A 19-YEAR STORY OF ADRENAL HEMORRHAGE, ADRENAL INSUFFICIENCY, AND ADRENAL RECOVERY: DYNAMIC COSYNTROPIN RESULTS WITH TREATMENT CONSIDERATIONS

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Abstract

There is limited information on the long-term natural history of adrenal function in adrenal hemorrhage following sepsis. The 19-year history of a patient is described who suffered adrenal hemorrhage during pneumococcal sepsis. Adrenal reserve using Cosyntropin testing with the 250 mcg dose was evaluated at seven time points during this interval, and a close observation of the patient enabled clinical correlation with adrenal status. The cosyntropin testing showed a 60 minute cortisol level post-hemorrhage of: 303.4 nmol/L (11.0 mcg/dL), one month; 656.6 nmol/L (23.8 mcg/dL), 1 year 10 months; and 714.5 nmol/L (25.9 mcg/dL), 19 years. Over the years the patient experienced hypoadrenal symptoms requiring both hydrocortisone and fludrocortisone until her adrenal function consistently demonstrated a 60 minute cortisol level of ~ 717.3 nmol/L (26 mcg/dL). Adrenal calcifications were visualized by ultrasound imaging and ultimately resolved. In conclusion, the patient's hypothalamic-pituitary-adrenal system appeared to have ultimately restored normal basal adrenal function 19 years after the initial hemorrhage, and the dynamic cosyntropin data indicate that normal adrenal function should not be assumed with a 60 minute cortisol level of 496.6 – 551.8 nmol/L (18 – 20 mcg/dL). Finally, mineralocorticoid as well as glucocorticoid may be important for improved mental acuity in primary hypoadrenalism.

Key words: adrenal insufficiency, adrenal hemorrhage, cosyntropin test.

INTRODUCTION

Acute adrenal hemorrhage and adrenal insufficiency resulting from sepsis, Waterhouse-Friderichsen syndrome, has been recognized for over a century (1, 2). It is usually fatal and a consequence of overwhelming sepsis, most frequently cited as originating from meningococcal infection, but can occur from streptococcal (pneumococcal) infection as well (3). There are causes of adrenal hemorrhage other than sepsis including anticoagulants, antiphospholipid

syndrome, trauma, surgery, and idiopathic (4). Although adrenal hemorrhage with adrenal insufficiency has been increasingly recognized in a wide range of clinical circumstances, long-term follow-up data in terms of: adrenal function quantitated by cosyntropin testing, adrenal imaging, and even appropriate glucocorticoid and mineralocorticoid replacement therapy are sparse and consist mainly of case reports (5, 6).

The following case report describes quantitative data on adrenal function vis-à-vis seven cosyntropin (250 mcg) stimulation tests during a time interval of 1 month to 19 years after an event of pneumococcal pneumonia, sepsis, and adrenal hemorrhage, and documents clinical findings from the initial near death experience to the probable normal restoration of adrenal function 19 years later. This case report enables a critique of the interpretation of the 250 mcg cosyntropin test and reviews literature relevant to this important diagnostic test. Furthermore, the clinical details, caveats, and nuances provided in this study were possible given that the patient is the wife of the author, an endocrinologist.

CASE PRESENTATION

In 1997 a healthy 45-year-old female, the mother of four children, underwent a routine radiological breast procedure; in retrospect, that visit was a point of contact with a virulent pneumococcus later identified in the community. She had no history of chronic medical illnesses, her PPD skin test had always been negative and she performed vigorous aerobic exercises for two to three hours daily, four to five days a week. Three days after this exposure she woke up with an explosive headache, shaking rigors, chattering teeth, and a fever of 39.4°C. She had nausea, but no vomiting. She was initially thought to have influenza. Two days after the onset of symptoms, the patient began hyperventilating and developed bilateral

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flank pain. She was brought to an outpatient clinic where initial blood work showed a white-cell count 9.5 per mm³, hematocrit 30.0%, platelet 214,000 per mm³, sodium 137 mmol/L, potassium 3.3 mmol/L, bicarbonate 20.2 mmol/L, creatinine 79.5 µmol/L (0.9 mg/dL), glucose 7.0 mmol/L (127 mg/dL); liver function tests were normal except for a low albumin of 32 g/L (3.2 g/dL). A chest radiograph showed a unifocal consolidated pneumonia. Because of hypotension and hypoxia, she was admitted to an intensive care unit, six days after exposure to pneumococcus and three days after onset of symptoms. Initial treatment included amantadine, erythromycin, and ceftriaxone. The flank pain worsened, but was attributed to menstrual cramps. Blood cultures drawn on admission were positive for streptococcus pneumoniae, and she was treated with ceftriaxone and hydration. After seven days of hospitalization the patient was discharged with a low-grade fever and continued intravenous ceftriaxone for a week at home.

After the first hospitalization, the patient

Figure 1. The faces of adrenal hemorrhage and hypoadrenalism (left) and recovery (right). The patient suffered adrenal hemorrhage in 1997 after contracting pneumococcal pneumonia. The photograph on the left was taken at home one week after adrenal hemorrhage, on the evening of hospital discharge; the patient could barely stand. The diagnosis of adrenal hemorrhage had been missed, and she was hospitalized two weeks later with syncope, diarrhea, and hypotension, at which time adrenal crisis was finally recognized and treated. The photograph on the right was taken in 2016, nineteen years after the adrenal hemorrhage, with recovery of adrenal function.

continued to be weak, tachycardic, shaky, extremely fatigued, very light-headed on standing, and felt nauseous, especially when she looked at food; she continued to experience flank pain, which eventually abated and low-grade fever (maximum temperature 38.4°C)(Fig. 1). Twenty-two days after the initial sepsis the patient had a syncopal episode and was again hospitalized, this time for diarrhea and dehydration. On admission her temperature was 36.7°C, pulse 88 beats per minute, respiratory rate 22 breaths per minute and blood pressure 98/60 mmHg; she would lose consciousness on standing. The admission laboratory results were: hematocrit 34.0%, white-cell count 17.500 mm³ with 22% bands, platelet count normal, sodium 139 mmol/L, potassium 3.9 mmol/L, creatinine 61.8 mmol/L (0.7 mg/dL). A random cortisol level was 333.8 nmol/L (12.1 mcg/dL). Following blood cultures, primaxin treatment (Imipenem and Cilastatin) was started empirically. Her condition worsened over the following twelve hours: she had difficulty maintaining consciousness, could not raise her head, repeatedly said she was 'so cold', and remained hypotensive despite normal saline volume expansion. An emergency echocardiogram showed left atrial enlargement.

Ironically, a copy of the original publication of Thomas Addison, Disease of the Renal Supra Capsules (7), which had been sitting on the author's desk, triggered realization of the diagnosis of adrenal crisis; the author requested and received permission to treat the patient, his wife, with hydrocortisone, 100 mg, every 8 hours intravenously. One hour after the first dose of hydrocortisone the patient was able to maintain consciousness and after four hours the level of her mentation increased to the point where she was conversant. She dramatically improved and was discharged 24 hours after stress dosing with hydrocortisone. During this 48 hour admission she was also diagnosed with pseudomembranous colitis by colonoscopy, and treated after discharge with oral vancomycin, 250 mg, four times daily. Blood cultures were negative and no other antibiotics were prescribed. On discharge the adrenal insufficiency was treated with hydrocortisone, 10mg, twice daily.

The clinical impression of adrenal insufficiency was confirmed one month after her episode of sepsis with presumptive adrenal hemorrhage and adrenal crisis by a cosyntropin test (250 mcg) with baseline, 30 minute, and 60 minute serum cortisol levels of 85.5 nmol/L (3.1 mcg/dL), 284.1 nmol/L (10.3 mcg/dL), and 303.4 nmol/L (11.0 mcg/dL), respectively. In addition, adrenal hemorrhage was further confirmed by

Figure 2. Adrenal calcification following adrenal hemorrhage. The ultrasound image shows a calcified right adrenal gland (arrow) 2 years 5 months after the pneumococcal sepsis and adrenal hemorrhage; the left adrenal was not studied. A cosyntropin test (250 mcg) the year of this ultrasound study showed 30 minute and 60 minute cortisol levels of 543.5 nmol/L (19.7 mcg/dL) and 648.3 (23.5 mcg/dL), respectively. An abdominal CT scan 10 years 10 months after the adrenal hemorrhage demonstrated no calcifications, and a bilateral adrenal ultrasound in 2016 (nineteen years after adrenal hemorrhage) also revealed no calcifications. At the time of these studies indicating resolution of adrenal calcification, the 30 minute and 60 minute cortisol levels by cosyntropin test had risen to ~ 552 nmol/L (20 mcg/dL) and ~ 717 nmol/L (26 mcg/dL), respectively.

ultrasound imaging in July 1999, 2 years 5 months after the pneumococcal sepsis, which showed calcification of the right adrenal gland (Fig. 2). The patient's pituitary function remained normal as indicated by normal thyroid function tests throughout the years and regular menses until menopause at age 56.

Adrenal function was periodically evaluated for nineteen years after the adrenal hemorrhage by the 250 mcg cosyntropin test. This enabled correlation of

Figure 3. Natural history of adrenal function after hemorrhage as evaluated by cosyntropin (250mcg) testing. The stimulated cortisol levels at 30 minutes and 60 minutes are shown over a time interval of nineteen years. Note there is an increase in adrenal function, as indicated by the 60 minute cortisol level, over a 63 month (5 years 3 months) period. Two further episodes of adrenal crisis occurred: 33 months (2 years 9 months) and 81 months (6 years 9 months) after the initial diagnosis, but no adrenal crisis for over the last twelve years.

stimulated 30 minute and 60 minute cortisol levels with actual clinical symptoms and signs and the replacement/supplementation doses of glucocorticoid and mineralocorticoid (Fig. 3 and Table 1).

Further treatment considerations and resolution of adrenal insufficiency

The patient's care was taken over by another endocrinologist. One month after discharge she demonstrated orthostatic changes, blood pressure 108/80 mmHg lying, blood pressure 98/76 mmHg sitting, but did not complain of dizziness. Her endocrinologist stopped the hydrocortisone and initiated treatment with dexamethasone, 0.5 mg, at bedtime, without fludrocortisone. For sixteen months after the adrenal hemorrhage on dexamethasone treatment the patient felt her exercise performance, which previously had

Table 1. Cosyntropin (250mcg) cortisol levels at 0, 30 and 60 minutes following adrenal hemorrhage

Time after hemorrhage	0 minute cortisol nmol/L (mcg/dL)	30 minute cortisol nmol/L (mcg/dL)	60 minute cortisol nmol/L (mcg/dL)
1 month	85.5 (3.1)	284.1 (10.3)	303.4 (11.0)
1 year 3 months	212.4 (7.7)	380.7 (13.8)	400.0 (14.5)
1 year 10 months	405.5 (14.7)	518.6 (18.8)	656.6 (23.8)
2 years 10 months	297.9 (10.8)	543.5 (19.7)	648.3 (23.5)
5 years 4 months	234.5 (8.5)	554.5 (20.1)	722.8 (26.2)
11 years 1 month	--	562.8 (20.4)	706.3 (25.6)
19 years	228.9 (8.3)	562.8 (20.4)	714.5 (25.9)

Most of the cortisol measurements were performed with a Siemens Immulite system where the coefficient of variation is cited as 7.3%. The renin at 2 years 10 months was 1.0 ng/mL/hr and at 3 years 2 months was 2.61 ng/mL/hr (normal range for upright, random dietary salt intake: 0 – 3.64 ng/mL/hr). 19 years 7 months post-hemorrhage the morning ACTH was 1.76 pmol/L (8 pg/mL) [normal range 1.32 – 11 pmol/L (6 – 50 pg/mL)] and cortisol 162.7 nmol/L (5.9 mcg/dL) [82.7 – 827.7 nmol/L (3 – 30 mcg/dL)].

been superior, was reduced and she would experience extreme nausea with vomiting after aerobics. In addition she would have episodic palpitations and reported abnormal sweating. She experienced 'foggy thinking' and difficulty concentrating. The patient therefore started fludrocortisone, 0.05 mg, daily, with dexamethasone, 0.375 mg alternating with 0.5 mg. This continued until two years after the adrenal hemorrhage. She was determined to 'get off' glucocorticoid and began treatment solely with fludrocortisone, 0.05 mg, daily. However, within two weeks of stopping the dexamethasone she developed hypoadrenal symptoms and started hydrocortisone, 10 mg, in the a.m., and 5 mg in the afternoon with fludrocortisone, 0.05 mg, daily, resulting in significant improvement. Approximately 4 years 4 months after the adrenal hemorrhage the patient began to taper her use of hydrocortisone and fludrocortisone. Eight years after the adrenal hemorrhage she was taking hydrocortisone, 10 mg, once or twice a week and fludrocortisone, 0.05 mg, once or twice a week. Seventeen years after adrenal hemorrhage she began taking hydrocortisone and fludrocortisone only occasionally, during viral syndromes such as shingles or influenza at doses of hydrocortisone, 20 – 40 mg, fludrocortisone, 0.05 mg, for two to three day periods.

Correlation of clinical adrenal status with cosyntropin results

After 23 months from adrenal hemorrhage the patient still could not discontinue her daily use of hydrocortisone, 10 mg, in the a.m., and 5 mg, in the afternoon, and fludrocortisone, 0.05 mg, daily, even with 30 min and 60 min cortisol levels of 518.6 nmol/L (18.8 mcg/dL) and 656.6 nmol/L (23.8 mcg/dL), respectively. Two additional events reflect on the interpretation of cosyntropin data and clinical adrenal status. In 1999 (2 years 9 months after adrenal hemorrhage) the patient was hospitalized in adrenal crisis and treated with stress doses of hydrocortisone and intravenous fluids; a cosyntropin test one month later showed 30 minute and 60 minute cortisol levels of 543.5 nmol/L (19.7 mcg/dL) and 648.3 nmol/L (23.5 mcg/dL), respectively. Interestingly, in 2002 a cosyntropin test revealed improved adrenal function with 30 minute and 60 minute cortisol levels of 554.5 nmol/L (20.1 mcg/dL) and 722.8 nmol/L (26.2 mcg/dL), respectively, but in 2003 (6 years 9 months after adrenal hemorrhage) she developed nausea, vomiting, and syncope and was hospitalized again for adrenal crisis and treated with stress doses of hydrocortisone

and intravenous fluids. She has suffered no episodes of adrenal crisis in the past twelve years, and repeated testing has shown 30 minute and 60 minute cortisol levels of ~ 552 nmol/L (20 mcg/dL) and ~717 nmol/L (26 mcg/dL), respectively.

DISCUSSION

The uniqueness of this case, the intimate clinical follow-up with serial measurements of increasing adrenal function after hemorrhage and an initial baseline of profound adrenal insufficiency, provide insights into the natural history of adrenal hemorrhage, the interpretation of the 250 mcg cosyntropin test, and the therapy of primary adrenal insufficiency.

The 250 mcg cosyntropin test—a single injection of ACTH1-24 administered either i.v. or i.m. as an out-patient procedure – is the gold standard procedure to evaluate for adrenal insufficiency; a stimulated serum cortisol level of 496.6 nmol/L – 551.8 nmol/L (18 – 20 mcg/dL) at 60 minutes is generally cited as indicating normal or at least 'adequate' adrenal function (8, 9). In interpretation of the 250 mcg cosyntropin test for the diagnosis of adrenal insufficiency one would want to know the normal range for the maximum cortisol level, which usually occurs at 60 minutes. Dorin *et al.* (10) provided a detailed review of 'adrenal normality' by cosyntropin testing in 2003; the lower limits of the 60 min cortisol levels from multiple studies were various 620 – 675 nmol/L (22.4 – 24.4 mcg/dL) and 500 – 725 nmol/L (18.1 – 26.2 mcg/dL). A more recent study in 2006 showed a range of 60 min cortisol levels of 926 – 1146 nmol/L (33.5 – 41.5 mcg/dL) for ten healthy volunteers (11), and another in 2007 reported mean maximum 60 minute cortisol levels of 31.6 – 42 mcg/dL (871 – 1158 nmol/L) for 175 non-diseased subjects stratified by different age groups (12). These normal ranges for the 60 minute 250 mcg stimulated cortisol would suggest that the often cited 496.6 – 551.8 nmol/L (18 – 20 mcg/dL) cortisol response as an indicator of sufficient adrenal function is not reassuring. There is not so much literature on this point for primary adrenal insufficiency, but case reports can be found; Oki *et al.* (13) discuss a patient clearly symptomatic with Addison's disease with an 'adequate' 60 minute cortisol response of 535.2 nmol/L (19.4 mcg/dL) using the standard 250 mcg cosyntropin test, although the 1 mcg ('low-dose') cosyntropin test showed a blunted response. The inadequacy of the 496.6 – 551.8 nmol/L (18 – 20 mcg/dL) 60 minute cortisol rule in the context

of secondary (pituitary-based) hypoadrenalism has been more rigorously shown (14,15); even 60 minute cortisol levels of 728 – 1092 nmol/L (26 – 39 mcg/dL) with the 250 mcg cosyntropin test did not signal sufficient adrenal function in certain patients with hypothalamic-pituitary dysfunction under physiologic stress (14).

The present longitudinal case report of the recovery of adrenal function after hemorrhage provides further information regarding the 496.6 nmol/L – 551.8 nmol/L (18 – 20 mcg/dL) benchmark in primary adrenal disease. After adrenal hemorrhage under the patient's endogenous ACTH stimulation according to her biologically determined hypothalamic-pituitary-adrenal set points, this patient's 60 minute cortisol rose to 656.6 nmol/L and 648.3 nmol/L (23.8 and 23.5 mcg/dL) at 1 year 10 months and 2 years 10 months, respectively, and to a plateau of ~ 717.3 nmol/L (26 mcg/dL) at 5 years 3 months. Thus, one would not infer the 648 nmol/L – 656.6 nmol/L (23.5 – 23.8 mcg/dL) cortisol levels at the 60 minute timepoint indicated adequate adrenal function given the later plateau to ~ 717.3 nmol/L (26 mcg/dL). Indeed this correlates with the patient's need for exogenous glucocorticoid and mineralocorticoid. It was only approximately eight years after the adrenal hemorrhage that the patient was able to reduce hydrocortisone and fludrocortisone use to weekly or less. She has not suffered hospitalization or adrenal crisis for over twelve years.

The best summary conclusion regarding interpretation of the 250 mcg cosyntropin test and the 496.6 – 551.8 nmol/L (18 – 20 mcg/dL) 60 minute cortisol rule to rule-out adrenal insufficiency (that is, it's unreliability) may come from Streeten *et al.* (14, 16): 'There is also nothing extraordinary about postulating the existence of partial failure of an endocrine function, which is more common than total failure in disorders such as hypothyroidism...' (14), and 'until a test becomes available to evaluate the ability of the entire hypothalamic-pituitary-adrenal axis to raise serum cortisol far above 630 nmol/L (23 mcg/dL), we have no recourse other than to rely on clinical assessment...' (16). Put simply, perhaps a level of 630 nmol/L (23mcg/dL) for a 60 min stimulated cortisol by the 250 mcg cosyntropin test can be a guide for adrenal adequacy, but must be put in the context of the patient's clinical status.

There is not much literature on long-term therapy after adrenal hemorrhage (6). The variable, increasing adrenal function during the 19 year interval presented unique therapeutic considerations. The patient during the

first year of severe adrenal insufficiency did not do well with dexamethasone alone, due to low mineralocorticoid activity of this steroid, but much improved when fludrocortisone, 0.05mg, daily, was added, especially in terms of mental acuity. In addition, she felt better still when hydrocortisone, 10 mg, in the AM, and 5 mg, at 1 PM, was substituted for the dexamethasone. Approximately eight years after the adrenal hemorrhage she was able to reduce hydrocortisone and fludrocortisone use to only once or twice weekly, and 17 years afterwards she only occasionally uses hydrocortisone and fludrocortisone for viral infections such as influenza and shingles; therefore, ultimately, there was significant improvement and probable normalization of basal adrenal function years after hemorrhage resulting from sepsis.

In retrospect, mineralocorticoid should have been started initially, and its continued use was important for years in the patients' health. Yet, other literature suggests that mineralocorticoid treatment is not typically needed in adrenal hemorrhage (6). It is important to note that there are mineralocorticoid receptors in the brain, and mineralocorticoid action may involve diverse physiological pathways other than vascular (17). Mineralocorticoid effects may confer resilience to stress-related psychopathologies and may be involved in such neurological properties as hippocampal memory (18). Clinically, as observed in the case presented here, fludrocortisone may improve concentration and other mental faculties in some patients with primary adrenal insufficiency.

Finally, this case shows that the doctor's wife does not always get the best of medical care; the diagnosis of adrenal hemorrhage and hypoadrenalism was initially missed by multiple physicians including the author. The author never expected such a healthy, vibrant woman to come so quickly so close to death from sepsis and adrenal insufficiency. Sometimes the doctor needs to be grateful for Providence.

Conflict of interest

The author declares that he has no conflict of interest concerning this article.

Acknowledgment

The author would like to acknowledge the expertise of Rakesh Shah, M.D., radiologist, Amarillo, TX, for review of the imaging studies discussed in this case report.

References

1. Hughes JF. Fulminating Septicaemia associated with Purpura and Adrenal Haemorrhage (Waterhouse-Friderichsen Syndrome). *Br Med J.* 1940;2(4158):353-354.

2. Arneil GC. Acute bilateral suprarenal haemorrhage. *Arch Dis Child.* 1946;21(107):171-417.
3. Hamilton D, Harris MD, Foweraker J, Gresham GA. Waterhouse-Friderichsen syndrome as a result of non-meningococcal infection. *J Clin Pathol.* 2004;57(2):208-209.
4. Dhawan N, Bodukam VK, Thakur K, Singh A, Jenkins D, Bahl J. Idiopathic bilateral adrenal hemorrhage in a 63-year-old male: a case report and review of the literature. *Case Rep Urol.* 2015;2015:503638.
5. Vella A, Nippoldt TB, Morris JC 3rd. Adrenal hemorrhage: a 25-year experience at the Mayo Clinic. *Mayo Clin Proc.* 2001;76(2):161-168.
6. Jahangir-Hekmat M, Taylor HC, Levin H, Wilbur M, Llerena LA. Adrenal insufficiency attributable to adrenal hemorrhage: long-term follow-up with reference to glucocorticoid and mineralocorticoid function and replacement. *Endocr Pract.* 2004;10(1):55-61.
7. Addison T. On the constitutional and local effects of disease of the supra-renal capsules. 1855, Special Edition 1980, publisher Adams LB Jr. The Classics of Medicine Library, Division of Gryphon Editions, Ltd, Birmingham, Alabama.
8. Neary N, Nieman L. Adrenal insufficiency: etiology, diagnosis and treatment. *Curr Opin Endocrinol Diabetes Obes.* 2010;17(3):217-223.
9. Nicolaidis NC, Chrousos, Charmandari E. Adrenal insufficiency. *Lancet.* 2014; 383(9935):2152-2167.
10. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. *Ann Intern Med.* 2003;139(3):194-204.
11. Alía P, Villabona C, Giménez O, Sospedra E, Soler J, Navarro MA. Profile, mean residence time of ACTH and cortisol responses after low and standard ACTH tests in healthy volunteers. *Clin Endocrinol (Oxf).* 2006;65(3):346-351.
12. Mansoor S, Islam N, Siddiqui I, Jabbar A. Sixty-minute post-synacthen serum cortisol level: a reliable and cost-effective screening test for excluding adrenal insufficiency compared to the conventional short synacthen test. *Singapore Med J.* 2007;48(6):519-523.
13. Oki K, Yamane K, Yoneda M, Nojima H, Watanabe H, Kohno N. A case of Addison's disease confirmed with low dose cosyntropin stimulation test. *Endocr J.* 2007;54(5):765-769.
14. Streeten DH, Anderson GH Jr, Bonaventura MM. The potential for serious consequences from misinterpreting normal responses to the rapid adrenocorticotropin test. *J Clin Endocrinol Metab.* 1996;81(1):285-290.
15. Kazlauskaitė R, Evans AT, Villabona CV, Abdu TA, Ambrosi B, Atkinson AB, Choi CH, Clayton RN, Courtney CH, Gonc EN, Maghnie M, Rose SR, Soule SG, Tordjman K. Consortium for Evaluation of Corticotropin Test in Hypothalamic-Pituitary Adrenal Insufficiency. Corticotropin tests for hypothalamic-pituitary adrenal insufficiency: a metaanalysis. *J Clin Endocrinol Metab.* 2008;93(11):4245-4253.
16. Streeten DH. Shortcomings in the low-dose (1 mcg) ACTH test for the diagnosis of ACTH deficiency states. *J Clin Endocrinol Metab.* 1999;84(3):835-837.
17. Mahfouz A, Lelieveldt BP, Grefhorst A, van Weert LT, Mol IM, Sips HC, van den Heuvel JK, Datson NA, Visser JA, Reinders MJ, Meijer OC. Genome-wide coexpression of steroid receptors in the mouse brain: identifying signaling pathways and functionally coordinated regions. *Proc Natl Acad Sci U S A.* 2016;113(10):2738-2743.
18. Kanatsou S, Fearey BC, Kuil LE, Lucassen PJ, Harris AP, Seckl JR, Krugers H, Joels M. Overexpression of mineralocorticoid receptors partially prevents chronic stress-induced reductions in hippocampal memory and structural plasticity. *PLoS One.* 2015;10(11):e0142012.