ACTH-Independent Macronodular Adrenal Hyperplasia

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ACTH-independent macronodular adrenal hyperplasia (AIMAH) is an uncommon cause of Cushing’s syndrome (CS). The pathophysiology of this disorder is heterogeneous in its molecular origin and also in its clinical presentation. AIMAH can present mainly as an incidental radiological finding with sub-clinical CS or rarely with overt CS. In a few familial cases reported with AIMAH, specific aberrant G-protein coupled receptors were expressed in the adrenals of all affected members, but sporadic cases are more common. The aberrant adrenal function of G-protein coupled receptors can lead to cell proliferation and abnormal regulation of steroidogenesis. Unilateral or bilateral adrenalectomy has been the most frequently used treatment for this adrenal disorder; alternatively, the identification of aberrant receptors using in vivo protocol of investigation can offer specific pharmacological approach to control abnormal steroidogenesis and possibly prevent AIMAH progression. (Endocrinol Metab 26:1-11, 2011)

Key Words: ACTH-independent macronodular adrenal hyperplasia (AIMAH), Aberrant adrenal G-protein coupled receptors, Cushing’s syndrome, Familial forms

INTRODUCTION

ACTH-independent adrenal etiologies account for 15–20% of endogenous Cushing’s syndrome (CS) [1]. Unilateral functional adenomas and, less frequently, adrenal carcinomas are responsible for the majority of them; however in 10–15% of cases, adrenal CS is due to bilateral adrenal lesions [1]. The adrenal hyperplasias are classified in two groups: micronodular if the nodules are less than 1 cm and macronodular when the nodules are larger. The micronodular forms include primary pigmented nodular adrenocortical disease (PPNAD) and primary non-pigmented micronodular hyperplasia [1]. The macronodular forms are most frequently referred to as ACTH-independent macronodular adrenal hyperplasia (AIMAH) [1]. The first case of AIMAH was described in 1964 and thirty years later, Lieberman et al. [2] were able to review only 24 published cases of AIMAH. A variety of terms have been used to report larger number of cases including “massive macronodular adenocortical disease”, “autonomous macronodular adrenal hyperplasia”, “ACTH-independent massive bilateral adrenal disease”, “giant or huge macronodular adrenal hyperplasia”, and “macronodular adrenal dysplasia” [3-7]. In this review, we will discuss the clinical characteristics of AIMAH, its diverse genetic or molecular mechanisms and therapy.

Epidemiology

AIMAH represents less than 1% of endogenous overt CS; considering the high prevalence of incidentally found adrenal lesions, of which 10% are bilateral, AIMAH with sub-clinical cortisol secretion is now increasingly recognized [1,2,4-8]. AIMAH should not be confused with bilateral diffuse nodular adrenal lesions following chronic stimulation by ACTH in Cushing’s disease or ectopic ACTH secretion as these conditions can rarely generate relatively autonomous nodules which secrete sufficient cortisol to partially suppress ACTH [1].

AIMAH can be present in the first years of life particularly with the McCune-Albright syndrome (MAS) [9]. Most AIMAH patients present in the fifth and sixth decades, a later age of onset compared with unilateral adenomas [1,2,4]. It is also later than PPNAD, which

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occurs at a mean age of 18 years [4,10]. In contrast to the predominant female distribution in most causes of CS, AIMAH is equally distributed between genders [1,2,4-8].

Genetic causes of AIMAH

AIMAH was most frequently reported as sporadic cases, but lately, there have been reports of familial forms with apparent autosomal dominant mode of transmission [11-17]. As systematic familial screening was not conducted, the prevalence of familial forms of AIMAH is not known yet. In recently studied families with AIMAH, aberrant hormone receptors have been identified in their adrenal tissues (see later section), but the genes implicated have not been identified until now [14-17]. Bilateral adrenal enlargement was found in 21% of a series of 33 multiple endocrine neoplasia 1 (MEN 1) patients and the majority of cases did not present CS [18]. Bilateral adrenal nodules have also been found in patients with familial adenomatous polyposis (FAP). However, sporadic somatic mutations have been only rarely found in both MEN1 and APC genes [19]. Mutations in the fumarate hydratase gene (FH) have also been described in AIMAH [19,20].

Clinical and laboratory features

AIMAH usually presents as sub-clinical CS and, less often, as overt CS. However, in some cases there is a co-secretion of cortisol and aldosterone, cortisol and estrone, or androgens only [2,4-8,21-24]. In many patients, the adrenal lesions are found incidentally in the process of radiological investigation of another disease not related to adrenal gland. The occurrence of sub-clinical CS is defined as the absence of classical clinical signs of CS associated with subnormal suppression of fasting plasma cortisol following the 1-mg overnight dexamethasone suppression test (>50 nmol/L or 1.8 µg/dL), a partially suppressed ACTH and/or elevated midnight plasma cortisol, and normal 24-hour urinary free cortisol production [25]. Depending on the extent of cortisol hypersecretion, plasma ACTH and its stimulation by CRH will become progressively suppressed in AIMAH [2,6,21,22,26]. Transient CS presentation was described during pregnancy and it became sustained after menopause in a patient with AIMAH expressing aberrant adrenal receptors for LH/hCG [27]. In patients with ectopic GIP receptors in AIMAH, food-dependent cortisol secretion occurs after meals and plasma cortisol may be low when the patient is fasting in the morning when ACTH is suppressed [28]. The natural history of AIMAH causing sub-clinical CS is largely unknown. Ohashi et al. [26] reported a 7-year follow-up during which a patient with sub-clinical CS developed overt CS.

The ACTH receptor gene (MC2R) remains expressed in AIMAH though at lower levels, but the majority of patients respond to ACTH pharmacological stimulus with large increase of cortisol [1,7,8,29]. This answer can help to distinguish it from other causes of bilaterally enlarged adrenals such as metastatic or infiltrative diseases [1]. The hormone secretion in AIMAH results from an increase in the number of adrenocortical cells rather than an augmented synthesis per cell; in fact there is a relatively inefficient hormonal synthesis in AIMAH with relatively decreased expression of ACTH receptor and several steroidogenic enzymes [29]. In addition, certain steroid precursors such as plasma 17-OH-progesterone or urinary 17-OH-corticosteroids (U17OHCS) are found at high levels which are proportionally more elevated than urinary free cortisol [19,22,29-33]. This inefficient steroidogenesis may explain the discrepancy between sub-clinical cortisol secretion despite massive adrenal enlargement.

Imaging in AIMAH

The adrenal glands are enlarged bilaterally (Fig. 1) with the presence of numerous nodules up to 5 cm in diameter; however, diffuse adrenal enlargement without nodules has also been described [34]. On CT, the nodules present hypodensity and can have marked contrast enhancement. On MRI, T1-weighted images are hypointense relative to the liver and isointense relative to muscle. T2-weighted images tend to be hyperintense relative to the liver [34,35]. This helps to differentiate the nodules of patients with chronic ACTH stimulation that appear isointense relative to the liver on T2-weighted MR images [5,34,35]. The glands can demonstrate a signal dropout at chemical shift imaging, suggesting the presence of intracellular lipid [35]. Occasionally there is an asymmetric development of nodules in AIMAH, leading to the erroneous diagnosis of unilateral pathology, as the development of macroscopic contralateral disease can occur several years later [4,36]. Iodine 131-i-β-iodomethyl-19-norcholesterol (NP-59) scintigraphy usually shows bilateral uptake [5].

Pathology

The mean combined weight of both adrenal glands in one series was 132 grams and could reach 200 grams per gland [34]. On cut sections, the nodules are yellow due to their high lipid content [33]. The nodules are composed of two cell types either with clear cyto-
plasm (lipid-rich) that form cordon nest-like structures, or with compact cytoplasm (lipid-poor) that form nest or island-like structures [30,33]. In contrast with MAS in which inter-nodular atrophy is present, in AIMAH a diffuse inter-nodular hyperplasia is found [31,33,37]. AIMAH is a benign neoplasia that has never been shown to acquire a malignant potential in long term follow-up of patients.

Pathophysiology of AIMAH

The regulation of cortisol hypersecretion in AIMAH independently of ACTH regulation has been clarified in the last decades. There are now several evidences that steroidogenesis in AIMAH is regulated by hormones other than ACTH as a result of the aberrant expression of their respective receptors in adrenocortical nodular glands; this is the most prevalent pathophysiology in patients with AIMAH [8].

A constitutive ACTH receptor (MC2R) mutation is not a common cause of adrenal hyperplasia or tumor formation [38,39]. In MAS, activating mutations of the Gsα subunit occur in a mosaic pattern in early post-zygotic embryogenesis resulting in constitutive activation of the cAMP pathway nodular hyperplasia and CS [9,37,40-44]. In the adrenal gland of 3 of 5 patients with CS due to AIMAH without classical MAS, two different gsp mutations at codon Arg201 were found [45]; these cases may represent variants of MAS or may be the result of late somatic mutations. Hsiao et al. [19] also reported one AIMAH case with a gsp mutation.

Aberrant hormone adrenal receptors in adrenal CS

Several groups have demonstrated that cortisol secretion in most patients with AIMAH and in a large proportion of unilateral adrenal adenomas with sub-clinical or clinical CS are regulated by hormones other than ACTH via the aberrant expression of G-protein coupled hormone receptors [8,19,22,46-49]. The cortisol secretion is regulated by the physiological fluctuations of the agonist of the aberrant receptor. The aberrant stimulation of steroidogenesis can be driven by two kinds of receptors: ectopic receptors which are not expressed in zona fasciculata cells, such as the glucose-dependent insulinotropic peptide or gastric inhibitory polypeptide (GIPR), β-adrenergic receptors, vasopressin (V2-V3-vasopressin receptor), serotonin (5-HT7 receptor) and probably angiotensin II receptor (AT1R) and glucagon. The second one, designed eutopic receptors can have increased expression or altered activity with increased coupling to steroidogenesis such as: vasopressin (V1-vasopressin receptor), luteinizing hormone/human chorionic gonadotropin (LH/hCGR), serotonin (5-HT4 receptor) and probably angiotensin II receptor (AT1R) and glucagon. The second one, designed eutopic receptors can have increased expression or altered activity with increased coupling to steroidogenesis such as: vasopressin (V1-vasopressin receptor), luteinizing hormone/human chorionic gonadotropin (LH/hCGR), serotonin (5-HT4 receptor) and probably angiotensin II receptor (AT1R) and glucagon.

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Investigation protocol for aberrant receptors

Investigative protocols have been developed to study patients with adrenal CS or sub-clinical CS to identify the regulation of steroid production by one or several aberrant receptor [46,47,51,52]. The strategy consists of modulating the plasma levels of diverse hormone (endogenous or exogenous) ligands for the potential aberrant receptors, while monitoring plasma levels of cortisol, other steroids and ACTH. All tests are performed following an overnight fast and in a supine position for at least 1 hour. For patients with sub-clinical CS, the studies are conducted under suppression with 1 mg dexamethasone every 6 hours, beginning 48-hours before the tests in order to avoid any effect of ACTH on steroidogenesis. The initial screening (Table 1) is performed in 3 days and involves during the first day a posture test to screen for receptors to angiotensin II, vasopressin, or catecholamines; a standard mixed meal to assess the presence of GIP or other gastrointestinal hormone receptors; and cosyntropin test (ACTH 250 μg IV) [52]. During the second day, the administration of GnRH 100 μg i.v. evaluates responses to LHRH, LH and FSH; TRH 200 μg i.v. screens for modulation by THR, TSH or prolactin. In the last day, the protocol is completed with the sequential administration of glucagon 1 mg i.m.; vasopressin 10 UI i.m. and 10 mg metoclopramide orally as a serotonin 5-HT4 agonist. Serial measurements of ACTH, cortisol and other steroids are performed at 30 to 60 minutes intervals during 2-3 hours following the intervention. The increment of 25-49% from the baseline of the steroid levels in the absence of an increase in ACTH level is defined as a partial response and an increase more than 50% is considered a positive response; the test should be repeated to confirm the response to the specific ligand and its reproducibility. Fluctuations of the putative ligand hormones of interest are also measured to better characterize the modulator of the response. When a positive response following this initial screening is confirmed, further stimulatory test should be undertaken to precisely define the hormone and the specific receptor type implicated (Fig. 3).

AIMAH with vasopressin--aberrant response

The most frequent aberrant response in patients with either AIMAH or unilateral adenomas with CS or sub-clinical CS has been the ACTH-independent increase of cortisol following exogenous vasopressin or physiological stimuli of vasopressin secretion such as upright posture [14-16,22,46,53-60]; this was found in close to 60% of patients in systematic screening studies [19,46,49,51]. Fluctuations of endogenous physiological levels of vasopressin (water and hypertonic sodium loading) resulted in parallel changes of plasma cortisol levels. The action of vasopressin was mediated via non-mutated V1-vasopressin receptors that are expressed at higher or similar levels compared with controls [56-60]. As the V1 receptor is normally expressed in the adrenal cortex and its activation leads to a modest in vitro increase in steroidogenesis, the observed exaggerated steroidalogenic response represents an aberrant response of a eutopic receptor. It was reported that a non-peptide V1 receptor antagonist was partially effective to reduce hypercortisolism due to AIMAH in an 8 day-test [57]. The ectopic expression of V2 and V3-vasopressin receptors has been documented in vitro in adrenal tissue from patients with AIMAH, the significance of this finding is unclear, because a cortisol response was not observed when desmopressin, a preferential V2-vasopressin receptor agonist, was administered to some of these patients [15,16].

Serotonin--responsive AIMAH

In the normal adrenal gland, 5-HT4 receptor agonists are potent

Table 1. In vivo screening protocol to detect the presence of aberrant hormone receptors in adrenal Cushings syndrome

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>-60</td>
<td>Fasting-supine</td>
<td>Fasting-supine</td>
<td>Fasting-supine</td>
</tr>
<tr>
<td>-15</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>0</td>
<td>Upright *</td>
<td>GnRH 100 μg i.v. *</td>
<td>Glucagon 1 mg i.v. *</td>
</tr>
<tr>
<td>+30</td>
<td>Upright *</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>+60</td>
<td>Upright *</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>+90</td>
<td>Upright *</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>+120</td>
<td>Upright *</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>+150</td>
<td>Supine *</td>
<td>(meal)</td>
<td>Vasopressin 10 IU i.m. *</td>
</tr>
<tr>
<td>+180</td>
<td>Mixed meal *</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>+210</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>+240</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>+270</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>+300</td>
<td>*</td>
<td>TRH 200 μg i.v. *</td>
<td>*</td>
</tr>
<tr>
<td>+330</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>+360</td>
<td>ACTH 1-24 250 μg iv*</td>
<td>*</td>
<td>Metoclopramide 10 mg orally *</td>
</tr>
<tr>
<td>+390</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>+420</td>
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<td>+450</td>
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<td>*</td>
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</tr>
<tr>
<td>+480</td>
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</tbody>
</table>

*Blood samples for determination of cortisol, ACTH, other hormones, and vital signs. Modified with permission from Lacroix et al. The Endocrinologist 9:9-15, 1999 [52].
stimulators of aldosterone secretion but only weakly affect cortisol secretion \textit{in vitro} [8]. In vivo, they normally do not produce an increase in plasma cortisol [8]. The second most frequent (approximately 40% of patients) aberrant response in patients with AIMAH or unilateral adenoma is that observed following administration of 5-HT4R agonists [19,46,49,51]. The first patient described had a combination of LH/hCG responsive AIMAH, but cisapride and metoclopramide also stimulated her plasma cortisol to a larger extent [27]. In 6 cases of CS and AIMAH with aberrant cortisol responses to cisapride or metoclopramide, adrenal overexpression of the 5HT-4 receptor was found in the adrenal glands of 4 of these patients [61]. The aberrant response to 5-HT4R agonists was also found in patients with familial AIMAH, sub-clinical production of cortisol and incidentally found AIMAH [16,22,62]. The ectopic expression of 5-HT7 receptors has also been demonstrated in a patient with AIMAH and CS [63].

GIP-dependent AIMAH

Patients with GIP-dependent CS can present low fasting plasma cortisol levels, which increase following meals, despite suppression of ACTH [28,64-70]. Cortisol increases following physiological elevation in plasma level of GIP after meals, as the result of the ectopic expression of non mutated GIP receptor in zona fasciculata-type cells in AIMAH or unilateral adenomas [8,36,64-70].

The expression of the GIP receptor can be detected in the early phases of adrenal hyperplasia [32,36]. The demonstration that bovine adrenal cells transfected with the GIP receptor and injected under the renal capsule in mice leads to the development of hyperplastic adrenals and hypercortisolism further supports the initiation role of the ectopic receptor in the pathophysiology of AIMAH [71].

Catecholamine-responsive AIMAH

The ectopic expression of $\beta$-adrenergic receptors was first reported \textit{in vitro} in adrenal tumors causing CS [8]. \textit{In vivo}, aberrant responses of cortisol following elevations of endogenous catecholamines induced by upright posture, insulin-induced hypoglycemia or exercise were documented in patients with AIMAH and CS
[14, 46, 72-74]. Isoproterenol infusion stimulated cortisol and aldosterone secretion in these patients but failed to do so in normal subjects. Aberrant cortisol responses mediated by β-adrenergic agonists were also found in families with AIMAH and were present in patients with sub-clinical stages of the disease [14]. These aberrant responses were reduced by pretreatment with propranolol, a β-adrenergic antagonist [72, 75]. Recently, an in vitro transcriptome study found the 2A adrenergic (ADRA2A) receptor in 13 of 18 AIMAH studied; in a perfusion of AIMAH tissue, the cortisol secretion was stimulated by the ADRA2A agonist clonidine, while it was reduced after the administration of an antagonist yohimbine [76].

LH/hCG-responsive AIMAH

Hypercortisolism due to aberrant LH/hCG receptors was first identified in a woman with transient Cushing’s syndrome during sequential pregnancies; persistent Cushing’s syndrome and AIMAH developed only after the postmenopausal sustained increase of LH secretion [27]. In this patient, cortisol secretion was stimulated by the exogenous administration of GnRH, hCG, or recombinant LH. Administration of the long-acting GnRH agonist, leuprolide acetate, resulted in suppression of endogenous LH and normalization of cortisol production [27]. A virilized woman with androgen-secreting AIMAH regulated by hCG was shown to express the LH/hCG receptor in one resected adrenal; suppression of endogenous LH with leuprolide acetate normalized androgen secretion from the contralateral adrenal, avoiding bilateral adrenalectomy [23].

In two independent reports, women with CS and aberrant adrenal LH/hCG receptor were also found to have a gsp mutation of Gsa in their unilateral adenoma [77, 78]. Other cases of aberrant receptors for LH/hCG either alone or in combination with serotonin 5HT4 or GIP receptors have been reported [22, 79, 80].

Angiotensin-responsive AIMAH

Adrenal hypersensitivity to angiotensin II was suggested in a patient with AIMAH and CS in whom a large increase in plasma aldosterone and cortisol were noted during upright posture [81]. The short-term oral administration of candesartan, an AT-1 receptor antagonist, eliminated the stimulation of these adrenal hormones. In vitro stimulation of cortisol secretion by angiotensin-II was also found in other patients with AIMAH and CS who had increases in cortisol levels with upright posture, but the presence of the AT-1 receptor has not been assessed directly in this study [79].

Others abnormal responses in AIMAH

In a patient with AIMAH and CS, GIP and leptin were shown to aberrantly increase cortisol production in vitro [82]. An increase in cortisol following in vivo administration of glucagon was found in two patients with CS and unilateral adenoma; glucagon receptor and glucagon were found in the tumor tissue, suggesting combined ectopic receptor and paracrine ligand production [83].

A recent transcriptome study [76] found several not previously identified GPCR genes that were highly expressed in a subset of 18 AIMAH, such as the receptors for motilin (MLN; three of 18 AIMAHs), g-aminobutyric acid (GABBR1; five of 18 AIMAHs) and the a2A adrenergic receptor (ADRA2A; 13 of 18 AIMAHs). They also showed a significantly reduced expression in all 18 AIMAH of three GPCRs: the IL-8 receptor, the chemokine receptor 5, and the MC2R [76].

Molecular mechanisms of aberrant hormone receptors

The molecular mechanism responsible for the aberrant adrenocortical specific expression of these receptors is not yet known. Their expression in bilateral hyperplasias suggests the occurrence of a germline mutation in the familial cases while an initial event occurring during embryogenesis could be responsible for the sporadic cases. Somatic mutations would result in the unilateral adenomas expressing aberrant receptors [50]. It was unclear whether aberrant hormone receptors are a primary phenomenon responsible for the pathogenesis of AIMAH or adenomas, or an epiphenomenon resulting from cell proliferation and dedifferentiation; several evidences are in favor of the former hypothesis. The reversal of hyperplasia between pregnancies in LH/hCG dependent CS favors the first hypothesis [27]. The germline transmission of the same aberrant receptors in all affected family members in familial AIMAH is another strong indication in favor of an initiating role of the aberrant receptor [14-16]. The demonstration that bovine adrenocortical cells transfected with the GIPR or LH/hcGR and injected under the renal capsule in immunodeficient mice lead to the development of hyperplastic adrenals and hypercortisolism further supports the initiation role of the ectopic receptor in pathophysiology of AIMAH [71, 84].

The aberrant adrenocortical expression of a receptor most probably is a primary phenomenon which initiates bilateral diffuse hyperplasias and CS. In addition to the initiating effect of aberrant receptor on hyperplasia formation, other somatic genetic events occur in time, as demonstrated by microarray data [32], generating
diverse monoclonal nodule formation resulting in the AIMAH phenotype (Fig. 4).

**Paracrine mechanisms in AIMAH**

Other paracrine regulatory mechanisms were suggested in some AIMAH cases after the demonstration of increased adrenocortical expression of pro-opiomelanocortin/ACTH, serotonin, vasopressin or glucagon in some affected adrenal tissues [60,61,63,85-88]. Thus, in addition to the aberrant expression of diversified hormone receptors, the local adrenal (adrenal cortex, adrenal medulla and adrenal tumor/hyperplasia) production of ligands for these receptors would allow an important contribution of paracrine or autocrine regulation in addition to the hormonal regulation of circulating hormones for these receptors. Recent preliminary data suggested that aberrant activation of GIPR and LH/hCGR in AIMAH tissues in perifusion stimulated local production of ACTH and that cortisol secretion was partially inhibited by the MC2R antagonists cortistatin and ACTH 7-38 [88]. Thus a complex interaction between aberrant receptors and ligands of endocrine and paracrine origin for those receptors could regulate local steroidogenesis.

**Treatment of patients with AIMAH**

Bilateral adrenalectomy has been the most utilized treatment in patients with AIMAH and hormonal hypersecretion including overt CS [2,4,6]. However, in patients with moderately increased hormonal production, unilateral adrenalectomy has been proposed as a safe and effective alternative [75,89-91]; it is expected that, as the cell mass increases in the contralateral adrenal, a second adrenalectomy may become necessary later. AIMAH is a benign process that has never been shown to become malignant. In sub-clinical CS with AIMAH, follow up with annual CT scan and biochemical assessment is sufficient.

The identification of aberrant adrenal hormone receptors in AIMAH provides new opportunities for specific pharmacological therapies as alternative to adrenalectomy (Table 2). Pharmacological blockade of post-prandial release of GIP using octreotide [67,92] or pasireotide [93] led to clinical and biochemical improvement of CS, although the benefit lasted only a few months, probably as the result of eventual desensitization of somatostatin-receptors in GIP-secreting duodenal K cells [67,92]. In catecholamine-dependent CS in AIMAH, β-adrenergic receptor antagonists were efficient in the long-term control of hormonal hypersecretion [17,72,75]. In LH/hCG-dependent AIMAH and CS or androgen excess, suppression of endogenous LH levels with long-acting leuprolide acetate con-

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**Fig. 4.** Hypothesis of sequential genetic events leading to AIMAH. The initial event is the aberrant expression of the LH/hCG receptor in the adrenal cortex during early embryonic life. Upon stimulation of this receptor, as during pregnancy (activation by hCG), diffuse adrenal hyperplasia (polyclonal) and transient CS occurs, but this is still reversible when hCG and LH levels are reduced following delivery. After menopause, the constant elevation of LH causes diffuse hyperplasia and CS. Other (second, third) somatic events occur progressively with time in a small number of cells; the monoclonal proliferation of these cells leads to appearance of several nodules which have maintained the expression of aberrant LH/hCGR. The inhibition of LH levels is able to control the excess production of steroids; this may be able to induce regression of adrenal growth at the stage of hyperplasia, but it may become insufficient to cause tumor regression when other oncogenic events have provided additional growth advantage to these cells. Reproduced with permission from Lacroix et al. Trends Endocrinol Metab 15:375-382, 2004 [47].

**Table 2.** Medical treatment options for identified aberrant adrenal hormone receptors using an *in vivo* screening protocol in AIMAH

<table>
<thead>
<tr>
<th>Aberrant receptor</th>
<th><em>In vivo</em> screening protocol</th>
<th>Medical treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIP</td>
<td>Mixed meal, oral glucose</td>
<td>Octreotide, GIPR antagonist</td>
</tr>
<tr>
<td>Vasopressin receptor (V1, V2, V3)</td>
<td>Upright posture administration of arginine-vasopressin or desmopressin</td>
<td>VP receptor antagonist</td>
</tr>
<tr>
<td>β-adrenergic receptor</td>
<td>Upright posture, isoproterenol infusion</td>
<td>β-blockers</td>
</tr>
<tr>
<td>LH/hCG receptor</td>
<td>GnRH administration; hCG, recombinant LH</td>
<td>Long-acting GnRH agonist</td>
</tr>
<tr>
<td>5-HT4 receptor</td>
<td>Administration of 5-HT4 receptor agonists</td>
<td>5-HT4 receptor antagonist</td>
</tr>
<tr>
<td>AT-1 receptor</td>
<td>Upright posture, angiotensin infusion</td>
<td>AT-1 receptor antagonist</td>
</tr>
</tbody>
</table>

GIP, gastric inhibitory polypeptide; LH/hCG, luteinizing hormone/human chorionic gonadotropin.
trolled steroid secretion and avoided bilateral adrenalectomy [23, 27]. It is possible that tumor regression might not occur, despite efficient blockade of the aberrant receptors, because other genetic events (other than aberrant receptors) inducing proliferation can appear over time [32,47] (Fig. 4).

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