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As physician co-leaders of Palmetto Health’s neuroscience service, we share a vision to provide the most advanced neurology and neurological surgery treatments available to the residents of South Carolina. We are excited to share this latest edition of our neuroscience journal featuring articles about early detection of age-related brain conditions and four cases of teenagers with headache, papilledema and visual impairment.
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Early detection and diagnosis of age-related brain conditions

Myriam Sollman, PhD, LP, clinical neuropsychologist and associate professor, Palmetto Health and University of South Carolina School of Medicine departments of neurosurgery and neurology

In the United States, the landscape of age is gradually changing, with a declining proportion of children due to fertility changes and a growing proportion of aging adults. In its 2015 report on world aging, the National Institutes of Health (NIH) stated that the U.S. population of individuals aged 65 and older will nearly double by 2050, from 48 million to 88 million. Non-communicable diseases, including things such as diabetes, vascular disease, cancer and dementia are identified as the greatest burden and threat in this population.¹

Health care professionals are well aware of the increased needs this population brings to their practices, including diagnostic skills, resources, interventions and patient/family education. While health care in North America has become highly specialized, it is the most generalized providers—including primary care and internal medicine physicians—who will bear the lion’s share of responsibility for promptly detecting neurological needs and ensuring they are met.

Age-related neurological change

“Dementia” is not a unidimensional disease. It affects cognition (thinking skills), movement, emotions and behaviors. It may be caused by one process, or an accumulation of several. Some dementias, for example, have been shown to affect how our brains develop in utero—leading to early-life individual differences in learning styles, strengths and personalities. Such “preprogrammed” neurological conditions may unfold very gradually throughout one’s lifetime, thus escaping detection until notable impairment. They may also emerge more noticeably in middle to later adult life. Other times, they may appear rapidly and forcibly. Alzheimer’s disease (AD) is the most well known and studied such condition, but there are myriad more including Parkinson’s disease (PD), Lewy body disease (LBD) and other forms of parkinsonism (ALS, corticobasal degeneration, progressive supranuclear palsy, multiple system atrophy), and the frontotemporal dementias such as Pick’s disease.

Genetically-driven dementias may be present in the family history, but more often they are not. This is because there is a complex interaction between genetics and the accumulation of exposures, illnesses and injuries one endures over time. In recent years, the role of the autoimmune system in the initiation and
recovery from neurological illness has become a central focus of understanding these interactions. Scientists also are highly focused on grouping the neurodegenerative dementias by the types of proteins that accumulate in the brain, with tau and alpha-synuclein being the most common pathology. This allows for crafting of disease-modifying treatments, such as vaccines.

Many other contributors to age-related neurological change warrant awareness and scientific study. These can be sole etiologies of neurological change, or factors that interact with the aforementioned neurodegenerative conditions. More often, these have an exponential effect on cognitive, physical and emotional/behavioral health.

**Premorbid (early life) deficits.** Individual differences in strengths and weaknesses are most apparent in elementary school settings. While individuals often “outgrow” specific deficits through the school years, these may re-emerge as a first sign of cognitive decline. Signs of early-life brain differences include left handedness without a family history of such, significant difficulties with penmanship or other fine motor skills, coordination/athletic deficits, attention deficit hyperactivity disorder (ADHD) and executive dysfunction, and subtle or true learning disabilities.

**Vascular disease** is the most prevalent contributor to neurological health over an American’s life span. This includes not only larger/identifiable strokes, but also insidious contributors such as migraine, sleep apnea, diabetes, cardiac arrhythmias, smoking, hypertension and high cholesterol (genetic or dietary). These diseases can constrict or block the flow of oxygenated and nutrient-rich blood within the brain, or rupture the tiniest to largest blood vessels, starting a biochemical cascade of other neuronal irritants.

**Psychiatric disease** is highly prevalent, with about one in five Americans experiencing a lifetime episode of major depression, and a similar number experiencing untreated anxiety. Unfortunately, untreated psychiatric disease can impact brain function and structure, accelerating neuronal aging. Even a first episode (cuing physicians or family that something has changed) can accelerate the progression of a dementia.²

**Autoimmune dysfunction** includes not only multiple sclerosis which creates lesions in the brain and spinal cord; but also antibody-mediated illnesses such as Hashimoto’s thyroiditis; and processes occurring post head injury or stroke that impact how well our brains are “cleaned,” so to speak.

**Cancer.** Some cancers metastasize to the brain and spinal cord more readily than others, creating lesional effects. Breast cancer, lung cancer and colon cancer are three common examples. Other cancers create harmful antibody-mediated autoimmune responses that can mimic a rapid dementia, infection or poisoning.

**Concussion and head injury.** Physical injuries to the brain, including concussions, create tissue bruising, blood vessel breakage, and shearing of white matter tracts, our “information superhighway.” New structural and functional brain imaging techniques are unveiling the microscopic yet long-lasting injuries. Media has drawn attention to the notion that these injuries, in accumulation, can create a neurodegenerative condition.

**Alcohol and drug use.** Over time, alcohol impacts “visuospatial” and “cerebellar” functioning, aging the brain. Substantial alcohol use can create amnestic memory loss due to nutritional deficiency. Alcohol and drugs interact with the psychiatric system to impact brain aging. Many drugs can create vascular lesions, as well.
**Epilepsy.** Over time, seizures have a cumulative effect on brain health. Additionally, they can kindle to impact other regions of the brain. When surgical intervention is not an option to stop seizure disorders, medications are imperative. However, these also can contribute to brain atrophy.

**Acquired diseases.** Various forms of the herpes virus, hepatitis, kidney disease, HIV and syphilis can have either gradual or rapid impact on central nervous system health.

**Finding the hidden disease**

There are four steps to early detection of age-related neurological decline. Awareness of the many conditions listed above, and how they manifest, is the first tool that providers can ensure they have in their repertoire. This includes knowing the common and the pathognomonic features of neurodegenerative conditions—such as loss of olfaction, constipation, slowed walking, decreasing handwriting size, or loss of facial expressivity which may happen years in advance of otherwise “symptomatic” Parkinson’s disease; new REM behavioral disorder (talking and/or acting out dreams), which happens in PD, LBD, and AD; slowed or unsteady walking, common to all subcortical diseases; and difficulty retrieving words or other “known” information from one’s mind, also prevalent in subcortical and vascular processes. As previously alluded to, a first or far more significant depressive or anxious episode can be a strong cue to the emergence of AD.

Taking time to identify and record an individual’s personal risk factors is another crucial step for early detection. This includes the early life differences noted above, as well as the prevalent vascular risk factors, neurological injury history (however mild), and any other medical or neurological contributors.

A picture is worth 1,000 words, and creating a strong record of how a person presents at the point in time you meet them is invaluable. Slowly unfolding changes are unlikely to be perceived. However, if you collect and record physical, cognitive and emotional data, you can detect system changes just as you would with blood lab changes.

**Physical data.** If you take a photo of your patient with resting face and one of your patient smiling, you can compare later expression to detect cranial nerve or subcortical influences. Timing walking speed over a set distance, and describing gait pattern, denoting seated posture, and recording other physical mannerisms also are helpful.

**Cognitive data.** How well does your patient communicate? Is their vocabulary and thought style simple or more complex? Does it flow freely? How well does your patient understand the concepts you discuss with them? How cognitively active is he or she in work or in seeking out mental stimulation? How complex are one’s preferred activities? In addition to answering questions such as these, test-based screening of cognition is beneficial. The preferred cognitive quick-screen, free for public use, is the Montreal Cognitive Assessment (MoCA). This takes about seven minutes to administer, and is much more sensitive than other methods, such as the Folstein Mini-Mental Status Exam (MMSE) or Saint Louis University Mental Status Examination (SLUMS), at detecting the executive skills changes that happen in subcortical and vascular disease.

**Emotional/Behavioral data.** Routinely measuring depression and anxiety, as well as quality of life, can help identify early changes and allow for early intervention. For older adults, the Geriatric Depression Scale (GDS) and the Geriatric Anxiety Scale (GAS) are highly sensitive, and ideal for precluding false positive due to physical symptoms from other disease states. In addition to measuring these states, collecting data on your patient’s level of social activity, their regular stress level, their degree of reactivity to stressors, the
presence of major stressors (such as caregiving), and personal characteristics such as initiative/motivation and follow-through are helpful to paint a picture of your patient's needs and risks.

Lastly, referral to a specialist for further work-up or characterization of a patient's status is beneficial. Neuropsychologists—doctoral-level providers skilled at collecting and sifting through risk factors, current symptoms, and objective data to describe a person—are invaluable in the earliest detection of dementias. A clinical neuropsychologist can provide a baseline examination for a patient at high risk for age-related neurological decline, prior to symptom emergence. This will qualify current skill sets, identify strategies for weaknesses, and target areas for which changes may reduce future risk. A neuropsychologist also can perform a detailed assessment early in a declining state to aid in differential diagnosis and management.

Neurologists can offer a thoughtful examination (via examination and imaging) of brain structure and function of psychiatric factors and medications that may be contributing to or creating symptoms, and of physical health markers that may be reversible. This includes testing for common nutritional deficiencies, autoimmune markers, substance accumulations and toxicities, hematological and endocrinological factors, infections, and fluid dynamics (i.e., to identify hydrocephalus or idiopathic intracranial hypertension). A neurologist is best able to direct medical intervention for complex conditions, and to rule out medical mimics—such as anti-NMDA receptor encephalitis which may look like young onset AD, while possibly due to an ovarian teratoma. Neurologists also can coordinate multidisciplinary treatment.

The case for early identification and intervention
Fortunately, awareness of the needs of our growing aging population has spurred research identifying medical and non-medical interventions to benefit our aging adults. These are broadly classified into symptom management strategies (such as the traditional cognitive enhancing agents like Aricept, psychiatric medications and the allied therapies: physical therapy, occupational therapy, and speech-language pathology), disease-modifying treatments (such as replacement therapies, vaccines, gene modification therapies, etc.), preventative strategies (vascular intervention, treatment of sleep apnea, nutritional supplementation), and disease-slowing interventions: exercise, sleep enhancement. Identifying care partner functioning (e.g., by a Zarit Caregiver Scale) and needs also is crucial to optimize a patient's long-term outcome.

As previously mentioned, quickly stabilizing and treating psychiatric symptoms can help reduce a patient's risk of diagnostic conversion from mild cognitive impairment to dementia.

There has been a boon of late in research showing the neuroprotective effects of exercise. Exercise is known to impact circulation of oxygen/nutrient-rich blood and endorphins, to reduce neuronally-toxic chemicals such as cortisol, and to increase neurotrophic factors important for plasticity, such as brain derived neurotrophic factor (BDNF). These affect key areas of the brain that are highly involved in cognition. Minimal amounts of exercise—about 30 minutes, five times weekly—have been shown to slow the progression of neurodegenerative conditions such as PD and AD, and to reduce population risk of a dementia diagnosis.3

Early referral for allied therapies also is invaluable in this process. A board-certified physical therapist (PT) who specializes in neurological or cognitive conditions will be primed to identify the most appropriate adaptive aides, as well as the safest and most ideal exercises for a patient, using an understanding of the sensory, motor and
cognitive factors impacting their movement. He or she also can offer specialized physical therapies, such as a mechanical balance tutor or a body-weight support treadmill that gradually increases a patient’s strength. This specialty practice is different from standard PT and home exercise programs, though it leaves the patient with long-term “homework.” A board-certified neurological or cognitive PT, such as ours at Palmetto Health Physical Therapy Specialists, is familiar with various neurological disease states. They are aware of neurobehavioral changes that may interfere with a patient participating in disease-slowing exercise, and can work with a care partner to help with compliance and carry-over. They also are alert to comorbid non-motor changes requiring intervention. This can signal referral to other allied practices such as OT, SLP and counseling.

The speech-language pathologist (SLP) likewise has invaluable offerings: swallow evaluation, dysphagia treatment and preventative strategies, speech therapy such as LSVT LOUD® for vocal quietening in PD, use of assistive communication devices, and cognitive therapy. Cognitive therapy includes things such as learning to “talk around” word-finding difficulty, developing strategies to memorize or to pull from memory, building insight, working around spatial dysfunction, and many, many others. The offerings of a skilled SLP are far from being limited to “speech.”

The occupational therapist (OT) is an ideal first resource when memory loss or executive dysfunction is detected. For memory loss, they can train a patient in strategies including use of routine and external memory aides. This requires development of new habits and therefore takes time. For executive dysfunction, such as disorganization that impedes staying atop appointments or bill-paying, they can evaluate the home environment to recommend changes, or develop personalized systems for increasing organization. A skilled OT also can devise schedules and other strategies to combat anhedonia and apathy that can interfere with maintenance and preventative self-care.

The SLP, OT, or neuropsychologist also can help those with cognitive decline to begin another home-based treatment: addition of cognitively stimulating activities. In recent research, this has been shown to slow progression of decline and reduce risk of mild cognitive impairment (MCI).4

Take home message

Just as the brain and spinal cord are responsible for multiple, highly varied human functions, early identification of age-associated cognitive decline—regardless of the etiology—requires attention to multiple factors. This is far less daunting than it seems when approached in a systematic manner. Assembling a diverse team of generalists and specialists around both our declining and at-risk patients is crucial to optimize quality of life for them and their families. It also will help modify the rate of patient decline and the experience of easily treatable symptoms. Neurological decline is a dynamic and highly treatable condition for our older adults. As disease modifying treatments become more available, early identification will be the single most important step in the health care of our aging and at-risk patients.

References

Four teenagers with headache, papilledema and visual impairment – *Idiopathic intracranial hypertension (pseudotumor cerebri) or NOT?*

by Stanley O. Skarli, FACS, FAAP, director of pediatric neurosurgery, and Brandi H. Martinez, APRN, FNP-BC, Palmetto Health-USC Pediatric Neurosurgery

The following case presentations of four teenagers presenting with headaches, papilledema and visual impairment demonstrate the importance of working through the process of making the correct diagnosis through utilization of the Dandy criteria.2 (See Table 4.)

Diagnosis of intracranial hypertension cannot be made without first identifying the correct terminology, which often is confusing. There are two types: primary and secondary. Primary intracranial hypertension (PIH) known as idiopathic intracranial hypertension (IIH), benign intracranial hypertension or pseudotumor cerebri is identified in the setting of normal brain and cerebrospinal fluid (CSF) studies. Terminology has changed over time and the most current terminology is idiopathic intracranial hypertension (IIH). IIH has an estimated incidence in the pediatric and adult population within the United States of 0.9 per 100,000.5 While patients will not die from this, they may go blind or live with chronic pain if not treated correctly.

Secondary intracranial hypertension (SIH) is specific to a treatable condition and may be reversed with treatment of the underlying problem.3 (See Table 1.) Pediatric cerebral sinovenous thrombosis (CSVT) is age dependent and may occur in varied conditions including dehydration, infection, renal failure, trauma, cancer and hematological disorders. It is estimated at 0.6 per 100,000 a year.6

**Clinical presentation**

A thorough history and physical will guide the evaluation and diagnosis. There are common characteristics of IIH, although diagnosis may be found in atypical patients. (See Table 2.)

**Examination and diagnostics**

Diagnosis of IIH is first based on the presence or absence of papilledema.1 Once confirmed, a full battery of examinations should be completed. (See Table 3.)

**Diagnosis and evaluation**

Diagnoses were initially made based on usage of the Dandy criteria developed in 1937. In 1985, Smith developed the Modified Dandy Criteria, used today. Although there has been discussion of further updating the criteria, there has been no consensus.2

**Treatment**

For all secondary cases, treatment of the underlying condition should be implemented. The basic treatment plan for IIH is to reduce CSF production or divert flow beginning with least invasive management. Often times multiple therapies are required. (See Table 5.)
### Table 1

**Most common causes of secondary intracranial hypertension**
- Cerebral venous abnormalities
- Sinus venous thrombosis
- Medications
- Tetracycline derivatives
- Vitamin A and retinoids
- Lithium
- Hormones
- Corticosteroids (withdrawal of chronic use)
- Human growth hormone
- Progestin

**Medical conditions**
- Addison’s disease
- Hypoparathyroidism
- Anemia (severe)
- Renal failure
- Down syndrome
- Turner syndrome
- Autoimmune disorders
- Prothrombotic state

### Table 2

**Physical characteristics**
- Female
- Obesity

**Symptoms**
- Headache
- Transient visual obscurations
- Pulsatile tinnitus
- Visual loss
- Orthostatic edema

**Minor symptoms of:**
- Diplopia
- Paresthesia
- Neck stiffness
- Arthralgia

**Signs**
- Papilledema

### Table 3

**Ophthalmology exam** – The exam should include visual acuity, dilated fundoscopy and visual fields. Extremely rare incidence of Charles Bonnet syndrome where patients who have had rapid vision loss feign normal vision and should be thoroughly evaluated.

**Laboratory** – Baseline CBC, chemistry panel, coagulation studies. Additional testing may include cortisol levels, protein C and S, antithrombin III, homocysteine, anticardiolipin, lupus anticoagulant and lipoprotein profiles.

**Neuroimaging** – CT or MRI signs of intracranial hypertension may include dilated optic nerve sheaths, empty sella or chiari malformation. MRV is recommended for atypical patients and to evaluate for venous outflow abnormalities. However, CTV may be superior to that of MR for detection of subtle areas of stenosis due to its superior spatial resolution and is institution dependent.

**Cerebral spinal fluid (CSF)** – Diagnosis should not be made without a lumbar puncture (LP). LP should be performed after neuroimaging has been completed in the lateral decubitus position with the legs relaxed. Prone and sitting positions are unreliable methods and will increase the intracranial pressure. Opening and closing pressures should be recorded. CSF studies for glucose, protein, cell count, VDRL, bacterial, fungal, tuberculosis cultures, and cytology should be sent. A therapeutic large volume tap may be completed, however these patients are not exempt from post spinal headache.
Table 4

**Modified Dandy Criteria**

1. Symptoms of raised intracranial pressure (headache, nausea, vomiting, transient visual obscurations or papilledema)
2. No localizing signs with the exception of abducens (sixth) nerve palsy
3. The patient is awake and alert
4. Normal CT/MRI findings without evidence of thrombosis
5. LP opening pressure of >25 cmH2O and normal biochemical and cytological composition of CSF
6. No other explanation for the raised intracranial pressure

Table 5

- Low sodium diet
- Weight loss
- Acetazolamide
- Topiramate
- Serial lumbar puncture
- Optic nerve sheath fenestration (best for vision loss)
- Shunt (best for headache alone)

Case Presentations

**Case 1:** 15-year-old thin white male presented with headache, nausea, weight loss, visual impairment and grade IV papilledema. Lumbar puncture showed elevated opening pressure of 62 cm of water. Initially he did not have significant improvement with CSF drainage via lumbar puncture. Magnetic resonance venography showed diffuse intracranial venous sinus thrombosis (Image 1). He failed a trial of Diamox. Endovascular venous sinus thrombectomy was attempted but aborted after finding solid organization of the thrombi. Because of his inconclusive response to lumbar puncture, a subsequent lumbar drain confirmed the benefit of CSF drainage. A lumbar peritoneal shunt with an Integra H-V valve has resolved his symptoms for the last 18+ months. After four months of Lovenox® therapy, his therapy was changed to aspirin. Hematologic testing off anticoagulation revealed a factor XII deficiency.

**Case 2:** 16-year-old obese black female presented with headache, visual impairment with bilateral sixth nerve palsies and grade IV papilledema. Lumbar puncture showed opening pressure greater than 55 cm of water. Routine MRI imaging showed a Chiari malformation with an upper cervical cord syrinx. CSF drainage only provided transient relief of headache, and transient improvement of her vision. Review of her history uncovered double dose birth control therapy for menorrhagia, which was causing significant anemia. Magnetic resonance venography showed bilateral transverse and sigmoid sinus thrombosis (Image 2). We discontinued hormonal therapy, instituting systemic anticoagulation with heparin, converted to Lovenox® and ultimately switched to Xarelto® after developing heparin-induced thrombocytopenia (HIT). These alterations in her medical therapy resolved her signs and symptoms. She returned a year later with classic suboccipital
Chiari headaches with Valsalva maneuvers, and an increase in the size of her cervical syrinx. She underwent a Chiari decompression with complete resolution of her symptoms.

**Case 3:** 17-year-old morbidly obese white female presented with headache, visual impairment and papilledema. Initial lumbar puncture data was inconsistent, employing a prone position. With an opening pressure of 34 cm of water and subsequently requiring two separate attempts at a blood-patch for symptoms that were interpreted as post lumbar puncture headache (intracranial hypotension), Magnetic resonance venography showed asymmetric transverse and sigmoid sinus outflow, with no thrombosis or focal stenosis (Image 3). This may well be congenital and unrelated to her symptoms, as asymmetry in venous outflow is not uncommon in asymptomatic patients. Repeated lumbar puncture in the lateral position and under anesthesia revealed opening pressure of 58 cm of water, however only gave transient relief of her symptoms. A lumbar peritoneal shunt utilizing an Integra™ H-V valve relieved her symptoms; however, it repeatedly failed due to mechanical issues related to her body habitus and her large abdominal girth. She has done well subsequently with a Codman CERTAS® (4) ventriculoperitoneal shunt.

**Case 4:** 17-year-old obese white female presented with 3–4 years of headache and anxiety. Formal ophthalmologic evaluation revealed visual impairment and grade IV papilledema. Lumbar puncture revealed elevated pressure of 60 cm of water, but was unreliable, performed in the prone position. She failed a trial of Diamox® with worsening vision. Lumbar puncture in the lateral position with mild sedation gave a pressure of 45 cm water. Magnetic resonance venography showed focal stenosis of the left transverse - sigmoid sinus junction (Image 4). Endovascular venous sinus pressure monitoring demonstrated a 10-mmHg gradient on the right and a 14-mmHg gradient on the left through the stenotic segment. Following left balloon dural angioplasty and stent placement the gradient was resolved. Subsequently, the patient has had complete resolution of her symptoms and papilledema. She remains on aspirin and Plavix® and will transition to aspirin alone.

**Conclusion**

IIH or pseudotumor cerebri as it is commonly known, is a diagnosis of exclusion. We cannot assume that all obese, teenage females have IIH and a thorough evaluation is imperative. Often there is a component of anxiety and depression associated with these patients related to chronic pain. For conditions that may require surgical intervention, consultation should be sought early.
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**Palmetto Health-USC Neurology**
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