International Psychogeriatrics (2023), 35:12, 679–681 © International Psychogeriatric Association 2023
doi:10.1017/S1041610223000868

COMMENTARY

The NIA-AA revised clinical criteria for Alzheimer's disease: are they too advanced?

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The National Institute on Aging and the Alzheimer's Association (NIA-AA) workgroups presented the revised guidelines for clinical diagnosis of Alzheimer's disease at AAIC 2023 for scientific input and review (see https://aaic.alz.org/nia-aa.asp).

The document, which is currently open for discussion, represents an updated synthesis of knowledge about the neurobiological basis of Alzheimer's disease and proposes innovations in the methods of diagnosing Alzheimer's disease and interpreting biological and clinical data, suggesting significant changes in management and clinical aspects.

Developments in the role and relevance of biomarkers are thoroughly discussed, and based on these innovations a new approach to Alzheimer's disease diagnosis is proposed. First and foremost, in the NIA-AA document, Alzheimer's disease is defined as a biological condition, detached from the presence of clinical symptoms. The presence of cognitive deficits or functional impairments is used only to define the stages of disease severity.

The authors stated that "*. . . disease exists when the first manifestation of the pathophysiology of Alzheimer's Disease (AD) can be detected by biomarkers, even though symptom onset may occur years in the future*" and proposed a distinction between a "*disease*" phase (asymptomatic) and an "*illness*" phase (in which cognitive complaints became evident).

This point is of particular relevance because the progression from the asymptomatic stage ("*disease*") to the symptomatic stage ("*illness*") is not simple to define and is conditioned not only by the neurobiological alteration typical of the Alzheimer's process but also by neuropathological and somatic comorbidity (Gottesman *et al.*, 2017), polypharmacy, frailty status (Wallace *et al.*, 2021), and variables related to sociocultural history and lifestyle factors (Fratiglioni *et al.*, 2020), cognitive reserve (Song *et al.*, 2022), psychic stress, age and gender, and probably many other variables. In the document, the role of these factors is not denied, but it is not operationalized in the recommendations.

The clinical phase of Alzheimer's disease may, therefore, manifest after several years (even beyond 15) and in a hardly predictable way based solely on the biological data of the individual (Dubois *et al.*, 2016).

Neuropathological studies have shown that approximately 50% of the brains of individuals of very advanced age with intact cognition have Alzheimer's-type neuropathology (Corrada *et al.*, 2012).

The risk of this approach is to create a large plethora of patients who will never develop the symptoms of the disease, with enormous individual and collective consequences (van der Schaar *et al.*, 2022).

A 70-year-old man has a 10-year survival probability ranging from 48 to 79% depending on the level of frailty and comorbidity (for a woman, it ranges from 61 to 80%) (Schoenborn *et al.*, 2022). Thus, we can consider that from 20 to 50% of people with biologically confirmed Alzheimer's disease at that age will never develop the clinical phase of the disease. Are we creating an army of patients awaiting their illness (Schermer and Richard, 2019)?

The authors point out that it is impossible to understand the role of co-pathology in the development of symptoms, and that *"with advancing age, co-pathologies are the rule and isolated AD is the exception."* The coexistence of non-AD pathologies (such as LATE, hippocampal sclerosis, argyrophilic grain disease, and vascular brain injury) is frequent in both early- and late-onset AD individuals and increases with age and predicts worse cognitive

https://doi.org/10.1017/S1041610223000868 Published online by Cambridge University Press

performance (Spina *et al.*, 2021). This has numerous consequences: difficulty in defining the prognosis, the involvement of the specific neuropathological alterations in symptom determinism, and the role of pharmacological and nonpharmacological interventions.

For many biomarkers, issues still exist regarding standardization and definition of meaningful cut-offs. This can lead to the emergence of gray areas, where uncertainty in the interpretation of biological data may result in clinically unacceptable ambiguity (Giangrande *et al.*, 2023).

In the real world, most patients arrive at medical care based on the presence of symptoms (cognitive and noncognitive) in their daily living, while the use of biomarkers is reserved for selected cases.

Do we really think that a person, in all his/her complexity, can be reduced to a single "biological" condition, without taking into consideration their history, their relationships, their culture, cognitive reserve, and all fundamental elements which can modulate the expression of the symptoms of the disease? Should we really be concerned only with biology, forgetting about the person? The distinction between disease and illness in Alzheimer's disease seems not to consider the fact that those extra-biological factors (somatic, psychological, and personal) and comorbidities other than Alzheimer's play a significant role in the determinism of symptomatology.

Regarding the distinction between disease and illness, a linguistic consideration might also arise. In Latin languages (e.g. Italian, Spanish, and Portuguese), it is not possible to effectively translate the English terms used to distinguish the asymptomatic phase ("*disease*") from the symptomatic one ("*illness*"). Words like *doença/maleita/enfermidade* (Portuguese), and *dolencia/mal/enfermedad* (Spanish), or *disturbo/malattia/infermità* (Italian), are interchangeable equivalents of the English term disease/illness. The use of expressions like "*prodromal phase*" or "*pre-symptomatic phase*" appears to be more informative in communicating with patients, avoiding unnecessary anxiety and fear.

From the document, two seemingly antithetical approaches seem to emerge. The first considers exclusively the biological basis of the disease and believes that the symptoms are a direct consequence of the biological alterations (although it then recognizes the existence of comorbidity, and its role is not easily definable). The other approach places the expression of the symptomatology in the foreground and the search for the biological cause (or causes, be they biological, somatic, or psychological) as secondary.

Finally, the issue of resource allocation must be considered. Should we allocate significant resources to treat a disease that we do not know when it will manifest itself clinically? Or should we invest more resources to treat the illness, which currently lacks sufficient services for families and patients?

From our point of view, the role of biology in the determinism of the syndrome is still too uncertain to consider individuals with a biological anomaly as affected by a "disease"; this categorical definition entails significant psychological and medico-legal repercussions and has relevant bioethical implications that perhaps should be taken into greater consideration.

Conflict of interest

None.

Acknowledgments

The authors thank Prof. Henry Brodaty for his important comments and suggestions.

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