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Research

Does Growth Hormone Therapy Enlarge Pituitary Adenomas?

Büyüme Hormonu Tedavisi Hipofiz Adenomlarını Büyütür mü?

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ABSTRACT

Objective: Pituitary adenomas are detected incidentally in some cases of childhood growth hormone deficiency. Growth hormones may affect tumor growth. This study analyzed the reliability of growth hormone therapy in patients with non-functioning pituitary adenomas.

Methods: The study group included 16 hypopituitary patients with incidentally detected non-functioning pituitary adenoma and treated with recombinant growth hormone. Age- and sex-matched 16 healthy children with incidental pituitary adenoma detected during investigation of chronic headache were selected as the control group. The data of the two groups were retrospectively reviewed and compared regarding the change in adenoma size over time.

Results: Changes in adenoma size in the patient and control groups were -0.1 (-0.8-0.3) mm and -0.1 (-0.5-0.3) mm, respectively (p=0.664). Adenoma size growth was detected in 3 patients in the patient group and 5 patients in the control group (p=0.685).

Conclusion: Our data suggest that recombinant growth hormone therapy does not produce pituitary adenomas, and thus its use is safe in growth hormone deficient children with incidentally detected non-functioning pituitary adenomas.

Keywords: Growth hormone therapy, pituitary adenoma, pediatric endocrinology

ÖZ

Amaç: Hipofiz adenomları çocukluk çağı büyüme hormonu eksikliği olan bazı olgularında tesadüfen saptanır. Büyüme hormonu tümör büyümesini etkileyebilir. Bu çalışma, non-fonksiyone hipofiz adenomu olan hastalarda büyüme hormonu tedavisinin güvenilirliğini analiz etmektedir.

Gereç ve Yöntem: Çalışma grubuna, insidental olarak saptanan ve non-fonksiyone hipofiz adenomu olan ve rekombinant büyüme hormonu ile tedavi edilen 16 hipopitüitarizmli hasta dahil edildi. Kronik baş ağrısı incelemesi sırasında insidental olarak hipofiz adenomu saptanan yaş ve cinsiyet açısından uyumlu 16 sağlıklı çocuk kontrol grubu olarak seçildi. İki grubun verileri geriye dönük olarak incelendi ve adenom boyutunun zaman içindeki değişimi karşılaştırıldı.

Bulgular: Hasta ve kontrol gruplarında adenom boyutundaki değişiklikler sırasıyla -0,1 (-0,8-0,3) mm ve -0,1 (-0,5-0,3) mm idi (p=0,664). Hasta grubunda 3, kontrol grubunda 5 hastada adenom boyutunda büyüme saptandı (p=0,685).

Sonuç: Verilerimiz rekombinant büyüme hormonu tedavisinin hipofiz adenomlarını büyütmediğini ve bu nedenle insidental olarak saptanan non-fonksiyone hipofiz adenomu olan büyüme hormonu eksikliği olan çocuklarda kullanımının güvenli olduğunu göstermektedir.

Anahtar Kelimeler: Büyüme hormonu tedavisi, hipofiz adenomu, pediatrik endokrinoloji

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INTRODUCTION

Recombinant growth hormone (rGH) therapy is used for treating short stature resulting from GH deficiency or other diseases during childhood (1). The causes of GH deficiency include space-occupying lesions and structural defects of the pituitary, and so pituitary magnetic resonance imaging (MRI) is used as a routine part of etiological evaluation before treatment (2). Pituitary adenomas are incidentally detected at a rate of 0.5%-20.3% in cases of childhood GH deficiency (3,4). GH is a mitogenic agent, that increases the levels of insulin-like growth factor-1 (IGF-1). This, in turn, raises concerns about its potential to be involved in tumor development and tumor growth (5). There are few data on the effect of rGH treatment on pituitary non-functioning adenoma (NFA) in children (4). This study examines the effect of rGH therapy on adenoma sizes in children diagnosed with GH deficiency.

METHODS

We retrospectively reviewed the file records of 87 patients who presented to the pediatric endocrinology outpatient clinic between 2011 and 2021 due to short stature, and that were diagnosed with GH deficiency. NFA was detected in the pituitary MRI of 16 patients. Age- and sex-matched 16 healthy children with incidental pituitary adenoma detected during investigation of chronic headache were selected as the control group.

rGH treatment was given to the patient group at a dose of 29.8 (26.3-33.5) µg/kg/day. IGF-1 levels were between +1 standard deviation score (SDS) and + 2 SDS during the treatment periods. Diagnoses of GH deficiency were established on the basis of short stature (height SDS <-2), growth rate SDS <-1 and a low level of IGF-1 for the child's age; and a low response (peak GH <10 ng/mL) to two GH provocation tests (L-dopa and clonidine). All patients underwent a pituitary MRI (Magnetom Amira, Siemens Medical Systems, Forcheim, Germany) before starting GH therapy. The pituitary MRI examination involved the measurement of the anteroposterior long diameter on the sagittal T1-weighted sequence (Figure 1). In the patient group and control group, all patients had microadenoma (<10 mm). For all cases, other anterior pituitary functions were evaluated by measuring the levels of IGF-1, IGF-binding protein 3, prolactin, adrenocorticotropic hormone (ACTH), cortisol, free thyroxine (fT4) and thyroid-stimulating hormone (TSH). The control pituitary MR images of the patient group and control group were reviewed, and changes in the size of the pituitary adenomas were recorded. The adenoma sizes in all patents were measured and compared before, and during the final treatment, by the same experienced radiologist. Approval for this study was obtained from the Van Yüzüncü Yıl University Clinical Research Ethics Committee (decision no: 2019/17-13, date: 06.12.2019).

Statistical Analysis

Statistical analyses were performed using the SPSS software version 15. Descriptive analyses were presented using medians and interquartile range due to the small number of cases. The Mann-Whitney U test was used to compare adenoma sizes at baseline and follow-up between the patient and control groups. Fisher's Exact test was conducted to compare the ordinal variables between groups. Also, the Wilcoxon test was used to compare the change in adenoma size between baseline and follow-up in each one group. A p-value of less than 0.05 was considered a statistically significant result.

RESULTS

NFA was detected in 16 (18.3%) of 87 patients diagnosed with GH deficiency. In the patient group, 5 patients had multiple pituitary hormone deficiency (3 patients had GH-TSH; 1, GH-TSH-gonadotropin; and 1, panhypopituitarism). The remaining 11 patients had isolated GH deficiency. In the patient group with multiple pituitary hormone deficiency, screening of *PROP1, POU1F1, HESX1, LHX3, LHX4, and OTX2* genes did not show any pathogenic variation. As shown in Table 1, there were no statistically significant differences between the patient and control groups regarding age, gender, location of pituitary adenoma, follow-up duration, and adenoma sizes at baseline and follow-up. The median treatment duration was 3.1 (1.4-5.0) years in the patient group. The median durations of interval between first and last MRI were 1.2 (0.8-3.9) and 1.6 (1.0-2.3) years in patient and control groups, respectively (p=0.649). Changes in adenoma size in patient and control groups were -0.1 (-0.8-0.3) mm and -0.1 (-0.5-0.3) mm, respectively (p=0.664). Comparisons of adenoma sizes between baseline and follow-up in each one group showed no statistically significant difference. Adenoma size growth was detected in 3 patients (19%) in the patient group and 5 patients (31%) in the control group, but this difference was not statistically significant (p=0.685).

DISCUSSION

Replacement therapy is commonly used in children with GH deficiency, although concerns have been raised about the safety of GHs due to their potentially stimulating effect on tumor growth (6).

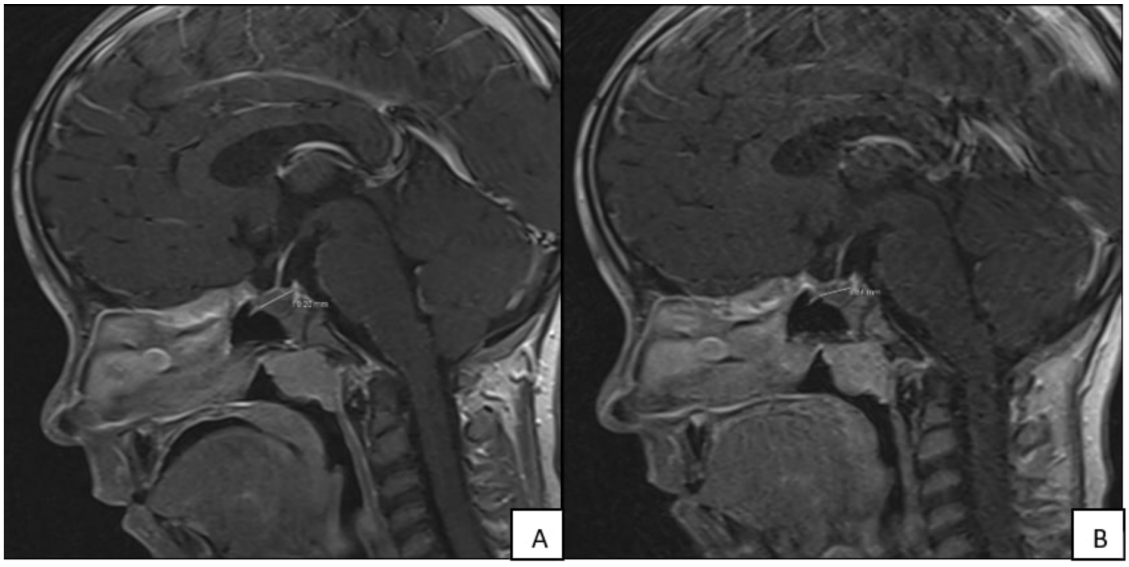

Figure 1. Pituitary MRI anterior-posterior image. A: before growth hormone therapy (10.2 mm), B: 1 year after growth hormone therapy (8.6 mm)
MRI: Magnetic resonance imaging

Table 1. Demographic data, and pituitary adenoma sizes at baseline and during follow-up

	Patient group (n=16)	Control group (n=16)	p-value
Age (years)	13.6 (10.7-14.5)	13.0 (12.2-15.4)	0.564
Gender (F/M)	6/10	7/9	0.719
Location of pituitary adenoma (C/R/L)	10/3/3	11/2/3	0.884
Duration of GH treatment (years)	3.1 (1.4-5.0)	-	-
Interval between first and last MRI (years)	1.2 (0.8-3.9)	1.6 (1.0-2.3)	0.649
Adenoma size at baseline (mm)	5.0 (3.5-5.1)*	4.3 (2.8-5.6)*	0.445
Adenoma size at follow-up (mm)	4.9 (3.5-5.6)*	4.3 (2.4-5.3)*	0.564
Change in adenoma size over time (mm)	-0.1 (-0.8-0.3)	-0.1 (-0.5-0.3)	0.664
Ratio of growing adenoma in size (%)	19	31	0.685

Data were presented using medians and interquartile range. *Comparisons of adenoma sizes between baseline and follow-up showed p-values of 0.22 and 0.795 in patient and control groups, respectively.

F: Female, M: Male, C: Central, R: Right, L: Left, MRI: Magnetic resonance imaging, GH: Growth hormone

NFAs can be detected on pituitary MRIs performed before GH therapy. Therefore, the possibility of GH therapy to enlarge concomitant pituitary adenoma is also of concern. Our study showed that GH therapy did not exert such an enlargement effect on concomitant pituitary adenoma size.

There have been very few studies addressing the effects of the GH treatment on adenoma size in childhood (4). In the study by Derrick et al. (4), the lesions did not grow after treatment in children with pituitary microadenoma who were treated with rGH and most of them were not observed on repeat imaging. In that study, the patient group was not compared with a control group that did not receive GH treatment. Additionally, it was reported that 17% of the patients did not start treatment because of the detection of NFA (4). Nonfunctional adenomas have potential disadvantages such as influencing the decision to initiate rGH treatment and patient/parent anxiety. Our study makes an additional contribution to the limited studies conducted on the effects of rGH treatment on NFA in children, and to the existing knowledge because it is a case-control study.

Basic research has shown that GH and IGF-1 are likely to play a role in tumor development and growth through cell proliferation and apoptosis regulation (6). Because of these effects of GHs, several studies have been conducted, but mostly with adults, regarding its reliability. The adult studies evaluating the effect of GH therapy, especially in NFA patients, were unable to establish any tumor growth or increased frequency of recurrence (6-9).

Buchfelder et al. (8) conducted a retrospective case control study to investigate the safety of GH in patients with NFA who were treated surgically. The authors identified no significant increase in tumor growth between the patients treated with GH and a control group who underwent no such treatment (8). Arnold et al. (7) evaluated the effect of GH therapy on tumor recurrence in 130 NFA patients who were treated only surgically and followed up at a single center. Tumor progression was noted in 35% of 23 patients undergoing GH therapy, and 36% of the 107 patients receiving no such therapy. Accordingly, the authors concluded that GH therapy did not cause progression (7). A previous meta-analysis of adults reported 10%-spontaneous growth of pituitary microadenomas (10). Previous adult studies investigating the effect of GH therapy on NFAs found them to contain more confusing factors (growth and pressure effects of NFA in advanced age and the development of other hormone deficiencies, possibility of surgical operation and radiotherapy due to pressure effects, etc.) compared to the pediatric patient group. We believe that the said study would provide more objective information on the pediatric patient group. The data in this study support the claim that GH therapy does not enlarge pituitary adenomas.

A previous meta-analysis used epidemiological, postmortem and radiological study data to estimate the prevalence of pituitary adenomas and reported an estimated prevalence of pituitary adenoma of 16.7% for the general population (11). A study of adults reported prevalence of microadenomas varying between 10% and 31.1% (10). Hirsch et al. (12), in turn, found microadenomas in 29% of children. A study by Derrick et al. (4) identified microadenomas in 20.3% of 261 patients with detected GH deficiency. A review of the Pfizer International Growth Database (KIGS database) examined 15,000 patients and identified pituitary microadenoma in 0.5% of the patients with GH deficiency (3). In this study, pituitary microadenomas were found in 16 (18.3%) of the 87 GH deficiency patients being followed up by our clinic. Our study presents new data on the incidence of microadenomas on pituitary MRIs of children with GH deficiency, and supports the study by Derrick et al. (4), which reported a relatively high rate. There is no clear difference in the prevalence of pituitary adenoma between the general population and GH deficiency patients. Nevertheless, the necessity to initiate treatment in patients with GH deficiency makes the pituitary adenoma more of a concern than it is for the general population (4). Therefore, in our study, we assessed whether such a concern is justified and observed that rGH treatment did not enlarge the size of pituitary adenomas and can be safely used in children with hypopituitarism and NFA.

Typical findings of microadenoma on a pituitary MRI include abnormal signal intensity on unenhanced images and delayed contrast enhancement after contrast administration (12). When a microadenoma is detected, the clinician must determine whether or not the tumor is functional. Functional microadenomas secrete extreme number of such pituitary hormones as, mostly, prolactin, and less frequently ACTH or GH (13,14). None of the children in the patient and control groups had any clinical signs of hormonal hyperfunction, and laboratory data showed that there was no hypersecretion of prolactin or ACTH. That said, NFAs may, theoretically, lead to hormone deficiencies through their mass effect on the adjacent pituitary tissue (13,14). Microadenomas are usually confined to sella turcica, and therefore, do not create a mass effect that can be detected through visual changes or other symptoms. Derrick et al. (4) demonstrated that pituitary microadenomas are common in cases of childhood GH deficiency; however, they are usually not the cause of the GH deficiency in childhood. In this study, most adenomas being microadenomas (<1 cm), their localization (not pressuring the stalk) and the lack of any identifiable visual changes gives the impression that it is not a prominent etiological factor.

The limitations of this study relate to its retrospective and the small number of cases.

CONCLUSION

As a result, this study identified non-functioning pituitary adenoma in 18.3% of children with GH deficiency. No significant difference was established in existing adenoma sizes after GH therapy. When the changes in adenoma size in both groups were compared, there was no significant difference. These data support the suggestion that GH therapy is safe in children with detected NFA, although there is a need for prospective randomized studies involving a larger number of cases.

ETHICS

Ethics Committee Approval: Approval for this study was obtained from the Van Yüzüncü Yıl University Clinical Research Ethics Committee (decision no: 2019/17-13, date: 06.12.2019).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.Ç.B., C.K., S.K., A.Y., Concept: E.Ç.B., C.K., O.T., Design: E.Ç.B., C.K., O.T., Data Collection or Processing: E.Ç.B., S.K., M.B., A.Y., Analysis or Interpretation: E.Ç.B., S.K., M.B., A.Y., O.T., Literature Search: E.Ç.B., S.K., M.B., A.Y., O.T., Writing: E.Ç.B., C.K., S.K., M.B., A.Y., O.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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