs such as Argyll-Robertson pupils and lost tendon reflexes in the lower limbs were required for the diagnosis.

The majority of the specimens were received from hospitals located in Southern Finland in an area covering about one-third of the population of Finland. The standard tests for syphilis were performed on all patients admitted to most of the hospitals. Treponemal tests were requested for some hospitals in virtually every case showing positive standard tests and from others only in problem cases. There was a great variation in requests concerning cases with negative standard tests but showing a clinical picture compatible with some late complication of syphilis. In general, the annual number of treponemal tests performed was increasing throughout the study period.

The VDRL test was performed by the standard technique (12) using either cardiolipin or sitolipin as antigen. The International Reference Preparation for Human Syphilitic Serum (1) was used, reconstituted and diluted to contain 8 units/ml giving a titre of 8.

Facilities for the TPI test were available during the entire study period and those for the FTA-ABS test from June 1966. After this date all sera sent for treponemal tests were examined in both the TPI and FTA-ABS tests. Quantitative Reiter protein complement-fixation (RPCF) test (11) was performed with virtually all specimens sent for treponemal tests.

Results

The present series comprised 94 patients with cardiovascular syphilis, 60 patients with various forms of neurosyphilis, and 6 patients with simultaneous cardiovascular and neurosyphilis. Table 1 shows that there were, in the series, slightly more males than females. The mean age in females at the time of diagnosis was slightly higher than in the males. The majority of the patients with cardiovascular syphilis had a complicated form of disease, either aneurysm or aortic regurgitation. Two-thirds of the patients with neurosyphilis had tabes dorsalis while the number with meningovascular syphilis or general paralysis was relatively small.

The youngest patient was a male aged 25. He had a somewhat atypical tabes dorsalis, possibly associated with congenital infection. The oldest one was a female aged 82 with an aortic aneurysm. The age distribution in different diagnostic groups (not shown in Table 1) reflected differences in the mean age. The age distribution was quite similar in patients with aneurysm and in those with aortic regurgitation.

The proportion of patients capable or willing to recall the initial infection was of the same order of magnitude in males and in females. However, it was somewhat greater in patients with tabes dorsalis than in those with cardiovascular syphilis (Table 2). The year of initial infection ranged from 1910 to 1947 in those cases in which accurate information was available. The mean age (60.4 years) and the age distribution in these patients did not differ significantly from the corresponding figures in patients without such information. The average time from the initial infection to the diagnosis was 33 years in cardiovascular syphilis and 34 years in tabes dorsalis.

About one-third of the patients had received some antisyphilitic treatment before the diagnosis of the late complication was made. Information of penicillin treatment was obtained in 17 cases, but none of the patients had received penicillin in the early (infectious) phase of the disease (Table 2). Four of the penicillin-treated patients had tabes dorsalis and the others cardiovascular syphilis, usually either uncomplicated aortitis or aortic regurgitation. Only 2 patients had aortic aneurysm. In 6 instances penicillin had been given for conditions other than syphilis. The majority of the patients treated for syphilis had received penicillin soon after it became available in Finland. Those patients had frequently previously received other type of treatment. One patient had been observed to have asymptomatic neurosyphilis at the time of penicillin treatment.

Table 1. *Distribution by diagnosis and sex of the patient series and the mean age in different groups at the time the diagnosis was made*

Diagnostic Group	Number of Patients			Mean Age in Years		
	Males	Females	Total	Males	Females	Total
Total cardiov. syphilis[1]	54	46	100	59.0	63.1	60.8
Aortic aneurysm	19	17	36	58.1	63.7	60.8
Aortic insufficiency	24	23	47	61.3	60.4	60.8
Uncompl. aortitis	11	6	17	55.4	71.0	61.0
Total neurosyphilis[1]	38	28	66	55.5	58.3	56.7
Meningovascular	6	1	7	55.2	61.0	56.0
General paralysis[2]	7	8	15	51.6	57.2	54.6
Tabes dorsalis[2]	25	19	44	57.0	58.5	57.6

[1] Six patients (three males and three females) with simultaneous cardiovascular and neurosyphilis (two with general paralysis and four with tabes dorsalis) were included in both cardiovascular and neurosyphilis groups.
[2] Two patients with taboparesis were classified in the group of general paralysis and one patient with optic atrophy in the group of tabes dorsalis.

Table 2. *Anamnestic information of initial syphilitic infection and of treatment in patients belonging to different diagnostic groups*

Number of patients with information of:	Diagnosis Group			
	Cardio-vascular	Meningo-vascular	General Paralysis	Tabes Dorsalis
Initial syphilitic infection	29	2	3	20
Treatment in the early stage				
Mercury, arsenicals and bismuth	17	1	2	14
Penicillin	0	0	0	0
Treatment in a later stage				
Arsenicals and bismuth	7	0	0	3
Penicillin	13	0	0	4
No information of treatment	68	6	13	26
Total number of patients	100	7	15	44

In the others there was no information of symptoms and signs related to active disease process. This does not imply that these cases represent failures of penicillin treatment. It is probable that the already existing late complication had been overlooked in some cases, possibly in the majority of them.

Table 3 shows the distribution of the VDRL titres in patients belonging to different diagnostic groups. Patients without information of previous treatment and those having such information were dealt with separately. It is seen that the titres in the latter group were, on the average, appreciably lower, even though high titres were encountered also in these patients. Further, it is apparent that patients with tabes dorsalis frequently had lower titres than patients with cardiovascular syphilis and especially those with general paralysis. However, a marked variation in the titres seemed to be a characteristic of each group. Completely negative results were recorded in previously untreated patients with either cardiovascular syphilis or tabes dorsalis.

Table 3. *Distribution of VDRL titres in untreated and treated patients belonging to different diagnostic groups*

	Number of Patients with VDRL Titre						Mean Titre[1]
	0	1—2	4—8	16—32	64—128	≧256	
Aortic aneurysm							
Untreated	2	5	5	6	5	3	12.7
Treated	1	5	3	0	0	0	2.8
Aortic insufficiency							
Untreated	1	7	5	6	8	1	13.3
Treated	1	8	7	3	0	0	3.4
Uncomplicated aortitis							
Untreated	1	4	1	5	2	0	8.0
Treated	0	1	2	0	0	1	9.5
Meningovascular syphilis							
Untreated	0	2	3	0	1	0	8.0
Treated	0	0	0	1	0	0	
General paralysis							
Untreated	0	2	2	4	4	1	26.5
Treated	0	0	0	1	1	0	
Tabes dorsalis							
Untreated	3	6	10	6	1	0	4.9
Treated	1	12	3	2	0	0	1.9

[1] Calculated as the logarithmic mean of the titres.

Table 4. *Correlation between VDRL and RPCF titres*

RPCF Titre	Number of Patients with VDRL Titre									
	0	1	2	4	8	16	32	64	128	256
4	10	13	9	15	5					
4		1	1	2	1	2		1		
8				1	1	2				
16		1	2	1		1	3			
32			1			2	1	1		
64							2	1	3	
128						1	1		1	1
256							1	1	1	1

No difference in the VDRL titres was observed between males and females. The possibility of correlation between age and the titre level was anticipated, but no such correlation was found.

The quantitative RPCF test was performed in 91 cases. It is seen from Table 4 that a high degree of correlation existed between the titres obtained in it and in the VDRL test. In previously treated patients both titres tended to be low, whereas in untreated patients they were both usually either high or low. There was no case showing high-titred reactivity in one test system and nonreactivity in the other.

Discussion

The selection of the present patient group has certain limitations. Conclusions can

therefore be derived from the data with reservations. Thus, the actual number of late complications diagnosed was certainly higher than that apparent from our figures. Also the proportion of cases with cardiovascular and neurosyphilis may have been different. Moreover, a thorough questioning of the patients in a uniform manner would presumably have revealed more information on initial infection and previous treatment. This is especially true concerning penicillin treatment given for conditions other than syphilis.

Certain features emerge which probably reflect a changing situation in regard to late complications of syphilis. The frequency of cardiovascular and neurosyphilis in untreated patients appears to be about twice as high in males as in females (2). In many large clinical series it has been higher. In the present study material, however, there were nearly as many females as males. A second point of interest is that information of initial syphilitic infection and of treatment in the early phase was obtained more frequently from patients with tabes dorsalis than from those with cardiovascular syphilis.

In untreated syphilis the average period from the initial infection to the diagnosis of its late complication is about 30 years in cardiovascular syphilis and in tabes dorsalis, while somewhat less in the other forms of neurosyphilis (2). In the present study this brings us to the years 1933–38. Combined treatment with arsenicals and bismuth was a common practice already some ten years before that. Such treatment was apparently fairly adequate and reduced the frequency of late complications (8). Thus, our material is related to the number of persons who escaped treatment rather than reflecting the total number of persons infected. The number of reported cases in Finland with infectious syphilis has been somewhat higher in males than in females (5). Since the occurrence of the late complications was about the same in females as in males one is inclined to assume that more females escaped treatment. Further, as discussed by Harrison (3), treatment inadequate for the prevention of neurosyphilis usually suffices to prevent the development of cardiovascular syphilis. This may explain the observed difference in the frequency of anamnestic information obtained from patients with cardiovascular syphilis from those with tabes dorsalis. Since the advent of penicillin, patients with late syphilis with history of early treatment should become exceedingly rare. The frequency of late complications should therefore reflect the number of patients escaping diagnosis and treatment.

A somewhat surprising feature was the small number of patients having meningovascular syphilis or general paralysis. These amounted together to only half the patients with tabes dorsalis. This is contrasted by figures about four times higher in the Oslo study of untreated syphilis (2) and by figures reported in many other studies. The difference may in part be due to the means by which the material was collected but certainly not completely. It has been suggested that treponemicidal drugs given for conditions other than syphilis may alter the clinical picture of neurosyphilis making the diagnosis more difficult (6). It seemed to the present authors that some hospitals were reluctant to make the diagnosis of general paralysis if the features of the disease did not completely fit its classical description.

The present study suggests that previous treatment, in any amount or at any time relative to serological testing, may markedly reduce the serum VDRL titres. This is in accordance with the view already reported by Moore and Eagle (9). Further it is apparent that great variation in titres occurred in patients without any information of previous treatment. The relative proportion of cases showing a completely negative VDRL test was probably higher than that apparent from our figures since they were included in the series only if the treponemal tests had been asked for and been positive. The observation that the VDRL titres in cardiovascular syphilis were higher than in tabes dorsalis is in keeping with that reported by Moore and Eagle (9). In the present work, the titre level in general paralysis was higher than in cardiovascular

syphilis, whereas such difference was not observed in the report of Moore and Eagle. It suggests that cases of general paralysis with low titres had been overlooked.

There is very little direct information on the quantitative relationship between lipoidal and treponemal antibodies in humans. The correlation observed between Wassermann titres and quantitative TPI titres in early syphilis is by no means impressive (4). This apparently is due to the circumstance that the immobilizing antibodies usually develop later than the antibodies reactive in the lipoidal tests. The TPI titres increase during the primary and secondary stages of the disease and tend to remain high in late syphilitic manifestations (10). Available evidence suggests that the lipoidal antibody titres also remain at a high level several years after the secondary stage and then gradually decline.

With the possible exception of secondary syphilis, antibodies detected by the FTA test are directed mainly against the group-specific rather than species-specific components of *Treponema pallidum* (13). Thus the titrated RPCF test (11) may be a suitable measure of the level of the treponemal antibodies. In old treated syphilis the titres obtained in the lipoidal tests and in the RPCF test were uniformly at a low level (7). The present study shows a high degree of correlation between the VDRL and RPCF titres in both untreated and treated late symptomatic syphilis. These findings may be helpful for the understanding of the stimulus leading to the development of these antibodies. Sera from a wider spectrum of clinical cases will have to be tested and the results compared before any conclusions in this respect can be drawn.

SUMMARY

The study included 94 cases of cardiovascular syphilis, 60 cases of neurosyphilis (predominantly tabes dorsalis), and 6 cases of simultaneous cardiovascular and neurosyphilis. There were 89 males and 71 females in the series with a mean age of 59.2 years. The cases had been diagnosed in 1963–68 and the infection acquired between 1910–47. The average time to the diagnosis of the late complication was 33 years in cardiovascular syphilis and 34 years in tabes dorsalis. Anamnestic information on initial infection and on treatment could be obtained more frequently from patients with tabes dorsalis than with cardiovascular syphilis. Seventeen patients had information of earlier penicillin treatment, but no one had received it in the early phase. The average VDRL titre was higher in patients without information of earlier treatment than in those giving this information. It was also higher in patients with cardiovascular syphilis than in those with tabes dorsalis. A high degree of correlation existed between the titres obtained in VDRL and RPCF tests.

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