STUDY OF SEROLOGY CHANGE IN IMMUNO-COMPETENT PATIENTS WITH ADEQUATELY TREATED SYPHILIS

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Summary

While syphilis etiology and pathogenesis are well described, and despite the existence of accurate and accessible serologic tests and effective treatment options, its incidence is continuously on the rise, representing a major public health issue, particularly in medical resources-strapped countries. The aim of this study is to conduct a thorough assessment of the change of syphilis serology results in a significant number of syphilis patients receiving adequate treatment under specialized super-vision. The subjects included in the study had different stages of syphilis progression.

The identified data show that VDRL (veneral disease research laboratory) test results with non-specific antigens become negative more often after adequate treatment used in stage I, the non-mandatory latent period and stage II syphilis, respectively. In more advanced stages, such as mandatory latent period and stage III, respectively, VDRL titres slowly decrease, but do not become negative after adequate treatment over a period of several years. Other relevant markers, using specific treponemal antigens such as TPHA (Treponema pallidum haemagglutination test) and IgM ELISA test system have a clearly predictable course. TPHA maintained positivity over the entire follow-up interval, possibly for the rest of the patient's life, while IgM ELISA became consistently negative one year after treatment at the latest.

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Introduction

Persistence of positive serology, both the specific treponemal antibody test and the non-specific cardiolipin antigen test, in immuno-competent patients who received adequate and complete treatment for syphilis is a practical fact well known to specialists in dermato-venereology, but other medical specialties seem to be less well informed (1).

VDRL or similar tests, such as specific anti-treponemal continue to be positive a long time after the patient is cured. Since these tests are routinely used during hospitalizations irre-spective of cause or mandatorily in different situations required by the law, we are frequently faced, at least in our medical unit, with the issue of whether these patients are cured or not, if their infection has relapsed and if pharmacological specific treatment, clinical surveillance or another

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medical approach is needed (2). This is the main rationale behind the conduct of his study.

Working hypothesis

We set out to assess the percentage of patients with persistently (which we termed residual) positive syphilis specific serology at 24 months after receiving adequate treatment and documented medical surveillance, who were deemed cured. In parallel we obtained the percentage of serologic tests results which turned negative in the respective patients, the interpretation being based on the disease stage when treatment was started.

Material and method

Data were collected from 2 syphilis diagnosis and treatment centres, Cluj-Napoca and Tg. Mureș during the period 2010–2012, from a total number of 1523 patients, with skin changes indicative of syphilis – 62 patients, as well as without skin signs, but with positive VDRL test results. The VDRL positive test was confirmed through the TPHA specific test. In most cases the latter turned out negative. If both tests were positive the IgG ELISA and IgM ELISA tests were performed. The positive IgM ELISA test equalled a clinical diagnosis, while negative IgM ELISA cases were excluded from the study, as they were considered cured with residual positive serology. Follow-up of the post-treatment VDRL and TPHA change was performed, by sampling every three months, for 24 months.

The positive VDRL and negative TPHA tests results were excluded from the very beginning as false-positive due to co-morbidities (autoimmune disease, antiphospholipid syndrome, malignancies, post-viral infection status and a case of normal pregnancy).

Results

In the end, 180 patients with active disease were selected. The male to female ratio was 1.3:1. Of the patients, 68.3% came from an urban environment, while 31.7% from the rural area. Overall, mean age was 30.5 years, with no significant gender differences (30.64 years in men vs 30.39 years in women).

Distribution based on disease stage is provided in Table 1. In fact, 10 patients were diagnosed with primary syphilis, 26 patients with fully blown secondary syphilis, 80 patients with early latent syphilis and 61 with late latent or uncertain syphilis, one patient with tertiary syphilis with gumma lesions and two patients with neurosyphilis, which were hospitalized.

Table 1: Case distribution based on disease stage

Disease stage	No. of cases	Percentage
Syphilis I (primary)	10	5.5%
Syphilis II (secondary)	26	14,4%
Early latent syphilis	80	44,4%
Late latent/uncertain syphilis	61	33,8%
Syphilis III (tertiary)	1	0,5%
Neurosyphilis	2	1,0%

The VDRL test was performed through dilutions in successive duplication. Based on the WHO guidelines, adopted by the Romanian Ministry of Health, a 4-fold decrease of the titre, i.e., a two-column left shift, equals cure of the disease, despite the persistence of a residual positive titre. In the study we monitored the cases where this test results reach full negativity, and findings at 24 months are presented in Table 2. In primary syphilis 20% of cases remained weakly positive, in secondary syphilis 53.8%, in early latent syphilis 71.2%, in late latent syphilis 81.9%, while the case of tertiary syphilis as well as the two cases of neurosyphilis showed a VDRL increase within normal ranges, however positive.

Table 2: Negative and residual positive VDRL test results (percentage)

Disease stage	Negative VDRL at 24 months	Residual positive VDRL at 24 months
S I	80%	20%
S II	46%	54%
Early latent S	29%	71%
Late latent S	18%	82%
S, other	0%	100% (3 cases)

For all syphilis cases we followed, irrespective of stage, the TPHA test remained consistently positive.

In parallel, for the IgG and IgM ELISA tests, in all cases, IgM reached negativity within 6 to 12 months post-treatment, while IgG ELISA continued to be consistently positive, which also explains why TPHA test results never reached negativity.

Discussions

The increase in the proportion of residual positive VDRL test results is clearly noticeable for increasing disease history and stage of disease when treatment is started respectively. Most cases were classified as mandatory latency timeframe of syphilis, both early as well as late or uncertain, with a total of 141 cases, 80.1% respectively, the timeframe when the disease is most frequently detected nowadays, for which the cumulative percentage of residual positive VDRL test results reached 76%. The usual specific confirmatory tests TPHA, and IgG ELISA respectively will also be inherently positive in these patients (3, 4). Under these circumstances we propose that specific tests which can detect the negative status of IgM antitreponemal antibodies be considered certainty confirmatory test for syphilis cure. We were able to use the IgM ELISA test during the study, however the fluorescent treponemal antibody absorbed (FTA-ABS) for IgG / IgM antibodies may prove just as useful (5).

If the treated patient may receive follow-up in the same centre, and the VDRL titres change may be registered over time, the disease is cured if there is 4-fold decrease (the most recent positive result shifts two columns to the left), while syphilis relapse is indicated by a two-fold titre increase (the most recent positive result shifts one column to the right). We recommend specific IgM antitreponemal antibodies test in patients with clinical or serological suspicion of disease in which a serology change history is not documented or unavailable.

Virtually, in a patient with positive VDRL test results (performed due to a legal obligation or a clinical suspicion) we recommend validation through a specific test such as TPHA (or IgG FTA-ABS or IgG ELISA). If uncertainty persists whether the disease is genuinely active or the results are only residual positive not indicative of disease, we recommend specific IgM ELISA or IgM FTA-ABS tests. If the latter are positive treatment is mandatory, while if they are negative the patient's syphilis may be deemed cured.

Conclusions

1. We noticed that in adequately treated syphilis patients the quantitative VDRL test becomes negative at 24 months of post-treatment follow-up in 80% of primary syphilis patients, 46% of secondary syphilis patients and only 24% of syphilis patients identified in the mandatory latency timeframe.
2. Irrespective of syphilis stage at treatment initiation, at 24 months of follow-up, an average 70% of syphilis cases have residual positive VDRL serology.
3. In patients with positive VDRL test results, irrespective of titre level, as well as a positive specific treponemal test, but no documented record of serology change and of the treatment used, we propose specific IgM treponemal tests for the unequivocal confirmation of disease activity status.

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Conflict of interest
NONE DECLARED

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