1. Introduction

Dementia is defined by a progressive loss of memory and cognition that severely affects the social, behavioral, occupational, and functional ability of the patient. Alzheimer’s disease (AD) is now assumed to constitute 60–80% of all dementia cases [1]. It is thus the leading dementia diagnosis and AD is becoming almost synonymous with dementia. Dementia due to AD is clinically defined by the cognitive impairments combined with signs of plaques and neurofibrillary tangles in the brain. Alois Alzheimer was the first to describe the neurofibrillary tangles in combination with plaques in 1907 [2] and later these were identified as protein aggregations and deposits of amyloid-β and tau respectively [3,4]. This is referred to as AD pathology and the amyloid cascade hypothesis has been the dominating explanation for the pathogenesis of AD and thus most dementia cases over the last four decades.

But there have been difficulties with the diagnosis of AD and its relation to other forms of dementia and old age [5,6]. AD pathology is neither sensitive nor specific for the development of dementia symptoms. Despite significant gains in the understanding of AD pathology, the causes of dementia in affected individuals are unknown, except for rare, fully penetrant genetic forms of early-onset dementia characterized by genetic defects in amyloid precursor protein (APP) and presenilin (PSEN1, PSEN2) [7]. Evidence from epidemiological and pathological studies indicates that damage to the vascular system is also associated with an increased risk of late-onset dementia, referred to as vascular contributions to cognitive impair-
of AD have changed over time. In the first half of the 20th century, a vascular etiology of late-onset dementia was the prevailing view, and the diagnosis of AD was considered an unusual early-onset neurological disorder [5,9]. Since the 1970’s, the AD diagnosis has been broadened to include most cases of late-onset dementia, a redefinition that is widely accepted in the scientific and clinical community along with amyloid-pathology as the underlying pathology. And in still more recent decades, new diagnostic methods have been introduced to standardize AD by detecting this pathology.

It is, we suggest, necessary to backtrack on some of these developments. First and foremost, we propose to disentangle AD from the heterogeneous category of late-onset dementia and reserve the diagnosis for the dominantly inherited types of early-onset. At the same time, we can draw important lessons from historical practices. In our approach to late-onset dementia we will I) Use ‘exploratory categories’ to approach the complex relations between biological mechanisms and late-onset dementia, as Alzheimer originally used AD as an ‘exploratory category’ in the early 20th century to challenge the undifferentiated category of senility with new clinical observations and causal pathophysiological mechanisms [19], II) Reject “normal” senility and combine a search for causal mechanisms with optimism about future treatment possibilities along the lines of the 1970’s redefinition of late-onset dementia as a disease that can be prevented and treated rather than an inevitable part of aging [20], And III) Retain the ambition to standardize pathophysiological mechanisms with a view to subdivide dementia patients – not just as has been done with focus on amyloid-β and tau but including other strands in the etiologies of late-onset dementia.

This will allow a renewed focus on the biological unravelling of the complex and yet-to-be understood etiology of late-onset dementia. We embrace the multicausal nature of late-onset dementia and consider late-onset dementia as a ‘black box disease’ – a level playing field where the full range of causal mechanisms are considered on equal footing.

2. The historical shaping of the AD diagnosis

The AD diagnosis we know today is a product of its history and of alternate subdivisions and extensions of the diagnosis. As we shall see, the development is shaped by reclassifications of biological/pathological mechanisms and clinical observations as well as social, political and technological changes [21]. Both the relationship between clinical symptoms and neuropathology as well as the role and definition of aging have played a role in the reconceptualization of AD through time.

2.1. AD as an ‘exploratory category’ for understanding dementia

In 1901, a 51-year-old woman named Auguste Deter was admitted to the Frankfurt mental hospital, where she became patient of the psychiatrist and neuropathologist Alois Alzheimer. He described her symptoms as a progressive cognitive disorder, including local neurological symptoms, hallucination, delusion, and psychological social disability. Auguste Deter progressively worsened until she lost almost all cognitive abilities and after 4 ½ years died of pneumonia. Still interested in the case, Alzheimer procured her brain. He conducted an autopsy and described an evenly atrophic brain with deposits of neurofibrillary tangles and plaques whereas the larger vessels showed arteriosclerotic change [2,22]. This combination of clinical symptoms and pathology constituted, Alzheimer and his mentor Emil Kraepelin argued, a new category of rapidly progressive early-onset dementia with a distinct disease process, and they discussed whether it should be considered as an atypical form of senile dementia or a disease not previously described [5,20]. At that time, dementia seen in elderly patients was referred to as senile dementia or just senility and was considered part of the normal aging process. Alzheimer presented the case of Auguste Deter to challenge this view and argued for paying attention to histology and the cases that did not provide an easy fit into known categories: “We should not be content to locate any clinically unclear cases of illness in one of the familiar categories of disease known to us to save ourselves the effort of understanding them” [5]. In 1910, Kraepelin then introduced the condition ‘Alzheimer’s disease’ in the eighth edition of his classic textbook *Psychiatrie: ein Lehrbuch für Studierende und Ärzte* but added the proviso: “The clinical interpretation of Alzheimer’s disease is still unclear at the moment”. As the historian of science Lara Keuck has pointed out, this lack of clarity is reflected in the way the diagnosis was used in practice in the years around the publication of the disease [19]. The original case notes added question marks or bracketed the AD diagnosis, and the patients included both early- and late-onset cases; at autopsy some revealed neurofibrillary tangles and/or plaques and some did not. The diagnosis was thus used, as Keuck has argued, as an ‘exploratory category’ [19]. It introduced new observations, indicating a specific pathology that might be relevant for understanding the disease process of dementia. Following the introduction of the diagnosis, the pathological significance of the plaques and neurofibrillary tangles and whether these represented a distinct disease process remained a subject of debate [5,20]. By the middle of the century however, AD settled as a rarely used diagnosis associated with early-onset dementia.

2.2. AD as a broad diagnosis with societal impact

AD was a rare diagnosis for early-onset dementia for decades, but in the 1970’s, a combination of technological, scientific, social and political changes resulted in the introduction of a radical biomedical reconceptualization of AD: The age of onset and thereby the distinction between AD and senile dementia was eliminated. Already in the 1960’s a renewed interest in neuropathology was sparked by the electron microscope, which allowed more refined differentiation of plaques and tangles. At the same time a series of brain autopsies carried out in England revealed AD pathology in the brains of older people. With the new pathological focus, the neurologist Robert Katzman then
suggested in the 1970’s that dementia in old age and AD were the same entity and should be viewed as distinct from normal aging [5,20,23]. Although dementia in old age was to some degree considered to be caused by cerebral atherosclerosis at the time [5,9], these cases were subsumed under the now broadened diagnostic category of AD. This unifying construct completely transformed what was considered ‘normal’ aging into a specific disease with a distinct underlying pathological mechanism. Katzman even wrote of its ‘malignancy’ further emphasizing its localized, pathological character [23].

Removing the age criterion resulted in diagnosing a far greater number of patients suffering from AD, and with Katzman billing it the fourth leading cause of death in the United States, AD was becoming appreciated as a significant public health problem [20]. This recategorization moreover resonated strongly with sociocultural changes in the perception of cognitive decline and with a conscious rejection of senility as an inevitable part of aging [5]. The reconceptualization of AD was supported and further taken up by the newly established National Institute of Aging (NIA), for which a specific disease with a distinct pathology in a large older patient group was an ideal opportunity to demonstrate the expected impact and importance of the research done by the institute. Substantial and successful efforts were made to increase funding of biomedical research into AD and the NIA established policies to boost AD at the federal level. Furthermore, dementia went from being viewed as a traditional geriatric disease with emphasis on nursing to a biomedical disease of the brain, which attracted a different set of scientists. This led to a social movement around AD and a dramatic increase in interest from research communities, the pharmaceutical industry, patient groups and politicians [20].

2.3. Standardization of AD and focusing on one pathophysiological mechanism

During the following decades, protein aggregations of amyloid-β and tau in the brain was identified as the plaques and tangles originally described by Alzheimer [3,4], thus fueling the hope for biomarker detection and treatment development. An aim to standardize AD diagnostics was set, and with new diagnostic technologies, magnetic resonance imaging (MRI), positron emission tomography (PET), cerebrospinal fluid (CSF) analysis and genomics, it was possible to detect the pathology prior to death. Additionally, AD started to be considered a continuum with a slowly progressive amyloid pathology, which would eventually lead to clinical symptoms and finally a diagnosis of dementia. This process could presumably be detected early before the presence of clinical symptoms and was considered unidirectional. The resulting shift in research and clinical focus, concentrating on the early disease stages before the onset of clinical symptoms, elicited the introduction of preclinical AD and prodromal AD, and the diagnosis of mild cognitive impairment (MCI) [24–26].

In 2018, the NIA and the Alzheimer’s Association (AA) suggested a research framework (the AT(N) biomarker system) in which AD should be considered a biological construct and should solely be defined by imaging and CSF biomarker detection with a focus on amyloid-β [A], tau [T], and neurodegeneration [N], because “cognitive symptoms are not an ideal way to define AD” [12]. The NIA-AA framework aimed to harmonize interventional and observational AD research, to distinguish AD from other pathological causes of dementia and to move AD research in the direction of precision medicine [12]. In a response to the AT(N) definition, Sweeney et al. proposed to incorporate biomarkers of vascular dysfunction to the research definition [10]. This was declined by the authors of the NIA-AA research framework, who rejected that vascular dysfunction represented a core feature of AD, though the authors agreed that measurement of vascular dysfunction was important in fully characterizing older people in terms of their risk for dementia [27]. Currently, AD is clinically still primarily defined by the presence of acquired cognitive impairments that impact daily living.

3. Rethinking late-onset dementia as a ‘black box disease’ and levelling the playing field

Over the last century, AD thus changed from a rare form of early-onset dementia, clinically defined and characterized by the presence of cognitive decline of which a certain diagnosis could be made only post-mortem, to a common biologically defined condition in older people with or without cognitive impairment. The logic and disease concept were transformed from identifying possible causal pathways of a clinically diagnosed cognitive syndrome into searching for the potential clinical implications of a biological mechanism of interest, i.e., the amyloid-β cascade. In this sense, the biomarkers and presumed disease mechanisms have taken priority over the clinical diagnosis. This fundamental shift in disease concept has led to a very narrow focus on the underlying pathological mechanisms as the amyloid biology on its own correlates poorly with the clinical symptoms and is neither sensitive nor specific for developing dementia. As stated earlier, there are cases with cognitive impairment without AD pathology as well as older adults with AD pathology who do not suffer cognitive impairment [11,12]. Furthermore, only 5–15% of older adults diagnosed with MCI develop dementia per year, depending on the population under study [28]. While loss of cognition might be the most important factor for the person suffering from late-onset dementia, challenges remain with respect to measurement and standardization.

Returning to Alzheimer’s original case of Auguste Deter, we find another indication that the exclusive focus on amyloid-β and tau deposits might not yield the key to understand late-onset dementia. Recent re-examination of Auguste Deter’s brain biopsy showed that she suffered from a mutation in the PSEN1 gene [29]. Mutations in this gene as well as PSEN2 and APP are commonly described in early-onset familial AD [7]. Hence, Auguste Deter was a case of a specific genetic variant of early-onset dementia. Thus, the amyloid cascade hypothesis was originally generated on the basis of the connection between genetic findings in APP and early-onset dementia [30]. As the dominant
theory of causal AD pathology is based on knowledge from historical early-onset dementia cases, where it was first found, we therefore suggest reserving the AD diagnosis for the dominantly inherited early-onset set with which it was historically associated. Late-onset dementia is then used for all other dementia cases, of which we do not yet know the etiology. What we maintain from the early history is the research attitude of Alzheimer’s, namely that of generating ‘explorative categories’ to challenge and differentiate late-onset dementia, which meant keeping the door open to novel hypotheses and thereby trigger research and innovation.

Leaving aside the reductionistic approach and embracing the complexity of the underlying pathologies, we consider late-onset dementia a ‘black box disease’ – a level playing field for all hypotheses about disease etiology. We know some of the elements going into ‘the box’ such as risk factors – age, cardiovascular disease, stroke, midlife-obesity, diabetes, the genetic APOE-ε4 allele [11]. We know what comes out of ‘the box’ – cortical atrophy, loss of memory and cognitive decline. What happens inside the box, the pathological mechanisms, is still to be illuminated and can be multiple, in several combinations and feeding into each other. Referring to the modern epidemiologist, Rothman and his conceptual framework of causes of diseases [31], late-onset dementia can best be described as the consequence of the accumulation of component causes, i.e. ‘risk factors’, and a complete set of component causes is sufficient to explain the disease. Patients diagnosed with one type of dementia do not always have the same set of underlying component causes, pointing to the heterogeneous complexity of dementia. Finally, the specific combination of component causes determines which symptoms becomes clinically apparent, a phenomenon that is recognized as different diseases share the same underlying pathophysiology. For example, problems with unfolded protein response, autophagy, inflammation, and mitochondrial dysfunction are observed in many patients, who are categorized in different age-related neurodegenerative disease clusters [32]. Dementia must be understood as a heterogeneous spectrum of complex biological systems with emergent characteristics.

4. Next steps – unfolding the ‘black box’

The suggestion to reject the amyloid cascade hypothesis as the main pathological cause of AD is by no means new, and it is widely debated whether pure AD ‘exists’ [5,6]. Yet to this day, the main focus of basic research and drug therapy in dementia is on the amyloid cascade hypothesis. Therefore, we would like to, once more, argue for the urgent redefinition of dementia. We would like to learn from both the uncertainties and successes of the history of dementia and the AD diagnosis, both by acknowledging the complex and multicausal nature of late-onset dementia as a ‘black box disease’ with several interlocking component causes, and by integrating approaches and insights from three different historical periods. Our approach to dementia is to:

I) Use exploratory categories to challenge existing notions of late-onset dementia.

In the early 20th century Alzheimer and Kraepelin used AD diagnosis with its combination of clinical representation and histopathological plaques and neurofibrillary tangles as an ‘exploratory category’ to investigate their understanding of dementia by considering unusual cases with particular care and connecting clinical and pathological observations. We suggest using this explorative attitude, but this time challenging the pathological role of plaques and neurofibrillary tangles in late-onset dementia and studying it at a level playing field along with other biomarkers and clinical observations. In this way, we want to create space and opportunity for new causal explanations and introduce other biomarkers and pathologies to disease etiology such as neuroinflammation, mitochondrial dysfunction, cerebral hypometabolism, cerebral vascular dysfunction, etc. Last, there are also social and environmental factors at play. These many theories can co-exist, because the biological mechanisms are not mutually exclusive, (partially) overlap, and may well interact, which emphasizes that the underlying pathological mechanisms of late-onset dementia are multifactorial, heterogeneous and complex. Opening up for more causal pathways also entails moving across a broader disciplinary landscape integrating different scientific fields such as epidemiology, systems biology, medicine, cellular- and molecular biology. And thus, as did Kraepelin and Alzheimer, we aim to estimate clinical prognosis anew and unravel the causal pathophysiological mechanisms.

II) Reject “normal” senility and combining a search for causal mechanisms with optimism about treatment

Until well into the 20th century, what was characterized as senile dementia was rarely regarded as pathology, but simply as part of aging itself. The relationship of ‘normal’ aging to dementia has never been adequately resolved and the debate of AD pathology revolves around interpretations of the significance of specific neuropathological changes associated with both aging and dementia. However, we wish to disentangle aging and dementia and to eliminate the concept of ‘normal’ cognitive decline and senility due to aging, as was effectively done in the 1970’s. Although we wish to sever the connection between AD and late-onset dementia, we do not take it to be part of a ‘normal’ aging’, as an age-related degenerative disease such as late-onset dementia is caused by a pathological process leading to the accumulation of permanent damages to the brain [33,34]. For Alzheimer, both presenile and senile dementia were pathological conditions; he wished that the medical community recognized that these clinically separate mental illnesses had an undeniable material reality that could be located in the brain [5]. It provides us with a window of opportunity to investigate different pathophysiological
mechanisms of cognitive impairment in old age and thereby bring us one step closer to potential drug targets and treatment for dementia.

III) Retain the ambition to standardize pathophysiological mechanisms with a view to subdivide dementia patients.

The current research definition, the AT(N) biomarker system, proposed by NIA-AA reveals the challenges in defining and standardizing AD and dementia. According to Jack et al., the distinction between neuropathologic changes and clinical symptoms in AD was becoming blurred, resulting in the term AD often being used to describe two very different entities: prototypical clinical syndromes without neuropathologic verification and AD pathology [12]. The framework was an attempt to standardize AD definition in research even though the authors acknowledged that deposits of amyloid-\(\beta\) and tau might not be causal in AD pathogenesis [12]. Consequently, the research definition of AD has become distinct from the diagnostic criteria used in general medical practice. This distinction is a hinderance for public health population and epidemiological research studies that often make use of the clinical definitions. While standardized diagnostic criteria are being discussed and developed for AD, differential diagnoses with incomplete knowledge of the underlying causes remain challenging across the dementia spectrum [9]. Focus on differential biomarker detection in the past decade creates the opportunity to stratify dementia patients and opens the door to precision medicine. Contrary to the recent approach in AD research with a focus on amyloid pathology alone, we suggest to openly study and aggregate clinical symptoms, biomarkers, and prognoses into syndromes without privileging a particular mechanism. When presenting the case with Auguste Deter, Alzheimer suggested that groups of patients with similar signs and symptoms should be subdivided into many smaller groups, by carefully correlating clinical observations and new pathological characteristics [5]. Thereby it will be possible to start anew with differentiating late-onset dementia into new patient subgroups and from here start new types of treatment testing, which in return can further define the diagnostic classification. This is aligned with the precision medicine approach, which has been suggested by others in relation to dementia [17,18,35–38].

Late-onset dementia is a devastating disease affecting millions of people, and it is urgent that we open up possibilities for investigating new disease mechanisms by severing its primary connection to AD pathology. It can seem like a step backwards to let go of the dream of a mono-causal relationship and obvious target for drug research. But more than ever, it is necessary to disentangle late-onset dementia from its historical association with AD. Instead, we follow Alzheimer’s explorative attitude to finding novel links between signs, symptoms and neuropathologies in patients who develop cognitive impairment at older age.

CRediT authorship contribution statement

Kristine F. Moseholm: Conceptualization, Writing - original draft. Karin Tybjerg: Conceptualization, Writing - review & editing. Majken K. Jensen: Writing - review & editing. Rudi G.J. Westendorp: Conceptualization, Writing - review & editing, Supervision.

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