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Drivers: A Biologically Contextualized, Cross-Inferential View of the Epidemiology of Neurodegenerative Disorders

Jesús de Pedro-Cuesta[a,b,*], Pablo Martínez-Martín[a,b], Alberto Rábano[b,c], Enrique Alcalde-Cabero[a,b], Fernando José García López[a,b], Javier Almazán-Isla[a,b], María Ruiz-Tovar[a,b], Maria-José Medrano[a], Fuencisla Avellanal[a,b], Olga Calero[b,d] and Miguel Calero[b,c,d]

[a]*Department of Applied Epidemiology, National Center for Epidemiology, Carlos III Institute of Health, Madrid, Spain*

[b]*Consortium for Biomedical Research in Neurodegenerative Diseases (CIBERNED), Madrid, Spain*

[c]*Alzheimer Disease Research Unit, CIEN Foundation, Queen Sofia Foundation Alzheimer Center, Madrid, Spain*

[d]*Chronic Disease Programme, Carlos III Institute of Health, Madrid, Spain*

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Abstract.

Background: Sutherland et al. (2011) suggested that, instead of risk factors for single neurodegenerative disorders (NDDs), there was a need to identify specific "drivers", i.e., risk factors with impact on specific deposits, such as amyloid-β, tau, or α-synuclein, acting across entities.

Objectives and Methods: Redefining drivers as "neither protein/gene- nor entity-specific features identifiable in the clinical and general epidemiology of conformational NDDs (CNDDs) as potential footprints of templating/spread/transfer mechanisms", we conducted an analysis of the epidemiology of ten CNDDs, searching for patterns.

Results: We identified seven potential drivers, each of which was shared by at least two CNDDs: 1) an age-at-exposure-related susceptibility to Creutzfeldt-Jakob disease (CJD) and several late-life CNDDs; 2) a relationship between age at onset, survival, and incidence; 3) shared genetic risk factors for CJD and late-life CNNDs; 4) partly shared personal (diagnostic, educational, behavioral, and social risk factors) predating clinical onset of late-life CNDDs; 5) two environmental risk factors, namely, surgery for sporadic CJD and amyotrophic lateral sclerosis, and *Bordetella pertussis* infection for Parkinson's disease; 6) reticulo-endothelial system stressors or general drivers (andropause or premenopausal estrogen deficiency, *APOEε*4, and vascular risk factors) for late-life CNDDs such as dementia/Alzheimer's disease, type-2 diabetes mellitus, and some sporadic cardiac and vascular degenerative diseases; and 7) a high, invariant incidence ratio of sporadic to genetic forms of mid- and late-life CNDDs, and type-2 diabetes mellitus.

Conclusion: There might be a systematic epidemiologic pattern induced by specific proteins (PrP, TDP-43, SOD1, α-synuclein, amyloid-β, tau, Langerhans islet peptide, and transthyretin) or established combinations of these.

Keywords: Amyloid, epidemiology, methods, neurodegeneration, risk factors

INTRODUCTION

It is increasingly accepted that failure in protein synthesis control, resulting in the aggregation and accumulation of misfolded proteins, and ultimately in impaired cell function and death in specific anatomical structures, characterizes a group of human disorders in

*Correspondence to: Jesús de Pedro-Cuesta, Department of Applied Epidemiology, National Center for Epidemiology, Carlos III Institute of Health, Av Monforte de Lemos 5, 28029 Madrid, Spain. E-mail: jpedro@isciii.es.

which approximately 30 different proteins are implicated [1, 2]. Among such ailments, this paper mainly concentrates on three groups of conditions: (a) those encompassing the majority of the protein-associated sporadic, conformational neurodegenerative disorders (sCNDDs), namely Alzheimer's disease (AD), late age-related macular degeneration (AMD), idiopathic Parkinson's disease (PD), Lewy body disease (LBD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), sporadic Creutzfeldt-Jakob disease (sCJD), and sporadic rapidly-progressing neurodegenerative dementia (sRPNDd); (b) some chronic vascular disorders, i.e., cerebral amyloid-β (Aβ) angiopathy (CAA), and those characterized by transthyretin deposits, associated with sporadic senile systemic amyloidosis (SSA), heart failure, and aortic aneurism; and, (c) type 2 diabetes mellitus (T2DM) [2]. These constitute examples of the group denoted as localized or organ-limited amyloid disorders, in which different, conformationally abnormal protein extracellular deposits or intracellular deposits such as fibrils, have been identified [2] (see Table 1 for a biochemical and epidemiologic outline). In the field of neurodegenerative disorders (NDDs), this expanding knowledge has recently been articulated in a new theoretical framework that incorporates two key elements, namely, one which is biochemical, i.e., pathogenic protein deposit, and the other which is anatomical and functional, i.e., neural networks [3].

In a previous report, we discussed some implications of the theoretical proposal [3] when interpreting incidence features of the abovementioned sCNDDs [4]. The aim of this paper is to group and discuss selected findings of the descriptive and analytical, general, and clinical epidemiology of sCNDDs, relevant both from the biochemical and pathophysiological perspective and for public health. A third, unpublished manuscript and end of the whole series, incorporates experimental, laboratory data supporting specific theory and two main testable hypotheses for late-life entities and disorders with onset mid-life.

METHODS

The driver concept

The rationale of our approach relies on the *driver* concept (first proposed by Sutherland et al. [5]). Bearing in mind the mixed molecular phenotype of some sCNDDs represented by the AD, PD, and FTD-ALS spectrum, and the fact that some conditions share one or more risk factors, the above authors argue that, instead of risk factors for single entities, there is a need to identify specific "drivers", i.e., risk factors or modifiers with impact on specific deposits, such as Aβ, tau, or α-synuclein, able to act across entities (i.e., history of head trauma) [5].

For the purpose of considering the presence of specific risk factors, we redefined "drivers" as "neither protein/gene- nor entity-specific epidemiologic features, i.e. time/place/person related, identifiable as potential footprints of templating/spread/transfer mechanisms, observed in the clinical and general epidemiology of several sCNDDs". Identification of potential drivers requires a targeted, in-depth review of both NDD epidemiology and the epidemiology of some essentially non-neurological, sporadic human amyloid disorders. Here we attempt an initial approach including selected entities listed in Table 1 [6–9].

We searched for epidemiologic features shared by at least two of the abovementioned disorders, supporting the view that a causally relevant "driver" or pathophysiological mechanism might underlie them. In line with the above definition, the remainder of this paper is devoted to identifying drivers and discussing their usefulness for selecting, assessing, and combining data in research populations and registries. Methodologically, we proceeded with a biologic-context-based conceptual overview of the literature on CNDDs, disregarding aspects of T2DM and vascular disease epidemiology unrelated to NDDs. We listed a potential number of drivers linking exposures to conditions, taking a life-course approach to allow for the recently analyzed influence of age at clinical onset on incidence features of CNDDs [4]. Age at onset is a variable used to facilitate research-resource identification (see "Longitudinal cohort studies in neurodegeneration research") [10].

Interpretation

On the basis of proposed drivers for sCNDDs, we outlined an epidemiologic complement to Warren et al.'s proposal for NDDs [3].

Ethics Statement

The study was based on reported data and neither animal nor human subject research was implicated. Accordingly, neither informed consent (Public Health General Law. BOE 2011, 240, Article 41.2 page 194613) nor ethical approval was required from

Table 1
Main biochemical, epidemiologic and inter-individual transmissibility features of sCNDDs and other sporadic human amyloid disorders

Entity or neuropathologically-related entities	Main protein deposit		Reported outbreaks	Annual incidence per million person-years or lesion prevalence at death*		M/F	Evidence of individual transmission
				Sporadic	Genetic		
Creutzfeldt-Jakob Disease (CJD)	APrP	vCJD	UK, Ireland, France, Spain, others	1	0.1	1.1/1	Yes
Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia	Ubiquitin, MAPT, SOD, TDP-43/FUS	ALS	Skaraborg county, Sweden [6]. US human growth hormone treated cohort [7].	10	1	1.5–2 / 1	No
Parkinson's disease and Lewy body disease	α synuclein	–	–	100	10	1.5–2.5 / 1	Yes**
Alzheimer's disease	Amyloid-β, Tau	–	–	1000	100	0.92 / 1	
Late age-related macular degeneration	EFEMP1 wild-type [8]		–	1000	Unknown	0.95 / 1	No
T2 diabetes mellitus	Langerhans Islet peptid	–	–	–	–	–	No
Sporadic cerebral amyloid angiopathy	Amyloid-β wild-type	–	–	–	–	–	
Senile systemic amyloidosis aortic aneurism	Transthyretin wild-type	–	–	–	25% ≥85y*	–	No
Medin arteriopathy [9]	Lactadherin	–	–	–	–	–	–

*Postmortem studies only. **From patients suffering from Parkinson's disease to fetal grafted cells.

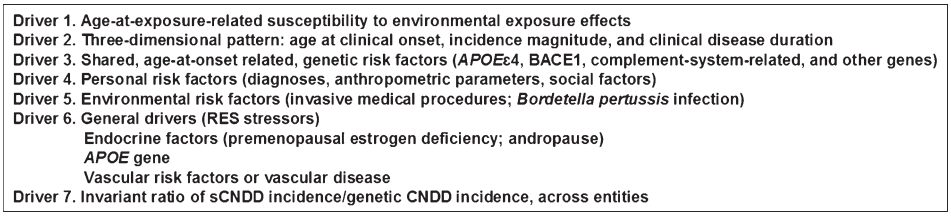

Fig. 1. Drivers proposed in this study.

the Carlos III Institute of Health Ethics Committee (*Comité de ética de la investigación y del bienestar animal*).

PROPOSED DRIVERS

See the list of seven proposed drivers in Fig. 1.

Driver 1 (D1). Age-at-exposure-related susceptibility to environmental exposure effects

Susceptibility to the effects of exposure (genetic or environmental) has been defined as the "underlying factor sufficient to make a person contract a disease following exposure" [11, 12], i.e., a precondition for causal action. While the factor determining susceptibility may be unknown, it would nonetheless appear to be partly age-related. Hence, age periods—traditionally defined and categorized as prenatal, postnatal, juvenile, and adult—constitute life-stage exposure strata that provide opportunities for experimentally or observationally detecting the presence of susceptibility by reference to a change in the stratum-specific effect measure [13, 14], i.e., relative risk.

Juvenile age at exposure to either diet containing bovine spongiform encephalopathy tissues (BSE-Diet) or treatment with human growth hormone increased the risk of variant CJD or accidentally transmitted (iatrogenic) iCJD, respectively [15–17]. High age at first-in-life whooping-cough epidemic increased risk of PD [18, 19]. Inverted V-shaped, age-at-exposure functions were suggested. Recently, a high risk of sCJD was observed for surgery undergone at ages up to 30 years, as compared to surgery undergone at ages above 31 years or non-exposure to surgery [20]. See Fig. 2 for a graphic outline [15–17, 19, 20]. This pattern, interpreted as susceptibility to exposure effects, might have diluted effect estimates in epidemiologic sCNDD research [21].

The existence of such a driver is consistent with some epidemiologic findings for other sCNDDs. For instance, smaller head size and shorter limb length associated with lower early-life socio-economic status appeared to be independent markers of risk for dementia among North Korean women [22]. The authors interpreted that these might indicate socioeconomic risk factors in childhood that affected both brain and skeletal development but were masked in men by preferential treatment of male children. A lower educational level in adulthood determined ethnic risk differences for cognitive decline or dementia [23]. Hall et al. suggested that, rather than being a risk factor of AD, low education (6 or fewer years of schooling) was a marker for associated deleterious rural socioeconomic or environmental influences in childhood [24]. Some established risk indicators, such as low educational level for AD and well water use for PD, are associated with rural residence and constitute exposures more frequent in early-life (before age 18 years) [25, 26]. These data support the contention that, as with cardiovascular disease, socioeconomic status in childhood or adolescence may constitute a risk factor for sCNDDs [27]. The presence of tauopathy, a hallmark of AD, observed in neurites as early as the second decade of life, would be consistent with an early in life induction of AD [28]. We propose that age-related susceptibility to exposure effects is a key element of an epidemiologic pattern shared by several sCNDDs.

Driver 2 (D2). Tridimensional pattern: Peak age-specific incidence (age at clinical onset), incidence magnitude, and survival (clinical disease duration)

For an outline of the tridimensional pattern, i.e., incidence, age at onset, and clinical disease duration, the reader is referred to Fig. 3 [4, 29–39], which shows data on selected sCNDDs extracted from those reported in de Pedro-Cuesta et al. [4]. The figure depicts normalized age-specific incidences, as well as selected reported age-adjusted incidences and clinical disease duration [29–31, 33, 35, 36,

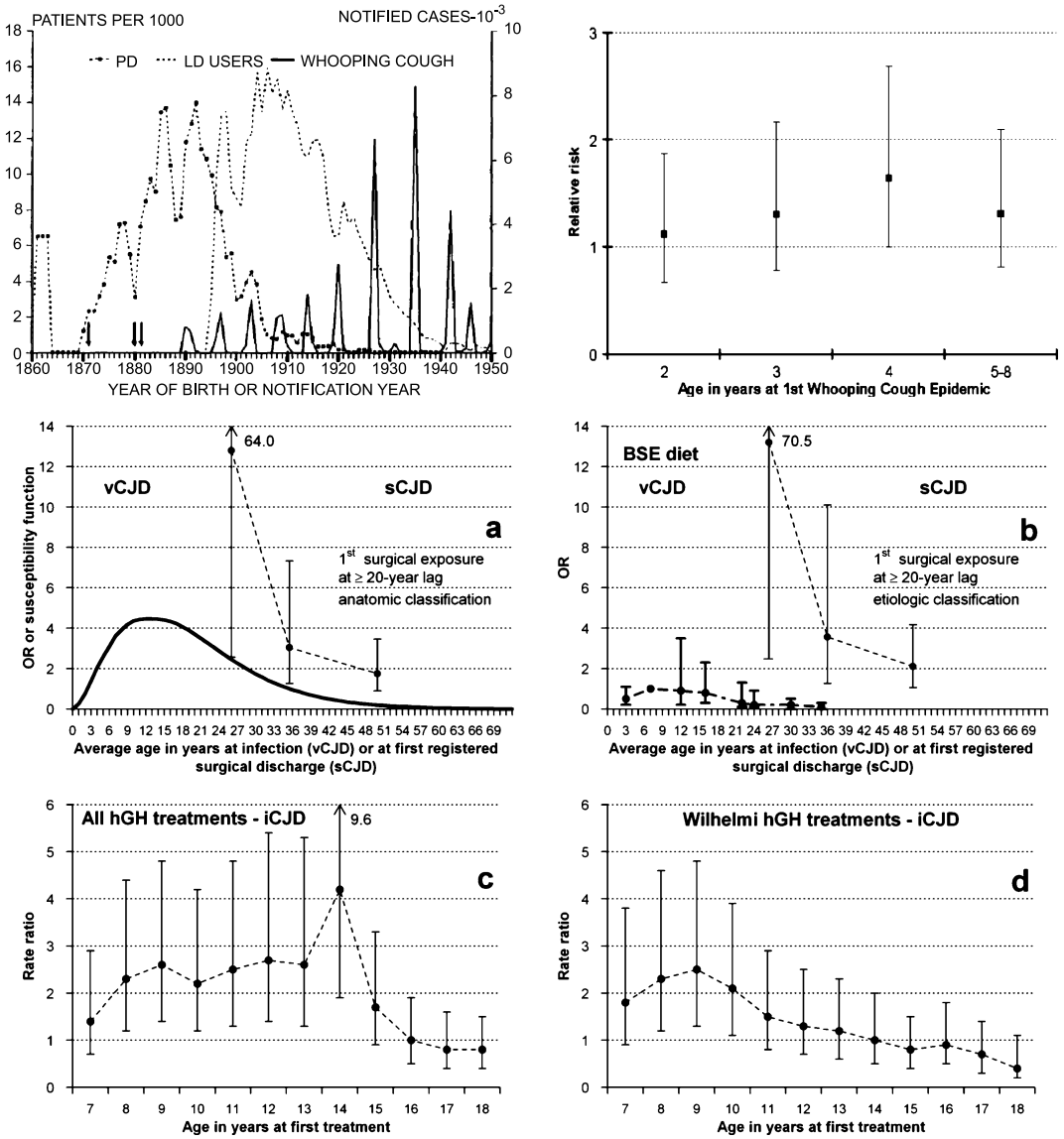

Fig. 2. Reported age-at-exposure-related patterns. (top) (left) Reported Parkinson's disease (PD) incidence and prevalence of levodopa users (left -Iceland- triennial moving averages) [19], and main whooping cough notifications in Iceland; and (right) risk of PD for lowest age at first whooping cough epidemic [19]. (bottom) (a) age-susceptibility function for variant Creutzfeldt-Jakob disease (vCJD) in the UK [15] and (b) risks after adjustment for dietary exposure to bovine material in the UK [17]; (a and b) risk of sporadic Creutzfeldt-Jakob disease (sCJD) from age at first hospital discharge associated with a registered main surgical procedure at a lag of $\geq$20 years, using an anatomical and etiologic classification [20]; and, (c and d) age at first treatment with pituitary growth hormone with the Hartree-modified Wilhelmi method and accidentally transmitted Creutzfeldt-Jakob disease (iCJD) [16].

38–40], suggesting that for sCJD, ALS, FTD, PD, LBD, AD, and AMD, there is a direct correlation between age at highest or peaking age-specific incidence (range 77.5 to $\geq$95 years), median clinical disease duration (range 0.4 to 8.9 years), and age-adjusted incidence (range $\leq$1.5–2589 $\times$ million person-years). The driver defined by "a tridimensional correlate of incidence magnitude, age at onset, and clinical course duration" can be simplified in ordinal terms as incidence spanning 1–1000 (1 for sCJD, 10 for ALS, 100 for PD, 1000 for AD and AMD), median age at onset ranging from almost 70 years for sCJD to 80 years at first visit for AD, and disease duration ranging from <1 year for sCJD to almost 10 years for PD. The pattern can be summarized using the driver notion in four parameters,

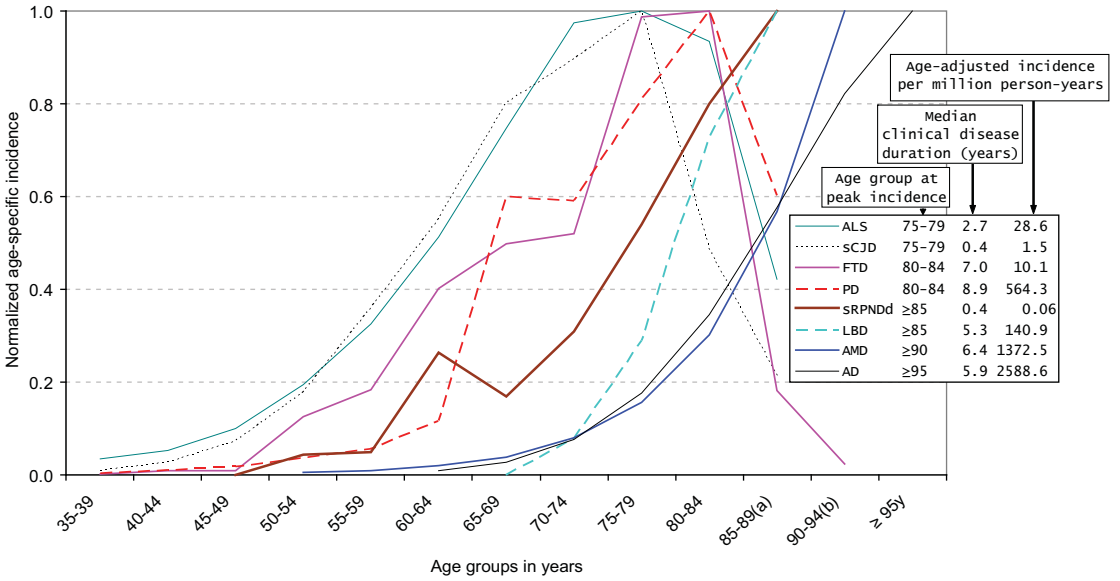

Fig. 3. Normalized age-specific incidence, incidence per million, and survival for selected neurodegenerative disorders. Modified from de Pedro-Cuesta et al. [4]. Normalized age-specific incidence, age-adjusted incidence, and median clinical disease duration of different sporadic protein-associated neurodegenerative disorders (sCNDDs), obtained either from reported data (amyotrophic lateral sclerosis (ALS), personally modified by Fang F, sporadic Creutzfeldt-Jakob disease (sCJD)) or from registries [rapid progressive neurodegenerative dementia (sRPNDd) notified as suspected sCJD in Spain for 1995–2011, obtained from the Spanish CJD surveillance registry]. References for Fig. 3 [29–39]. (a) 85–89 years is equivalent to 85 years and older for sCJD, ALS, Lewy body disease (LBD), Parkinson's disease (PD), and sRPNDd; (b) 90–94 years is equivalent to 90 years and older for age-related macular degeneration (AMD) and frontotemporal dementia (FTD).

i.e., age at onset and age at death, both measured in general and clinical populations.

Driver 2 is most relevant when combined with driver 1. Firstly, this is because it may define life-course references for subclinical disease or clinical progress, i.e., how templating and self-propagation is phenotypically manifested. Secondly, the notion that early- versus late-life onset corresponds to rapidly versus slowly progressive and to short versus long clinical-course duration is not difficult to reconcile with views from neuropathology on neurodegeneration progression or cell-to-cell spread, particularly in late-life NDDs [41]. Thirdly, the fact that high sCNDD incidence requires late onset may suggest that ubiquitous or widespread, tiny exposures correspond to high attack rates and lifetime risks.

Driver 3 (D3). Shared, age-at-onset-related, genetic risk factors (APOEε4, BACE1, complement-system-related, and other genes)

Mutations and common polymorphisms constitute biologically similar variations in the human genome determining CNDDs. The most common pattern linking genetic variations to CNDDs is where a number of different mutations in the same or different genes determine similar familial CNDD forms. A considerable number of mutations have been described for PD [42]. However, only a few of these result in α-synuclein deposits, a feature of Lewy body lesions in PD [43]. Mutations in the Cu/Zn superoxide dismutase (SOD) gene, the FUS/TLS gene, the TDP-43 gene and, in particular, GGGGCC (G4C2) repeat expansion in the C9orf72 gene have been seen in ALS, and the latter two and the MAPT gene in FTD [44–46]. Conversely, albeit infrequently, point mutations are present in cases with different phenotypes. For instance, in human prion diseases, mutations at codon 178 of the PRNP gene have been described as generating pathologically confirmed cases of either CJD or fatal familial insomnia, depending on codon 129 status on the same allele containing the mutation [47]. In other instances, the disease phenotype appears to uncover a similar abnormal protein deposit, with the cellular subsystem being the determinant for clinical expression as cerebellar ataxia or ALS [48–51]. Mutations at different codons of the *PRNP* gene were identified in neuropathologically different forms of CJD or AD, with deposits of PrP or Aβ, respectively [52]. For the purposes of

driver identification, some polymorphisms determining excess risk shared by sCNDDs are paramount, i.e., *APOEε*4, BACE1, and those related to the complement system [53–56].

APOEε4

Recent reports have repeatedly indicated that *APOEε*4 is a shared genetic risk polymorphism for AD, LBD, and sCJD [53, 54, 57], for mild cognitive impairment (MCI), LBD, and vascular dementia (VaD), and for dementia in PD but not PD itself [5, 58–60]. From a genetic standpoint, AD is considered to be heterogeneous, with *APOEε*4 constituting a risk factor for the most frequent AD form able to account for 50% of the etiologic fraction [53]. Moreover, it is well established that the *APOEε*4 allele and homozygosity at polymorphic codon 129 in the *PRNP* gene are the major genetic risk factors for AD and human prion diseases, respectively [54]. A synergistic age-dependent interaction was seen between *APOE* and *PRNP* in both AD and sCJD, suggesting shared genetic factors paving the way for shared genetic susceptibility to environmental causes [54].

BACE1

The β-site AβPP cleaving enzyme 1 (BACE1) appears to be the rate-limiting β-secretase enzyme in the amyloidogenic processing of AβPP and Aβ formation, and thus plays a prominent role in AD pathology. Recent evidence suggests that the PrP protein interacts directly with BACE1, regulating its β-secretase activity. The *BACE1* rs638405 C-allele is associated with an increased risk of developing both sCJD [61] and sporadic AD [62].

Complement-system-related genes

Multiple genetic risk factors related to the complement system have been associated with AMD (see references [58] and [63] for recent reviews). For example, the functional polymorphism rs2230199 in the complement C3 gene was linked to AMD [64]. In contrast, modest associations between such genes and AD were seen, and their direction and genetic model differed from that observed for AMD [65].

Other genetic factors

Shared genetic factors for PD and other selected NDDs are not common. Genome-wide association studies suggest that SNCA and LRRK2 polymorphisms constitute modest risk factors for PD [66–68], and that PD variants around the 17q21 are associated with gene expression suggestive of AD risk [69]. The H2 variant in the MATP (tau) gene is protective for PD [70]. C9orf72 expansion (G4C2 repeats) was strongly associated with ALS and FTD, though not with AD or PD [71]. The opposite effects of *APOEε*4 and *APOEε*2 in AD and AMD, i.e., *APOEε*2, protective for AD and causal for AMD, and *APOEε*4, causal for AD and protective for AMD, are well established [58]. Clusterin and PICALM (phosphatidylinositol binding clathrin assembly protein) behave as different risk factors for AMD and AD [58].

Genetic exposures might constitute the paradigm of the driver notion in NDDs. The idea of a univocal correspondence between genes and entities has long been abandoned. Here evidence is gathered on three genes, *APOEε*4, BACE1, and *PRNP*, which, separately or by interaction, cause the risk of several sCNDDs to increase, e.g., AD, CJD, LBD, and, probably mediated by serum lipids, atherosclerosis [72, 73]. Positive findings in sCJD for CALHM1-3 and BACE-1 polymorphisms underscore the interplay among AβPP, Aβ oligomers, *APOE*, PrP, and BACE1 in sCJD and AD, and suggest that aging, and perhaps vascular risk factors (VRF), may partly modulate disease pathologies through these key players [61, 74]. It would appear that a few genes, *APOE* and *PRNP*, constitute a driver for entities with midlife and late-life onset, with CJD, LBD, and AD constituting a genetically differentiated group.

Driver 4 (D4). Personal risk factors (diagnoses, anthropometric parameters, social factors)

Personal factors encompass a set of multiple variables, such as clinical signs and symptoms (i.e., diagnoses), behavioral patterns (i.e., health-related habits), and educational factors, which constitute the group of best-established associations with specific sCNDDs. A large number of these have been studied. Associations with multiple personal variables have been found for NDDs exhibiting peak incidences at very similar ages, e.g., PD and LBD [75]. Recently, a case-control study on LBD concluded that the risk factors were an amalgam of those described for PD and AD [59]: many of them (history of depression, educational level) were personal variables.

Diagnoses

Perhaps the first variable to be considered is a second sCNDD diagnosis. For instance, PD is associated with AD [76], and essential tremor is associated with increased risks of both PD and AD [77]. The inverse overall co-occurrence of cancer in patients with either

AD or PD, shown by a recent meta-analysis of 50 studies, is consistent with a lower exposure to environmental carcinogens in early decades of life, i.e., due to rural residence [78].

Vascular risk factors

The concept of VRF of sCNDDs encompasses different forms of high blood pressure (HBP), dyslipidemia, obesity, T2DM, physical inactivity, hypothyroidism, and vascular diseases such as coronary disease, stroke, or heart failure. In all probability, the liveliest debate in the context of personal risk factors for NDDs turns on VRF. This in part may be due the association being masked by study designs' sensitivity to bias: (a) selection secondary to impact of vascular disease on taxonomy, e.g., for vascular or mixed dementia or for vascular parkinsonism [79]; (b) use of hospital controls, as seen in sCJD studies [80], and; (c) exposure measurement after clinical onset, i.e., arterial hypertension in PD, LBD, and hereditary dysautonomy, NDDs which may result in vascular pathology or dysregulation. Finally, non-causal interpretations of positive associations can be reconciled with etiologic mechanisms acting on the vascular wall decades before neurological and vascular symptom onset for single disorders (see reference [81] for a discussion on VRF preceding sCJD onset) or shared by, say, AD and sCJD (see driver 6). Bearing such problems in mind, a brief overview now follows.

Little is known about VRF for sporadic ALS, FTD, and PD. Controversial results are reported for VRF and risk of ALS (see a review by Hardiman [82]), and for T2DM and risk of PD, with both positive [83] and negative findings [84, 85]. No cardiovascular risk factors, including *APOEε*4 [86] and hypertension [87], have been reported for PD, whereas the protective factor of smoking—a risk factor for AD, at least in *APOEε*4 carriers—has been well established (see Sutherland et al. [5] for a review). Risk of FTD from T2DM increases twofold [88]. When compared with AD and vascular parkinsonism, both FTD and PD had a lower prevalence of VRF (systolic blood pressure and *APOEε*4 allele) [79, 89].

VRF associations have traditionally been reported for dementia and AD. For instance, with regard to late-life AD, this association has been established for high midlife systolic blood pressure, elevated midlife total cholesterol, the *APOEε*4 allele [90], and T2DM [90]. Microvascular brain lesions as well as VRF underlie vascular dementia and mixed (vascular and AD) dementia [91, 92]. Obesity, arteriosclerosis, diabetes, hypertension, and hypercholesterolemia predispose to AMD [93–95]. However, a recent meta-analysis still casts doubts on links between hypertension and incident AD [96], and some reports (see Kravitz et al. [97] for a review) question its value for dementia with onset after age 90 years. A review of method- and quality-stratified studies on VRF and AD by Chui et al. concluded that VRF predicted vascular pathology linked to dementia rather than determining plaques and tangles, with such associations being attributed to selection [98]. Coronary artery disease is associated with AD neuropathology in *APOEε*4 carriers [99]. We described a significantly high frequency of coronary surgery during the ten years preceding clinical onset of sCJD [100].

In brief, various VRF, including hypertension and hypercholesterolemia in particular, have been found to be directly associated with AD and AMD, while coronary disease has been found to be associated with AD-*APOEε*4 carriers and coronary surgery with sCJD. One of these, smoking habit, has repeatedly been found to be negatively associated with PD.

Vascular disorders and proteinopathies

Discussion on VRF and NDDs largely preceded recent knowledge of proteinopathies. Similar misfolded protein deposits in nervous system and vascular structures, i.e., Aβ in AD [101, 102] and APrP in sCJD [103], challenge the concept of such entities as organ-limited amyloidoses, and suggest that some factors or a proportion of the excess vascular risk, well known for AD, might be attributable to the vasculopathy that precedes clinical expression of central nervous system lesions [104]. Therefore, associations between coronary surgery and sCJD [100], and coronary surgery and AD pathology in *APOEε*4 carriers [99] might correspond to vascular comorbidity potentially determined by similar or different causes in sCJD and AD acting at long latency periods. Furthermore, the fact that Aβ vasculopathy in neurodegenerative dementia appears to be linked to AD pathology, that a large majority of AD patients present with Aβ vasculopathy, and that AD and sCJD share genetic predictors [54, 61, 74] may support the view that there is a conformational protein-related vasculopathy in both AD and sCJD, partially accounting for the associations between vascular risk factors and each of the two disorders. To sum up, all the above indicates that there might be biologically shared mechanisms of misfolded protein accumulation in the brain and the vascular wall, affecting Aβ, PrP, and a few other proteins and, to a less clear degree, α-synuclein.

In addition, the fact that T2DM is classified within the group of disorders presenting similar pathologic toxic deposits of misfolded proteins [105–107] adds evidence for existing, albeit complex, links between T2DM, angiopathy, and sCNDDs, and motivates the section below on General Drivers. It would appear that the driver concept proposed for etiologic inference in the field of shared risk-factor epidemiology [5], may be expanded to cover a proportion of vascular disease and, to a possibly different extent, selected sCNDDs, particularly sCJD, sRPNDd, LBD, AD, and AMD, entities in which a small vessel vasculopathy of the brain or retina have been described. The *driver* concept might provide a rationale for prevention, complementing, insofar as dementia is concerned, strategies aimed at promoting healthy lifestyles, e.g., by multi-domain interventions [108].

Driver 5 (D5). Environmental risk factors (invasive medical procedures; Bordetella pertussis infection)

Despite intensive efforts, environmental factors continue to be an elusive research field for sCNDDs. For instance, although higher exposure to or use of agrochemicals (herbicides, fertilizers, pesticides, and solvents) has been described as being linked to AD, PD, ALS, etc. [109], not a single chemical product has ever been unequivocally identified as a risk factor for AD, PD, or ALS, mainly due to poor measurements of exposure [110, 111]. Head trauma, has been singled out by Sutherland et al. as a pluripotential risk factor for several sCNDDs, and therefore proposed as a driver valid for AD, PD, and other disorders [5]. We will focus on two other drivers, namely, invasive medical procedures and, bearing recent findings in amyloid research in mind, infection.

Invasive medical procedures (surgery and blood transfusion)

Neurosurgery has been linked to CJD after a few reports on the use of instruments potentially contaminated by surgery on a CJD patient, and an experimental study based on one such report, focusing on re-used electrodes. However, this association has never been demonstrated in epidemiologic controlled studies. In contrast, a number of associations and epidemiologic features potentially underlying or masking surgery as a risk factor have been reported for sCJD and ALS. There is increasing epidemiologic evidence of significant etiologic links: in the case of sCJD, to history of general surgery [100] with long incubation periods [100, 112], and to surgery of the retina and peripheral nerves after shorter incubation intervals [112]; and in the case of ALS, to cervical compression with and without spinal surgery [113], and to occupations with high levels of physical activity [114, 115], e.g., Italian football players [116]. Whether surgical history might underlie reported associations with agricultural or non-specialized work [117], war veterans [118, 119], history of cranial or other trauma [120, 121], or history of repeated or severe trauma [122], is a matter of speculation, yet it cannot be ignored. Since none of the abovementioned approaches to studying associations between medical procedures and ALS used latency analysis, the results suggest that surgery as a risk factor for ALS may have confounded some of the reported associations. The role of surgical history in sRPNDd, PD, or AD has not been explored in depth [123].

A recent review has shown inconsistent results for blood transfusion as a potential risk factor for sCJD after a 10-year lag [80]. Blood transfusion was not linked to AD [124], and its link with PD and sRPNDd has probably not been well studied [123]. The abovementioned, recently reported significant excess risk for motor neurone disease (3 cases) in a cohort of human growth hormone recipients opens up the question of accidental transmission of ALS [7]. All the above suggests that invasive medical procedures followed by a considerable lag may constitute D5 drivers for mid-life sCNNDs.

Bordetella pertussis (BP) infection

The association between age at first major whooping cough outbreak and PD constitutes a single observation in Iceland, reinforced by negative results for birth-cohort effects in continental populations. Considered as a natural quasi-experiment, it is consistent with the high prevalence and incidence of PD among the Färoe Islanders and Greenland Inuit reported from direct surveys [125, 126]. While the excess risk of PD as a long-term biological effect of BP infection was attributed to Pertussis toxin [19], there is recent evidence to propose prion-like mechanisms. For instance: (a) PD shares protein deposits (see Sutherland et al. [5] for a review) with LBD and AD, BP; (b) amyloidosis by various amyloid fibrils is best induced by mouse AApoAII(C) amyloid [127] and A amyloidosis in mice was enhanced by cross seeding curli of *Escherichia coli* (a human adapted pathogen like BP) [128]; and, (c) multiple

system atrophy, an α-synucleinopathy, has recently been transmitted in cell and mouse models [129].

To sum up, host-adapted human pathogens such as BP might constitute D5 drivers for PD, LBD, and AD and other late-life sCNDDs induced by infection in genetically susceptible young individuals. Invasive procedures sharing similar mechanisms might be proposed for sCJD, ALS and sRCNDd.

Driver 6 (D6). General drivers.
Reticuloendotelial system (RES) stressors:
1) Endocrine factors (premenopausal estrogen deficiency; andropause); 2) APOE gene;
3) Vascular risk factors and vascular disease

We define general drivers as any driver, whether personal, environmental, or genetic, which, in accordance with (a) the theory attributing protein misfolding, aggregation, and deposit to an RES dysfunction [105, 107], and (b) the molecular nexopathy expanded paradigm, exhibits associations with variables related to onset and progression of different sCNDDs or entities of the amyloid spectrum [130]. We perceive three fields in which general drivers might be manifested: endocrine factors; the *APOE* gene; and risk factors or progression biomarkers potentially reflecting extraneuronal amyloid deposits in vascular wall and pancreas.

Endocrine factors

An as yet incomplete association array may be structured around the two axes, i.e., premenopausal estrogen deficiency and testosterone deficiency.

Premenopausal estrogen deficiency

From single studies and recent reviews on the interplay between natural or surgical menopause, oophorectomy, and hormonal therapies, and its potential impact on vascular risk [131] and dementia [132], it might be pointed out: (a) that bilateral oophorectomy not followed by post-menopausal estrogen therapy doubled the risk of coronary disease (two cohort studies) [133] and of cognitive decline or dementia [134]; and, (b) in the Danish national population, premenopausal bilateral oophorectomy doubled the risk of dementia, with this risk increasing with younger age at surgery [135]. In two US populations, age at surgical menopause was associated with a faster decline in global cognition, and in the case of the sample studied postmortem, was associated with AD neuritic plaque burden [136]. When controlling for estrogen therapy, analyses in most studies [133, 134, 136] indicate either an absence of associations, or associations that are in part mediated. Despite the fact that not all studies support the excess risk for cardiovascular conditions [137], premenopausal oophorectomy might illustrate the existence of drivers shared by NDDs and vascular disease.

Andropause

The combination of short androgen receptor CAG alleles with lower levels of serum testosterone increased the risk of AD in men fourfold [138]. A second line of observations linking andropause to AD and T2DM was recently reviewed [139]. Low testosterone precedes cognitive [140] and neuropathologic [141, 142] diagnoses of AD, suggesting a direct causal role in AD. Additionally, low testosterone levels predict metabolic syndrome, preceding the onset of metabolic and cardiovascular symptoms by 5–10 years [143, 144], and testosterone depletion due to prostate cancer therapy increases the incidence and prevalence of T2DM [145, 146].

The fact that estrogen and testosterone deprivation at a certain age might result in increased risk of AD, coronary disease, and T2DM would support the view that modest associations among these entities might be partly due to confounding.

APOE gene

The *APOEε*4 allele has been described as one of the genetic risk factors for different sCNDDs, namely, AD and sCJD (see Driver 4). Nevertheless, it must also be considered as a *general* driver, since many other associations with it as a predictor of sCNDD progression or as a risk factor for potentially conformational disorders have been described. For instance, the *APOEε*4 allele was found to be a risk factor: for VaD and mixed dementia [147]; for AMD, AD, and VaD [148]; for LBD, pure Lewy body dementia, and dementia in PD [57]; for amnestic MCI [149]; for dementia in PD; and, interacting with *PRNP*, for late-onset sCJD [54]. The *APOEε*4 allele predicts conversion from MCI to AD [148] as well as microbleeds in AD [150]. On the one hand, the *APOEε*4 allele has been shown to constitute a risk factor for death from coronary heart disease [151], and a risk factor for T2DM with and without coronary artery disease [152]. However, a large-sized prospective study failed to show an association between *APOEε*4 and risk of coronary heart disease, after a mean follow-up of 11 years [153]. It is possible that the *APOEε*4 allele effect in coronary heart disease

or T2DM may require a longer latency, as seen for late-life NDDs. The *APOEε*4 allele, whether alone or interacting with other cholesterol genes, affects memory [154]. On the other hand, a role for the *APOEε*4 allele in T2DM and AD is recognized, since the presence of *APOEε*4 allele in T2DM patients raises the risk of AD [155]; and in T2DM patients with AD, *APOEε*4 is associated with increased neurofibrillary tangles, amyloid plaques, and CAA [156]. In brief, the *APOEε*4 allele, in addition to constituting a driver shared by AD and CJD, may play a wider role in determining risks of T2DM and vascular disease.

Vascular risk factors and vascular disease

An arteriosclerotic disease indicator for AD [157], midlife untreated high diastolic blood pressure and high systolic blood pressure for AD and VaD, respectively, in the Honolulu study [158], or the set of high body mass index, blood pressure, serum cholesterol, or impaired glucose regulation in midlife for AD [90], constitute examples of multiple VRF associations. On the other hand, VRF have been associated with conversion from MCI to dementia [148] and have predicted natural history patterns from normal cognition to dementia [159]. Other examples include: (a) white matter hyperintensities and conversion from MCI to dementia; (b) T2DM, carotid stenosis, HBP, white matter lesions, a VRF score, and vascular disease scores and conversion from MCI to dementia [160, 161]; and, (c) untreated arterial hypertension, cholesterol, and diabetes and conversion from MCI to AD [162]. When examined from a different, possibly statistically unopposed view, obesity, metabolic syndrome, and T2DM not only contribute to impaired cognitive function, but also increase the risk of AD [139].

Drawing on Finnish studies on the prevalence at death of biochemically characterized vascular lesions, two highly frequent, unassociated angiopathies, SSA and CAA (linked to wild-type transthyretin deposit and heart failure/myocardial infarction, and associated with Aβ, dementia, or AD, respectively), illustrate different mechanisms underlying atherosclerosis among the very old [163–165].

To sum up, VRF constitute a complex array of exposures or vascular effects of exposures, and some VRF constitute a complex group of elements acting midlife as risk factors for—and, at a later stage, as confounding and competing risk associations with—a number of dementing NDDs, and with AD and mixed dementia in particular. The failure of controlled experiments to prevent AD through targeting major cardiovascular risk factors (e.g., using antihypertensive drugs, lowering cholesterol, and anti-inflammatory therapies reviewed by Qiu [166]), despite imaging and other evidence suggesting a role for VRF in dementia, would support the view that translation of NDD proteomics to epidemiologic research is required. We outline an incomplete epidemiologic/etiologic scenario where different amyloid deposits (wild-type transthyretin, lactadherin, and Aβ), sometimes shared by sCNDDs, vascular disorders, and a number of endocrine entities or functions, might determine late-life human pathology. The complex D6 might thus represent the puzzle resulting from the multiple effects of RES stressors.

Driver 7 (D7). Invariant ratio of sCNDD incidence/genetic CNDD incidence, across entities

Some authors have given special attention, early as well as recently, to the invariant ratio of sporadic to genetic sCNDD forms [167]. This ratio would correspond to the inverse value of the proportion of genetic forms in CJD, MND, PD, and AD in community-based case series including sporadic and familial/genetic forms, usually reported to range from approximately 10% to 20%, amounting to a four- to ninefold higher number of sporadic than familial cases [168]. Incidence, as a proxy mortality-based figure of purely familial/genetic forms, has been reported for PrP-related NDDs [169]. The expected annual incidence range of genetic CNDD forms corresponding to the sCNDD forms in Fig. 2 would be approximately 0.1–100 per million.

Maturity-onset diabetes of the young (MODY) and autosomal dominant, early-onset T2DM unlinked to known MODY genes (MODY gene-negative families) constitute more than 5% of all cases of T2DM [170]. The most common form of CAA is due to Aβ deposition, which occurs sporadically in the elderly or in association with AD [171]. Aβ-CAA may also be prominent in variants of familial AD, with mutations of the AβPP, presenilin-1 (PSEN1) or presenilin-2 (PSEN2) genes. Other familial CAA forms present protein deposits different from Aβ. Hereditary forms of CAA constitute a non-negligible proportion of both AD and sCAA. Familial forms of retinal atrophy have been traditionally described as retinal dystrophies. Mutations have been described in the *EFMP1*, *SEMA4A*, and other genes [172], with the deposit being semaphorin. More than one hundred mutations have been described in the transthyretin

gene [173]. In essence, driver 7 appears to be shared by sCNDDs, T2DM, and a substantial proportion of atherosclerosis lesions represented by angiopathies resulting from protein elimination failure.

Despite the fact that the invariant ratio of genetic/sporadic cases across entities has not been formally studied and that observations rely on case series or unrefined figures, this type of ecological observation (absent or rare in some entities, such as Huntington's disease) warrants detailed attention: phenotypical similarities between genetic and sporadic forms are evident. An etiologic link between the genetic and sporadic forms would require the presence of vectors of transferred human pathologic genetic material from human ancestors resulting in prion-like processes driven by human adapted organisms. A tantalizing field of knowledge anticipating the role of driver 7 in sCNDDs and other conformational disorders is horizontal gene transfer from human to prokaryotic and other human pathogens, which constituted a major force in prokaryotic evolution [174] perceived at an early stage [175]. The final step would require the presence of infectious natural protein aggregates resulting from human transferred active sequences, acting as inoculum able to cross the species barrier back to the original human source.

SUGGESTIONS FROM NDD EPIDEMIOLOGY

Neuroepidemiologic knowledge in the field of NDDs is ultimately a form of biological interpretation of the findings yielded by social science (i.e., population) research, currently in its initial stages. Relations may emerge that will erase the limits of the initial outline. Here a number of sCNDDs have been selected, though the number of entities to be included for inference remains open. For instance, one may consider the appropriateness of AMD, generally neglected when discussing NDDs. Similarly, a number of relationships or elements have to be proposed in order to define the boundaries of such knowledge. Arguably, analysis of epidemiologic events will never be definitive or absolutely valid. The proposal set forth here should be useful for designing non-experimental research aimed at testing the epidemiologic dimensions of an expanded NDD paradigm [3], thereby providing reoriented cumulative knowledge. Traditional work on the epidemiology of NDD clinical entities may benefit from the proposed biochemical perspective, by providing a more stable structure, i.e., in Foucault's terminology, "*from the tangled mass of discontinuities to the great, uninterrupted unities*" [176]. The above observations may suggest that the traditionally accepted epidemiologic traits of single NDDs need to be revised toward the epidemiology of a continuum, and redefined by including links with T2DM and atherosclerosis. On the basis of our recently systematic incidence review [4] and this analysis, we propose that:

1) Incidence of single sCNDDs in the general population increases with age at onset.
2) Age-specific incidence of single sCNDDs increases with age at onset following an inverted V-shaped function, only in part perceived for late-life sCNDDs.
3) Normalized age-specific incidences of acquired CNDDs and sCNDDs follow an age-at-onset (peak incidence) and protein-related pattern. Differences for the same protein, i.e., for CJD, would reflect different causal mechanisms or protein strain.
4) Environmental risk factors may preferably act when exposed at infantile and juvenile ages or in early adulthood through being mediated by genes and shared susceptibility to effects.
5) Not being entity-specific, genetic risk factors for sCNDDs do not systematically refer to genes affected in the corresponding genetic form.
6) Risk factors and preclinical or clinical biomarkers of disease progression may correspond -albeit not systematically- to the same parameter, i.e., genes, and determine incidence as well as progression of subclinical and clinical course.
7) Age determines risk as a result of age at exposure, age-related susceptibility, and latency.
8) Sex is a risk modifier for specific sCNDDs. Some endocrine drivers may be sex- and age-at-onset specific, i.e., for late-life NDDs. The male versus female sex incidence ratio for different late-life sCNDDs may vary reflecting occupation, endocrine, and other factors. Endocrine disorders might also constitute genuine endocrine proteinopathies, such as T2DM sharing biological RES pathophysiological mechanisms.
9) Etiologic or pathophysiological mechanisms may be shared by different proteinopathies, including sCNDDs. Consequently, prevention strategies might be shared, not only for NDDs

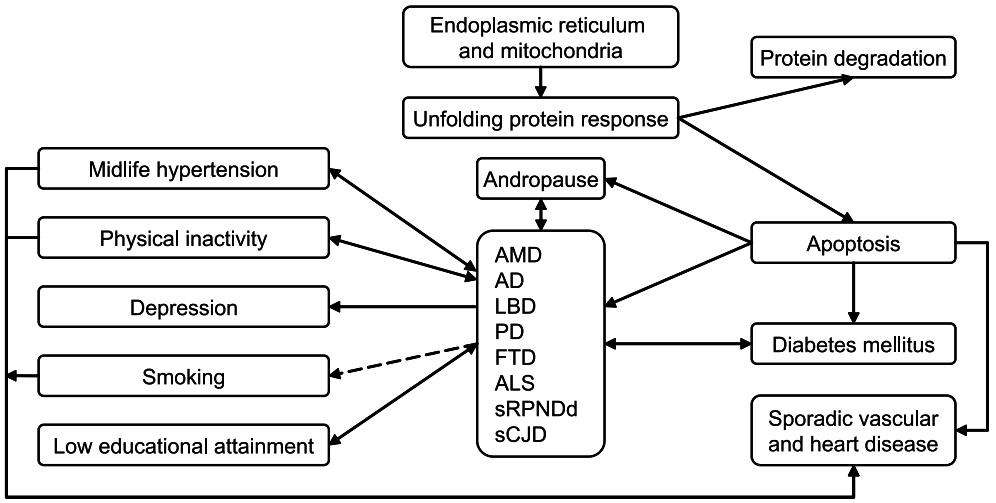

Fig. 4. Outline of an epidemiologic model for sCNDDs on the basis of drivers. Here we assume that there is an age-at-onset-related continuum for various late-age neurodegenerative disorders, and that the unfolded protein response explains, at least in part, the reported associations for diverse conformational neurodegenerative, vascular degenerative, and metabolic (T2DM) disorders. Arrows represent different potential types of associations, i.e., inverse (dashed line), bidirectional, etc.

and mixed NDD forms, but also for T2DM and a proportion of atherosclerotic lesions.

10) Control of vascular risk factors may or may not determine sCNDD prevention. The causal weight of selected vascular risk factors in sCNDDs would require reassessment.
11) The present view of sCNDDs reinforces the notion of a set of neurodegenerative processes in which continuity as a form of overlap, and competition—with earlier and more lethal NDDs, T2DM, or vascular disease, removing persons at high risk of other less lethal NDDs—act on the age axis. Potential chronic RES stressors, i.e., obesity, may have acted simultaneously on different target cells.
12) Should early-age susceptibility drivers be present in sCNDDs with long latency periods, this may imply that there could be a short lifetime for primary, and a protracted lifetime for secondary sCNDD prevention.

As a summary outline, we propose the epidemiologic model shown in Fig. 4. Accordingly, we would give particular consideration to research lines, such as: (a) well-assessed incidence studies on sRPNDd, FTD, and LBD, supported where possible by postmortem biochemical analysis; (b) incidence and analytical studies of combined forms, such as MND + FTD, in the same population; (c) taxonomy-oriented studies facilitating a converging, interrelated view of sCNDDs, likely within the field of organ-limited amyloidoses, e.g., sRPNDd, including sCJD and vascular dementia; (d) studies on environmental factors, where epistasis with selected genes and epigenetic aspects can be explored; (e) targeted cohort availability and resource access [10], despite the fact that diagnostic criteria, and exposure variables may not have been well defined at baseline; and, (f) studies on specific causal hypotheses, supported where possible by experimental data, requiring tailored combinations of cohorts and registries for testing.

CONCLUSION

There might be a systematic epidemiologic pattern induced by specific proteins (PrP, TDP-43, SOD1, α-synuclein, Aβ, tau, Langerhans islet peptide, and transthyretin) or established combinations of these, as a result of molecular templating. New biologic paradigms proposed for CNDDs may encompass other organ-limited disorders associated with amyloid deposits.

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