THINK AGAIN

A pair of researchers approaches Alzheimer's disease with new perspective

Research on Alzheimer's disease (AD) has historically cut a swath up the middle of the condition. Although patterns of decline are well documented across all phases of AD (a test categorizes AD patients according to disease progression: mild, moderate or severe), few studies have sought to characterize the cognitive and functional abilities of patients in its later stages. This oversight has been deliberate, says Dr. Sandra Black, a senior scientist and director of the neurosciences research program at Sunnybrook Research Institute (SRI). "No one has wanted to touch this [severe-stage] population." That's because, just as drugs delivered too early in AD's progression might fail to inspire a response, drugs delivered too late might miss the window of opportunity, she says. Thus, almost every man-made innovation designed to mitigate the devastation of this neurological nightmare has focused on its mild-to-moderate stage.

Until recently.

Acetylcholine is a neurotransmitter that plays an important role in how the brain functions. It affects certain cerebral tasks, including attentional focus, intentional thinking, memory and maintaining vigilance. In the 1970s, researchers identified that this system was a target of AD, gradually destroyed as the disease progresses, for reasons no one entirely understands. This realization, says Black, "led to the idea that a strategy to restore its function might help to combat the symptoms of AD."

Scientists conducted the first clinical trials with a drug that inhibits the breakdown of acetylcholine in the 1980s. The thinking, says Black, was that inhibiting its breakdown at synapses would help the neurotransmitter to last longer, to activate cholinergic receptors, thereby giving "a bigger bang for the buck." The drug—tacrine was first on the scene, marketed under the trade name Cognex—helped, but with caveats. Patients had to take it four times a day. And tacrine appeared to be toxic to the liver. Some also experienced nausea and diarrhea.

In the late 1990s, the second generation of these drugs appeared, donepezil being the first. Typically, the trials exploring this new generation of drugs, called cholinesterase inhibitors, focused on the middle band of severity. There, they showed a modest benefit. Says Black, "You could stabilize the symptoms for a period. But a big unanswered question was: Would these drugs make any difference in severe-stage disease?"

She was keen to find out.

Black headed up an international multicentre pharmaceutical trial, which led to a 2007 *Neurology* paper, "Donepezil preserves cognition and global function in patients with severe Alzheimer's disease." The research team found that donepezil has "beneficial effects, slowing decline in cognitive and overall functioning in severe-stage AD." This study, conducted in patients still living at home, demonstrated that this drug could also be helpful in late-stage disease.

Still, response to such promise has been halting. While donepezil's use for this late-stage purpose was approved, the formularies in most provinces do not cover the cost of the cholinergic drugs or another new drug for moderate to severe disease, called memantine, which is about $5 a day. "For people who can afford it, it's a no-brainer, but it's a cost that many families can't afford," says Black.

On another front, Black and her team have been actively investigating interactions between AD and cerebrovascular disease, especially small-vessel brain disease, which increases with aging and is becoming prevalent in developed societies.

Historically, researchers have approached the two conditions independently, failing to exploit the potential of modern computerized analysis and to acknowledge new data showing the most common cause of dementia is a combination of the two diseases. "There's a lot of 'silent' brain vascular disease that's visible on brain scans but ignored because it's so common," Black says. "But Alzheimer's and cerebrovascular disease, including stroke, can no longer be regarded as two separate disorders, because there's a lot of interaction between them."

Drs. Sandra Black and Fuqiang Gao

"Silent strokes" may occur up to 10 times more often than symptomatic strokes.

In a paper published in *Stroke* in March 2008, Black and lead author Dr. Richard Swartz — an MD-PhD student, supervised by Black during the research — analyzed both disorders and explored their combined impact on neurological deterioration.

Swartz, now a final-year resident in neurology at the University of Toronto, says that any other approach is folly. The two diseases are common afflictions of the aged. Dementia affects one in three people aged over 85, and AD and strokes accelerate as we age. Because they can affect thinking, memory and cognition, understanding how stroke disease and degenerative pathologies interact has become an important and urgent goal, says Swartz. To appreciate how brain changes contribute to cognitive impairment, he says, scientists need to move away from diagnostic groupings and look at different measures of atrophy, vascular disease and cognition, and work to understand how they all relate.

What's more, population studies have revealed that lots of folk are walking around with vascular changes in their brains, but no symptoms. These "silent strokes," says Swartz, may occur up to 10 times more often than symptomatic strokes (those everyone notices because they cause sensory loss or weakness). "Silent stroke disease is very common in the elderly, and may subtly affect functions like abstract thinking, planning and motivation, even though they don't wipe out the ability to, say, move your arm."

In their research, the team sought to understand how brain shrinkage interacts with some of these silent strokes and incidental white matter findings (as we age, many of us develop structural abnormalities on the brain — white matter hyperintensities — that show up as white spots on imaging). "We wanted to tease out which of the changes we see on imaging are most important to mental functioning, and to evaluate the correlation of these different types of pathology with different mental tasks," says Swartz.

Using measures of global severity that rated functional impairment and cognition, along with cognitive tests that analyzed participants' short-term memory and language, working memory and mental flexibility, the researchers found that measures of atrophy were the strongest correlates of all cognitive domains. Measures of small-vessel disease (white matter changes and small strokes in the brain's deep grey matter) were correlated with memory, language and mental flexibility. "Furthermore," says Swartz, "our data show that the more of one type of change you have, the more of the other you have. Studies that try to tease out which is the most relevant are highly flawed."

They showed that small-vessel disease affects the ability of anterior brain regions to plan, shift attention and multitask. In contrast, they found that large-vessel strokes contribute to memory, language and working memory, but not to mental flexibility.

It's not all brand new, Swartz admits, of their research. "But it's the first time it's all been tied together." Armed with specifics on which brain measures matter most for understanding breakdown of particular areas of cognitive function, doctors can gain new insight into why a patient's abilities are disappearing in a certain way. "And the results," says Swartz, "argue that treatments aimed at preventing vascular disease should help to prevent some of the [breakdown] of cognition."

The most critical finding of the research, says Black, is that, "to understand the relationship between brain tissue volumes and cognitive abilities, you need to look at all the brain tissue compartments, including the white matter lesions. You can't just ignore the lesions, as many people do in studies of Alzheimer's, or ignore the rest of the brain if you focus on white matter disease. If you do, you'll miss the fuller explanation of what's going on." LP

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