Memory Care Monthly

Supporting Healthcare Professionals in Caring for the Aging October 2006

Cancer-Related Cognitive Impairment (CRCI)

October is National Breast Cancer Awareness Month. In commemoration, this month we focus our attention on the link between cancer and cognitive impairment.

Cancer treatment has made great strides since the initial clinical trials of the National Cancer Institute were begun in the 1960s. Many fatal cancers in the 1960s are now routinely curable or have very good prognoses. As a consequence of the longer survival in a variety of cancers, new issues have arisen. One of those is cancer-related cognitive impairment (**CRCI**). The importance of CRCI is underscored by the fact that life expectancy due to cognitive impairment is the same as that due to cancer[1]. CRCI is a common complaint. Detecting and diagnosing CRCI will allow use of treatment that can ameliorate cognitively related functional disability and may improve quality of life.

Published studies examining the occurrence of CRCI have identified the following:

Whole Brain Irradiation produces CRCI in a dose dependent fashion[2].

Low dose irradiation to the frontal or posterior brain areas of infants produces CRCI during their adulthood[3].

Methotrexate, cytosine arabinoside and ifosfamide can cause acute encephalopathy, aseptic meningitis, plus delayed syndromes of cognitive impairment, hemiparesis, aphasia and progressive dementia. They are most likely to occur when these treatments are given in high doses, high frequency or co-administered with radiation therapy.

Primary CNS lymphoma patients surviving ≥4 years who are treated with methotrexate and radiation therapy develop leukoencephalopathy associated with impaired attention and memory[4].

Opiates increase the likelihood of CRCI in early stage cancer patients and delirium in advanced stage cancer patients[5]

Cancer survivors ≥65 years old and cancer patients who survive longer than 5 years are more than twice as likely to have CRCI or dementia[6].

Nonmetastatic breast cancer patients, prior to receiving chemotherapy, show CRCI in verbal learning and memory[7].

Breast cancer patients two years after adjuvant high-dose cyclophosphamide, thiotepa, or carboplatin chemotherapy or after conventional cyclophosphamide, methotrexate, or 5-fluorouracil chemotherapy have a higher risk of CRCI compared to breast cancer stage 1 patients. Whether CRCI lasts longer than two years in these patients is not settled[8].

Long-term survivors of childhood acute lymphoblastic leukemia and solid tumors have a significantly increased prevalence of CRCI[9].

Among **acute myelogenous leukemia and myelodysplastic syndrome patients prior to treatment**, higher IL-6 levels associate with poorer executive function, and higher IL-8 levels associate with better memory performance[10].

Tuberous Sclerosis increases the risk of autism[11].

Neurofibromatosis type 1 greatly increases the risk of CRCI[12]

Among **long-term survivors of childhood brain tumors**, CRCI is more likely to occur with younger age at time of treatment, longer survival time, in females, and in the presence of hydrocephalus. CRCI is related to loss of white matter or failure to myelinate in the frontal lobe and cingulated gyrus[13;14].

The likelihood of CRCI is a function of both radiation dose and the volume of brain irradiated[13]. CRCI progresses faster during the first few years after radiation therapy and more gradually later on[15].

Primary CNS Hodgkin's lymphoma patients who survive longer than 1 year virtually all develop cognitive impairment[16].

Low grade gliomas of the brain produced CRCI that is exacerbated by high dose cranial irradiation and by anticonvulsants[17].

Brain tumors in the frontal or temporal lobes impair executive function, attention and memory[18].

Small cell lung cancer patients frequently have CRCI[19].

Pancreatic cancer patients are more likely to develop Alzheimer's disease[20].

Familial adenomatous polyposis patients frequently have CRCI[21].

Patients with **paraneoplastic syndromes** develop CRCI and other psychopathology[22].

The mechanisms underlying CRCI include:

Slowing of nerve conduction velocity in the brain as measured by event related potentials during learning[9].

Leukoencephalopathy in long-term survivors treated with methotrexate and radiation therapy or methotrexate and cytosine arabinoside. The leukoencephalopathy of methotrexate may be due to disturbed folate metabolism leading to decreased folate and S-adenosylmethionine levels plus increased homocysteine and adenosine levels[23;24].

Gliosis leading to cognitive impairment can occur in patients treated with cisplatin in a dose- and frequency-dependent manner[25]. In culture and animal models, cisplatin induces apoptosis, which can be reduced by NMDA receptor modulating agonists, possibly memantine[26].

Chemotherapy delivered directly into the cerebrospinal fluid (i.e., by Ommaya reservoir) leads to clinically significant leukoencephalopathy in more than half of long-term treatment survivors and has a significant negative impact on quality of life[27].

Fludarabine and possibly other immunosuppressive chemotherapeutic agents increases risk for infection with the JC virus, which leads to progressive multifocal leukoencephalopathy[28]. Fludarabine is used to treat low-grade lymphoproliferative diseases such as chronic lymphocytic leukemia and follicular lymphoma.

Published studies of the effects of treating CRCI:

1. Cancer patients treated with **recombinant human erythropoietin** (epoetin alfa) show a reduction in cognitive impairment, possibly related to reduction of hypoxia-induced neuronal damage from various therapeutic protocols.
2. Administration of low molecular weight sulfur-containing agents that increase cellular glutathione levels has been shown to reduce the in vitro toxicity of the alkylating agents, melphalan, carboplatin, and cisplatin. Of sodium thiosulfate, N-acetylcysteine, and glutathione ethyl ester, N-Acetylcysteine was the most effective protectant tested[29].

The issue of identifying and treating CRCI is in its infancy. However, some existing treatments may counteract underlying mechanisms of CRCI to improve outcomes. Without further knowledge, the use of such treatment needs to be done safely on a trial and error basis.

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Potential agents that could improve function in CRCI:

1. Glutamatergic Modulation of Long-Term Potentiation
   a. Memantine (Namenda)
   b. Amantadine (Symmetrel)
2. Cholinesterase Inhibitors
   a. Rivastigmine (Exelon)
   b. Galantamine (Razadyne)
   c. Donepezil (Aricept)
   d. Huperzine alpha
3. ADHD Medications
   a. Methylphenidate (Ritalin, Concerta, Focalin)
   b. Dexedrine (Adderal)
   c. Atomoxetine (Strattera)
4. Dopaminergic therapy
   a. Dopamine precursors: Levodopa (Sinemet, Stalevo)
   b. Dopamine agonists: Pramiprexole (Mirapex)
   c. Catechol O-Methyl Transferase inhibitors (COMTAN)
   d. Monamine Oxidase Inhibitors: Selegeline (Eldepryl, Deprenyl)
5. Selective Serotoninergic antidepressants
   a. Paroxetine (Paxil)
   b. Sertraline (Zoloft)
   c. Escitalopram (Lexapro)
6. Selective Noradrenergic/Dopaminergic antidepressants
   a. Duloxetine (Cymbalta)
   b. Mirtazapine (Remeron)
   c. Venlafaxine (Effexor)
   d. Desipramine (Norpramin)
   e. Bupropion (Wellbutrin)
7. Antihypoxia Treatment
   a. recombinant human erythropoietin
8. Glutathione antioxidant therapy with alkylating chemotherapeutics
   a. N-Acetylcysteine
   b. R-alpha lipoic acid
9. Hypothalamic Nuclear Stimulation
   a. Modafinil (Provigil)
10. Cognitive Therapy
    a. Sudoku
    b. Posit Science Program to improve executive dysfunction
11. Physical Exercise[30]

Research Update

Cognitive Complaints in Older Adults May be Associated with Underlying Neurodegenerative changes

New research shows brain atrophy in older adults with cognitive complaints similar to that in subjects with amnestic types of mild cognitive impairment (aMCI). Saykin et al from Dartmouth Medical School have compared structural brain MRI scans of 40 euthymic individuals with cognitive complaints (CC) who had normal neuropsychological test performance with those of 40 patients with aMCI and 40 healthy controls (NL) using voxel-based morphometry and hippocampal volumes analysis. The CC and aMCI groups showed similar patterns of decreased grey matter, compared to the NL group, with differences evident in the medial temporal, frontotemporal, and other regions. The degree of grey matter loss was associated with extent of both memory complaints and performance deficits. This study suggests that cognitive complaints in older adults may be associated with underlying neurodegenerative changes.

Reference

Saykin AJ, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. Neurology. 2006; 67 (September 1 of 2): 834-42.

Research Shows High Interest among Older Adults in Screening and Treatment for Mild Cognitive Impairment

A recent study conducted by Dale et al at the University of Chicago found strong interest among healthy adults aged 35+ in being tested and treated for mild cognitive impairment (MCI) (n=149).

This study was conducted at two university-based geriatric waiting rooms in Chicago, and subjects were asked 12 attitudinal questions toward MCI and Alzheimer's disease (AD). These questions included "If you began to notice problems with your memory, would you go see your doctor to see if you have MCI?," "Would you want your doctor to test your memory to see if you have MCI as part of the medical exam even if you had not noticed any memory loss?," and "Would you want to know as early as possible that you had AD?."

Ninety-nine percent of respondents would be willing to be tested for MCI if a family member suggested they had memory problems, 99% were willing to take a medication if it would cut the risk to conversion from MCI to AD in half, and 92% would take a medication to delay the conversion from MCI to AD by 1 year.

In conclusion, the authors raised a concern about such high interest across the population given the limited ability to treat and delay the progression of some memory disorders. However, with rapidly advancing research on MCI and a promising pipeline of new treatments, public acceptance of early detection and treatment is encouraging.

Reference

Dale W et al. High Interests in Screening and Treatment for Mild Cognitive Impairment in Older Adults: A Pilot Study. JAGS. 2006;54:1388-94.

November
is
Alzheimer's Awareness Month

Look for an e-mail in your in-box in October with a suggestion of how you can use the opportunity to educate your patients about the importance of early detection and treatment of Alzheimer's Disease

Share Your Experience

How have your patients benefited from early detection of memory disorders?

How has your practice incorporated memory assessment services?

If you are available to share your experiences, please send an email to customerservice@mccare.com and let us know what is a good time to call you.

We are looking forward to hearing from you.

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