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Caroline Moreau

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**Immunoassays disruption by high dose biotin therapy: fair warning for neonatal care pediatricians**

Charles R. Lefevre<sup>1,2</sup>, Lucas Peltier<sup>1</sup>, Léna Damaj<sup>3</sup>, Jessica Valaize<sup>1</sup>, Claude Bendavid<sup>1,4</sup>, Caroline Moreau<sup>1,2</sup>

<sup>1</sup> Laboratoire de Biochimie – Toxicologie, Hôpital Pontchaillou, CHU Rennes, France

<sup>2</sup> Univ Rennes, CHU Rennes, INSERM, EHESP, IRSET (Institut de Recherche en Santé, Environnement et Travail) UMR\_S 1085, F-35000 Rennes, France

<sup>3</sup> Service de Pédiatrie, Hôpital Sud, CHU Rennes Boulevard de Bulgarie, 35000 Rennes, France

<sup>4</sup> Univ Rennes, CHU Rennes, INSERM, NUMECAN (UMR 1241), 35000 Rennes, France

Corresponding author : Dr. Caroline Moreau

Service de Biochimie – Toxicologie

Hôpital Pontchaillou CHU Rennes

35000 Rennes, France

[caroline.moreau@chu-rennes.fr](mailto:caroline.moreau@chu-rennes.fr)

## Clinical Letter

Very high-dose biotin therapy is sometimes prescribed in newborns with pharmacoresistant neonatal epileptic encephalopathy or with suspicion of inherited metabolic disorders such as biotinidase deficiency, holocarboxylase synthetase deficiency or LEIGH syndrome (in Biotin-Thiamine-Responsive Basal Ganglia Disease due to *SLC19A3* mutation) (1,2). Regardless of the child's weight (2-10 kg), tremendous doses of biotin are administered (10-300 mg/day *e.g.* 3-100 mg/kg/day for a 3 kg newborn).

## Patient description

We presented the case of a dichorial diamniotic pregnancy involving a 795g extremely premature newborn (26 weeks + 2 days). An inherited metabolic disorder was suspected because of the history of several miscarriages in the mother (G7P2), the outcome of the pregnancy, and the presence of a dilated cardiomyopathy and a mild hyperlactacidemia in the neonate. According to biological and clinical data, the neonate was treated with biotin 10mg per day, *e.g.* 12.5 mg/kg/day, which is a tremendous amount. The urinary organic acids, the plasmatic acylcarnitines, and the plasmatic and urinary amino-acid profiles were normal. Metabolic hypothesis has been ruled out. A non-exhaustive biological assessment was carried out, including in particular the exploration of thyroid function (*i.e.* Thyroid Stimulating Hormone -TSH-, Free Thyroxin -FT4-, and Free Tri-iodothyronine -FT3- dosages). The results were completely disrupted leading to a biological neonatal hyperthyroidism profile, which is very rare. Only our clinical discernment and communication with pediatricians enabled us to spot the issue. The hypothesis of an analytical interference because of biotin-treatment was retained. Biotin may be neutralized from blood sample and biological thyroid

profile was normal. Today, at the age of 7-months, the patient still presents an unexplained dilated cardiomyopathy.

## Discussion

Even if no direct adverse effect of this treatment is described to date for the patient, high-dose biotin therapy may have a significant indirect impact through biological analysis, because of analytical interferences with some immunoassays. Briefly, biotin excess in the patient sample competes with biotinylated antibodies used as a reagent, thereby causing falsely low results with sandwich immunoassays (*e.g.* TSH assay) and falsely high results in competitive immunoassays (*e.g.* FT4 assay). Moreover, these false results can still be consistent with the patient's clinical state and lead to misdiagnosis and inappropriate care. Such situations occurred during large scale clinical studies of biotin therapy in adults with multiple sclerosis using 300 mg per day in adults (4-5 mg/kg/j). Analytical interferences involved routine or emergency biomarkers, including cardiac biomarkers (troponin, N-Terminal-pro-Brain Natriuretic Peptide -NT-pro-BNP-), thyroid function markers (TSH, FT4), vitamins (B9, B12) or serology. To date, Piketty *et al.* reported the case of an adult treated by 300 mg/day of biotin with undetectable TSH and very elevated FT4 that perfectly mimicked hyperthyroidism, but without dysthyroidism (3). Dramatic outcomes with false-negative troponin results leading to death were also reported (4).

Biotin interference with immunoassays is now a well-known pitfall for the manufacturers, some of whom have elaborated new more robust assays that are not biased by high-level biotin therapy for multiple sclerosis in adults. However, this may still be insufficient in newborn cases whose dose/weight ratio is, as mentioned above, far higher than for adults with multiple sclerosis. Consequently, erroneous clinical management related to biotin interfered

results can still be encountered in newborns supplemented with biotin for rare disease management, even if the immunoassay is labeled “biotin proof”.

In samples containing biotin, biotin may be neutralized by clinical pathologists with a simple and short – less than 1h30 – preanalytical treatment that can be adapted to neonatal biotin intake (3). We followed and adapted the protocol to neutralize the interference in the sample. We extrapolated adults' values and hypothesized that, according to therapeutic intake, biotin-concentration in this infant plasma would be five times higher than in an adult. So as a precaution, we decided to use fivefold more reagent to ensure the success of the preanalytical treatment. TSH, FT4, and FT3 resulted in the normal range.

The take-home message is that pediatricians must be very cautious of the disrupting potential of biotin therapy in immunochemistry and must, therefore, contact systematically their clinical pathologists in case of biotin supplementation to discuss every biological prescription to evaluate potential interference.

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