CASE REPORT

Positive serological tests for syphilis and administration of intravenous immunoglobulin

S A Constable, C M Parry, T P Enevoldson, M Bradley

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We report the case of a man who tested positive for syphilis following the intravenous administration of human normal immunoglobulin as part of the treatment of Guillain-Barré syndrome. The chronology of the testing suggested the passive acquisition of treponemal antibody. This phenomenon is not widely documented in the medical literature, but is a theoretical risk of treatment, and serves as a reminder to be cautious in the interpretation of such serological tests.

A 32-year-old man, previously healthy, presented with a progressive bilateral lower motor neuron facial weakness. Lumbar puncture demonstrated an elevated cerebrospinal fluid (CSF) protein without pleocytosis and nerve conduction studies were consistent with demyelination. A diagnosis of early stage Guillain-Barré syndrome (GBS) was made and the patient was treated with a 5 day course of intravenous human normal immunoglobulin (HNIG) (in this case, Flebogamma 5%) at a dose of 0.4 g/kg/day. This treatment was well tolerated and he made a full recovery.

Serological testing for syphilis, as part of the initial diagnostic evaluation, was undertaken on a blood sample taken (inadvertently) after the diagnosis of GBS had already been established, and 24 hours after the final dose of HNIG had been given. The enzyme immunoassay (EIA, Bioelisa Syphilis 3.0, Biokit) was positive, the *Treponema pallidum* haemagglutination assay (TPHA, Biokit Syphagen TPHA) was positive (titre 320), but the rapid plasma reagin (RPR, Biokit RPR Reditest) test was negative. The results suggested a previous treponemal infection that was neither active nor current. Testing of the same sample at the regional reference laboratory confirmed these results—the EIA (ICE, Murex Diagnostics) and fluorescent treponemal antibody absorbed test (FTA abs) were positive, the TPPA was positive (titre 160), and the RPR was negative. The patient had no clinical evidence of syphilis or history of previous syphilis exposure. Insufficient CSF was available for testing, but further lumbar puncture was deemed clinically unnecessary and ethically inappropriate. As a result of these findings, and in the period of recovery from GBS, the patient underwent further counselling and testing in the genitourinary clinic. Subsequent tests, 8 weeks and 13 weeks after the initial diagnosis, were negative (negative EIA, TPHA, and RPR), and this was confirmed by the reference laboratory. No antibiotic therapy was administered at any stage.

DISCUSSION

HNIG is prescribed for a wide ranging list of indications in a variety of specialties. It is a pasteurised preparation of highly purified immunoglobulin (IgG) obtained from pools of donations of human plasma, containing the antibody specificities found in the donor population, including measles, mumps, varicella, and hepatitis A. The source plasma is collected by apheresis in dedicated centres inspected and approved by the regulatory authorities (in this case, the Food and Drug Administration in the United States). As a blood product, all source plasma is tested using standard serological tests for blood borne viruses. The plasma donors themselves are screened regularly (once every 4 months) for syphilis, using the RPR test. Neither the pooled plasma nor individual units of HNIG are rescreened for syphilis. Pasteurisation would be expected to destroy all pathogenic vegetative micro-organisms including *Treponema pallidum*, but this process is only validated in a model replicating the environment required for the inactivation of certain model viruses and not specifically for *Treponema pallidum*.

Patients who receive infusions of HNIG may subsequently have misleading positive serological results for a variety of viral, bacterial, and other infectious diseases,[1] and this is specifically advised in the summary of product characteristics (SmPC, or datasheet).[2] However, to the best of our knowledge, there is only one previous report in the literature recording the passive acquisition of treponemal antibody as a result of immunoglobulin therapy.[3] Interpretation of blood tests for syphilis can be difficult and a variety of conditions, including autoimmune diseases, can give rise to false positive tests, particularly with the non-treponemal tests, such as the Venereal Disease Research Laboratory (VDRL) or RPR tests.[4] However, testing here was with sensitive and specific tests for the presence of the antibody to *Treponema pallidum*, and included confirmatory testing at a reference laboratory. Furthermore, the chronology of the testing would suggest the passive acquisition of treponemal antibody rather than false positive results. Unfortunately, no premorbid blood sample was available for testing.

We highlight this case because of the potential for clinical confusion and misinterpretation of infectious disease testing in a patient who has received HNIG. More importantly, these test results led to a significant amount of anxiety and distress for a patient and his family caused by concern about a sexually transmitted disease.

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CONTRIBUTORS

All authors were responsible for the clinical care of this patient during his admission and subsequent follow up period, and contributed to the preparation and review of the manuscript for submission.

Abbreviations: CSF, cerebrospinal fluid; EIA, enzyme immunoassay; GBS, Guillain-Barré syndrome; HNIG, human normal immunoglobulin; RPR, rapid plasma reagin; TPHA, *Treponema pallidum* haemagglutination assay; VDRL, Venereal Disease Research Laboratory

Key messages

- Serological test results should be interpreted with caution once human normal immunoglobulin has been administered to a patient
- The datasheet for pharmaceutical agents may provide valuable assistance in the evaluation of such diagnostic problems
- Screening for syphilis, for any indication, is best done with specific tests for treponemal antibody (for example, EIA or TPPA) rather than using VDRL or RPR, that may lead to false negative results

Authors' affiliations
S A Constable, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK
C M Parry, Department of Medical Microbiology and Genito-urinary Medicine, University of Liverpool, Liverpool, UK
T P Enevoldson, The Walton Centre for Neurology and Neurosurgery, Liverpool, UK
M Bradley, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK

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Correspondence to: S A Constable, Department of Pharmacology and Therapeutics, University of Liverpool, Ashton Street Medical School, Ashton Street, Liverpool L69 3GE, UK; s.constable@liverpool.ac.uk

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