Central Hypothyroidism related to Pituitary Adenomas:
Resistance to Central Hypothyroidism in patients with GH secreting pituitary adenomas.

下垂体腺腫と中枢性甲状腺機能低下症:
GH 産生下垂体腫患者は中枢性甲状腺機能低下症に抵抗性を示す。

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平成 31 年 1 月 23 日

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Abstract

Background: The most frequent cause of central hypothyroidism (CeH) is pituitary adenomas, but the mechanisms remain unclear. We investigated thyroid status and GH/IGF-1 in CeH in untreated patients with pituitary non-functioning and GH-secreting adenomas.

Methods: This was a retrospective cross-sectional study of cases collected from two Hospitals between 2007 and 2016. One hundred-thirty-nine cases of non-functioning (NFPA) and 150 cases of GH-secreting pituitary adenoma (GHPA) were analyzed. The correlations between the thyroid status, several clinicopathological parameters, and GH/IGF-1 were examined.

Findings: Twenty-four percent of NFPA patients had CeH. The severity did not correlate with tumor size and age, and all cases had normal TSH levels. In contrast, only 8.7% of GHPA patients had CeH; about half had normal TSH levels and about half had low TSH levels. Serum TSH levels in GHPA patients were significantly lower and free T4 (FT4) and free T3 levels were higher than those in NFPA patients. One-fourth of GHPA patients had normal FT4 levels and low TSH levels. In addition, serum FT4 levels and serum TSH levels were positively and negatively correlated, respectively, with serum IGF-1 levels. Furthermore, IGF-1 levels in patients with GHPA decreased with age.

Interpretation: 1) NFPA patients with CeH had TSH levels within a normal range. 2) GHPA patients were resistant to CeH, which may be a result of stimulated thyroid function by GH/IGF-1. 3) We found an age-dependent decrease in serum IGF-1 levels in a large cohort of GHPAs.

A. Introduction

Central hypothyroidism (CeH) is defined as hypothyroidism because of insufficient stimulation of the thyroid grand by TSH for which secretion and activity can be impaired at either the hypothalamic or pituitary level. The clinical manifestations of CeH are similar to those of primary hypothyroidism. A diagnosis of CeH is difficult because serum TSH cannot be used as a diagnostic marker: TSH levels can be low, normal, or even elevated in CeH patients. Although hypothalamic and pituitary disorders can induce central hypothyroidism, the most frequent cause is pituitary adenomas, which account for 60% of cases (1). A highly sensitive assay for serum TSH has been used for the last 20 years, but there are only several cases of treated or untreated pituitary adenomas were studied in the literature. In addition, the effect of secreted hormones from pituitary adenomas on thyroid hormone status remains unclear. In previous reports, 8% to 81% of 1,911 assessed patients with NFPA exhibited central hypothyroidism (2). However, because most of these reports referred only to the complication of central hypothyroidism, there is little information on serum TSH or thyroid hormone levels in patients with pituitary adenomas. In 1973, Faglia et al. reported that central hypothyroidism was associated with pituitary adenomas, but they included post-operation and radiation patients, and the assay for serum TSH was not sensitive, particularly for low values of TSH (3). Subsequently, a small number of cases of central hypothyroidism associated with acromegaly or non-functioning adenomas have been reported (4). Therefore, detailed changes in serum TSH and thyroid hormone levels in central hypothyroidism induced by pituitary adenomas remain unclear.

Patients with acromegaly exhibit increased thyroid vascularity compared with healthy individuals (5), and both thyroid size and nodularity are associated with disease activity and duration in acromegaly patients (6, 7). A clinical study evaluating the associations between GH administration and thyroid size as a function of serum TSH levels in hypopituitary patients indicated that IGF-1 not only independently stimulates thyroid growth but also enhances the proliferation of thyroid cells by potentiating the mitogenic effects of TSH (8). Organ-specific IGF-1 has substantial effects on thyroid morphology and function, but there is controversy on whether serum IGF-1 levels are associated with thyroid function and its disorders.

Here, we evaluated thyroid status in patients with pituitary adenomas, particularly in non-functioning pituitary adenomas (NFPAs) in which excess hormone secretion did not affect thyroid status, and investigated the association between serum GH/IGF-1 levels and thyroid
function in GH-secreting pituitary adenomas (GHPAs). We retrospectively reviewed thyroid status in untreated patients with NFPA and GHPA.

**B. Patients and Methods**

*Study population and design*

We retrospectively reviewed the medical charts before the operation of 288 patients with pituitary adenomas (139 patients with NFPA and 149 patients with GHPA) operated between 2007 and 2016 at Gunma University Medical hospital or Toranomon Hospital. All patients taking medication of thyroid hormone and concomitant primary hypothyroidism or primary hyperthyroidism were excluded. Basal hormone measurements were performed for all patients, and in some patients, complete dynamic testing for the pituitary-gonad, pituitary thyroidal, and pituitary-adrenal axes, and GH reserve was performed. GHPA was diagnosed by a lack of suppression of nadir serum GH <1 ng/mL in a 75 g oral glucose tolerance test (OGTT) (9) and clinical manifestations.

Patients were divided into four groups according to the thyroid hormone and serum TSH levels before the operation: Group 1, normal serum FT4 and serum TSH levels; Group 2, normal FT4 and low TSH levels; Group 3, low FT4 and normal TSH levels; and Group 4, low FT4 and low TSH levels. There was no patient with either high FT4 or high serum TSH. Diagnosis of CeH was made on the basis of a low FT4 level, which corresponded to Groups 3 and 4 (Fig. 1).

Some patients were receiving hormonal replacement treatments. Specifically, 12/139 (8.7%) and 2/149 (1.3%) patients in the NFPA and GHPA groups, respectively, were treated with physiological doses of cortisone acetate/hydrocortisone (10–20 mg/day). Furthermore, 1/139 and 0/149 in the NFPA and GHPA groups, respectively, were receiving a nasal DDAVP injection.

Neuroradiological studies included magnetic resonance imaging. The presence of a microadenoma (maximum diameter, less than 10 mm), a macroadenoma (maximum diameter, more than 10 mm), and the maximum diameter of the tumor were recorded.

*Ethical approval*

The studies were conducted in accordance with the principles of the Declaration of Helsinki and were approved by the Ethics Committee on human research of Gunma University (Approval number 535: Gunma University Human Genome Ethics Committee).
Hormones assay

Serum TSH was measured by an immunoradiometric assay (IRMA) method using LUMIPULSE g (forte) (FUJIREBIO) for TSH, FT3, and FT4 with detection limits of 0.003-200 µU/mL, 0.1-30.0 pg/mL, and 0.05-10.0 µg/dL, respectively. The reference ranges for TSH, FT3, and FT4 were 0.54-4.26 mU/mL, 0.72-1.52 ng/dL, and 2.29-4.17 pg/dL, respectively. Serum GH and IGF-1 were also measured by IRMA methods (TOSOH E test TOSOH II and BML, respectively), and the reference ranges were 2.10 ng/mL or less (10). All other biochemical parameters were analyzed according to standard laboratory methods.

Statistical analysis

Data on hormone levels from clinical studies were expressed as medians (interquartile range). Comparisons of proportions were made with the Pearson Chi-square test, and comparisons of the continuous variables between two groups were made with the non-parametric Wilcoxon test as all the variables analyzed did not show a normal distribution. Independent effects of parameters on hormone profile at diagnosis were tested by a multiple logistic stepwise regression analysis. The odds ratio was calculated using a logistic regression model. JMP pro version 12.0.1 was used for all statistical analyses. Differences were considered significant if \( p < 0.05 \).

C. Results

Patient profiles with pituitary adenomas

The patient profiles, laboratory data, and MRI studies are summarized in Table 1. The mean age of NFPAs was slightly higher than that of GHPAs (53.6 ± 13.2 vs. 47.6 ± 13.8 years, mean ± SD). The sex of NFPAs and GHPAs did not significantly differ (male percentage, 53.2 vs. 46.9%). The percentage of microadenomas was significantly lower in the NFPAs (4.5%) compared to that in GHPA (37.1%). As expected, median serum GH levels in GHPAs (11.03 (5.11-24.33) ng/mL) were significantly higher than that in NFPAs (0.18 (0.08-0.50) ng/mL). Median serum IGF-1 levels in GHPAs (624.50 (491.50-838.50) ng/mL) were significantly higher than in NFPAs (117.65 (76.55-160.00) ng/mL). Median serum cortisol levels did not significantly differ between patients with NFPA (11.2 (7.6-14.4) ng/mL) and GHPA (12.0 (9.1-15.1) ng/mL). Median serum testosterone levels in male patients also did not significantly differ between patients with NFPA (187.0 (54.5-382.8) ng/mL) and GHPA (278.0 (144.9-361.8) ng/mL).
Central hypothyroidism (CeH) induced by NFPAs showed normal serum TSH levels.

We first examined thyroid status in patients with NFPAs and classified them into four groups according to serum TSH and FT4 levels. As shown in Fig 1a, among 139 patients with NFPA, 70.5% of patients showed normal thyroid function with normal serum TSH and FT4 levels. In the remaining 29.5% of patients, about one-fourth of patients (24.5%) exhibited CeH with low FT4 levels.

Among these CeH patients, 94.1% had normal TSH levels (Group 3), and only 5.9% had low TSH levels (Group 4). Two patients in Group 4 were a 61-year-old male with a microadenoma and a 33-year-old male with a 15-mm adenoma. Their serum TSH levels were 0.145 and 0.264 μU/mL, respectively. The former patient was treated with 5 mg/day of hydrocortisone, and the pituitary adenoma in the latter patient was immunopositive for GH, PRL, and FSH. Therefore, after exclusion of these two cases, all CeH induced by NFPA had serum TSH levels within a normal range.

Furthermore, only seven patients (5.0%) with NFPA belonged to Group 2 with normal FT4 levels but low TSH levels. Among these seven patients, three patients received replacement therapy with hydrocortisone, and five were male with macroadenomas.

Patients with GHPA showed resistance to central hypothyroidism

Next, we examined the thyroid status of 149 patients with GHPA. The percentage of CeH in GHPA patients was lower (8.7%) compared to that in patients with NFPA (Fig. 1b). Median GH levels were 11.0 (5.11-23.82) ng/mL in Group 1, 10.94 (4.99-29.65) ng/mL in Group 2, 11.9 (10.91-23.31) ng/mL in Group 3, and 14.38 (5.14-21.36) ng/mL in Group 4. Statistical analysis revealed that patients with GHPA were significantly resistant to CeH compared to those with NFPAs with an odds ratio of 0.29 (95% CI: 0.13 to 0.62, p < 0.01) after adjusting for age, sex, and tumor size. Furthermore, in contrast to CeH in NFPAs with normal serum TSH levels, about half of CeH in GHPA (53.8%) had TSH levels within a normal range (Group 3), and about half (46.2%) had low TSH levels (Group 4). In contrast to NFPAs, about one-fourth (23.5%) of the patients with GHPA had low TSH levels and normal FT4 levels (Group 2). Overall, the thyroid profiles of patients with GHPA differed from those of patients with NFPA.

Thyroid status in patients with NFPA and GHPA.

A comparison of serum TSH and thyroid hormone levels among pituitary adenomas revealed
that median serum TSH levels in GHPAs were significantly lower than those in NFPAs (1.59 (0.99-2.19) and 0.691 (0.481-1.07) µIU/mL, n = 139 and n = 149, \( p < 0.01 \), respectively) (Fig. 2a and Table 1). Serum FT4 levels in GHPAs (median 0.99 (0.85-1.1) ng/mL) were significantly higher than those in NFPAs (0.88 (0.73-1.0) µg/dL, \( p < 0.01 \)) (Fig. 2b and Table 1). In addition, serum FT3 levels in GHPAs (3.3 (2.99-3.62) pg/mL) were significantly higher than those in NFPAs (2.84 (2.57-3.1) pg/mL, \( p < 0.01 \)) (Fig. 2c and Table 1), but the FT3/FT4 ratio did not differ between the two groups (Fig. 2d). These findings suggested that the increased serum thyroid hormone levels may downregulate serum TSH levels in patients with GHPA, and that a high level of GH and/or IGF-1 may increase thyroid hormone production in thyroid glands.

**Effect of serum growth hormone and IGF-1 levels on thyroid status**

Next, we evaluated the relationship between thyroid status and GH and IGF-1 levels in all cases. As shown in Fig 3a and 3b, serum TSH levels were negatively correlated with serum GH and IGF-1 levels, particularly serum IGF-1 levels (\( r = -0.39, p < 0.01 \)). Serum FT4 levels were weakly but significantly positively correlated with serum IGF-1 levels (\( r = 0.27, p < 0.01 \)) (Fig. 4d), but not with serum GH levels (\( r = 0.11, p = 0.06 \) (Fig. 3C). Furthermore, as shown in Fig 3e and f, serum FT3 levels more significantly correlated with IGF-1 levels (\( r = 0.44, p < 0.01 \)) and than with GH levels (\( r = 0.23, p < 0.01 \)). These correlations were also observed when examined only in NFPA patients where serum GH and IGF-1 levels were almost within a normal range (Sup. Fig. 1). Taken together, these findings suggested that a high concentration of serum IGF-1 may stimulate thyroid hormone production in the thyroid gland and enhance conversion of T4 to T3, which decreased serum TSH levels in GHPA patients.

**Effect of tumor size on hormone levels**

We evaluated the effect of tumor size on hormone levels in patients with GHPA because almost all NFPAs examined in this cohort were macroadenomas. Because it was difficult to measure tumor size in several cases, we classified patients into groups with tumor sizes greater or lesser than 10 mm and analyzed GH/IGF-1 and thyroid hormone levels.

As shown in Fig. 4a, serum GH levels in patients with a tumor size less than 10 mm were significantly lower than in patients with tumor size over 10 mm. A similar tendency was observed for IGF-1 levels; serum IGF-1 levels in patients with a tumor size of 30-39 mm were significantly higher than in patients with a tumor size under 29 mm, which suggests that larger
tumors secreted more growth hormone. On the other hand, as shown in Fig. 4c and 4d, although serum TSH and FT4 levels in macroadenomas were lower than in those in microadenomas, there was no significant difference among all groups, except that the serum TSH levels in patients with a tumor size under 20 mm were significantly higher than in patients with a tumor size of 40-49 mm. These findings suggested that tumor size weakly affected thyroid levels in patients with GHPA.

**Relationship between age and serum IGF-1 levels**

There is a negative correlation between age and serum IGF-1 levels in healthy subjects (10). Therefore, we examined the relationship between age and serum IGF-1 levels in patients with NFPA and GHPA. As shown in Fig. 5a, a negative correlation between serum IGF-1 levels and age was observed among all patients with NFPA and GHPA. In patients with NFPA whose IGF-1 levels were in the low-to-normal range, serum IGF-1 levels were negatively correlated with age (r = -0.38, n = 139, p < 0.01) (Fig. 5b). Surprisingly, this relationship was also observed in patients with GHPA. Serum IGF-1 levels were negatively correlated with age (r = -0.47) (Fig. 5c) and had a stronger correlation than in NFPA patients (Fig. 5d). These findings showed that even in GHPA secreting excess GH autonomously, age was the major parameter for determining serum IGF-1 levels.

**D. Discussion**

We found that approximately 30% of patients with pituitary adenomas had either abnormal serum TSH or thyroid hormone levels. About one-fourth of the patients with NFPA had CeH with low FT4 levels. Recent reports since 2000 showed the prevalence of NFPA patients with CeH is 12–43% (11-15), which is comparable the frequency in this study.

Faglia et al. reported that TSH levels were undetectable in 35% of patients, within a normal range in 41%, and above a normal range in 24% of 89 CeH patients with various pituitary diseases (3). We found that almost all NFPAs represented serum TSH levels within a normal range. Previously, we cloned human and mouse TRH genes and established TRH-deficient mice, which showed typical tertiary hypothyroidism with low serum thyroid hormone levels but slightly elevated serum TSH levels (16). In these mice, a TRH test revealed an exaggerated response of serum TSH, but the increase of serum T3 in response to elevated TSH was significantly impaired, indicating reduced biological activity of serum TSH (3). Adenomas may cause increased intrasellar pressure, which leads to the compression of portal vessels and
impairs the delivery of hypothalamic hormones including TRH to the anterior pituitary. Therefore, central hypothyroidism caused by the mechanic pressure by pituitary adenomas show normal serum TSH levels with low FT4 levels.

In contrast to the high prevalence of CeH in patients with NFPA, we found CeH in only 8% of patients with GH-secreting adenomas. TSH deficiency complications increase in NFPA patients with tumor size (12, 17). Although tumor sizes in NFPA were larger than those in GHPA, we found no significant difference in serum TSH levels and thyroid hormone levels with tumor size. Furthermore, GHPA patients had significantly decreased TSH levels and significantly increased thyroid hormone levels compared to those in NFPA patients, even for GHPA and NFPA patients with only macroadenomas (Sup. Table 1). Central hypothyroidism from pituitary adenoma is also observed in microadenomas of non-functional, ACTH-secreting, and prolactin-secreting pituitary adenoma (17, 18). Therefore, the difference in CeH prevalence was a result of factors other than tumor size.

What are the factors that affect thyroid status in patients with GHPA? We investigated the correlation between serum GH and IGF-1 levels and serum TSH, FT3, and FT4 levels. There were significant correlations, particularly between IGF-1 and FT3 levels. This was further supported by Wu et al. showing that in patients with acromegaly, the group with higher serum IGF-1 levels had elevated serum thyroid hormone levels, especially FT3 levels (7). A similar change of thyroid function was observed when growth hormone deficiency (GHD) patients were treated with recombinant human GH (rhGH) therapy, which reduced reverse-T3 (rT3) and increased the T3/T4 ratio after rhGH administration (19-24). Conversely, in untreated GHD patients, a decreased conversion of T4 to T3 was observed with an increased rT3 (25). These findings suggest that extra-thyroidal conversion of T4 to T3 was upregulated by GH and IGF-1. In acromegaly patients, serum TSH levels are increased, and serum T3 levels and the T3/T4 ratio are decreased after transsphenoidal surgery (TSS) (26). We also showed that serum TSH levels in GHPA patients were significantly lower than in NFPA patients. In fact, patients classified into Group 4 with low TSH levels and normal FT4 levels were significantly more common in GHPAs than in NFPA. However, Karlberg et al. demonstrated that the diminished TSH response to TRH only occurs in acromegalic patients, not in patients with NFPA and prolactinoma (27). Taken together, excess GH/IGF-1 increased the conversion of T4 to T3, and then T3 negatively regulated TSH production and synthesis in the pituitary.

In acromegaly patients, 25-70% of patients have thyroid goiter, which is a result of chronically elevated IGF-1 levels because elevated IGF-1 levels positively correlate with
thyroid volume (28-31). Therefore, IGF-1 may increase thyroid volume, which increases thyroid hormone levels. These findings suggest that long-term exposure to excessive GH and IGF-1 may cause an increase in thyroid hormone levels. IGF-1 induces thyroid hyperplasia in transgenic mice overexpressing IGF-1 and the IGF-1 receptor (32). Furthermore, an in vitro study demonstrated synergistic cell proliferation induced by TSH and IGF-1 using FRTL-5, a non-transformed line of rat thyroid follicular cells (33). Prolonged pretreatment of cells with TSH or other agents that increased intracellular cAMP potentiated DNA synthesis induced by IGF-1. Prolonged cAMP or IGF-1 stimulus induces phosphatidylinositol (PI) 3-kinase activation through a novel mechanism, which potentiates DNA synthesis in FRTL-5 cells (34). IGF-1 induces the proliferation of WRT cells, a thyroid epithelial cell line from Wister rats (35). These findings suggest that long-term excessive IGF-1 promotes the proliferation of thyroid follicular cells and increases thyroid hormone synthesis.

We found an age-dependent decrease in serum IGF-1 levels in GHPA patients similar to that in healthy subjects. An increase in GH resistance with age in the normal population was suggested by Lieberman et al. (36), but A. J. van der Lely et al. reported that both serum GH and IGF-1 levels were negatively correlated with age in acromegaly. We found a weak correlation between serum GH levels and age (\( r = -0.18, \ p = 0.026 \), data not shown), which suggests that the activity of acromegaly may be lowered in elderly patients (37). Further studies are needed to investigate this mechanism.

Several limitations need to be considered to interpret our findings. First, this study was a cross-sectional retrospective design and evaluated only symptomatic patients with GHPA and NFPA who needed TSS at two hospitals. Therefore, we may have overestimated the prevalence of CeH in patients with NFPA because of Berkson's bias (admission rate bias) and excluded asymptomatic acromegalic patients. Second, because we limited our investigation to overt cases of CeH with low serum FT4 levels, mild CeH with FT4 concentration in a normal range was not examined.

E. Summary

In conclusion, CeH is complicated in patients with NFPA, and serum TSH levels in CeH patients are within the reference range. In contrast to NFPA, thyroid function is better preserved in GHPA, and this difference is independent of tumor size, which may be a result of stimulated thyroid gland function by a high level of GH and/or IGF-1. Our data may be useful to manage pituitary adenomas, especially NFPA and GHPAs.
Acknowledgements

We thank all medical and co-medical staff and graduate students involved in patient care. This work was supported by JSPS KAKENHI Grants 16K15493, 23591345, and 20591087 (to M.Y.) and 16K19551 (to K.H.). This work was partially supported by the Advancing Care of Hypothalamic-Pituitary Dysfunction in Japan Study (to M.Y.) from the Japan Agency for Medical Research and Development, and the Research on Rare and Intractable Disease, Health and Labour Sciences Research Grants (to M.Y.).

Disclosure Summary The authors have nothing to disclose.
F. References


Effects of growth hormone on thyroid function are mediated by type 2 iodothyronine deiodinase in humans. *Endocrine*. 2018;59(2):353-63.


G. Figure Legend

Fig. 1 Thyroid levels in patients with NFPA and GHPA

Thyroid levels in patients with a) NFPA and b) GHPA were classified into four groups according to thyroid hormone and serum TSH levels before operation.

Group 1, normal serum FT4 and serum TSH levels; Group 2, normal serum FT4 and low serum TSH; Group 3, low serum FT4 and normal serum TSH; Group 4, low serum FT4 and TSH. The patients in Groups 3 and 4 were diagnosed as central hypothyroidism (CeH) because of low FT4 levels. CeH complications were found in 24.0% of patients with NFPA and 8.7% of patients with GHPA, which was significantly lower in patients with GHPA than in patients with NFPA.

Fig. 2 Serum TSH and thyroid hormone levels in NFPA and GHPA

Thyroid hormone levels were compared between patients with NFPA and GHPA. a) Serum TSH, b) serum FT4, c) serum FT3, and d) FT3/FT4 ratio are shown. The box plots show the median levels (middle horizontal line in each box), the interquartile range (delineated by the top and bottom of each box), and outlines falling below the 5th percentile or above the 95th percentile (points below or above the vertical lines, respectively).

Serum TSH levels were significantly lower in GHPA than in NFPA, whereas both serum FT4 and FT3 levels were significantly higher in GHPA than in NFPA. The FT3/FT4 ratio was not significantly different between NFPA and GHPA.

***, p < 0.01.

Fig. 3 Correlations between GH/IGF-1 and TSH and thyroid hormone levels

The correlations between each thyroid parameter (TSH, FT4, and FT3) and GH or IGF-1 in all patients with NFPA and GHPA. The correlations between a) serum TSH and GH (n = 283), b) serum TSH and IGF-1 (n = 266), c) serum FT4 and GH (n = 283), d) serum FT4 and IGF-1 (n = 266), e) serum FT3 and GH (n = 283), and f) serum FT3 and IGF-1 (n = 266). The diagonal line in the figure shows the approximate curve.

Fig. 4 Correlations between tumor sizes and serum GH and IGF-1 levels

Comparison of serum GH, IGF-1, TSH, and FT4 classified by tumor size in patients with GHPA. a) Serum GH levels, b) serum IGF-1 levels, c) serum TSH levels, and d) serum FT4 levels classified by tumor size are shown. The box plots show the median levels (middle
horizontal line in each box), the interquartile range (delineated by the top and bottom of each box), and outlines falling below the 5th percentile or above the 95th percentile (points below or above the vertical lines, respectively).

*, $p < 0.05$. **, $p < 0.01$. ***, $p < 0.001$.

Fig. 5 Correlations between age and serum IGF-1 and GH levels

The correlation between serum IGF-1 levels and age in patients with NFPA and GHPA. a) The correlation between serum IGF-1 levels and age in all patients ($n = 266$). A significantly negative correlation was found between serum IGF-1 levels and age ($p < 0.001$). b) The correlation between serum IGF-1 levels and age in NHPA patients ($n = 125$). c) The correlation between serum IGF-1 levels and age in GHPA patients ($n = 141$). A significantly negative correlation was found between serum IGF-1 levels and age ($p < 0.001$). The diagonal line in the figure shows the approximate curve. d) Combined figure of Fig. 5b) and c). Circles represent NFPA, and dots represent GHPA. The lower diagonal line shows the approximate curve for NFPA, and the upper diagonal line shows that for GHPA.

Supplemental Figure Legends

Sup. Fig. 1 Correlations between serum TSH and FT4 levels and GH/IGF-1

The correlations between thyroid parameters (TSH and FT4) and GH or IGF-1 in patients with NFPA. The correlations between a) serum TSH and GH ($n = 135$), b) serum TSH and IGF-1 ($n = 126$), c) serum FT4 and GH ($n = 135$), and d) serum FT4 and IGF-1 ($n = 126$). The diagonal line in the figure shows the approximate curve.
H. 発表予定論文

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Lancet Diabetes & Endocrinology（投稿中）

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