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LETTER TO THE EDITOR

Assessment of long-term efficacy and safety of metyrapone monotherapy in a patient with ACTH-independent macronodular adrenal hyperplasia

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To the Editor,

ACTH-independent macronodular adrenocortical hyperplasia (AIMAH) is a rare form of Cushing's syndrome (CS), characterized by macronodular enlargement of the bilateral adrenal glands. Although an 11β-hydroxylase inhibitor, metyrapone, has been used in inoperable CS cases, its efficacy and safety for AIMAH are still unclear. The curative therapy for AIMAH is bilateral adrenalectomy; however, because AIMAH usually occurs in elderly persons, patients often have high operation risks.

A 69-year-old woman, with apparent cushingoid features, was referred to us for hypokalemia (2.1 mEq/l) after coronary artery bypass graft surgery for triple-vessel disease. She received insulin therapy for diabetes (HbA1c, 8.8%). Abdominal computed tomography revealed macronodular enlargement of the adrenal glands (right, 48 × 31 mm; left, 55 × 33 mm). Morning plasma ACTH and cortisol levels were <5.0 pg/ml (reference 7.4–54.7) and 19.0 μg/dl (reference 4.0–18.3), respectively. The cortisol level did not show circadian variation. Urinary free cortisol (UFC) level was 328 μg/day (reference 11.2–80.3). Dexamethasone suppression tests (DSTs) with 2 and 8 mg indicated unsuppressed morning cortisol levels (29.6 and 34.2 μg/dl, respectively). Rapid ACTH (250 μg i.v.) test showed overreaction of cortisol levels (26.2 to 110.0 μg/dl). Vasopressin (10 U i.m.) administration increased the cortisol levels (32.7 to 53.5 μg/dl). ^{131}I-adosterol scintigraphy showed strong uptake in the bilateral adrenal glands. These findings indicated vasopressin-responsive AIMAH.

The patient had severe coronary disease and underwent metyrapone therapy. Ten-day metyrapone (750 mg) administration decreased UFC level (110 μg/day) and improved diabetes. To prevent adrenal insufficiency, 0.5 mg dexamethasone was administered with 750 mg metyrapone (block and replacement); however, cortisol level increased. Ten days after dexamethasone was discontinued, high UFC level (364 μg/day) improved again (51.4 μg/day). Because dexamethasone induces the expression of UDP-glucuronosyltransferases and cytochrome 3A enzymes [1], it might accelerate metyrapone elimination via glucuronidation or affect cortisol metabolism in this case. Thereafter, 1000 mg metyrapone was administered and cortisol levels were normalized (7.8–19.1 μg/dl). Cross-reactivity of the antibody used for the cortisol assay with 11-deoxycortisol was 17.8%.

After 7 years of metyrapone treatment, its therapeutic effect was re-evaluated. Plasma ACTH and cortisol levels at 0700 and 2300 h were 6.0 pg/ml and 13.9 μg/dl, and 6.0 pg/ml and 7.0 μg/dl, respectively, and UFC level was 38.5 μg/day. One-mg DST indicated unsuppressed cortisol level (11.8 μg/dl). HbA1c level was 6.2% with pioglitazone (15 mg) treatment. AST and ALT levels were 17 U/l (reference 13–33) and 11 U/l (reference 6–27), respectively. Liver enzyme levels were within the reference ranges during the course of treatment. Adrenal lesion enlargement, adrenal insufficiency, and hirsutism were not observed. Metyrapone inhibits aldosterone synthesis; plasma renin activity and aldosterone concentration were 4.9 ng/ml/h (reference 0.3–2.9) and 30.0 pg/ml (reference 30–159), respectively. Accumulated aldosterone precursor,

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11-deoxycorticosterone (6.35 ng/ml; reference 0.03–0.33) showed no adverse effect.

The effect of metyrapone administration for several months in an AIMAH patient has been reported [2]; however, its long-term outcome remains unknown. According to some reports on long-term (3–4 years) metyrapone therapy for bilateral adrenal hyperplasia because of ACTH-dependent CS and McCune-Albright syndrome, the hypercortisolemia improved [3, 4], whereas the unexpected development of pituitary and adrenal lesions was observed in 1 case [5].

In this case, low-dose metyrapone improved severe hypercortisolemia without adverse effects for 7 years. In AIMAH patients, key steroidogenic enzymes such as 17α-hydroxylase and 3β-hydroxysteroid dehydrogenase are expressed differentially between compact and clear cells, resulting in inefficient cortisol production. Therefore, metyrapone may efficiently block the cortisol synthesis. Metyrapone therapy is a useful therapeutic option for AIMAH, especially in inoperable cases.

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