

**American Academy of Neurology
Section on Neuroendocrinology
Resident Core Curriculum**

1. Introduction

Clinical Neuroendocrinology is a discipline that deals with the role of hormones in the pathophysiology and treatment of neurological and neuropsychiatric disorders, as well as the impact of neurological and neuropsychiatric disorders on endocrine function.

2. Goals and Objectives

Goal – To prepare neurology residents to recognize and manage clinically relevant interactions between the nervous system and the endocrine system.

Objectives – During residency training, the resident should become familiar with

1. The anatomy and physiology of the neuroendocrine regulatory and feedback systems
2. The basic mechanisms involved in the reciprocal interactions between the nervous system and the endocrine system
3. Hormonal, imaging and electrophysiologic diagnostic tests that complement the clinical assessment
4. Principles of hormonal treatment of neurological and neuropsychiatric disorders

3. Curriculum

1. Anatomy and physiology of the neuroendocrine regulatory and feedback systems
2. Neuroactive and psychoactive properties of hormones
3. Diagnosis and management of basic neuroendocrine disorders in various subspecialties:

Behavior

- 1) Limbic system and brain circuitry for representation of emotions
- 2) Effects of reproductive state (adrenarche, puberty, menstrual cycle phase, pregnancy, perimenopause, menopause/andropause) on emotions and behavior
- 3) Catamenial exacerbation of anxiety and mood disorders
- 4) Role of anomalous brain substrates (e.g. temporolimbic dysfunction)
- 5) Hormonal treatment

Bone Health

- 1) Bone physiology
 - a. Growth and resorption; radiological and serum/urine markers
- 2) Clinical screening
 - a. risk factors for altered bone health
 - b. patient groups for which laboratory screening for osteoporosis is important
e.g patients who take corticosteroids or enzyme inducing antiepileptic drugs, patients with stroke

- c. Risk of falls
- 3) Laboratory testing
 - a. DXA bone scan and definition of osteopenia and osteoporosis
 - b. Measurements of serum concentrations of vitamin (vitamin D, calcitrol) and hormone (estradiol, testosterone) levels
- 4) Management
 - a. Diet and exercise
 - b. Drugs

Dementia

- 1) Alzheimer's Disease
 - a. Gender differences for Alzheimer's Disease – women/men : 2/1
 - b. Neurotrophic and protective effects of estrogen vs oxidative effects of estrogen metabolites, e.g catechol estrogens
 - c. Lack of substantial or lasting efficacy of acute estrogen treatment
 - d. Increased risk of cognitive decline with postmenopausal HRT in women over 65
 - e. Protection of younger women (50-63 years of age) with postmenopausal HRT

Epilepsy

- 1) Role of the temporolimbic substrate in hormonal regulation and feedback
- 2) Role of epilepsy in the development of reproductive and reproductive endocrine disorders in men and women with epilepsy
 - a. Men
 - i. Hypogonadotropic Hypogonadism
 - ii. Hypergonadotropic Hypogonadism
 - b. Women
 - i. Polycystic Ovarian Syndrome (PCOS)
 - ii. Hypothalamic Amenorrhea
 - iii. Functional Hyperprolactinemia
 - iv. Premature Menopause
 - c. Sexual function: relationship to EEG laterality and androgen levels in men and women with epilepsy
- 3) Role of antiepileptic drugs (AEDs) in the development of reproductive and reproductive endocrine disorders in men and women with epilepsy
 - a. Men
 - i. Role of enzyme inducing vs non inducing AEDs in hypogonadism and sexual dysfunction
 - c. Women
 - i. Role of AEDs in the development of PCOS
- 4) Catamenial epilepsy
 - a. patterns and diagnosis
- 5) Pregnancy and Teratogenesis
 - a. Effects of pregnancy on seizures
 - b. Role of seizures and various AEDs in teratogenesis

- c. Effects of seizures and AEDs on neurocognitive outcome of offspring
 - d. Effects of AED exposure through breast milk on infants
- 6) OCP use and AEDs
 - a. AED effects on OCPs
 - b. OCP effects on AEDs
 - 7) Hormonal treatment in men and women (investigational)
 - a. progesterone, depomedroxyprogesterone and leuprolide treatment in women
 - b. testosterone and aromatase inhibitor treatment in men

Headache

- 1) Migraine
 - a. Female/male : 3/1
 - b. Menstrually Related Migraine (MRM) i.e. catamenial exacerbation (2 days before to 3 days after onset of menses) in 67% and exclusively perimenstrual in 15% (Pure Menstrual Migaine)
 - c. Role of estrogen withdrawal in pathophysiology
 - d. Preventive treatment of menstrual migraine: short term NSAIDS, triptans, continuous active OCP for 3-4 months at a time (risks & benefits), estrogen patch, bromocriptine, depot lupron with stable HRT.

Immune Disorders

- 1) General
 - a. More common among women than men
 - b. Role of reproductive steroids (estrogen, testosterone and progesterone) and pregnancy in immunological processes, inflammation and tissue repair
 - c. Role of prolactin in promoting autoimmune responses in experimental models; benefit of bromocriptine in lessening prolactin mediated immune responses
- 1) Multiple Sclerosis
 - a. More common in women than men; HLA DR2 more common in women
 - a. Onset peaks in early and late reproductive years
 - d. Catamenial exacerbation in a small proportion, less than with epilepsy and migraine
 - e. Improvement during pregnancy; relapse postpartum within 3 months; decreased long-term risk with history of pregnancy
 - f. Correlations between reproductive steroid levels and number of lesions (investigational)

Movement Disorders

- 1) Relationship of reproductive hormones to Parkinson's disease (preliminary investigational findings)
 - a. Improvement in motor function (UPDRS score) with conjugated estrogen use vs placebo in postmenopausal women
 - b. Estrogen may reduce minimal effective dosage of L-Dopa

- c. Estrogen use does not affect the risk of developing PD but may be protective against the development of PD-related dementia
 - d. Testosterone supplement lessens hypogonadal symptoms in men with PD and is associated with trends toward improvement in other nonmotor and motor symptoms of PD
 - e. Hypogonadism may play a role in the pathogenesis of PD vs may just be a comorbidity
- 2) Relationship of reproductive hormones to other movement disorders including focal dystonias, choreoathetosis, essential tremor, Tourette's
- a. Higher prevalence of adult onset cranial and cervical dystonia in females than males, e.g spasmodic torticollis (ST): female/male : 1.6/1
 - b. ST onset peaks in the 5th decade, the same decade as perimenopause, and reproductive disorders and hysterectomy are significantly more common than in neurological and normal controls. ST features are commonly exacerbated perimenstrually; oral contraceptive use and pregnancy have not been demonstrated to have adverse effects
 - c. Choreoathetosis is more common with OCP use and pregnancy (chorea gravidarum)
 - d. Neuroleptic-induced tardive dyskinesia occurs with higher frequency in women than men
 - e. In essential tremor, hand tremor may be more notable in men and head or voice tremor in women
 - f. Tourette's occurs more commonly in boys than girls and may possibly be affected by testosterone

Neoplasms

- 1) Intracranial meningiomas
 - a. Incidence women/men: 2/1
 - b. Estrogen and progesterone receptors in the tumors
 - c. Frequent exacerbation of symptoms during pregnancy
 - d. Retardation of growth by the competitive progestin inhibitor mifepristone
 - e. Progesterone receptor positive tumors are less likely to recur
- 2) Neurofibromas
 - a. Remarkable growth acceleration under the influence of female reproductive steroids, including during pregnancy
 - b. First appear during puberty and shrink postpartum
 - c. Neurofibromatosis association with an elevated risk of intrauterine growth retardation, pregnancy-related hypertension (including an exacerbation of pre-existing chronic hypertension), abortion, stillbirth and oligohydramnios
 - d. Majority of neurofibromas (75%) express progesterone receptors whereas only a minority (5%) expressed estrogen receptors
 - e. Possibility that antiprogestational agents may show efficacy in treatment
- 3) Pituitary tumors
 - Hormone Secreting:*
 - a. Prolactinoma

- i. Presentation – galactorrhea, menstrual disorder, infertility, headache,
 - ii. Tests – hyperprolactinemia, MR cranial imaging to detect tumor
 - iii. Differential of hyperprolactinemia - medications, seizures, ectopic PRL production e.g. fibroid
 - iv. Treatment: dopaminergic agents, surgery
- b. Growth Hormone Secreting Pituitary Adenoma (Acromegaly)
 - i. Presentation – acromegaly, dysmorphic features, gigantism, bone or joint pain due to excessive cortical bone growth,
 - ii. Tests: elevated GH and IGF-1 levels, MR cranial imaging to detect tumor
 - iii. Pharmacodynamics and kinetics of serum GH and IGF-1: GH level but not IGF-1 level is affected by glucose load; therefore, IGF-1 is a more accurate diagnostic test and less sensitive to timing of blood draw
 - iv. Treatment - surgical resection of the tumor (transphenoidal or craniotomy), GH-hormone antagonist (Somatostatin), radiation.
 - v. Risks of long-standing GH and IGF-1 elevation include accelerated arteriosclerosis with increased risks of cardiovascular and cerebrovascular disease.
- c. ACTH-Secreting Pituitary Adenoma (Cushings Syndrome):
 - i. Presentation – Cushing’s syndrome
 - ii. Tests - elevated serum cortisol, elevated 24-hr urinary cortisol, elevated serum ACTH, positive dexamethasone test, MR cranial imaging
 - iii. Differential – depression, epilepsy, exogenous steroid, ectopic ACTH production e.g. lung tumor
 - iv. Treatment – surgical resection, radiation
- d. Thyrotropin-Secreting Pituitary Adenoma
 - i. Presentation – hyperthyroidism
 - ii. Tests – increased serum levels of TSH and T4, MR cranial imaging
 - iii. Treatment – surgical resection, radiation

Non-Hormone Secreting:

- a. Non-Secreting Pituitary Adenoma
 - i. Presentation – hypopituitarism, headache, visual field defect
 - ii. Tests – trophic hormone levels normal or decreased
 - iii. Treatment - surgical resection, radiation therapy (stereotactic radiation therapy, proton beam irradiation, intensity-modulated radiation therapy)
- b. Peripartum Pituitary Hypertrophy
 - i. Presentation - during pregnancy or puerperium, headache, hypopituitarism, visual field deficits
 - ii. Tests - combination of clinical, endocrine and radiologic findings
- c. Sella/Parasellar Meningioma or Chordoma

- i. Treatment - surgical resection via pterional rather than transphenoidal approach, radiation therapy (stereotactic radiation therapy, proton beam irradiation, intensity-modulated radiation therapy) may be necessary.
- d. Inflammatory Diseases of the Sella Mimicking Pituitary Adenoma (rare)
 - i. Presentation – panhypopituitarism
 - ii. Differential - lymphocytic adenophypophysitis, sarcoidosis, and idiopathic hypertrophic pachymeningitis
 - iii. Treatment - corticosteroids or cytotoxic chemotherapies.

Other Neuroendocrine Disorders

- 1) SIADH
 - a. Presentation – headache, confusion, seizure
 - b. Differential: head injury, subdural, seizures
 - c. Treatment: fluid restriction, diuresis
- 2) Adrenal Disorders (relevant to neurological or psychiatric disorders)
 - d. Nonclassic Congenital Adrenal Hyperplasia (CAH)
 - i. Presentation – menstrual disorder, hirsutism, emotional (refractory anxiety or rapid cycling mood disorders) or behavioral (impulsive aggressive) disorders
 - ii. Tests – screen precursors of cortisol e.g. 17 hydroxyprogesterone, Cortrosyn stimulation test with measurement of precursors at baseline, 30, 60 and 80 minutes
 - iii. Treatment – partial adrenal suppression (hydrocortisone, dexamethasone or prednisone) or ketoconazole
 - b. Hypercortisolism related to epilepsy or depression
- 3) Precocious Puberty
 - e. Presentation – early puberty
 - f. Tests – accelerated timetable of adrenal and or gonadal reproductive steroid production and levels, early pulsatility of gonadotropin secretion
 - g. Differential: CAH, pituitary gonadotropin-secreting tumor, brain disorders (e.g. neurofibromatosis)

Sleep

- 1) Sleep apnea (obstructive)
 - a. More common in men than in women
 - b. More common in women with hyperandrogenism (e.g. PCOS)
 - c. More common in women postmenopausally; benefited by HRT
 - d. Exacerbated by treatment of hypogonadal men with testosterone
- 2) Restless legs syndrome (RLS)
 - a. High frequency during pregnancy, approaching 30% in the third trimester
 - b. >1/3rd of cases represent exacerbation of preexistent, presumably familial RLS

Stroke

- 1) Significant differences exist between men and women in stroke susceptibility and outcome

- a. Stroke is more prevalent in men in younger age groups, but this difference dissipates with increasing age
 - b. Risk factors, such as diabetes, CAD and blood pressure, differ in their impact on vascular disease between men and women
 - c. There are sex-based differences in large artery stiffness (atherosclerosis)
 - d. Women often have worse outcome and increased mortality after stroke than men
 - e. Gender differences in fibrinolysis and coagulation; impact of OCPs, pregnancy and HRT
- 2) Oral Contraceptives (OCPs)
- a. The use of oral contraceptives is associated with increased risk for subarachnoid hemorrhage, venous sinus thrombosis, and stroke in migraine patients
 - b. Early formulations of OCPs contained high levels of estrogens and were known to be associated with a higher incidence of stroke
 - c. Newer formulations have lower doses of estrogen and may be safer overall except in women with known stroke risk factors, primarily smoking, hypertension, age >35, obesity and diabetes
 - d. Estrogen only, progestin only pills remain to be evaluated
- 3) Pregnancy
- a. Pregnancy is a high estrogen, high progesterone state that causes an increase in coagulation factors and leads to a hypercoagulable state
 - b. Both ischemic and hemorrhagic stroke are more frequent in pregnancy, often later in the third trimester and especially cerebral venous thrombosis in the postpartum period
 - c. Postpartum angiopathy
 - d. While creating a hypercoagulable state, estrogen also leads to a fibrinolytic state, primarily at the utero-placental interface, recreating a low level DIC
- 4) Menopausal Hormone Replacement Therapy (HRT)
- a. Nurses Health Study showed an increased risk of ischemic stroke with use of HRT
 - b. Heart and Estrogen-Progestin Replacement Study (HERS) showed a slight increase in risk of fatal stroke in women on HRT
 - c. Women's Estrogen for Stroke Trial (WEST) trial showed no increased risk of stroke
 - d. Women's Health Initiative (WHI) showed a significant increased risk of ischemic stroke regardless of underlying risk factors
- 5) Reproductive Steroids in the Treatment of Stroke (Experimental Animal Studies)
- a. Estrogens may increase brain perfusion and reduce infarct size, apoptosis and inflammation
 - b. Progesterone may decrease infarct size by lessening excitotoxic damage

4. Prerequisites for the trainee

The trainee should be in an approved neurology residency

5. Training Methods

The residency training director at each institution should be responsible for making this curriculum outline available to each resident and training faculty member. Since there is a paucity of neurologists who have extensive experience in neuroendocrinology, some training will likely be required by faculty as well as residents. This can be achieved by referral to the reading material that is referenced as part of this curriculum and also by attendance at neuroendocrine courses offered by the AAN.

6. Evaluation

The section will make available a self-administered online test that will evaluate the level of current neuroendocrine knowledge. This will become available on the AAN website and will be updated annually.

7. Teaching Resources and References

General

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- 2) Roussouw JE and the Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321-33.
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Behavior

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Bone Health

- 1) Physician's Guide To Prevention And Treatment Of Osteoporosis National Osteoporosis Foundation <http://www.nof.org/physguide/index.htm>
- 2) Lloyd ME, Spector TD, Howard R Osteoporosis in neurological disorders *J Neurol Neurosurg Psychiatry* 2000; 68:543-547.
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Dementia

- 1) Henderson VW. Hormones and dementia. *JNNP* 2005;76:103-5.
- 2) Rapp SR and WHIMS investigators. Effect of estrogen on global cognitive function in post menopausal women: the Women's Health Initiative Memory Study; a randomized controlled trial. *JAMA* 2003;289:2663-72.
- 3) Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. *JAMA* 2000; 283(8):1007–1015.
- 4) Seshadri S, Zornberg GL, Derby LE, et al. Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease. *Arch Neurol* 2001;58(3):435–440.

Epilepsy

- 1) Herzog AG, Klein P, Ransil BJ. Three patterns of catamenial epilepsy. *Epilepsia* 1997; 38:1082-1088.
- 2) Herzog AG. Progesterone therapy in women with complex partial and secondary generalized seizures. *Neurol* 1995; 45:1660-1662.
- 3) Herzog AG, Coleman AE, Jacobs AR, Klein P, Friedman MN, Drislane FW, Schomer DL. Interictal EEG discharges, reproductive hormones and menstrual disorders in epilepsy. *Ann Neurol* 2003;54:625-37.
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Headache

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Immune Disorders

- 1) Riskind PN, Massacesi L, Doolittle TH, Hauser SL. The role of prolactin in autoimmune demyelination: suppression of experimental allergic encephalomyelitis by bromocriptine. *Ann Neurol* 1991;29:542-7.

Movement Disorders

- 1) Okun MS, Walter BL, McDonald WM, Tenover JL, Green J, Juncos JL, DeLong MR. *Arch Neurol*. 2002 Nov;59(11):1750-3. Beneficial effects of testosterone replacement for the nonmotor symptoms of Parkinson disease.

- 2) Tsang KL, Ho SL, Lo SK. Estrogen improves motor disability in parkinsonian postmenopausal women with motor fluctuations. *Neurology* 2000;54:2292-8.
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Neoplasms

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Other Neuroendocrine Disorders

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Sleep

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- 8) See general references 2 & 3.

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