Evidence of seropersistent VDRL test reactivity in an elderly Treponema pallidum-infected population

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Abstract

Background. Using the VDRL test as the only one, or the first in a series of tests, leads to a diagnostic miss in the serological detection of latent and late syphilis, especially among older age group. We compared the age of 518 *Treponema pallidum*-infected individuals with their VDRL test results. This was aimed at determining the proportion of VDRL reactors who were suspected of having a persistently active syphilitic process.

Methods. Our retrospective analysis of archival data on subjects' age and VDRL serotest outcomes for the 518 *Treponema pallidum*-infected (who were reactors in the TPHA reference test) covered the period 1974-98. They were selected from a nonvenerological population routinely tested at a public health laboratory.

Results. Data analysis revealed the subjects' high mean age (53.13 years in VDRL reactors and 51.87 years in nonreactors), and an unexpectedly high proportion of VDRL reactors (49%) among those tested.

Conclusion. It may be presumed based on the 49% persistence of VDRL reactivity coupled with the subjects' high mean age (53.15 years), which is appropriate to latent and late syphilis, that most subjects (70%) had either been untreated or insufficiently treated. This view is based on the Bayes' theorem, which takes account of the generally accepted percentage of VDRL reactivity for latent and late syphilis.

KEY WORDS

VDRL seropersistence, syphilis

Introduction

In the course of proficiency testing program for the serological diagnosis of syphilis in Croatian laboratories from 1993 to 1995 we noted occasional differences in indications for the VDRL serological test (1,2). The first stage of that survey checked how proficient routine laboratories were in detecting the infected (3), then the size of diagnostic miss in detecting the latent and late (and possibly active) syphilis. The then small sample uncovered a disproportion between the age of serologically stabilized patients (VDRL nonreactors, but TPHA reactors) and that of potentially active (VDRL and TPHA reactors); also, we noticed the high proportion

of the latter among the infected. Analysis only included the results of a one-turn (actually the last) serological testing. Beside the demographic data there were no clinical or epidemiological data available on any of the subjects tested. Analyzing the above mentioned phenomena the present paper attempts to establish the causes of the unexpected test reactivity of some population subgroups, as well as obtain more information about the disease and the affected population.

Materials and methods

Tested population. A retrospective analysis of archival data on 518 serologically tested persons, 275 (53%) males and 243 (47%) females, covered a 22-year period (1976-98). They underwent two parallel tests for syphilis each: the nontreponemal VDRL test and the treponemal TPHA test.

A public health population was tested whose sera are usually studied in public health laboratories: non-venereal inpatients, chronic psychiatric asylum patients, patients from psychiatric wards and homes, persons from conscription centers, prisons etc.; persons undergoing pre-employment examinations, persons seeking medical certificates or international health documents, pregnant women, etc. Statistical analysis covered the items of age, year of testing (1976 through 1998), sex and the result of parallel testing by the VDRL and TPHA tests.

Tests. Both the VDRL and the TPHA test, which came from the Croatian Institute of Immunology, respectively BAG GmbH, Germany (TPHA) were done in the standard way (4). Qualitative expression of the results enabled the use of literature data from nosological sensitivity and specificity tables in function of the stage of syphilitic process and subject status as treated or untreated. Throughout the period studied (1974-98), the problem sera were subject to proficiency testing performed by N.A. Johnston of the V.D. Reference Laboratory P.H.L.S., The London Hospital, London, E.1, Great Britain.

Statistical procedures. In addition to the standard statistical methods an own statistical procedure was used which is based on the Bayes' theorem (5). In the absence of clinical data this allowed us to assess the proportion of untreated among the infected.

Results

For greater clarity the tested population was divided into 3 groups by time periods, thus permitting a statistical evaluation to detect eventual differences. Table 1.

During the 1976-1979 period 77 patients' sera were tested: 59 were VDRL+ TPHA+; the arithmetical mean value of their ages was 50.45 years. In the same period 18 sera were VDRL- TPHA+, their ages giving the mean value of 52.59 years. Figure 1.

There were 130 patients' sera tested during the 1990-98 period: 52 were VDRL+ TPHA+, their mean ari-

Table 1. The number of persons tested by test period from 1976 to 1998, and the arithmetic mean age for persons with differing results of combined parallel testing: VDRL+ TPHA+ and VDRL-TPHA+.

No. of persons tested in the period	N	Group	Arithmetic mean age (yr.) VRDL+ TPHA+ N=254 (49%)	VDRL- TPHA+ N=264 (51%)
1976-1979	77	1	50.45	52.59
1980-1989	311	2	52.54	53.27
1990-1998	130	3	58.56[a]	49.06
Weighted arithmetic mean age (N=254, N=264 and N=518)			53.13[b]	51.87[c]
			52.69[d]	
TOTAL	518			

[a] The dividing of this group by sex uncovered a female VDRL and TPHA reactive group with high arithmetic mean age of 63.94 years, as well as its highly statistically significant ($p<0.008$) age difference in relation to the all-subject (518) arithmetic mean age of 52.69 years.
[b] The data relate to N=254.
[c] The data relate to N=264.
[d] The data relate to N=518.

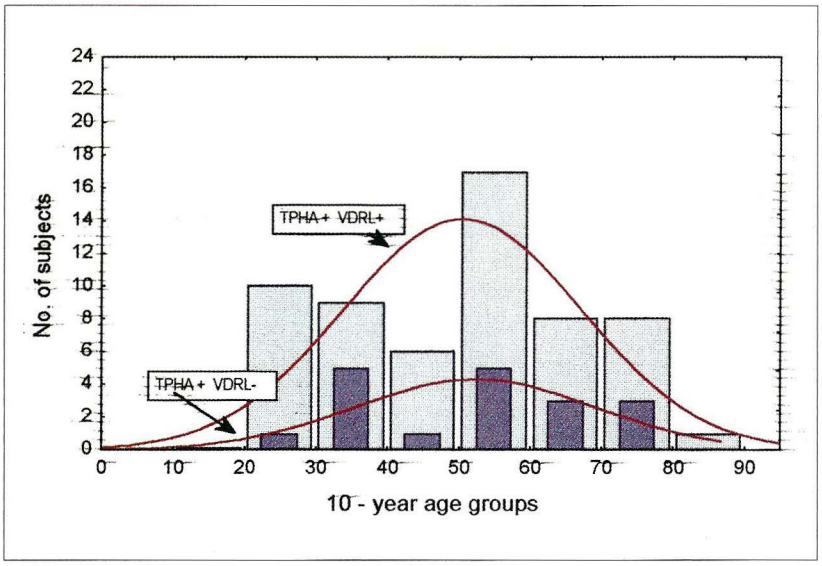
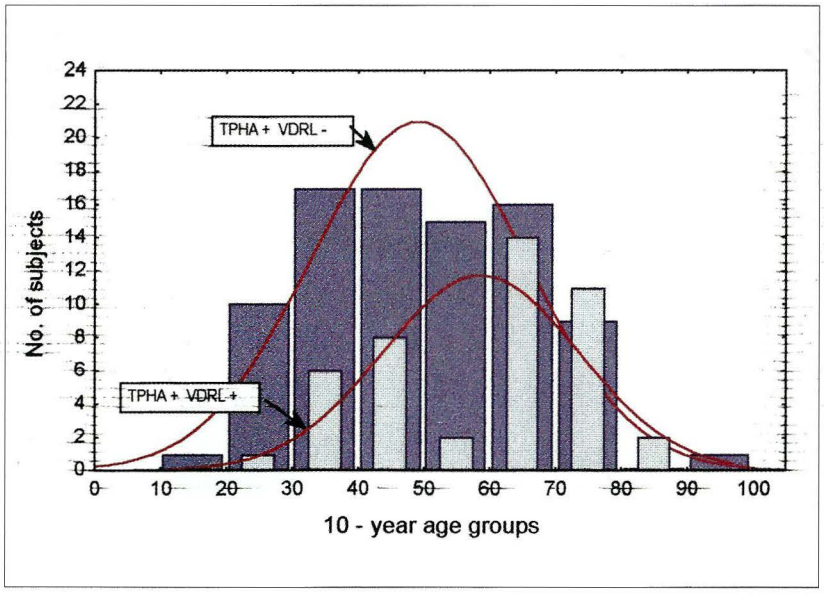


Figure 1. The number of subjects with VDRL+ TPHA+ test results (N=59; arithmetic mean age = 50.45 yr.) and VDRL- TPHA+ results (N=18; arithmetic mean age = 52.59 yr.) by 10-year age groups in the 1976-79 period.

thmetical age was 58.56 years, while 78 were VDRL- TPHA+ with a mean arithmetical age of 49.06 years. Figure 2.

Inserting our data on VDRL positive tests amounting to 49% (VDRL sensitivity) of all the infected (TPHA positives) into the Bayes theorem-based formula (5), together with VDRL sensitivity data for treated (1%) and untreated (70%) yielded a proportion of 0.7, an indication that 70% of our infected subjects had probably not been treated. Inserting in the same formula for the sensitivity of the treated a value of 10%, this would still give a high value of 65% for the untreated.

Figure 2. The number of subjects testing VDRL+ TPHA+ (N=52, arithmetic mean age = 58.56) and VDRL- TPHA+ (N=78, arithmetic mean age = 49.06) by 10-year age groups in the period 1990-98.



Discussion

The presence for 22 years in public health laboratory's records of a high percentage (49%) of VDRL reactors with an average age of over 50 years could be considered unexpected. Actually, it is assumed that for seropositive cases aged 50 years sufficient time has elapsed since their infection and treatment (which most probably happened in their 20s) for VDRL findings to turn negative. However, in contradiction to the available literature stating that persistent serological reactivity on the VDRL test is a rare phenomenon (6), through subsequent decades (probably during some 30 years) only half our subjects tested negative on the VDRL. The literature VDRL reactor values for treated late latent syphilis and treated late manifest syphilis are 1% only (7). Though higher values may have been reported, they were unaccompanied by a specification as to the interval lapsed between the times of treatment and testing (6,8). Moreover, not even untreated latent syphilis or late syphilis exceed the VDRL reactivity of 70% (30% of the diseased spontaneously become negative) (6). Based on the above, one could hypothesize that a large portion of our subjects had either received no treatment or an inadequate one. The successfully treated minority probably contributed 20% of the negative tests, thus rounding up the VDRL nonreactors to about 50%. Nevertheless, it would be more correct to assess the old population of the infected with regard to previous treatment, or no treatment, by means of the Bayes' theorem-based procedure which we used in the No. 3 (1997) issue of this review, presenting the results of the first part of the same study (5). Inserting the 1% reactivity to the VDRL reported in the literature for the treated (7), and the 70% reactivity to the VDRL test for the untreated who have latent and late syphilis (6), as well as our figure of 50% for theprevalence of the VDRL reactors, yields, in terms of proportion, a result of 0.7. In other words, it would appear that 70% of our VDRL positive population have not been treated. Had we inserted 10% instead of the value of 1% for VDRL test reactors in the treated that would still produce as many as 65% untreated!

An off hypothesis, i.e., that our patients had acquired syphilis not in their 20s but after turning 40, might be proffered to explain the high proportion of VDRL reac-

tors among our infected subjects. If true, it could be argued that despite the patients receiving adequate treatment, the reactivity on the VDRL test had not disappeared yet.

Even less probable is the assumption that our patients had started their treatment only some 10 years after developing the infection, i.e., at the stage of late latency and late syphilis. Some authors feel that VDRL reactivity could stay in as many as half such subjects longer than 2 years (6) or "for years" (8). Nevertheless, a growing trend in the number of VDRL nonreactors among the infected observed over 22 years points to the fact that in the past few years the treatment of syphilis has become increasingly effective.

In addition to the unusually large portion of VDRL reactors noticed at the first stage of this study (5), also recorded was their higher average age. Statistical analysis on a bigger sample of 518 infected has shown this phenomenon to be significant only in one subgroup of women tested between 1990 and 1998 (Table 1). One explanation might be the coincidence between their time of infection and the start of the penicillin era in Croatian hospitals. In fact, the abandonment of strongly treponemocidal (but toxic for body) arsenobenzolic preparations and bismuth salts, coupled with the use of the then insufficient penicillin concentrations and length of treatment could have contributed to the phenomenon. Another extra factor possibly having the same effect was the use of benzathine penicillin, which is known for low penetration into some tissues and body systems (7). To this one should add the known difficulties of detecting syphilis in women with the resulting later start of treatment.

A possibly active syphilitic process could account for the high-recorded percentage of VDRL reactors (49% of the 518 tested) among the infected and for their high mean age (53.13 yr.). This might have public health repercussions. The above phenomenon warrants further corroboration and analyses (clinical follow-up and CSF evaluation). It also impresses on nonvenereologists the need to cautiously order and interpret serological tests for the demonstration of syphilis (6). This subsumes quantifying the VDRL among the infected and the use of modern tests to determine the intensity of syphilitic process.

Conclusion

Analyzing for 22 years (1976-96) the relationship between the patient's age and VDRL test results on a large sample of 518 *T. pallidum*-infected persons revealed a high proportion (49%) of subjects (with a mean age above 50 years) potentially affected by an active syphilitic process (VDRL reactives). Conspicuous among them was a female subgroup statistically significant for its high age (64 vs. a general average of 52.7 years) ($p<0.008$). It was probably infected and insufficiently treated in the arsenobenzol-penicillin switch period. As well as indicating a possible presence of an unrecognized active syphilis in elderly age, the results point to the need for nonvenereologists to exercise care in ordering and interpreting syphilis serotests.

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REFERENCES

1. Anonymous. Serological screening methods for the most relevant microbiological diseases of organ and tissue donors. European Health Committee, Council of Europe, 25-27 June 1996, CDSP (96) 21, p.5.

2. Muić V, Vodopija I. Serotesting for syphilis, diagnostic proficiency and health care quality surveillance (in Croatian). Liječ Vjesn 1996; 118: 184-6.

3. Muić V, Vodopija I, Ljubićić M, Mayer V, Janković V. Interlaboratory differences in VDRL test nosologic sensitivity in syphilis serodiagnosis in Croatia from 1993 to 1995. Period biol 1997; 99: 45-8.

4. Larsen S, Hunter E. Syphilis Diagnosis. In: Isenberg H (ed). Clinical Microbiological Handbook. Washington DC, American Society for Microbiology, Supplement 1, 1994, Section 9.7.

5. Muić V, Vodopija I, Ljubićić M, Mayer V. Limitations and consequences of basing late syphilis seroassessments on VDRL test. Acta Dermatoven APA 1997; 6: 87-91.

6. Larsen S. Steiner E, Rudolph A. Laboratory diagnosis and interpretation of tests for syphilis. Clin Microbiol Rev 1995; 8:1-21.

7. Tramont E. *Treponema pallidum* (Syphilis). In: Mandell GI, Benett JE, Dolin R, eds. Mandell, Douglas and Benett's Principles of Infectious Diseases. New York, NY: Churchill Livingstone, 1995: 2117-33.

8. Lukehart S, Holmes K. Syphilis. In: Isselbacher K (ed) Harrison's Principles of Internal Medicine. New York, McGraw Hill, 1994; 726-37.

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