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Editorial

Dementia: Should We Reorient Our Approach to Treatment?

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The World Health Organization (WHO) defines dementia as "an umbrella term for several brain diseases that manifest themselves by a group of symptoms affecting memory, other cognitive abilities, and behavior". To this definition other symptoms must be added such as emotional problems, language difficulties, and decreased motivation. Memory loss is not synonymous with dementia; rather, it is an indication of the need for professional treatment. All in all, dementia is a progressive neurodegenerative disease that interferes significantly with the affected person's daily living activities.

Because of economic development and increasing lifespan, dementia in its several types and forms has surfaced as a major global public health concern. According to the WHO "...worldwide, in 2010, 35.6 million people had dementia, increasing steadily to 46 million in 2015 and around 50 million in 2017 with rates increasing significantly with age… (further), in 2013, dementia resulted in about 1.7 million deaths up from 0.8 million in 1990… and every year, there are now nearly 10 million new cases projected to reach 82 million in 2030 and 152 million in 2050". The sharpest increases in numbers of people living with dementia are predicted for low- and middle-income countries. Further, as the combined result of a decrease in risk factors and a greater longevity, dementia is becoming more common.

For 2016, Global Health Estimates ranks "...Alzheimer's and other dementias as fifth among the top 10 global causes of mortality costing annually $818 billion (excluding the majority of care that is provided by family carers)".

But dementia is not an emerging disease! It has been with us since at least the 7th century BC when the Greek philosopher Pythagoras described old age (63 - 79 years) and advanced age (80 to death) as the *senium,* a period of mental and physical decay. In the centuries following, it was discussed by the Greek Athenian statesman and poet Solon, and the ancient Greek philosopher Plato. It was also mentioned in Chinese medical texts in the 6th century BC and since then by others (Cicero, a Consul of the Roman Republic; Celsius, another Greek philosopher; and Galen, the Greek physician considered the father of modern-day medicine). Even during the early Ottoman Empire (end 13th century to mid 20th century AD), Byzantine physicians wrote of dementia because seven of the Byzantine Emperors displayed signs of cognitive decline. During the 19th century until the first half of the 20th century, doctors (erroneously) used interchangeably schizophrenia and precocious dementia*. They even* came to believe that dementia in the elderly was the result of either blockages of the major arteries supplying the brain or small strokes within the vessels of the cerebral cortex (cerebral atherosclerosis).

While dementia has been referred to in medical texts since Antiquity, 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, any type of psychosocial incapacity, and cerebral atherosclerosis. 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 identified.

After all these past centuries, dementia remained (and continues to be) one of the most misunderstood diseases in medicine. It is only in the 1960s that the link between age-related cognitive decline and neurodegenerative diseases was established. Since then, the medical

community maintained that Alzheimer's disease was the cause of the vast majority of mental impairments rather than vascular disease, which is rarer than previously thought. It also thought that senile dementia could be linked to Alzheimer's disease dementia, and that dementia is a mixture of both Alzheimer's disease dementia and vascular disease dementia. Further, other dementia types have been identified.

Most dementia types are slow, progressive, and varying from person to person and according to their type and stage. A diagnosis is based on two considerations: greater decline than expected from normal aging and change in the mental functioning. The disease also affects significantly a person's caregivers.

In addition to the obvious physical signs and symptoms, others evolve in three consecutive phases (early, middle, and late phase) that end up in near total dependence and inactivity, and serious memory disturbances. In addition, in all types of dementia, behavioral and psychological symptoms of dementia occur almost always, manifesting as agitation/aggression, anxiety, apathy, appetite changes, behavioral changes, delusions/hallucinations, depression, disinhibition, impulsivity, irritability, mood elations, motor abnormalities, psychosis, and sleep disturbances.

Whereas each dementia type has its own risk factors, most forms have several risk factors in common including age (the biggest of them all), family history, high blood pressure, diabetes, smoking, and lifestyle. It is not known how treatment for some or all of these problems influences the risk of developing dementia. Nonetheless, people who remain physically active, socially connected, and mentally engaged seem less likely to fall prey to dementia (or develop dementia later) than others. To compound things, the same person may show more than one type of dementia.

Further, symptoms are not the whole story! Being very similar in all types of dementia, they cannot by themselves help in distinguishing between the different types of dementia and thereby reach the correct diagnosis of what type of demential affects the individual being examined. At present, the main types are Alzheimer's disease dementia (50 - 70% of cases), vascular disease dementia (25%), Lewy body dementias (15%), others of unspecified types including Parkinson's disease dementia, frontotemporal disorders dementia, and still others (mixed, senilitic, syphilitic, progressive supranuclear palsy, corticobasal degeneration, encephalopathy and Creutzfeldt-Jacobs disease dementia). Chronic inflammatory conditions that are immunologically mediated 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.

Because the symptoms of various dementias can make it hard to get an accurate diagnosis and because the different diseases are treated differently, it is important to be able to make the correct diagnosis. Indeed, a correct diagnosis is a prerequisite to get the right treatment.

Inherited conditions include various diseases (Alexandre's, Krabbe's, Niemann-Pick type C, maple syrup urine, Pelizaeus-Merzbacher), 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 such as hypothyroidism, Vitamin B_{12} deficiency, Lyme disease, and neurosyphilis. All people with memory difficulty should be checked for hypothyroidism and B_{12} 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 psychoneurosis 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 above treatable types of dementia, 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. More recently, I have posited that the root cause (not a risk factor) of Alzheimer's and other neurodegenerative diseases is but a runaway autoimmune disease.

Nonetheless, to this day, the cause of many types of dementia, including the most prevalent Alzheimer's disease, remains unclear. Many theories (rather hypotheses) have been advanced, but these are largely based on risk factors, associations or correlations. However, signs and symptoms, risk factors, associations, correlations... are not causation and their management is not cure...merely palliative treatments! What is going on? Have we got the cause of dementia all wrong? I believe so. Rather than remaining focused on the primary endpoint of a cure, we have meandered around and shifted the emphasis to surrogate endpoints even though the latter had not been clinically demonstrated to correlate well with the disease. In brief, we lost the proverbial forest for the trees! Unfortunately, this often happens in medicine when the endpoint (a cure) had not been attained.

Yet, billions of dollars are spent each year in rising healthcare costs relating to dementia, in addition to the financial and emotional burdens on families, friends, and care partners/givers. Irrespective of geographical location, racial/ethnic background, and cross-cultural and socioeconomic divides, one can die prematurely of dementia because there still are no cures or effective long-term treatments. 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. For most neurodegenerative disorders, including dementia, there is a ray of hope in my recent suggestion that the root cause may be an autoimmune disease having gone rogue, and that protein deposits (or plaques) including interactions between them and other proteins (tau, etc.) may only be the signs of a brain homeostasis that had broken down under an avalanche of brain insults. Similar innovative ideas and suggestions are direly needed and should be doggedly pursued.

I believe we should reorient our approach to dementia along a different path, one that devolves from a runaway autoimmune disease as the root cause. Such an approach will be more successful in leading us to a cure, at least for several dementia types (Alzheimer's, Parkinson's, Lewy body, and perhaps others) [1].

Bibliography

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