Defying Gravity

Article:
Jordan E. Baum, Stephen R. Master.
Defying Gravity.
J Appl Lab Med 2016;1:247-249.
http://jalm.aaccjnls.org/content/1/3/247

Guest:
Dr. Stephen Master is an associate professor of pathology and laboratory medicine at Weill Cornell Medicine in New York.

Randye Kaye: Hello, and welcome to this edition of "JALM Talk" from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

It's well known in the laboratory medicine field that immunoassays are prone to a number of interferences. However, it can sometimes be difficult to elucidate if there is an analytical interference and exactly what is causing it. A Case Report entitled, "Grave Clinical Pathologic Correlation: A Case of Hyperthyroxinemia" was published in the November 2016 issue of JALM, and it discussed a young female patient who had thyroid testing carried out by a family physician and due to abnormal results, she was subsequently referred to an endocrinologist. When the laboratory test results didn't match the clinical picture, the endocrinologist asked the laboratory for help in resolving this discordance.

The Case Report discusses the investigations the laboratory undertook to determine what was causing interference in the immunoassays for free thyroxin, free triiodothyronine, and thyroid stimulating hormone receptor antibody that caused falsely elevated results in competitive electrochemiluminescent immunoassays. Dr. Stephen Master, an associate professor of pathology and laboratory medicine at Weill Cornell Medicine in New York was invited to write an editorial regarding this Case Report. Dr. Master is our guest for today's podcast. Welcome, Dr. Master.

Our first question is, what are immunoassay interferences? And, why are they important?

Dr. Steven Master: Well, for quite some time, we've known that immunoassay results are susceptible to interferences from other factors, so the classic example being patient-specific antibodies that bind to the animal antibodies that are used to construct an assay. The lab always needs to be mindful of this possibility, since there are cases that have been described where significant medical harm came from false results with

interferences. But of course, while we recognize the importance of immunoassay interferences, finding them and characterizing them is often more easily said than done.

Randye Kaye: Well, this Case Report describes the particular case of a patient with lab results suggesting the presence of hyperthyroidism, but who didn't appear to have symptoms that would be consistent with this diagnosis. So what happened?

Dr. Steven Master: Well, this paper by Mattman and colleagues provides an interesting example of an unusual immunoassay interference. In this case, it's one in which the incorrect assay results were confusing because they partially mimic a known aspect of human physiology. So specifically, the patient was found to have a low TSH with an elevated free T4, and further testing was positive for TSH receptor antibodies. Now of course, low TSH with a high free T4 is the general reciprocal trend that you would expect with hyperthyroidism, but it didn't match the patient's clinical euthyroid picture. And as a result, the authors considered a number of disorders that would account for this mismatch.

But as part of that broader workup, they also explored whether a lab error or artifact could cause these results. They eventually concluded that the patient had anti-streptavidin antibody which have been previously described in the literature, but has not been widely recognized. Streptavidin is often used in constructing laboratory assays due to its affinity for biotin. In this case, the interesting aspect is that the Roche immunoassay system that the authors were using has a competitive assay for free T4 and a sandwich assay for TSH. Because the chemiluminescence signal is inversely proportionally to analyted and competitive immunoassay, but directly proportional in a sandwich assay, this provided a nice single cause that could explain the apparently physiological reciprocal results for these analytes seen in the patient.

I should mentioned that a similar picture can actually be seen when the patient is on high dose biotin supplementation, but this patient, the patient in this Case Report, was not taking biotin. And at least one of the cases of possible anti-streptavidin antibody reported in the past few years, the lab was able to correct the erroneous result by preclearing the antibodies from the sample using protein A, providing evidence the interference was in fact the antibody mediate, so the cumulative evidence for this anti-streptavidin antibody seems strong.

Randye Kaye: I would say so. So, for this particular case, what would say are the lessons you can take from this case for the laboratory?

Dr. Steven Master: Well, one point that I think always needs to be emphasized is the importance of a strong working relationship between the laboratory and clinicians. In many cases of interference, the only clue that anything is wrong comes from that astute physician who notices that the lab value doesn't fit the clinical picture. We, in the lab have a number of tools to investigate interferences, but these often require that we're first informed that something seems wrong.

Randye Kaye: Okay. So when you're considering the possibility of anti-streptavidin antibody, are there any other concerns that the patient should have?

Dr. Steven Master: Well, this is a second major point about this is case, which is that in some cases of interference, there are broader implications beyond a single lab value for a patient. In the case of something like of an anti-streptavidin antibody, there may be a number of other assays that are constructed using a similar principle that are also affected.

In a prior case of anti-streptavidin antibody that my lab had handled, we wrote a letter for the patient documenting the interference and explaining the implications for certain test platforms. Certainly if that patient required emergency treatment in an institution that was using a susceptible platform, it will be extremely important to know about the potential for diagnostic interference.

Randye Kaye: Yes, I agree, it certainly would. Is there anything else that the lab can do to detect or characterize these types of interferences?

Dr. Steven Master: I do think that it's important to make sure that the lab has access to a diverse set of testing methodologies. As healthcare systems have centralized and standardized to a common platform, there have certainly been cost savings and the ability to share expertise that have resulted from that. But I think we have to recognize that this consolidation has risks, if there are subsets of patients that receive incorrect results using a given methodology. So having some degree of access to multiple platforms not only facilitates patient care, but also allows the lab to more easily identify interferences. You know, of course, every platform has its own strengths and weaknesses, but I guess I'm just trying to argue that clinical lab testing within a given geographical region is a little like biology, where some degree of ecological diversity would be a good thing.

Randye Kaye: Okay, very interesting and very important. Thank you so much for joining us today, Dr. Master.

Dr. Steven Master: Thank you very much.

Randye Kaye: That was Dr. Steven Master from Weill Cornell Medicine in New York talking about the JALM Case Report, "Grave Clinical Pathologic Correlation: A Case of Hyperthyroxinemia" for this podcast. Thanks for tuning in for "JALM Talk." See you next time, and don't forget to submit something for us to talk about.