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Dementia Treatment: Where Do We Stand?

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Dementia has been referred in medical texts since Antiquity (see the writings of Pythagoras, Solon, Plato, Cicero, Celsus, Galen, Bacon and others in Asia and China) although the disease was comparatively rare before the 20th century. Until the end of the 19th century, it was a much broader clinical concept that encompassed mental illness and any type of psychosocial incapacity. In the elderly, it was also believed to be the result of cerebral atherosclerosis (whether blockages of the major arteries supplying the brain or small strokes within the vessels of the cerebral cortex).

It was only recently, on the basis of pathological examination of brain tissues, symptomatology, and different patterns of brain metabolic activity that a number of other types of dementia have been differentiated from Alzheimer disease and vascular dementias. However, the causal etiology of many types of dementia including Alzheimer disease remains unclear and many hypotheses (theories) have been advanced but these are largely based on risk factors. More recently, this author has posited that the root cause (not a risk factor) of Alzheimer and other neurodegenerative diseases is an autoimmune disease having gone rogue.

With increasing lifespan in the developed world, dementia has emerged as an increasing public health concern. It was uncommon in pre-industrial times and relatively rare before the 20th century. As more people are living longer, dementia is becoming more common in the population as a whole due to a decrease in risk factors. *Global Health Estimates* 2016 lists Alzheimer and other dementias as fifth among the top 10 global causes of mortality costing $818 billion (the majority of care provided by family carers).

Worldwide, in 2017, around 50 million people have dementia, an increase from 46 million in 2015 and 35.6 million in 2010, slightly higher in women than men at ages 65 and older, resulting in about 1.7 million deaths up from 0.8 million in 1990. Rates increase significantly with age. Every year, there are now nearly 10 million new cases projected to reach a total of 82 million in 2030 and 152 million in 2050. Much of this increase is attributable to the rising numbers of people with dementia living in low- and middle-income countries (nearly 60% of people affected), where the sharpest increases in numbers are predicted.

Most dementia types are slow and progressive. Symptoms vary across types and stages and vary with the individual. A diagnosis requires a change from a person's usual mental functioning and a greater decline than one would expect due to aging. The disease also has a significant effect on a person's caregivers. The signs and symptoms evolve in three consecutive phases (early, middle and late phase) ending up in near total dependence and inactivity, serious memory disturbances, and more obvious physical signs and symptoms. Behavioral and psychological symptoms of dementia occur almost always in all types of dementia and may manifest as: abnormal motor behavior;

agitation; anxiety; apathy; changes in sleep or appetite; delusions or hallucinations; depression; elated mood; disinhibition and impulsivity; irritability; psychosis; and agitation/aggression.

Each form of dementia has its own risk factors, but most forms have several risk factors in common. These are: age (the biggest risk factor), family history, and other factors including lifestyle, high blood pressure, smoking, and diabetes although it is not known how treatment for these problems influences the risk of developing dementia. It seems as though people who remain physically active, socially connected, and mentally engaged seem less likely to fall prey to dementia (or develop dementia later) than others. More than one type of dementia may exist in the same person.

Dementia has four progressive and subsequent stages quantified by scores, for example, in the Mini-Mental State Examination: mild cognitive impairment (score: 27-30), early stage dementia (score: 20-25), middle stage dementia (score: 6-16), and late stage dementia (score: <<6).

Symptoms are very similar in all types of dementia and thus cannot by themselves help in reaching the correct diagnosis of demential type(s). Diagnosis is usually based on (a) the history of the illness, (b) preliminary tests (niacin, folate or vitamin B12 deficiency, delirium, mental illness, paralytic dementia, and infective conditions such as cryptococcal meningitis, AIDS, Lyme disease, subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy, syphilis, and Whipple disease); (c) various cognitive tests of memory, executive function, processing speed, attention, and language skills, and emotional and psychological adjustment to rule out other etiologies and determine relative cognitive decline over time or from estimates of prior cognitive abilities (modified and mini-mental state examinations, abbreviated mental test score, cognitive abilities screening instrument, clock drawing test, Montreal cognitive assessment test, self-administered questionnaire, informant questionnaire on cognitive decline in the elderly, Alzheimer disease caregiver questionnaire, and general practitioner assessment of cognition). The sensitivity and specificity of several of these tests have been established; (d) laboratory tests (vitamin B12, folic acid, thyroid-stimulating hormone, C-reactive protein, and full blood count) to evidence deficiencies or other problems that commonly cause confusion or disorientation in the elderly. It is recommended to administer some of the above tests to those people over the age of 65 (including demented patients) with memory complaints. However, screening the general population for dementia is not recommended; and (e) imaging brain scans (computed tomography, single photon emission computed tomography, magnetic resonance imaging, functional magnetic resonance imaging, and positron emission tomography) may help in the diagnosis or even provide an accurate one. However, only a brain biopsy (not recommended, but can be performed at autopsy) can lead to an absolutely accurate diagnosis.

The main contributors to dementia are Alzheimer disease (50-70% of cases), vascular dementia (25%), Lewy body dementia (15%), and others of unspecified contribution including Parkinson disease, frontotemporal dementia, mixed dementia, senilitic dementia, syphilis, progressive supranuclear palsy, corticobasal degeneration, encephalopathy, and Creutzfeldt-Jacobs disease. Immunologically mediated, chronic inflammatory conditions include Behcet disease, multiple sclerosis, sarcoidosis, Sjogren syndrome, systemic lupus errhythematosus, and celiac and non-celiac diseases. There are still many other medical and neurological conditions in which dementia only occurs late in the illness.

Inherited conditions include various diseases (Alexandre, Krabbe, Niemann-Pick type C, maple syrup urine, Pelizaeus-Merzbache), syndromes (fragile X-associated tremor/ataxia, San Filippo type B), epilepsy, and many other disorders (cerebrotendinous xanthomatosis, dentatorubal pallidoluysian atrophy, fatal familial insomnia,, glutaric aciduria type 1, neuronal ceroid lipofuscinosis, neuroacanthocytosis, organic acidemias, spinocerebellar ataxia type 2, and urea cycle).

There are, nonetheless, some reversible conditions: hypothyroidism, Vitamin B12 deficiency, Lyme disease, and neurosyphilis. All people with memory difficulty should be checked for hypothyroidism and B12 deficiency. For Lyme disease and neurosyphilis, testing

should be done if there are risk factors for those diseases. Because risk factors are often difficult to determine, testing for neurosyphillis and Lyme disease, as well as other unmentioned factors, may be undertaken as a matter of course in cases where dementia is suspected.

Except for the treatable types of dementia listed above, and in the absence of a thorough understanding of the deep biology of this disease, there is currently no cure. Medical interventions remain heretofore palliative in nature with aim to alleviate pain and suffering. They include: cognitive and behavioral interventions, education and support for the patient and the patient's family and caregiver(s), and activity and exercise program.

There are also psychological, psychiatric and reminiscence therapies which, while offering small benefits, can improve the quality of life, communication, and possibly mood in some circumstances. Adult daycare centers and special care units in nursing homes provide specialized care while home care can provide one-on-one support and allow for the more individualized attention that is needed as the disorder progresses.

The psychopharmacotherapy for dementia includes (a) several (optional) medicines for treating Alzheimer disease including cholinesterase inhibitors such as Donepezil (Aricept®), Rivastigmine (Exelon®), and Galantamine (Razadyne®), Memantine (Namenda®), N-methyl D-aspartate receptor blockers (folate or Vitamin B12 and statins show no benefit, and there is no clear link of dememntia with blood pressure medications).

Behaioral symptoms are cautiously treated with antipsychotics. Of common occurrence, especially in the early phases of dementia, depression may be managed with behavioral therapy and/or with selective serotonin reuptake inhibitors including Fluoxetine (Prozac®), Sertraline (Zoloft®), Paroxetine (Paxil®), Citalopram (Celexa®), and Escitalopram (Lexapro®). Anxiety and aggression and sleep problems can likewise be medicated. Alternative therapies are also available (aromatherapy ad massage, cannabinoids, and omega-3 fatty acid supplements). Complementary treatments have also been developed for pain, eating difficulties, and palliative care.

Interestingly, there is limited evidence linking poor oral health to cognitive decline. Poor oral hygiene can have an adverse effect on speech and nutrition causing general and cognitive health decline. Indeed, oral bacteria (*P. gingivalis, F. Nucleatum; P. intermedia, T. Forsythia*; trepomena spirochetes) and oral viruses have been observed in the brains of Alzheimer patients. While no medications or supplements have shown good preventative evidence, including blood pressure medications, efforts to prevent dementia include: early education, decrease of risk factors, lifestyle changes, and computerized cognitive training.

In summary, whereas much is known about dementia and the underlying and contributing factors, and much has been published on the subject, we still do not understand the deep biology of the disease. Lacking this understanding, we have so far failed to find a cure and continue to be limited to symptomatic treatments that have limited or no effect. In the case of Alzheimer dementia, the main contributor, there is a ray of hope in the recent suggestion (Fymat, 2018) that the root cause of Alzheimer may be an autoimmune disease gone rogue, and that deposits (or plaques) of beta-amyloid (a protein) and the neurofibrillary tangles (disorganized masses of protein fibers within the brain cells) may only be the signs of a brain homeostasis that had broken down under an avalanche of brain insults. Similar innovative ideas and suggestions should be pursued for the other contributors to dementia.

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