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Dementia: A Public Health Challenge

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Dementias, including Alzheimer's disease (AD), that is the most common form of progressive neurodegenerative disorders, are characterized by a severe decline in mental ability that interferes with daily living. The loss of cognitive functioning, such as thinking, remembering and reasoning, coupled with deterioration in emotional control, social behaviour and social communication, is due to irreversible loss of neurons and brain functions. Currently, there are no resolutive therapies for AD since the available drugs are mainly active against the symptoms and unable to inhibit disease progression.

The day-to-day caring of patients has high physical, emotional and financial costs. The economic impact, already difficult to sustain in Western countries, is unmanageable in developing countries, where there is a steady rise in life expectancy, increasing age-related diseases.

At present, there are more than 36 million people living with Alzheimer's disease in the world and, owing to the global ageing of the population, it is estimated that each day more than 6,000 new cases are diagnosed, increasing this number to 115 million by 2050. Therefore, the public health challenge in the coming years is certainly to develop new therapeutic treatments but, above all, to prevent these age-related diseases, causes of disability.

The challenge, though ambitious, is not entirely unfeasible because the development of omics approaches allows a better understanding of the cellular metabolic impairment that triggers dementia pathogenesis.

As is known, the neuropathology hallmarks of AD are severe atrophy of the cortex and hippocampus, and the accumulation of amyloid-beta (Aβ) into senile plaques and of hyperphosphorylated tau into neurofibrillary tangles. In the molecular mechanisms of this multifactorial proteinopathy several pathways, including oxidative stress, mitochondrial impairment, microglia activation with release of pro-inflammatory cytokines and dysregulation of metal homeostasis, play relevant roles.

On the basis of newly acquired knowledge about the mechanisms that regulate cellular metabolism, it seems clear that we must restore the balance between the biosynthesis of new macromolecules and the re-use of damaged macromolecules. The caloric excess, favouring biosynthesis at the expense of re-use, determines, especially in differentiated cells (such as neuronal cells), the accumulation of old and damaged components that is the common pathogenetic mechanism in many age related diseases, including AD. This pathway triggered by mTOR (mammalian target of rapamycin), promoting the *de novo* synthesis of cellular components, produces chronic inflammation and oxidizing conditions due to an excess of oxidized or aggregated proteins and accumulation of damaged organellae, not subject to autophagy. In particular, damaged mitochondria are the main source of oxidative stress and their impairment alters cellular energy metabolism (i.e. uncoupling between the electron transport chain and oxidative phosphorylation) and neuronal cell survival–death pathways. Moreover, the oxidizing conditions mTOR-induced favour sequestration of trace and heavy metals that can be accumulated in the cells reaching toxic amounts, while under reducing redox conditions these electrophiles are readily excreted. Other than their pro-oxidant properties, the toxic metals, owing to their positive charge, show a high affinity for free thiols. The metals, forming sulfides after reaction with cysteine and glutathione, reduce the normal metabolic reactions of these thiol compounds. A further damage, caused by dyshomeostasis of metal in AD (metallopathy), seems to be the pivotal role of metals in protein misfolding and aggregation, as highlighted by metal colocalization in Aβ plaques.

Conversely, AMPK (AMP activated protein kinase), triggered by fasting, stimulates the autophagic recycling of cellular materials, optimizing energy efficiency. Decreasing the load of damaged proteins, lipids, glycans, RNA and DNA, the AMPK-activated pathways counteract phlogosis. In the central nervosus system (CNS), the innate immune cells (i.e. microglia) mediate inflammatory responses by releasing pro-inflammatory cytokines that amplify and aggravate inflammation throughout the brain. In turn, cytokines can induce degeneration of normal neurons through upregulation of nuclear factor kappa B (NF-κB).

By limiting calorie intake throughout the day, also helping the energy expenditure by physical exercise, and ensuring a more prolonged period of fasting overnight, an optimal cycle between new biosynthesis and re-use can be ensured, preventing the accumulation of damaged components.

As stated, this clearly highlights how it would be rather simple to prevent AD as well as many other chronic degenerative diseases, typical of the elderly. A substantial "overhaul" of the diet, meaning by this term not only dietary habit but more generally lifestyle, could certainly reduce or even simply delay the onset of dementia in elderly people. This would allow significant cost savings and, above all, to improve the quality of life of patients and their caregivers. In recent decades, life expectancy has increased beyond all expectations but, as pointed out by the WHO, about a decade is spent with disabilities, including dementia. It is the task of public health to add quality to the gained years by promoting, with all the necessary tools, a healthy way of life.

A dietary habit more in line with energy requirements must necessarily be coupled to regular exercise and must prioritize food rich in micronutrients such as vitamins, minerals and phytochemicals that assist cellular metabolic pathways and promote the redox balance. Due to the established use of a high-calorie diet in developed countries, overhauling the diet will be more difficult to promote, while in developing countries it is absolutely necessary to prevent Western diets becoming consolidated in the population. Following a healthy diet from childhood will more likely achieve the goal of stemming the dementia epidemic in the elderly.