Letter to the Editor

False hypercortisolemia due to abnormal albumin-cortisol binding in a patient with familial dysalbuminemic hyperthyroxinemia

Running title: Hypercortisolemia with FDH

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Dear Editor,

The report of familial dysalbuminemic hyperthyroxinemia (FDH) due to Pro^{218} (R218P) mutant albumin that caused hypercortisolemia in Swiss family members by Moran et al. (1) was of great interest to us. FDH subjects with R218P have been reported in Swiss and Japanese families (2)(3), and here, we report to our knowledge the first Japanese FDH case of false hypercortisolemia.

A 46-year man, previously diagnosed with FDH due to R218P (TSH 2.2 mU/L, FT3 8.2 pmol/L, FT4 >103.0 pmol/L) by genetic testing (3), developed hypercortisolemia with normal adrenocorticotropic hormone (ACTH) level (ACTH 14.2 pmol/L, cortisol 957.3 nmol/L) during an investigation for Parkinson's syndrome and was referred to our department for further examination. His cortisol level was 195.9 nmol/L at midnight and 411.1 nmol/L after a low dose dexamethasone overnight test. ACTH and cortisol responded to CRH load, although basal and peak cortisol levels were high (976.6 and 1487.0 nmol/L, respectively). A high dose dexamethasone overnight test showed suppressed ACTH and cortisol levels, and MRI showed no obvious pituitary adenoma. Despite a significantly high cortisol level, no Cushing signs or metabolic abnormalities were observed and urinary free cortisol was within the normal range (30.7 μg/day),

suggesting the presence of factors affecting the laboratory testing. We removed albumin from the patient serum using an immunoprecipitation method (Pierce Direct Magnetic IP/Co-IP Kit; Thermo Fisher Scientific, Waltham, MA, USA) and anti-albumin antibody (Proteintech, Rosemont, IL, USA). Cortisol levels were measured by LC-MS/MS performed using a Dionex Ultimate 3000 liquid chromatography system coupled to a TSQ Quantum Access Max triple stage quadrupole mass spectrometer containing a heated-electrospray ionization (HESI-II) probe (Thermo Fisher Scientific).

His serum cortisol decreased by 38% after removing albumin despite unremarkable changes in the controls such as ectopic ACTH syndrome, primary hyperparathyroidism and resistance to thyroid hormone beta (Table 1), suggesting the binding rate of cortisol to mutant albumin in the patient was increased, leading to false hypercortisolemia.

R218P causes a missense mutation (G to C) of the same nucleotide, which leads to the replacement of normal Arg218 with a proline. This mutation results in the presence of a restriction site for *Ava*II (4). The presence of R218P is characterized by extremely high concentrations of total T4 compared with other FDH types. Regarding cases of R218P, moderate conformational changes are combined with a concomitant distortion of the helix main chain, which promotes the translation of T4 toward the mutated residue. This closer contact results in very strong T4 binding (5).

In our patient, the binding rate of cortisol to mutant albumin might be increased, leading to false hypercortisolemia, and the degree of cortisol reduction after albumin removal was similar to that of the Swiss case. Our case highlights Japanese individuals with FDH due to R218P mutant albumin develop hypercortisolemia, confirming the results of the Swiss case. More detailed molecular studies on cortisol binding to albumin are required.

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Author Contribution statement

Koki Chiba and Hiraku Kameda wrote the manuscript. Shigeki Jin and Kotaro Matoba measured cortisol levels. All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

Author Disclosure Statement

The authors have nothing to disclose.

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Table 1. Cortisol levels after pre/post albumin removal.

Case	Pre-cortisol (nmol/L)	Post-cortisol (nmol/L)	% Change
This study	1117.3	692.5	−38.0
Control 1	1131.1	1087.0	−4.0
Control 2	168.3	231.7	38.7
Control 3	63.5	69.0	8.2

Pre-cortisol: amount of cortisol before removing albumin. Post-cortisol: amount of cortisol measured by LC-MS/MS after removing albumin by immunoprecipitation using an anti-albumin antibody. % Change: percentage change in cortisol before and after albumin removal. Control 1: ectopic ACTH syndrome. Control 2: primary hyperparathyroidism. Control 3: resistance to thyroid hormone beta.