

# Alberta Doctors' Digest

## The evil empress of all maladies

If cancer is the emperor of maladies, then neuro-degenerative disease, particularly Alzheimer's disease (AD) is the evil empress.

A Case: Alan and Ann (not their real names) live in Calgary. We are good friends. Alan is a retired radiologist who is amiable, sociable and particular about detail. Ann was an effective school psychologist. But the hours spent on the public schools computer system had become draining with frequent changes of layout without adding value. She retired at 65, six years ago.

There had been times when she'd come out with strange observations: for example, she'd insisted that we'd been on a hike earlier that year with her and Alan – we knew that hadn't happened. It seemed harmless enough, a slip in memory – but Ann would not even consider that she might have imagined the hike or made a mistake. She *knew* it had happened.

Shortly after retiring, Ann went for a consultation at the Seniors Health Clinic at Rockyview Hospital. Alan had told her they might ask her to subtract sevens from a hundred, so she had better practice that. She did. An MRI was unremarkable, and she was told she might have some minor age-related cognitive impairment.

Then a year later, she had an irrational memory that was persistent despite all appeals to logic. She could not find a sofa blanket. She accused Alan of taking it to the hospital for a patient.

"But why would I do that?" said Alan.

"I don't know. But I do know you did it. I saw you putting it into your car. I don't mind but would prefer you ask permission first," she said.

Alan talked to me about that. I suggested he should get his kids to talk to Ann about it, explaining it didn't make any logical sense. This they did, to no avail.



Alzheimer's disease is an international calamity needing a huge effort from the public and especially researchers. (Photo credit: Mabel Amber, Pixabay.com)

Four years ago, they went on a summer trip to Europe visiting friends and relatives. This went well, but on return Ann insisted they had taken a large black suitcase of sheets, pillows, blankets and sleeping bags that she had checked in at Calgary Airport; it was now missing. Alan said there never had been a large black suitcase – it didn't make any sense taking sleeping bags when they were staying with friends and in hotels. This had no effect on Ann. Again, she *knew* they had taken a suitcase. She contacted everyone: had it been left behind at their house? Alan then spent time contacting them and apologizing for this strange request.

Alan and the kids noticed about three years ago that Ann, previously particular with household activities like washing dishes, would often unload the dishwasher without the dishes having been washed. Misplacing things around the house increased: her glasses, gloves, shoes, hat. Ann would even insist that she'd given them to Alan or one of the children to look after. What had they done with them?

My wife mentioned that Ann's memory for dates like going for a walk with friends was faulty. Ann would phone a friend to confirm a meeting, forget she'd done that, and phone again – and again. Friends called Alan: did he know that Ann had memory problems, that she was missing meetings despite having been reminded several times?

Alan had a long talk with me at that time. He was distressed and struggling. He found the incessant misplacing of her belongings trying to his patience. It was clear that something serious was wrong, and the dreaded diagnosis was emerging. The family doctor did blood tests – Ann had a low serum B12 and then took B12 shots. There was initially a sense of relief: something reversible had been found.

But there was no real change in Ann's short-term memory loss, though she could recite poems learned from childhood. The family doctor referred Ann to a seniors health clinic. Memory tests were again done, which showed a decline in cognitive abilities compared to tests done three years before. The psychiatrist thought Alzheimer's dementia likely and broke the news to Ann. This went badly. Ann stormed out refusing to accept this diagnosis and refused to see the psychiatrist again – a case of shooting the messenger.

A PET-CT was booked. Ann, who had problems with claustrophobia, took the injection of F18-fluorodeoxyglucose but refused to go into the scanner at the Foothills Hospital.

She had always loved golf, but her golfing partners complained she would lose her ball, hit someone else's ball and muddle her score. Some refused to play with her. Others understood it was not her fault. She now plays with a unique colored ball. Around this time, Ann started to have paresthesia-like symptoms on the top of her head. She fell more often. An MRI was done, and now there had been some shrinkage of the cerebral and cerebellar cortex. The diagnosis was never really in doubt, but this test result supported it.

Alan mentioned that strange nocturnal events from Ann were wearing him down: wandering in the house at night, sometimes taking a picture down, sometimes falling on the floor and refusing to get up. He thought Ann had been drinking more alcohol than usual. She had bursts of inexplicable anger. I told him this was "sun-downing" where a fugue-like state can occur with no memory of it in the morning.

A crisis occurred three months ago. Ann, who had refused to stop driving to the gym and local shops, had a serious traffic accident. She drove through a red light and crashed her car as well as the car crossing on the green light. The insurance company covered the cost. But Ann has now forgotten the details of that event – or has re-arranged it in her mind. She was furious and insisted on continuing to drive with no insight into the calamity that could occur. She then talked about ending her life since she was no longer independent.

The Sheldon Chumir geriatric psychiatry team who saw Ann after her accident suggested mirtazapine 7.5-15 mg for its sedative and anti-depressant properties but were required to inform the police of the diagnosis. Ann merely saw this as an interference – still with no insight into the dangers of her driving – or indeed insight that there was anything the matter.

She currently requires companionship, and Alan has caregivers coming in two days a week. Ann has recently had a review at a specialist clinic including assessment of her capacity and her ability to look after her finances. This was handled with great sensitivity and skill by the staff there. Personal directives and an enduring power of attorney have been signed over to Alan.

AD is an evil disease. It robs humans of their personality, their individuality, their self-confidence, their reason, their emotions. Alan was finding it hard to adapt to this new person he was living with. Treatment is symptomatic at best. Drugs have been disappointing. Choline-esterase inhibitors such as Aricept may slow progress in some cases, but it caused Ann to have nausea and agitation. AD is a perfect disease for the fraudsters, grifters, mountebanks, quacks and blood-suckers of the Internet feeding on the sufferers of this nightmare of a disease.

We know so little of the causes – likely multifactorial – of AD. The impairment of cognitive functions has traditionally been thought to result largely from a reduction in neuronal and synaptic activities, and ultimately neuronal cell death, with the peptide

amyloid- $\beta$  playing a role in pathogenesis – a cascade of events associated with excessive deposition of amyloid- $\beta$  – but is it cause or effect?

The genetics are unclear – better understood in the early-onset form (comprising <1% of cases), which typically follows an autosomal dominant pattern with gene mutations altering beta-amyloid metabolism to form intra-cerebral plaques. The genetics of later-onset AD (age 65 and older) are more complex, possibly with in-born errors of neuro-metabolism conferring susceptibility through more common but less penetrant genetic factors, for example, apolipoprotein E alleles allowing accumulation of intra-cerebral beta-amyloid. However, not all cases of human AD have observable plaques of beta-amyloid deposition nor, if present, does the amount of beta-amyloid present easily correlate with symptoms.

Another molecular mechanism of neuronal and synaptic disruption involves build-up of Tau protein filaments. This protein normally stabilizes neuronal microtubules, but in some dementia cases these proteins clump together forming long filaments of neuro-fibrillary “tangles” disrupting the neurone’s intercellular communication.

Is there a lack of an unknown vitamin or other food component? The dementia associated with excessive alcohol intake might suggest poor diet is a factor here. The MIND diet, based on a Mediterranean diet with plenty of greens, fish and olive oil and even a glass of red wine, seems, in a recent study, to slow the progress of AD.

Is there a transmissible factor, a “prion?” Prions are robust, hard-to-denature, misfolded protein molecules that can gain entry into cerebral tissues and are able to trigger and transform wild-type proteins into prionic forms by prion/protein-protein interactions forming plaques that interfere with neural circuits.

Kuru, a now-rare dementia in New Guinea, was likely caused by a prion from contaminated human brain tissue among natives who practiced a form of cannibalism in which some participants ate the brains of the dead as a funeral ritual.

The late Ralph Klein, usually a sensible man, said (jokingly) in the middle of the 2003 mad cow disease crisis in the UK that all a rancher had to do instead of slaughtering the herd was to “shoot, shovel and shut-up.” Canada can be a country that’s irony deficient at times – and this “advice” sent shivers down my spine – just one pre-clinically infected cow might allow penetration of bovine spongiform encephalopathy (BSE) prions into the food supply. (This has never been shown to occur in North America.)

Scrapie, a transmissible spongiform encephalopathy thought likely involving ingestion of prions, is a neuro-degenerative disease of sheep and goats. I recall in Scotland smart restaurants serving up “sheep’s head” and “brain cakes” as delicacies. A top restaurant in New York used to keep a soup stock of animal brains to enhance the exclusive taste of their pricey soup. The direct transmission of a natural classical scrapie isolate to macaque monkeys (a relevant model for human brain diseases) has been recently reported to cause dementia after a 10-year silent incubation period with features similar to human cases of sporadic Creutzfeld-Jacob disease (s-CJD) – a rapidly evolving dementia with myoclonus, extra-pyramidal and cerebellar symptoms occurring annually in 1:1,000,000 population.

Tragically, variant CJD (likely BSE prions) was transmitted to humans through the use of pooled, infected growth hormone extracts from cadaver pituitary glands in the 1990s – cases are still being diagnosed. Neither Scrapie nor BSE has never been formally shown to be orally transmissible to humans – though any epidemiological studies are

difficult with such long incubation periods and spotty recall of diets 10-20 years in the past. Recently reported in the UK are four cases of variant-CJD (thought caused by BSE prions) linked to past blood transfusions – a reason CJD is now screened for in the blood supply.

Several hypotheses are driving research into AD. Currently a dominant theory (according to *The Economist*, February 16, 2019, that dilettante journal of medical breakthroughs) is the prionic theory of Stanley Prusiner, who has argued that most neuro-degenerative diseases are prionic in origin. An emerging hypothesis is the relationship between neuronal hyperactivity and AD, observable in early stages of AD – normal activity being important for the formation of new memories and the retrieval of old ones. Clinical trials of levitracetam (Keppra), an anti-epileptic, are ongoing.

The evil irony of this awful disease is not lost on physicians: the more our research has improved outcomes in cancer, heart disease and infectious diseases, the longer people live and become susceptible to brain disease. The Alzheimer Society of Canada reckons that currently in Canada some 500,000 souls (two-thirds of them women) are living with AD (with 10% institutionalized.) Each year, some 25,000 new cases are diagnosed. In 20 years, we may have nearly a million sad souls living with AD with all the silent suffering and sorrow – and the family and societal disruption that goes with them.

Seniors' psychiatric teams are struggling. More support, including payment for caregivers, is required. This wicked disease is an international calamity needing a huge effort from the public and especially researchers. Causes and practical treatments must be found. Just as important, though achingly difficult, we must find a way to carry through the personal directives of patients (while they are able to give consent) to end their suffering – including medical assistance in dying (MAID). Would you want to end your life in a dementia ward? Not me.

Thank you to Drs. Wayne Chen and Alexandra Hanson, University of Calgary, for expert help.

---

References available upon request.