Percutaneous Bilateral Adrenal Radiofrequency Ablation in Severe Adrenocorticotropic Hormone-dependent Cushing Syndrome

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ABSTRACT

Objectives: The objectives of the study were to evaluate adrenal radiofrequency ablation (RFA) as a method of treatment in patients with severe adrenocorticotropic hormone (ACTH)-dependent Cushing syndrome, among whom bilateral adrenalectomy is not a suitable option.

Material and Methods: Five patients with ACTH-dependent Cushing syndrome underwent RFA of both adrenal glands. Four of them presented with Cushing disease unsuccessfully treated with pituitary surgery and medical therapy, while one patient had ACTH-dependent Cushing syndrome due to pancreatic endocrine tumor with liver metastases. All patients were disqualified from adrenalectomy due to morbid obesity or lack of consent.

Results: A technical success was obtained in all cases, with only one re-intervention necessitated by a cooling effect of the inferior vena cava. Despite pre-procedural adrenergic blockade, severe hypertension was noted during the procedure in three cases, this being treated immediately using direct-acting vasodilators. No complications occurred otherwise. In all cases, significant improvement of clinical symptoms was observed, as well as marked decreases in levels of serum cortisol, free urine cortisol, and dehydroepiandrosterone sulfate.

Conclusion: Bilateral RFA under CT-guidance is technically feasible and clinical improvement can be achieved using the method. In patients disqualified from adrenal surgery, RFA might be considered as an alternative method of ACTH-dependent Cushing syndrome treatment.

Keywords: Cushing syndrome, Cushing disease, Adrenal ablation, Adrenalectomy, Radiofrequency ablation

INTRODUCTION

Cushing syndrome is a disorder characterized by prolonged glucocorticoid excess. It can be caused by exogenous steroid use, adrenocorticotropic hormone (ATCH) producing pituitary adenoma (Cushing disease), ectopic production of ACTH, or adrenal tumors.

The main signs and symptoms of Cushing syndrome include obesity, edema, cardiovascular events, diabetes, infections, muscle weakness, and depression. Some of these symptoms, especially cardiovascular events and infections, can prove life-threatening.

Typical treatment of ACTH-dependent Cushing syndrome involves surgical removal of a pituitary adenoma or ectopic ACTH-secreting tumor. While medical therapy is a typical treatment for patients with persistent hypercortisolism following pituitary surgery, it fails frequently.¹
Should these therapies fail, bilateral adrenalectomy can be used as the next treatment; though some patients are not good candidates for this procedure on account of their marked obesity. Moreover, while peptide receptor radionuclide radiotherapy (PRRT) can also be effective in these patients, this is associated with significant risk of hypopituitarism.\(^2\)

Case reports have been published on microwave adrenal ablation in ectopic Cushing syndrome,\(^3,4\) but no radiofrequency ablation (RFA) cases have so far been reported. Furthermore, lacking is published data on adrenal ablation in patients with Cushing disease. Under those circumstances, the work detailed here has sought to evaluate the efficacy and safety of adrenal RFA in five patients with Cushing syndrome (including four with Cushing disease).

**MATERIAL AND METHODS**

The study was approved by the Warsaw Medical University Bioethical Committee. Five patients (three women and two men; mean age 44; range 25–70) who had undergone CT-guided RFA of both adrenal glands were included in this study and four of them presented with Cushing disease. All had been treated by means of pituitary surgery (one of them 3 times), while two had also received peptide receptor radionuclide therapy. The fifth patient suffered from ACTH-dependent Cushing syndrome due to unresectable pancreatic neuroendocrine tumor (NET) with liver metastases. He was treated surgically (with primary tumor resection), followed by PRRT. The inclusion criteria were morbid obesity or lack of consent that disqualified the patient from adrenalectomy.

Lack of follow-up was the exclusion criterion, and two patients with ectopic Cushing syndrome treated with RFA were excluded from the study for that reason.

The most common symptoms the patients presented with were obesity, diabetes, hypertension, osteopenia, and depression [Table 1].

The procedures were conducted in an interventional CT suite, under general anesthesia with intra-arterial blood-pressure monitoring. Doxazosin mesylate was administered for 2 weeks before the procedure, to limit hypertensive crisis during the ablation. In all cases, the posterior approach was chosen in ipsilateral decubitus to prone position. The procedures were performed under CT guidance (Aquilion One, Toshiba/Canon). During ablations StarBurst Talon Semi-Flex electrodes were used with 9 min ablation time and with end point temperature of 105°C. The “heat sink” effect generated by IVC proved a significant limiter of right-adrenal ablation, and the procedure had to be repeated in the first patient. In the following four patients, the “heat sink” effect was reduced by displacing IVC with hydrodissection (5% Glucose, 100–300 ml). In two patients, hydrodissection was used to displace splenic vessels and the pancreas [Figure 1].

Ablation required multiple applications of heat to achieve overlapping ablation zones covering long, hyperplastic adrenal glands. The mean number of applications per procedure was 4.6.\(^3\)\(^4\)\(^6\)

![Figure 1: A 43-year-old woman with Cushing syndrome presented with diabetes and hypertension. Non-enhanced CT showing an electrode (white arrow) targeting the left adrenal and Chiba needle (black arrow) for hydrodissection (arrowhead), to displace the splenic artery and pancreas (asterisk).](image-url)
Rosiak, et al.: Percutaneous bilateral adrenal radiofrequency ablation in severe ACTH-dependent Cushing syndrome

Serum cortisol, free urine cortisol, dehydroepiandosterone sulfate (DHEA-S), and ACTH levels were all measured ahead of the procedure and at follow-up times ranging from 18 to 24 months.

In all patients with osteopenia, bone mineral density was measured using densitometry.

Post-procedural contrast-enhanced CT was carried out immediately after the procedure, to exclude potential complications and allow for the assessment of the volume of the adrenal ablation zone [Figures 2 and 3].

Due to the high probability of hypertensive crisis arising, the patients were screened pre-procedurally for intracranial aneurysms, using MR angiography without contrast administration (time of flight sequence).

**RESULTS**

The complete ablation zone was defined as a lack of contrast enhancement (coagulated tissue) on contrast-enhanced CT in the venous phase. Due to prominent enhancement of hyperplastic adrenal glands before the procedure, assessment of the ablation zone proved relatively easy.

A technical success was taken to have been achieved where ablation of at least 80% of adrenal gland volume had taken place.

On this basis a technical success rate of 100% was obtained, with only one re-intervention necessary, due to a cooling effect of the internal vena cava.

Despite pre-procedural preparation through adrenergic blockade, severe hypertension was noted in three patients. Radiofrequency current was terminated and direct-acting vasodilators (nitroprusside) administered immediately. Maximal systolic pressure ranged from 180 to 300 mmHg. RFA was continued with following blood pressure normalization. None of the patients presented with Nelson syndrome and no other complications occurred. No patient required antibiotic therapy.

Clinical improvement was observed in all cases [Tables 2 and 3]. Effects in all patients included reduction in body weight, blood pressure normalization, and improved carbohydrate metabolism. In two out of four patients, densitometry confirmed improvements as regards bone mineral density.

Follow-up also revealed significant improvement in terms of laboratory results. While before the procedure the mean morning serum cortisol level was 39.8 (28.8–61.6) μg/dl, by follow-up this had declined to 8.66 (4.7–16) μg/dl. Likewise, the mean free urine cortisol level pre-procedure was 402 (188.9–820.2); as opposed to 38.2 (20.5–57.2) at follow-up. Mean morning DHEA-S before the procedure was in turn 285.5 (195–450), as opposed to 22.8 (10–41) at follow-up. Morning serum ACTH went up in four of the patients with Cushing disease, while decreasing slightly (from 350 to 310 pg/ml) in the patient with NET.

At follow-up, two patients were found to require hydrocortisol supplementation.

**DISCUSSION**

Cushing syndrome is a debilitating, potentially life-threatening disease. There is, furthermore, a small group of patients in whom all treatment methods (pituitary surgery,
adrenalectomy, radiotherapy, or medical therapy) have either failed or have not proved feasible. In that light, this report has sought to document the efficacy of bilateral adrenal ablation as an alternative treatment in such patients. Specifically, four patients with Cushing disease and one with ectopic Cushing syndrome presented, in the light of a failure of the typical modes of treatment referred to. Notably, adrenalectomy in these patients was ruled out by their morbid obesity or lacks of consent, with the result that bilateral adrenal RFA was performed instead.

In all of the patients reported on here, adrenal ablation had the effect of reducing levels of serum cortisol, free urine cortisol, and DHEA-S significantly. Furthermore, the decreases in question were found to be present 18 or even 24 months after ablation. ACTH levels increased in all of the patients other than the ectopic Cushing syndrome patient. There was also considerable improvement regarding such clinical symptoms as body weight, diabetes, hypertension, and mineral bone density [Tables 2 and 3].

RFA of adrenal glands in tumor treatment has been reported widely,[5-10] and multiple publications describe ablation of functioning adrenal tumors.[11-15] In turn, the few published reports on microwave adrenal ablation in ectopic Cushing syndrome[3,4,16] note a significant decrease in serum cortisol levels, although with follow-up periods only between a week and 5 months in length. Sarma et al.[4] reported how adrenal ablation in two patients with ectopic Cushing syndrome resulted in normalization of serum cortisol. However, the follow-up period was again a relatively short one (at 2–3 months). A second report[3] presented a patient

| Table 2: Clinical and laboratory effects of ablation. |
|-----------------------------------------------|
| Patient | Serum cortisol 8 AM (5–22 μg/dl) | Free urine cortisol (1–111 μg/24 h) | DHEA-S (8 AM) F (58–227 μg/dl) | M (41–405 μg/dl) | ACTH (8 AM) (5–46 pg/ml) | Clinical effects |
|---------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|         | Before | After | Before | After | Before | After | Before | After | Before | After | Before | After | Before | After | After | After | Before | After | Before | After | Before | After | Before | After | Before | After |
| 1       | 39.4   | 5.1 (sup) | 310.5 | 20.5 | 450   | 36   | 56   | 79   | Body weight reduction, blood pressure normalization, bone mineral density improvement |
| 2       | 36.3   | 9.7   | 285.2 | 57.2 | 195   | 41   | 59   | 120  | Body weight reduction, blood pressure normalization, improvement of carbohydrate metabolism |
| 3       | 28.8   | 7.5   | 188.9 | 44.8 | 228   | 15   | 54   | 75   | Body weight reduction, blood pressure normalization, bone mineral density improvement, improvement of carbohydrate metabolism |
| 4       | 31.9   | 4.7 (sup) | 405.3 | 25.0 | 243   | 10   | 94   | 341  | Body weight reduction, no depression, normal carbohydrate metabolism, hydrocortisol supplementation |
| 5       | 62.6   | 16 | 820.2 | 43.3 | 310   | 12   | 350  | 310  | No carbohydrate metabolism disorders, normal blood pressure, normal potassium levels |

sup: Hydrocortisol supplementation needed at follow up. after: 18–24 months after ablation. Normal values in parentheses

| Table 3: Clinical effects of ablation. |
|-----------------------------------------------|
| Patient | Body weight (kg) | Blood pressure (mmHg) | Glucose levels (mg/dl) |
|---------|-----------------|-----------------|-----------------|
|         | Before | After | Before | After | Before | After |
| 1       | 95     | 82    | 150/100 | 125/85 | 105   | 92   |
| 2       | 93     | 85    | 160/110 | 130/80 | 120   | 89   |
| 3       | 88     | 76    | 150/110 | 130/80 | 180   | 98   |
| 4       | 78     | 69    | 130/88  | 125/80 | 110   | 90   |
| 5       | 79     | 77    | 170/110 | 120/80 | 159   | 91   |
with ectopic Cushing syndrome treated by way of right adrenal microwave ablation. Before this, the patient had had pancreatic tumor resection, as well as a splenectomy, left adrenalectomy, and left nephrectomy. Following ablation, his serum-cortisol level decreased from 1976 to 74 nmol/L (71.6–2.6 μg/dl).

The results of our study have proved to be consistent with such past research, sustaining a theory that, where other methods have failed, adrenal ablation can be an effective method of treating Cushing syndrome. The fact that it can also be effective in patients with Cushing disease is something that has not been published on previously.

Incidences of hypertensive crisis are a well-known complication in patients undergoing percutaneous adrenal ablation procedures.\cite{17,18} This complication was also present in our group of patients. The most severe hypertension was noted in our first patient, in whom the procedure commenced with adrenal-limb ablation. Our view is that it is worth first ablating the adrenal body, with the probable result of thrombosis of adrenal veins and prevention of extensive catecholamine release in the course of the procedure. Even though pre-procedural adrenergic blockade does not eliminate the risk hypertensive crisis, it can be effectively managed with nitroprusside sodium.

This is the first report on adrenal ablation as a method of treating Cushing disease. It furthermore details by far the largest group of patients with Cushing syndrome to be treated in this manner, and also extends to the longest-ever follow-up. In addition, this is the first report on RFA in patients with Cushing syndrome (as opposed to the microwave ablation detailed in the previous reports).

The small number of patients is nevertheless the main limitation of this study.

CONCLUSION

Radiofrequency ablation is shown to be effective in patients with severe, drug-resistant, ACTH-dependent Cushing syndrome, among whom adrenal surgery is precluded. Further studies on larger numbers of patients will nevertheless be necessary if the role of ablation in such cases is to be determined fully.

Declaration of patient consent

Institutional Review Board permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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