Acta Biomed 2024; Vol. 95, N. 2: e2024094 DOI: 10.23750/abm.v95i2.15930

Dementia: A crazy enigma

Domenico Cucinotta

Former Chairman, Department of Internal Medicine and Ageing, University Hospital of Bologna, Italy

Memory continuously declines as people age, but age-related memory impairment is not necessarily a prodrome of dementia. It may be senescent forgetfulness and can be reversed or [can] become stable. However, in Europe, the number of people at risk of severe cognitive impairment is expected to rise significantly in the coming years because of increased longevity (1).

Dementia affects 5–8% of the population aged over 65 years (~50 million worldwide), and according to the World Health Organization it is the third leading cause of mortality in Europe and the seventh globally (1,2). By 2050, this number will almost double every 20 years, reaching 82 million in 2030 and 152 million in 2050. Much of the increase will be in developing countries.

Dementia is an umbrella term for several progressive diseases. It affects memory, other cognitive abilities, and behaviour and significantly interferes with a person's ability to maintain daily living activities.

Many types of studies and research have been carried out in the last decades to identify an effective treatment capable toreversing functional impairment, but up to now, the results have been very poor.

In 2006, I was invited to speak at an international meeting organized by Ljubljana University; the title of my lecture was: "*Pharmacological Treatment of Dementias", A Crazy Pathogenetic Puzzle* (Figure 1) (3). My final message was that the available drugs and supplements were not capable to reverse the progression of the syndrome despite some initial partial benefits. These observations further underlined the variability of cognitive and functional impairment, particularly in older persons where the clinical aspects can be due to frailty and multimorbidity.

Numerous neuropathological and neuroimaging studies indicate that at least one-third of AD cases are complicated by some degree of vascular pathology. AD changes rarely occurred on their own, so only 9% of people with dementia had pure AD pathology. The other common types are vascular dementia (VD), mixed dementia (MD), Levy body dementia (LBD), frontotemporal dementia (FTD), mild cognitive impairment (MCI), and other dementias]. Young-onset dementia (YOD) is a neurological syndrome that affects the behaviour and cognition of patients between the ages of 45-64 years. Common symptoms include behavioural changes, psychiatric manifestations, and cognitive decline (4).

Early diagnosis and new therapies of pathogenetic factors?

The major neuropathological lesions defining AD include neurofibrillary tangles and amyloid plaques,

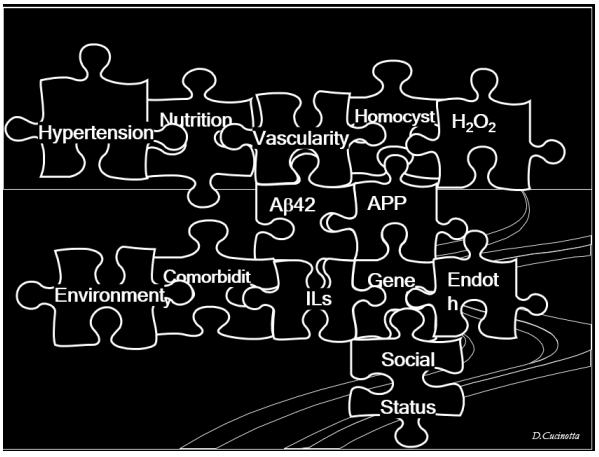

Figure 1. The crazy pathogenetic puzzle of dementia.

composed of abnormally phosphorylated tau and amyloid beta (Aβ), respectively. The accumulation of soluble and insoluble Aβ aggregates may initiate or potentiate pathologic processes (5).

Recent treatments are based on humanized IgG1 monoclonal antibody that binds with high affinity the Aβ soluble protofibrils. The advent of these disease-modifying drugs (DMD) has offered some hope to people with YOD. Aducanumab, lecanemab and donanemab have been shown in clinical trials to remove amyloid from the brain during the earliest stages of AD and slow cognitive decline (6-8). However, the benefits and risks of initiating DMD are questionable, multifaceted and complex, as are the patterns of evidence and effectiveness from clinical trials. Moreover, DMDare associated with severe adverse events such as brain edema or effusion, and the costs of treatments are very high. Aducanumab is out from research and marketing from February 2024. Therefore, longer trials are warranted to determine the efficacy and safety of this category of drugs, and the research is progressing at pace.

The Alzheimer Europe position paper has addressed anti-amyloid drug efficacy, safety, and cost questions, highlighting three priority areas: effective communication of risks and benefits; an accurate, timely diagnosis; and healthcare systems preparedness. To address these challenges, Alzheimer Europe calls for concrete actions from industry, regulators, payers, healthcare systems and governments (9).

The diagnostic problem in a very early stage

Access to DMD hinges entirely on a timely and accurate diagnosis of light to mild AD, which remains challenging in clinical practice. Recently, a randomized clinical trial demonstrated that performing amyloid PET early in the diagnostic workup allowed 40% of memory clinic patients to receive an etiological diagnosis with very high diagnostic confidence, adding evidence to previous studies showing that amyloid PET has a relevant diagnostic value. But its relevance concerns younger patients, a small group (10). Another multidisciplinary working group has defined recommendations for the effective and individualized use of biomarkers for AD diagnosis in memory clinics. Putting patients, instead of the disease or a test, at the centre of doctors' diagnostic considerations constitutes a turning point in the currently applied clinical approaches. The objective is to overcome the current limitations of the recommendations and guidance for diagnosing AD. It will promote consistency of neurocognitive disorders, reduce the cost of analyses, and identify those eligible for treatments with more precision. In the future, it will avoid up to 70% of invasive tests such as lumbar punctures and PETs, helping to reduce costs and expanding diagnoses in the general population (11). It could also be useful to start treatment with DMD.

The real world of evidence

Frailty and multimorbidity are a huge challenge in dementia, with difficulties in organizing care. Older people with dementia might forget to tell their family or health professionals of symptoms, struggle to understand or follow agreed plans, and are more likely to forget to drink or eat, to perform physical activity, with the results of increasing falling, malnutrition, and infection rates.

Healthcare professionals need education to be more comfortable, understanding, and positive in communicating with patients with dementia, considering the link between very old age, frailty, multimorbidity and dementia (4,5). This approach suggests a new type of comprehensive care, focusing on specific age-related processes that might reduce the functional impact or severity of dementia. Many classical vascular risk factors such as hypertension, diabetes mellitus, and hypercholesterolemia have recently been shown also to increase the risk of any type of dementia.

Modifiable, personalized multi-domain risk-reduction strategies should be considered for all at-risk subjects. A large population-based study suggests six healthy lifestyle behaviours are linked to slower memory decline in older adults. Investigators found that adhering to healthy diet, cognitive activity, regular physical exercise, not smoking, and abstaining from alcohol were significantly linked to slowed cognitive decline in older adults, irrespective of APOE4 status (12). APOE4 is one of the prominent genes involved

in the increased risk of developing dementia, but its effect on cognition in patients who are not yet diagnosed with dementia or mild cognitive impairment is relatively understudied.

After adjusting for health and socioeconomic factors, investigators found that each individual healthy behaviour was associated with a slower-than-average decline in memory over a decade. The healthy diet emerged as the strongest deterrent, followed by cognitive activity and a physical-cognitive integrated treatment approach (12).

The Mediterranean diet (MeDi) may offer a defence against cognitive deterioration: people who follow a MeDi have a lower risk of developing cognitive problems. Adherence to MeDi could be an effective non-pharmacological measure to reduce the burden of dementia, even among oldest (13,14).

The Mediterranean diet: a historical perspective (15)

The MeDi, born in the Mediterranean basin, was initially quite poor and simple, essentially based on the products that grew almost spontaneously along the shores of the Mediterranean, i.e., olives, grapes, and wheat, which were long cultivated in that region. The invasions of the Roman Empire by barbarian populations between 400 and 800 enriched the diet with products from wild, uncultivated areas, meat from game and pigs, and vegetables. With the arrival of the Arabs in southern Italy in the ninth century, the diet shifted to carbohydrates, particularly dried pasta and other new ingredients. The Arabs primarily brought a new imaginative spirit to the kitchen by introducing and using an infinity of condiments and seasonings. The discovery of the Americas and the arrival of new ingredients from the New World brought the final adjustments to the MeDi: new meat (turkey), new vegetables (potatoes, broad beans, corn, tomatoes,) new fruits (strawberries, pineapples, coconuts, peanuts), chocolate, coffee and sugar completed the list of components of the MeDi as we know it today.

Reduced vascular risk factors and favourable effects on glucose and lipid metabolism may also contribute to a lower risk of dementia. However, other aspects of the Mediterranean lifestyle, such as regular exercise and robust social networks, might help lower the risk of the syndrome.

Previous studies have reported that excessive caloric intake could increase oxidative stress injury and βamyloid accumulation, which harms nerve cells and increases the risk of MCI (2). An excessive intake of saturated fatty acids will increase the risk of MCI and dementia; conversely, an increase in dietary unsaturated fatty acids can reduce the risk of cognitive impairment. The possible mechanism was regulating the anti-inflammatory response and endothelial function through cyclooxygenase and lipoxygenase.

A recent research has positioned the gut microbiota (GM) as an important susceptibility factor in dementia by showing specific alterations in AD patients. However, it is unknown whether GM alterations are causal in the manifestation of AD symptoms. Serum from Alzheimer's patients decreased neurogenesis in human cells in vitro and was associated with cognitive scores and key microbial genera. These findings reveal for the first time that AD symptoms can be transferred, confirming a causal role of GM, and highlight hippocampal neurogenesis as a converging central cellular process regulating systemic circulatory and gut-mediated factors in AD/16).

Conclusion

Knowledge about risk factors and potential prevention, detection, and diagnosis of dementia is improving, although significant gaps remain regarding the necessity of policy and individual changes to delay the onset of cognitive and functional impairment. A better approach could be to support and treat people with dementia and their families and improve their quality of life. Primary prevention through risk factor modification and behaviour change is crucial if we want to improve global (brain) health, reduce health inequalities, and contain healthcare costs worldwide.

Without specific and effective medications to improve memory (1-3), it is clear that healthcare professionals can do several things to improve cognition and support abilities,including managing the treatable causes and multimorbidities, recommending MeDi, exercise, cognitive stimulation therapy, using reminiscence therapy, and offering caregiving support (17,18). Sadly, most of these are never done.

It is important to recognize that there are multiple approaches to enhancing outcomes that do not involve medications in the care of old patients. The ambition is for worldwide provision of resources for adequate well-being to people with dementia and their careers

with a better evidence base to guide individual care and policy -making. Interventions, including organization of complex physical illness and social needs, to support people affected by dementia and relatives, can have a huge effect when taken as a whole (19). With good quality care, people can live well with dementia and families can feel supported.

Conflict of interest: The Author declares that he has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connectio with the submitted article.

References

1. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019. Lancet. Public Health 2022, 7, e105–e125.
2. Nucci D, Sommariva A, Degoni LM, et al. Association between Mediterranean diet and dementia and Alzheimer disease: a systematic review with meta-analysis. Aging Clin Exp Res 36, 77 (2024). https://doi.org/10.1007/s40520-024-02718-6.
3. Cucinotta D. Pharmacological treatment of dementias.. Lecture. Abstract Book. XXXVIIth Janez Plocnick Memorial Meeting, University of Ljubljana, Dec 7, 2006 (Slides are available on request).
4. Hendriks S, Peetoom K, Bakker C, et al. Global Prevalence of Young-Onset Dementia: A Systematic Review and Meta-analysis. JAMA Neurol. 2021;78(9):1080–1090. doi:10.1001/jamaneurol.2021.2161.
5. Livingston G, Huntley J, Sommerlad A, et al.. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020 Aug 8;396(10248):413-446. doi: 10.1016/S0140-6736(20)30367.
6. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023 Jan 5;388(1):9-21. doi: 10.1056/NEJMoa2212948. Epub 2022 Nov 29. PMID: 36449413.
7. Cummings J, Aisen P, Lemere C, Atri A, Sabbagh M, Salloway S. Aducanumab produced a clinically meaningful benefit in association with amyloid lowering. Alzheimers Res Ther. 2021 May 10;13(1):98. doi: 10.1186/s13195-021-00838-z. PMID: 33971962.
8. Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimers Dement. 2021 Apr;17(4):696-701. doi: 10.1002/alz.12213..
9. Alzheimer Europe position on anti-amyloid therapies. https://www.alzheimer-europe.org/ policy/ positions/ alzheimer-europe-position-anti-amyloid-therapies,2024. www.alzheimer-europe.org: Public Call for Action, March 22,2024. www.alzheimer-europe.org: Public Call for Action, March 22,2024.
10. Altomare D, Barkhof F, Caprioglio C,; et al. Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) Consortium. Clinical Effect of Early vs Late Amyloid Positron Emission Tomography in Memory Clinic Patients: The AMYPAD-DPMS Randomized Clinical Trial. JAMA Neurol. 2023 Jun 1;80(6):548-557. doi: 10.1001/jamaneurol.2023.0997..
11. The Lancet Neurology. Dementia diagnosis in the anti-amyloid era. Lancet Neurol. 2024 Mar;23(3):219. doi: 10.1016/S1474-4422(24)00041-3.
12. Yaffe K, Vittinghoff E, Dublin S, et al. Effect of Personalized Risk-Reduction Strategies on Cognition and Dementia Risk Profile Among Older Adults: The SMARRT Randomized Clinical Trial. JAMA Intern Med. Published online November 27, 2023. doi:10.1001/jamainternmed.2023.6279
13. Nien SW, Lin IH, Wu HC, Chen YH, Yang SC. Evaluation of Dietary Intake in Individuals with Mild Cognitive Impairment. Nutrients. 2023 Aug 23;15(17):3694. doi: 10.3390/nu15173694. PMID: 37686726; PMCID: PMC10490258.
14. Meshram A, Yadav D, Song M. Investigating the Mediterranean diet's role in Alzheimer's disease prevention: a review. Progr Nutr [Internet]. 2023 Dec. 13 [cited 2023 Dec. 15];25(4):e2023057.
15. Capurso A. The Mediterranean diet: a historical perspective. Aging Clin Exp Res.2024;36:78 (2024). https://doi.org/10.1007/s40520-023-02686-3.
16. Grabrucker S, Marizzoni M, Silajdžić E, et al. Microbiota from Alzheimer's patients induce deficits in cognition and hippocampal neurogenesis. Brain. 2023 Dec 1;146(12):4916-4934. doi: 10.1093/brain/awad303. PMID: 37849234; PMCID: PMC10689930.
17. Morley JE. Editorial: Management of Cognitive Dysfunction. J Nutr Health Aging. 2021;25(7):819-820. doi: 10.1007/s12603-021-1654-y. PMID: 34409959.
18. Lin FR, Pike JR, Albert MS, et al.. Hearing intervention versus health education control to reduce cognitive decline in older adults with hearing loss in the USA (ACHIEVE): a multicentre, randomised controlled trial. Lancet. 2023 Sep 2;402(10404):786-797. doi: 10.1016/S0140-6736(23)01406-X.
19. New dementia strategy for Scotland: Everyone's Story. Published on www.gov.scot/publications 31 May 2023.

Received: 11 March 2024
Accepted: 11 April 2024
Correspondence:
Prof. Domenico Cucinotta, MD, MPH
Former Chairman, Department of Internal Medicine and Ageing, University Hospital of Bologna, Italy.
E-mail: cucin.d@libero.it