Henry Ford Hospital Medical Journal

Volume 2 | Number 3 Article 7

9-1954

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THE VALUE OF THE TREPONEMA PALLIDA IMMOBILIZATION TEST (T.P.I.) IN THE DIAGNOSIS OF BORDERLINE CASES OF SYPHILIS

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It has become customary to consider syphilis a vanishing disease. It is true that early syphilis is now rarely seen in the average practice. There is still, however, a large reservoir of late forms of syphilis that frequently present serious diagnostic problems. Most of this late syphilis falls within one of four groups:

(1) Syphilis of the central nervous system.

(2) Syphilis involving the cardiovascular tract.

(3) Late latent syphilis characterized by positive standard tests for syphilis (S.T.S.) with or without a history of syphilis but showing on physical examination no demonstrable focus of infection. To be placed in this classification, the spinal fluid must be examined and found to be negative.

(4) A group of borderline cases where the decision as to whether the patient has or ever has had syphilis requires the most painstaking study. This borderline group can again be subdivided as follows:

(a) History, physical examination and spinal fluid negative. S.T.S. weakly positive and non-diagnostic.

(b) History, physical examination and spinal fluid negative. S.T.S. weakly positive, but with a history of past treatment for syphilis. A history of treatment does not establish a diagnosis of syphilis. In the past, many patients have been treated because a weak, non-diagnostic S.T.S. was found, or the patient had a biologic false positive S.T.S.

(c) A history and/or evidence of past syphilis. These patients have usually been treated, but the S.T.S. is so weak as to suggest a residual type of serologic reaction without remaining viable spirochetes.

(d) A positive S.T.S. that is strong enough to suggest an active infection, but with a negative physical examination, including a spinal fluid examination, and with the patient flatly denying any possibility of a venereal infection.

This borderline group is an extremely important one; both because of its large and growing numbers, and because every effort should be made not to attach the diagnosis of syphilis to a patient who does not now have, or never has had the disease. Furthermore, these tests that are not due to syphilis may give some clue to other disease processes.

That, numerically, this group is important has been shown by our own experience. The laboratory reports on 1747 different consecutive individuals showing any

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degree of positive reaction to the S.T.S., from a weakly positive with one antigen only to strongly positive reactions to all antigens, were studied. In this series, the Kline Exclusion test was done as a screen test. The Kolmer, Kahn and Eagle were done as diagnostic tests. In this series, 891 cases, or 51% of the entire group, a diagnosis of syphilis could be made with reasonable certainty. In 856 of these cases, or 49%, no diagnosis of syphilis was justified.

This is not to say that 49% of the laboratory tests for syphilis gave false reactions. Very few of these tests were biologic false positive in the sense that a strong diagnostic S.T.S. was reported in a patient not having syphilis. In most of these cases, the titres reported were so low or there was so much disagreement between the diagnostic antigens that it was at once apparent that additional evidence would be necessary to establish a diagnosis of syphilis. In fact, the accuracy of the laboratory in doing these sensitive tests and in recording the fluctuating titres, so characteristic of some of these cases, was of the greatest value in reaching a clinical diagnosis.

These results do show, however, that an increasing number of these non-diagnostic reactions are being reported; and as Magnuson[1] points out, as the actual amount of syphilis decreases, this group will remain stationary and so show a relative increase in numbers. We believe that this point has already been reached. Two other factors must also be considered. One is that the older age group is becoming larger and, secondly, a larger portion of the population is having blood tests for syphilis done. It is also obvious that any new diagnostic tests with increased specificity, even at the expense of some sensitivity, would be of great value in complimenting our present S.T.S. The Treponema Pallida Immobilization Test (T.P.I.) seems to be such a test.

It appears that we are to have this problem of the borderline cases as a continuing problem. A closer scrutiny of this group of 856 individuals is of value.

Moore[2] and others have emphasized the value that these non-specific positive reactions have in recognizing other diseases then syphilis. Lupus erythematosus, infectious mononucleosis, malaria, herpiforme diseases and "virus" pneumonia, among others, have been pointed out as being responsible, at times, for false positive S.T.S. All of these diseases appear in this group of 856 cases. The most numerous are the cases of lupes erythematosus; there being 8 cases, including both the discoid and disseminated varieties. All of the other diseases mentioned appeared in smaller numbers in this borderline group.

The age incidence is of interest and is as follows:

Decade	Number	Per cent
0–9	21	2.4%
10–19	11	1.2%
20–29	66	7.7%
30–39	180	21+%
40–49	181	21+%
50–59	196	22.8%
60–69	156	18%
70–84	45	5.2%
	856	99.3%

It is noted that 46% of this group are over 50 years of age. This is the group where the degenerative diseases would be expected. Their frequency and distribution are noted. In the interest of brevity, the following diseases have been grouped together:

1. Arthritis.
2. Arteriosclerosis.
3. Hypertension.
4. Heart disease.
5. Diabetes.
6. Obesity.
7. Malignancy.
8. Chronic infection including tuberculosis.
9. Thrombophlebitis and stasis dermatitis.

There were 271 individuals or 31.7% of the entire group showing one or more of these diseases. This is the largest of any of the divisions in this group and, as would be expected, individuals over 50 years of age predominated. 76.4% of the group were over 50 years old and 23.6% were under 50. It would seem that the degenerative diseases as a group might be responsible for more aberrant reactions then the acute diseases mentioned above.

The second largest group contained those individuals who had had or had been treated for syphilis, but who now showed no evidence of active disease except an uncertain S.T.S. There were 157 cases in this group, with 52.8% under 50 years of age and 47.2% above 50 years. As 46% of the entire borderline group are over 50 years of age, it would appear that the incidence of a history of syphilis or treatment for syphilis does not increase in the older age group.

There were 33 cases of pregnancy in this group of 856 cases. While the number was small, it was important that prompt decisions be made as to their status. The T.P.I. test would be of great value in making such a decision.

The introduction of the Triponema Pallida Immobilization Test (T.P.I.) by Nelson and Mayer[3] in 1949 added a powerful diagnostic agent to the S.T.S. already available. In this test, living pathogenic spirochetes obtained from inoculated rabbit testes are placed in the blood serum of the patient to be tested. The serum is divided into two parts. In one part, active complement is added to the blood serum to be tested; and in the other part, inactive complement is added. Both parts are then incubated for from 16 to 18 hours and the number of viable (motile) organisms is counted in both lots of serum. If the test is positive, most of the spirochetes in the serum containing the active complement will be immobilized or killed. The spirochetes in the serum containing the inactive complement will be active and motile. If the spirochetes remain motile in both lots of serum, the test is negative.

The antibody present in syphilitic serum that gives a positive reaction with the standard antigens used in tests for syphilis is known as reagin. It has been found that this is not the antibody that is responsible for immobilizing the spirochetes

in the T.P.I. test. A distinct immobilizing antibody is present and this antibody is not present in serum giving a false biologic reaction. Therefore, false positive tests are rare or even absent in sera that are not hemolyzed or contaminated.

This test as at present constituted is, in practice, both complicated and expensive. It is still in the research category and must be carried out by thoroughly qualified serologists. It is time consuming and the number of tests that can be done is strictly limited. It should, therefore, be used as a control test after all possible information has been obtained from the S.T.S.

The following facts should be kept in mind:

(1) The immobilization antibody appears in early syphilis shortly after the reagin that gives the positive S.T.S.

(2) If treatment is instituted promptly and the S.T.S. is rendered negative, the T.P.I. may also become negative.

(3) In late syphilis, however, although treatment may reverse the S.T.S. to negative, the T.P.I. will remain positive. Thus, a positive T.P.I. may mean that the patient has or has had syphilis and a reversal to negative is not to be expected even if treatment is successful.

Through the courtesy of Dr. Curtis and Dr. Wheeler of the Department of Dermatology and Syphilology at the University of Michigan, we have had 33 T.P.I. tests done. These were all on problem patients. Of these 33 tests, 16 were positive and 15 were negative. In only one case where the T.P.I. was negative were all the antigens of the S.T.S. strongly positive. This was in the case of a woman who was found to have a strong positive S.T.S. on pre-marital examination.

In no case where the T.P.I. test was positive was the S.T.S. completely negative. In the 16 cases showing positive T.P.I. tests, six had been previously diagnosed as probably not having syphilis. In the 15 cases showing negative T.P.I. tests, three had been previously diagnosed as probably having syphilis.

In all of these cases, the decision as to the presence of syphilis was recognized as uncertain, but the probable diagnosis differed from the T.P.I. test in 9 of the 31 cases.

In all borderline cases where a definite decision cannot be made through the usual diagnostic approach, a T.P.I. test should be done if possible.

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