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Serological Syphilis Testing in Brazilian Older Adults

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Methods: A retrospective study was conducted in Curitiba, Brazil, involving individuals over 60 years old, of both sexes, who tested positive for CMIA syphilis tests but negative for VDRL. FTA-ABS was performed as a confirmatory test, and demographic/clinical data were collected from medical records.

Results: A total of 311 patients were studied, 53.1% male, with a median age of 69 years. No significant differences were found between sexes or ages. Previous syphilis diagnoses were found in 7.4% of patients, and 10.2% had undergone prior treatment for syphilis. Of the patients, 23.4% came from internal medicine, 18.3% from neurology, and 17.3% from infectious disease clinics. False-positive CMIA results were observed in 14.1% of cases.

Keywords: *syphilis, serologic test, aging adults.*

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Conclusion: No significant differences were found between sexes or ages in patients with positive serologic syphilis tests. False-positive CMIA results were observed in 14.1% of cases, most of which had borderline values.

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I. INTRODUCTION

Syphilis is a systemic, chronic, and curable bacterial infection that, when untreated, can progress to severe stages, affecting various body systems, including the cardiovascular and nervous systems. [1] In Brazil, the detection rate of syphilis rose by 32.9% in 2021, particularly in patients over 60, increasing from 59.1 to 78.5 cases per 100,000 inhabitants. [2,3] Between June 2011 and June 2022, over 1.1 million cases of acquired syphilis were reported, with the majority being male (60.6%) and within the age groups of 20-29 (35.6%) and 30-39 (22.3%). [2]

To diagnose syphilis, two types of serological tests are used: non-treponemal tests (e.g., VDRL) and treponemal tests (e.g., CMIA and FTA-ABS). Treponemal tests, which are more specific, have been recommended as the first diagnostic step in Brazil since 2011. [4,5] A positive result in both non-treponemal and

treponemal tests indicates active syphilis. [6] However, an isolated positive treponemal test may signal a past infection or a false-positive result. [5]

Routine syphilis testing in older adults is often performed to investigate conditions such as dementia or cardiovascular diseases. [7] However, diagnosing syphilis, especially in its late latent stage or in cases of neurosyphilis, poses clinical challenges. [8] VDRL positivity tends to decline over time, even without treatment, particularly in tertiary syphilis. [4]

Despite these challenges, few studies have focused on syphilis in older adults. In clinical practice, serological tests are the primary diagnostic tool, but limitations in non-treponemal test specificity and weak correlations between treponemal test results and disease activity complicate diagnoses. [8] Therefore, this study aimed to assess the epidemiological profile and laboratory findings in older adults with positive serological tests for syphilis and to evaluate the frequency of false-positive CMIA results.

II. METHODS

a) Study Design and Ethical Considerations

This cross-sectional study, utilizing retrospective data collection, was approved by the local Research Ethics Committee (protocol number 4.754.505). The study adhered to the Good Clinical Practice guidelines and the ethical principles outlined in the Declaration of Helsinki.

b) Participants

This study utilized a convenience sample of patients aged 60 and older, of both sexes, drawn from the database of the Clinical Laboratory at the Complexo Hospital de Clínicas of the Federal University of Paraná (CHC-UFPR) between March 2019 and October 2022. Included were cases with divergent results, specifically positive treponemal (CMIA) and negative non-treponemal (VDRL) tests for syphilis. A third treponemal test (FTA-ABS) was performed to confirm the serological results. Additional demographic and clinical data, including sex, age, previous syphilis diagnosis, and prior treatment history, were extracted from medical records.

c) Serological Testing For Syphilis

All serological tests were conducted at the Clinical Analysis Unit Laboratory of Hospital de Clínicas, Curitiba, Brazil. The precision of the quantitative tests

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was evaluated following Clinical and Laboratory Standards Institute (CLSI) guidelines (EP15-A3). [9] Three levels of quality control materials were used. Treponemal tests were performed using CMIA (Alinity System, Abbott, USA), with a manufacturer-defined cutoff point of 1.0. Patients with positive CMIA results underwent a non-treponemal VDRL test (Wierner, Argentina) at dilutions of 1:1 and 1:10 to avoid the prozone effect. Additionally, FTA-ABS tests (Wama Diagnostic, Brazil) were performed with an initial dilution of 1:4, and samples were treated with an absorbent buffer for 30 minutes. The indirect immunofluorescence reaction was observed under a microscope (Olympus, Japan) by a single examiner. As per Brazilian Ministry of Health guidelines, a false-positive syphilis result is determined when a positive CMIA is not confirmed by FTA-ABS. All non-concordant cases were retested for verification.

d) Statistical Analysis

Data were collected in frequency and contingency tables. Nominal and categorical data are expressed as percentages. The distribution of numerical data was performed using the Shapiro-Wilk test and central tendency expressed as means and standard deviations for parametric data and median and interquartile range (IQR) for non-parametric data.

The chi-squared test was used to compare nominal data, while the unpaired t-test and Mann-Whitney test were used to compare numerical data. The adopted significance level was 5%.

III. RESULTS

A total of 311 patients with positive CMIA anti-treponemal tests were included in the study, comprising 146 females (46.9%) and 165 males (53.1%; $p = 0.12$), with a median age of 69 years (IQR = 64-75). No significant differences were found when comparing age and sex ($p = 0.35$). Of the patients, 23 (7.4%) reported prior syphilis diagnosis, and 30 (10.2%) had received treatment. Among those treated, 63.3% were male (19/30) and 36.6% were female (11/30).

Tests were performed on patients from various departments: 73 (23.4%) from internal medicine, 57 (18.3%) from neurology, and 54 (17.3%) from infectious diseases, all with a median age of 69 years. Of the 54 infectious diseases patients, 28 (12.3%) were HIV follow-up patients, of which 16 were male (57.2%) and 12 female (42.8%). Across the hospital, 14 medical specialties requested syphilis tests.

As shown in *Figure 1*, in 44 patients (14.1%), there was a discordance between treponemal test results: positive CMIA and negative FTA-ABS, indicating a false-positive result as per Brazilian guidelines (2022). [2] Among the group with both reactive treponemal tests ($n = 267$), 58% were male, while the discordant group had 40.1% males and 59.9% females ($p = 0.07$).

The median age in the false-positive CMIA group was 67 years (IQR = 65-74), while the group with both positive tests had a median age of 69 years (IQR = 64-75), showing no significant difference ($p = 0.86$). Of the 311 patients, 46 (14.8%) had CMIA values between 1.1 and 2.0, considered positive. In this subgroup, 24 (52.1%) tested negative on FTA-ABS, 13 (28.2%) tested mildly positive, and 9 (19.5%) were weakly positive, leading to diagnostic uncertainty in over half of these cases.

Chemiluminescence values (*Figure 2*) showed a median optical density (OD) of 4.9 (IQR = 2.6-8.8) in the true-positive group, while the false-positive group had significantly lower OD values (median 1.9; IQR = 1.2-2.4; $p < 0.0001$). However, it is noteworthy that some cases with low CMIA values also yielded positive FTA-ABS results.

IV. DISCUSSION

The findings from this study contribute to a deeper understanding and expand discussions on interpreting syphilis serological tests in older adults. The increased likelihood of false-negative results in non-treponemal tests, especially in this population, raises concerns about distinguishing between a serological scar and late latent syphilis. In the late latent phase, the sensitivity of the VDRL test ranges from 34-94% in the general population, and even without treatment, non-treponemal test titers may revert to negative. [1] This makes accurate diagnosis challenging, particularly in older individuals.

Since 2013, Brazil has experienced a marked rise in syphilis cases, particularly among older adults. This trend underscores the need to include syphilis in the differential diagnosis of other systemic diseases in this population and to raise awareness about transmission and prevention. According to the Brazilian Institute of Geography and Statistics (IBGE), by 2050, older adults will represent 30% of Brazil's population.[7] This demographic shift, coupled with increased longevity, improved quality of life, and extended sexual activity, emphasizes the importance of addressing syphilis in older adults. Notably, studies suggest individuals aged 50-64 are least likely to use condoms globally. [10, 11].

In our sample, no significant differences were found in the positivity of syphilis serological tests between males and females. However, Ministry of Health data indicate that men over 50 are more likely to be diagnosed with syphilis than women.[2] This disparity may be related to the setting of the study, which was conducted in a tertiary hospital, potentially reflecting a higher male representation in more complex or advanced cases referred for specialized care.

In terms of prior syphilis diagnosis awareness, only 7.4% of patients reported a previous diagnosis in

their medical records. Bastos et al. found that around 68% of older adults were unaware of syphilis, and 70.9% did not know how the disease is transmitted. [12] Additionally, healthcare providers often feel uncomfortable discussing STIs with older patients, which can contribute to underreporting and insufficient communication regarding syphilis and its transmission in this age group.

Internal medicine, neurology, and infectious diseases were the specialties that most frequently requested syphilis testing in this study. In contrast, specialties that commonly order tests in younger adults, such as gynecology, urology, and dermatology, were less represented in the sample. The high number of requests from neurology can be attributed to the protocol recommendation for syphilis testing in patients with dementia or suspected neurosyphilis. [13] Treponemal antibody tests typically remain positive long-term, whether the infection is treated or not, while non-treponemal tests may become negative in late neurosyphilis. [14] In cases where both treponemal tests (CMIA and FTA-ABS) are positive but VDRL is negative, a lumbar puncture is advised for confirmation. It's important to note that while VDRL is the recommended test for cerebrospinal fluid, it has low sensitivity (about 53%) but high specificity. [15]

In the studied sample, following Brazilian guidelines, 14.1% of CMIA tests were negative on the FTA-ABS, indicating false-positive results. This is likely due to the high sensitivity of CMIA, which may detect non-specific anti-treponemal antibodies during FTA testing. [16] False-positive reactions occur in about 1% of the general population in treponemal tests. [17] The age of the sample may contribute to the presence of non-specific antibodies, as previous studies have shown that the risk of false positives increases with age. [18] Additionally, CMIA OD values were significantly higher in cases where both treponemal tests were positive. It is important to note that many false-positive cases had CMIA values close to the cutoff threshold. Transient false-positive results can also arise due to infections, vaccinations, medications, blood transfusions, or pregnancy. [17] However, limited research on syphilis serological tests in older adults makes comparisons with other studies challenging.

This study has certain limitations due to its retrospective design. The lack of access to full medical records prevented us from gathering detailed information about the final diagnoses and whether syphilis treatment was administered. Despite these limitations, the findings underscore the need for the development of new and more reliable diagnostic tests for syphilis, particularly in older adults, where interpretation can be challenging.

Our study also contributes to the growing body of knowledge regarding the interpretation of syphilis serological tests in older populations. The higher

likelihood of false-negative results in non-treponemal tests in this age group raises concerns about accurately distinguishing between a serological scar and late latent syphilis. As a result, careful interpretation is crucial to avoid misdiagnosis and ensure appropriate treatment decisions.

V. CONCLUSION

This study found that the median age of older patients with positive serologic tests for syphilis was 69 years, with no significant differences between sexes. The medical specialties with the highest number of positive syphilis tests were internal medicine, neurology, and infectious diseases. False-positive results were observed in 14.1% of CMIA cases, with most having borderline values. There were no significant associations between age or sex and the occurrence of false-positive serologic tests for syphilis in this older population.

Funding Information

This study had no specific funding.

Conflict of Interest Statement

All authors declare that we have no potential conflict of interest.

Ethics Approval: All procedures performed in studies involving human participants were in accordance with the institutional research ethics committee standards and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the Research Ethics Committee from the Evangelic Mackenzie School of Medicine under protocol number 4.754.505.

Transparency Declaration

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Abbreviations:

CMIA= Chemiluminescent microparticle immunoassay (treponemal test)

FTA-ABS= Fluorescent treponem antibody absorption (treponemal test)

VDRL= Veneral Disease research in the laboratory (non-treponemal test)

