Factitious Increase in Thyrotropin in a Neonate Caused by a Maternally Transmitted Interfering Substance

To the Editor:

Patient 1 was born at 41 weeks of gestation by normal delivery and had a normal birth weight of 3000 g. He had an increased thyrotropin (TSH) on day 3 after routine neonatal screening, using blood spots in the Elegance Neonatal TSH ELISA [TSH, 25.4 mIU/L; upper reference limit (URL), 13.0 mIU/L]. As per the standard newborn screening procedure (1,2), the neonatal screening test was repeated on day 17, and although lower than the previous measurement, the TSH was again above the URL (TSH, 19.6 mIU/L; URL, 10.0 mIU/L). On day 21 of life, the child was euthyroid, had thrived since birth with a current weight of 3600 g, and was feeding well. No jaundice, palpable goiter, or other abnormalities were detectable. His mother had not been given iodine or other medications. She had no family history of thyroid disorder and was euthyroid on history and examination. However, both mother and child had markedly increased TSH values as measured by the laboratory Dade Behring Dimension TSH assay (mother’s TSH, 35.0 mIU/L; reference interval, 0.3–5.0 mIU/L; patient’s TSH, 60.9 mIU/L; URL, 13.0 mIU/L) but with normal free thyroxine (FT4) and free triiodothyronine (FT3) results measured on the Abbott AxSYM analyzer. Thyroid autoantibodies were negative for both mother and child, and a thyroid scan of the child was normal.

TSH was measured in serum samples from patient 1 taken on days 22, 24, 51, and 98 by the Dade Behring Dimension assay. TSH values decreased over this time, decreasing to within reference values by day 98 (Fig. 1). Also shown in Fig. 1 are the Elegance Neonatal TSH results at days 3 and 17. FT4 remained within reference values during this time.

Serum specimens from the mother collected over a 5-month period were also referred to other laboratories for TSH analysis. TSH values measured by the DPC IMMULITE 2000 and Abbott AxSYM were also increased; however, TSH results from the Abbott Architect, Bayer ACS:180, and Bayer ADVIA Centaur were all within reference values. FT4 was also within reference values over this time period.

Recently, a second child, patient 2, was born at term to the same mother by normal delivery with normal birth weight. Routine neonatal screening by the Elegance Neonatal TSH ELISA revealed a markedly increased TSH (113.8 mIU/L; URL, 13.0 mIU/L). Further testing with the Beckman Coulter Dxi assay revealed a TSH concentration of 262 mIU/L, whereas the value obtained with the Bayer ADVIA Centaur assay was within the reference interval (11.1 mIU/L), as was the FT4 concentration. No further testing has been performed in this euthyroid infant.

Further investigations were carried out on the mother’s serum. Neither the heterophilic blocking reagent (Scantibodies) nor protein A-Sepharose (3) was able to remove the interfering substance; however, this lack of reduction does not rule out a nonspecific binding antibody or agent. Linearity studies of the mother’s serum (serial dilutions from 1:2 to 1:64) showed a good linear response after dilution, which is usually not seen if human anti-mouse antibodies are causing the interference. Human chorionic gonadotropin, follicle-stimulating hormone, and luteinizing hormone (hormones with α subunits similar to that of TSH), immunoglobulins, rheumatoid factor, and electrophoresis of the mother’s serum were all normal.

The interference seen with the TSH assays (Elegance Neonate, Dade Behring Dimension, Abbott AxSYM, DPC IMMULITE, and Beckman Dxi assays) in samples from our patients appears to have been transmitted transplacentally from the mother’s blood. This interference had a time course of decay in the serum of patient 1 consistent with an immunoglobulin. It is likely that this interfering substance had high affinity and was very specific for common antibody epitopes present in the reagents of the affected assays but absent from at least one of the antibodies in the unaffected assays. Alternatively, proprietary additives in the unaffected assays may have been blocking the interfering substance. It was not possible to define the susceptible reagents in terms of the monoclonal or polyclonal antibody animal sources.

Interference in immunoassays has been the subject of several reviews (4–10). Although there have been several reports of transient neonatal hypothyroidism in the literature (11–15), we believe that this case is unusual because the mother had not received any previous medications or iodide treatment and had no known exposure to animals, and the interfering substance could not be identified as being a heterophile antibody.

We believe that, even with modern technologies aimed to eliminate such interference, to prevent adverse treatment of patients, it is imperative for clinicians to be aware of the possibility of interfering antibodies in immunoassays. The importance of confirming hypothyroidism detected on screening with both TSH and FT4 must be emphasized, as well as resolution of any discrepancies before long-term replacement therapy is determined. It is
also important for clinicians to alert the laboratory if biochemical data do not agree with the clinical findings, as recommended by Ismail and Barth (8), so that such interfering substances can be identified and documented. This problem is best managed by promoting open dialog between clinical users and laboratory providers, as all analytical systems seem to be at risk and conventional quality assurance procedures do not detect such errors.

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References


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