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Letter to the Editor

Familial dysalbuminemic hyperthyroxinemia coexisting with a Grave's disease: a Belgian case report

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To the Editor,

More than 99 % of thyroid hormones (TH) circulate in the bloodstream bound to thyroxine-binding globulin (TBG), transthyretin (TTR) and human serum albumin (HSA). Depending on its affinity for transport proteins, 75 % of thyroxine (T4) is bound to TBG, 20 % to TTR and only 5 % to HSA [1].

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Genetic mutations of these binding proteins alter their synthesis or their affinity for TH and may be suspected in euthyroid patients having normal thyroid stimulating hormone (TSH) with altered total T4 or triiodothyronine (T3) concentrations. Identifying those conditions can be challenging because deficiency of TBG [2] or increased affinity TTR as well as HSA variants can coexist with thyroid disorders including Grave's or Hashimoto disease [3–5].

Familial dysalbuminemic hyperthyroxinemia (FDH) is an autosomal dominant syndrome and is the most common cause of inherited euthyroid hyperthyroxinemia in Caucasian. The prevalence of FDH is estimated around 1:10,000 in the Caucasian population and can reach 1–1.8 % in Hispanic population [6]. This disorder is characterized by mutations of HSA gene leading to variants having a higher affinity for TH. FDH patients present altered thyroid function tests (normal TSH with increased T4 and/or T3), but are, most often, clinically euthyroid [3]. The discordant TH tests can mimick thyroid disorders such as TSH adenoma or resistance to thyroid hormone (RTH).

A 55-year-old Caucasian Belgian female with a history of recurrent Grave's disease underwent a thyroidectomy 10 years ago. She was treated with variable doses of levothyroxine and the TH tests, performed regularly during the follow-up, showed discordant results with a high free T4 concentration, a normal free T3 and a normal or slightly increased TSH level. The discrepancy of thyroid tests was first attributed to the fact that the daily levothyroxine dose (100 µg) was taken before the blood withdrawal. Free T4 concentration can indeed increase about 40 %, 3 or 4 h following the levothyroxine ingestion [7]. Despite taking standardized levothyroxine after blood tests, free T4 concentrations failed to normalize. Serum concentrations of TSH (Elecsys TSH) and free T4 (Elecsys FT4 IV, one step assay) were measured on an electrochemiluminescent immunoassay e801 analyser (Roche Diagnostics, Mannheim, Germany) and were as follows: 4.31 mUI/L for TSH [95 % central reference interval (RI): 0.27–4.2 mUI/L] and 27.5 pmol/L for free T4 (95 % central RI: 11.9–21.6 pmol/L). At the same time, her 27-year-old daughter was referred to the endocrinology department for a chronic fatigue assessment. She was clinically euthyroid and did not take any medication, oral contraceptives included. Thyroid tests carried out twice on this patient showed a marked elevation of free T4, almost twice as high as the upper normal values (FT4: 38 pmol/L), with a TSH and a free T3 concentration within physiological limits on the Roche analytical platform. Given this picture of inherited abnormality of thyroid tests, FDH was suspected. In the meantime, the daughter was referred to the emergency department after fainting. Due to the results of high FT4

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value, the emergency physician wanted to initiate an antithyroid treatment, but the patient, who was aware of its potential FDH diagnosis, warned the clinician and prevented this. DNA sequencing of HSA gene demonstrated the known R218H albumin mutation for the mother and her daughter. Free T4 concentrations were measured on different analytical platforms: Alinity I (Abbott Diagnostics, Wiesbaden, Germany, 2 two steps assay), Lumipulse G1200 (Fujirebio, Gent, Belgium, one step assay) and Atellica IM analyser (Siemens Healthineers, Erlangen, Germany, one step assay). The normal RI for FT4 provided by Abbott was 9–19.5 pmol/L (99 % central RI), 9.7–19.8 pmol/L (95 % central RI) for Fujirebio and 11.5–22.7 pmol/L (95 % central RI) for Siemens. Figure 1 summarizes the FT4 concentrations measured with different assays. Total T4 levels were quantified on an e602 analyser (ECLIA, Roche Diagnostics) and were respectively 265 nmol/L and 267 nmol/L (95 % RI: 66–181 nmol/L) for the mother and her daughter.

Genetic HSA variants present a substitution of the arginine residues in position 218 or 222 and of the lysine in position 66, causing familial dysalbuminemic hyperthyroxinemia and hypertriiodothyroninemia, respectively. The most common mutation found in FDH is a substitution of arginine 218 with histidine (R218H) and produces conformational changes creating a high affinity site for T4 [6]. The presence of high affinity HSA variants is probably underdiagnosed; Dieu et al. identified the variant R218H in 18 % of French patients referred for a suspicion of RTH without the presence of a thyroid hormone receptor β gene variant [8]. In addition, the allele frequency of R218H in the global population is 0.03274 % (gnomAD v3.1.2) according to the Genome Aggregation Database. The FDH patients present an increase in total TH concentration with a normal TSH response to the TRH administration [6]. Free T4 levels can be elevated depending on the analytical platform used. Assays based on the competition of a T4 analog tracer with unbound T4 can yield to apparent high free T4 levels because albumin binding with the T4 analog is enhanced in FDH. Theoretically, two steps assays should be less impacted in FDH due to the absence of contact between the T4 analog tracer and HSA variant. Different authors studied the susceptibility of common free T4 immunoassays in FDH patients and found that two steps assays (Abbott) seemed to be less impacted by the presence of a high affinity HSA variant compared with one step assays [9]. On the contrary, Li et al. described high free T4 levels in a R218H patients whatever the test design used, highlighting that FDH could not be solely identified by comparing free T4 values measured by one step vs. two steps assays [4]. Beside the

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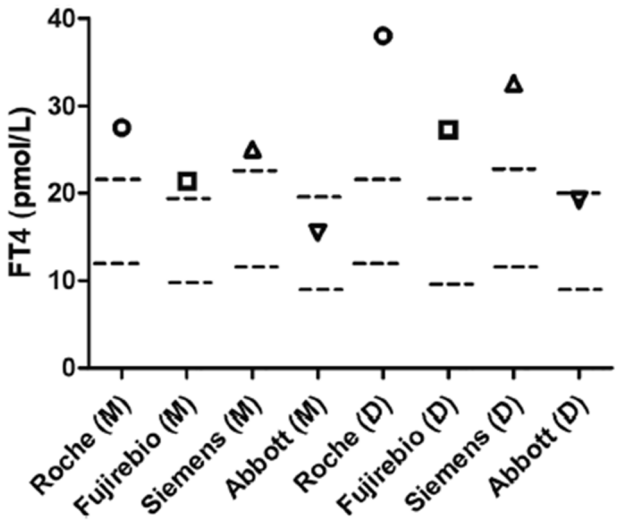
impact of the assay design, the normal free T4 concentrations measured in our patients with the two steps assay could also be attributed to the fact that the Abbott assay measured markedly lower free T4 levels compared to other immunological and mass spectrometry methods [10]. In addition, some two steps methods are altered in FDH because they use inhibitors of T4 binding to albumin (i.e. chloride) that will release a higher amount of the T4 for FDH samples [9].
Designing immunoassays for free T4 measurement is indeed complicated as the equilibrium between the free and bound hormone can be easily altered by small changes in temperature, pH or buffer composition [10].

Figure1*: Concentrations of free thyroxine (FT4 in pmol/L) measured with different assays in the mother (M) and her daughter (D). The dashed lines represents the reference values provided by each manufacturer. The free T4 levels measured for the mother on the Fujirebio, Siemens and Abbott platforms were respectively: 21.4 pmol/L (RI: 9.7–19.8 pmol/L), 25 pmol/L (RI: 11.5–22.7 pmol/L), 15.5 pmol/L (RI: 9–19.5 pmol/L) and, for the daughter: 27.3 pmol/L (RI: 9.7–19.8 pmol/L), 32.6 pmol/L (RI:11.5–22.7 pmol/L),19.2 pmol/L (RI: 9–19.5 pmol/L). For all methods except the Alinity from Abbott Diagnostics, free T4 concentrations were above the normal RI.*



We reported the case of a 55-year-old Belgian woman presenting a Grave's disease associated with FDH (R218H). As the prevalence of hyperthyroidism ranges from 0.2 to 1.3 %, it is not surprising

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to find both conditions coexisting. The presence of genetically proved FDH in a patient with Grave's disease was described by few authors [4, 5]. For the two cases previously published, the patients were females carrying the R218H HSA variant.

In conclusion, FDH is a syndrome that is probably underestimated given the frequency of the R218H allele in the population. This condition may be suspected in patients, usually clinically euthyroid, having an increase in total TH, possibly accompanied by an elevated free TH concentration, with a TSH within normal limits. The high concentration of total TH allowed to exclude free TH tests abnormalities due to drugs that alter the binding between TH and their binding proteins [7]. Due to the lower frequency of RTH (incidence of 1:40,000) and TSH adenoma (incidence of 1:1,000.000 individuals), FDH should be excluded before considering those rare thyroid disorders.

The comparison of free T4 levels measured by one step vs. two steps assays is not particularly useful given that the operating conditions seems to have a greater impact on the final free T4 concentration than the type of assay design. The final diagnosis requires a sequencing of HSA gene to avoid inappropriate treatment.

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Research ethics: The local Institutional Review Board deemed the study exempt from review.

Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.

Author contributions: Wolff Fleur wrote the draft. Fery Françoise and Désir Julie gave all the clinical data (case description and genetics results). Gadisseur Romy, Cavalier Etienne and Cotton Frédéric reviewed the letter to editor. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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