Published in final edited form as:

World J Surg. 2016 March ; 40(3): 683–689. doi:10.1007/s00268-015-3242-y.

FDG PET/CT Scan and Functional Adrenal Tumors: A Pilot Study for Lateralization

Dhaval Patel¹, Sudheer Kumar Gara¹, Ryan J. Ellis², Myriem Boufraqueh¹, Naris Nilubol¹, Corina Millo³, Constantine A. Stratakis⁴, and Electron Kebebew¹

¹Endocrine Oncology Branch, Clinical Research Center, National Cancer Institute, NIH, Building 10-CRC, Room 3-5840, Bethesda, MD 20892, USA

²Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA

³PET Department, Clinical Center, NIH, Bethesda, MD 20892, USA

⁴Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD 20892, USA

Abstract

Background—Patients with Cushing’s Syndrome (CS) and Conn’s Syndrome with bilateral adrenal masses pose a dilemma. Uptake of 18F-FDG by hyperfunctioning adrenal glands has not been previously reported and may help lateralize. The aim was to determine if 18F-FDG PET/CT scan could identify hyperfunctioning adrenal masses and determine a biological basis for uptake.

Methods—Patients with nonfunctional adenomas ($n = 9$), CS ($n = 11$), and Conn’s syndrome ($n = 4$) underwent an 18F-FDG PET/CT scan with a volume of interest circumscribing each mass to obtain a maximal standardized uptake value (SUV_{max}). Thirty-two adrenal masses were analyzed. Genome-wide expression data from an independent cohort were analyzed in nonfunctioning adenomas ($n = 20$), Conn’s syndrome ($n = 29$), and CS ($n = 24$) focusing on *GLUT* genes. For genes differentially expressed, immunohistochemistry was performed on tissue samples.

Results—Cortisol-secreting masses ($n = 16$) had a higher average SUV_{max} of 5.9 compared to nonfunctioning masses ($n = 11$, average SUV_{max} 4.2) and aldosterone-hypersecreting masses ($n = 5$, average SUV_{max} 3.2) ($p = 0.007$). SUV_{max} cut-off of 5.33 had 50.0 % sensitivity and 81.8 % specificity in localizing a cortisol-secreting mass. *GLUT3* expression was 2.19-fold higher in patients with CS compared to patients with nonfunctioning adenomas ($p = 0.003$) and 2.16-fold higher in patients with CS compared to Conn’s syndrome ($p = 0.006$). *GLUT3* immunohistochemistry showed 2.2-fold higher staining in CS tumor samples compared to nonfunctioning adenomas.

Conclusions—Differential 18F-FDG PET/CT uptake was observed in patients with nonfunctioning, aldosteronehypersecreting, and cortisol-secreting masses. *GLUT3* overexpression in cortisol-secreting tumor likely accounts for the differential uptake. Future larger cohort studies will need to be conducted to determine if 18F-FDG PET/CT uptake can lateralize cortisol-secreting adrenal masses in patients with bilateral adrenal masses.

Introduction

Determining the appropriate surgical treatment in patients with hyperfunctioning adrenocortical tumors causing Cushing's syndrome (CS) and Conn's syndrome can be challenging. CS results from excessive endogenous or exogenous glucocorticoids and is estimated to affect 10–15 persons per million population in the United States [1]. Conn's syndrome results from excessive endogenous aldosterone. Previously estimated to affect one to two percent of patients with hypertension [2], recent cross-sectional and prospective studies have identified the disease in more than 10 % of patients with hypertension [3].

After the diagnosis of ACTH-independent CS and Conn's syndrome is biochemically established, radiological imaging helps direct the need for and the appropriate surgical therapy. Patients with bilateral adrenal masses, though, pose a clinical dilemma. Kasperlik-Zaluska and colleagues reported a large cohort of 1790 patients, of which nearly 20 % had bilateral adrenal incidentalomas [4]. In cases of Conn's syndrome, the introduction of adrenal venous sampling (AVS) has led to accurate determination of whether patients have unilateral or bilateral hypersecreting adrenal glands [5]. However, in ACTH-independent CS, there is no standard of care to lateralize the hyperfunctioning side in patients with bilateral adrenal masses. Young and associates have used AVS to lateralize the hyperfunctioning side in patients with bilateral adrenal masses and hypercortisolism for surgical intervention [6], but this is invasive and not the current standard of care. Thus, noninvasive modalities to lateralize cortisol-secreting tumors are needed.

18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) scanning, which combines functional and anatomical imaging, has been used to characterize adrenal lesions and masses. 18FFDG, a glucose analog, is taken up by cells with increased glycolysis, which are typically malignant cells [7]. Groussin and colleagues showed that 18F-FDG PET/CT can be used to distinguish between patients with adreno-cortical adenomas and adrenocortical carcinomas [8]. Thus, the primary use of 18F-FDG PET/CT has been focused on evaluating malignant adrenal disease. The biological mechanism of glucose uptake in patients with cancer undergoing 18F-FDG PET/CT scan has been studied in various cancers such as metastatic pulmonary tumors [9], high-grade gliomas [10], and melanoma [11]. These studies have examined the mechanism of glucose uptake by assessing the biological correlation of glucose transporters, hexokinase, Ki-67, hypoxia-inducible factor-1 α (HIF-1 α), and vascular endothelial growth factor and 18F-FDG uptake [9–11]. The utility of using 18F-FDG PET/CT to evaluate the functional status of adrenal tumor has not been previously reported.

The specific aim of this pilot study was to evaluate whether 18F-FDG PET/CT can differentiate between patients with nonfunctional adrenal masses, Conn's syndrome, and patients with adrenal CS. Genome-wide expression data were used to determine the biological rationale for the observed 18F-FDG uptake focusing on the glucose transporter genes with validation of the data in patients who had 18F-FDG PET/CT.

Materials and methods

Patients

Demographics, genetic tests, pathology, radiology, and operative history were reviewed in patients who were evaluated at the National Institutes of Health (NIH) Warren Magnuson Clinical Center on Institutional Review Board-approved prospective clinical research protocols (NCT01348698, NCT01005654, NCT00005927, NCT020 01051). All patients with adrenal masses (Table 1) were evaluated and screened for hyperaldosteronism, pheochromocytoma, and hypercortisolism with plasma renin activity/plasma aldosterone concentration, plasma normetanephrine and metanephrines, and urinary free cortisol (UFC). Screening UFC higher than upper limit normal of 45.0 mcg/24 h resulted in a confirmatory 1 mg dexamethasone suppression test (DST, cut-off [3.0 mcg/dl). Patients with a genetic predisposition or strong family history underwent both screening UFC and 1 mg DST. Subclinical hypercortisolism was diagnosed in patients without clinical signs and symptoms of hypercortisolism with at least two out of three positive biochemical tests: DST > 3.0 mcg/dl, elevated UFC, and/or morning suppressed basal ACTH < 2.2 pmol/l with elevated cortisol. Hyperaldosteronism was confirmed with either the oral sodium loading test or sodium infusion test. As part of the NIH clinical protocol, all patients underwent an adrenal protocol CT scan and an 18F-FDG PET/CT scan. Unilateral or bilateral adrenalectomy was offered to all patients when clinically indicated.

18F-FDG PET/CT

All patients with adrenal masses underwent an 18F-FDG PET/CT prior to surgery. The scans were performed approximately 60 min after intravenous administration of 10 mCi of 18F-FDG for patients less than 90 kg of weight and 15 mCi of intravenous 18F-FDG for patients greater than 90 kg of weight. Blood glucose levels were less than 150 mg/dl for each patient prior to radiotracer administration. The patients were scanned from the base of the skull to the mid-thighs. A noncontrast CT scan was used for attenuation and anatomical localization. A volume of interest was drawn on the primary adrenal mass and the SUV_{max} recorded. The values were reviewed and reported by a nuclear medicine radiologist (CM) blinded to the clinical data.

Genome-wide gene expression profiling

Genome-wide gene expression data from an independent cohort in patients with adrenal CS ($n = 24$), Conn's syndrome ($n = 29$), and nonfunctioning adrenocortical tumors ($n = 20$) were analyzed to determine the biological basis for differential 18F-FDG uptake focusing on the glucose uptake transporter (*GLUT*) genes. Raw microarray data were analyzed using the Affy package (Affymetrix Gene-Chip Operating software; Affymetrix Inc) and R/Bioconductor with multiarray average method with default variable normalization [12, 13]. Normalized gene expression data were analyzed by comparing tumors from CS with Conn's syndrome and with nonfunctioning tumors, respectively. The P values were adjusted for multiple testing using the Benjamini–Hochberg method and a false discovery rate of 5 % [14].

Immunohistochemistry (IHC)

Unstained paraffin-embedded tissue sections were deparaffinized and rehydrated stepwise through xylene and graded alcohol solutions. Peroxidase activity was blocked with 6 % H₂O₂ for 5 min. Antigen retrieval was performed with 10 % citrate buffer in a water bath at 120 °C. Sections were blocked for 1 h with 2 % goat serum and then incubated overnight at 4 °C with anti-GLUT3 polyclonal antibody (ab103890, AbCam, Cambridge, UK; 1:100 dilution). Staining was performed using the biotin-free polymer detection system (DAKO, Glostrup, Denmark). Counterstaining was performed using hematoxylin. Negative controls were used without using the primary antibody. Twenty-two samples from patients with 18F-FDG PET/CT scanning results were stained for GLUT3 protein expression: 9 CS samples, 4 Conn's syndrome samples, 4 nonfunctioning adrenal adenoma samples, and 5 normal adrenal samples.

An independent observer who was blinded to the PET data and the functional data of the tumors scored each stained slide. The entire tumor slide was scanned and scored from 0 to 4 based on the percentage of cells that stained positive for GLUT3 protein. Scores were assigned as 0 with no cells positive, 1 with 1–25 % of cells positive, 2 with 26–50 %, 3 with 51–75 %, and 4 with 76–100 % of cells positive for GLUT3 protein staining.

Statistical analysis

The one-way ANOVA test was used to compare SUV_{max} between groups. The Mann–Whitney *U* test was used to compare SUV_{max} between groups. An unpaired *t* test was used to compare gene expression between groups. The relationship between tumor size measured in the longest dimension and 18F-FDG uptake was assessed by Spearman correlation. The relationship between GLUT3 staining and SUV_{max} was assessed by the exact two-tailed Jonckheere–Terpstra trend test. A *P* value of <0.05 was considered statistically significant. All calculations were performed using GraphPad software (La Jolla, CA, USA).

Results

The demographic and clinical characteristics of the study cohort are summarized in Table 1. Nine patients had nonfunctioning unilateral adrenal masses. Four of the nine patients underwent unilateral adrenalectomy secondary to growth or risk of malignancy based on imaging features and/or tumor size. These four patients were found to have benign adrenocortical adenomas or adrenal hyperplasia. The other five patients had adrenal tumors less than 4 cm or had imaging indicating a likely benign tumor. These five patients were managed by active surveillance. Four patients had aldosterone-hypersecreting adrenal masses, one had bilateral masses on anatomic imaging, and three patients had unilateral adrenal masses. The patient with bilateral adrenal masses underwent AVS with lateralization to the right adrenal gland and was cured after adrenalectomy. All four patients underwent unilateral adrenalectomy. Eleven patients had cortisol-hypersecreting adrenal masses, of which six had bilateral masses and five patients had a unilateral adrenal mass. All eleven patients were biochemically confirmed to have hypercortisolism by 1 mg dexamethasone suppression test. Three patients had massive macronodular adrenal disease, one had medically refractory ACTH-dependent Cushing's disease, and one patient had diffuse

macronodular adrenocortical hyperplasia. These patients underwent a bilateral adrenalectomy. One patient with a unilateral adrenal mass had Carney's complex and also underwent a bilateral adrenalectomy for definitive treatment. One patient with bilateral masses underwent a right adrenalectomy secondary to suspicious imaging characteristics concerning for adrenocortical carcinoma. The tumor was found to be benign by pathology and had lateralized by 18F-FDG PET scan. Three patients with unilateral masses had ACTH-independent CS and underwent unilateral adrenalectomy. One patient with a unilateral adrenal mass had subclinical hypercortisolism and underwent a unilateral adrenalectomy.

Cortisol-secreting masses ($n = 16$) had a higher average SUV_{max} of 5.9 compared to nonfunctioning adrenocortical masses ($n = 11$) with an average SUV_{max} of 4.2 and aldosterone-secreting masses ($n = 5$) with an average SUV_{max} of 3.2 (Fig. 1, $p = 0.007$). A subanalysis of the data comparing nonfunctioning and cortisol-secreting adrenal masses was significant ($p = 0.035$). An outlier analysis was performed and showed no change in statistical significance for either of the analyses. An SUV_{max} cut-off of 5.33 demonstrated a sensitivity of 50.0 % and specificity of 81.8 % in identifying a cortisol-secreting mass. There was no significant correlation between tumor size as measured and SUV_{max} . All patients with CS and Conn's syndrome were biochemically cured on clinical follow-up.

Analysis of genome-wide gene expression data from an independent cohort showed that *GLUT3* expression was 2.19-fold higher in patients with CS compared to nonfunctioning adenomas ($p = 0.003$), and 2.16-fold higher in patients with CS compared to patients with Conn's syndrome ($p = 0.006$). This relative difference in expression is presented visually with a heat map (Fig. 2). GLUT3 immunohistochemistry performed on the cohort with 18FFDG PET/CT scanning results showed 2.2-fold higher staining in patients with CS ($n = 9$) compared to patients with Conn's syndrome ($n = 4$) and a 2.2-fold higher staining in patients with nonfunctioning adrenocortical tumors ($n = 4$) (Fig. 3). There was no significant association between SUV_{max} and IHC staining scores ($p = 0.17$).

Discussion

This study demonstrates that 18F-FDG PET/CT uptake in patients with cortisol-hypersecreting adrenal tumors is higher than in patients with nonfunctioning adrenal masses and aldosterone-hypersecreting adrenal masses. This suggests that 18F-FDG PET/CT may be a potential tool to identify cortisol-hypersecreting adrenocortical tumors. The data also demonstrate that GLUT3 overexpression may be a plausible biological reason for our clinical findings. To our knowledge, this is the first report of patients with benign functional adrenal masses who have undergone 18F-FDG PET/CT scan compared to patients with nonfunctioning adrenal masses.

Although the management of patients with CS with biochemical evidence, clinical signs and symptoms, and a unilateral adrenal mass is relatively straightforward, patients with bilateral adrenal masses without a genetic predisposition can pose a clinical dilemma [6]. Kasperlik-Zaluska and colleagues reported 1790 patients with unilateral adrenal incidentalomas, of which 351 (19.6 %) patients had bilateral adrenal incidentalomas. Of these 351 patients, 14

patients (4 %) had subclinical hypercortisolism requiring surgery. In these patients, the larger tumor, more rapidly growing tumor, or the tumor with the higher density in the first phase of CT were initially surgically resected. However, 2 of these 14 patients had persistent subclinical hypercortisolism, and 1 of these 14 patients had recurrent subclinical hypercortisolism within three years requiring resection of the contralateral adrenal gland [4]. Preoperative lateralization by 18F-FDG PET/CT may be beneficial for this subset of patients but will require further study. In comparison to patients with a unilateral adrenal mass, Vassiliadi and colleagues found that patients with bilateral adrenal masses have an odds ratio of 5.50 of having sub-clinical hypercortisolism [15]. Young and associates have used AVS to lateralize the hyperfunctioning side in patients with bilateral adrenal masses and hypercortisolism for surgical intervention [6]. Although AVS was successful in lateralizing the hyperfunctioning side in this study, diagnostic [18] FDG PET/CT is noninvasive and widely available, and would avoid the potential morbidity associated with AVS. Preoperative iodocholesterol adrenal scintigraphy has been used preoperatively to lateralize adrenal tumors [16]. However, this imaging modality is not widely available. In fact, a patient with bilateral adrenal masses in this study underwent a unilateral right adrenalectomy that showed differential uptake by [18] FDG PET/CT scan. The [18] FDG PET/CT findings in this study would be applicable and may either lateralize to identify the cortisol-hypersecreting adrenal mass or indicate to the clinician that the patient would benefit from a bilateral adrenalectomy.

A second potential use of 18F-FDG PET/CT involves patients with subclinical hypercortisolism. Unlike CS, subclinical hypercortisolism is defined as a patient with biochemical evidence of excess cortisol without overt clinical signs and manifestations [17–19]. The disease is estimated to be found in 0.2–2.0 % of the adult population [18]. SUV findings in benign CS have previously been limited to a single case report detailing a 48-year-old woman with subclinical hypercortisolism and a left adrenal tumor showing increased 18F-FDG uptake [20]. In the current study, one patient had subclinical CS and evidence of increased uptake with a normal contralateral adrenal gland. Thus, this suggests that utilizing 18F-FDG PET/CT scanning in patients with subclinical CS may be useful. Patients with subclinical hypercortisolism would be an excellent cohort to study, if FDG PET/CT can potentially help differentiate if these patients are indeed secreting excess cortisol versus presenting with false-positive biochemical findings.

Patients with cyclic CS may also benefit from an 18FFDG PET scan showing avidity within the adrenal glands. Patient's with cyclic CS have irregular hormonogenesis with constant or intermittent clinical signs and symptoms [21]. These patients may have a normal dexamethasone suppression test result due to cycling out of hypercortisolism. Measuring UFC or salivary cortisol may identify these patients, but may also result in normal findings [22]. One of the potential pathophysiological mechanisms of cyclic CS involves necrosis and hemorrhage within the adrenal tumor resulting in intermittent release of cortisol. Indeed, pathological analysis from resected cyclic CS adenomas has shown the presence of necrosis in resected adrenal glands [21]. 18F-FDG uptake is facilitated by areas of hypoxia and increased glycolysis [7]. Therefore, given this potential mechanism and difficulty in diagnosis of cyclic CS, 18F-FDG PET/CT could potentially be a very valuable diagnostic adjunct tool in these patients.

The biological mechanism of glucose uptake in patients with cancer undergoing 18F-FDG PET/CT scan has been studied in various cancers [9–11]. Our data show a higher proportion of cells with positive staining for GLUT3 in patients with CS compared to Conn's syndrome and nonfunctioning adrenocortical tumors. There was no significant association between the proportion of GLUT3 cells staining positive and 18F-FDG uptake. A significant correlation may not have been detected due to the small sample size and would require further study to validate the biological underpinnings of FDG uptake in patients with CS. However, given the genome-wide expression data, and the validation of this by immunohistochemistry, FDG uptake is likely accounted by overexpression of GLUT3 in patients with hypersecreting cortisol tumors.

The limitations of this study include small sample size and specifically a small number of patients with bilateral adrenal masses without genetic predisposition. One patient in this study was able to lateralize with 18F-FDG PET/CT scan, and this supports our hypothesis that cortisol-secreting tumors have higher SUVmax. Whether 18F-FDG PET/CT scan can lateralize cortisol hypersecretion in patients with bilateral adrenal masses will require further study. The optimal cut-off value will also require further study prior to applying this to clinical practice.

In conclusion, in this pilot study, 18F-FDG PET/CT uptake in patients with cortisol-hypersecreting adrenal tumors is higher than in patients with nonfunctional adrenal masses and aldosterone-hypersecreting masses. 18F-FDG PET/CT could potentially serve as an adjunct lateralizing tool in patients with CS and bilateral adrenal masses, or cyclic CS but will require further study. Furthermore, *GLUT3* overexpression in cortisol-secreting tumor likely accounts for the observed differential 18F-FDG uptake in cortisol-secreting tumors.

Acknowledgments

Financial support This research was supported by the intramural research program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health.

References

1. Guaraldi F, Salvatori R (2012) Cushing syndrome: maybe not so uncommon of an endocrine disease. *J Am Board Fam Med* 25: 199–208 [PubMed: 22403201]
2. Ganguly A (1998) Primary aldosteronism. *N Engl J Med* 339:1828–1834 [PubMed: 9854120]
3. Funder JW, Carey RM, Fardella C et al. (2008) Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 93:3266–3281 [PubMed: 18552288]
4. Kasperlik-Zaluska AA, Slowinska-Srzednicka J, Roslonowska E et al. (2010) Bilateral, incidentally found adrenal tumours—results of observation of 1790 patients registered at a single endocrinological centre. *Endokrynol Pol* 61:69–73 [PubMed: 20205107]
5. Kempers MJ, Lenders JW, van Outhousden L et al. (2009) Systematic review: diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism. *Ann Intern Med* 151:329–337 [PubMed: 19721021]
6. Young WF, Jr, du Plessis H, Thompson GB et al. (2008) The clinical conundrum of corticotropin-independent autonomous cortisol secretion in patients with bilateral adrenal masses. *World J Surg* 32:856–862. doi:10.1007/s00268-007-9332-8 [PubMed: 18074172]

7. Naji M, Hodolic M, El-Refai S et al. (2010) Endocrine tumors: the evolving role of positron emission tomography in diagnosis and management. *J Endocrinol Invest* 33:54–60 [PubMed: 19820296]
8. Groussin L, Bonardel G, Silvera S et al. (2009) 18F-Fluorodeoxyglucose positron emission tomography for the diagnosis of adrenocortical tumors: a prospective study in 77 operated patients. *J Clin Endocrinol Metab* 94:1713–1722 [PubMed: 19190108]
9. Kaira K, Okumura T, Ohde Y et al. (2011) Correlation between 18F-FDG uptake on PET and molecular biology in metastatic pulmonary tumors. *J Nucl Med* 52:705–711 [PubMed: 21498541]
10. Charnley N, Airley R, Du Plessis D et al. (2008) No relationship between 18F-fluorodeoxyglucose positron emission tomography and expression of Glut-1 and -3 and hexokinase I and II in high-grade glioma. *Oncol Rep* 20:537–542 [PubMed: 18695903]
11. Park SG, Lee JH, Lee WA et al. (2012) Biologic correlation between glucose transporters, hexokinase-II, Ki-67 and FDG uptake in malignant melanoma. *Nucl Med Biol* 39:1167–1172 [PubMed: 22901702]
12. Fernandez-Ranvier GG, Weng J, Yeh RF et al. (2008) Identification of biomarkers of adrenocortical carcinoma using genomewide gene expression profiling. *Arch Surg* 143:841–846 [PubMed: 18794420]
13. Bolstad BM, Irizarry RA, Astrand M et al. (2003) A comparison of normalization methods for high density oligonucleotide array data based on variance and bias. *Bioinformatics* 19:185–193 [PubMed: 12538238]
14. Benjamini Y, Drai D, Elmer G et al. (2001) Controlling the false discovery rate in behavior genetics research. *Behav Brain Res* 125:279–284 [PubMed: 11682119]
15. Vassiliadi DA, Ntali G, Vicha E et al. (2011) High prevalence of subclinical hypercortisolism in patients with bilateral adrenal incidentalomas: a challenge to management. *Clin Endocrinol* 74:438–444
16. Yu KC, Alexander HR, Ziessman HA et al. (1995) Role of pre-operative iodocholesterol scintiscanning in patients undergoing adrenalectomy for Cushing's syndrome. *Surgery* 118:981–987 [PubMed: 7491543]
17. Reincke M (2000) Subclinical Cushing's syndrome. *Endocrinol Metab Clin N Am* 29:43–56
18. Chiodini I (2011) Clinical review: diagnosis and treatment of subclinical hypercortisolism. *J Clin Endocrinol Metab* 96:1223–1236 [PubMed: 21367932]
19. Young WF, Jr (2000) Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota. *Endocrinol Metab Clin N Am* 29:159–185
20. Shimzu Y, Matsui S, Harada J (2003) Evaluation of micro-organic pollution in lake sediments: application to Akanoi Bay Lake Biwa, Japan. *Environ Technol* 24:889–896 [PubMed: 12916840]
21. Meinardi JR, Wolffenbuttel BH (2007) Dullaart RP cyclic Cushing's syndrome: a clinical challenge. *Eur J Endocrinol* 157: 245–254 [PubMed: 17766705]
22. Nieman LK, Biller BM, Findling JW et al. (2008) The diagnosis of Cushing's syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 93:1154–1526

Fig. 1.

A comparison of FDG PET/CT SUV_{max} values of patients with nonfunctioning adrenal masses, patients with hyperaldosteronism, and patients with hypersecreting cortisol adrenal masses SUV_{max} ($p = 0.007$)

Fig. 2.

Genome-wide expression data presented as a heat map with *shades of red* showing increased gene expression and *shades of blue* showing decreased gene expression. Selected heat map of *GLUT3* probes with expression that was **a** 2.19-fold higher in patients with CS compared to nonfunctioning adenomas ($p = 0.003$), and **b** 2.16-fold higher in patients with CS compared to patients with Conn's syndrome ($p = 0.006$)

Fig. 3.

Representative immunohistochemistry (100 μ m scale) for GLUT3 protein a in **a** patient with Conn's syndrome, **b** in a patient with Cushing's syndrome, and **c** in a patient with nonfunctioning adrenocortical tumors. Negative controls **d** in a patient with Conn's syndrome, **e** in a patient with Cushing's syndrome, and **f** in a patient with nonfunctioning adrenocortical tumors

Table 1

Clinical, radiological, and biochemical characteristics of the study cohort

	Nonfunctioning	Conn's syndrome	Cushing's syndrome
Number of patients	9	4	11
Sex (Female/Male)	7/2	2/2	7/4
Age (Ave. $\pm$ SD)	58.1 $\pm$ 9.5	48.0 $\pm$ 13.2	44.0 $\pm$ 15.7
Number of adrenal masses on CT scan	11	5	16
Laterality (unilateral/bilateral)	9/0	3/1	5/7
Size of adrenal masses (cm, Ave. $\pm$ SD)	3.6 $\pm$ 1.2	1.2 $\pm$ 0.4	4.5 $\pm$ 2.8
24-h urinary free cortisol reference range: 3.5–45.0 mcg/24 h (Ave. $\pm$ SD)	18.3 $\pm$ 5.05	12.8 $\pm$ 9.2	154.2 $\pm$ 183.1
1-mg dexamethasone suppression test	2.1 $\pm$ 1.4	1.0 $\pm$ 0.0	14.4 $\pm$ 7.4
Reference range <3 mcg/dl) (Ave. $\pm$ SD)			
PAC/PRA (ng/dl/ng/ml/h, Ave. $\pm$ SD)	10.2 $\pm$ 6.3	37.8 $\pm$ 11.4	4.8 $\pm$ 2.9