Factors independently related to mortality with bacterial meningitis in the elderly are age, pneumonia as a predisposing factor, coma on admission, and heart failure and/or seizures after therapy.

**Background:** There are an estimated 1000 to 3000 cases of bacterial meningitis in older patients in the United States each year, and the incidence is higher in other countries.

**Objective:** To define the etiology, clinical features, evolution, and prognostic factors of bacterial meningitis in older adults.

**Design:** Retrospective chart review.

**Participants:** 910 cases of community-acquired bacterial meningitis were identified between 1977 and 2006; 675 of these cases were in patients aged ≥18 years.

**Results:** Among these 675 adult patients, 185 (27%) were aged ≥65 years (76 males, 109 females; mean age, 73 ± 6 years; age range, 65 to 93 years). The percentage of patients aged >64 years increased from 22% in 1977-1986 to 36% in 1997-2006. About one third of these 185 patients had 1 or more underlying diseases associated with bacterial meningitis: diabetes mellitus (n=50), alcoholism (n=10), neoplasm (n=9), chronic liver disease (n=5), myeloma (n=4), renal failure (n=4), corticosteroid therapy (n=4), and splenectomy (n=2). Fever at home or in the emergency department (ED) was documented for 91% of patients, although only 70% had fever in the ED. On admission, 23% of these elderly patients were in coma, and 9% presented with seizures. Shock was present in 8% of cases. Blood and cerebrospinal fluid cultures were positive in 69% and 76% of patients, respectively. Causative microorganisms were *Streptococcus pneumoniae* (n=74), Neisseria *meningitides* (n=49), Listeria *monocytogenes* (n=17), other streptococci (n=9), Escherichia coli (n=6), Haemophilus *influenzae* (n=4), Klebsiella pneumoniae (n=2), *Staphylococcus aureus* (n=2), *Capnocytophaga canimorsus* (n=1), Enterococcus *faecalis* (n=1), and unknown organisms (n=20). Overall mortality rate was 31%, being highest for *S pneumoniae* (36%), *N meningitides* (24%), and *L monocytogenes* (29%). Compared with patients aged <65 years, elderly patients had a significantly higher frequency of pneumonia and otitis as a primary infection; diabetes and neoplasm as underlying disease; absence of headache, nausea, vomiting and nuchal rigidity on admission; hypernatremia; and more prevalent hemiparesis, seizures, positive blood cultures, and complications, including renal failure, urinary tract infection, and overall mortality. Factors independently related to mortality were age, pneumonia as a predisposing factor, coma on admission, and heart failure and/or seizures after therapy. Treatment with dexamethasone along with antimicrobials was a protective factor.

**Conclusions:** Bacterial meningitis in elderly patients is associated with greater diagnostic difficulties and neurologic severity, more complications, and increased mortality. The authors recommend use of anti-seizure prophylaxis and dexamethasone, along with antimicrobial therapy, in these patients.

**Reviewer's Comments:** It appears that the elderly represent an increasing percentage of patients afflicted with bacterial meningitis. This very useful study delineates the etiology, clinical features, evolution, and prognostic factors of bacterial meningitis in this population. This should help all neurologists who treat these patients. (Reviewer-W. Steven Metzer, MD).

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Keywords: Community-Acquired Bacterial Meningitis

Print Tag: Refer to original journal article
In selected patients with intractable epilepsy, lesionectomy of insular lesions is acceptably safe and provides a high rate of satisfactory seizure relief.

Objective: To determine clinical features and long-term outcomes in patients who undergo insular lesionectomy for refractory seizures.

Participants/Methods: 24 patients aged 1 to 62 years (mean, 27 years) underwent epilepsy surgery for a lesion involving the insula.

Results: The most frequently experienced symptoms were viscerosensory or emotional, including ictal fear. In none of the patients were these initial symptoms, which were variable and included somatosensory or motor symptoms and auditory or visual symptoms. Three patients had initial loss of consciousness. Viscerosensory and emotional symptoms occurred both in patients whose lesions extended into the temporal lobe and those whose lesions were restricted to the insula. Lesion location according to preoperative MRI did not correlate well with surface electroencephalogram (EEG), which variably showed no clear seizure origin or patterns implicating mesial temporal, frontotemporal, frontocentral, or temporo-occipital areas. In all patients, preoperative MRI showed a circumscribed lesion either restricted to the insula or additionally involving inferomedial temporal lobe and amygdala. Seventeen patients had surgical resection of their lesions; the rest had subtotal resection. Histopathologically, 6 patients had cortical dysplasia, 3 had gliosis, 2 had cavernous angioma, 2 had dysembryonic neuroepithelial tumors, 6 had gangliogliomas, 2 had oligoastrocytomas, 1 had astrocytoma, 1 had oligodendroglioma, and 1 had pleomorphic xanthoastrocytoma. Surgical morbidity was low: 1 patient had hemihypesthesia, 1 had deterioration of a pre-existing hemiparesis, and 2 had a hemianopia as a "calculated deficit." During follow-up of 12 to 168 months (mean, 38 months), two thirds of patients were completely seizure-free, and 79% were rated as having a satisfactory seizure outcome, which included patients with subtotal lesion resections.

Conclusions: In selected patients with intractable epilepsy, lesionectomy of insular lesions is acceptably safe and provides a high rate of satisfactory seizure relief. Neither ictal surface EEG nor seizure semiology reliably differentiates insular seizure origin from temporal or frontal lobe origin. In reviewing other reports of seizures with insular lesions, such ictal phenomena as dysgeusia, vomiting, and laryngeal constriction are described. Proof of insular seizure origin requires depth electrode EEG, and continuous intraoperative electrophysiological monitoring reduces surgical morbidity.

Reviewer's Comments: Of note is that semiology can point to the insula as the source of seizures, but it does not predict the extent of the lesion. (Reviewer-John C. Brust, MD).

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Keywords: Insular Lesionectomy

Print Tag: Refer to original journal article
Epilepsy Affects 6% of Children With Down Syndrome

Clinical and EEG Features of Epilepsy in Children and Adolescents in Down Syndrome.

Smigielska-Kuzia J, Sobaniec W, et al:

J Child Neurol 2009; 24 (April): 416-420

There is an increased risk for epilepsy in children with Down syndrome, and seizure control can be difficult in those with epilepsy.

Background: Children with trisomy 21 (Down syndrome) are at increased risk for epilepsy, but seizures are not considered to be a common feature.

Objective: To evaluate the prevalence of epilepsy, seizure type, electroencephalogram (EEG) findings, and antiepileptic drug (AED) therapy in a large cohort of children with Down syndrome.

Participants: A group of 252 children with Down syndrome included 155 boys and 97 girls who were evaluated by pediatric neurologists at a center in Poland over a 13-year period. Ages ranged from 1 to 20 years.

Methods: A retrospective chart review was performed with attention to history of seizures, seizure type, age at onset, AED therapy, seizure control, and possible etiology. An EEG was performed on all patients with seizures. A comparison of EEG findings was made with an age- and gender-matched control group of 10 children with Down syndrome who did not have seizures, and a second group of 28 children with epilepsy who did not have Down syndrome. EEG findings were noted and compared.

Results: 15 children were identified who had epileptic seizures, which represented 6% of the cohort with Down syndrome. Partial seizures occurred in 8 children, primary generalized seizures in 5, and infantile spasms and Lennox-Gastaut syndrome in 1 each. All children with Down syndrome who had experienced epileptic seizures had an abnormal EEG. Generalized slowing or epileptiform discharges were noted in 6 patients, focal or multifocal abnormalities were noted in 8, and a hypsarrhythmia pattern was present in 1. Seizures were controlled with medication in about 40% of children with epilepsy, and 60% were uncontrolled. AED monotherapy was used in 13 patients, and only 2 were treated with 2 AEDs. Quantitative EEG analysis revealed several findings with comparison of the 3 groups. The primary finding was that Down syndrome children with epilepsy had less alpha activity and more delta activity compared to the other 2 groups. Results of neuroimaging studies that included either CT or MRI scans of the brain were available on 10 children with Down syndrome and epilepsy, and 2 were abnormal: 1 had agenesis of the corpus callosum and 1 had periventricular leukomalacia.

Reviewer's Comments: In this cohort of children with Down syndrome, 6% had epilepsy. When epilepsy was present, seizures were not controlled with AED therapy in almost 60%. Seizures are more common in children with Down syndrome. Adult studies have revealed that the risk of seizures increases significantly when patients with Down syndrome reach age ≥50 years. One study reported that the prevalence of epilepsy approached 50% in adult Down syndrome patients aged >50 years. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Epilepsy & Down Syndrome

Print Tag: Refer to original journal article
Peripartum Migraine Strongly Associated With Increased Stroke Risk

Migraines During Pregnancy Linked to Stroke and Vascular Diseases: US Population Based Case-Control Study.

Bushnell CD, Jamison M, James AH:

BMJ 2009; 338 (March 10): b664

**Background:** An estimated 11% to 26% of women of childbearing age are afflicted with migraine. The conventional wisdom is that migraine generally improves during pregnancy, although objective evidence of this has been inconsistent. A previous population-based study of migraine in pregnancy reported a 17-fold increased risk of pregnancy-related stroke and a 4-fold increased risk of acute myocardial infarction.

**Objective:** To investigate the relationship between migraine, pregnancy, and vascular disease.

**Design:** Retrospective database review of discharge diagnoses from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality, a database of discharge diagnoses from about 1000 hospitals in the United States.

**Results:** Investigators were able to identify 18,345,538 pregnancy-related discharges from 2000-2003 using this database. Among these pregnancy-related discharges from the hospital, 33,956 migraine codes were identified (185 per 100,000 deliveries). Diagnoses that were jointly associated with migraine during pregnancy included stroke (odds ratio [OR], 15.0), myocardial infarction (OR, 2.1), venous thromboembolism and pulmonary embolus (OR, 3.2), and hypertension (OR, 8.6). Coexistent migraine and pregnancy were also associated with an increased occurrence of preeclampsia (OR, 2.3) and with smoking (OR, 2.8). Migraine was not found to be associated with several other nonvascular diagnoses.

**Conclusions:** There is a strong relationship between active peripartum migraine and vascular diagnoses during pregnancy, in particular with stroke (OR, 15), independent of preeclampsia. The investigators recommend aggressive recognition and treatment of modifiable cardiovascular risk factors for pregnant women with active migraine.

**Reviewer's Comments:** This study has some limitations, the most obvious being selection bias. Women with a pregnancy-related hospital discharge for whom migraine was listed as comorbidity most probably represent patients with most severe migraine. Women with less severe migraine are probably under-represented in this study. However, these results are compelling that active migraine most probably significantly increases the risk of peripartum stroke. Neurologists who manage migraine in women of childbearing age should be aware of these findings and, when necessary, freely communicate them to our obstetrical colleagues. (Reviewer-W. Steven Metzer, MD).

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Keywords: Pregnancy

Print Tag: Refer to original journal article
In frontotemporal lobar degeneration with right temporal lobe atrophy, behavioral symptoms are prominent, including social disinhibition, depression, and aggressive behavior.

**Objective:** To identify the clinical profile associated with frontotemporal lobar degeneration (FTLD) and asymmetric predominantly right-sided temporal lobe atrophy (RTLA).

**Participants/Methods:** 20 patients aged 52 to 85 years were identified from a dementia registry with predominant RTLA on the basis of blinded assessment of MRI scans. Patients were tested for cognitive and behavioral change, and results were compared to semantic dementia patients with predominantly left-sided temporal lobe atrophy and a group of healthy control subjects.

**Results:** Among the RTLA group, volume loss was 37% in the right temporal lobe and 19% in the left temporal lobe, with severe atrophy in the right hippocampus and amygdala. Six RTLA patients had at least 1 first-degree family member with dementia, and in 2 of these, there was a strong likelihood of familial FTLD. Autopsies in 2 patients revealed ubiquitin-positive, tau-negative inclusions in 1, and combined Alzheimer and cortical Lewy body changes in the other. Ninety percent of RTLA patients had impaired episodic memory, and in 35%, it was the presenting symptom. Other cognitive and behavioral abnormalities included topographical disorientation (“getting lost”) in 65%, prosopagnosia in 60%, disinhibition in 65%, and obsessional behavior in 50%. Less-often encountered were problems with naming, apathy, behavioral rigidity, loss of insight, loss of empathy, aggression, hyper-religiosity, loss of libido, decline of personal care, depression, somatization disorder, overeating, altered food preference, complex visual hallucinations, and abnormal "cross-model" perception of sensory stimuli. In nearly half the patients with RTLA, behavioral disorders predated cognitive deficits. The clinical profile of patients with semantic dementia and predominantly left temporal lobe atrophy was quite different. Every semantic dementia patient had problems with naming, and none had topographical disorientation. The clinical profile of patients with semantic dementia and predominantly left temporal lobe atrophy was quite different. Every semantic dementia patient had problems with naming, and none had topographical disorientation. Somatic dementia patients were as likely as RTLA patients to have impaired episodic memory and twice as likely to have behavioral rigidity. They were less likely to have prosopagnosia, disinhibition, obsessional behavior, aggression, or loss of libido. None of the semantic dementia patients had somatization disorder, loss of insight, hyper-religiosity, visual hallucinations, or abnormal perception of visual stimuli.

**Conclusions:** FTLD with predominantly RTLA produces symptoms that differ significantly from syndromes associated with other focal degenerations of the frontal and temporal lobes.

**Reviewer's Comments:** Of note is that behavioral abnormalities that characterize the syndrome of RTLA would not be detected on a mini-mental status evaluation. (Reviewer-John C. Brust, MD).

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Keywords: Right Temporal Lobe Atrophy

Print Tag: Refer to original journal article
Benefits of tight blood sugar control in elderly diabetics have to be weighed against the risk of triggering severe hypoglycemic events and increasing the chance of dementia.

**Background:** Patients with diabetes have an increased risk for dementia. The reason for this is not clear but most probably involves multiple mechanisms mediating Alzheimer disease and diabetic comorbidities such as stroke. One modifiable mechanism is hypoglycemia arising from aggressive glycemic control. Acute hypoglycemia has been associated with cognitive impairment in children with type 1 diabetes. Whether hypoglycemia in elderly patients with type 2 diabetes predisposes to dementia has not been previously investigated.

**Objective:** To examine if hypoglycemic episodes severe enough to bring the patient to the hospital increase the risk of dementia in a population of older type 2 diabetics followed over 27 years.

**Methods:** From the Kaiser Permanente Northern California Diabetes Registry, the authors identified patients with type 2 diabetes diagnosed between 1980 and 2002, and who were cognitively intact in 2002. They stratified patients into 2 groups: patients who had experienced 1 or more severe hypoglycemic event between 1980 and 2002, and those who had not. Hypoglycemia was considered severe if it required an emergency department visit and/or hospitalization. Dementia cases were identified by reviewing inpatient and outpatient ICD-9 codes for senile dementia—uncomplicated, Alzheimer disease, vascular dementia, and dementia not otherwise specified. Cox proportional hazard regression models were used to assess dementia risk, adjusted for age, sex, race/ethnicity, education, body mass index, duration of diabetes, 7-year mean hemoglobin A1c (HbA1c) diabetes treatment, duration of insulin use, hyperlipidemia, hypertension, cardiovascular disease, stroke, transient cerebral ischemia, and end-stage renal disease.

**Results:** 16,667 patients (mean age, 65 years) had type 2 diabetes diagnosed during 1980-2002 and were cognitively intact in 2002; 1465 patients (8.8%) had experienced 1 or more severe hypoglycemic episodes during 1980-2002. From 2003-2007, 1822 patients (11%) were newly diagnosed with dementia; 250 of 1465 hypoglycemic patients (17%) developed dementia. In contrast, among 15,202 patients without hypoglycemic events, only 1572 (10%) developed dementia. The risk for dementia increased with the number of hypoglycemic episodes. With no episodes, dementia appeared in 10%; 1 episode, 15%; 2 episodes, 22%; and ≥3 episodes, 20%. The absolute risk of dementia per year of follow-up rose by 2.4% for hypoglycemic patients when compared with patients free of such events. The findings were independent of HbA1c levels, types of treatment, and diabetic comorbidities. Results were not affected by medical utilization rates, duration of health plan membership, or time from initial diabetes diagnosis.

**Conclusions:** Among older type 2 diabetics, 1 or more severe hypoglycemic episode increases the risk of a subsequent diagnosis of dementia.

**Reviewer’s Comments:** One treatment group within the ACCORD trial was recently stopped 18 months early due to increased mortality rates in patients receiving intensive blood glucose-lowering therapy. The authors urge caution in tight glycemic control of elderly type 2 diabetics. Whether more minor hypoglycemic episodes affect cognition is unknown. (Reviewer-Michael Jacewicz, MD).

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Keywords: Diabetes & Dementia Risk

Print Tag: Refer to original journal article
Can Stroke Therapy Be Used in an Extended Time Window AND Be Safe?

Effectiveness and Safety of Transcranial Laser Therapy for Acute Ischemic Stroke.

Zivin JA, Albers GW, et al:

Stroke 2009; 40 (April): 1359-1364

Transcranial near-infrared laser energy after acute ischemic stroke increases adenosine triphosphate production and inhibits apoptosis.

**Background:** Transcranial near-infrared laser energy (NIRLE) increases adenosine triphosphate production and inhibits apoptosis, and it improves outcomes in animal models of cerebral ischemia, possibly through beneficial effects on mitochondria.

**Objective:** To investigate the safety and efficacy of NIRLE in patients with acute cerebral ischemia.

**Design:** Double-blind, randomized, sham-controlled clinical trial.

**Participants:** 660 patients aged 40 to 90 years with acute hemispheric cerebral ischemia of any etiology, except septic emboli, with baseline National Institutes of Health Stroke Scale (NIHSS) scores of 7 to 22. Major exclusions were intracranial hemorrhage, severe pre-stroke disability, seizures at onset, severe uncontrolled hypertension, glucose >400 or <60, prior use of tissue plasminogen activator (tPA) or other thrombolytic drugs, or brain tumor. The nature of treatment necessitated exclusion of patients with cranial foreign bodies, such as aneurysm clips or shunt valves, scalp disorders, and those who had received other types of light therapy.

**Methods:** NIRLE at 808 nm was applied for 2 minutes at each of 20 predetermined sites on the scalp following shaving the hair. NIRLE is known to penetrate the skull to a depth of about 2 cm. Sham patients received identical applications of the probe, without any energy delivery. Treatment had to be initiated within 24 hours of stroke onset. Outcome measures included the modified Rankin Scale (mRS) and the NIHSS, assessed at baseline and at intervals up to 90 days after treatment. Usual clinical, demographic, medical history, exam, and risk factor data were collected. Neuroimaging (not further specified) was done at baseline and 5 days after therapy. Statistical analysis was by intention to treat. The primary outcome measure was the 90-day mRS, dichotomized into 0-2 versus 3-6. Many other NIHSS and mRS outcomes were analyzed.

**Results:** Sham and active treatment groups were similar at baseline. Mean NIHSS at baseline was 13. Mean onset-to-treatment time was about 15 hours. Neither the primary outcome measure, nor any prespecified secondary outcome measure, favored either group. Strong trends were seen favoring active treatment for many subgroups. Post hoc analysis, excluding about 225 patients (one third of the cohort) with baseline NIHSS scores of >15, was statistically significant, favoring the active treatment ($P=0.044$). NIRLE was not effective for "deep infarcts" (not otherwise defined). There were no serious adverse events attributed to NIRLE; rates of hemorrhagic transformation at day 5 were the same in both groups.

**Conclusions:** NIRLE at 808 nm applied transcranially within 24 hours of acute ischemic stroke is safe but not effective. Because of trends favoring treatment versus sham treatment in subgroups of patients with less severe strokes, a larger trial is certainly warranted and probably will be forthcoming.

**Reviewer’s Comments:** Several of the co-authors, including the lead author, have financial interest in the company that manufactures the NIRLE delivery device tested in this trial. (Reviewer-James W. Schmidley, MD).

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Keywords: Acute Ischemic Stroke

Print Tag: Refer to original journal article
In this case report of a Parkinson's disease patient, the amount of painting and associated disruptive behaviors induced by dopamine agonists was dose-related.

**Background:** Observations of artistic skill and production in patients with neurological diseases have opened a window on the underlying brain areas involved with creativity. Degeneration of language areas in the temporal lobe variant of frontotemporal dementias can lead to the emergence or improvement of creative endeavors. Processes affecting visuospatial areas can cause changes to more abstract art, and Parkinson's disease can result in compulsive art production.

**Objective:** To present the authors' experience of an amateur artist who developed idiopathic Parkinson's disease. **Case Report:** A 47-year-old man was noted to lose interest in painting 8 months prior to diagnosis of Parkinson's disease and mild depression. Treatment with levodopa led to improvement of motor symptoms, but the patient did not resume painting. After beginning cabergoline 4 mg daily 2 years later, he resumed painting and even developed a selective interest in this activity. His quantity of paintings increased, and his style changed from realistic to impressionistic. He felt a need to express refreshed inner emotions. He was otherwise apathetic with no other daily activities arousing his interest. Painting became his only activity, interfering with sleep and disrupting family activities. There was no mania, impulse control disorder, or dopamine dysregulation. Cabergoline was discontinued over 6 weeks, with resultant apathy, worsened depression, and decreased artistic activity. Increasing the levodopa dosage did not change this. With restarting cabergoline 4 mg/day, he resumed the same pattern of painting as previously. Cabergoline was replaced by pramipexole 0.7 mg 3 times daily with the same disruptive painting pattern. Decreasing this medication to 0.35 mg 3 times daily resulted in a self-satisfactory daytime painting pattern without continuation of this activity until the night.

**Conclusions:** Changes in creativity in Parkinson's disease are related to dopaminergic imbalance in the limbic system.

**Reviewer's Comments:** It is presumed that dopaminergic stimulation of hypersensitized mesolimbic pathways is responsible for impulse control disorders, dopamine dysregulation, punding, mania, and changes in creative, artistic processes in Parkinson's disease. What determines which of these will occur in any given Parkinson's patient remains a mystery. (Reviewer-John Schwankhaus, MD).

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Keywords: Parkinson's Disease

Print Tag: Refer to original journal article
Compensation is likely a strong contributor in explaining the dramatic increase in military post-concussive symptoms in veterans as compared to their civilian counterparts.

**Background:** An estimated 300,000 veterans of the wars in Iraq and Afghanistan have sustained a so-called mild traumatic brain injury (TBI). The Departments of Veterans Affairs and Defense, therefore, enacted screening, disability, and specialty care services.

**Objective:** To address the flawed foundation and consequences of the present approach.

**Results:** The definition of mild TBI or concussion used by these programs implies an unhealed brain injury with persistent cognitive and behavioral symptoms of the post-concussive syndrome (headache, sleep disturbance, irritability, dizziness, imbalance, fatigue, inattention, and poor concentration or memory). Concussion, on the other hand, is defined as brief loss of consciousness or posttraumatic amnesia caused by physiologic changes at the time of injury. In two thirds of cases identified as mild TBI, it was solely on the basis of a positive response when asked if they recalled being dazed or confused at the time of injury or blast (an invalidated question). During war, several factors could lead to a positive response, including a normal response to injury, dissociation, acute stress, sleep deprivation, or the confusion of war. Several past studies have failed to show a causal relationship between concussive head injuries and post-concussive symptoms. These symptoms are found just as frequently with injuries not involving the head and in the general population. Post-deployment screening done in a structure of care with both treatment and disability, and complicated by psychological factors, compensation, and patient expectations, have shown that 40% of service members experience persistent symptoms compared to 3% to 5% of their civilian counterparts. A previous study by these authors linked post-concussive symptoms in this population more strongly to posttraumatic stress disorder (PTSD) and depression. In the VA system, "Residuals of TBI" carries a 40% disability rating and is based on ≥3 subjective symptoms that interfere with functioning or objective evidence of impairment of memory, attention, concentration, or executive function. This approach blatantly ignores extensive literature showing a strong association between compensation and persistence of symptoms after concussion. Non-specific post-concussion symptoms are treated the same whether occurring in the presence or absence of head injury. Instead, veterans are sent to specialty TBI clinics designed to treat much more severe injuries. This approach fails to address the real underlying condition (PTSD, depression, substance abuse) and tends to reinforce negative perceptions of illness.

**Conclusions:** The authors put forth several recommendations with the goals of enhancing the expectation of recovery, decreasing severity of symptoms, preventing long-term disability, and providing optimal care.

**Reviewer's Comments:** As elucidated well in this editorial, the present approach to so-called "mild TBI" is not based on scientific fact and is potentially disabling for veterans. A more comprehensive approach to all post-deployment concerns is desperately needed. (Reviewer-John Schwankhaus, MD).

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Keywords: Mild Traumatic Brain Injury

Print Tag: Refer to original journal article
Paraneoplastic neurological syndromes are a potential cause of oligoclonal banding in the cerebrospinal fluid.

**Background:** No detailed analysis of cerebrospinal fluid (CSF) abnormalities in a large unselected cohort of patients with paraneoplastic syndromes of the nervous system (PSNS) has been published.

**Objective:** To describe CSF findings in PSNS patients from a paraneoplastic neurological syndromes database.

**Design:** Retrospective observational study.

**Participants:** 295 patients with at least 1 full CSF exam, including white cell count and protein determination. Patients had antibodies to Hu, Yo, Ri, Ma/Ta, CV2, or Tr, and neurologic disease definitively attributable to PSNS.

**Methods:** The PSNS encountered included limbic encephalitis, encephalomyelitis, brainstem encephalitis (including opsoclonus), cerebellar degeneration, and a "lumped" category of peripheral nerve disorders.

**Results:** A broad overview of these patients produced no surprises: 170 had anti-Hu (these had the widest variety of clinical syndromes and mainly had SCLC), and 59 had anti-Yo antibodies and largely had cancer of the breast or gynecologic cancers and cerebellar degeneration. The other antibodies were represented by <25 cases each. CV2 patients tended to have small-cell lung cancer and peripheral nerve disorders; anti-Ma/Ta patients tended to have limbic encephalitis and testicular cancer; anti-Ri patients had brainstem encephalitis and breast cancer; and anti-Tr patients had cerebellar degeneration and Hodgkin's disease. As always, with PSNS, there were variable correlations among type of antibody, type of tumor, and type of clinical syndrome produced. As usual with a large cohort of such patients, 14% had no tumor, despite having a serum antibody and a clinical illness. Overall, CSF had an elevated white count about 40% of the time and an elevated total protein about two thirds of the time. Of patients whose CSF was tested for oligoclonal bands, 63% were positive. Only 7% had a completely normal CSF, and only 3% had a normal CSF if spinal fluid was sampled within the first 3 months after onset of symptoms. The frequency of abnormal CSF was the same with all antibodies, as was the frequency of oligoclonal bands. There was a statistically significant tendency for CSF cell count to be higher in the first 3 months after onset of PSNS.

**Conclusions:** CSF abnormalities are common in PSNS, especially early after onset of symptoms. The tendency for CSF to be more inflammatory early in the course of PSNS is consistent with pathological findings. CSF findings did not correlate with antibody, clinical syndrome, or tumor type.

**Reviewer's Comments:** Our investigations start with a clinical syndrome in a patient, prompting a search for tumor and/or antibody. CSF is often studied to rule out other diseases, but CSF abnormalities of the type described increase the likelihood that the final diagnosis will be a PSNS; persistently negative CSF would make the diagnosis less likely. The study is useful, despite being non-systematized and retrospective. (Reviewer-James W. Schmidley, MD).

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Keywords: Paraneoplastic Neurological Syndromes

Print Tag: Refer to original journal article
In children with myasthenia gravis, response to thymectomy tended to be better when it was performed early during the course of the disease.

**Objective:** To evaluate the response to thymectomy as treatment for juvenile myasthenia gravis (MG) in children.

**Design/Participants:** Retrospective review of records of all children with a diagnosis of MG at Children's Memorial Hospital in Chicago from 1982 to 2007 and who had undergone thymectomy as therapy for MG.

**Methods:** The severity of MG was classified according to the established Osserman criteria as follows: grade I, focal disease (such as ocular); grade IIa, mild generalized disease; grade IIb, moderate generalized disease; grade III, severe generalized disease; and grade IV, myasthenic crisis with respiratory compromise requiring intubation. Typically, patients were treated initially with pyridostigmine followed by prednisone as clinically indicated. A response to oral therapy scale rating was assigned to each patient prior to and following thymectomy. Response to thymectomy was also evaluated based on the number of hospital days, ICU days, and intubation days prior to and following thymectomy.

**Results:** A total of 50 children with a diagnosis of MG were identified who ranged in age at the onset of symptoms from 15 months to 18 years, with a mean of about 8 years. Overall, a good response to standard therapy was achieved in approximately half the patients who were rendered asymptomatic. About one third of patients successfully got off all medications. Thymectomy had been performed in 13 patients, including 11 females and 2 males. Age at time of thymectomy ranged from 17 months to 18 years. Severity of symptoms following thymectomy based on the Osserman rankings were grade I in 2 patients, grade IIa in 1, grade IIb in 4, grade III in 1, and grade IV crisis in 1; 4 patients were in remission. On the response to therapy scale, 4 children were grade A (complete remission, no medication), 3 were grade B (some improvement, lower dose of medication), 3 were grade C (slight improvement, no change in medication), and 3 were grade D (no improvement). Days of hospitalization, ICU stay, and intubation were significantly decreased post-thymectomy. Response to thymectomy tended to be better when it was performed early during the course of the disease. Only about half of these children had positive acetylcholine receptor antibodies, and presence or absence of antibodies was not predictive of response to thymectomy. Thymectomy was judged to be effective in about two thirds, and one third experienced remission.

**Reviewer’s Comments:** Thymectomy is a viable therapy to be considered in children with MG, especially when response to medical therapy is not satisfactory. Early thymectomy is more likely to yield a positive response. (Reviewer-Gregory B. Sharp, MD)

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Keywords: Thymectomy

Print Tag: Refer to original journal article
Pathologic gambling and hypersexual behavior are highly associated with use of dopamine agonists but not levodopa. The effect is dose-related and reversible upon stopping the drug.

**Background:** Referral center specialty clinics have reported compulsive behavior, including pathologic gambling and hypersexuality, in patients treated with dopamine agonists (DA) for idiopathic Parkinson’s disease (PD). **Objective:** To assess the true frequency of compulsive behavior. **Design:** Retrospective community-based study. **Participants:** All patients from the environs of the Mayo Clinic who were treated there for PD from 2004 to 2006. **Methods:** Patients were identified by chart review. Behavior was considered pathologic if it impaired social or occupational function. A therapeutic dose of pramipexole was considered to be at least 2 mg/day and, of ropinirole, at least 6 mg/day. No patient was taking another DA. **Results:** There were 267 patients: 66 (25%) who took a DA but only 38 (14%) in a therapeutic dose, and 178 (67%) who took levodopa but no DA. Five patients had new-onset pathologic gambling or hypersexuality. All 5 were taking a DA, and 1 was not taking levodopa. Furthermore, all 5 patients were taking their DA in a therapeutic dose, and none exceeded the usual recommended dose. Thus, 8% of patients taking a DA, and 13% of those taking it in a therapeutic dose developed hypersexuality or pathologic gambling. Two of these 5 patients developed other compulsions: lawn care, eating, alcoholism, and hobbies. Compulsive behavior disappeared gradually after stopping the DA. The 5 affected patients were not demented, had relatively mild PD, and were significantly younger than unaffected patients, but there were no differences in gender or history of substance abuse or psychiatric illness. **Conclusions:** Pathologic gambling and hypersexual behavior are highly associated with use of DA but not levodopa. The effect is dose-related and reversible upon stopping the drug. **Reviewer's Comments:** An exhaustive review of the literature on DAs and impulse-control disorders, by Weintraub, can be found in the *Annals of Neurology* 2008; 64 (December; suppl 2): S93-S100. (Reviewer-Marc D. Winkelman, MD).
Sustained-release fampridine provides clinically meaningful benefit by improving ambulatory disability in patients with multiple sclerosis.

**Background:** Several studies have shown that fampridine (4-aminopyridine), a potassium-channel blocker, improves visual function, ambulation, fatigue, and endurance in multiple sclerosis (MS) patients. However, a Cochrane systematic review of 6 randomized studies (198 subjects) published in 2002 could not draw any conclusions as to efficacy or safety, mainly due to small sample sizes.

**Objective:** To report on the findings of a phase III trial using sustained-release fampridine in patients with MS, assessing safety and effectiveness on ambulation and leg strength.

**Design:** Randomized, multicenter, double-blind, controlled phase III trial.

**Methods:** Patients were randomly assigned to receive oral fampridine (10 mg twice a day) or placebo. The proportion of patients with consistent improvement on timed 25-foot walk (T25FW) was the primary outcome. A 12-item MS walking scale (MSWS-12) was used to validate the clinical significance of the T25FW response.

**Results:** Of 301 patients with any type of MS, 229 were randomized to the fampridine arm and 72 to the placebo arm. The fampridine group had a higher proportion of timed walker responders compared to placebo (78 of 224 [35%] vs 6 of 72 [8%]; \( P < 0.0001 \)). Maintained improvement in walking speed in timed walk responders was seen 25.5% in the fampridine group and 4.7% in the placebo group. Timed walk responders showed significantly greater improvement in MSWS-12 scores. Overall, the incidence of adverse events was higher in the fampridine group, but only 2 serious adverse events could be specifically attributed to the medication: focal seizure in 1 patient and severe anxiety in another (recurred on re-challenge with fampridine).

**Conclusions:** In some patients with MS, fampridine improves ambulation in a clinically meaningful way. An additional phase III trial is needed to confirm these observations.

**Reviewer’s Comments:** In this study, there was no difference in demographics and clinical characteristics between responders and non-responders to fampridine. It is probably due to differences in neuropathology. Patients with more demyelination (as opposed to more secondary axonal loss) probably respond better, due to improvement in conduction through demyelinated pathways via potassium-channel blocking action of fampridine. (Reviewer-Chitharanjan Rao, MD).

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Keywords: Fampridine

Print Tag: Refer to original journal article
Lancinating facial pain is a good predictor for a good outcome following microvascular decompression in patients with trigeminal neuralgia.

**Background:** Trigeminal neuralgia (TN) is treated with anticonvulsants, gamma knife, or microvascular decompression (MVD). Compression of the TN by a blood vessel at or near the root entry zone is the causative theory that justified MVD.

**Objective:** To analyze outcome predictors in TN patients treated with MVD.

**Design/Participants:** Retrospective analysis of TN patients treated with MVD at 1 U.S. university medical center.

**Methods:** Patients who underwent MVD were contacted by phone. They were retrospectively classified into TN1, if they had a preponderance of typical lancinating TN pain (shock-like, electrical, shooting, stabbing), or TN2, if they had atypical constant facial pain (aching, burning, throbbing, stinging). Patients were asked about the duration of their preoperative pain (≥36 or <36 months), presence of absence of trigger points, pain-free intervals, response to anticonvulsants, and a memorable onset of pain. Outcome was defined as excellent (long-term relief without medication), good (mild or intermittent pain controlled with low-dose medication), or poor (severe persistent pain or need for additional surgical treatment).

**Results:** Among 167 patients contacted, 121 agreed to participate, and 95 were included in this analysis. Mean age was 54.3 years. The only predictor for outcome, using multiple regression analysis, was TN pain type ($P<0.05$). Outcome was excellent, good, and poor for TN1 versus TN2 patients in 60% versus 25%, 24% versus 39%, and 16% versus 36%, respectively (relative risk 2.39; 95% CI, 1.66 to 11.9). Patients with lancinating pain (TN1) without a component of constant pain (TN2) had a greater likelihood of excellent outcome. In contrast, those with constant pain (TN2) without a component of lancinating pain had a lower likelihood of good or excellent outcome. Arterial compression was associated with TN1 symptoms more so than venous compression, and it predicted a slightly better overall outcome but was not by itself statistically significant. There were trends toward better outcome in patients with shorter preoperative duration of symptoms, presence of trigger points, positive response to anticonvulsant agents, pain-free intervals, and memorable onset of pain.

**Conclusions:** The type of pain (typical and lancinating versus atypical and constant) was the only significant and independent predictor of outcome following MVD in patients with TN.

**Reviewer’s Comments:** This study supports prior clinical studies that distinguished the general outcome of patients with classical TN from those with “atypical facial pain.” In contrast to TN, patients with atypical facial pain usually respond poorly to medical therapy. This study not surprisingly confirmed prior observations that MVD is also more effective in TN than in atypical facial pain. Shortcomings of this study are its retrospective design, high number of patients who refused to participate (58 of 179), and reliance on patients’ subjective recollection of the preponderance of pain type and intensity. (Reviewer-Bashar Katirji, MD).

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Keywords: Neuralgia

Print Tag: Refer to original journal article
Skin Necrosis, Low C4 Level Characteristic of Malignancy in Older DM Patients

Factors Associated With Underlying Malignancy in a Retrospective Cohort of 121 Patients With Dermatomyositis.

Fardet L, DuPuy A, et al:

Medicine (Baltimore) 2009; 88 (March): 91-97

Rapid onset of dermatomyositis in patients aged >50 years with skin necrosis or low C4 level portends a higher incidence of malignancy.

Background: Patients with dermatomyositis (DM) have a 3- to 6-fold increase in the risk of underlying malignancy compared to the general population. Apart from age, there are no well-defined clinical factors that favor underlying malignancy and justify surveillance for occult cancer.

Objective: To identify factors associated with an underlying malignancy in patients diagnosed with DM.


Participants: Patients who fulfilled the criteria of Bohan and Peter as definite DM or probable DM as well as patients with dermatitis and without muscular weakness (amyopathic DM) were included, while patients with polymyositis were excluded.

Methods: Muscle biopsy was available on 74 patients, while 33 were diagnosed with DM based on clinical criteria. A malignancy was considered to be associated with DM when diagnosed <1 year prior to or within 5 years of DM diagnosis. A variety of clinical findings were assessed using multivariate analysis and hazard ratios were calculated.

Results: Of 121 patients, 75 had definite DM, 32 probable DM, and 14 amyopathic DM. The majority of patients in the study were women (70%). Malignancy in a wide range of organs was detected in 29 patients, while 92 were free of cancer. Of those with malignancy, 18 of 29 (62%) were diagnosed within 3 months of DM diagnosis. The following were independent factors associated with malignancy: age >52 years (P ≤0.01; hazard ratio [HR], 7.24), time between onset of symptoms and DM diagnosis of <4 months (P ≤0.03; HR, 3.11), skin necrosis (P ≤0.05; HR, 3.84), periungual erythema (P ≤0.02; HR, 3.93), and low (<16 mg/L) C4 (P ≤0.02; HR, 2.74). A low (<1500/mm3) lymphocyte count had a protective value against malignancy (P ≤0.01; HR, 0.33).

Conclusions: Factors that favor an underlying malignancy in DM include age at diagnosis of >52 years, rapid onset of skin and/or muscular symptoms, presence of skin necrosis or periungual erythema, or low complement factor C4 level. A low lymphocyte count is protective against cancer.

Reviewer’s Comments: This study is a good attempt at trying to identify patients who might benefit from extensive evaluation for underlying malignancy. It also shows that most associated malignancy occurs within 3 months of DM diagnosis. Guidelines regarding screening are still vague since cancer source is variable, and optimal interval for rescheduling malignancy workup is yet to be determined since only two thirds of patients in this series were diagnosed with cancer within 3 months of DM diagnosis. (Reviewer-Bashar Katirji, MD).

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Keywords: Underlying Malignancy

Print Tag: Refer to original journal article
All children with sickle cell disease should be followed at a center where transcranial Doppler screening is performed to identify those at increased risk for stroke.

**Background:** One of the primary causes of mortality, and especially morbidity, in children with sickle cell anemia is stroke. In untreated patients, about 10% of children with sickle cell disease (SCD) experience stroke by age 20 years. In the Stroke Prevention Trial in Sickle Cell Anemia (STOP) that was completed in 1998, transcranial Doppler ultrasonography (TCD) screening was used to identify children with SCD who were at high risk for stroke. These children were then placed on a hypertransfusion protocol that resulted in an >90% reduction in the rate of stroke.

**Objective:** To determine if TCD screening is effectively being used in children with SCD to identify those at increased risk for stroke.

**Design/Methods:** A retrospective review of records was performed that included a cohort of children with SCD within a large managed care plan from 1993 through 2005. Statistical analysis was performed to determine the rates of TCD screening and the annualized stroke incidence rate before and after the first TCD.

**Results:** A cohort of 157 children with SCD was identified and studied. The average annual rate of TCD screening prior to 1998 was 1.8 per 100 person-years. During 1998 and 1999, the rate increased to 5.0; after 1999, it increased to 11.4 per 100 patient-years. During the study period, subjects were followed for a mean of 8.5 years at 26 different facilities within the managed care organization. One third of children received a first TCD evaluation. An additional 6 children were referred for TCD screening but did not have the study done. The only independent predictor of having TCD screening performed was proximity to the vascular laboratory. The annualized stroke rate prior to the first TCD was 0.44 per 100 person-years, and this rate decreased to 0.19 following the first TCD.

**Conclusions:** The rate of TCD screening in children with SCD has increased 6-fold within this managed care plan since the STOP trial was completed in 1998.

**Reviewer’s Comments:** TCD screening is very effective in identifying children with SCD at risk for stroke, and although TCD is being used more readily, it is still underused. Increased availability within more cities or communities would likely increase utilization. (Reviewer-Gregory B. Sharp, MD).

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**Keywords:** Transcranial Doppler Ultrasonography

**Print Tag:** Refer to original journal article
Children with an absence of any additional white matter abnormalities when presenting with an initial episode of idiopathic optic neuritis appear very unlikely to develop multiple sclerosis, and presence of white matter lesions is associated with an increased risk.

Background: Optic neuritis is a common presenting feature of multiple sclerosis (MS), especially in adult patients. A baseline MRI of the brain that reveals additional white matter lesions has been determined to be a strong predictor of the development of MS in adults. In children, this association has not been firmly established.

Objective: To examine the association of brain MRI findings with the development of MS in children at first episode of optic neuritis.

Design/Methods: A retrospective record review was performed at the Children's Hospital of Philadelphia that identified children who presented with optic neuritis as a first demyelinating episode prior to age 18 years over a 10-year period between 1993 and 2004. MRI of the brain was obtained at baseline at the time of presentation with optic neuritis and attention was paid to identify white matter abnormalities on T2 and/or FLAIR sequences in addition to abnormalities within the optic nerves. Identified symptoms, ophthalmologic findings, MRI results, and clinical outcomes were all noted and recorded.

Results: 29 children presented with signs and symptoms consistent with idiopathic optic neuritis during this period and did not have a history of prior optic neuritis or demyelinating episode. Just over half had bilateral optic neuritis at the time of initial presentation. Additional white matter abnormalities were identified in approximately 40%. Follow-up for >24 months was achieved in 18 patients, and 3 of 18 (just under 20%) developed clinical MS. All 3 of these patients had additional white matter abnormalities present on their initial MRI. The group of patients without white matter abnormalities on MRI at the time of presentation with optic neuritis were followed for a mean of >7 years, and none had developed MS. Thus, in patients followed for >2 years, 3 of 7 with ≥1 white matter abnormalities on MRI developed MS compared to 0 of 11 whose initial MRI was normal from that perspective.

Reviewer's Comments: Conclusions/Reviewer's Comments: All children who present with signs and symptoms of optic neuritis should obviously have an MRI scan of the brain. The absence of additional white matter abnormalities is a good prognostic factor in that these patients are unlikely to develop multiple sclerosis. Presence of additional white matter abnormalities is indicative of an increased chance for the development of MS. Based on this small number of patients, these potential probabilities are obviously not absolute. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Pediatric Optic Neuritis

Print Tag: Refer to original journal article
Etiology Predicts Long-Term Outcome in Childhood Epilepsies

Early Seizure Frequency and Aetiology Predict Long-Term Medical Outcome in Childhood-Onset Epilepsy.

Sillanpää M, Schmidt D:

Brain 2009; 132 (April): 980-998

Long-term outcome in childhood epilepsies is determined by early seizure frequency and etiology.

**Background:** Approximately two thirds of treated epileptic patients experience remission lasting several years. However, it is not clear which factors forecast an unfavorable long-term outcome and increased mortality in new-onset childhood epilepsy. Early identification of such features may encourage more aggressive seizure management, besides helping provide parents with answers.

**Objective:** To identify early clinical features that predict seizure outcome and mortality.

**Participants/Methods:** Children aged <16 years with epilepsy evaluated at the University of Turku Central Hospital in Finland between 1961 and 1964 were studied. Seizures and epilepsies were defined per guidelines of the International League Against Epilepsy. Remission was defined as the first seizure-free year. Terminal remission (TR) was defined as remission at the end of follow-up, and could have a remitting or remitting-relapsing course. Complete seizure control from the start of first adequate treatment was called early uninterrupted terminal remission. Epilepsy was considered drug-resistant if 1-year remission (1YR) was not achieved at all during a follow-up of at least 10 years. Sudden unexpected death (SUDEP) was defined per guidelines.

**Results:** 102 patients were eligible for inclusion; 66 had idiopathic/cryptogenic etiology, and 36 had symptomatic etiology. At the end of a 40-year median follow-up, 95 (93%) of 102 subjects had achieved ≥1 1YR. The remaining 7 patients (7%) were drug-resistant. Twenty patients achieved early uninterrupted terminal remission. Weekly seizures during the first year of treatment increased the risk of drug-resistant epilepsy 8 times (hazard ratio [HR], 8.2; \( P =0.0125 \)). Weekly seizures prior to treatment did not significantly affect the probability of achieving 1YR. However, the idiopathic/cryptogenic group had a higher probability of achieving 1YTR than the symptomatic group (59% vs 22%). Of 13 patients who died during follow-up, etiology in 6 was epilepsy, including 3 SUDEPs. The mortality risk was 9 times higher in the symptomatic group (HR, 9.0; \( P =0.0071 \)); the risk was not affected by pretreatment or early posttreatment seizure frequency.

**Conclusions:** In this long-term follow-up study of childhood epilepsies, etiology predicted seizure outcome and mortality. Early posttreatment seizure frequency predicted seizure outcome, but not mortality.

**Reviewer's Comments:** This unique, long-term follow-up study of childhood epilepsies (possible only in countries with national health service) showed that remission is predicted by early posttreatment seizure frequency, and not by pretreatment seizure frequency, as is commonly believed. Not surprisingly, a symptomatic etiology is associated with lower remission rates and higher mortality. The major strength of this study (very long-term follow-up) is also its weakness. Investigative tools such as MRI, newer medications, vagal nerve stimulation, and resective surgical methods were not available for a major period of the study. (Reviewer-Chitharanjan Rao, MD).

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Keywords: Seizure Outcome & Mortality

Print Tag: Refer to original journal article
Parkinson's disease patients are unable to lie due to prefrontal executive dysfunction.

**Background:** Parkinson's disease (PD) patients are said to possess certain personality traits, e.g., industriousness, seriousness, and inflexibility. They are also described as "honest," as they tend not to tell untruths. It is possible that PD patients, rather than choosing not to tell lies, have difficulty in telling lies. One potential mediator for complex cognitive process requiring executive function such as deception is the prefrontal cortex, as this area supports processes such as response inhibition and cognitive control. Thus, impairment in the prefrontal executive function can affect the flexible and goal-directed behaviors that are essential for human deceptive behavior. In PD patients, prefrontal cortex has been implicated in executive dysfunction. Functional imaging studies in normal subjects have shown that prefrontal cortex is active during deceptive responses.

**Objective:** To test the hypothesis that PD patients seem relatively honest, as they have difficulty in making deceptive responses due to prefrontal executive system dysfunction. This hypothesis was tested using a novel cognitive task and 18F-deoxyglucose (FDG)-PET imaging.

**Participants/Methods:** 32 PD and 20 control subjects were included. The inclusion criteria for PD patients consisted of: age 40 to 75 years, age at onset >40 years, Hoehn-Yahr stage 1 to 3, and MMSE score ≥24. Standard neuropsychological tests were administered to all subjects. Fourteen PD patients were on dopaminergic medications, which were discontinued at least 5 hours prior to the PET scanning. PET control data were obtained from 14 healthy subjects. The experimental deception task consisted of an incidental study phase and a recognition memory test phase (details provided in the article).

**Results:** During the standard neuropsychological testing, PD subjects performed worse on the digit span, verbal fluency (for syllables), and trail-making tests compared with control subjects. On the deception task, PD patients had impaired ability to lie ($P=0.0003$), which was due to failure to inhibit true responses and make deceptive responses. This performance correlated well with performances on verbal fluency for syllables and trail-making test. There was no correlation between te performances on the deception task and the digit span test. Performance on the deception task correlated significantly with prefrontal (right anterior prefrontal and left dorsolateral prefrontal cortices) hypometabolism on resting state FDG-PET.

**Conclusions:** Honesty in PD patients is due to prefrontal executive dysfunction resulting in diminished ability to produce deceptive responses as shown by the deception task results and metabolic studies.

**Reviewer's Comments:** This elegant study shows that PD patients are "honest," not by choice, but rather due to prefrontal cortex dysfunction. It would be interesting to study these patients in an "on" medication state to see if dopaminergic medications make them "less than honest." What about patients with other disorders affecting the prefrontal cortex? (Reviewer-Chitharanjan Rao, MD).

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Keywords: Deceptive Behavior

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