Fall 2008

front line

A PUBLICATION OF ABBOTT NORTHWESTERN HOSPITAL'S NEUROSCIENCE INSTITUTE

Corticosteroids in the Management of Cerebral Edema: A Neurosurgical Perspective

by Charles R. Watts, MD, PhD Neurological Associates, Ltd.

Corticosteroids are 21-carbon steroid hormones derived from cholesterol and synthesized in the adrenal cortex in response to the release of either adrenocorticotropic hormone or vasopressin from the hypothalamic pituitary axis. They are divided into two classes based on primary physiologic function.

This article does not cover nor pertain to the use of corticosteroids in the setting of bacterial or viral meningitis, cerebritis, intracranial abscesses, autoimmune disease, or spinal cord injury.

Mineralocorticosteroids (aldosterone) act on the cells of the distal renal tubule and collecting duct, and play an important role in Na+, K+, and water homeostasis. Glucocorticosteroids (cortisol) have widespread effects on metabolism, immune modulation, and the endocrine system. They play an important role in the body's ability to adapt to noxious stimuli, environmental changes, and stress. The mineralocorticosteroids and glucocorticosteroids have cross reactivity to each others' receptors and synthetic analogs used in medicine are classified with respect to their relative potency for Na+ retention, effects on glucose metabolism, and inflammation.

Corticosteroids are highly protein-bound in the plasma and highly lipid-soluble, passing easily through the cell membrane. They interact with specific nuclear binding proteins within the cytosol. These nuclear binding proteins are members of a family of transcription factors that bind small lipid-soluble ligands that include the steroid hormones. With binding of corticosteroid, the nuclear-binding protein translocates across the nuclear membrane of the cell and interacts with short sequences of exposed DNA that are recognized by the specific receptor. Binding of the corticosteroid receptor to DNA may either induce or inhibit gene transcription altering protein expression in the cell. This mechanism of action explains the widespread and various effects of corticosteroids throughout the body on different tissue types and the several hour delay between administration and apparent therapeutic effect.

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Dear Colleagues,

Once again, I am pleased to report that Abbott Northwestern Hospital has been ranked among the top 50 hospitals in the country for neurology and neurosurgery by *U.S. News & World Report*. This report is based on the resources of the Neuroscience Institute, the number of patients we see, the complexity of the cases we treat, and the results we have obtained. This is indeed an honor for our neurologists, neurosurgeons, nurses and other staff who have achieved this ranking six years in a row.

Please note the enclosed *Neuroscience Institute Overview and Outcomes Report 2008.* It highlights the many features of our outstanding programs. We are proud of the services and care that we provide for our patients.

I hope you enjoy reading the articles in our fall publication. As always, if you have any suggestions or questions regarding this publication or wish to speak to one of our authors, please call 612-863-3200.

Best regards,

Mahmoud Nagib, MD

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Corticosteroids, *continued from page 1*

The pioneering work demonstrating the efficacy of glucocorticosteroids in the treatment of cerebral edema was published in 1964 and performed at the University of Minnesota by Dr. French and Dr. Galicich. Dexamethasone was used due to its high anti-inflammatory potency and low mineralocorticoid effects. The initial study was small (147 patients), non-randomized, treated patients with various etiologies (neoplasm, post-operative edema, closed head injury, subarachnoid hemorrhage and radiation injury), and did not examine patient outcomes. Efficacy was defined as an improvement in neurologic examination after the initiation of therapy. The study demonstrated the ability of these agents to reduce edema, particularly in the setting of neoplasm and post-operative edema, as well as the resulting rebound edema that may occur with rapid withdrawal of treatment. These results prompted the widespread use of glucocorticosteroids in operative neurosurgery and corresponded with a significant historic decrease in the perioperative mortality of patients undergoing craniotomy.

The pioneering work demonstrating the efficacy of glucocorticosteroids in the treatment of cerebral edema was published in 1964 and performed at the University of Minnesota by Dr. French and Dr. Galicich. Dexamethasone was used due to its high anti-inflammatory potency and low mineralocorticoid effects.

This initial work was followed by multiple studies investigating the effects of glucocorticosteroids on cerebral edema secondary to a variety of intracranial pathologies. For ischemic stroke, intracranial hemorrhage, and subarachnoid hemorrhage, there appears to be no substantial benefit. In the setting of traumatic brain injury, administering glucocorticosteroids failed to control elevations in intracranial pressure. Their use also correlates with an increased risk of death and poor clinical outcome. Areas that have demonstrated efficacy are in the setting of primary and metastatic brain tumors, radiation therapy of intracranial tumors, radiation injury, and operatively induced trauma (extensive brain retraction).

The exact gene expression patterns and pathways that are important for the control of cerebral edema are largely unknown. The effects appear to be limited to the setting of vasogenic (interstitial) edema where the permeability of the blood brain barrier has been altered or disrupted, resulting in a net flow of water into the extracellular space. Potential mechanisms are: inhibition of gene expression for the arachidonic acid cascade, decreased expression of the VEGF receptor, and altered expression of the proteins that make up the endothelial tight junction.

Complications of therapy include: hyperglycemia, redistribution of body fat to the face and trunk ("moon facies" and "buffalo hump"), electrolyte and water imbalances (water and Na+ retention and hypokalemia), hypertension, skeletal muscle wasting (myopathy), alterations in mood and behavior, gastric ulceration, osteoporosis, aseptic bone necrosis, cataract formation, and immunosuppression with resulting opportunistic infections. Rapid withdrawal of therapy may result in rebound cerebral edema and, in the setting of long-term therapy, may precipitate acute adrenal insufficiency, a potentially life-threatening condition.

In patients undergoing uncomplicated craniotomy with minimal risk of prolonged post operative edema, steroids may be weaned rapidly over the course of five to seven days. Longer tapers may be necessary depending on the degree of brain retraction, post-operative course, pathology encountered, and expected chance of neurologic decline or rebound edema. In those patients with a stable neurologic condition, a 50 percent dose reduction every four days may be used. In patients with poorly controlled edema or significant pathology, a 25 percent dose reduction every eight days may be attempted. The goal of therapy should be to eventually remove all steroids or if long-term maintenance therapy is used, to limit the dose to one to two milligrams per day of dexamethasone.

For those patients who require long-term therapy, particularly in the setting of palliative medicine, care should be taken to use the lowest possible effective dose while minimizing the systemic side effects. Serum electrolytes should be monitored regularly since disturbances in Na+ and water balance may contribute to

Charles R. Watts, MD, PhD, graduated from the University of St. Thomas in St. Paul, Minn. in 1991 with a degree in chemistry. Dr. Watts received his PhD in biophysical chemistry from the University of Minnesota in 1998 and his medical degree from Creighton University School of Medicine in 2000. He finished his neurosurgical residency at the University of Minnesota in June 2006 and has also completed a fellowship in Surgery Critical Care at the University of Minnesota. In 2006, Dr. Watts joined Neurosurgical Associates and sees patients at the Edina location. Some of his clinical interests include brain tumors, complex spine surgeries, neurocritical care of severely injured patients secondary to ischemic stroke, intracranial and subarchanoid hemorrhage and trauma, and cervical arthroplasty (artificial cervical disc replacement). ■

hypertension and cause increased somnolence, cognitive disorders, or encephalopathy. Hypokalemia may cause myocardial irritability with resulting dysrrhythmias. Hyperglycemia should be controlled either with dietary measures or the use of insulin therapy. Prolonged blood sugar levels above 180 milligram/dL have been demonstrated to impair white blood cell function and have other deleterious systemic effects. Patients who are bed-ridden or experiencing weakness due to myopathy should be considered for DVT prophylaxis either with anticoagulation, pneumatic or elastic compression stockings, or an inferior vena cava filter.

Moderate daily activity and physical therapy also play an important role in recovery. To prevent osteoporosis, calcium supplementation with vitamin D should be instituted and consideration given to the addition of a bisphosphonate. Hypertension should be treated when appropriate, particularly if intracranial hemorrhage is a significant risk. Stomach acid production should be suppressed with either an H2-receptor antagonist (ranitidine) or proton pump inhibitor (omeprazole) to decrease the risk of gastric ulceration. Patients with significant immunosuppression should also be considered for antimicrobial, antifungal, and antiviral prophylaxis. Trimethoprim-sulfamethoxazole may be used to prevent pneumocystis carinii pneumonia and other opportunistic bacterial infections. An antifungal agent such as fluconazole may be necessary in patients who have a high risk of fungal infection and antiviral therapy in those patients with a history of herpes simplex or varicella zoster infection.

Appropriate use and dosing of glucocorticosteroids in patients with neurosurgical pathology will provide optimal control of symptoms while minimizing potentially life threatening or debilitating complications of therapy. ■

Pituitary Tumors: Diagnosis and Surgical Treatment

by Hart Garner, MD

Diagnosis

Pituitary gland tumors are a distinct set of nervous system tumors characterized by a wide range of symptoms. They make up between 10 and 15 percent of tumors originating in the central nervous system. These tumors are almost always benign, but their fast growth can invade and compress surrounding structures. As a result, the behavior of the tumor may be malignant even though the tumor itself does not fully meet the pathologic definition of malignancy.

Pituitary tumors can be divided into:

1) Those that are active (functioning) and secrete hormones at an abnormal level. These tumors often are found when they are small because the abnormal levels of hormones result in significant symptoms affecting many body systems.

2) Those that are inactive (nonfunctioning), and often grow abnormally large. These tumors tend to present clinically at a more advanced stage because the symptoms they cause are primarily due to their size and the resulting compression of surrounding structures such as the optic nerves.

Common active (functioning) tumor types include:

- Tumors that secrete Prolactin (prolactinoma). This type makes up almost two-thirds of functioning tumors and results in a clinical syndrome characterized by impotence and decreased libido in men; and galactorrhea, infertility, irregular menstruation, and decreased libido in women.
- Tumors that secrete growth hormone (causing acromegaly). This is the next most common type and is characterized by enlarged facial features and hand size. Acromegaly affects almost all systems of the body and can lead to complications like heart disease, lung disease, diabetes, carpel tunnel syndrome and goiter.
- Tumors that secrete adrenocorticotropin. This is the least common type and results in elevated glucocorticoid levels (causing Cushing's disease). It can result in a clinical syndrome similar to that seen in patients who are prescribed glucocorticoid medications including weight gain with truncal obesity, glucose intolerance, abdominal striae, hypertension, and increased susceptibility to infections.

The other distinction made in the classification of pituitary tumors is based on size. Microadenomas are less than one centimeter in diameter, whereas macroadenomas are larger than one centimeter in diameter. As tumors grow, they can be more difficult to surgically remove or treat with radiation, thus increasing the likelihood that the tumor may not be completely removed, treated and cured. As tumors in this region of the brain enlarge, they begin to compress the optic chiasm and nerves resulting in a visual deficit where the temporal visual field in both eyes is reduced. Before they develop focal deficits, patients often experience frontal headaches as the tumor grows larger and compresses the dura and arachnoid membranes above the pituitary gland. Pressure and distension of these structures causes pain. Other less common problems that can occur from these large tumors

Epilepsy in the Elderly

by Lizbeth S. de Padua, MD MINCEP Epilepsy Care

Incidence

There are two periods in one's life when a person is most likely to develop epilepsy. Though most physicians are aware that epilepsy frequently begins in childhood, the incidence of epilepsy in older adults is often misperceived as being a rare occurrence. In fact, numerous recent epidemiologic studies and the Centers for Disease Control and Prevention have found that though many newly diagnosed cases of epilepsy occur in children, there is an even higher incidence of new onset epileptic seizures in people over the age of 65. Indeed, the incidence of epilepsy in the elderly may even be higher than that of Alzheimer's disease (134/100,000 for epilepsy versus 123/100,000 for Alzheimer's). It is estimated that every year, over 50,000 older Americans have their first seizure.

Since the mid-1990s, when the frequency of epilepsy development in the elderly was first recognized, much work has been done to better understand the nature of seizures in this age group and the differences in diagnosing and treating this age group as compared to others.

Etiology

The causes of epilepsy over age 65 are more easily identified, and differ from the

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are compression of the nerves that control eye movement resulting in double vision or ptosis. Occasionally, the tumors enlarge quickly when there is bleeding into them. This can compress all of the above-mentioned surrounding structures and cause acute deficits. This is called pituitary apoplexy, and often requires urgent neurosurgical evaluation and surgery as soon as possible to relieve pressure.

Treatment

Once a tumor is diagnosed, the best course of treatment must be determined. Often collaboration and agreement between a neurosurgeon and endocrinologist results in the best recommendation. Treatment options include observation with serial MRI scans at six-month to yearly intervals, medical treatment (prolactinomas respond very well), surgical resection of the tumor, and focused radiation treatments of the tumor. Surgical resection is most often performed with a combined surgical team that includes a neurosurgeon and an ear, nose, and throat surgeon.

Because the pituitary gland is located at the base of the brain between the eyes and just above the nose, the best way to access it is either through the nasal cavity, or just under the nasal cavity by opening the sphenoid sinus, which makes up the floor of the bony structure that houses the pituitary gland. Once the sphenoid sinus is entered, a microscope or endoscope is used to assist in the removal of the tumor through a small opening in the bone that makes up the floor of the sella turcica.

The accuracy of the surgery and the completeness of tumor removal can be augmented using intra-operative image guidance with MRI scans. Using a pre-surgical MRI, a specialized navigation system can compare the location of equipment and instruments in surgery to the location of anatomic structures and the tumor identified on the MRI. A more involved application of MRI technology available at Abbott Northwestern Hospital is the use of intra-operative MRI (iMRI) which produces scans during surgery to check the amount of tumor remaining. This technique gives the surgical team certainty that it has completely removed the tumor, or as much of the tumor as possible, before the surgery is finished. This technology is most useful for larger and more difficult-to-treat tumors.

The primary complications associated with surgery include infection, spinal fluid leak, hormonal imbalance and chronic sinus drainage. Close monitoring for these problems is performed in the immediate post-operative period while the patient is still hospitalized. If they occur and are identified, they are treatable and should not lead to any major, long-term problems.

In general, the surgical treatment of pituitary tumors is safe when an experienced team of surgeons is orchestrating the treatment and has access to a full range of surgical tools and image guidance equipment. It should be noted that the most important decision in treating pituitary tumors is determining which treatment option will be most beneficial with the lowest amount of risk given the tumor's type, size and behavior, as well as the patient's life situation. ■

Hart Garner, MD, received a BA in Biology from Miami University and graduated from the University of Minnesota Medical School. Dr. Garner then completed a surgical internship followed by a neurosurgical residency. His medical interests include brain and spine tumors and the full range of spine surgeries. Dr. Garner is a partner at Metropolitan Neurosurgery and practices at Abbott Northwestern Hospital. ■

Sources:

Batjer, H. Hunt, Loftus, Christopher M. . Textbook of Neurological Surgery: Principles and Practice. Pages 1395-1400. 2003.

Epilepsy, *continued from page 4*

causes of epilepsy that begin in childhood. In an Olmsted County population study, the major causes of epilepsy in the older adult were: cerebrovascular disease (33 percent), dementia (11.7 percent), neoplasm (4 percent), infection (0.6 percent) and trauma (1 percent). Up to 16 percent of people who have had a cerebral infarction will eventually develop epilepsy, more if the infarct was cortical in location (27 percent) or embolic in nature (up to 43 percent).

Diagnosis

The cause of a person's seizures can determine the types of seizures he will have. Since most seizures in the older population originate from areas of prior focal neurologic damage, such as strokes, traumatic injury and tumors, it is not surprising that about 70 percent of them are either complex partial (49 percent) or simple partial seizures. Thus, if one thinks of seizures mainly in terms of convulsions, seizures in the elderly can easily be missed.

Furthermore, unlike complex partial seizures in children and younger adults, most of which originate in the temporal lobe, complex partial seizures due to previous strokes are more likely to originate from the frontal and parietal lobes.

Correction: Epileptologist

Lizbeth S. de Padua, MD, ~~Epidemiologist,~~ received her neurology training at Temple University Hospital in Philadelphia followed by her epilepsy fellowship training at MINCEP® Epilepsy Care in 1988. Prior to joining MINCEP in 2007, de Padua was the medical director of the Mid-America Brain and Stroke Institute's Comprehensive Epilepsy Program in Kansas City, Mo. She sees adolescents and adults who have seizures and seizure-like episodes. MINCEP is a Level four medical and surgical epilepsy center. ■

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Therefore, they may not present with déjà vu–like auras or lipsmacking, chewing and swallowing automatisms typically associated with seizures arising from the temporal lobe. Instead, complex partial seizures in the elderly most often present with an aura of "dizziness" or paresthesias, with the seizures themselves causing only obtundation, delay in responses and confusion. Seizures in the elderly are also distinctive in that 30 percent of them present in the form of non-convulsive status epilepticus, such that the changes in mentation characterizing these seizures can persist for hours or even days at a time, and can easily be mistaken for strokes or delirium.

The long duration and/or frequent recurrence of these seizures provides a diagnostic advantage, however, in that it gives the physician an opportunity to perform an emergent EEG or to have the patient undergo video EEG monitoring that can immediately establish seizures as a readily treatable basis for the mental status change. In fact, an expeditiously performed EEG can reveal the cause of an acute mental status change in up to 30 percent of patients, whereas the CT scan almost invariably ordered in such emergency room situations will yield an etiologic diagnosis less than five percent of the time.

The challenge lies in recognizing the possibility that acute changes in mentation can be caused by seizures and in arranging for an EEG to be done while the patient is still acutely confused.

Treatment

Choice of treatment for epilepsy in the elderly is complicated by the decreased rates of gastrointestinal absorption, hepatic metabolism and renal clearance, and the increased likelihood of hypoalbuminemia that comes with aging. Also, older individuals are more likely to have concomitant medical problems for which they take several medications that could potentially interact with anti-epilepsy drugs (AEDs). A community-based study in the Twin Cities showed that over two-thirds of adults over 60 take an average of seven medications at any given time and up to 13 different medications in a year.

Choice of treatment for epilepsy in the elderly is complicated by the decreased rates of gastrointestinal absorption, hepatic metabolism and renal clearance, and the increased likelihood of hypoalbuminemia that comes with aging.

The ideal AED for the elderly would be one that does not cause side effects of dizziness or dysequilibrium, sedation, or cognitive deficits. Additionally, it would be highly water-soluble, have predictable pharmacokinetics, not be extensively metabolized in the liver, not affect the metabolism of other drugs, not be highly protein-bound, have a long half-life, and not contribute to bone loss. Currently, there are no AEDs available that fulfill all of these criteria, but second-generation AEDs are better tolerated and have fewer drug-drug interactions than do older AEDs. For instance, multi-center, head-to-head comparisons of AEDs in the elderly population have shown that

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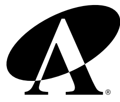

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Epilepsy, *continued from page 5*

levetiracetam and lamotrigine are just as effective and are much better tolerated in this age group than are phenytoin, phenobarbital and carbamazepine.

Current management of epilepsy in the elderly still leaves much to be desired. Apart from having a long half-life, phenytoin, with its complex pharmacokinetics, its interactions with many different classes of drugs, and its propensity for decreasing bone mineral density, does not meet any of the criteria for the ideal AED for use in the elderly. Despite a growing list of clinical recommendations and guidelines citing phenytoin as suboptimal for the treatment of epilepsy in the elderly, a study published in May 2008 reviewing Veterans Administration and Medicare data for 72,358 patients over 60 who were prescribed AEDs for new onset epilepsy revealed that phenytoin remains the most commonly prescribed AED for new onset epilepsy in adults over 60, with little change in its use from 2000 through 2004 (70.6% vs. 66.1%).

Current management of epilepsy in the elderly still leaves much to be desired. Apart from having a long half life, phenytoin, with its complex pharmacokinetics, its interactions with many different classes of drugs, and its propensity for decreasing bone mineral density, does not meet any of the criteria for the ideal AED for use in the elderly.

As our elderly population continues to grow, it becomes increasingly important for physicians to keep in mind that seizures frequently occur de novo in this age group, and can be the cause of acute or recurrent mental status changes, such that a well-timed EEG or video EEG monitoring is an essential part of patient care in such situations. Physicians also need to be sensitive to the potential consequences of using older AEDs to treat these patients, including fluctuating efficacy and toxicity due to unforeseen effects of other drugs on AED absorption, protein binding, metabolism, and excretion, and the possible loss of efficacy of concomitant medications when enzyme-inducing AEDs are added to the mix. The management of epilepsy in older adults is challenging and may be handled best by epilepsy specialists familiar with the best treatment options for this population. ■

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