CT Very Sensitive for Subarachnoid Hemorrhage

Determining the Sensitivity of Computed Tomography Scanning in Early Detection of Subarachnoid Hemorrhage.

Cortnum S, Sorensen P, et al:

Neurosurgery 2010; 66 (May): 900-903

Newer CT scanners appear to have a higher sensitivity for identifying subarachnoid hemorrhage.

**Background:** Early detection of subarachnoid hemorrhage (SAH) leads to improved outcomes. Previous guidelines, based on studies from the 1980s and 1990s, suggest that lumbar puncture is needed to rule out this entity if the CT scan is negative. Previous sensitivity of CT scanning ranged from 93% to 95% in the first 24 hours, 85% at 3 days after symptom onset, and 50% after 1 week.

**Objective:** To test the sensitivity of CT scanning using newer high-resolution multidetector CT scanners and to reevaluate the need for lumbar puncture.

**Design:** Retrospective study.

**Participants:** All patients referred to the neurosurgical unit for suspected SAH from 2000 to 2005.

**Methods:** The medical records were reviewed as well as the CT scan, angiography, and results of the lumbar puncture. Those with a negative CT scan had a lumbar puncture with cerebrospinal fluid (CSF) sent to the lab for cell counts and analyzed for xanthochromia by spectrophotometry. These were done no earlier than 12 hours after the onset of symptoms.

**Results:** Of 510 patients admitted, 8 were excluded because there was no clinical suspicion of SAH, and 2 were excluded because their CT scan showed a capillary hemangioblastoma. A patient with a spinal hemorrhage on MRI with no vascular abnormality on angiography was also excluded. Of the remaining 499 patients, 203 had the diagnosis excluded by CT scan and negative lumbar puncture, and 296 had a SAH. SAH was diagnosed on positive CT scan in 295 of 296 patients. The remaining patient with SAH was diagnosed by lumbar puncture on day 6. From day 1 to day 5, CT scanning had 100% specificity and 100% sensitivity. Overall, CT scanning had 99.7% sensitivity and 100% specificity. In those who underwent a lumbar puncture, 4 had viral meningitis and 15 had a post-spinal headache.

**Conclusions:** CT scanning is excellent for diagnosing SAH and appears sufficient to exclude this entity in the first few days after ictus.

**Reviewer's Comments:** This study is very encouraging because many patients with sudden, severe headache presently undergo only a CT scan without lumbar puncture. I would like to see further studies confirming this finding before changing my present diagnostic approach. (Reviewer-John Schwankhaus, MD).

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Keywords: Subarachnoid Hemorrhage, Detection, CT Scanning, Lumbar Puncture

Print Tag: Refer to original journal article
Virtual reality systems like the Nintendo Wii™ can safely be used as an adjuvant to traditional rehabilitation therapies in patients after stroke.

**Objective:** To determine if the virtual reality Nintendo Wii™ gaming system (VRWii) can be used safely to improve motor recovery after stroke.

**Design:** Single-blind trial.

**Participants:** Patients whose ages ranged from 18 to 85 years and who were within the first 6 months of a first-ever stroke.

**Methods:** Patients were randomly assigned to either using the VRWii or recreational therapy (RT) to augment motor performance. Exclusion criteria included being unable to follow instructions, having significant pre-stroke disability, having poor upper extremity function or shoulder instability, having a history of seizures, having medical instability, or having a poor prognosis for survival. The primary outcomes were feasibility and safety of the intervention. The secondary outcome was change in motor performance on the Wolf Motor Function Test (WMFT), Box and Block Test, as well as the quality of life measure Stroke Impact Scale (SIS) at 4 weeks after intervention.

**Results:** 22 subjects were randomly assigned, but 5 dropped out of the study. Nine subjects were randomly assigned to VRWii, and 8 subjects were randomized to RT. At baseline, the VRWii group was younger than the RT group (55 vs 67 years, respectively), and they had more severe strokes. Time of participation was similar for both interventions during the 14-day study period (VRWii, 364 minutes; RT, 388 minutes). No serious adverse events occurred in either group. After adjusting for baseline factors, the VRWii group had a mean 7.4-second improvement in motor function on the WMFT (95% CI, -14.5 to 0.2) when compared to the RT group.

**Conclusions:** Virtual reality Wii gaming is feasible in the subacute phase after stroke and may lead to better motor function.

**Reviewer's Comments:** In this small pilot study, the authors showed that VRWii can be safely used in conjunction with standard rehabilitation therapy in stroke patients. In our own center, we have implemented the use of this technology in select patients. In general, patients have expressed positive comments about using the VRWii system as part of rehabilitation therapy. This study showed a modest improvement in motor function with this intervention compared to RT. Motor improvement was not the primary outcome of interest, and further studies will be needed to see if this intervention truly leads to better motor performance and, more importantly, less disability. Limitation of this study includes its small sample size, differences in baseline characteristics between groups, and the comparison of VRWii to RT, which is an intervention unlikely to augment motor recovery. There are growing data that mass practice is useful remediating the effects of stroke. The VRWii system has great potential to improve outcome after stroke by augmenting current rehabilitation practice. (Reviewer-Aninda B. Acharya, MD, MSPH).

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Keywords: Rehabilitation

Print Tag: Refer to original journal article
Childhood Seizures—Hypoxemia Common, Bradycardia Is Not

How Common Is Ictal Hypoxemia and Bradycardia in Children With Partial Complex and Generalized Convulsive Seizures?

Moseley BD, Nickels K, et al:

Epilepsia 2010; 51 (July): 1219-1224

Hypoxemia is common in generalized convulsive seizures in children and is more likely with prolonged complex partial seizures. Bradycardia is relatively uncommon and is more likely with partial seizures of extratemporal origin.

**Background:** Respiratory compromise, hypoxemia, and cyanosis are commonly present in children during seizures. Bradycardia occurs less commonly. Abnormalities in cardiac rate and rhythm may be involved in sudden unexplained death in epilepsy (SUDEP). The incidence of SUDEP in children has been estimated to be 1 to 2 per 10,000 patient-years.

**Objective:** To determine the prevalence and risk factors for ictal hypoxemia and bradycardia in children during seizures.

**Methods:** A medical record review was performed on all children between the ages of 1 month and 18 years who were admitted for prolonged video EEG (VEEG) monitoring at a single tertiary center during a 16-month study interval. All children who had at least 1 recorded complex partial or generalized convulsive seizure and who had pulse oximetry and heart rate data recorded in the medical records were included in this study. An oxygen saturation of <90% and a drop in heart rate below the second percentile for age during the seizure were considered to represent ictal hypoxemia and bradycardia, respectively.

**Results:** The study group included 49 children, and a total of 225 seizures were analyzed. Hypoxemia occurred in 49% of children and during 27% of recorded seizures. Ictal hypoxemia with oxygen saturation of <60% occurred in one-third of seizures with hypoxemia. Occurrence of ictal hypoxemia was far more common during generalized convulsive seizures than during seizures that remained partial (44% vs 19%, respectively). Hypoxemia was also more likely to occur when antiepileptic drugs were being decreased for the purpose of recording seizures during VEEG. The likelihood of hypoxemia increased during complex partial seizures with prolonged seizure duration. The presence of ictal hypoxemia did not correlate with age. Localization or lateralization of focal seizures was not related to hypoxemia. Ictal bradycardia occurred in about 8% of children and during 4% of seizures. Ictal bradycardia was only observed during complex partial seizures that were extratemporal in origin. Bradycardia during a seizure was primarily seen in younger children, with a mean age of 1.2 years. Because the number of cases of ictal bradycardia was so small, there was no statistical significance in regards to these findings.

**Reviewer’s Comments:** For the most part, the findings of this study were predictable. Hypoxemia during seizures is common, especially during generalized convulsive seizures. Ictal bradycardia occurs, but only in a small percentage of children with seizures. In my experience, ictal bradycardia is more common in infants and younger children than in older patients. The one interesting finding was that ictal bradycardia was only noted in partial seizures of extratemporal origin. Whether bradycardia plays a role in SUDEP remains unknown. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Sudden Unexplained Death in Epilepsy, Hypoxemia, Bradycardia

Print Tag: Refer to original journal article
Acute Neuropathy Is Likely Immune-Mediated Ganglionopathy

Clinicopathological Features of Acute Autonomic and Sensory Neuropathy.
Koike H, Atsuta N, et al:

Brain 2010; August 23 (): epub ahead of print

Objective: To describe clinical and pathological features in 21 patients with acute autonomic and sensory neuropathy.

Methods: Patients had neuropathy with monophasic progression of autonomic and sensory symptoms and signs in the absence of weakness or EMG evidence of motor involvement. Patients with diabetes mellitus, amyloidosis, Sjögren syndrome, Fabry disease, and alcoholism were excluded.

Results: In the group studied, 6 patients were men and 15 were women. The mean age at onset was 29 years (range, 6-65 years). Fifteen reported an antecedent event, most often an upper respiratory or gastrointestinal (GI) infection. Initial symptoms were numbness or pain in the extremities or trunk or autonomic dysfunction. Nine patients presented with vomiting, abdominal distention, or diarrhea, and 1 of these had abdominal surgery for paralytic ileus. In 16, neurogenic flaccid bladder required urethral catheterization. Of 18 patients with orthostatic hypotension, 17 had frequent syncope on sitting or standing. Hypohidrosis or anhidrosis affected the whole body in 18 patients. Mydriasis, with or without loss of pupillary light reflex, was bilateral in 13 and unilateral in 2 patients. Initial sensory loss was for pinprick, temperature, and light touch in all patients; proprioceptive loss and sensory ataxia subsequently appeared in 12. Sensory loss included proximal limbs, face, scalp, and trunk, and tended to be asymmetric and segmental rather than glove/stocking. All but 1 patient experienced spontaneous pain. Nine patients had attacks of coughing related to discomfort in the pharynx. Other symptoms included myalgia, depression, difficulty communicating because of deep sensory impairment in the tongue, sleep apnea, seizure due to hypoxia, and aspiration pneumonia. In patients with sensory ataxia, nerve conduction studies revealed reduced sensory nerve action potentials, and MRI revealed abnormal signal in the dorsal column of the spinal cord. All patients had elevated CSF protein without an increased cell count. Sural nerve biopsy revealed predominantly small fiber axonal loss without evidence of regeneration. Autopsy on a patient with both superficial and deep sensory loss showed neuronal cell loss in thoracic sympathetic and dorsal root ganglia and Auerbach's plexus in the GI tract. Duration from the initial symptoms to peak severity ranged from 6 to 25 days. Most patients received IVIg, plasma exchange, or IV methylprednisolone, but because the diagnosis of neuropathy was often late, only 11 received treatment before symptoms peaked. In several, symptoms stopped progressing soon after treatment was started. Recovery was gradual and incomplete, with sensory symptoms, including sensory ataxia, often outlasting autonomic symptoms. Three patients died within 3 years from sepsis.

Conclusions: Acute autonomic and sensory neuropathy is an immune-mediated ganglionopathy rather than a polyneuropathy.

Reviewer's Comments: A striking observation in this report was the number of patients presenting with abdominal symptoms, the neurological basis of which was not initially recognized. (Reviewer-John C. Brust, MD).

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Keywords: Acute Autonomic & Sensory Neuropathy, Characteristics, Causes

Print Tag: Refer to original journal article
Suspect SD When Patient Asks the Meaning of Words


Kertesz A, Jesso S, et al:
Arch Neurol 2010; 67 (April): 483-489

Behavioral and personality changes are an early feature of semantic dementia. Asking the meaning of words is very common and apparently specific to this disorder.

Background: Semantic dementia (SD) is a variety of frontotemporal dementia. Patients lose the meaning of words, but language is fluent with normal phonology and syntax.

Objective: To delineate SD from the behavioral variant of frontotemporal dementia (FTD), progressive non-fluent aphasia (PNFA), and Alzheimer disease (AD).

Methods: Patients from a cognitive neurology clinic were diagnosed with SD, PNFA, FTD, or AD based on interview, neurological examination, and neuropsychological evaluation. All patients underwent the Mini-Mental State Examination (MMSE), Dementia Rating Scale (DRS), Clock Drawing Test, Category Fluency tests, and the Western Aphasia Battery (WAB). Behavior and personality changes were rated on the Frontal Behavioral Inventory (FBI).

Results: 48 patients with SD were clinically diagnosed from a cohort of 361 with FTD using Neary and colleagues’ criteria. Of these 48 patients, 37 were thought to have probable SD, and 11 were considered “possible SD” due to atypical features (episodic memory loss, Capgras syndrome, significant vascular disease, panic attacks, predominant behavioral changes with incipient SD by first visit, mixed non-fluent and SD features). The FTD group performed significantly better on the MMSE and DRS than did the AD and PNFA patients, while those with SD were also better, but not significantly. Patients with SD performed significantly worse on animal fluency than did AD and FTD patients. SD patients had preserved visuospatial function, and 9 had an obsessive inclination to paint and complete jigsaw puzzles. Of 37 SD patients, 13 had visual object agnosia and 15 had prosopagnosia. The speech output in SD patients was fluent, but 18 of 37 had semantic jargon (meaningless and irrelevant speech output that is grammatically and phonologically correct), 9 had thematic or semantic perseveration, and 8 had excessive output. Questioning the meaning of words heard in conversation occurred in 34 of 37 patients. The AD and FTD groups had significantly less language deficit than did the SD group. The PNFA patients were significantly less fluent than AD and FTD groups but not significantly different from the SD group. The SD group was significantly worse in naming than all other groups. On the FBI, both the FTD and SD groups had significantly more behavioral abnormalities than AD and PNFA groups. Only 6 patients presented with pure SD without behavioral change.

Conclusions: SD is distinguishable from other FTDs and AD by fluent speech, impaired comprehension, no loss of episodic memory, syntax, and phonology, and empty garrulous speech with thematic perseverations, semantic paraphasias, and poor category fluency. Questioning the meaning of words in conversation is common and not seen in other groups. Behavioral change is prevalent.

Reviewer’s Comments: This study helps better define patients with SD. Asking the meaning of words is very common and apparently specific to this disorder. (Reviewer-John Schwankhaus, MD).

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Keywords: Semantic Dementia, Frontotemporal Dementia, Diagnosis

Print Tag: Refer to original journal article
Cerebrospinal venous insufficiency and cerebral venous congestion do not appear to play a significant role in the pathogenesis of multiple sclerosis.

**Background:** Several recent studies have advanced the controversial notion that multiple sclerosis (MS) occurs in the context of chronic cerebrospinal venous insufficiency (CCSVI). Thus, internal jugular venous (IJV) stenosis promotes CCSVI with perivenular congestion of the brain, inflammation, and demyelination. That would explain the long known venocentric nature of MS plaques. Proposed criteria for diagnosing CCSVI include the demonstration of reflux of the deep cerebral veins and/or the internal jugular veins (IVJs) and vertebral veins (VVs), IJV stenosis, missing flow in IJVs and VVs, and inverse postural response of the cerebral venous drainage. Opening IVJ stenosis with stenting has reportedly improved some MS patients, and that has energized the MS population to seek out the procedure despite limited evidence for its efficacy. Most MS experts recommend that the provocative findings be confirmed before resorting to potentially dangerous endovascular manipulations.

**Objective:** To determine if drainage of the cerebrospinal venous system in MS patients differs from controls.

**Methods:** 56 MS patients and 20 controls were subjected to ultrasound examination. Extended extra- and transcranial color-coded sonography was used to characterize the extracranial venous blood volume flow (BVF), cross-sectional areas, IJV flow in supine and upright positions and during Valsalva maneuver (VM), and to examine if proposed CCSVI criteria were fulfilled uniquely in the MS group.

**Results:** In all but 1 patient, the direction of blood flow was normal in the IJVs and VVs. IVJ stenosis was not detected in anyone. In both MS patients and controls, IJV and VV BVF were similar in the supine body position. On assuming an upright position, the decrease of total jugular BVF was less pronounced in MS patients (173 ±235 mL/min) than in controls (362 ±150 mL/min, \(P<0.001\)), and the cerebrocervical drainage for MS patients in the upright position was higher (318 ±242 mL/min) than in controls (123 ±109 mL/min; \(P<0.001\)). There were no differences between the 2 groups during Valsalva maneuver.

**Conclusions:** Cerebrospinal venous drainage in MS patients does not differ from normal subjects except in the upright position, when cerebrospinal venous drainage in MS surpasses that of controls. To explain this finding, the authors suggest that vascular dysregulation occurs when MS affects the autonomic nervous system.

**Reviewer's Comments:** In their discussion, the authors review the intracranial venous anatomy, emphasize the enormous capacity of extrajugular pathways for cerebral venous drainage, and explain why IVJ stenosis, even if present, should not result in CCSVI. As an example, most patients who lose one or both IVJs in radical neck dissection do not develop intracranial venous hypertension. And for the few that do, not one has been reported to develop MS. (Reviewer-Michael Jacewicz, MD).

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**Keywords:** Chronic Cerebrospinal Venous Insufficiency,

**Print Tag:** Refer to original journal article
High vitamin D status provides protection against developing Parkinson disease, but animal data show a U-shaped curve for the neuroprotective effects of vitamin D. Both low and very high levels should probably be avoided.

**Background:** Vitamin D deficiency has been associated with increased risk of cancer, cardiovascular disease, and type 2 diabetes. Recently, great interest has been seen in the role that vitamin D might play in multiple sclerosis (MS). It has been hypothesized that gestational vitamin D deficiency might predispose to autism and schizophrenia. Both basic science and clinical evidence suggests that gestational and neonatal vitamin D status affects neurodevelopment, including dopaminergic neuronal development. A study published in 2007 suggested that chronically inadequate vitamin D intake might play a role in the pathogenesis of Parkinson disease (PD). Other cross-sectional studies have supported this concept.

**Objective:** To investigate whether serum vitamin D level predicts risk of PD.

**Design:** Longitudinal population cohort study.

**Participants:** 3173 men and women (age range, 50-79 years) not diagnosed with PD and not using antipsychotic medications. They were drawn from a total of 7217 individuals who participated in the Mini-Finland Health Survey of Finnish adults >30 years old from 1978 to 1980 in 40 areas of Finland. This included the banking of serum samples.

**Methods:** In 2002, the 25-hydroxyvitamin D concentrations were determined for these stored serum samples. During a 29-year follow-up through the end of 2007, individuals diagnosed with PD were identified through the Finnish health care system database. These cases were reviewed, with 80% meeting diagnostic criteria for PD. During follow-up, 50 incident cases of PD occurred in the cohort.

**Results:** Baseline characteristics associated with the development of PD included being a nonsmoker, the absence of hypertension and diabetes, and lower serum vitamin D levels. The relative risk between the highest and lowest serum vitamin D quartiles was 0.33 (95% CI, 0.14-0.80) after adjusting for gender, age, marital status, education, alcohol consumption, leisure time physical activity, smoking, BMI, and month of blood draw. Individuals with a serum vitamin D concentration of ≥50 nmol/L had a 65% lower risk for developing PD than those with values <25 nmol/L after adjustment for several potential confounding variables.

**Conclusions:** These researchers conclude that high vitamin D status provides protection against developing PD. They comment that vitamin D has been shown to exhibit neuroprotective effects through antioxidative mechanisms, neuronal calcium regulation, immunomodulation, enhanced nerve conduction, and detoxification mechanisms.

**Reviewer’s Comments:** This article is accompanied by an informative editorial. Neurotoxin models of PD generally indicate that vitamin D may offer neuroprotection for dopaminergic neurons. Pretreatment of animals with vitamin D mitigates toxin-induced dopaminergic cell death induced by both 6-hydroxydopamine and MPTP, associated with increases in various neurotrophic factors and glutathione levels, and decreased levels of pro-inflammatory cytokines and microglial activation. These neuroprotective effects exhibit a U-shaped curve, with loss of neuroprotection or even toxicity at higher doses. (Reviewer-W. Steven Metzer, MD).
Recent primate work suggests the existence of 5 separate cortical areas influencing function of facial muscles, with areas controlling the upper face muscles in the anterior cingulate and mesial frontal cortex.

**Background:** Typical patients with hemispheric strokes have contralateral facial weakness, with severe involvement of lower facial movements and sparing of upper facial muscles. Classically this has been explained by invoking bilateral control of the upper facial muscles, which certainly does exist. However, recent primate work suggests the existence of 5 separate cortical areas influencing function of facial muscles, with anterior cingulate and mesial frontal cortical areas (in the anterior cerebral artery [ACA] territory) controlling muscles of the upper face. These would be spared in middle cerebral artery (MCA) territory infarcts.

**Objective:** To determine correlations between brain lesions and loss of distinct contralateral facial movements following a first cerebral infarct.

**Participants:** Consecutive cerebral infarct patients seen at 1 institution. Exclusion criteria were intracranial hemorrhage, prior stroke or facial nerve palsy, and deep white or gray matter infarction.

**Methods:** Patients were evaluated by blinded examiners at 2 to 5 days following stroke using a semiquantitative exam that compared affected and unaffected sides. “Upper” facial functions studied included forehead elevation and eyelid closure, and “lower” facial functions included elevation, abduction, depression, and closure of the lip. Lesion localization used the Alberta Stroke Program Early CT Score (ASPECTS) system applied to scans done 2 to 3 days after stroke. ASPECTS divides the MCA territory into 6 cortical segments, with additional segments for ACA and posterior cerebral territories, and deep structures. The authors examined only patients with involvement of territories thought to contain “face” motor representations, based on primate studies. These were the ACA territory (including mesial motor areas such as the supplementary motor area and the anterior cingulate gyrus), premotor areas of frontal cortex, and primary motor cortex. Clinical findings were correlated with CT findings using ordinal logistic regression.

**Results:** 28 patients had facial weakness and met inclusion and exclusion criteria. Of these, only 7 had facial weakness confined to the lower facial muscles, and 3 had isolated upper facial muscle weakness. Of the 4 cases of emotional facial palsy uncovered in screening, 3 had brainstem, basal ganglia, or internal capsule lesions. Only 1 of 28 patients with facial weakness had emotional facial palsy. No examples of emotional facial palsy dissociated from volitional paralysis were noted. Ordinal logistic regression found correlations between infarction in the ACA territory and weakness of lid closure, and between infarction of primary motor cortex (in the MCA territory) and weakness of lip elevation, abduction, and depression.

**Conclusions:** Sparing of the upper facial muscles in MCA infarcts is explained by a second motor area for these movements in the ACA territory.

**Reviewer's Comments:** This paper represents a start at sorting out a very complex clinical phenomenon. Lesion localization, including identification of the acute stroke, can be accomplished much better with MRI, including diffusion weighted images. (Reviewer-James W. Schmidley, MD).

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Keywords: Facial Palsy, Neuroanatomy

Print Tag: Refer to original journal article
Lesions of CA1 Neurons in Hippocampus Lead to TGA

Focal Lesions of Human Hippocampal CA1 Neurons in Transient Global Amnesia Impair Place Memory.

Bartsch T, Schoenfeld R, et al:

Science 2010; 328 (June 11): 1412-1415

This work highlights the critical relay function of hippocampal CA1 neurons within a hippocampal-parietal network important to spatial memory tasks.

**Background:** Transient global amnesia (TGA) is characterized by sudden onset of a selective antegrade and retrograde amnesia without other neurological deficits, usually lasting 6 to 10 hours. Most patients experience a single episode. The pathology and pathophysiology of TGA have been poorly understood. It is known that hippocampal lesions in animals produce impairment in spatial memory.

**Objective:** To investigate if spatial memory disruption due to hippocampal lesions underlies TGA in humans.

**Design:** Case-controlled study.

**Participants:** 6 men and 8 women (mean age, 67.8 ±7.6 years) presenting with an acute episode of TGA. They were compared to a control group of 10 healthy adults (5 men, 5 women; mean age, 67.0 ±7.1 years).

**Methods:** All TGA subjects underwent brain MRI within 72 hours of symptom onset. TGA subjects and controls completed a virtual water maze test of spatial memory, with TGA subjects tested during the acute episode. TGA subjects also completed declarative verbal and visuoconstructive memory tests during the acute episode.

**Results:** All TGA subjects were found to have hippocampal lesions selectively involving the CA1 sector (Sommer sector) on DWI and T2 MRI images within 48 to 72 hours after symptom onset. The lesion sizes ranged from 1 to 7 mm² (left, 4 mm²; right, 7 mm²; bilateral, 3 mm²). TGA subjects were found to have substantial deficits in both declarative verbal and visuoconstructive memory. Compared to controls, TGA subjects had profound deficits in completing the virtual water maze test. The degree of impairment on measures of verbal and spatial learning correlated with size of the hippocampal lesion on MRI and duration of the TGA episode.

**Conclusions:** These findings show that acute and focal lesions of CA1 neurons in the human hippocampus lead to a profound impairment of place learning. TGA is a natural lesion model of disturbance of CA1 hippocampal neurons.

**Reviewer's Comments:** This very elegant research provides a great deal of information about the site of transient pathology in TGA, and it also highlights the critical relay function of hippocampal CA1 neurons within this hippocampal-parietal network. The pathogenic mechanism of TGA remains unknown. Focal MR spectroscopy of lesions in TGA patients have revealed a lactate peak, suggesting that anaerobic glycolysis as a cellular stress response of CA1 neurons is the metabolic correlate of the diffusion changes seen in TGA. However, the pathogenic mechanism of this change remains elusive. (Reviewer-W. Steven Metzer, MD).

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Keywords: Hippocampus, Memory, Transient Global Amnesia

Print Tag: Refer to original journal article
Cognitive Impairment a Feature of Both MSA, PSP

Cognitive Impairment in Patients With Multiple System Atrophy and Progressive Supranuclear Palsy.

Brown RG, Lacomblez L, et al:

Brain 2010; 133 (August): 2382-2393

Cognitive impairment is more prevalent among patients with progressive supranuclear palsy compared to multiple system atrophy, but the cognitive profile is similar in both disorders.

Objective: To describe cognitive performance in a prospective large-scale study of patients with progressive supranuclear palsy (PSP) and multiple system atrophy (MSA).

Methods: 372 patients had MSA and 311 had PSP, based on standard clinical criteria. MSA patients with “severe dementia,” defined as a Mini-Mental State Examination score <20, were excluded. The mean age was 62 years for MSA patients and 68 years for PSP patients. Cognition was assessed using the Frontal Assessment Battery (FAB) and Dementia Rating Scale (DRS).

Results: On clinical neurological examination, 77% of PSP patients and 38% of MSA patients were considered cognitively impaired. On the DRS, 57% of PSP patients and 20% of MSA patients scored below the 5% cut-off score. On the FAB, 62% of PSP patients and 32% of MSA patients scored at a level indicative of impaired performance. The most prevalent impairment in both groups involved initiation and perseveration. Other impairments included memory, conceptualization, construction, and attention. One-fifth of PSP patients showed no impairment on any of the DRS subscales, and 39% showed impairment restricted to a single domain. Two-thirds of MSA patients showed no impairment on any of the DRS subscales, and 29% showed impairment restricted to a single domain. Patients with cognitive impairment were significantly older and had more severe disease and disability, but cognitive impairment was observed in patients with early mild disease in both groups. During the course of the study, autopsies were performed on 112 patients. Of cognitively impaired patients considered to have PSP, the diagnosis was confirmed in 89%, and alternative diagnoses included corticobasal degeneration, Lewy body disease, amyotrophic lateral sclerosis, and MSA. Of cognitively impaired patients considered to have MSA, the diagnosis was confirmed in 64%, and alternative diagnoses included amyotrophic lateral sclerosis, Lewy body disease, and PSP. Of those with a pathological diagnosis, 80% of PSP patients and 18% of MSA patients were cognitively impaired at initial examination. Conclusion: Cognitive impairment is more prevalent in PSP than in MSA, but it does occur in both disorders, sometimes early in the course of the illness.

Reviewer’s Comments: Although the degree of cognitive impairment is greater in PSP than in MSA, the cognitive profiles are identical, with executive dysfunction probably reflecting subcortical and frontal cortical pathology. (Reviewer-John C. Brust, MD).

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Keywords: Multiple System Atrophy, Progressive Supranuclear Palsy, Cognitive Impairment

Print Tag: Refer to original journal article
In patients at high risk for cerebral ischemia, platelet aggregation may occur through cyclooxygenase-independent mechanisms. In addition, platelet function assays are not ready for use in managing stroke patients taking ASA.

**Objective:** To examine the evidence for and against the use of platelet function assays (PFA) to manage antiplatelet (AP) therapy in patients at high risk for cerebral ischemia.

**Design/Methods:** This article and accompanying editorials were part of a published series called “Controversies in Stroke.” The controversy was introduced with a case study (a patient with a recurrent lacunar infarct that occurred while taking 1 baby aspirin [ASA] daily), followed by questions (whether and how AP therapy should be altered, and whether PFA would be the useful in selecting further treatment).

**Results:** A patient such as the hypothetical patient would be deemed an “ASA failure.” It is first important to ensure that this “failure” is not the result of poor compliance or drug interactions impairing the AP effect of ASA. It may also be important to reconsider etiology of the stroke and rule out a non-atherothrombotic mechanism, if appropriate. These things having been done, a neurologist might be tempted to employ PFA as a guide to optimizing AP therapy. The first problem arises with the many definitions of “ASA resistance,” based on aspects of the many different PFA systems. Among these are whether the assay used blood or platelet-rich plasma, what agonist/concentration was used to induce aggregation, and whether results from a single test or panel of tests were considered. Even after having discovered “ASA resistance” in vitro, there is nothing to guide clinicians concerning the next step. Adding clopidogrel to ASA or switching to clopidogrel would introduce a new set of problems: increased bleeding caused by dual AP therapy and/or the growing list of drug/genetic interactions with clopidogrel. Switching to ASA/extended-release dipyridamole would entail prescribing the very low dose of ASA in this combination. Increasing the ASA dose, presumably to the point where an AP effect was achieved, would entail the risk of increased side effects with the higher dose of ASA and perhaps concomitant decreased compliance. The proponent of using PFA to direct AP therapy after stroke stressed the high incidence of and poor outcomes associated with ASA resistance, yet acknowledged that the definition of ASA resistance varied and the lack of a validated approach to modifying AP therapy proven to improve outcomes in patients with ASA resistance.

**Conclusions:** Both sides in the debate agree that ASA resistance is not all-or-nothing and that more study is needed.

**Reviewer's Comments:** A further complicating point is that ASA may be doing what it is intended to do (fully inhibiting cyclooxygenase), yet platelet aggregation may still occur through cyclooxygenase-independent mechanisms, such as shear stress. Is this aspirin resistance? (Reviewer-James W. Schmidley, MD).

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Keywords: Platelet Function Assays, Antiplatelet Therapy, Cerebral Ischemia

Print Tag: Refer to original journal article
Early IVIg treatment delays permanent deficits and axonal loss in multifocal motor neuropathy.

**Background:** Multifocal motor neuropathy (MMN) mimics motor neuron disease, responds to IV immunoglobulin (IVIg), and may be elusive to diagnose.

**Objective:** To describe MMN's clinical manifestations, response to IVIg, and outcome as observed in patients with MMN in the Netherlands.

**Methods:** All Dutch neurologists participated in this cross-sectional study from January to December 2007. Patients with definite MMN had at least 1 definite motor conduction block (>50% drop in amplitude and area), while possible MMN was defined by an amplitude and area drop of 30% to 50%. Distal motor amplitudes were scored and reflected the severity of axon loss. Muscle strength was assessed using a modified 10-grade MRC scale with a maximum sum score of 180. Functional impairment was assessed using the Overall Disability Sum Score (ODSS) ranging from 0 (normal) to 5 in the arms and 7 in the legs.

**Results:** In a population of 16.4 million people, 97 patients were identified (prevalence 0.6 per 100,000 inhabitants). Of these, 88 (91%) participated in the study, 64 were men (73%), and the mean disease duration was 11 years (range, 2 to 43 years). The median delay to diagnosis in 1988 to 1995 was 5 years (range 1-15 years) and was 2 years in 2001 to 2006 (range, 1-5 years; P<0.0001). Motor neuron disease was the most common initial misdiagnosis (28 patients, 32%). Muscle weakness started in the distal arm (61%) or distal leg (34%), but it rarely started in the proximal arm (5%), and it never started the proximal leg. One or more reflexes were absent in 73 patients (83%), all reflexes were normal in 7 (8%), and all reflexes were brisk but none were pathological in 8 (9%). In 38 patients (43%), anti-GM1 antibody was elevated (titer ≥1:400). Conduction block was mostly detected in the median and ulnar nerves (77% and 80%, respectively), while low distal motor amplitude was detected mostly in peroneal and median nerves (66% and 60%, respectively). Multivariate analysis revealed that more severe weakness and disability were associated with axon loss (P<0.0001) and years without IVIg treatment (P=0.07). IVIg was infused in 84 patients (95%) and was effective in 79 (94%). Lack of response correlated with more axon loss (P<0.01) and longer time before treatment (P=0.03). IVIg median dose (converted to weekly dose) increased over the years from 12 g to 17 g per week (P<0.01).

**Conclusions:** MMN is more prevalent in men (M:F ratio = 2.7:1). Early IVIg treatment may help to delay the occurrence of axonal loss and irreversible neurological deficits.

**Reviewer's Comments:** This is a welcome neurological review of a large number of MMN patients treated for many years. It reinforces the importance of early treatment and the consistent response to IVIg. (Reviewer-Bashar Katirji, MD).

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**Keywords:** Multifocal Motor Neuropathy, Therapy, IVIg

**Print Tag:** Refer to original journal article
The anti-tumor necrosis factor agent adalimumab is useful in relieving pain in acute lumbosacral radiculopathies.

Background: Experimental studies suggest that tumor necrosis factor α (TNFα) plays an important role in the development of clinical symptoms in radiculopathy.

Objective: To determine if adalimumab is efficacious for the treatment of radicular pain in patients with lumbar disc herniation.

Design: Multicenter, randomized, double-blind, placebo-controlled trial in Switzerland.

Participants: Adults with leg pain for <12 weeks due to lumbosacral radiculopathy (L3 through S1). All enrolled patients had significant disability (>50) based on the Oswestry disability index (ODI), which ranges from 0 (no disability) to 100 (extreme disability).

Methods: Patients received 2 subcutaneous injections (separated by 1 week) of adalimumab or placebo. The primary outcome was leg pain intensity using a visual analog scale (VAS) ranging from 0 to 100. The average score was recorded for 10 days and again at weeks 6 and 24. Secondary outcomes include low back pain and the level of disability based on the ODI score. Responders were defined as patients in whom the VAS scores for leg pain, back pain, or ODI improved >30%. Low disease impact was defined as residual VAS score of <20 without surgery.

Results: Of 265 patients screened, 61 were randomized into adalimumab (n=31) or placebo (n=30). Four patients in the placebo arm were lost to follow-up. Baseline characteristics were similar, except that the ODI score was higher in the placebo group. Overall, the outcome of leg pain and back pain was more favorable in the adalimumab group than in the placebo group (P=0.002 and P<0.0001, respectively). At 6 months, the number of responders with regard to leg pain was significantly higher in the adalimumab group (71%) than in the placebo group (43%, P=0.03). Significantly more responders with regard to back pain were found in the adalimumab group (65%) than in the placebo group (27%, P<0.01), and significantly more responders with regard to ODI were found in the adalimumab group (71%) than in the placebo group (43%, P=0.03). The proportion of patients fulfilling the criteria for low residual disease impact at 6 months was 58% with adalimumab versus 30% with placebo for leg pain, was 52% with adalimumab versus 30% with placebo for back pain, and was 42% with adalimumab versus 20% with placebo for ODI. Fewer surgeries were required for the adalimumab group (n=6, 20%) than for the placebo group (n=13, 42%; P=0.04). Conclusion: A short course of adalimumab resulted in a small decrease in pain and fewer surgeries in patients with acute lumbosacral radiculopathy due to a herniated disc.

Reviewer's Comments: Until now, we have used corticosteroids and NSAIDs as the only pharmacologic treatment to combat inflammation caused by disk herniation. TNFα antibodies may prove to be an effective alternative. Larger confirmatory studies are needed. (Reviewer-Bashar Katirji, MD).

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Keywords: Sciatica, Lumbar Radiculopathy, Treatment

Print Tag: Refer to original journal article
GBP and MNT Improve Vision in Acquired Nystagmus

*Crossover Trial of Gabapentin and Memantine as Treatment for Acquired Nystagmus.*

Thurtell MJ, Joshi AC, et al:

Ann Neurol 2010; 67 (May): 676-680

Both gabapentin and memantine can suppress nystagmus and improve vision in patients with acquired nystagmus. Gabapentin may be preferable in MS patients because MS symptoms may worsen with memantine.

**Background:** Past studies have shown that gabapentin (GBP) and memantine (MNT) are effective treatments of nystagmus.

**Objective:** To compare the 2 drugs in treating acquired forms of nystagmus.

**Design:** Prospective, double-masked, crossover, treatment trial. **Setting:** Tertiary referral neuro-ophthalmology program.

**Participants:** 3 men and 7 women (age range, 28-61 years) with blurred vision or oscillopsia caused by acquired nystagmus. The nystagmus was “pendular” in 6 patients (4 with oculopalatal tremor and 2 with multiple sclerosis [MS]) and was “jerk” in the remaining patients (upbeat, hemi-seesaw, torsional, upbeat-diagonal). The cause of nystagmus was MS (n=3), stroke (n=6), and trauma (n=1).

**Methods:** Patients were examined at baseline, after treatment with each drug, and again after the washout period between the drugs. Patients were randomly assigned to take GBP 300 mg 4 times daily or MNT 10 mg 4 times daily for 2 weeks. After a washout period of 2 to 3 weeks, they crossed over to the other drug and took it for 2 weeks. The primary outcome measures were median eye speed and distance visual acuity. The median eye speed was measured by recording eye movements during attempted fixation of near and distant central visual targets and eccentric targets.

**Results:** Both drugs significantly reduced median eye speed ($P<0.001$): GBP by an average of 32.8% and MNT by 27.8%. Visual acuity improved significantly with both GBP ($P=0.02$) and MNT ($P=0.011$). Pendular nystagmus improved equally with both drugs, and jerk nystagmus improved unpredictably with 1 or the other drug. Both drugs were well tolerated: the most common adverse effects were unsteadiness with GBP and drowsiness with MNT. Eight patients continued their preferred drug after the trial ended.

**Conclusions:** Both GBP and MNT can suppress nystagmus and improve vision in patients with acquired nystagmus.

**Reviewer’s Comments:** In choosing which drug to try, the authors point out that GBP may be preferable in MS patients because MNT has been reported to cause worsening of MS symptoms. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Acquired Nystagmus, Gabapentin, Memantine, Symptom Control

Print Tag: Refer to original journal article
Paralytic Rabies May Mimic Guillain-Barre Syndrome

Rabies Viral Encephalitis: Clinical Determinants in Diagnosis With Special Reference to Paralytic Form.

Gadre G, Satishchandra P, et al:

J Neurol Neurosurg Psychiatry 2010; 81 (July): 812-820

Paralytic rabies resembles Guillain-Barré syndrome but differs by including fever, fasciculations and paresthesias in the bitten limb, CSF pleocytosis, and eventually, a reduced level of consciousness.

**Background:** Rabies can begin with cerebral symptoms (encephalitic or furious rabies) or limb weakness (paralytic or dumb rabies). The encephalitic form includes limbic symptoms, hydrophobia, aerophobia, and inspiratory spasms, which are all well known phenomena that lead to the diagnosis. However, the paralytic form is harder to recognize because it resembles Guillain-Barré syndrome (GBS).

**Objective:** To present the clinical features of paralytic rabies.

**Design:** Retrospective study conducted at 2 neurology referral centers in India where rabies is endemic.

**Participants:** 47 autopsy-confirmed cases of rabies, 13 with encephalitic onset and 34 with paralytic onset.

**Results:** 34 of the 47 patients had a history of dog bite. The median incubation period between dog bite and symptom onset was 2 months (range, 1 week to 4 years). The median duration of illness from onset to death was 11 days (range, 2 days to 6 months). Prodromal symptoms consisted of fever (n=24) and headache (n=11). Among the patients with paralytic rabies, weakness began in 1 limb, usually the bitten limb (n=14), both limbs (n=14), or all limbs (n=6), and progressed rapidly. The authors did not report whether the weakness was upper or lower motor neuron in type. “Bulbar involvement” (not further described) followed limb weakness within a week, and impaired consciousness followed within another. Nine of the 34 patients with paralytic rabies had paresthesias, 8 had fasciculations, 2 had hallucinations, and 5 had hydrophobia. Seventeen of them had CSF pleocytosis (median, 30 cells/mL; range, 8-770 cells/mL; predominantly lymphocytes), and 5 had albuminocytologic dissociation. Neutralizing antibody to rabies was found in the CSF of 40% of patients. Nuchal skin biopsy and corneal smear did not lead to the diagnosis because they were “not consistent.” EMG and MRI were done on only 3 patients.

**Conclusions:** Paralytic rabies resembles GBS but differs by including fever, fasciculations and paresthesias in the bitten limb, CSF pleocytosis, and eventually, a reduced level of consciousness. Unlike the encephalitic form, paralytic rabies is unlikely to present with hydrophobia.

**Reviewer's Comments:** Especially in the United States where rabies infection is not endemic, paralytic rabies is a very difficult diagnosis to make because of the absence of classic features of encephalitic rabies, such as hydrophobia and inspiratory spasm, and the absence of a history of a dog bite, as seen in many patients in this series. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Rabies, Paralytic Form, Diagnosis

Print Tag: Refer to original journal article
**Objective:** To identify clinical and imaging predictors of recurrence of lobar intracerebral hemorrhage (ICH) caused by cerebral amyloid angiopathy (CAA).

**Design:** Prospective longitudinal cohort study conducted at a single-center academic stroke program.

**Participants:** All patients, aged ≥55 years who presented from 1994 to 2006 with symptomatic cerebral lobar ICH caused by CAA. The diagnosis of CAA was made when other causes of lobar ICH (coagulopathy, trauma, and vascular malformation) had been ruled out.

**Methods:** Lobar microbleeds detected on gradient-echo MRI were defined as hemorrhages <5 mm in diameter. Hypodensity of cerebral white matter was assessed on CT scans.

**Results:** The cohort contained 104 patients (age range, 64-80 years) who were followed up for a median of 3 years. There were 29 recurrent lobar ICHs, yielding a 2-year recurrence rate of 16%. In univariate analysis, significant predictors of recurrence were a lobar hemorrhage preceding the index hemorrhage (HR 9.8; 95% CI, 3.3-28.8; \( P < 0.0001 \)), the presence of cerebral white-matter hypodensity (HR 3.7; 95% CI, 1.3-11.1; \( P = 0.01 \)), posterior cerebral white-matter hypodensity (HR 5.7; 95% CI, 2.2-15.3; \( P = 0.001 \)), and the number of lobar microbleeds. For 2 to 4 microbleeds, the HR was 3.3 (95% CI, 1.1-14.4; \( P = 0.03 \)), and for ≥5 lobar microbleeds, the HR was 5.2 (95% CI, 2.1-14; \( P = 0.001 \)). In a multivariate Cox regression model controlled for lobar microbleed count, treatment with aspirin after the index event became a predictor for recurrent lobar ICH (HR 4; 95% CI 1.6-8.3; \( P = 0.02 \)). The magnitude of the effect of aspirin varied directly with the number of microbleeds: the HR was 1.9 for no microbleeds, and it rose to 5.3 for ≥5 microbleeds.

**Conclusions:** In patients with CAA, recurrence of lobar ICH is common. Past large lobar ICHs and microbleeds and hypodensity of cerebral white matter on CT scan predict recurrent lobar ICH. The use of aspirin after a lobar ICH may also increase the risk of recurrence, especially in patients with numerous microbleeds.

**Reviewer’s Comments:** The data suggest that lobar microbleeds and white matter hypodensity are markers of the severity of CAA and, as the severity of CAA increases, aspirin becomes an increasingly more potent a promoter of lobar ICH. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Cerebral Amyloid Angiopathy, Recurrent Lobar Hemorrhage, Predicting

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Some New AEDs Increase Risk of Suicidal Behavior

Use of Antiepileptic Drugs in Epilepsy and the Risk of Self-Harm or Suicidal Behavior.

Andersohn F, Schade R, et al:

Neurology 2010; 75 (July 27): 335-340

In patients with epilepsy, current use of new antiepileptic drugs (AEDs) with a high risk of depression is associated with a nearly 3-fold increased risk of self harm and suicide attempt.

**Background:** The Food and Drug Administration (FDA) performed a meta-analysis of 199 clinical trials of antiepileptic drugs (AEDs), and in 2008, they issued a safety alert that AEDs were associated with suicidal behavior.

**Objective:** To determine if the use of AEDs in patients with epilepsy is associated with an increased risk of suicidal behavior in clinical practice.

**Design:** Nested case-control study.

**Participants:** Participants were gathered from the United Kingdom General Practice Research Database, which contains the computerized medical records of 6.4 million people. The database contained information on 44,300 people with epilepsy, and 453 of them had harmed themselves or attempted suicide, which comprised the cases for this study. For each case, 20 controls who had not harmed themselves or had not attempted suicide were randomly selected from the same cohort and matched for gender, age, and year of cohort entry.

**Methods:** AEDs were divided into old AEDs (phenobarbital, primidone, carbamazepine, valproic acid, phenytoin, ethosuximide) and new AEDs. The new AEDs were subdivided into 2 groups: those with a low risk of causing depression (oxcarbazepine, lamotrigine, gabapentin, pregabalin) and those with a high risk (levetiracetam [LEV], tiagabine, topiramate [TPM], vigabatrin [VGB]). The risk of depression was taken from clinical trials: a frequency ≤1% was considered low, and a frequency >1% was considered high.

**Results:** More cases than controls had psychiatric comorbidity. Current use of new AEDs with a high risk of depression was associated with a high risk of suicide attempt or self harm (OR 3.1, 95% CI, 1.2-7.8), but there were only 6 such cases (2 each for LEV, TPM, and VGB). Current use of new AEDs with a low risk of depression and of old AEDs was not associated with an increased risk of self harm or suicide attempt.

**Conclusions:** In patients with epilepsy, current use of new AEDs with a high risk of depression is associated with a 3-fold increased risk of self harm and suicide attempt, as compared to patients not currently treated with AEDs. Old AEDs and new ones with a low risk of depression do not increase the risk of self harm or suicide attempt.

**Reviewer's Comments:** The FDA safety alert covered all AEDs. The present study exonerates most of them and implicates only new AEDs with a high risk of causing depression. In an accompanying editorial, Mula and Sander cast doubt on even that. They point out that the conclusion was based on a very small number of cases (2 cases per high-risk drug). They also point to the high psychiatric comorbidity in the cases and wonder whether this comorbidity, rather than the AEDs, might have played the major role. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Antiepileptic Drugs, Suicidality, Suicide Risk

Print Tag: Refer to original journal article