Commentary on the Abuse of Metal Chelation Therapy in Patients with Autism Spectrum Disorders

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Abstract Approximately half a million patients with autism spectrum disorders are subjected to chelation therapy in the US annually. The overwhelming majority of such cases are chelated for non-accepted medical indications. These patients may seek evaluation when a urine sample is assayed after the administration of a chelating agent and the values obtained have been improperly compared to reference ranges for non-chelated urines, causing falsely elevated results. Legitimate practitioners confronted with such data must decide, preferably in consultation with the patient or their guardian(s), whether to do further testing using legitimate methodology or to simply dismiss the results of the improper testing. Bayesian principles tell us that further testing is likely to yield results within normal reference ranges. However, under some circumstances, it is useful to do such testing in order to demonstrate that there is no need for chelation therapy. Unnecessary chelation therapy is expensive, can cause significant acute adverse effects, and may be associated with long-term consequences.

Keywords Autism spectrum disorder · Chelation therapy · Mercury · Metal toxicity · Elevated body burden of metal

Multiple epidemiological studies have provided a very strong body of evidence rejecting any association between receiving vaccines containing the mercurial preservative thimerosal and

the subsequent development of autism spectrum disorders (ASDs) [1, 2]. Despite this incontrovertible body of epidemiological data, it is still common for certain physicians and websites to recommend chelation therapy for mercury removal in these patients. The frequency with which patients with ASD are chelated has been reported to be in the 7–8 % range [3, 4]. Assuming the prevalence of ASD to be 1 %, that translates into approximately 500,000 children in the US that have received chelation treatment for this condition.

While it is prudent for the evidenced-based physician to discourage chelation for mercury based on a large and consistent body of scientific data [1, 2, 5], there are other circumstances where questions of toxicity or elevated body burdens of other metals are frequently encountered in individuals with ASD. Unlike the large database on mercury and ASD, the body of scientific information upon which to rely when making decisions about other metals is insufficient to provide absolute recommendations. Therefore, the physician confronted with such data must make informed decisions based on the clinical scenario, the desires of the patient, and, where applicable, their parents or guardians. Importantly, fundamental principles of Bayesian logic are particularly helpful in making these decisions.

The greatest ambiguity in decisions about how to proceed regarding questions of metal toxicity or chelation in patients with an ASD is when they present for evaluation accompanied by laboratory data which, if truly reflective of the patient's physiological state, could be interpreted as a biomarker for an elevated body burden of one or more metals. Typically, such data come from studies done by one of a variety of laboratories that aggressively advertise on the internet and that cater to both the general public and the small group of unorthodox practitioners who shun mainstream science. Rather, the latter subscribe to studies, generally of marginal quality, often published in low-quality journals, suggesting that metal toxicity in patients with ASD is a significant problem.

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Testing results for metals done by one of these laboratories, and which physicians may be confronted with, are usually one of two kinds: hair testing, or more commonly, urine assays where the patient has been pretreated by a metal chelating agent prior to sample collection.

While some hair testing, when done carefully, can be useful and valid, there are a number of pitfalls in such evaluations. For many metals, there are not well established and validated reference ranges for hair samples. Where such reference ranges do exist, they may be different from those used by certain laboratories. Hair testing is also notoriously susceptible to environmental contamination; separating external material that has settled on the hair from that which is endogenously excreted into the hair matrix through the hair follicle can be difficult and is technique-dependent [6–8]. Thus, insufficient separation of exogenous from endogenous components may lead to falsely elevated results. In contrast, overly aggressive methods to remove surface contamination may cause liberation of metals of endogenous origin, thus resulting in falsely low concentrations.

Similarly, there are many problems with so-called “provoked” urine specimens which are based on urine collections done after a chelating agent is administered. Usually, the time period of urine collection under these circumstances is such that it encompasses the period of expected greatest metal excretion, commonly for the first 6 h.

There are no validated post-chelation urine metal reference ranges with the exception of an antiquated test for lead body burden after a calcium edetate challenge [9]. Therefore, the values obtained for the concentrations of metals in chelated urines are often inappropriately compared to those that have been validated for non-chelated specimens. Doing so clearly injects a strong positive bias in the sample interpretation, since it would be expected that all individuals, whether they have ASD or not, and whether they have an elevated body burden of any metals or not, might exceed the reference range for basal urinary metal excretion after a chelator has been given. This practice, therefore, has no scientific validity, and values obtained in provoked urine samples should be considered to be uninterpretable unless they fall within the reference range of non-provoked urinary excretion. Recently, the American College of Medical Toxicology has issued a position statement condemning the use of provoked urine samples for the assessment of metal toxicity or body burden [10]. A similar cautionary statement has been issued jointly by the American Academy of Clinical Toxicology and the Association of Occupational and Environmental Clinics [11].

While values obtained on tests of chelated urine samples are uninterpretable when they are elevated compared to reference ranges, they can be interpreted as not being elevated when they do fall into the normal reference range. This is

because chelating agents would not be expected to reduce the concentrations of metals in the urine. Therefore, it is possible to take assurance when a chelated urine sample is not elevated above reference values. Potential clinical ambiguity arises, however, when the value of a provoked urine sample is elevated. Theoretically, there are two possible interpretations. One is that the sample simply represents a false elevation on the basis of the fact that it was provoked. In the writer’s experience, this is the most common explanation. However, an elevated value on a chelated sample cannot a priori be taken as assurance that it would not have been elevated on a non-chelated specimen. This injects a degree of ambiguity into the interpretation of laboratory data that has the potential to be uncomfortable to desperate and concerned families of individuals of an ASD.

The evidence-based practitioner has little to rely on other than Bayesian logic under these circumstances. Although a true quantitative Bayesian analysis can be daunting, doing so is often unnecessary in clinical scenarios. Bayesian thought, as it applies to medicine, refers to the concept of the posterior probability of disease. A specific example would be an assessment of the likelihood that a positive test result reflects a true positive result. Although this is the most common medical application of Bayesian thought, it can be used in the opposite way for the interpretation of a negative test. An easy example of Bayesian logic can be applied to the results of HIV immunoassays. Here, there is a substantial likelihood that a positive HIV immunoassay in a patient who has never been sexually active, never received a blood transfusion, and never used injectable substances of abuse is a false positive result. In contrast, exactly the same test result in a patient with at-risk sexual practices and a history of intravenous substance abuse while sharing needles has a high likelihood of being a true positive.

This same Bayesian approach can be utilized to address the ambiguities of potentially falsely positive metal test results from a provoked urine sample in a patient with ASD. Such a result clearly does not rule out an elevated body burden of metals but, in the absence of history of substantial pica, is unlikely to represent a true positive. The likelihood that an appropriate sample, such as a non-chelated urine, will be elevated is low. However, it is best to discuss the pros and cons, including the expense, of additional and appropriate testing with the patient or, where necessary, the patient’s family or guardians. A joint decision should be made such that if they desire further testing using correct methodology, it should be made available to them. In this writer’s experience, following a frank discussion, such testing is not often requested, and, if done, the result is usually within the range of the general population. Doing such testing, if desired by the patient or relevant guardians, is likely to reduce the risk of patients subsequently getting inappropriate chelation therapy. Inappropriate chelation treatment can be dangerous [12–17].

Animal data has raised the possibility of long-term adverse cognitive effects from unnecessary chelation [18].

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