Memory Care Monthly

Supporting Healthcare Professionals in Caring for the Aging February 2007

Chronic Disease and Cognitive Impairment: Focus on Diabetes

It is not widely appreciated that diabetes mellitus (DM) impairs cognition. Approximately 100 million people in the USA have either diabetes or pre-diabetes. Type 2 diabetes, the most common form of diabetes, causes cognitive impairment in a number of ways. Diagnosis of the underlying cause, followed by the proper treatment, is essential to minimizing disability.

EPIDEMIOLOGY

DM is an independent risk factor for cognitive impairment or dementia due to either Alzheimer's disease (AD) or cerebrovascular disease (CVD). Type 2 DM increases risk of lacunar infarcts by 1.6-fold and increases risk of hippocampal atrophy by 1.7-fold [3]. The risk of cognitive impairment is increased in patients not receiving anti-DM treatment, in patients with insulin resistance (hyperinsulinemia) or insulin dysregulation, and in patients with longer duration or greater severity of DM [3,6].

Pathophysiology of Cognitive Impairment in Diabetes

The most likely pathophysiologic mechanisms are as follows:

- Decreased cerebral perfusion can result from accumulation of advanced glycosylation end products and atherogenesis [1].
- Beta amyloid deposition may result from advanced glycosylation end products or insulin resistance [1].
- Reduced cholinergic transport across the BBB can impair cognition [1].
- Homocysteinemia approximately doubles risk for AD and CVD, and diabetic microangiopathy associates with homocysteinemia [2].

EVALUATION

Impaired glucose regulation is a significant risk factor for MCI in both DM and non-DM patients. DM patients with fasting plasma glucose in the 135 -180 mg/dl range and with the tightest glucose control—as measured by HbA1c levels—show the best overall cognitive function [4]. A study of 1983 postmenopausal women with osteoporosis found that HbA1c blood levels ≥ 7% increased risk of MCI 1.6- and 3.7-fold among non-diabetics and diabetics respectively [5]. These findings suggest that it is useful to measure fasting plasma glucose and HbA1c blood levels in elderly patients, in AD patients, in postmenopausal women with osteoporosis and in DM patients.

Homocysteine blood levels should be monitored annually to keep homocysteine levels below 10.

DIFFERENTIAL DIAGNOSIS

Since the treatments for cognitive impairment/dementia due to AD and CVD differ, it is important to diagnose the underlying cause of impairment when detected.

Cognitive findings in patients with impairment due to CVD consist largely of a subcortical pattern of memory impairment, in which delayed free recall is impaired but delayed recall with a cue or hint is preserved. Executive function—consisting of difficulties with sustained concentration, organization, planning, judgment and decision-making and task execution—are typically more impaired early on in CVD than in AD patients. On the MCI Screen, a typical subcortical pattern would consist of impaired delayed free recall, preserved delayed cued recall, underestimate or normal estimate of delayed free recall ability, and sometimes impaired immediate free recall on wordlist learning trials 1, 2 and 3.

Cognitive findings in patients with impairment due to AD consist largely of a cortical pattern of memory impairment in which newly learned information is simply not stored and therefore can not be retrieved later even with cues or hints. Sustained concentration is often less impaired, but the patient may show poor insight in assessing their own abilities. On the MCI Screen, a typical cortical pattern would consist of impaired delayed free and cued recall, relatively normal immediate free recall on wordlist learning trials 1-3, and an overestimate of delayed free recall ability relative to the actual number of words recalled.

Patients identified to have cognitive impairment or dementia should all have a structural brain image consisting of a non-contrast MRI with coronal slices if possible, or a spiral CT with coronal slices otherwise. The key findings to look for are cortical and subcortical ischemic disease, hippocampal infarcts and hippocampal atrophy. Hippocampal atrophy argues strongly for a diagnosis of AD if it is not explained by an extensive amount of cerebrovascular ischemic disease, there is no hydrocephalus, and there is no history of major depressive disorder that had gone untreated for many years.

Laboratory studies to identify contributing causes include homocysteine, HbA1c, fasting plasma glucose and lipids, B12, folate, free T4, TSH, C-reactive protein, erythrocyte sedimentation rate, a CBC with differential, a standard chemistry panel, and a urinalysis. In postmenopausal women, particularly those with hysterectomy including the ovaries, a highly sensitive estradiol level may be useful as there is evidence of increased risk of dementia in hysterectomized women as well as in women with estradiol levels below 40 pg/ml [7]. In persons with a history of head trauma, stroke, cardiovascular disease, hyperlipidemia, a family history of dementia, or with age of onset before 65 years old, it is worth considering ordering an apolipoprotein E genotype. This is not only useful to determine if there is a more rapidly progressive form of AD, as is seen in those with one or two apolipoprotein e4 alleles, but it also provides the children of the patient with useful knowledge about their risk for developing AD, cerebrovascular or cardiovascular disease, and hyperlipidemia. Given that each of these diseases has risk factors that can be identified and reduced, it is worth considering ordering an apolipoprotein E genotype in such individuals.

TREATMENT

Although not conclusively established, treating homocysteinemia may delay the onset and progression of diabetic microangiopathy and treating homocysteinemia with B12, B6 and folate therapy is reasonably safe.

Tight glycemic control should be the goal in patients with abnormal fasting plasma glucose (<100 or >180 mg/dl) or HbA1c levels ≥ 7%.

To the extent that insulin resistance can be treated, it may delay the progression of AD by retarding beta amyloid formation.

Currently, there is both clinical and basic science evidence that cholinesterase inhibitors delay AD progression by 33-54% for three or more years. The mechanisms by which they accomplish this disease delaying effect are most likely to be: 1) Aricept weakly inhibits acetylcholinesterase for 1-3 years to reduce beta amyloid formation and delay AD progression by approximately one year [8]; 2) Razadyne allosterically modulates nicotinic cholinergic presynaptic receptors to trigger multiple mechanisms (reduced cholinergic neuron loss, reduced beta amyloid toxicity, reduced apoptosis, reduced glutamate toxicity) that delay AD progression by up to 50% for four or more years [9]; and 3) Exelon strongly inhibits acetyl- and butyrylcholinesterase to reduce beta amyloid formation, retard neuritic plaque production, and delay AD progression by up to 54% for five or more years [10]. Given a recent consensus article that disease-delaying effects with cholinesterase inhibitors are likely [11], treatment should be initiated with one of them as early as possible if the diagnosis is AD. The fact that DM patients may have further reduction in cholinergic activity suggests that Exelon, which is the most potent augmentor of acetylcholine, may be the first choice amongst them.

Namenda offers promise in cognitively impaired DM patients because it can block glutamate mediated excitotoxicity due to pathologically elevated levels of glutamate in the synapse. CVD mediates its damage in part via glutamate-mediated excitotoxicity, such that Namenda may play a protective role in preventing future damage due to CVD in DM patients. The additional value of Namenda is that it can enhance cognitive, functional and behavioral abilities by augmenting glutamatergic function when given at the right dose. It is not widely appreciated that the optimal Namenda dose is highly variable across patients, and that some patients may require up to 30 mg per day. Given a 3-4 day half-life, dose changes of 5 mg should not be done more frequently than every two weeks, which also gives adequate time to evaluate the symptomatic benefits at each dose. Assessing with the MCI Screen after each dose change will help identify when cognition is optimal, and avoid higher doses that can actually impair cognition.

Diagnosing and treating cognitive impairment in DM patients can be highly rewarding as it can help preserve a patient's livelihood or favorite pastimes.

REFERENCES

[1] Pasquier F, Boulogne A, Leys D, Fontaine P. Diabetes mellitus and dementia. Diabetes Metab. 2006;32:403-14.

[2] Araki A. Homocysteine and diabetic macroangiopathy Nippon Rinsho. 2006;64:2153-8.

[3] Korf ES, White LR, Scheltens P, Launer LJ. Brain aging in very old men with type 2 diabetes: the Honolulu-Asia Aging Study. Diabetes Care. 2006;29:2268-74.

[4] Shorr RI, de Rekeneire N, Resnick HE, Yaffe K, Somes GW, Kanaya AM, Simonsick

EM, Newman AB, Harris TB. Glycemia and cognitive function in older adults using glucose-lowering drugs. J Nutr Health Aging. 2006;10:297-301.

[5] Yaffe K, Blackwell T, Whitmer RA, Krueger K, Barrett Connor E. Glycosylated hemoglobin level and development of mild cognitive impairment or dementia in older women. J Nutr Health Aging. 2006;10:293-5.

[6] Debling D, Amelang M, Hasselbach P, Sturmer T. Diabetes and cognitive function in a population-based study of elderly women and men. J Diabetes Complications. 2006;20:238-45.

[7] McCleary, R., Mulnard, R.A., and Shankle, W.R. Reproductive Health Risks in Dementia: Evidence From the 1986 National Mortality Followback Survey. Alzheimer's Research (1996).

[8] Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, Wetterholm AL, Haglund A, Zhang R, Schindler R. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement Geriatr Cogn Disord. 2006;21:353-63.

[9] Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Arch Neurol. 2004;61:252-6.

[10] Farlow MR, Lilly ML; ENA713 B352 Study Group. Rivastigmine: an open-label, observational study of safety and effectiveness in treating patients with Alzheimer's disease for up to 5 years. BMC Geriatr. 2005;5:3.

[11] Geldmacher DS, Frolich L, Doody RS, Erkinjuntti T, Vellas B, Jones RW, Banerjee S, Lin P, Sano M. Realistic expectations for treatment success in Alzheimer's disease. J Nutr Health Aging. 2006;10:417-29.

Research Updates

Childhood Cancer Treatment May Increase Risk of Stroke

Brain cancer and leukemia account for more than half of all childhood cancers. As its survival rate improves, long-term effects of cancer treatment become important issues for patients. New research conducted by Bowers et al. from the University of Texas Southwestern Medical School links childhood cancer treatment for brain cancer or leukemia with an increased risk for stroke later in life. Data from 4,828 childhood leukemia survivors and 1,871 childhood brain tumor survivors was examined and compared to that of a random sample of 3,486 siblings of childhood cancer survivors. All cancer survivors had received a diagnosis when they were younger than 21, and all three groups were interviewed in their mid to late 20s. Strokes were reported in 1.5% of the leukemia survivors and 6.3% of the brain tumor survivors and only 0.2% of the siblings. Likewise, childhood cancer increased the relative risk of developing a late-occurring stroke, defined as those experienced 5 or more years after the cancer. Leukemia survivors had a relative risk of 6.4 and brain cancer survivors, a relative risk of 29 when compared to the siblings. Treatment methods also impacted the risk of stroke. Of those treated with chemotherapy, leukemia survivors had a 4.0 relative risk and brain cancer survivors a 12. Use of cranial radiotherapy (CRT) increased the relative risk to 5.9 for leukemia survivors and 37.5 for brain cancer survivors.

Bowers, D. et al. *J Clin Oncol.* (2006) 24: 5277-82.

Increased Rates of AD and MS Prevalence Reported in U.S.

A study conducted by the National Institutes of Neurological Disorders and study updated US prevalence data for 12 neurological conditions including Alzheimer's disease (AD), multiple sclerosis (MS) and Parkinson's disease. New report estimates AD prevalence of 67 per 1,000 population compared to 50 per 1,000 in 1982, which makes 25% increase in AD prevalence. The study also reported approximately 50% increase in MS population. The study, published in the January 30 issue of *Neurology*, was based on strongest available evidence. In some cases, the best available data came from Western European studies and was extrapolated to the U.S. population.

Hirtz, D. et al. *Neurology*. (2007) 68: 326-37.

Decline in Total Cholesterol Levels May Precede Diagnosis of Dementia

According to a study published in the January Issue of *Archives of Neurology*, a decline in total cholesterol levels precedes the diagnosis of dementia by at least 15 years. Dr. Robert Stewart and colleagues, from King's College in London UK, analyzed the data from the Honolulu-Asia Aging Study. They compared the natural history of cholesterol level change during the course of 26 years between two groups who did (N=56) or did not (N=971) develop dementia 3 years after the last measurement. Researchers found that the decline in cholesterol levels were significantly steeper among men who went on to develop dementia.

Stewart, R. et al. *Arch Neurol.* (2007) 64: 103-7.

Higher Plasma Cortisol Levels Linked to Dementia Progression

Increased levels of plasma cortisol, associated with higher hypothalamic-pituitary-adrenal (HPA) axis activity, may be associated with faster progression of Alzheimer-type dementia. 33 subjects with very mild or mild Alzheimer-type dementia and 21 subjects without dementia were evaluated annually for 4 years. Plasma samples were obtained and assayed for cortisol and the subjects were tested with the Clinical Dementia Rating Scale and other neuropsychological tests. In patients with dementia, higher plasma cortisol levels were associated with rapidly increasing symptoms of dementia as well as more rapidly decreasing performance on neuropsychological tests associated with temporal lobe function. In non-demented patients, there was no such association. No associations were observed between plasma cortisol levels and clinical and cognitive assessments obtained at the single assessment closest in time to the plasma collection. The findings of this study suggest that high levels of stress which increase glucocoticoid hormones may accelerate the progression of Alzheimer's disease. The study was led by Dr. John G. Csernansky and colleagues from Washington University School of Medicine, St. Louis, Missouri.

Csernansky, J.G. et al. *Am J Psychiatry.* (2006) 163: 2164-9.

Folate Intake and Cognitive Functions

Two recent studies on foliate intake give conflicting results. A study led by Luchsinger, et al. from Columbia University followed 965 persons over 65 years old without dementia to evaluate whether higher intake of folate and vitamins B_6 and B_{12} would reduce the risk of Alzheimer's disease (AD). While researchers found folate intake was independently associated with lower AD risk, they found a very weak association between vitamin B_6 and B_{12} intake and AD. Interestingly, the other study by Morris, et al. from Rush University Medical Center suggested that higher folate intake was associated with a higher risk for cognitive decline. These conflicting results highlight the need for newer results from ongoing randomized controlled trials.

Luchsinger, J.A. et al. *Arch Neurol.* (2007) 64: 86-92.
Morris, M.C. et al. *Arch Neurol.* (2005) 62: 641-5.

2007 Billing, Coding and Reimbursement Update

UPDATED REIMBURSEMENT ESTIMATOR

In our ongoing effort to keep you abreast of changes, we have uploaded the 2007 Medicare RVU rates into our Reimbursement Estimator. Please visit our website at www.mccare.com and click on the button marked "Reimbursement" to use our Reimbursement Estimator.

DIAGNOSIS CODES

It has come to our attention that some Medicare carriers have adopted Local Coverage Determination(s) which include a very specific list of Diagnosis Codes to be used for Psychiatry and Psychological Services, which include the CPT codes 96118, 96119, 96101 and 96102 for our procedures. We suggested that you check to see if your carrier has adopted such a policy before billing for any of these procedures.

FREE MEMORY QUIZ:

We have a new Memory Quiz which is available for use in your practice. It is intended as a tool to help increase patient awareness, and establish medical necessity. It is available electronically and you can request it by contacting customerservice@mccare.com

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