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IS DESMOPRESSIN USEFUL IN THE EVALUATION OF CUSHING'S SYNDROME?

¹Frederic Castinetti, ²André Lacroix

¹Department of Endocrinology, Aix Marseille University, Assistance Publique-Hopitaux de Marseille, INSERM, Marseille Medical Genetics, Marmara Institute, French Reference Center for Rare Pituitary Diseases, Endo-European Reference Network and EURACAN European Expert Center on Rare Pituitary Tumors, La Conception Hospital, Marseille, France.

²Division of Endocrinology, Department of Medicine Research Center, Centre hospitalier de l'Université de Montréal (CHUM), Montréal, Québec, Canada.

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Corresponding authors:

Frederic Castinetti – Department of endocrinology, La Conception Hospital, 145 Boulevard Baille, 13385 Marseille Cedex 05, France. Frederic.castinetti@ap-hm.fr. ORCID **0000-0002-1808-8800**

André Lacroix – Division of Endocrinology, Department of Medicine, Research center, Centre hospitalier de l'Université de Montréal (CHUM), 900 Saint-Denis Street, H2X 0A9, Montréal, Québec, Canada. andre.lacroix@umontreal.ca. ORCID **0000-0003-4137-3025**

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ABSTRACT

The desmopressin test was first described 30 years ago. Based on the differential secretagogue properties of desmopressin on ACTH release between normal and corticotroph tumor cells, this test was intended to facilitate the diagnosis of Cushing's syndrome. The distinct expression of the various arginine vasopressin receptors between normal pituitary, corticotroph tumors, or neuroendocrine tumors cells secreting ACTH ectopically suggested that this test could facilitate the etiological diagnosis of ACTH-dependent Cushing's syndrome. In this review, we have analyzed the merits and pitfalls of desmopressin use in the diagnostic procedures of Cushing's syndrome. Desmopressin response is not able to completely differentiate the various etiologies of Cushing's syndrome; its wider availability has allowed to use it for inferior petrosal sinus sampling confirmation of pituitary source of ACTH excess. In addition, desmopressin can be useful to demonstrate adequate corticotroph tumor resection when its stimulatory effect is lost following pituitary surgery of patients with Cushing's disease. Desmopressin response can also be a marker of the risk of longer-term postoperative recurrence. However, this review also highlights the lack of consensual criteria of normal or abnormal response to desmopressin in its various uses and requirement for further research on its usefulness.

Introduction

Desmopressin (1 deamino-S-D-arginine vasopressin), a long-acting synthetic analogue of vasopressin (also called arginine vasopressin), was synthesized in 1967 for the treatment of diabetes insipidus¹. It was not until 1974 that Coslovsky et al. reported a stimulatory effect of lysine-vasopressin on the corticotroph axis, through the excretion of 17-urinary hydroxycorticosteroids in 7 patients with Cushing's disease (CD) compared with 11 healthy subjects². The hypothesis then accepted was that lysine-vasopressin either caused a secretion of CRH or directly stimulated the secretion of ACTH². Almost 20 years later, Malerbi et al. reported that in contrast to vasopressin, desmopressin did not stimulate ACTH secretion in most normal subjects, while it led to ACTH stimulation in a large proportion of patients with CD³. In this review, we summarize the pathophysiological mechanisms of desmopressin use, the usefulness of desmopressin response in the positive and etiological diagnosis of CS (including its role as a secretagogue in bilateral intrapetrosal sinus sampling, BIPSS), as well as its role as a predictor or marker of recurrence in the postoperative surveillance of patients with CD following their initial corticotroph tumor resection. For this review, a systematic search was performed on Pubmed using the terms "Desmopressin", "Vasopressin" and "Cushing" from 1993 to 2021.

1. Vasopressin receptors in normal pituitary and in CS

Vasopressin acts through different G-protein coupled receptors. The V1 or V1a receptor (AVPR1A) is present in the liver, brain, smooth muscle, mesangial cells and platelets: it stimulates the phospholipase C pathway. The V2 receptor (AVPR2) is expressed in the kidney tubule, predominantly in the distal convoluted tubule and collecting ducts, where binding of arginine vasopressin (AVP) leads to G α and adenylyl cyclase activation and mechanisms that concentrate the urine and maintain water homeostasis. The V3 (or V1b, AVPR1B) receptor is expressed at a low level in pituitary corticotroph cells⁴.

The pathophysiological mechanisms explaining the response to desmopressin in CD remain controversial. As early as 1996, Dahia et al. reported an ectopic expression of the AVPR2, and

overexpression of the AVPR1B in corticotroph tumor tissues ⁵. These results were confirmed by Luque et al. by transcriptional profiling (mRNA): they reported a low expression of the AVPR2, and a higher expression of the AVPR1B in CD tumor tissues ⁶. However, Pecori-Giraldi et al. reported the lack of systematic correlation between the *in vivo* and the *in vitro* response in cell culture: based on 14 cultures of corticotroph tumors incubated with desmopressin, the authors did not find a correlation between *in vitro* ACTH secretion and the desmopressin response performed in patients before surgery ⁷. Interestingly, some tumors with ectopic ACTH secretion (EAS) can also express ectopic AVPR1B (or even AVPR2) ⁸: some studies reported up to 19% positive response to desmopressin in mostly benign neuroendocrine tumors with EAS ⁹.

Recently, Schichi et al. reported a link between AVPR1B receptors and *USP8* mutations, proposing a pathophysiological mechanism explaining an increased corticotroph stimulation by DDAVP in *USP8*+ vs. *USP8*- tumors: transient transfection studies showed activation of the promoter of the gene encoding the V1b receptor in the presence of activating mutations of *USP8* ¹⁰.

A summary of the potential pathophysiological mechanisms is provided in Figure 1.

2. Desmopressin test in the diagnosis of CS (figure 2)

The desmopressin test was reported for the first time 30 years ago: the objective of the original study reported by Malerbi et al. was to describe the response of the corticotroph axis in patients with CS, with or without an ACTH-dependent mechanism, and compare it with 15 normal controls ³. A dose-response curve testing 5 and 10 micrograms of desmopressin intravenous bolus was also performed. As suggested by Scott et al., the strongest response was observed with 10 micrograms which is the dose now used in all centers for the desmopressin test ¹¹. The principle of the test is to measure ACTH and cortisol before the injection and then every 15 minutes for 2 hours, even if, as discussed later, the value of both ACTH and cortisol remains debated. While symptomatic hyponatremia might actually occur after desmopressin injection, it was actually rarely reported in the literature and patients should be advised to restrict fluid intake for 12 hours. Malerbi et al. first described a stimulation of ACTH

and cortisol in 15/16 patients with CD.³ A few years later, the same team compared the ACTH and cortisol response in subjects with hypercortisolism vs. normal controls and patients with depression (functional non-neoplastic hypercortisolism, previously termed pseudo-Cushing's syndrome). A positive response, defined by an increase in cortisol greater than 4 times the basal value, was observed in 15/16 cases of hypercortisolism, versus 2/15 controls, and 4/11 patients with depression¹².

Subsequently, published data have complicated the interpretation of the test, not in its discriminative value, but in the definition of the "positive response", i.e, the response allowing to confirm the diagnosis of CS, not its etiology. Tsagarakis first defined new criteria using an increase in peak-base cortisol greater than 20%, or ACTH greater than 50%: with cortisol, a positive response was observed in 21/25 patients with CD, vs. 3/20 obese patients; with ACTH, a positive response was observed in 23/25 CD vs. 3/20 obese patients¹³. When the criteria used by Malerbi and Tsagarakis were used by Moro et al. in a larger cohort of 173 patients (including 76 with CD, 30 with functional non-neoplastic hypercortisolism, 36 with obesity and 31 controls), the results were disappointing: most patients had a positive response using the Malerbi criteria, whereas almost half of the patients (71/173) were misclassified using the Tsagarakis criteria. Moro et al. defined new criteria for positivity based on ROC curves: the positive response should be defined by an ACTH increment superior to 6 pmol/l: a positive response was observed in 66/76 patients with CD, and 9/97 in the 3 other groups¹⁴. Using the same criteria, Pecori-Giraldi et al. reported a sensitivity of 81.5% in the diagnosis of CS in a cohort of 55 patients, including 23 with functional non-neoplastic hypercortisolism¹⁵. A few years later, Tirabassi et al. defined new criteria of positivity based on a cohort of 52 patients with CD, compared to 28 patients with functional non-neoplastic hypercortisolism and 31 normal control subjects: while the criteria of Moro et al. gave a sensitivity of 75% and a specificity of 89.8%, a composite criterion combining a basal cortisol of more than 331 nmol/l and an absolute increase in ACTH of more than 4 pmol/l gave a sensitivity of 90.3% and a specificity of 91.5%. The comparison with the other classical tests used in the first line for positive CS diagnosis and for which a ROC curve was also performed showed that the desmopressin test compared well with other first-line screening tests: midnight

plasma cortisol higher than 207 nmol/l (Se 94.2% and Sp 83.1%), overnight dexamethasone suppression with cortisol < 50 nmol/l (Se 78.8%, Sp 94.9%) or urinary free cortisol (Se 78.8%, Sp 52.5%)¹⁶. Other criteria established from ROC curves have been defined since then in smaller cohorts, such as an ACTH peak greater than 15.8 pmol/l or an absolute increase in ACTH greater than 8.1 pmol/l¹⁷.

If these different studies underline the benefit of the desmopressin test in the diagnosis of CS, none of them agrees on the thresholds to be used to define a positive response to desmopressin. Concordant with this, recent guidelines on the diagnosis of CS do not consider the desmopressin test as a first-line screening test: the results of the literature however suggest that it might be useful in patients for whom the differential diagnosis with functional non-neoplastic hypercortisolism is difficult^{18,19}. As such, the diagnostic procedure of CS might include first-line screening tests (1 mg overnight dexamethasone suppression test, urinary free cortisol, late night salivary cortisol): in case of discordance between clinical probability and tests, or in case of discordance of first line screening tests, the desmopressin test could be used after a second round of first line screening tests (figure 2).

3. Desmopressin response in the etiological diagnosis of ACTH-dependent CS (figure 2)

- As a stimulation test in the diagnostic procedure

Since the initial negative results of two studies^{20,21}, which failed to differentiate between CD and EAS, several studies emphasized the contribution of the desmopressin response in the etiologic diagnostic approach of ACTH-dependent CS. Few studies evaluated the desmopressin response without comparison with other tests^{17,22,23}. More than 25 years ago, Newell-Price et al. reported the combination of 2 tests by injecting CRH and desmopressin simultaneously, using positivity criteria based on the original work of Nieman et al. on the CRH test (20% rise in plasma circulating cortisol and 35% rise in circulating ACTH cortisol)^{24,25}. Since then, a sequential approach became preferred, within which the place of the desmopressin use remains debated. Two large studies were reported over the last 5 years on this topic. From a large cohort of 170 patients (149 CD), Barbot et al. positioned the desmopressin response after the combination of a high dose dexamethasone suppression test

(Sensitivity, 88%; Specificity, 90%; diagnosis of CD if basal cortisol decreased by more than 52.7%) and a CRH test (Sensitivity, 76%; Specificity 100%; diagnosis of CD if basal ACTH increased by more than 72.4%). In this study, an ACTH increase superior to 32.4% after desmopressin led to a diagnosis of CD with a sensitivity of 83% and a specificity of 62%, far below the performance of the other 2 tests ²⁶. In contrast, Frete et al. made the desmopressin response one of the main components of their two dynamic tests (CRH and desmopressin without high dose dexamethasone suppression test) and imaging (pituitary and thoracic) approach in the diagnosis of ACTH dependent hypercortisolism²⁷. With a positive response to the desmopressin test, defined by a 33% increase in ACTH and an 18% increase in cortisol, and a positive response to the CRH test defined by a 37% increase in ACTH and a 17% increase in cortisol, the combination of the 2 tests provided a sensitivity of 73% and a specificity of 98% for the diagnosis of CD ²⁷. The positivity of the 2 tests indicated CD in 98.4% of cases (whatever the result of the pituitary MRI); the negativity of the 2 tests associated with a negative pituitary MRI indicated EAS in 90% of cases. The authors concluded that the combined approach of tests and imaging would avoid 47% of the current indications of BIPSS ²⁷.

- **As a stimulatory agent during BIPSS**

CRH has been the most widely used secretagogue during BIPSS and remains the gold-standard ¹⁸; recent loss of availability of ovine CRH in North America and several other countries raised the interest of using desmopressin in this setting. As early as 1993, Malerbi et al. had suggested the possibility of using desmopressin with ACTH measurements basally and then (after 5 and 15 minutes after bolus injection) during BIPSS by reporting stimulation in 3 patients ³. These results were confirmed by 2 studies based on 80 patients with ACTH-dependent hypercortisolism: in the first, with a peak/base ACTH ratio greater than 2, only one patient with CD (n=33) did not respond to desmopressin injection, whereas a lack of response was observed in 7 patients with EAS. Desmopressin injection corrected the diagnosis in 5 cases ²⁸. In the 2nd study, with a peak/base ACTH ratio greater than 3, desmopressin stimulation corrected the diagnosis in 7 cases, but the test was falsely negative in 4 cases of CD (n=47), and falsely positive in 4 cases of EAS (n=9) ²⁹. With this latter criterion of positivity, comparable efficacy

was reported by Deipolyi et al. based on 20 patients with a sensitivity of 94.5% for the diagnosis of CD³⁰. Even though desmopressin is a procoagulant agent, no thrombotic side effect was reported during the procedure. The most recent study, based on 226 patients with CD and 24 patients with EAS, described a sensitivity of 94.7% of the BIPSS without stimulation (ACTH ratio > 1.4, n=214/226), of 97.8% with desmopressin stimulation (ACTH ratio > 2.8, n= 221/226), and a specificity of 100% (n=25/25) for the diagnosis of CD. Of note, the benefit of the desmopressin stimulation was questioned in patients with an MRI pituitary finding larger than 6 mm, as all patients who required stimulation to confirm the diagnosis of CD had a pituitary image on MRI inferior to 6 mm³¹.

To our knowledge, only 2 studies specifically compared the results of BIPSS stimulated with desmopressin vs. CRH. The first was a retrospective study, in which the result of BIPSS were analyzed depending on the secretagogue used: there was no significant difference in the result in 20 patients with desmopressin stimulation vs. 16 with CRH stimulation³⁰. The second one was a prospective study in which 29 patients (27 with Cushing's disease and 2 with ectopic ACTH secretion) were randomized to receive CRH or desmopressin during BIPSS: the source of ACTH (confirmed after the BIPSS by surgery) was correctly identified in all the patients, whatever the secretagogue³². Very recently, a meta-analysis and review did not show any significant difference when comparing the accuracy of CRH vs desmopressin (11 different studies were pooled, with 612 patients): the pooled sensitivity and specificity of BIPSS using desmopressin was 0.96 and 1, respectively, while it was 0.98 and 1 when using CRH. The authors concluded that desmopressin could be considered an effective alternative to CRH³³. Of note, desmopressin stimulated BIPSS was also considered a safe approach: while hyponatremia could theoretically happen after desmopressin injection, none of the study evaluating the efficacy of BIPSS stimulated with desmopressin reported such a side effect. However, we always recommend restricting fluid intake in the following 12 hours.

4. Desmopressin response as a surveillance marker for recurrence of CD following initial corticotroph surgical resection

While transsphenoidal surgery is the first line treatment for CD¹⁸, there is a risk of recurrence in 5-30% of cases after this treatment, requiring prolonged follow-up of all patients treated for CD³⁴. Immediate post-operative corticotroph deficiency defined as low serum cortisol values (< 50 nmol/L or 1.8 mcg/dL) and low or normal ACTH level is one of the best predictors of outcome (with the presence of a prolonged serum cortisol deficit being predictive of surgical success) even if the absolute level of cortisol does not seem to be an accurate marker³⁵. Of note, 15-20% of patients with a postoperative serum cortisol deficit will present a recurrence during follow-up¹⁹. The accuracy of the desmopressin test in the diagnosis of CD raised the possibility of using this test as a predictive marker of persistent corticotroph tumor tissue after transsphenoidal surgery: a persistent response to desmopressin, even in patients with post-operative cortisol insufficiency, or the appearance of a positive response during follow-up would suggest a risk of recurrence in the intermediate or short term. Note that in this setting, hydrocortisone should not be given in the morning the day of desmopressin injection.

The main bias of the studies that reported this benefit is that some did not include systematic preoperative desmopressin response: as 10 to 20% of patients with CD do not show a positive response to preoperative desmopressin administration (for instance, n=5/16 CD patients without response in the study by Colombo et al.³⁶), this might underestimate the accuracy of the test. Moreover, since recurrence of CD is often late, studies with a long follow-up should be necessary; however, most of the reported studies had a follow-up of less than 10 years. Some studies used post-hoc ROC curves to define the best threshold of positivity, without proposing a second validation cohort. Finally, the use of absolute values of ACTH and cortisol increment make it difficult to use these thresholds in every center because of different ACTH and cortisol assay methods; however, percent increments between baseline and peaks are always difficult to interpret immediately after surgery, because ACTH and cortisol levels are usually very low at that stage.

- **As an early predictor of recurrence**

For this approach, desmopressin injection should be performed early, within 1-6 months after surgery, in patients at the stage of postoperative cortisol deficit. There is no data in the literature showing that

the response to desmopressin injection would be modified by the presence or absence of cortisol deficiency. The aim here would be to have a predictor of delayed recurrence, which would be useful to tailor the follow-up of operated patients, at a stage they usually have low serum cortisol levels. In a study on 24 patients operated on for CD, Colombo *et al.* reported for the first time a negative desmopressin response postoperatively (compared to the positive preoperative response) in 14 patients in remission; the desmopressin response remained positive in 5 patients not cured by surgery, and in 5 eucortisolemic patients after surgery, including 2 of whom who presented with a recurrence of hypercortisolism in the next 36 months³⁶. Following these results, Losa *et al.* suggested that the persistent response in 30% of patients operated on for CD could predict a higher risk of recurrence in these patients³⁷. Since then, the data in the literature provided contradictory results: moreover, results were difficult to compare because of the variable thresholds used to define positivity. Positive response was either defined by an increase in peak-base cortisol greater than 193 nmol/l, or an increase in ACTH greater than 30%, or an increase in ACTH greater than 27 pg/ml³⁷⁻⁴⁰. Authors disagreed on the accuracy of a positive response in predicting recurrence vs. a negative response in predicting long-term remission³⁷⁻³⁹. When combining all these results, whatever the threshold used, Vassiliadi *et al.* reported a negative predictive value of 92%, with a specificity of 95%, and a positive predictive value of 77% with a sensitivity of 68% for predicting long-term recurrence⁴¹. The most recent study reported encouraging results, using exclusively cortisol increase: 95 patients, with a positive response to desmopressin before surgery, and with immediate postoperative cortisol deficiency (early morning cortisol below 138 nmol/l), were evaluated with a mean follow-up of 61 months after surgery. They all had a desmopressin stimulation test in the first 3 months after surgery. Seventeen patients showed recurrence during follow-up. Patients with a cortisol peak below 100 nmol/l or an increment below 30 nmol/l after desmopressin injection were at lower risk of recurrence with an odds ratio at 0.12 and 0.11, respectively, compared with patients with a higher cortisol increment. Interestingly, within this group of patients with cortisol deficiency, the level of cortisol (below 50 nmol/l or between 50 and 138 nmol/l) had no predictive value for the risk of recurrence³⁵.

Performed early after surgery, desmopressin could allow to differentiate patients at a higher risk of recurrence despite immediate post-surgical cortisol deficiency, or at the opposite, to reassure patients with a negative response to desmopressin, and maybe organize an individual and less frequent surveillance, but still long-term; those with response to desmopressin should be monitored more frequently for clinical and hormonal recurrence.

- **As an early marker of recurrence**

For this approach, the desmopressin injection would be performed at least 1 year after surgery, and often on a regular (annual) basis, with a positive response in favor of an increased risk of recurrence. Studies indeed emphasized the early positivity of the test compared with conventional markers of hypercortisolism (such as 1-mg overnight dexamethasone suppression test, 24-hour urinary free cortisol, or late-night salivary cortisol) in still asymptomatic patients^{42,43}. A correct evaluation of the desmopressin stimulation requires a positive response prior to pituitary surgery: Ambrogio et al. indeed pointed out that preoperative desmopressin non-responders did not show a positive response postoperatively when they recurred³⁸. The issue of thresholds for defining a positive response to desmopressin also arises in this setting. For instance, Valero et al. defined a positive response by an increase in ACTH greater than 22 pg/ml or more than 35% and cortisol greater than 350 nmol/l or more than 14%: from 22 patients operated on for CD, 4/5 patients had a positive response and recurrence, while no unresponsive patients had recurrence with a mean follow-up greater than 2 years⁴⁴. Vassiliadi et al. defined a positive response by an increase in cortisol superior to 200 nmol/l, from 39 patients with a mean follow-up of 63 months; the risk of recurrence was multiplied by 24.7 in case of positive response⁴⁵. Barbot et al. defined a positive response by an ACTH peak-base increment superior to 9 pg/ml in a cohort of 57 patients, of whom 15 had a recurrence: the risk of recurrence was 18.6 times higher in patients with a positive response³⁹. In these studies, the positive response to desmopressin occurred on average 6 months to 3 years before other markers of hypercortisolism. To date, no study has been performed to demonstrate a benefit to initiate treatment aimed at lowering cortisol level at this stage. The benefit of desmopressin could thus be to adapt the follow-up of these patients on a

long- term basis, to provide the optimal treatment as soon as a classical marker of hypercortisolism become positive.

- **The coupled dexamethasone-desmopressin test**

The rationale for a coupled dexamethasone-desmopressin test was based on the suppression of ACTH secretion by normal corticotroph cells by the dexamethasone, and stimulation of residual tumor cells by desmopressin. Serum cortisol obtained at 08:00 am after 1 mg-overnight dexamethasone suppression test would be the t0 of the classical desmopressin test ⁴⁶. The test has only been described as a predictive marker of recurrence in patients. Le Marc'hadour et al. showed the potential benefit of this coupled test in 67 patients in remission of CD, 11 of whom had a recurrence. While the desmopressin test showed a positive predictive value of 20% and a negative predictive value of 72%, the coupled test showed a positive predictive value of 44% and a negative predictive value of 100% for recurrence. Positive response was defined by an increase in ACTH and cortisol superior to 50%. When the authors combined the coupled test with the immediate post-surgical cortisol value (threshold of 35 nmol/l), none of the 24 patients with low cortisol and lack of response had recurrence with a median follow-up of 60 months. This could thus modify the frequency of follow-up of these patients considered at low risk of recurrence ⁴⁷.

Conclusions and perspectives

The use of desmopressin in the diagnosis of CS might have many benefits as a second-line in the diagnosis of CS, and probably as a first-line in the diagnosis of ACTH-dependent CS. The desmopressin test has, however, an obvious limitation, which is the definition of its positivity threshold (summarized in table 1). Each study indeed defined its own criteria for positivity, based on a ROC curve, without a validation cohort. Moreover, the use of absolute values of ACTH and cortisol makes inter-center reproducibility difficult because of the use of different assay methods. A re-evaluation of each study with a single ROC curve could allow the definition of universal criteria to be validated on an external cohort thereafter.

The interest of evaluating the response to desmopressin preoperatively is also based on its predictive role in defining the risk of recurrence, an event occurring in 20 to 30% of patients operated for CD, and for which regular monitoring is currently proposed to all patients. The pre-selection of patients at a low or high risk of recurrence, in the immediate post-operative period, could allow individualization of the monitoring in combination with the post-operative cortisolic status (ACTH deficiency). In contrast, the use of desmopressin as an early marker of recurrence (as the response to the test seems to occur before other markers of hypercortisolism) is more questionable, as no data in the literature suggest that management should be initiated as soon as the test becomes positive: at most, surveillance could be more closely monitored in this situation.

To conclude, controversies remain on the value of desmopressin in patients with CS. Further research is thus needed to clarify its roles in the diagnosis, localization, and follow-up of patients with Cushing's disease, ectopic ACTH or functional non neoplastic hypercortisolism syndrome. However, considering the limited access to CRH in several countries, and the incomplete reliability of the diagnostic procedures (CRH test, dexamethasone tests, imaging for the differential diagnosis of CS etiology), we think that desmopressin should be considered a valuable resource. Desmopressin could also be performed in the pre-operative evaluation of ACTH dependent CS, and in the first 3 months after surgery of CD to individualize the surveillance of the patients, even though the lack of clear thresholds and large cohorts make it difficult to recommend it systematically.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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LEGEND TO FIGURES

Figure 1: Proposed mechanisms of action of desmopressin in corticotroph tumors, depending on *USP8* status. AVPR, Arginine vasopressin receptor (type 1b or 2). WT, wild-type.

Figure 2: Proposed diagnostic algorithm defining the role of desmopressin in patients with a suspicion of Cushing's syndrome. First-line screening tests: 24h-urinary free cortisol, late night salivary cortisol, 1 mg-overnight dexamethasone suppression test. Etiological/localization step in ACTH-dependent hypercortisolism would be performed to determine whether ACTH secretion is due to a pituitary adenoma or an ectopic ACTH secretion. BIPSS, bilateral intra-petrosal sinus sampling; *Note that the thresholds defining a positive response are the ones which were used in the largest series reported in the literature; these thresholds remain controversial. **Based on Reference #27 (Frete et al.).

Table 1: Main criteria used to define a positive response to the desmopressin test in the different indications in Cushing's syndrome

Indication	Author, year	Number of patients	Threshold for positive response
Positive diagnosis	Malerbi, 1993 ³	16 CS, 15 normal controls	Peak/base cortisol > 4
	Malerbi, 1996 ¹²	14 CD, 11 depressed, 20 normal controls	Peak/base cortisol > 4
	Tsagarakis, 1999 ¹³	25 CD, 20 obese subjects	Peak/base cortisol > 20% and peak/base ACTH > 50%
	Moro, 2000 ¹⁴	76 CD, 30 FNNH, 36 obese, 31 normal controls	Peak/base ACTH increment > 6 pmol/l
	Pecori-Girardi, 2007 ¹⁵	33 CS, 22 FNNH	Peak/base ACTH increment > 6 pmol/l
	Tirabassi, 2010 ¹⁶	52 CD, 28 FNNH, 31 normal controls	Basal cortisol > 331 nmol/l and peak/base ACTH increment > 4 pmol/l
ACTH dependent etiological diagnosis	Barbot, 2016 ²⁶	149 CD, 21 EAS	Peak/base ACTH increment > 32.4%
	Frete, 2020 ²⁷	167 CD, 21 EAS	Peak/base ACTH increment > 33% and peak/base cortisol increment > 18%
BIPSS secretagogue	Machado, 2006 ²⁹	47 CD, 9 EAS	Peak/base ACTH > 2
	Castinetti, 2007 ²⁸	33 CD, 7 EAS	Peak/base ACTH > 3
	Chen, 2019 ³¹	226 CD, 24 EAS	Peak/base ACTH > 2.8
Early predictor	Romanholi, 2008 ³⁸	57 CD	Peak/base cortisol increment > 193 nmol/l
	Losa, 2009 ³⁵	174 CD	Peak/base ACTH increment > 30%
	Cambos, 2020 ³³	95 CD*	Peak cortisol > 100 nmol/l or peak/base cortisol increment > 30 nmol/l
Early marker of recurrence	Valero, 2004 ⁴²	22 CD operated	Peak/base ACTH increment > 22 pg/ml or > 35% and peak/base cortisol increment > 350 nmol/l or > 14%
	Barbot, 2013 ³⁷	57 CD operated	Peak/base ACTH increment > 9 pg/ml
	Vassiliadi, 2016 ⁴³	39 CD operated	Peak/base cortisol increment > 200 nmol/l

Table 1: Main criteria used to define a positive response to the desmopressin test in the different indications in Cushing's syndrome. Abbreviations: CS: Cushing's syndrome; CD: Cushing's disease; FNNH: functional non neoplastic hypercortisolism; BIPSS: bilateral inferior petrosal sinus sampling; EAS: ectopic ACTH secretion. Early predictor: the desmopressin test was performed in the first 3 months after the surgery to determine long-term outcome. Early marker of recurrence: the desmopressin test was performed during follow-up and became positive before the classical markers of recurrence of hypercortisolism. *All had corticotroph deficiency (early morning cortisol < 138 nmol/l).

Figure 1

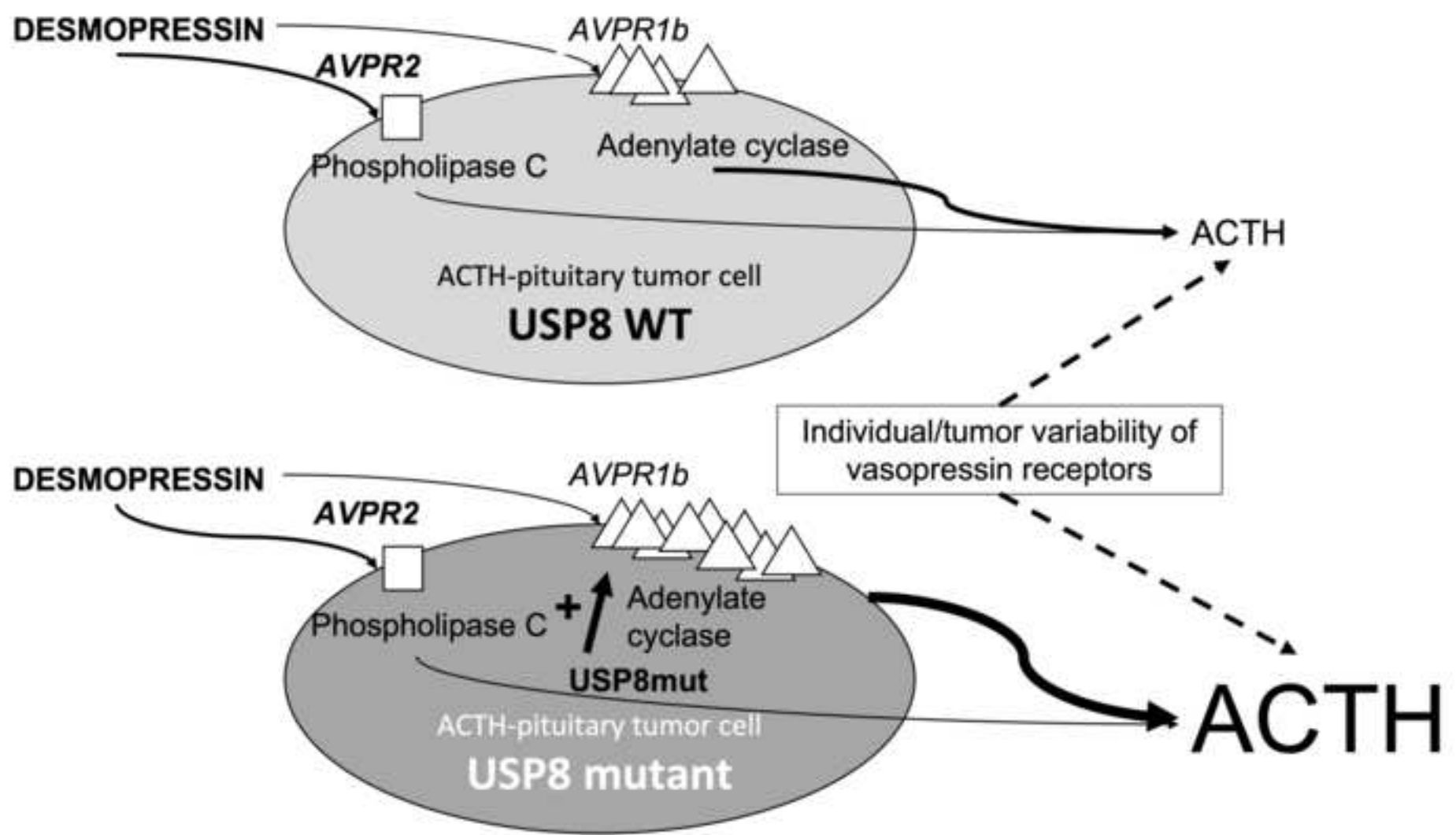


Figure 2

