

Chemo Brain

Cognitive problems after cancer treatment are not imaginary.

BY DEBRA GORDON, M.S.

“I can’t find the right words when I’m having a conversation. **I forget what I wanted to say** by the time the other person finishes talking.”

—LINDA JAMES

When Linda James, 67, was diagnosed with a rare type of reproductive cancer in July 2013, she expected the pain, fatigue, nausea, and hair loss from the surgery, chemotherapy, and radiation. What the Williamsburg, VA, retiree *didn't* expect was that she would feel like she was losing her mind.

“I can’t find the right words when I’m having a conversation. I forget what I wanted to say by the time the other person finishes talking,” James says. The wrong words come out of her mouth, like “thermometer” when she means to say “thermostat,” she explains. James also has difficulty with short-term memory, which is why she immediately logs all appointments in her phone, a device she is never without.

It might sound like James is experiencing the normal, occasional forgetfulness that most of us experience in late middle age. She is not. Her symptoms didn’t appear until her third chemotherapy treatment and worsened significantly after her sixth and final treatment in December 2013. James is experiencing cancer-related cognitive dysfunction (CRCDD), commonly referred to as chemo brain. It’s a condition that affects up to 75 percent of cancer patients, but one that physicians have only recently begun to recognize as an actual consequence of cancer and its treatment.



SURPRISING SIDE EFFECTS Linda James didn't expect her chemotherapy treatment to have cognitive effects.

NO LONGER CONTROVERSIAL

Cancer patients have reported cognitive changes after chemotherapy for decades. Physicians, however, chalked up the memory loss and other symptoms to fatigue, depression, anxiety, and the stress of the cancer and treatment. That's changing, however, as more rigorous studies, including brain imaging, confirm its existence.

“Chemo brain has been a controversial area for a long time,” says John W. Henson IV, M.D., Fellow of the American Academy of Neurology (FAAN), a neuro-oncologist at Swedish Medical Center in Seattle, WA. “In part, that’s because it’s a difficult condition to study. But increasingly, we’re learning that chemotherapy does have an effect on cognitive function in some patients.” Evidence is accumulating from laboratory, animal, and human studies, such as MRI studies of breast can-

cer patients. Researchers have found very selective changes in the cognitive functioning of animals that can’t be written off as a side effect of chemotherapy, he says. Similar evidence in humans has convinced Dr. Henson “that chemo brain is a real toxicity of chemotherapy.”

Marc W. Haut, Ph.D., a neuropsychologist at West Virginia University School of Medicine, agrees. “We’d see these patients in the office, and many of us felt certain their symptoms were not due to just being depressed, anxious, or fatigued,” he says. “In fact, the symptoms were similar to what we see in people with subcortical white matter disease”—small strokes deep inside the connecting fibers of the brain, away from the thinking cells in the gray matter.

Estimates of the prevalence of chemo brain in cancer patients vary considerably. Data from the National Health and Nutrition Examination Survey, which included 1,300 people with a history of cancer and 8,500 without, found 14 percent of those with a history of cancer had memory problems, compared to 8 percent of those without a history of cancer—a 40 percent increased risk. Studies in breast cancer patients find rates of chemo brain ranging between 17 and 75 percent. As might be expected, people 55 and older are more likely to experience cognitive deficits.

Chemotherapy is not the only cancer treatment associated with cognitive problems. Chemo brain also occurs with targeted biologic therapies such as trastuzumab (Herceptin) and hormonal therapies, like tamoxifen. One study found worse deficits in women who received chemotherapy followed by tamoxifen than in women who received chemotherapy only. The difference could be due to the anti-estrogen effects of tamoxifen, a hormone that is important for brain health.

Cognitive deficits can occur even in the absence of chemotherapy. A study in young men (average age of 31) with testicular cancer found that 40 percent exhibited cognitive impairment *after* surgery but before chemotherapy. The authors theorize that the deficits could be related to the effects of inflammatory cytokines (chemicals released by the body because of stress that can cause inflammation), which are associated with cognitive decline, or to an immune response to the cancer itself that damaged brain cells.

“Clinicians need to understand that **cognitive loss is like pain**; it is whatever the patient says it is.”

—LYNNE P. TAYLOR, M.D.

CHANGES IN THE BRAIN

One reason for greater acceptance of chemo brain as a real condition, according to Lynne P. Taylor, M.D., FAAN, a neuro-oncologist and director of the brain tumor clinic at Tufts Medical Center in Boston, MA, is better imaging of the brain. Imaging studies show white matter changes in the brains of people who report symptoms of chemo brain, particularly in the hippocampus and prefrontal cortex. Both areas of the brain are involved in higher-level cognitive functioning. For

Do You Have Chemo Brain?

Studies find that various realms of cognition are affected by chemo brain, including verbal learning, the ability to navigate within one's environment (visuospatial function), and the ability to recall things one sees visually (visual memory). But what does that look like in daily life?

According to Marc W. Haut, Ph.D., of West Virginia University School of Medicine, chemo brain can cause you to:

- ▶ Lose track of what you're saying in the middle of a conversation
- ▶ Go into another room and forget why you went there
- ▶ Get distracted in the middle of one chore or task so you never finish the original task
- ▶ Feel sluggish with your thinking, like your car's engine on a cold winter day

One clue that “fuzzy thinking” is related to cognitive deficits and not depression or anxiety, says neuro-oncologist Lynne P. Taylor, M.D., FAAN, is that with true memory impairment, “you put something into your memory and can demonstrate that it's there, but when you go to pull it out, it's gone. But in depression and anxiety, you can't demonstrate that it ever went into memory because your concentration is so poor and scattered.”

Dr. Taylor uses the Montreal Cognitive Assessment (MoCA) to screen patients for chemo brain. The 15-minute test assesses concentration, executive functioning (mental processes involved in activities such as planning, organizing, and time management), short-term memory, language, visuospatial skills, and orientation. She also assesses them for depression and anxiety. Whether the tests find depression, anxiety, or chemo brain, she says, patients are often “very relieved” to learn their deficits are real.

instance, one study using diffusion tensor imaging, which highlights the structure of white matter tissue, found significant damage in chemotherapy-treated breast cancer patients with cognitive deficits compared to healthy individuals.

In addition, functional imaging studies, which track blood flow in the brain during cognitive exercises, also find differences in brain activity between chemotherapy-treated individuals and healthy controls.

One unanswered question is how long the damage persists. A study in 42 women with breast cancer found that 65 percent had a decline in cognitive function during or just after finishing chemotherapy (compared to 21 percent before). However, even nearly eight months after finishing chemo, 61 percent of patients continued to show cognitive decline, and nearly a third had developed new deficits. Meanwhile, an imaging study found brain volume reductions in breast cancer survivors even 20 years after chemotherapy ended.

However, some patients return to normal as early as a year after chemotherapy. “We think it does get better, just like chemotherapy-related peripheral neuropathy, but it may take years,” says Dr. Taylor. That's because the brain retains some plasticity even as we age, she notes, so it can rewire itself. “It just depends on your age and how much chemotherapy you received,” she says.

Despite the growing body of evidence on chemo brain, however, many patients still find their symptoms dismissed. “They have a lot of frustration and anger towards the medical community for not believing them,” says Dr. Taylor. And even if chemo brain couldn't be measured objectively—such as through images of the brain—that wouldn't mean it isn't real. “Physicians need to understand that cognitive loss is like pain,” Dr. Taylor says. “it is whatever the patient says it is.”

PREDICTING CHEMO BRAIN

Researchers still don't understand exactly how chemotherapy and cancers other than brain tumors damage thinking. One possibility is that it results from the neurotoxic effects of certain chemotherapy drugs on brain cells. For instance, 5-fluorouracil (5-FU), an older chemotherapeutic agent that is still used to treat many solid tumors, crosses the blood-brain barrier and, in animal models, damages brain cells.

Other possible causes include hormonal changes (particularly in breast cancer patients), immune-related dysfunction, and tiny strokes. Studies also find certain genetic fingerprints in people who are most vulnerable to chemo brain, including the presence of genes that are associated with a higher risk of Alzheimer's disease (AD).



STAYING SHARP Linda James regularly does crossword puzzles to improve her cognitive function. Many neurologists encourage patients with chemo brain to flex their mental muscles.

Other risk factors associated with developing chemo brain include high-dose chemotherapy, multi-agent chemotherapy, combined chemotherapy and radiation (in brain cancer patients), and administration of drugs directly into the brain. In addition, individuals with a history of head injuries, depression, learning disabilities, and other neurologic disorders may have an even higher risk, but they have been excluded from studies on chemo brain.

Another unanswered question is why only some cancer patients experience cognitive impairment.

It could be related to a greater genetic vulnerability to the damage, according to Dr. Haut. His group is planning to learn more about individual vulnerability to chemo brain by comparing positron emission tomography/computed tomography scans that all patients receive prior to chemotherapy with post-

treatment scans and neuropsychological testing to see if they can predict who is most likely to develop impairment during treatment. “If you could predict it, perhaps you could intervene,” Dr. Haut says.

WHAT CAN PATIENTS DO?

So if chemo brain is real, what does that mean for patients and physicians? For one, experts say, oncologists should include the potential for cognitive changes in their discussions with patients about the risks and benefits of systemic chemotherapy, particularly with older patients, for whom cognitive changes are particularly feared.

Patients at high risk of chemo brain might benefit from preventive approaches such as cognitive training—brain exercises

that teach you how to remember lists of words, as well as reasoning training that helps you recognize number and word patterns. Studies find such approaches can help people without cancer maintain cognitive health, even up to 10 years after the program ends. Only a few studies have been done with cancer patients, however, with mixed results.

One advantage of cognitive training, however, is to help patients manage their expectations, said Jennifer Wiener, Ph.D., a postdoctoral resident in clinical neuropsychology at West Virginia University School of Medicine. That way they don't automatically assume they'll have deficits. Otherwise, she says, concern over developing the cognitive changes "can turn into a self-fulfilling prophecy," just as patient expectations that they will be nauseous after chemotherapy are the best predictors of nausea.

Other preventive options include exercise, which has been shown to prevent chemo brain in mice and overall cognitive decline in healthy individuals; and diets high in antioxidants, like the Mediterranean diet, which is high in whole grains, fruits, vegetables, olive oil, and lean protein. Animal studies also find that fluoxetine (Prozac) can prevent deficits in older chemotherapy regimens such as 5-FU, but no human trials have been conducted.


"We're really in our infancy about how to help people," says Dr. Taylor. Education and reassurance are among the most important approaches, she says. "One thing people can do is tell their neurologist which areas they're having trouble with. That way, we can suggest strategies, such as keeping notes on

their smart phone." In patients with visuospatial deficits, for instance, she recommends games in which they pick out words in a cube of letters. One advantage of this approach, she says, is the ability to track any progress.

Certain medications may also help. Physicians may prescribe psychostimulants like methylphenidate (Ritalin), certain antidepressants, or modafinil (Provigil) or armodafinil (Nuvigil), which are approved for excessive daytime sleepiness.

Dr. Taylor urges patients to advocate for themselves. "If they find themselves being brushed off about the existence of chemo brain, then they should ask to see a neurologist or neuro-oncologist."

Dr. Henson tells his patients to remain as engaged in daily life as they can. And despite the plethora of "brain games" available today, he says, "It's hard for me to imagine anything a whole lot better than a crossword puzzle."

Linda James is a crossword fanatic, but she finds even that beloved pastime frustrating. "I have to wait a lot longer for my brain to remember what the word is," she says. The good news is that she's seen some improvement since her last treatment in November 2013. "My doctor says it will take at least a year, but I'm only giving it until June. Then I want to be back to normal." 

FOR MORE INFORMATION

- ▶ For a Patient Page on chemo brain from the American Academy of Neurology, go to bit.ly/1n2Hy7T
- ▶ For a full collection of *Neurology Now* articles on brain tumor, go to bit.ly/1oxqLoY