The Dementia Antipsychotic Withdrawal Trial (DART-AD): Long-Term Follow-Up of a Randomised Placebo-Controlled Trial.

Ballard C, Hanney ML, et al:

Lancet Neurol 2009; 8 (February): 151-157

Try psychosocial interventions or non-antipsychotic medications (divalproex, acetylcholinesterase inhibitors, etc) before resorting to antipsychotic medications in AD patients with behavioral problems.

**Background:** A meta-analysis suggested a 1.5-fold to 1.7-fold increase in mortality risk in randomized, placebo-controlled trials of Alzheimer's disease (AD) patients on antipsychotic medications compared with those not receiving these medications throughout a 6-week to 12-week period.

**Objective:** To determine if long-term use of antipsychotics in AD patients is associated with a continued risk of increased mortality.

**Methods:** Patients with dementia due to AD who were taking the antipsychotics thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone for at least 3 months were enrolled from long-term care facilities. For inclusion, participants had to be living in a residential or nursing home; met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for AD; had a mini-mental status score >6 points or a severe impairment battery score >30 points, and were on at least 10 mg chlorpromazine equivalents of an antipsychotic medication. They were excluded if unable to complete the primary outcome measures at baseline or had any physical condition that would make participation in the study unsafe (extrapyramidal symptoms or prolonged QT interval on ECG). Patients were randomly assigned to receive active treatment with ongoing antipsychotic medication as close to present dose as possible or to a placebo which resembled their pre-study antipsychotic dose (very low, low, or high dose). The antipsychotic dose was the same throughout the 12-month follow-up. The primary end point was mortality at 12 months. Additional follow-up was completed for a minimum of 2 years. Investigators attempted to get the death certificate for each deceased individual to ascertain cause of death.

**Results:** 165 patients were randomized (83 to continue antipsychotics and 82 to placebo). Ten patients continuing treatment and 16 patients switched to placebo were on high-dose medications, all others were in the low-dose group. At 12 months, the cumulative probabilities of survival were 70% in the antipsychotic and 77% in the placebo group. For continued treatment, the survival rates of antipsychotic versus placebo groups were 46% versus 71% at 24 months, 30% versus 59% at 36 months, and 26% versus 53% at 42 months. Death certificates were obtained in 78% of deaths but failed to show more vascular deaths in the antipsychotic group.

**Conclusions:** There is an increased long-term risk of mortality in patients with AD who are prescribed antipsychotic medications.

**Reviewer's Comments:** Antipsychotic medications should only be used in AD patients after other medical and non-medical approaches fail, and then only at as low a dose and for as short a time as possible. (Reviewer-John Schwankhaus, MD).

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Keywords: Antipsychotic Medications

Print Tag: Refer to original journal article
Aβ Immunization for AD Increases Vascular Amyloid Load

Consequences of Aβ Immunization on the Vasculature of Human Alzheimer's Disease Brain.
Boche D, Zotova E, et al:

Brain 2008; 131 (December): 3299-3310

Amyloid immunization for treatment of Alzheimer’s disease may remain a potentially viable future treatment, if the inflammatory process resulting in some cases of encephalitis can be mitigated.

Background: The amyloid hypothesis for the pathogenesis of Alzheimer’s disease (AD) states that abnormal aggregation of the amyloid-β peptide (Aβ) in the brain triggers the downstream effects of tau aggregation, microglial activation, synaptic dysfunction, and neuronal loss, cumulatively resulting in cognitive decline. In 2000, this led to a trial of Aβ immunization to treat AD, with about 50% of immunized patients developing Aβ antibodies. A larger clinical trial was subsequently halted because encephalitis developed in about 6% of immunized patients. Published postmortem results reported reduction in cortical amyloid plaques among patients who were immunized.

Objective: To investigate the pathophysiological mechanism of this reduction in cortical amyloid plaques among immunized AD patients.

Methods: These investigators examined postmortem brains from 9 patients who had received Aβ42 immunization and who died between 4 and 64 months after the first immunization dose. Selected sections were immunostained for Aβ, tau, and α-synuclein. These brains were compared to a control group of 11 unimmunized AD control brains.

Results: Compared to unimmunized AD brains, the brains from immunized patients contained significantly less parenchymal Aβ42 and significantly higher levels of vascular Aβ42 and Aβ40. The immunized AD group had about 14 times as many blood vessels containing Aβ42 in the cerebral cortex and approximately 7 times more in the leptomeninges. Immunized patients showed a higher density of cortical microhemorrhages and microvascular lesions than the unimmunized controls, although none of the subjects had major congophilic angiopathy related intracerebral hemorrhages, and the structural integrity of the blood vessels appeared to be preserved, despite the increased amount of amyloid in their walls. Two of the longest survivors, who had been immunized 4 to 5 years previous to pathological examination, had virtually complete absence of both plaques and congophilic amyloid angiopathy, suggesting that, over time, Aβ may eventually be cleared from the cerebral vasculature.

Conclusions: These findings are consistent with the hypothesis that Aβ immunization results in solubilization of plaque Aβ42, which exits the brain via the perivascular pathway, causing a transient increase in the amount of cerebrovascular amyloid.

Reviewer’s Comments: This study adds to our knowledge of the mechanism by which Aβ immunization for AD may lead to a reduction in cortical load of amyloid plaque. These limited data suggest that a transient increase in cortical and leptomeningeal amyloid angiopathic changes may not be of any clinical significance. Amyloid immunization for treatment of AD may remain a potentially viable future treatment, if the inflammatory process resulting in some cases of encephalitis can be mitigated. (Reviewer-W. Steven Metzer, MD).

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Keywords: Cerebral Amyloid Angiopathy

Print Tag: Refer to original journal article
In patients who underwent angioplasty and stenting for intracranial atherosclerosis, the restenosis rate was significantly higher with self-expanding stents than with balloon-mounted stents.

**Background:** Medical therapy of symptomatic intracranial atherosclerosis remains inadequate, with stroke rates of about 12% per year.

**Objective:** To determine the outcomes associated with angioplasty and stenting of atherosclerotic intracranial stenoses.

**Methods:** A literature search identified studies describing angioplasty and stenting of atherosclerotic intracranial stenoses >50%, documented by angiogram. Included papers described >5 patients undergoing both angioplasty and stenting and reported periprocedural stroke and death rates. Excluded were papers that described treatment of acute stroke. The 30-day (periprocedural) and long-term stroke and death rates were tracked. Restenosis rates were also considered.

**Results:** The review encompassed 1,134 patients with 1,177 stenoses, about equally divided between anterior and posterior circulation. Of these patients, 98% were symptomatic. Mean pre-intervention stenosis of 78% was reduced to 14% post-intervention. The median technical success rate for deployment of the stent was 97%. Most stents were balloon-mounted, and 23% were self-expanding. Only 6% of the stents were drug-eluting. Balloon-mounted stents produced a larger reduction of stenosis than did self-expanding stents (11% residual stenosis vs 30%, respectively). The median 30-day stroke and death rate was 7.7% (interquartile ratio 4%-14%), but stroke/death rates up to 50% were reported in some series. The stroke and death rate was higher for posterior procedures (8.3%) than for anterior procedures (5.1%), but there was no difference in 30-day stroke and death rates between balloon-mounted and self-expanding stents. Few papers described extended clinical follow-up (mean clinical follow-up, 13.5 months). By 15 months, approximately 12% of patients, cumulatively, had suffered either stroke or death. Methods, indications, and timing of investigations to determine restenosis were extremely variable. In patients with long-term follow-up (>1 year), the restenosis rate was 14%, with a symptomatic restenosis rate of 5%. The restenosis rate was significantly higher with self-expanding stents than with balloon-mounted stents.

**Conclusions:** Angioplasty and stenting for symptomatic intracranial stenosis is associated with high rates of initial technical success, but also with high initial periprocedural stroke and death rates, and a high incidence of restenosis, about a third of which is symptomatic. Self-expanding stents are associated with greater residual stenosis and higher rates of restenosis.

**Reviewer’s Comments:** Neither clinical nor radiologic follow-up was standardized in the studies, nor was post-stent medical management. Angioplasty and stenting for symptomatic intracranial atherosclerotic stenosis is not of proven value and its use outside of randomized control trials is discouraged. (Reviewer-James W. Schmidley, MD).

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Keywords: Intracranial Atherosclerosis

Print Tag: Refer to original journal article
In this small series, new lesions were not found on follow-up MRI scans in the relevant deep middle cerebral artery (MCA) perforator territory following angioplasty and stenting of MCA stenosis.

**Background:** As soon as radiologists began deploying stents in the intracranial circulation, particularly the basilar artery (BA) and middle cerebral artery (MCA) stem, the question arose: what would happen to the origins of perforating vessels, which are very dense in these arterial segments, as the angioplasty balloon was inflated and the stent deployed in proximity to atherosclerotic plaque? This effect, nick-named “snow plowing,” is acknowledged in the stenting literature, but its frequency is not known. Of further concern is the susceptibility of perforating arteries (which may not be occluded by the original procedure) to late occlusion by in-stent endothelial hyperplasia.

**Objective:** To determine if perforating arteries are occluded by stent placement in intracranial arteries.

**Methods:** Patients with recent stroke or transient ischemic attack (TIA) attributable to severe MCA stenosis (>60%) were subjected to angioplasty and stenting. Patients were excluded if the stenosis was not atherosclerotic, if the NIH stroke scale was >8, or if they had contraindications to antiplatelet therapy or heparin. All patients underwent MRI scan with diffusion-weighted imaging before and after the angioplasty/stenting procedure. Timing of the "before" scan was not given. Follow-up scans were done at 4 months. The patients were followed up clinically at 30 days, 3 months, and 6 months. Any new infarct in the ipsilateral striatocapsular region was attributed to the interventional procedure. Self-expanding stents were used in all procedures. During the periprocedural period and for 6 months afterward, the patients took aspirin and clopidogrel.

**Results:** 24 patients were studied (median age, 65 years). Twenty-one patients had recurrent strokes, and the remainder had refractory TIAs. Twenty-three patients underwent successful balloon dilatation and stenting, with median stenosis reduction from 74% to 20%. There were no periprocedural strokes, and no new lesions were found on follow-up MRI scans in the relevant deep MCA perforator territory.

**Conclusions:** Self-expanding stents do not pose a major risk to perforators, at least in the proximal MCA.

**Reviewer’s Comments:** This report is at variance with the findings of the previously reviewed paper and is strikingly at odds with my own, limited experience. Of course, the stroke risk with interventional procedures encompasses microembolic or macroembolic occlusion of other intracranial vessels as well as the perforators originating from the area of the stent. This is not specifically addressed. The issue of late reocclusion by in-stent endothelial hyperplasia was not addressed either. (Reviewer-James W. Schmidley, MD).

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Keywords: Intracranial Stenosis

Print Tag: Refer to original journal article
Distal hyperintense vessels on FLAIR provide one of the earliest signs of acute ischemia on MRI and may be a marker for favorable collateral circulation in acute middle cerebral artery stroke.

**Background:** In acute middle cerebral artery (MCA) stroke, MRI fluid-attenuated inversion recovery imaging (FLAIR) frequently discloses hyperintense vessels (HV) in the periphery of the ischemic territory. One hypothesis suggests that HV represent vascular collaterals bringing blood flow from other arterial sources. The collateral blood flow moves retrograde and slowly, hence its detection by FLAIR.

**Objective:** To better define the relevance of HV to other imaging parameters and to determine if patients with HV have smaller infarctions and better outcome than patients without HV.

**Methods:** HV prominence and their vascular topography were characterized in 52 consecutive patients with MCA stroke prior to treatment. HV locations were correlated to the pretreatment diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), MCA occlusion site, recanalization status 2 hours after thrombolysis, and infarct size on follow-up imaging.

**Results:** The mean patient age was 69 years. The median initial NIHSS score was 8 (range 1-28). Both subtle and prominent HV were observed distal to arterial occlusion in 73% of patients. HV were more often associated with proximal (M1) than distal MCA occlusion. Among 38 patients with proximal MCA occlusion, the initial PWI volumes were comparable, regardless of whether distal HV were subtle or prominent. However, patients with prominent distal HV had lower NIHSS scores and smaller initial DWI volumes, indicating a greater diffusion-perfusion mismatch. Also smaller were the 24-hour DWI, the 3-day to 7-day ischemic volumes identified by FLAIR, and the 5-day NIHSS score.

**Conclusions:** In acute MCA stroke, prominent distal hyperintense vessels on MRI FLAIR are associated with a larger diffusion-perfusion mismatch and smaller subacute ischemic lesion volumes following thrombolysis. HV may reflect improved collateral blood flow distal to the arterial occlusion, attenuating ischemic injury.

**Reviewer’s Comments:** Coyle in the 1980s found that MCA occlusion produced much larger infarct volumes in spontaneously hypertensive rats (SHR) when compared to normotensive Wistar rats (from which the SHR strain was bred). What determined infarct size was not the degree of hypertension nor the number of collaterals between the anterior cerebral artery and the MCA, but the fact that SHR pial-collaterals had smaller lumen diameters compared to their genetically closely related Wistar brethren. If similar genes govern human collateral development, the FLAIR HV may be detecting the larger lumen vascular collaterals that can carry more retrograde blood flow and are, therefore, more likely to protect against ischemic injury. (Reviewer-Michael Jacewicz, MD).

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**Keywords:** Acute Stroke

**Print Tag:** Refer to original journal article
Psychogenic Tremor Has Poor Long-Term Prognosis

Psychogenic Tremor: Long Term Prognosis in Patients With Electrophysiologically-Confirmed Disease.
McKeon A, Ahliskog JE, et al:

Mov Disord 2009; 24 (January 15): 72-76

The mean duration of tremor prior to diagnosis with psychogenic tremor is significantly shorter for patients with mild or no tremor at follow-up.

Background: An estimated 2% to 4% of patients in movement disorder centers have psychogenic movement disorders, with psychogenic tremor being most common. Reports of the long-term prognosis for these patients have been variable.

Objective: To investigate long-term outcome of electrophysiologically confirmed psychogenic tremor.

Participants: 62 patients diagnosed at the Mayo Clinic with psychogenic tremor during a 2-year period.

Methods: These patients met accepted clinical diagnostic criteria for established, documented, probable or possible psychogenic movement disorder. In addition, this diagnosis was supported by accepted electrophysiological evidence of psychogenic tremor. Long-term follow-up information was obtained by questionnaire. Of the 62 patients, 33 provided follow-up information.

Results: Tremor onset was acute in 16 (49%), insidious in 9 (27%), and subacute in 8 (24%). Median symptom duration prior to initial evaluation was 1.6 years (range, 0.1-15 years). Other psychogenic findings were present in 24% of these patients, including gait disorder, dystonic-type posturing, eye movement abnormalities, and dysarthria. A further 27% of these patients had indeterminate clinical findings, but a psychogenic etiology was suspected. Of these patients, 94% were counseled that they had a definite diagnosis of psychogenic tremor and were offered psychiatric consultation. Only 36% of these subjects agreed to follow-up with psychiatric consultation. Psychiatric diagnoses included conversion disorder, depression, anxiety disorder, obsessive compulsive disorder, and bipolar affective disorder. Major life stressors were identified in only 7 of the 33 respondents. After a median follow-up of 3.2 years from diagnosis (range, 2.8-4.8 years), 21 of the 33 respondents (64%) reported persistent tremor and rated their disability as severe or moderate. In addition, 15 of the 33 respondents (45%) reported new tremor involving limb parts not affected previously. In 12 patients, the tremor remained present but with mild or no disability (n=10) or resolved (n=2). Mean duration of tremor prior to diagnosis with psychogenic tremor was significantly shorter for patients with mild or no tremor at follow-up.

Conclusions: Physiologically confirmed psychogenic tremor carries a poor prognosis with unremitting or worse tremor persisting 3 years after diagnosis in most patients.

Reviewer’s Comments: Attempts at intervention in this study were typically unsuccessful. A major drawback of this study is that almost half of the patients failed to respond with follow-up information. The authors address this and note that there were no significant differences between responders and nonresponders with respect to baseline demographic and clinical characteristics. Patients with psychogenic movement disorders remain a very difficult group of patients to help. (Reviewer-W. Steven Metzer, MD).

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Keywords: Psychogenic Tremor

Print Tag: Refer to original journal article
X-linked adrenoleukodystrophy presented as rapidly progressive dementia in a 57-year-old man.

Case Report: A 57-year-old man being treated for recurrent melanoma of the right eyelid became abruptly incoherent, and the next day had a nocturnal convulsive seizure. A lumbar puncture was negative, CT of the brain revealed generalized atrophy, and EEG showed diffuse slowing. MRI/FLAIR showed abnormal confluent white matter signals most prominent in the parietal and temporal lobes, the posterior corpus callosum, and cerebropontine projections. Peripheral gadolinium enhancement indicated an outer rim of inflammation. He received lorazepam, haloperidol, phenytoin, levetiracetam, acyclovir, and ceftriaxone, but his mental status deteriorated. His wife reported occasional episodes of confusion and disorientation during the previous 5 years (more frequent in past 2 months) and progressive memory impairment. He had abused alcohol, cocaine, and intravenous heroin, but not within the past 10 years. He also had been exposed to industrial solvents. Hepatitis C was diagnosed 15 years earlier, and a recent HCV RNA level was 1.6 million units. On examination, the patient was cachectic and agitated, with markedly impaired attention, fluent meaningless speech with paraphasias, and inability to follow simple commands, read, or write. He was considered to have advanced leukoencephalopathy. Diagnostic considerations included HCV infection, progressive multifocal leukoencephalopathy, a mitochondrial disorder, illicit drug-related leukoencephalopathy, solvent-related leukoencephalopathy, X-linked adrenoleukodystrophy, and metachromatic leukodystrophy. A stereotactic brain biopsy was performed. Pathologically, there was gliotic white matter, myelin and axonal loss, and macrophages filled with periodic acid-Schiff-positive material. Ultrastructurally, the macrophages contained lamellar structures, consistent with adrenoleukodystrophy. Very long-chain fatty acids were then found elevated in the plasma, and the gene mutation responsible for adrenoleukodystrophy was identified on chromosome Xq28. This gene, called ABCD1, codes an ATP-binding cassette transporter protein necessary for peroxisomal degradation of very long-chain fatty acids. The patient died of pneumonia 10 months after presentation. Atypical features for adrenoleukodystrophy in this case include advanced age, fulminant deterioration, apparent absence of affected family members, and lack of spasticity and sphincter dysfunction. Approximately a third of patients with X-linked adrenoleukodystrophy develop dementia and adrenal insufficiency between 4 and 8 years of age. In 35% to 40%, onset is in young adulthood, with myeloneuropathy, slowly progressive paraparesis, and sphincter disturbance. Twenty percent of these patients have rapidly progressive inflammatory demyelination with death in 1 to 2 years.

Reviewer's Comments: This patient's course was most atypical, but if the possibility of X-linked adrenoleukodystrophy had been more seriously considered and plasma levels of very long-chain fatty acids obtained, a brain biopsy could have been avoided. (Reviewer-John C. Brust, MD).

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Keywords: Dementia

Print Tag: Refer to original journal article
The single leg stance time may identify elderly at risk for falls.

**Background:** Age-related white matter changes (ARWMC) are associated with progressive gait disturbances and falls and are thought to result from interruptions of cortical-subcortical circuits controlling balance, posture, and locomotion.

**Methods:** Present study data were derived from the Leukoaraiosis and Disability (LADIS) study. Elderly patients with no or mild disability on the instrumental activities of daily living (IADL) were included. MRI was performed at baseline with ARWMC severity rated as mild, moderate, or severe using the visual scale of Fazekas. An extensive set of clinical and functional tests were performed at baseline and at yearly follow-up for 3 years. These included a questionnaire to assess vascular risk factors and comorbidity, as well as global functioning, cognitive, motor, and quality of life measures. Physical performance and postural control were assessed with the short physical performance battery (SPPB) and the single leg stance time, including walking speed, tandem stance, and chair stands, which were all believed to be controlled by cortico-subcortical loops.

**Results:** 639 individuals were included in the study. According to the Fazekas scale, 284 had mild, 197 had moderate, and 158 had severe ARWMC at baseline. A statistically significant association of global ARWMC with a positive history of falls was found for the year prior to study inclusion. Complaints of gait disturbance and female gender were identified as risk factors for falls in the year prior to study, while memory impairment, syncope, and vertigo were not. Physical activity was associated with a significantly lower rate of falls. The mean single leg stance time was significantly reduced in those with a history of a single or multiple falls as compared to those without falls in the previous year. In each of these 3 groups, the single leg stance time was significantly correlated with the severity of ARWMC. The standing balance subscore of the SPPB was significantly reduced in those with single or multiple falls. On MRI, only periventricular and frontal deep ARWMC were significantly associated with falls using a multivariate binary logistic regression model.

**Conclusions:** Frontal and periventricular ARWMC are associated with falls, supporting the hypothesis that interruption of frontal subcortical motor circuits leads to balance disturbance and falls.

**Reviewer’s Comments:** ARWMC in specific areas are associated with balance difficulties and falls in the elderly. Clinically, the single leg stance time can identify those at risk for falls. (Reviewer-John Schwankhaus, MD).

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Keywords: Age-Related White Matter Changes

Print Tag: Refer to original journal article
Four Health Behaviors Influence Stroke Risk

Combined Effect of Health Behaviours and Risk of First Ever Stroke in 20,040 Men and Women Over 11 Years' Follow-Up in Norfolk Cohort of European Prospective Investigation of Cancer (EPIC Norfolk): Prospective Population Study.

Myint PK, Luben RN, et al:

BMJ 2009; February 19 (epub ahead of print):

Small differences in lifestyle could have a substantial impact on stroke risk in our growing and aging population. However, modification of even simple behavior is often very difficult.

Objective: To investigate the impact of selected health behaviors on stroke risk.

Participants: 20,040 men and women (age range, 40-79 years at baseline) from a British population cohort for a prospective cancer investigation that was comparable to the national British population with respect to baseline characteristics. The 913 subjects with a history of stroke and myocardial infarction and another 9,492 subjects with missing information at baseline were excluded.

Methods & Results: Four health behaviors were recorded at entry into this study: smoking, physical activity, alcohol intake, and fruit and vegetable intake. Subjects were assigned 1 point for each of the following behaviors: current nonsmoker; not inactive (nonsedentary occupation or regular exerciser); moderate alcohol consumption (1-14 units of alcohol per week); and at least 5 servings daily of fruits & vegetables (inferred from serum vitamin C levels). Average follow-up was 11.5 years (almost 230,000 person-years). There were a total of 599 strokes, of which 28% were fatal. Type of stroke was not determined. These 4 health behaviors were found to significantly influence the relative risk of stroke in a linear fashion, with a dose-response relationship. Current non-smoking, being physically active, moderate alcohol intake, and plasma vitamin C concentrations >50 micromoles per liter significantly reduced the risk for stroke. Compared to people with these 4 health behaviors, the relative risks for stroke for men and women were 1.15 with 3 health behaviors, 1.58 with 2 health behaviors, 2.18 with 1 health behavior, and 2.31 with none of these health behaviors. This relationship was independent of other risk factors for stroke, including blood pressure, cholesterol, diabetes, and obesity.

Conclusions: These 4 health behaviors combined predict more than a 2-fold difference in incidence of stroke in men and women.

Reviewer's Comments: This study has several limitations. There is no assurance that the health behaviors recorded at baseline were maintained throughout the follow-up period. A large number of subjects were not included for analysis because of incomplete data. The types of strokes were not ascertained. However, this study has important public health implications. Modification of these 4 behaviors in the general population might have a greater overall impact on the incidence of stroke than addressing medical risk factors in selected patient populations. Small differences in lifestyle could have a substantial impact on stroke risk in our growing and aging population. However, modification of even simple behavior is often very difficult. (Reviewer-W. Steven Metzer, MD).

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Keywords: Risk

Print Tag: Refer to original journal article
Impaired memory in thiamine-deficient alcoholics correlates with reduced functional connectivity between the mammillary bodies and the anterior thalamus.

**Objective:** To test the hypothesis that amnesia in Wernicke-Korsakoff syndrome is the result of impaired mammillothalamic functional connectivity.

**Methods:** Seven chronic alcoholics during recovery from acute Wernicke encephalopathy were compared to 14 alcoholics without Wernicke encephalopathy and 14 healthy subjects. Alcoholic patients were abstinent for at least 1 month at testing. Wernicke patients had received thiamine replacement therapy for at least 1 month and no longer exhibited an acute confusional state. Patients with a history of head injury, hepatic encephalopathy, or other neurological or psychiatric disorders were excluded. All subjects underwent functional MRI and neuropsychological testing. Imaging consisted of determining functional MRI signal levels in the mammillary bodies and the anterior nucleus of the thalamus during a 5-minute passive viewing task. Temporal correlations between these 2 regions were then calculated to determine resting functional connectivity strength. Subjects were then tested for immediate and delayed verbal and nonverbal recall and verbal recognition.

**Results:** Connectivity strength between the anterior thalamus and the mammillary bodies was more reduced in Wernicke patients than in healthy subjects, and the connectivity strength of the non-Wernicke alcoholics fell between these 2 groups. Statistical significance, however, was achieved only in the left hemisphere. The strength of left-sided connectivity correlated significantly with delayed verbal recall and verbal recognition scores. Results were not influenced by the duration of abstinence or the amount of lifetime alcohol consumption.

**Conclusions:** Memory function in patients recovering from Wernicke encephalopathy parallels the level of mammillothalamic functional connectivity. The authors note that nonverbal memory was also impaired in their Wernicke patients and that lesions in Wernicke-Korsakoff syndrome are nearly always bilateral and symmetric. The left-right differences in the present study might be attributed to small sample size. The functional role of the mammillary bodies and their relation to the thalamus and the hippocampus has been debated ever since Papez described his circuit in 1937. The results of the present study suggest that one need not choose between brain regions to explain the memory deficits of Wernicke-Korsakoff disease, but that connectivity between regions is what matters. Consistent with this view is a case report of Wernicke-Korsakoff syndrome in which there was no medial temporal lobe damage, yet hippocampal activation did not occur during memory tasks. (Caulo M, van Hecke J, et al. Brain. 2005;128:1584-1594).

**Reviewer's Comments:** Connectivity strength was also reduced in non-Wernicke alcoholics. Could this have resulted from either a subclinical thiamine deficiency or from a direct effect of alcohol? (Reviewer-John C. Brust, MD).

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Keywords: Wernicke's Encephalopathy

Print Tag: Refer to original journal article
MRI Abnormalities Seen in 20% of IS Cases Receiving Vigabatrin

Magnetic Resonance Imaging Abnormalities Associated With Vigabatrin in Patients With Epilepsy.

Wheless JW, Carmant L, et al:

Epilepsia 2009; 50 (February): 195-205

Objective: To identify the frequency of the development of signal abnormalities on cerebral MRIs in children with infantile spasms (IS) and in children and adults with refractory complex partial seizures (CPS).

Methods: MRIs and medical records were reviewed from multiple study sites in the United States and Canada that evaluated vigabatrin therapy for infants with IS younger than 24 months of age and for children and adults treated for medically refractory CPS. Comparison was made between those treated with and without vigabatrin. MRI abnormalities were prespecified to include any hyperintensity on T2-weighted or FLAIR sequences with or without restricted diffusion not explained by any other pathology. The typical abnormalities as previously described tend to occur in the globus pallidus, thalamus, dorsal midbrain, and cerebellar nuclei. MRIs were reviewed by 2 neuroradiologists who were blinded regarding treatment. Prevalence and incidence of MRI abnormalities related to therapy with vigabatrin were estimated. The study included examination of 332 MRIs from 205 infants with IS and 2,074 scans from 668 children and adults with CPS.

Results: 93 infants with IS were treated with vigabatrin and 112 never received vigabatrin. Prespecified MRI-signal abnormalities were seen in about 3% of MRIs obtained at baseline prior to treatment. The prevalence of MRI signal abnormalities in those treated with vigabatrin was 22% compared to 4% in those treated otherwise without vigabatrin exposure. The attributable risk associated with vigabatrin therapy was about 14%. There was a suggestion that the occurrence of abnormality on MRI was dose-related, but the findings were not statistically significant. Resolution of the signal abnormalities occurred in two-thirds of those with an abnormality on MRI who were followed up with subsequent scans. Resolution occurred both in patients in whom vigabatrin was discontinued and in those in whom it was continued. In children and adults with refractory CPS, there was no significant difference in the incidence and prevalence of prespecified MRI abnormalities in those treated and not treated with vigabatrin.

Reviewer's Comments: Signal abnormalities on MRI may develop in approximately 20% of infants treated with vigabatrin for IS but appear to be asymptomatic and are often transient. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Vigabatrin

Print Tag: Refer to original journal article
Vigabatrin for IS Therapy Has Little or No Impact on Vision

Visual Fields at School-Age in Children Treated With Vigabatrin in Infancy.

Gaily E, Jonsson H, Lappi M:

Epilepsia 2009; 50 (February): 206-216

Vigabatrin is an effective antiepileptic drug for many children with infantile spasms and appears to have little impact on peripheral vision.

**Background:** Vigabatrin is not approved in the United States due to associated visual field deficits that have been reported to develop in 20% to 40% of children and adults treated for epilepsy chronically with vigabatrin. The impact on visual fields has not been determined in children treated as infants with vigabatrin for infantile spasms (IS). Formal visual field testing requires a cooperative patient and is not possible in infants and young children or in older children with significant cognitive compromise. In older patients, visual field loss has been linked to a relationship with cumulative dose over time.

**Objective:** To investigate the impact of vigabatrin on peripheral vision in children treated for IS.

**Methods:** Assessment of visual fields was performed on 16 children between 6-12 years of age who had been treated with vigabatrin for IS during infancy. Data concerning exposure to vigabatrin was collected from review of the medical record. Visual fields were evaluated using Goldmann kinetic perimetry. Normal visual fields were defined as the temporal meridian extending to >70°. Restriction of the temporal meridian to between 50° and 70° was deemed to be consistent with mild visual field loss attributed to vigabatrin.

**Results:** In this group of 16 children with a confirmed diagnosis of IS, vigabatrin therapy was initiated between 3 to 20 months of age (mean, 7 months). The mean duration of vigabatrin therapy was 21 months (range, 9-30 months). Spasms remitted in all patients in this study group in response to vigabatrin or other therapy. Vigabatrin was effective in 10 children (approximately 60%). The cumulative vigabatrin dose ranged from about 200 to 1100 grams. Vigabatrin was the only antiepileptic drug (AED) used in 8 children. Adrenocorticotropic hormone was used in addition to vigabatrin in 5 children, and 3 had been treated with additional AEDs. About 80% (n=13) had remained seizure-free at the time visual field testing was performed. Visual fields were normal in 15 of 16 of these children (approximately 90%). One child had mild visual field loss. That child was treated with vigabatrin for a total of 19 months with a cumulative dose of just over 570 grams.

**Reviewer's Comments:** Although the group of children included in this study is relatively small, the findings are very important and encouraging. It has been very difficult to ascertain what impact treatment of IS with vigabatrin might have on vision. This study suggests that vigabatrin therapy during infancy may only rarely impact visual field integrity. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Vigabatrin

Print Tag: Refer to original journal article
Amphiphysin antibody-associated stiff person syndrome is a rare paraneoplastic disorder that affects women only and is strongly associated with breast cancer.

**Background:** Stiff-person syndrome (SPS) is a rare autoimmune neurological disorder characterized by muscle stiffness, often triggered by emotional stress, which involves predominantly the legs and trunk muscles. SPS is often associated with high levels of antibodies against glutamic acid decarboxylase (GAD). A variant of SPS is associated with antibodies to amphiphysin and possibly with breast cancer.

**Objective:** To identify the distinctive clinical features of SPS associated with amphiphysin antibodies compared to those with anti-GAD antibodies.

**Participants/Methods:** Retrospective analysis of records collected at the Yale SPS Project. This database included patients from 6 continents acquisitioned between 1986 and 1999. Of 845 case records maintained by the Yale SPS Project, 621 patients had antineuronal antibodies measured. Of these, 116 patients had elevated GAD antibodies, while 11 patients had elevated amphiphysin antibodies. The clinical information was analyzed with regard to neurological findings, distribution of muscle stiffness, association with cancer, and response to benzodiazepines and other treatment.

**Results:** All amphiphysin antibody-associated SPS patients were women who were significantly older (age range, 39-75 years) than patients with GAD antibodies (age range, 14-82 years). Breast cancer was found in 10 of 11 women with amphiphysin antibodies while only 1 of 112 patients with GAD antibodies had breast cancer. None had diabetes mellitus. The distribution of muscle stiffness was also significantly different. Stiffness in the neck and arms was found in 80% of patients with amphiphysin antibodies and in 37% of patients with GAD antibodies. Treatment with tumor excision and chemotherapy produced dramatic improvement in 3 of 5 patients with breast cancer, and 4 patients were described as steroid responsive.

**Conclusions:** Amphiphysin antibody-associated SPS affects women exclusively and is strongly associated with breast cancer, neck and arm stiffness, and advanced age. The disorder may respond to cancer treatment and steroids.

**Reviewer's Comments:** This is an important paper despite the rare occurrence of amphiphysin antibody-associated SPS. This syndrome should be added to the growing list of paraneoplastic neurological disorders. This antibody should be considered and measured in all women with SPS, particularly in older women when it predominantly involves the upper arms and neck. Although a larger study would be useful for confirmation, I do not expect this in the near future due to the rarity of this syndrome (11 of 845 patients [1%] with SPS).

(Reviewer-Bashar Katirji, MD.)

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**Keywords:** Stiff Person Syndrome

**Print Tag:** Refer to original journal article
Stroke Prevention With Atorvastatin Good for All Stroke Subtypes

Results of Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial by Stroke Subtypes.
Amarenco P, Benavente O, et al:

Stroke 2009; February 19 (epub ahead of print):

Stroke subtype does not influence the benefits of atorvastatin treatment in stroke prevention.

Background: The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial demonstrated that, in patients with recent stroke or transient ischemic attack (TIA) and without known coronary artery disease, 80 mg of atorvastatin per day reduced the incidence of strokes (5-year absolute risk reduction, 2.2%) and cardiovascular events (5-year absolute risk reduction, 3.5%). In one secondary analysis, the group that showed the largest decline in low-density lipoprotein cholesterol (LDL-C) levels experienced the most benefit.

Objective: To perform a post hoc analysis of the SPARCL trial data to determine whether stroke subtypes responded differently to the atorvastatin treatment.

Methods: All patients older than age 18 years who had a stroke (ischemic or hemorrhagic) or TIA were included in the SPARCL study. Stroke subtypes were defined per TOAST criteria (Trial of ORG 10172 in Acute Stroke Treatment), and included hemorrhagic, small vessel disease (SVD), large vessel disease (LVD), ischemic stroke with multiple causes, or ischemic stroke of unknown cause. The patients had to be ambulatory (modified Rankin score, 3) and have LDL-C levels >100 mg/dL and <190 mg/dl. Cardioembolic strokes were excluded. Primary endpoint was fatal or nonfatal stroke. Secondary endpoints included major cardiovascular events (MCVE; stroke plus major coronary events).

Results: 4,728 patients were included in the post hoc analysis. Stroke subtype classification showed 15.8% LVD (n=749), 29.8% SVD (n=1,409), 2% hemorrhagic (n=93), 21.5% ischemic stroke of unknown cause (n=1,017), and 30.9% TIA (n=1,460). When comparing the atorvastatin versus placebo groups, the primary endpoint was reached in 13.1% versus 18.6% for LVD, in 13.1% versus 15.5% in SVD, in 11.2% versus 12.7% in ischemic stroke with unknown cause, 22.2% versus 8.3% in hemorrhagic, and in 7.6% versus 8.8% with TIA. Similarly MCVEs showed comparable reductions for various stroke subtypes.

Conclusions: Atorvastatin was similarly effective across all stroke subtypes in reducing the risk of stroke and MCVEs. The tendency of atorvastatin to increase hemorrhages had already been noted.

Reviewer's Comments: Regardless of stroke subtype, the addition of statins reduces the risk of stroke and other cardiovascular events. The limitations of this analysis include post hoc design, exclusion of cardioembolic strokes (thus skewing the distribution of stroke subtypes), and absence of power in the SPARCL trial for subgroup analysis. Overall, the SPARCL study results should prompt us to consider statins at hospital discharge following stroke. Only a third of patients have statins in their discharge orders even when they are eligible per ATP II guidelines. (Reviewer-Chitharanjan Rao, MD).

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Keywords: Prevention

Print Tag: Refer to original journal article
Knee pain, neuropathic pain, or fluctuating weakness in peroneal neuropathy should prompt imaging using MRI or high-resolution ultrasound.

**Background:** Common peroneal neuropathy (CPN) is the most common compressive neuropathy in the lower extremity. Intraneural ganglia (IG) are increasingly recognized as a cause of CPN, reported in 18% to 60% of patients.

**Objective:** To determine the clinical or electrodiagnostic factors that could distinguish CPN due to IG from compressive causes.

**Design:** Retrospective review of Mayo medical records from 1998 to 2007.

**Methods:** Adults with CPN, EMG findings consistent with peroneal nerve lesions around the knee, and who underwent knee MRI or high-resolution ultrasound imaging were included. CPN from blunt trauma was excluded. All patients had normal EMG of the biceps femoris (short head) and medial gastrocnemius. All patients with IG had findings confirmed at the time of surgery. Of 310 patients, 50 CPN were only screened since others had confounding factors, such as underlying peripheral polyneuropathy, myopathy, compartment syndrome, or sciatic neuropathy.

**Results:** The clinical or electrodiagnostic findings of 22 patients with CPN due to IG were compared to 11 patients with CPN and negative MRI. There were no differences in age, gender, degree of weakness, and degree of sensory loss between the two groups. The onset was subacute over days in both groups. Patients with CPN due to IG were less likely to have a history of weight loss (0% versus 36%), immobility (0% versus 21%), or leg crossing (0% versus 80%). The IG group had more pain at the knee (52% versus 0%), more neuropathic pain in the peroneal distribution (76% versus 27%), and higher body mass index (30 versus 24). The IG group had more fluctuating weakness than did patients with CPN and negative MRI (48% versus 0%), usually with weight bearing (38% versus 0%). A palpable mass only was detected in 47% of IG patients. The electrodiagnostic studies showed no significant differences between both groups, except for a trend of increased frequency of conduction block at the fibular neck in patients with CPN and negative MRI (64% versus 25%).

**Conclusions:** Pain, fluctuating weakness, and lack of precipitating factors for CPN (weight loss or immobility) increase the likelihood of IG in patients with CPN.

**Reviewer’s Comments:** There is increasing interest in performing imaging in patients with peripheral nerve compression. IG of the peroneal nerve originates from the superior tibiofibular joint after disruption of its capsule. This study predicted clinical features that may distinguish patients with compressive CPN from those with IG. Although a mass could only be palpated at the fibular neck in 47% of cases, knee pain, neuropathic pain, and fluctuating weakness as well as the lack of precipitating factors (such as weight loss or immobility) were good predictors for IG. (Reviewer-Bashar Katirji, MD).
Background: Two well-recognized components of Tourette syndrome, the involuntary expression of socially unacceptable words (coprolalia) or gestures (copropraxia) are known together as coprophenomena. 

Objective: To evaluate the prevalence and associations of coprophenomena in people with Tourette syndrome.

Methods: The Tourette Syndrome International Database Consortium (TIC) was established in 1991 and descriptive data are currently collected on about 800 new cases per year. For this study, an expanded version of the TIC data collection form was used at 15 TIC sites in 7 countries, and detailed coprophenomena data were collected prospectively from 648 consecutive patients with Tourette syndrome based on established diagnostic criteria. Reasons for exclusion included intellectual disability, pervasive developmental disorder, and psychosis. The final sample of 597 patients included 506 children under 18 years of age and 91 adults.

Results: Approximately 20% of males and 15% of females had experienced coprolalia at some point, and copropraxia had occurred in 6% of males and 5% of females. Overall, coprolalia was about 3 times more common than copropraxia. Onset of each was at a mean age of about 11 years and tended to occur about 5 years after the onset of motor tics. Coprolalia and copropraxia each occurred early as one of the initial symptoms in just over 10% of subjects. Other features that were strongly associated with coprophenomena were smelling of objects, spitting, and inappropriate sexual behavior. Long-term persistence of coprophenomena did not appear to be associated with early onset.

Reviewer's Comments: Coprophenomena can represent the most socially disturbing component of Tourette syndrome but fortunately occurs in only 15% to 20% of patients with Tourette syndrome. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Tourette Syndrome

Print Tag: Refer to original journal article
Transcranial laser therapy is safe and modestly effective in acute ischemic stroke. Further studies are needed to find the most optimum treatment population.

**Background:** Fewer than 4% of acute ischemic stroke patients receive any treatment other than rehabilitation and prophylaxis despite the evidence supporting the use of tissue plasminogen activator (tPA). One likely reason is the short window of opportunity. Transcranial laser treatment (TLT) is a new noninvasive method which affects biochemical changes in the ischemic neurons by delivering near-infrared laser energy. TLT has shown considerable and lasting benefits in animal stroke models, with efficacy when used up to 6 to 24 hours after onset. TLT is probably neuroprotective and perhaps acts by increasing ATP formation. Results of the NeuroThera Effectiveness and Safety Trial-1 (NEST-1) published in 2008 suggested that TLT is safe and effective for treatment of humans with ischemic stroke. NEST-2 includes a larger number of patients.

**Objective:** To evaluate the safety and efficacy of TLT in acute ischemic stroke.

**Design:** Double-blind, placebo (sham) controlled trial.

**Participants:** 660 patients were included at 57 centers in 4 countries.

**Methods:** All patients underwent the same TLT procedure within 24 hours, but the patients in the sham arm received no laser energy via the device. The primary endpoint was a good 90-day score of 0-2 on modified Rankin scale (mRS). The other endpoints included overall shift in mRS and changes in NIHSS score.

**Results:** The primary endpoint was met by 36.3% of the TLT group and by 30.9% of the sham group. The difference in benefit did not reach statistical significance. A post hoc, stratified analysis showed a favorable outcome in the TLT subgroup with entry NIHSS score <16. Mortality rates and serious adverse events were the same in both groups.

**Conclusions:** Both NEST-1 and NEST-2 confirmed the safety of TLT while showing some favorable trends regarding outcome.

**Reviewer’s Comments:** This is an important preliminary study of a novel therapeutic modality using electromagnetic energy aimed at neuroprotection (in contrast to use for its destructive abilities) following an acute ischemic stroke. The study was obviously designed to establish safety and was not sufficiently powered, as the current human experience is fairly limited. Further studies are needed to find the most optimum treatment population. In this regard, the evidence of higher benefit in patients with an NIHSS score of <16 is pertinent. Since the adverse effect profile for TLT is highly favorable (as opposed to that of tPA), the entry barrier to studies will be much lower. (Reviewer-Chitharanjan Rao, MD).

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Keywords: Transcranial Laser Therapy

Print Tag: Refer to original journal article
PH Associated With Epilepsy and 5q14.3-q15

Periventricular Heterotopia, Mental Retardation, and Epilepsy Associated With 5q14.3-q15 Deletion.
Cardoso C, Boys A, et al:

Neurology 2009; 72 (March 3): 784-792

Microarray-based comparative genomic hybridization can be used to detect specific genetic mutations responsible for neurologic abnormalities in children.

**Background:** Screening MRI of the brain performed on patients with epilepsy will sometimes reveal periventricular heterotopia (PH). These are nodules of gray matter or neurons that lie ectopically along the lateral ventricles as the result of an abnormality in neuronal migration during brain development in utero. Mutations in two different genes have previously been identified as causing PH. In X-linked bilateral PH, mutations in FLNA (Xq28) and ARF-GEF2 (20q13) have been identified. There is also a rare autosomal recessive with associated microcephaly. Several chromosomal rearrangements have also been associated with PH, including involvement of 1p36, 5p15, and 7q11, but the specific gene mutations have not been identified. Another 14 anatomoclinical PH syndromes have also been described, but associated genetic abnormalities have not been identified.

**Objective:** To describe a new, genetically identifiable PH syndrome marked by severe mental retardation, epilepsy, and bilateral PH.

**Methods:** Microarray-based comparative genomic hybridization defined a specific de novo deletion in the 5q14.3-15 region in three unrelated patients with PH, epilepsy, and mental retardation. Clinical and imaging features of these patients were collected and described.

**Results:** These patients had bilateral PH along the walls of the temporal horns of the lateral ventricles. Each of these patients had a common deleted region that spanned 5.8 Mb in the 5q14.3-15 region and contained 14 candidate genes. These patients had severe developmental compromise, some minor dysmorphic features, and seizures. One patient had infantile spasms, one had episodes of unresponsiveness with onset at 8 months of age and myoclonic seizures at 18 months, and one had febrile seizures at age 1 year and generalized tonic clonic seizures with onset at 6 years of age.

**Reviewer's Comments:** This represents a new and distinct syndrome with bilateral PH, mental retardation, epilepsy that maps to 5q14.3-15. As we go forward, microarray techniques will reveal the mystery regarding the etiology of many neurodevelopmental syndromes in children. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Periventricular Heterotopia

Print Tag: Refer to original journal article
An autosomal-recessive disease with its genetic locus on chromosome 20 resembles Refsum disease in its multisystem clinical picture but does not cause elevation of plasma phytanic acid.

**Background:** Refsum disease is an autosomal-recessive disorder comprising retinitis pigmentosa, sensorimotor demyelinating polyneuropathy, ataxia, deafness, cataracts, cardiomyopathy, ichthyosis, and elevated plasma phytanic acid.

**Objective:** To describe a new disease that is clinically similar to Refsum disease but is also biochemically and genetically distinct from it.

**Design:** Study of one family.

**Participants:** The 3 affected patients (2 siblings and their third cousin) are from a Norwegian family in which all 4 parents of the patients were descended from a man born in 1585.

**Methods:** The authors hypothesized that the disease was autosomal recessive and that the patients were homozygous for the same mutation (identical by descent). They used the technique of "homozygosity mapping" to find the genetic locus of the disease (Science 1987;236:1567-1570).

**Results:** In all 3 patients, symptoms were noticed in early childhood and included delayed walking, pes cavus and heel-cord shortening, and sensorineural deafness. The disease was slowly progressive, and as years passed, cataracts, a demyelinating sensorimotor polyneuropathy, ataxia of gait and limb movements, retinitis pigmentosa, dysarthria, and corticospinal tract signs appeared. Cognition was unaffected. The following diseases were ruled out: Refsum disease and another peroxisomal disorder; α-methylacyl-CoA racemase deficiency; mitochondrial disorders, including NARP (neuropathy, ataxia, and retinitis pigmentosa); vitamin E deficiency; and other ataxias, including Friedreich ataxia and SCA 7. A genome-wide scan using microsatellite markers followed by linkage analysis disclosed a locus for the disease on chromosome 20: a 9.88-cM segment that spans the centromere. All 3 patients (but not their healthy siblings) were homozygous in this region. Twenty-three of the 216 genes in the region were directly sequenced, but no detrimental sequence variants were found.

**Conclusions:** The clinical picture of Refsum disease is genetically heterogeneous. The authors suggest naming the new disease PHARC (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, cataract).

**Reviewer's Comments:** In an accompanying editorial, Thomas Bird points out that the new disease, unlike Refsum disease, includes corticospinal-tract signs but does not involve the heart or skin. (Reviewer-Marc D. Winkelman, MD.)
Nonviolent Behavior Can Be Manifestation of RBD

Nonviolent Elaborate Behaviors May Also Occur in REM Sleep Behavior Disorder.

Oudiette D, De Cock VC, et al:

Neurology 2009; 72 (February 10): 551-557

Although less common than violence, nonviolent behavior can be the manifestation of REM sleep behavior disorder.

**Background:** REM sleep behavior disorder (RBD) involves the enactment of a dream while it is going on. The prevailing notion is that the content of the dream and, hence, the behavior are violent.

**Objective:** To describe nonviolent behavior in RBD.

**Design:** A retrospective study and a prospective study.

**Participants:** The retrospective study included 13 patients with nonviolent RBD (age range, 33-86 years). Four of them had idiopathic RBD, and the others had secondary RBD, caused by Parkinson's disease (PD; n=4), narcolepsy/cataplexy (n=2), and dementia with Lewy bodies (n=2). The prospective study included 100 consecutive patients with PD, of whom 60 had RBD.

**Methods:** RBD was diagnosed when videopolysomnography showed enhanced chin muscle tone or complex movements during REM sleep or when a bed partner reported purposeful movements during sleep and the patient recalled a fitting dream. Patients with a history of sleepwalking, confusional arousals, or night terrors were excluded.

**Results:** The nonviolent behavior documented in the 2 studies included masturbating, coital pelvic thrusting, mimicking eating and drinking, collecting apples, making a business deal, shaking hands, crying, laughing, singing, dancing, urinating, defecating, mimicking smoking a cigarette, clapping, gesturing "thumbs up," flying, giving a speech, giving orders to soldiers, recording a movie, talking with a child-like voice, and giving lessons. All the patients in the prospective study (but not all those in the retrospective study) who had nonviolent REM behaviors also had violent episodes. In the prospective series of PD patients with RBD, 18% had nonviolent episodes, and 82% had only violent ones. Those with nonviolent episodes were significantly older, but there was no difference between the 2 groups of patients in gender, severity of RBD, PD motor disability, depression, cognitive ability, or daytime sleepiness.

**Conclusions:** Although less common than violence, nonviolent behavior can be the manifestation of RBD.

**Reviewer's Comments:** These observations expand the spectrum of behavior that a physician can plausibly ascribe to RBD. As the authors point out, some cases of nocturnal enuresis or encopresis in the elderly might be due to RBD. (Reviewer-Marc D. Winkelman, MD).

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Keywords: REM Sleep Behavior Disorder

Print Tag: Refer to original journal article