なクッシング徴候を呈するが，グルココルチコイド過剰分泌と正常分泌を繰り返す，周期性クッシング症候群を呈することがある．病理像は，色素沈着を伴う副腎皮質小結節の多発と，副腎皮質の萎縮像を示す．副腎皮質結節が自律的にグルココルチコイド過剰分泌することにより，ACTH 分泌が抑制され，副腎皮質萎縮をきたすと考えられている．

ACTH 非依存性大結節性副腎皮質過形成(ACTH-independent macronodular adrenocortical hyperplasia: AIMAH)は，副腎皮質における G 蛋白共役型受容体の異所性発現で生じると考えられている．40～50 代の発症が多く，小児では非常にまれである．病理像は，色素沈着を伴わない 5 mm 以上の結節の多発を示す．

McCune-Albright 症候群は体細胞モザイク *GNAS* 機能亢進変異で生じる．カフェオレ斑，線維性骨異形成および機能亢進型の内分泌障害が 3 主徴である．McCune-Albright 症候群に伴う内分泌障害として，クッシング症候群はまれである．McCune-Albright 症候群に伴うクッシング症候群は，生後 6 か月未満に発症することが多い．その約 4 割で，グルココルチコイド過剰分泌が自然に改善すると報告されている．

疫学

小児クッシング症候群全体の頻度は不明である．最も多い原因は医原性クッシング症候群である．小児の内因性クッシング症候群はまれである．全年齢の内因性クッシング症候群罹患率は 100 万人年あたり 2～5 人と推定されており，そのうち約 10% が小児期および青年期に発症する．

小児の内因性クッシング症候群は，年齢により原因疾患の割合が異なることが知られている．7 歳未満の小児では，副腎腫瘍(癌および腺腫)の割合が多い．7 歳以上では，クッシング病が大半を占める．小児クッシング症候群の原因として，異所性 ACTH 症候群，PPNAD，AIMAH や McCune-Albright 症候群はまれである．

症状

成人クッシング症候群の多くに認められるような中心性肥満，満月様顔貌，多毛，顔面紅潮，皮膚線条，高血圧，筋力低下，野牛肩，精神障害や面皰といった典型的な症状を小児でも呈する(表 2)．ただし，これらの症状がそろうのは，クッシング症候群が進行してからである．時に副腎癌や異所性 ACTH 症候群によるクッシング症候群は急速に症状が進行するが，多くの小児クッシング症候群は 5 年間以上かけて緩徐に症状が進行する．そのため，小児クッシング症候群ではしばしば典型的なクッシング様の外見を示さない．最も早期に現れ，かつ頻度が高い小児クッシング症候群の症状は，体重増加と成長率低下である．よってすべての成長率低下を伴う肥満児は，クッシング症候群を疑って評価する必要がある．単純性肥満では，逆に体重増加と成長率増加を示すことが多い．

表② 小児クッシング症候群の症状頻度

症状	頻度(%)
体重増加	92
成長障害	84
骨減少症	74
疲労感	67
高血圧	63
思春期遅発または停止	60
多血症	46
面皰	46
多毛	46
強迫行動	44
皮膚線条	36
紫斑	28
野牛肩	28
頭痛	26
骨年齢遅延	13
夜間頻尿	8

〔文献 2 より引用〕

小児クッシング症候群も成人と同じように精神障害を呈しうる．しかし，小児クッシング症候群の精神障害は典型的には強迫行動を示し，成人クッシング症候群が示すうつ病とは異なることに注意が必要である．また，小児クッシング症候群では過小評価される傾向にあるが，骨減少症の頻度が高いので注意が必要である．

診断(表 3，図 1)

小児のクッシング症候群の確立された診断基準はなく，成人の診断基準や小児クッシング症候群における検査感度および特異度を参考に診断を進めるほかない．

前述したように，クッシング症候群の最も多い原因は医原性クッシング症候群であり，診断検査を始める前に，まず医原性クッシング症候群を鑑別することが重要である．

クッシング症候群の診断は 2 つステップに分けられる．1 つ目のステップで，クッシング症候群であるか確定診断する．2 つ目のステップで，クッシング症候群の病型診断を行う．1 つ目のス

表③ クッシング症候群診断に使用される検査(＊は成人のデータ)

	検査名	判定基準	感度	特異度
確定診断	24 時間蓄尿中遊離コルチゾール	70 μg/m^2/ 日未満なら異常なし(3 日間)	88	90
	深夜血清コルチゾール	PM11:30 ～ 12:00 の間に検査 睡眠時　4.4 μg/dL 未満で異常なし	99	100
	2 日間少量デキサメタゾン抑制試験	デキサメタゾン 30μg/kg/ 日(最高 2mg) を分 4 で 2 日間内服．内服終了後 AM9 時の血清コルチゾール値 1.8 μg/dL 未満なら異常なし	94	ND
	一晩少量デキサメタゾン抑制試験	AM11 時にデキサメタゾン 15 μg/kg/ 日(最高 1mg) 内服．翌朝 AM8 時の血清コルチゾール値 1.8 μg/dL 未満なら異常なし	95*	80*
	深夜唾液中コルチゾール	PM11 時に採取．2.8 ng/mL 未満なら異常なし(最低 2 検体以上)	100	95.2
	少量デキサメタゾン抑制 -CRH 試験	デキサメタゾン 30μg/kg/ 日(最高 2mg) を分 4 で 2 日間内服．最終内服 2 時間後に CRH 負荷．その 15 分後の血清コルチゾール値 1.4 μg/dL 未満なら異常なし	98*	60*
病型診断	一晩大量デキサメタゾン抑制試験	PM11:00 にデキサメタゾン 120 μg/kg/dose(最高 8mg) 内服．翌朝午前 8 時の血清コルチゾールが前日の 0.8 倍未満ならクッシング病	97.5	100
	朝血中 ACTH	ACTH 5pg/mL 未満なら ACTH 非依存性 ACTH 29pg/mL 以上なら ACTH 依存性	68 70	100 100
	CRH 試験	CRH 1μg/kg/dose 静注後の血中 ACTH が 1.35 倍以上ならクッシング病	81	ND
	2 日間大量デキサメタゾン抑制試験	デキサメタゾン 120μg/kg/ 日(最高 8mg) を分 4 で 2 日間内服．24 時間蓄尿遊離コルチゾールが投与前の 0.1 倍未満ならクッシング病(異所性 ACTH 症候群との鑑別)	83*	100*
	選択的静脈洞サンプリング(海綿静脈洞，下錐体静脈洞)	血中 ACTH 中枢 / 末梢比が基礎地で 2 以上，CRH 負荷後頂値で 3 以上ならクッシング病(左右差の判定は 1.4 以上，異所性 ACTH 症候群との鑑別)	95*	93*

〔文献 3 より引用〕

テップでは，24 時間蓄尿中遊離コルチゾール(3 日間)，深夜血清コルチゾール，深夜唾液中コルチゾール(少なくとも 2 回)，一晩または 2 日間少量デキサメタゾン抑制試験や少量デキサメタゾン抑制 -CRH 試験などが用いられる．2 つ以上の検査を行ったほうが確実である．2 つ目のステップでは，まず，朝血中 ACTH を測定し，ACTH 依存性か ACTH 非依存性かを鑑別する．結果が確定的でない場合には，CRH 試験を行い，ACTH 反応の有無で鑑別する．ACTH 非依存性であった場合さらに画像検査を行い，病因を特定する．ACTH 依存性であった場合，さらに一晩または 2 日間少量デキサメタゾン抑制試験，CRH 試験，選択的静脈洞サンプリングや 画像検査を行い，クッシング病と異所性クッシング症候群を鑑別する．小児では異所性クッシング症候群がまれなため，クッシング病と異所性クッシング症候群を鑑別する検査の感度および特異度に関する信頼性の高いデータはない．

治療

医原性クッシング症候群の治療は基本的に ACTH やグルココルチコイド投与の中止であるが，原病のコントロールも合わせて考慮する必要がある．

クッシング病の治療としては，小児も成人と同じく経蝶形骨洞手術による腫瘍摘除が第一選択となる．前述のように，ACTH 産生下垂体腫瘍の多くはミクロアデノーマであり，術前に画像で局在を特定できるものは約半数である．そのため腫瘍のみの摘除は小児では難しく，治癒の割合は 45 ～ 78% と報告されている．選択的静脈洞サンプリングを併用することで治癒の確率を上げられるとする報告もある．経蝶形骨洞手術による腫瘍摘除の合併症としては，術後の下垂体機能低下症がある．経蝶形骨洞手術による腫瘍摘除以外の治療法としては，放射線療法と両側副腎摘除術がある．放射線療法に対する反応は成人よりも早いとされる．放射線療法には下垂体機能低下症，両側

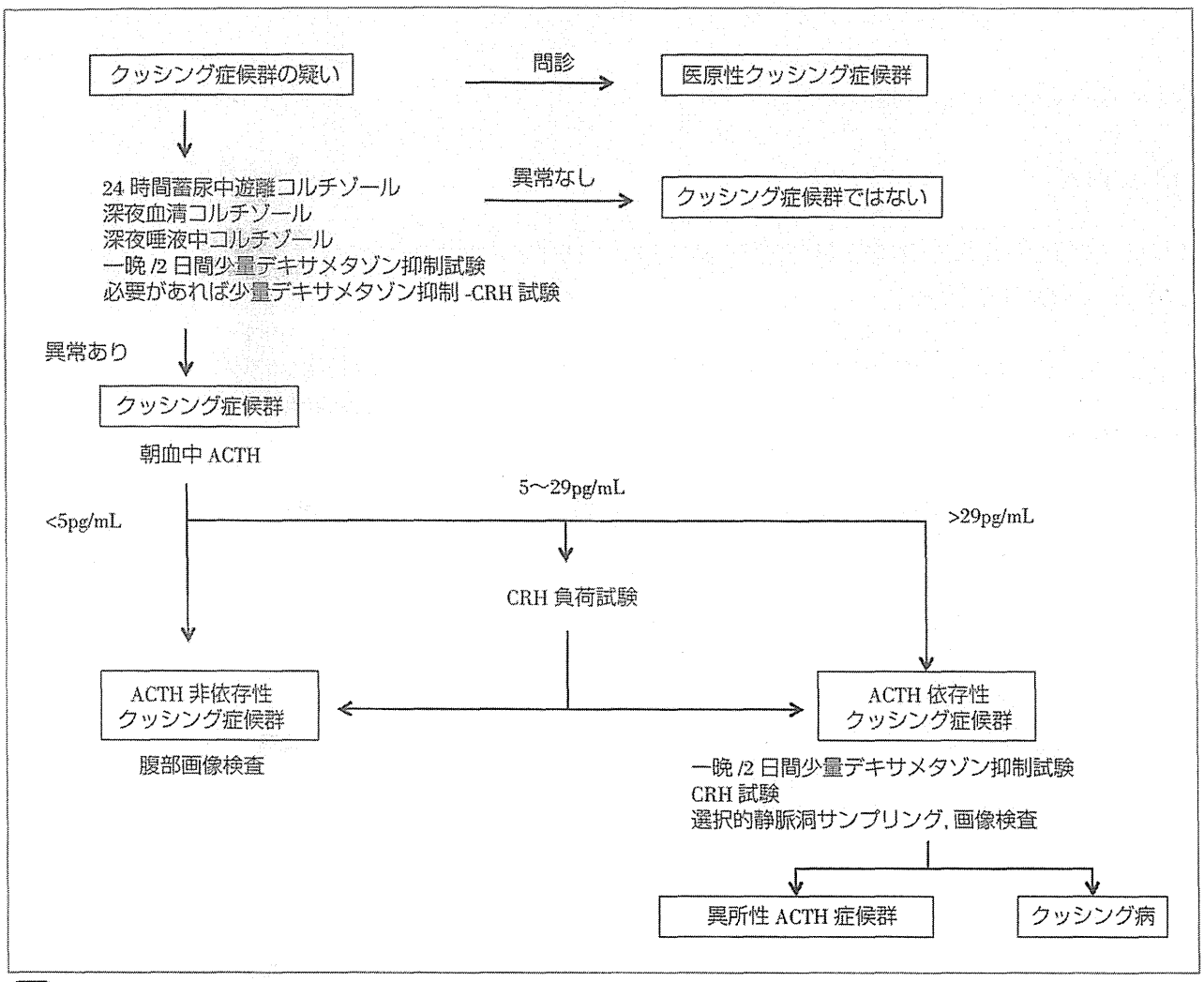

図1 クッシング症候群診断のフローチャート
〔文献 3 より引用〕

副腎摘除術にはネルソン症候群が合併する可能性がある．両側副腎摘除術後はグルココルチコイド補充療法が必要となる．

異所性クッシング症候群の治療は原因腫瘍により異なる．原因腫瘍が限局している場合には腫瘍摘除術で治癒可能である．

ACTH 非依存性クッシング症候群，すなわち副腎皮質病変が原因である場合は副腎摘除術が第一選択の治療法となる．副腎腫瘍の場合は患側の，PPNAD や AIMAH の場合は両側の副腎摘除術を行う．両側副腎摘除術周術期だけではなく，片側副腎摘除術周術期にも，健側の副腎皮質機能が抑制されているため，グルココルチコイド補充療法が必要である．手術前にコルチゾール濃度を改善させる目的でメチラポンなどの薬物治療を行うことがある．転移のある副腎癌に対しミトタンを含む化学療法を用いることがあるが，小児副腎癌に対する効果については結論が得られていない．

予後

内因性小児クッシング症候群の治癒後に，身長および体組成が正常化することは難しいと考えられている．治癒後に身長の catch-up を認めるが，成人身長は target height に達しないことが多い．また，小児クッシング症候群患者は治癒後も肥満であることが多く，その体脂肪量および内臓脂肪割合が高いと報告されている．一方，腰椎骨密度は治癒後 3 年で正常範囲内に改善することが多いとされる．

クッシング症候群の早期診断および早期治療が，身長および体組成の予後改善に重要と考える．

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ORIGINAL

The prevalence of acromegaly in hospitalized patients with type 2 diabetes

Kentaro Suda[1)], Hidenori Fukuoka[2)], Genzo Iguchi[2)], Yushi Hirota[2)], Hitoshi Nishizawa[1)], Hironori Bando[1)], Ryusaku Matsumoto[1)], Michiko Takahashi[3)], Kazuhiko Sakaguchi[2)] and Yutaka Takahashi[1)]

[1)] *Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Japan*
[2)] *Division of Diabetes and Endocrinology, Kobe University Hospital, Japan*
[3)] *Department of Nutrition, Kobe University Hospital, Japan*

Abstract. The prevalence of acromegaly is estimated to be 8–24/100,000, but several recent studies suggest it is underestimated. In particular, acromegaly is considered more prevalent in patients with type 2 diabetes mellitus (T2DM) than in the normal population. This study aimed to evaluate the prevalence of acromegaly in hospitalized patients with T2DM. A total of 327 hospitalized patients with T2DM were recruited as subjects. If serum insulin-like growth factor 1 (IGF-1) levels were found to be elevated, random GH level was measured or oral glucose tolerance test (OGTT) was performed. Five patients with elevated serum IGF-1 levels and random GH level or inadequate suppression of GH in the OGTT underwent pituitary magnetic resonance imaging. Of those patients, pituitary adenoma was detected in 2 patients. These 2 patients were diagnosed with acromegaly, as they also exhibited mild acromegalic features. Intriguingly, both these patients exhibited severe macroangiopathy and an absence of microangiopathy. The prevalence of acromegaly in the hospitalized patients with T2DM in this study was therefore 0.6%, suggesting a higher prevalence than that predicted. Although a large-scale prospective study is required to clarify the precise prevalence of acromegaly in hospitalized patients with T2DM, the present study shows that it is useful to screen hospitalized patients with T2DM for acromegaly by measuring their serum IGF-1 level.

Key words: Acromegaly, Type 2 diabetes, Glucose intolerance, Prevalence

ACROMEGALY is a rare disease characterized by excess secretion of GH and increase in the level of circulating insulin-like growth factor 1 (IGF-1). The disease is associated with several morbidities including cardiovascular diseases [1]. The prevalence of acromegaly is estimated to be 8–24/100,000 [2-4]. Owing to the slow onset and poor familiarity of non-specialist physicians with the disease, patients are often diagnosed in the advanced stage; therefore, acromegaly may be underdiagnosed [4-6]. Recent studies also suggest that the prevalence of acromegaly is underestimated. A simple questionnaire given to 17,000 patients in primary health-care clinics led to the estimated prevalence of acromegaly to be revised to 29/100,000 [7]. In another study, the results of screening of 6,773 adults from a general primary care population in Germany for serum IGF-1 levels suggested a prevalence of acromegaly as high as 103/100,000 [8].

Excessive secretion of GH in acromegaly induces insulin resistance [9]. In approximately 55% of the patients with acromegaly, the disease is complicated by type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (IGT) [10, 11]. On screening 2,270 Caucasian individuals with T2DM or IGT, GH-producing pituitary adenoma was detected in 3 patients (132/100,000 individuals), demonstrating that the prevalence of acromegaly in T2DM patients is higher than that in the normal population [12]. However, the prevalence of acromegaly in hospitalized patients with T2DM remains unclarified.

In this study, we analyzed the prevalence of acro-

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Correspondence to: Yutaka Takahashi, Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. E-mail: takahash@med.kobe-u.ac.jp

megaly in Japanese hospitalized patients with T2DM. We also investigated the status of micro- and macro-angiopathy in these patients.

Patients and Methods

Patients

This was a retrospective study. A total of 327 consecutive hospitalized patients with T2DM, diagnosed according to the criteria of the American Diabetes Association at Kobe University Hospital from April 2010 to March 2013 were analyzed. Generally, the patients were hospitalized because of poor glycemic control. Nine patients with pituitary disease or hyperthyroidism and 1 pregnant patient were excluded.

Protocol

For screening the patients, serum IGF-1 levels were measured on the second day after admission and IGF-1 SD score (SDS) were calculated according to the age- and sex-matched references [13], and if IGF-1 SDS was elevated, the oral glucose tolerance test (OGTT) was preformed, when it was considered necessary and safe. For the OGTT, serum GH levels were measured at 0, 30, 60, 90, and 120 min. If the OGTT was not performed, random GH level was measured. Patients with elevated serum IGF-1 and nadir GH levels >0.4 ng/mL in the OGTT [14] or random GH level >1.0 ng/mL further underwent pituitary magnetic resonance imaging (MRI) and were examined by an endocrinologist to check for the clinical characteristics of acromegaly. The complications of microangiopathy and macroangiopathy were evaluated in these patients as previously described. Retinopathy was diagnosed using bilateral digital images by an ophthalmologist, and staged as non-diabetic, simple, preproliferative, and proliferative [15]. Nephropathy was assessed by 24-h urine collection. Microalbuminuria and macroalbuminuria were diagnosed when the albumin content in the urine collection was more than 30 mg/day and more than 300 mg/day, respectively [16]. Neuropathy was assessed by reduction of Achilles tendon reflex, inability to sense vibration, and symptoms of neurological damages, and diagnosed by either abnormal nerve conduction in two different peripheral nerves [17], or unequivocally abnormal autonomic test results such as coefficient of variation in R-R intervals [18], or Shellong test [19]. The degree of carotid narrowing was assessed by carotid ultrasonography and the diagnosis of carotid stenosis was confirmed using carotid magnetic resonance angiography (MRA). Exercise treadmill testing and stress myocardial scintigraphy were performed to diagnose ischemic heart disease. The ankle-brachial pressure index and MRA findings of the peripheral artery were used to diagnose peripheral arterial disease.

Assays

Serum GH levels were measured by immunoenzymometric assay (Tosoh, Shiba, Japan) and IGF-1 levels, by immunoradiometric assay (Daiichi, Daiichi Isotope Research, Tokyo, Japan).

Results

We analyzed 317 consecutive hospitalized patients (184 men and 133 women; mean age, 60.7 ± 14.2 years) with T2DM. Acromegaly was not suspected by the physician who had treated diabetes at admission. The clinical profile, risk factors for arteriosclerosis, and diabetic angiopathies of these patients are described in Table 1. Twenty out of 317 patients (6.3%) exhibited elevated serum IGF-1 levels (Table 2); 6 out of 20 patients (cases 1–4, 6, and 7) underwent OGTT, and 4 patients showed nadir GH level of >0.4 ng/mL, indicating inadequate suppression of GH (Table 2). The other 14 patients did not undergo OGTT at the physician's discretion but were screened by the random GH level; 2 patients (case 4 and 5) had random GH levels >1.0 ng/mL. Five patients (cases 1–5, 1.6%) underwent pituitary MRI. Pituitary adenoma was detected in 2 (cases 3 and 4) out of 5 patients (0.6%) (Fig. 1), and the tumor sizes were 0.7×0.5×0.4cm and 0.6×0.4×0.6cm, respectively. At that time, the endocrinologist pointed out the mild acral changes in the face and extremities in cases 3 and 4. As a result, cases 3 and 4 were diagnosed with acromegaly (Fig. 2). Random GH levels were 0.49 ng/mL in case 3, and 1.15 ng/mL in case 4. Colon polyps and left ventricular thickness were detected in case 3. Both of these patients with acromegaly were treated with cabergoline therapy because of their mildly elevated IGF-1 levels and age.

We examined the extent of micro- and macro-angiopathy in these patients. Intriguingly, both of these patients had no microangiopathy associated with T2DM; however, these patients had advanced macroangiopathy: carotid artery stenosis, angina pectoris, and peripheral artery disease (Table 3). In addition to diabetes, dyslipidemia, and smoking were found to be

Table 1 Clinical characteristics including risk factors for arteriosclerosis and diabetic angiopathies in the patients with T2DM

Charecterictics and risk factors	Ratio or mean ± SD	Diabetic angiopathies	Ratio or mean ± SD
Gender (M/F)	184/133	Retinopathy (%)	42
Age (year)	60.7 ± 14.2	Simple diabetic retinopathy	18
T2DM duration (year)	11.2 ± 9.8	Preproliferative diabetic retinopathy	9
Body mass index (kg/m^2)	26.9 ± 5.9	Proliferative diabetic retinopathy	15
Fasting plasma glucose (mg/dL)	134.4 ± 44.9		
HbA1c (%)	8.9 ± 2.0	Creatinine clearance (mL/min)	88.9 ± 43.9
Systolic blood pressure (mmHg)	128.1 ± 19.4	Urine albumnin (mg/day)	167.5 ± 495.0
Diastolic blood pressure (mmHg)	70.7 ± 10.1	Urine protein (mg/day)	267.4 ± 698.7
Hypertension with medicine (%)	59	Nephropathy (%)	29
Total serum cholesterol (mg/dL)	181.7 ± 48.6	Microalbuminuria ≥30-299	18
Serum LDL cholesterol (mg/dL)	108.1 ± 36.4	Macroalbuminuria ≥300	11
Serum HDL cholesterol (mg/dL)	49.3 ± 14.5		
Serum triglycerides (mg/dL)	158.5 ± 236.6	Neuropathy (%)	37
Dyslipidemia with medicine (%)	48		
Smoking (%)	45	Carotid stenosis or stroke (%)	21
GH (ng/mL)	0.5 ± 1.0	Angina or myocardial infarction (%)	17
IGF-1 (ng/mL)	134.5 ± 60.6	Peripheral arterial disease (%)	14
IGF-1 SDS	-0.09 ± 1.47		

Table 2 Clinical features of the patients with elevated IGF-1 levels

No	Age (years)	Gender	BMI (kg/m^2)	HbA1c (%)	FPG (mg/dL)	GH (ng/mL)	IGF-1 (ng/mL)	IGF-1 (SDS)	Nadir GH (ng/mL)
1	34	F	34.4	7.7	186	<0.1	381	3.6	0.78
2	41	M	24.3	11.9	105	0.17	311	2.9	0.74
3	82	M	21.5	8.5	150	0.49	166	2.4	0.41
4	73	M	23.5	6.8	107	1.15	355	5.3	0.72
5	51	F	44.6	5.1	73	1.17	245	2.6	ND
6	65	M	22.5	9.3	91	0.22	247	2.5	0.11
7	65	F	26.7	7.5	76	0.15	200	2.3	0.16
8	64	M	27.0	10.2	199	0.3	226	2.1	ND
9	90	M	19.1	7.2	133	0.97	213	ND	ND
10	69	M	20.7	7	166	0.28	236	2.6	ND
11	62	F	30.4	10.7	174	0.54	218	2.4	ND
12	61	M	29.0	7.4	106	0.15	275	2.8	ND
13	74	M	27.4	9.3	134	<0.1	234	3.0	ND
14	62	F	31.9	6.4	95	0.17	219	2.4	ND
15	42	F	28.4	11	164	0.33	258	2.4	ND
16	28	M	23.6	6.6	120	0.38	328	2.2	ND
17	37	F	26.8	10.9	195	0.28	271	2.2	ND
18	71	F	24.5	9.1	103	0.17	280	4.0	ND
19	68	M	41.5	8.8	171	0.42	226	2.3	ND
20	40	F	32.0	11.1	201	0.56	277	2.6	ND

Four patients had nadir GH levels of >0.4 ng/mL on OGTT, and 2 patients showed random GH level >1.0 ng/mL.
ND, not determined

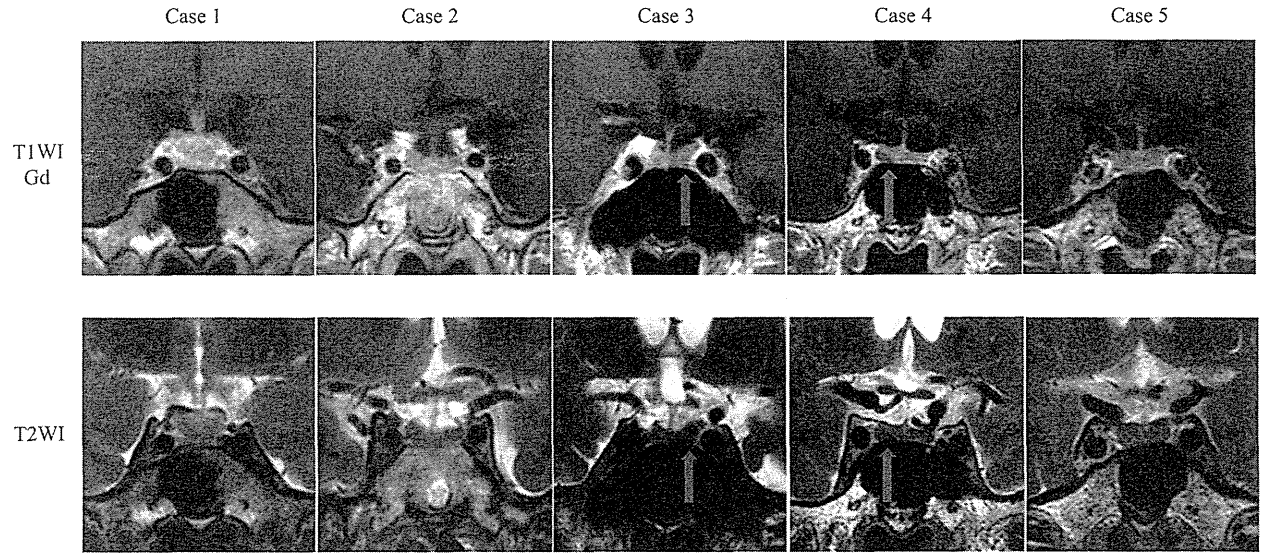

Fig. 1 Gd-enhanced pituitary MRI
No abnormalities were found in cases 1, 2, and 5. T2WI shows a low-intensity tumor in the left lobe of the pituitary with a midline shift of pituitary stalk in case 3. T1WI shows a low-intensity tumor in the right lobe of the pituitary in case 4. The tumor sizes were 0.7×0.5×0.4cm and 0.6×0.4×0.6cm, respectively. T2WI, T2-weighted imaging; T1WI, T1-weighted imaging

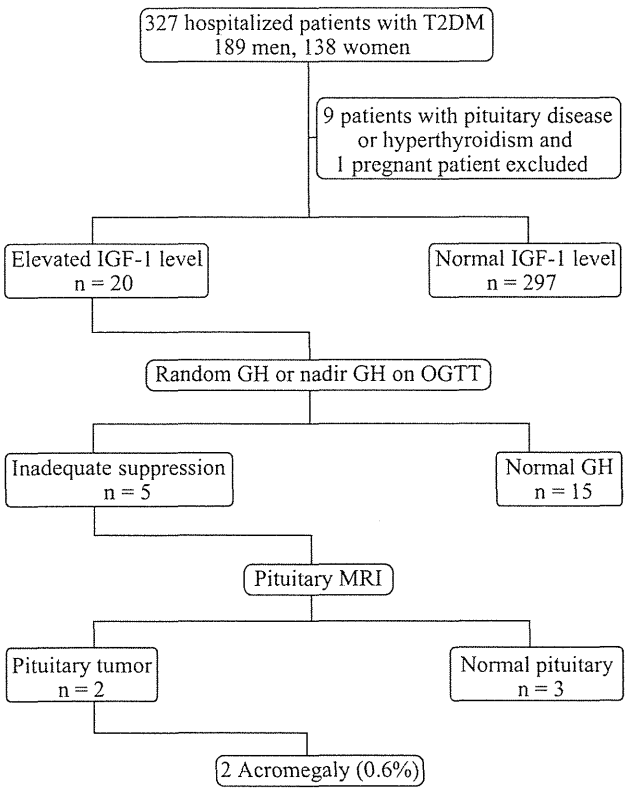

Fig. 2 Diagnostic work-up of patients with IGF-1 and GH
OGTT, oral glucose tolerance test; MRI, magnetic resonance imaging

the risk factors for case 3, and dyslipidemia, for case 4 (Table 3).

Discussion

In this study, after screening 317 hospitalized patients with T2DM, we found that 20 patients (6.3%) had elevated serum IGF-1 levels. Among these 20 patients, 2 patients (0.6%) had acromegaly, and they demonstrated severe macrovascular complications but absence of microangiopathy.

Both acromegaly patients exhibited autonomous GH secretion, as evidenced by the high nadir GH levels on OGTT: GH levels of 0.41 ng/mL and 0.72 ng/mL. The reference value of nadir GH of <1.0 ng/mL [20] was recently revised to <0.4 ng/mL, because of the sensitivity of the diagnostic methods used now [21]. In fact, normal individuals have nadir GH levels of <0.4 ng/mL [14], and this level is also considered a criterion for the resolution of acromegaly [20]. On the other hand, the levels of nadir GH suggest that the degree of autonomous GH secretion and the elevation of IGF-1 were mild in these patients. In addition, the acromegalic features were mild; hence, acromegaly was overlooked in the differential diagnosis at the admission.

In the present study, random GH levels were mea-

Table 3 Risk factors and clinical features of angiopathy in the cases 3 and 4

Case	HbA1c (%)	Smoking	Diabetes Duration (year)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	Statin therapy	Microangiopathy			Macroangiopathy		
								Retino-pathy	Nephro-pathy	Neuro-pathy	Carotid artery	Cardio-vascular	Peripheral vascular
3	8.5	(+)	39	58	87	83	(+)	(-)	(-)	(-)	Stenosis of right carotid artery	(-)	Peripheral arterial disease
4	6.8	(-)	8	75	29	149	(+)	(-)	(-)	(-)	Stroke	Angina pectoris	Peripheral arterial disease

Diabetes, hyperlipidemia, and smoking were present in case 3 and diabetes and hyperlipidemia in case 4.

sured in the patients with elevated IGF-1 levels, and 2 out of 20 patients showed random GH levels of >1ng/mL. Although case 4 showed random GH levels of >1ng/mL, in case 3, random GH levels were <1ng/mL. While impaired GH suppression can occur in conditions including chronic renal insufficiency, liver failure, hyperthyroidism, anorexia nervosa, malnutrition and adolescence [22], there are patients of active acromegaly with clearly elevated IGF-1 concentrations with apparently 'normal' plasma GH concentrations [23], suggesting that GH concentrations vary depending on conditions. Taken together, it might be useful to screen for acromegaly by measuring serum GH levels in patients with T2DM, but it requires further investigation.

IGF-1 levels can be elevated in some adolescents, patients with hyperthyroidism, and pregnant women but are rarely elevated in conditions other than acromegaly [22]. We excluded these conditions in this study; finally, 20 out of 317 patients (6.3%) showed elevated serum IGF-1 levels. It is reasonable that 2.5% of patients are considered to have elevated IGF-1 levels because of the definition of normal range (SD: ± 2.0); however, the ratio of 6.3% is higher than that predicted. We performed pituitary MRI in 5 patients and found pituitary tumor in 2 patients. We could not find any abnormalities in the other 3 patients. Generally, pituitary adenoma is detected on MRI in acromegaly patients [24], but considering the possibility of early-stage acromegaly with small adenoma, an invisible tumor cannot be ruled out. Therefore, it is suggested that these patients be followed up.

Three out of 2,270 individuals with T2DM or IGT have GH-producing pituitary adenoma (132/100,000 individuals) [12], suggesting that acromegaly is more prevalent in patients with T2DM than in the normal population, and T2DM or IGT is a representative complication in acromegaly [10]. In this study, we showed that the prevalence was 2/317, that is 631/100,000, much higher than that reported in previous report. The reason behind this discrepancy may be that the study subjects were hospitalized patients with T2DM, who generally presented more severe T2DM. Taken together, the prevalence of acromegaly might be underestimated especially among T2DM patients.

Acromegaly causes diabetes, and acromegaly complicated by diabetes has a poor prognosis [5, 25]. Additionally, the long duration for detection of acromegaly and diagnosis of cardiovascular disease and diabetes mellitus is related to increased mortality [26]. Both patients with acromegaly in this study revealed a microadenoma, suggesting an early diagnosis and high expectancy for cure [27]. These data suggest that a careful screening for acromegaly to enable early diagnosis in patients with T2DM is important.

Acromegaly is associated with increased morbidity and mortality of patients with atherosclerotic diseases. Excess GH and IGF-1 promote atherosclerotic changes *via* various mechanisms. It has been reported that GH increases the collagen deposition rate in the aorta [28], and IGF-1 promotes matrix formation and induces vascular smooth muscle cell migration and proliferation, associated with atherosclerosis [29, 30]. In the screened T2DM patients, 42%, 29%, and 37% of patients showed retinopathy, nephropathy, and neuropathy defined as microangiopathy related with T2DM. In contrast, 2 acromegaly patients showed no microangiopathy, rather showed severe macroangiopathy. Although it cannot be ruled out that the macroangiopathy was a coincident finding because of the presence of several risk factors including diabetes, smoking, and dyslipidemia, it is speculated that acromegaly might promote the progression of macroangiopathy in addition to these risk factors. It is also suggested that in T2DM patients with predominant macroangiopathy, acromegaly should be ruled out.

The present findings are limited in several respects.

This was a retrospective study, analyzing a relatively small number of patients. The diagnosis was not definitely verified by pathological findings because these patients were treated with primary medical therapy. Serum IGF-1 levels were measured at the second day after admission, in which serum IGF-1 levels might have been affected by uncontrolled diabetes, and the screening for autonomous secretion of GH by OGTT was not performed in all the patients with elevated IGF-1 levels, so latent acromegaly might have been overlooked. Nevertheless, the results in this study clearly showed the possibility of a higher prevalence of acromegaly in hospitalized patients with T2DM.

In conclusion, we showed a high prevalence of acromegaly in hospitalized patients with T2DM. Although a large-scale prospective study is required to clarify the precise prevalence of acromegaly in hospitalized patients with T2DM, the present study highlights that it is useful to screen hospitalized patients with T2DM for acromegaly by measuring their serum IGF-1 levels.

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Disclosure

The authors declare no conflict of interest.

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Endoscopic endonasal transsellar approach for laterally extended pituitary adenomas: volumetric analysis of cavernous sinus invasion

Masaaki Taniguchi · Kohkichi Hosoda · Nobuyuki Akutsu · Yutaka Takahashi · Eiji Kohmura

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Abstract
Purpose The authors conducted a statistical analysis of surgical results of the endoscopic endonasal transsellar approach to provide quantitative indices for selection of the approach in the treatment of laterally extended pituitary adenomas.
Methods Surgical results of 25 patients with laterally extended pituitary adenomas of Knosp grade 3 or 4 were retrospectively analyzed. The removal rate was evaluated by the volumetric change of the lateral tumor compartment.
Results The transsellar approach was used exclusively in all cases. Gross total removal of the lateral tumor compartment was achieved in 14 (56.0 %). Factors affecting the tumor removal through the transsellar approach were lateral tumor volume ($p = 0.006$), maximal distance to the cavernous sinus outer wall ($p = 0.004$) and history of previous surgery ($p = 0.017$). The cut-off values for the lateral tumor volume and maximal distance to the cavernous sinus outer wall predicting the gross total removal were 0.479 ml and 8.1 mm, respectively. The surgical complications of the transsellar approach included each case of anterior lobe function insufficiency and liquorrhea.
Conclusions The transsellar approach is adequate for removal of lateral tumor compartment in the majority of cases with laterally extended pituitary adenomas. The tumor compartments dorsal and ventral to the horizontal portion of the intracavernous carotid artery are amenable to the removal. But for removal of the tumor compartment lateral to the carotid siphon requires additional use of the parasellar approach.

Keywords Cavernous sinus · Endoscopic endonasal surgery · Pituitary adenoma · Transsellar approach

Introduction

Cavernous sinus extension of the pituitary adenoma still constitutes a limiting factor of tumor removal. Whether the complete removal of the intra-cavernous compartment should be strived despite the inherent surgical risk is a matter of debate. Still, as the ultimate treatment of benign tumors is the total removal, the attempt of surgical removal within the cavernous sinus seems to be justified as far as the risk can be reduced to an acceptable level. Several those attempts have been reported with the improved results by the application of extended transsphenoidal technique [1]. The recent evolution of the endoscopic technique is expected to further improve the treatment results [2–5]. Besides the direct ventral approach into the cavernous sinus lateral to the carotid siphon of the intracavernous carotid artery, which is called the parasellar approach, an approach from the sella through the cavernous sinus medial wall, which is called the transsellar approach, became reliable with the application of the angled scopes [6]. The previous papers reporting the surgical results of laterally extended pituitary adenomas, however, do not

M. Taniguchi (✉) · K. Hosoda · N. Akutsu · E. Kohmura
Department of Neurosurgery, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan
e-mail: mtani@med.kobe-u.ac.jp

Y. Takahashi
Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

distinguish both approaches precisely. Also in the most recent paper by Woodworth et al. [7] reporting the result of the transsellar approach in detail, the tumor was approached through the cavernous sinus incision lateral to the carotid artery in 23 among the 36 cases. As the two approaches are distinct in terms of invasiveness and usefulness, we advocate for the necessity to evaluate both approaches separately. Moreover, to adequately assess the efficacy of an approach to the cavernous sinus, the removal rate of lateral tumor compartment should be evaluated separately to the removal rate of the whole tumor. We herein describe the surgical features of the transsellar approach and evaluate their usefulness and limit by performing a pre- and postoperative volumetric analysis of the laterally extended tumor compartment.

Methods

Clinical materials

Among the pituitary adenomas treated at the Kobe University Graduate School of Medicine from February 2009 to December 2013, 41 adenomas demonstrated cavernous sinus extension classified as grade 3 or 4 according to Knosp et al. [8]. Excluding 11 cases, in which the aim of the surgery was the biopsy or partial mass reduction due to the patient's condition or already extensive recurrent tumor, and another 5, in which the parasellar approach was employed in addition to the transsellar approach, total of 25 patients treated exclusively by the transsellar approach were eligible for retrospective analysis of their surgical results. Cavernous sinus was evaluated on both sides in each patient, but lateral extension corresponding to Knosp grade 3 or 4 was evident only on one side, resulting in grade 3 in 23 patients and grade 4 in 2 patients. Thirteen tumors demonstrated high intensity and 12 demonstrated iso ~low intensity on T2 weighted MR-images. Four tumors were endocrinologically active with elevated plasma level of growth hormone (GH). Nine patients had previous history of surgical treatment (all by microscopic transsphenoidal surgery). Eighteen patients presented with impaired visual function and in four patients, the regrowth of the residual tumor was the only reason for surgery. The study was approved by the Institutional Review Board of the Kobe University Graduate School of Medicine.

Surgical technique

All patients were operated upon by a single surgeon using the binostril endoscopic endonasal approach. Surgical maneuver was performed bimanually with the endoscope fixed to a dedicated holding system (EndoArm, Olympus Co., Japan) [9]. The bony sellar floor was widely opened until the medial margin of the internal carotid artery. The exposed dura was incised at the sellar floor and the tumor within it was removed including the superiorly extended compartment. After certain amount of the tumor was removed, the laterally extended compartment was approached through the space dorsal and ventral to the horizontal portion of the intracavernous carotid artery and was removed under the 30- and 70-degree angled endoscopes using various curved and steerable instruments. If dural incision lateral to the carotid siphon was mandatory to address the tumor in the most lateral compartment of the cavernous sinus, this was defined as parasellar approach and was excluded from the series.

Evaluation of the surgical results

A line connecting the medial border of the intracavernous segment of the carotid artery (inter-carotid line) was drawn, and the tumor lateral to the line was considered as lateral tumor compartment (Fig. 1). The size of the tumor was estimated from the volumetric measurement of the coronal plane Gadolinium (Gd)-enhanced T1-weighted MRI with the slice thickness of 3 or 5 mm (Achieva 3T, Philips Electronics Japan, Japan) using the ImageJ software (version 1.47; http://rsbweb.nih.gov/ij/). First, the tumor area was figured out by tracing its contour on each MRI slices, and the volume was calculated by multiplying the sum of the areas by the slice thickness. The degree of tumor removal was quantitatively evaluated from the resultant volume change of the lateral tumor compartment. The removal rate was considered gross total (GTR) if there was no evidence of tumor residual on postoperative Gd-enhanced T1-weighted MRI performed within 3 months after surgery. For hormonally active tumors, the endocrinological results were also taken into account to assess the tumor removal. Criteria for cure according to the 2010 consensus guideline was used in GH-secreting adenomas, i.e. 75 g-oral glucose tolerance test (OGTT) nadir <0.4 ng/ml or random GH <1.0 ng/ml and insulin-like growth factor (IGF)-1 level within ±2 SD adjusted to sex and age [10]. Each case was also evaluated for ophthalmological sequelae.

To investigate the factors affecting the removal of the lateral tumor compartment, differences in the followings were evaluated between the GTR and non-GTR groups: volume of the lateral tumor compartment, maximal distance from the inter-carotid line to the cavernous sinus lateral wall, history of previous surgery, number of functioning versus non-functioning tumor, tumor consistency estimated from the T2-weighted MRIs (T2-high vs. T2-iso ~low). Student's t test and Fisher's exact test were used for continuous and for categorical variables,

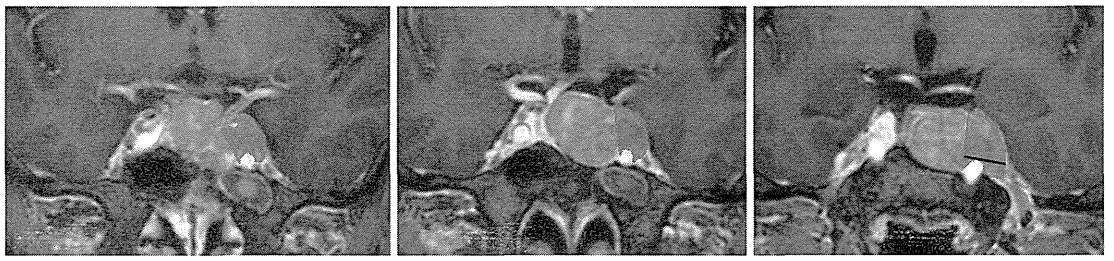

Fig. 1 An example of delineation of the lateral tumor compartment on Gd-enhanced T1-weighted MRIs. A line connecting the medial border of the intracavernous segment of the carotid artery (inter-carotid line) was drawn, and the volumetric measurement of the tumor compartment lateral to the line (indicated as shaded area in *red*) was conducted (1.762 ml in the present case). The *dotted vertical line* to the inter-carotid line in the *right* MRI indicates the maximal distance from the inter-carotid line to the cavernous sinus outer wall (12.3 mm in the present case)

Table 1 Summary of the clinical results

Mean volume of lateral tumor compartment ± SD	0.773 ± 0.507 ml
Mean maximal distance to the cavernous sinus outer wall ± SD	8.2 ± 2.3 mm
No. of cases with GTR	14/25 (56.0 %)
No. of Knosp 3 tumor (GTR/total)	14/23 (60.9 %)
No. of Knosp 4 tumor (GTR/total)	0/2
Endocrinological remission achieved by surgey/total	3/4
Complication	
Anterior pituitary insufficiency	1
Liquorrhea	1

respectively. The optimal cut-off values for tumor volume and maximal distance to the cavernous sinus outer wall were estimated from the receiver operating characteristic (ROC) curve analysis by taking the value with the highest sum of sensitivity and specificity. All statistical analyses were done by MedCalc (ver.12.7.1.0). A p value <0.05 was considered statistically significant.

Results

The mean volume of the lateral tumor compartment was 0.773 ± 0.507 ml. The GTR of the lateral tumor compartment was achieved in 14 cases accounting for 56.0 %. Considering the Knosp grading, the GTR of the lateral tumor compartment was achieved in 14 cases out of 23 Knosp 3 tumors (60.9 %) and in none out of 2 Knosp 4 tumors (Table 1). Cavernous sinus invasion was confirmed intraoperatively in 15 cases (13 Knosp grade 3 and 2 Knosp grade 4 tumors). Removal of the intracavernous compartment was accomplished through the already existing laceration of the medial wall in all but one case of GH secreting adenoma, in which seemingly intact medial wall had to be incised to remove the tumor within the cavernous sinus. In other 4 cases, the tumor only compressed the cavernous sinus leaving intact the medial wall, and in the residual 6 cases, the medial wall was not fully exposed due to the subcapsular or partial removal of the tumor. Of the four functioning adenomas, endocrinological remission was achieved in three cases. The follow up period ranged from 15 to 67 months with the median of 36 months.

Of the 18 patients presented with impairment of visual function, all demonstrated postoperative improvements. Surgical complications included each case of anterior lobe function insufficiency and liquorrhea, which had to be revised surgically. There was no patient complicated by the cranial nerve injury, neither temporary nor permanent. During the follow up, one case with the GH secreting adenoma, who did not reach the modern criteria for cure, required repeat surgery for the recurrence of the tumor 19.5 months after the initial surgery.

Among the factors evaluated, the lateral tumor volume, maximal distance to the cavernous sinus outer wall and history of previous surgery exhibited statistically significant difference between the GTR and non-GTR groups ($p = 0.006$, 0.004 and 0.017, respectively) (Table 2). The cut-off values for the lateral tumor volume and maximal distance to the cavernous sinus outer wall predicting the GTR according to the ROC curve analysis were 0.479 ml (57.1 % sensitivity and 100.0 % specificity, AUC 0.805, $p = 0.001$, 95 % CI 0.599–0.935) and 8.1 mm (85.7 % sensitivity and 72.7 % specificity, AUC 0.825, $p = 0.0001$, 95 % CI 0.621–0.946), respectively (Fig. 2).

Illustrative cases

Case 1

In this 61-year old woman, an acromegalic feature was pointed out when she visited a primary care clinic for palpitation and tremor of the hand. The MRI demonstrated

Table 2 Summary of statistical evaluation

Parameters	GTR (n = 14)	Non-GTR (n = 11)	*p* value
Mean volume of lateral tumor compartment ± SD (95 % CI)	0.539 ± 0.392 ml (0.313–0.765)	1.071 ± 0.492 ml (0.740–1.402)	0.006[a]
Mean maximal distance to the cavernous sinus outer wall ± SD (95 % CI)	7.075 ± 1.910 mm (5.972–8.178)	9.605 ± 2.061 mm (8.220–10.989)	0.004[a]
No. of cases with previous surgery	2/14	7/11	0.017[b]
No. of functioning tumor	4/14	0/9	0.105[b]

[a] Student's *t* test

[b] Fisher's exact test

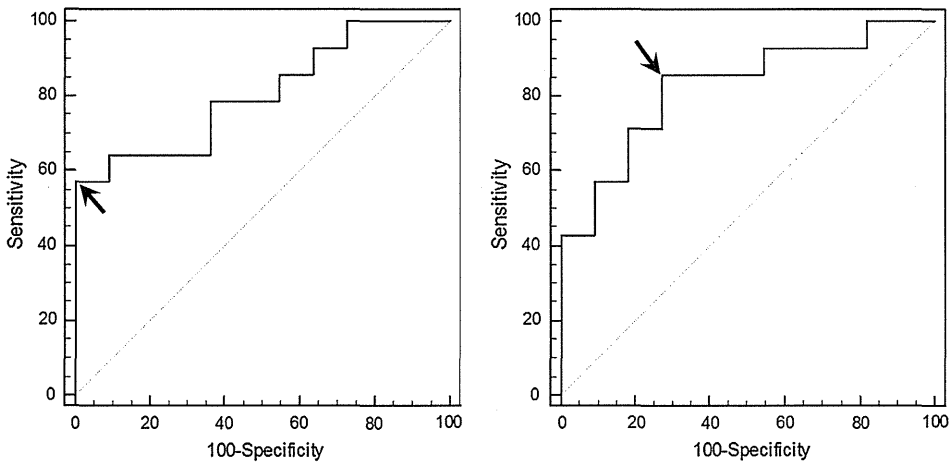

Fig. 2 Receiver operating characteristic curve of lateral tumor volume (*left*) and maximal distance (*right*) cut-off points with respect to gross total removal. The optimal cut-off point is indicated by an *arrow* within the respective graphs

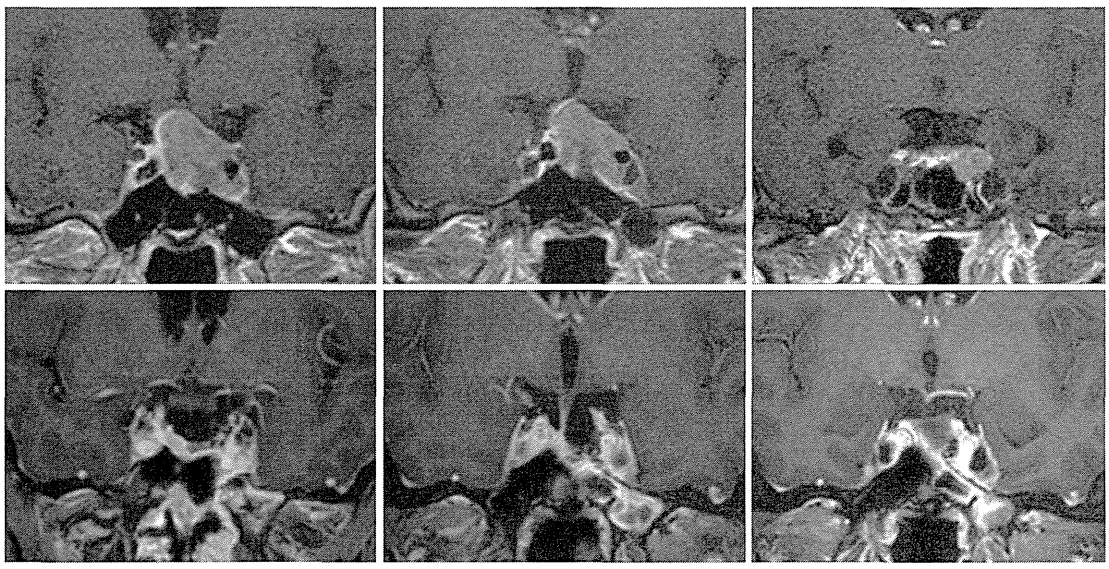

Fig. 3 The pre- (*upper row*) and post-operative (*lower row*) Gd-enhanced T1-weighted MRIs of the illustrative case 1 with GH-secreting adenoma. The tumor was gross totally removed with the use of the transsellar approach, and endocrinological remission was achieved

a pituitary tumor, and the endocrinological examination demonstrated elevated plasma level of random GH (25.47 ng/ml) and IGF-1 (1,509.6 ng/ml, +12 SD). She was at first treated with long acting octreotide injection for 1 year with the final dose of 40 mg/month. After some shrinkage of the tumor, the Gd-enhanced T1-weighted MRI

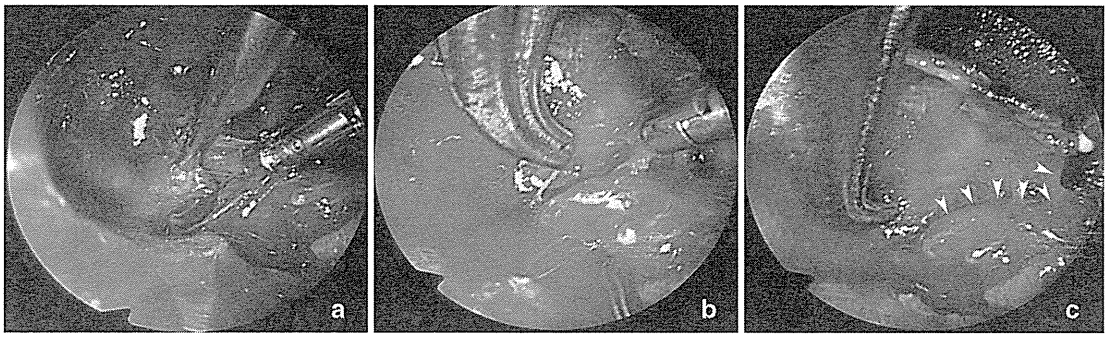

Fig. 4 Intraoperative photographs of the illustrative case 1. The lateral tumor compartment is removed through the transsellar approach under the 30-degree endoscope. The tumor capsule was grasped by the steerable forceps (**a**) and gently removed from the cavernous sinus compartment dorsal to the carotid artery (**b**). After gross total tumor removal, entire course of the intracavernous carotid artery (indicated by *white arrow heads*) is confirmed with the Doppler probe (**c**)

still demonstrated an intrasellar mass extending to the left cavernous sinus diagnosed as Knosp grade 3 (Fig. 3, upper row). The volume of the lateral tumor compartment was 1.120 ml and the maximal distance from the inter-carotid line to the cavernous sinus lateral wall was 11.8 mm. The patient was thus operated upon her pituitary tumor through the binostril endoscopic endonasal approach. The lateral tumor compartment was removed under the angled endoscopes using various curved and steerable instruments through the transsellar approach (Fig. 4). There were some fibrous components within the tumor potentially due to preoperative administration of the octreotide, but they were not far beyond the range of those in other pituitary tumors. The postoperative Gd-enhanced T1-weighted MRI demonstrated no apparent residual of the tumor (Fig. 3, lower row). The plasma level of random GH and IGF-1 levels 15 months after surgery decreased to 0.27 and 74 ng/ml (−1.8 SD), respectively, indicating endocrinological remission.

Case 2

This 53-year old woman was operated upon for her nonfunctioning pituitary adenoma 5 years ago. She was followed up since then for the residual tumor, which showed gradual regrowth finally reaching the optic chiasma and causing visual field defect. The preoperative Gd-enhanced T1-weighted MRI demonstrated recurrent pituitary adenoma with left lateral extension diagnosed as Knosp grade 4 (Fig. 5, left). The volume of the lateral tumor compartment was 1.541 ml and the maximal distance from the inter-carotid line to the cavernous sinus lateral wall was 13.1 mm. The tumor was removed with binostril endoscopic endonasal approach. After removing the intrasellar compartment, the lateral tumor compartment was removed through the transsellar approach. The postoperative Gd-enhanced T1-weighted MRI demonstrated removal of the major tumor compartment except the tiny residual in the ventral portion of the cavernous sinus, and her visual symptom resolved soon after surgery (Fig. 5, right). The result was judged as partial removal for lateral tumor compartment.

Discussion

Surgical results of laterally extended pituitary adenomas in the previous reports vary considerably due to the different definition of gross total or radical tumor removal, difference in the calculating method of the tumor volume and also due to whether the analysis is conducted for the whole tumor or only for the lateral tumor compartment. Detailed information about the degree of lateral extension is also sometimes lacking. As such, simple comparison of the results may be not adequate, but taken all the issues into consideration, the rate of gross total or radical removal of laterally extended pituitary adenomas ranged from 4.3 to 65.0 % for endoscopic [2, 7] and 17.6 to 34.2 % in the microscopic series [1, 11]. When focusing on the Knosp 3 tumors, the GTR rate of the lateral tumor compartment in the present series being 60.9 % was rather comparable with those reported in the recent papers of endoscopic series being 51.9–88.9 % [2, 5, 12].

The statistical analysis of the results provided several quantitative indices for selecting the transsellar approach in the treatment of laterally extended pituitary adenomas. Among the factors evaluated, the volume of the lateral tumor compartment, maximal distance to the cavernous sinus outer wall from the inter-carotid line and history of previous surgery were the factors affecting the removal rate. The tumor consistency may surely be one important factor affecting the tumor removal, but its exact estimation from the preoperative images is presently not possible [13, 14]. The consistency of the tumor was also not uniform

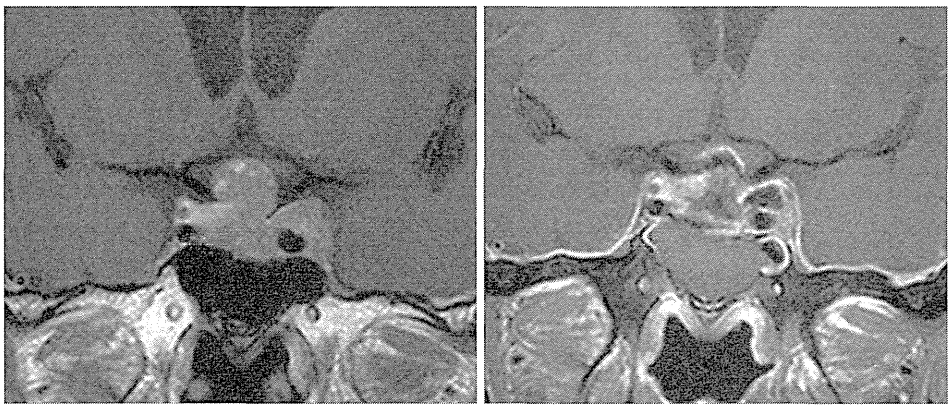

Fig. 5 The pre- (*left*) and post-operative (*right*) Gd-enhanced T1-weighted MRIs of the illustrative case 2 with recurrent non-functioning pituitary adenoma. The Knosp 4 tumor at the left cavernous sinus was removed through the transsellar approach

within a tumor in most of our series, and the comparison of the removal rate between T2-high and T2-iso ~low tumors exhibited no statistical significance. The cut-off value of 0.479 ml for lateral tumor volume to achieve GTR is rather small, but it has sensitivity of 57.1 % and specificity of 100.0 %, indicating that about 40 % of the cases with GTR had greater tumor volume than 0.479 ml, and if the lateral compartment was smaller than the cut-off value, the tumor was removed in all cases. And the cut-off value of 8.1 mm for maximal distance to the cavernous sinus outer wall may indicate present limit of the range of access by the transsellar approach. But as the shortage of appropriate surgical instruments is one of the present constraints of surgical maneuver under the angled endoscopes during the transsellar approach, there is a potential for further improvement of those cut-off values by the future development of the surgical instruments. And though the number is very limited, when considering the results of recent papers reporting 14.3–45 % cure rate using the modern criteria for GH secreting tumors with cavernous sinus extension [15–17], three cases fulfilling the critria out of four in the present series may suggest promising role of the described approaches in aiming the endocrinological cure for functioning adenomas.

When considering the invasive nature of the pituitary adenoma, the microscopically complete tumor removal can not always be achieved. Therefore, controversy exists how far the risk would be accepted by insisting on removal of the intracavernous sinus compartment in the non-functioning adenomas. As the transsellar approach uses the course of tumor extension as the surgical trajectory, the anatomical structures hindering the entry are scarce. The cranial nerves also run in the most lateral wall of the cavernous sinus and rarely encountered during the tumor removal when entering the sinus dorsal to the horizontal portion of the carotid artery. Thus, the risk to the cranial nerves and carotid artery is rather limited compared to the parasellar approach, which requires bone drilling over the carotid siphon and surgical maneuver in close proximity to the abducens nerve. From the result of the present series without any morbidity associated with the injury to the cranial nerves and carotid artery, the use of this approach may be considered acceptable. Moreover, from the result of the extensive investigation about the types of lateral extension of the pituitary adenomas by Knosp et al. [8] which indicated that lateral extension occurs mostly, and more prominently, dorsal to the intracavernous carotid artery, transsellar approach alone is sufficient to remove major part of the lateral compartment in many cases. Even for tumors with Knosp 4 cavernous sinus invasion, the transsellar approach may be sufficient as demonstrated in illustrative case 2, if complete removal of the tiny residual ventral to the carotid artery is not insisted on.

The disadvantage of the transsellar approach might be the non-linear approaching route, which has to be visualized with the angled endoscopes. Even though the straight instruments can reach certain area within the lateral compartment, use of curved/steerable instruments becomes mandatory, if surgical maneuver in the most lateral compartment is required [18, 19]. The present armamentarium of such instruments, however, has not yet reached the level of satisfaction, and further development of surgical instruments would be an urgent requirement. And for large adenomas, for which the extensive mass reduction beyond the intracavernous carotid artery is necessary, the additional use of the parasellar approach would be indispensable. The indication of such additional approach, however, must be determined by weighing the potential complication against the need for extensive cavernous sinus exploration in each individual case. And finally, as the follow up period is limited, the long term results of the transsellar approach need still to be evaluated.

Conclusions

In the present series of pituitary adenomas with Knosp grade 3 and 4, the transsellar approach was used for removal of laterally extended tumor compartment. The removal rate was evaluated by the volume change of the lateral tumor compartment, being comparable to those of the recent endoscopic series. The factors affecting the tumor removal were volume of the lateral tumor compartment (cut-off; 0.479 ml), maximal distance from the inter-carotid line to the cavernous sinus outer wall (cut-off; 8.1 mm) and history of previous surgery. Though the approach to the lateral tumor compartment has to be selected according to the required extent of cavernous sinus exploration, the transsellar approach would be adequate in the majority of cases.

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Conflict of interest The authors declare that they have no conflict of interest.

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The prevalence and associated factors of colorectal neoplasms in acromegaly: a single center based study

Masaaki Yamamoto · Hidenori Fukuoka · Genzo Iguchi · Ryusaku Matsumoto · Michiko Takahashi · Hitoshi Nishizawa · Kentaro Suda · Hironori Bando · Yutaka Takahashi

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Abstract
Purpose Colorectal neoplasms are well known to be a complication in cases of acromegaly; however, data on the prevalence of colorectal neoplasms in Asian patients with acromegaly are limited. Further, the factors associated with colorectal neoplasms in cases of acromegaly are controversial. Therefore, we aimed to clarify the prevalence of and factors associated with colorectal neoplasms in Japanese patients with acromegaly in a single center.
Methods We analyzed consecutive 57 patients who had undergone full-length colonoscopy at the time of diagnosis at Kobe University Hospital between 1986 and 2012.
Results Of the 57 patients, 22 (38.6 %), 18 (31.6 %) and 3 (5.3 %) patients were diagnosed with hyperplastic polyps, adenomas, and adenocarcinomas, respectively and the prevalence was significantly higher than in a historical control group, Chinese patients with irritable bowel syndrome (The odds ratio was 4.0, 8.7, and 17.5, respectively). The prevalence of adenocarcinomas was also significantly higher in these patients than in the general Japanese population (odds ratio 14.5). Patients with acromegaly who had colorectal neoplasms had longer disease duration than those without colorectal neoplasms. Of note, the area under the growth hormone (GH) concentration–time curve (GH AUC) during the oral glucose tolerance test was significantly higher in patients with adenocarcinomas than in those with no colonic lesion or those with hyperplastic polyps.
Conclusion Japanese patients with acromegaly exhibited an increased risk of colorectal neoplasms, especially colorectal adenocarcinomas. An increased GH AUC was associated with an increased risk for colon adenocarcinomas in patients with acromegaly.

Keywords Acromegaly · Colon cancer · Colon neoplasm · Colon polyps · GH

M. Yamamoto · H. Fukuoka · G. Iguchi · R. Matsumoto · M. Takahashi · H. Nishizawa · K. Suda · H. Bando · Y. Takahashi (✉)
Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan
e-mail: takahash@med.kobe-u.ac.jp

Background

Acromegaly is caused by the excess secretion of growth hormone (GH) and is characterized by acral enlargement, coarse facial features, and visceromegaly. Patients with acromegaly have a reduced life expectancy, primarily due to cardiovascular, cerebrovascular, and respiratory disease [1]. Further, acromegalic patients are well known to be at an increased risk for malignancies in several organs including thyroid, breast, and prostate [1]. With regard to the digestive tract, patients with acromegaly exhibit an increased risk for hyperplastic polyps, colonic adenomas, and adenocarcinomas and therefore, an increased mortality due to colon cancer. Similar findings have been reported in a meta-analysis [2–4]. However, most data are based on Caucasian patients with acromegaly, and data on the prevalence of colorectal neoplasms in Asian acromegalic patients are limited, and these few studies include only a small number of patients [5–7].

In patients with acromegaly, several factors have been reported to be associated with the presence of colorectal neoplasms. A high serum insulin-like growth factor I (IGF-I) level and a high IGF-I to IGF-binding protein 3 ratio were

associated with an increased prevalence of colorectal adenomas and adenocarcinomas, respectively [8, 9]. In another study on patients with acromegaly, those with impaired glucose tolerance (IGT) or diabetes had a 2.4–5.8 times higher risk of colonic lesions than those with normal glucose tolerance, and an elevated fasting insulin level was associated with the increased prevalence of colonic lesions, particularly adenomas and adenocarcinomas, independent of body mass index [10]. However, whether the excess secretion of GH itself is associated with the development of colorectal neoplasms is unclear.

In this study, we aimed to clarify the prevalence of colorectal neoplasms in Japanese patients with acromegaly in a single center and to elucidate the factors associated with the presence of colorectal neoplasms.

Subjects and methods

This was a retrospective cross-sectional study. We analyzed the data of consecutive 57 patients with acromegaly (24 male, 33 female; age, 22–80 years) who had undergone full-length colonoscopy at the time of diagnosis at Kobe University Hospital between 1986 and 2012. The diagnosis of acromegaly was based on clinical signs, the lack of serum GH level suppression to <1 ng/mL during a 75-g oral glucose tolerance test (OGTT), serum IGF-I levels beyond the normal range for age- and sex-matched control individuals, and the presence of a pituitary tumor. The duration of disease was determined by comparing photographs and by conducting patient interviews to determine the onset of acral enlargement, as previously described [11]. Height and weight were measured to calculate the body mass index [weight (kilograms)/height (meters)^2]. In the 75-g OGTT, blood samples were collected before and at 30, 60, 90, and 120 min after glucose ingestion for the measurement of plasma glucose and serum insulin and GH concentrations. The area under the serum concentration–time curve of GH (GH AUC) during the 75-g OGTT was calculated by applying the trapezoid rule to both positive and negative GH concentrations increments between 0 and 120 min as previously reported [12]. By using fasting plasma glucose and serum insulin concentrations, we calculated the homeostasis model assessment of β-cell function {HOMA-β; [360 × serum insulin level (μU/mL)/plasma glucose level (mg/dL)] − 63} and the homeostasis model assessment of insulin resistance {HOMA-IR; [serum insulin level (μU/mL) × plasma glucose level (mg/dL)]/405}. The insulinogenic index was calculated as the change in the serum insulin concentration divided by the change in the plasma glucose concentration between 0 and 30 min during the OGTT [13]. Colonoscopy was performed by several experienced gastroenterologists after careful bowel preparation with 2 L of a polyethylene glycol–electrolyte oral lavage solution (Niflec, Ajinomoto-Farma, Inc., Japan). All lesions visualized on colonoscopy were recorded individually, and, when possible, the lesions were biopsied and subjected to histological examination. Detailed analysis for colon polyps such as localization and diverticulum was performed in the patients, whose detailed record was available. The clinical characteristics of all the patients in this study are shown in Table 1.

Assays

The serum GH concentration was measured using the IRMA kit (Daiichi Radioisotope Laboratories, Tokyo, Japan) until March 2005 and subsequently, using the immunoenzymometric assay kit (Tosoh Co. Ltd, Tokyo, Japan). The standard form of GH for analysis changed from pituitary-derived GH to recombinant human GH (rhGH) in April 2005 in Japan [14]. Therefore, measurements made prior to April 2005 were adjusted to those made using the rhGH standard. The serum IGF-I concentration was measured using the IRMA kit (Daiichi Radioisotope Laboratories). The IGF-I standard deviation (SD) score was calculated with age- and sex-matched healthy Japanese individuals used as Ref. [15] (http://ghw.pfizer.co.jp/adult/information/igf-i/index.html).

Statistical analysis

All statistical analyses were performed using StatView 5.0 (Abacus Concepts Inc., Berkeley, CA, USA). Data are represented as mean ± SD. For continuous variables, differences were analyzed using the Mann–Whitney U test for nonparametric data. For categorical variables, differences were analyzed using the χ^2 test and Fisher's exact test. Continuous variables were tested for differences between patients with hyperplastic polyps, adenomas, and adenocarcinomas and those without neoplasms using the Kruskal–Wallis test followed by the Dunn's multiple comparison test (Table 5; Fig. 2). Significance was established at $P < 0.05$.

Results

Differences in characteristics between patients with or without colorectal neoplasms

The colon was visualized up to the caecum in all 57 patients. First, we compared endocrinological and clinical parameters between acromegalic patients with or without colorectal neoplasms (Table 2). Elevated IGF-I levels and the presence of IGT or diabetes are reported to be associated with an increased risk of colorectal neoplasms in patients with acromegaly [10]. Most parameters did not

Table 1 Profile of patients at diagnosis

No. of patients	57
No. of males/females	24/33
Age (years)	50.3 ± 12.9
Disease duration (years)	10.1 ± 8.1
BMI (kg/m^2)	25.3 ± 4.2
Basal GH levels (ng/mL)	28.6 ± 32.0
Nadir GH levels during OGTT (ng/mL)	21.3 ± 25.6
GH AUC during OGTT	3,691 ± 4,416
IGF-I levels (ng/mL)	775 ± 340
IGF-I levels (SDS)	8.1 ± 3.0
HbA1c (%)	6.21 ± 2.15
Fasting glucose level (mg/dL)	108 ± 56
Fasting insulin level (mU/mL)	10.8 ± 11.2
HOMA-R index	2.88 ± 4.02
HOMA-β index	132 ± 119
Insulinogenic index	0.9 ± 1.1

Data are shown as mean ± SD. *AUC* the area under the concentration–time curve, *SDS* standard deviation score

differ between these groups of patients including these parameters; however, disease duration was significantly longer in patients with colorectal neoplasms than in those without these lesions.

The pathological classification based on endoscopic findings

Patients were classified according to the histological classification of their colonic lesions (Table 3a). Hyperplastic polyps, adenomas, and adenocarcinomas were present in 22 (38.6 %), 18 (31.6 %) and 3 (5.3 %) patients, respectively. Then we compared the prevalence of colonic lesions in this study with Chinese patients with irritable bowel syndrome (IBS), which is a common functional but not organic bowel disease [16] (Table 3b). The prevalence of each colonic neoplasm in our study was significantly higher than that in the patients with IBS. The odds ratios of hyperplastic polyps, adenomas, and adenocarcinomas were 4.0, 8.7 and 17.5, respectively (Table 3b). The prevalence of colonic neoplasms according to age in acromegaly is shown in Table 3c. The prevalence rates of colon neoplasms in patients aged <40, 40–49, 50–59, and ≥60 years were 58.3, 75.0, 85.7, and 80.0 %, respectively. We also analyzed the number and site distribution of colorectal polyps in the patients, whose detailed record was available. Single hyperplastic polyp was detected in three patients (21.4 %) and multiple hyperplastic polyps were in 11 patients (78.6 %). Single adenoma was in four patients (36.4 %) and multiple adenomas in seven patients (63.6 %; Table 3d), indicating that multiple lesions were predominant. All three cases with adenocarcinoma revealed as a single lesion (data not shown). With regard to the site distribution of polyps, hyperplastic polyps distributed predominantly in rectum (55.0 %) and adenomas distributed evenly in the colon (Table 3d). In addition, we examined colon diverticulum because a recent paper suggested that the patients with acromegaly exhibited increased frequency of colonic diverticulum [17]. Six out of 28 patients exhibited colon diverticulum (21.4 %; Table 3e). Most of the patients revealed single diverticulum (66.7 %) and the

Table 2 Profile of the patients with or without colorectal neoplasms

	Patient with colorectal neoplasms	Patient without colorectal neoplasms	*P* value
No. of patients (%)	43 (75.4 %)	14 (24.6 %)	
No. of males/females	18/25	6/8	0.95
Age (year)	51.3 ± 12.1	47.1 ± 15.2	0.22
Disease duration (years)	11.4 ± 8.6	6.4 ± 5.2	0.02*
BMI (kg/m^2)	24.9 ± 3.5	26.6 ± 6.0	0.60
Basal GH levels (ng/mL)	32.0 ± 17.1	18.4 ± 17.1	0.24
Nadir GH levels during OGTT (ng/mL)	24.2 ± 28.7	13.2 ± 9.4	0.37
GH AUC during OGTT	4,346.0 ± 4,890.5	1,771.5 ± 1,444.2	0.07
IGF-I levels (ng/mL)	750.0 ± 309.2	852.5 ± 426.4	0.24
IGF-I levels (SDS)	8.0 ± 2.7	8.5 ± 3.9	0.92
HbA1c (%)	6.4 ± 2.4	5.6 ± 0.9	0.24
Fasting glucose level (mg/dL)	113.5 ± 62.4	92.6 ± 19.2	0.10
Fasting insulin level (mU/mL)	10.7 ± 12.3	11.3 ± 7.7	0.50
HOMA-R index	3.0 ± 4.5	2.6 ± 1.7	0.87
HOMA-β index	115.7 ± 102.2	183.1 ± 151.2	0.11
Insulinogenic index	0.8 ± 0.8	1.1 ± 1.6	0.51

Data are shown as mean ± SD. *P* values show the results of the mann–whitney test