

## Cross-Fertilization of Studies in Neurodegeneration

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Chen et al. [1] demonstrated that curli (a natural bacterial amyloid fibril) expressed by many Enterobacteriaceae, including *E. coli*, was capable of enhancing alpha-synuclein (AS) aggregation in both aged rats and the nematode *C. elegans* overexpressing alpha-synuclein. They suggested that amyloid proteins in the microbiota might be involved in the triggering of neurodegenerative diseases [1]. In this letter, we wish to draw attention to the wide potential for reciprocal fertilization of experimental and observational research in organ-limited amyloid disorders. By way of reference, we take our recent review on the epidemiology of different conformational neurodegenerative disorders (CNDD) undertaken from a biological perspective, which incorporated descriptive and analytical elements of both the general and clinical epidemiology of CNDD [2].

Chen et al. [1] conclude that bacterial amyloid can transmit amyloid conformation to AS at distant places by cross-seeding (the process whereby an amyloidogenic protein, such as curli, causes another to adopt a beta-sheet structure). Moreover, they suggest that protein misfolding in neurodegenerative disorders may be triggered by cross-seeding through exposure to exogenous microbial amyloids in the nose, mouth, and gut. The rationale of these experiments can be ascribed to a wider etiological framework, where the accumulation in the brain of diverse pathogenic aggregated amyloid proteins with prion-like properties plays an early central role in the development of different neurodegenerative disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and other ailments. This molecular view is in sharp contrast to our review's most illustrative finding, which corresponded to the update of the driver concept 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 conformational disorders". Here, we briefly discuss three of these drivers (following the original description and numbering) [2] in relation to the findings of Chen et al. [1].

Driver 1 is defined as age-at-exposure-related susceptibility to environmental exposure effects. Low age at exposure and an inverted V-shaped susceptibility function are supported by epidemiologic observations of childhood age at whooping cough epidemics and PD in Iceland, Creutzfeldt-Jakob disease accidentally transmitted by growth-hormone treatment, and dietary exposure to bovine spongiform encephalopathy, as well as age at surgery and risk of sporadic CJD at least 20 years later. The relevance of driver 1 for PD and AD is supported by multiple experimental data relating to: (a) the potential host-to-graft induction of AS degeneration from patients diagnosed with PD who received tissue grafts, and disease induction by seeding in the AS and tau mouse models [3,4]; (b) the age-at-exposure-related effect on neurodegeneration induced by neurotropic agents [5,6]; (c) the fact that intracerebral injection of brain extracts containing aggregated AS into young AS-transgenic mice stimulates the formation of AS lesions in the host [7]; and, (d) a similar feature displayed by the male-mouse castration model of PD, which is only efficient when castration is performed on 4-6 week old mice [8]. With regard to this driver, we wonder whether the authors explored a similar experimental approach with younger rats exposed to *E. coli* curli, with different or clearer results.

Driver 5 is related to environmental risk factors. Two of these were proposed, namely, invasive medical procedures for rapidly progressing CNDD and *Bordetella pertussis* (BP) infection. The latter, selected as an example of host-adapted human pathogen, was considered to be relevant for late-life sporadic neurodegenerative disorders. Since both *E. coli* and BP are host-adapted human pathogens, driver is relevant for cross-seeding AS studies.

The association between age at first major whooping cough outbreak and PD in Iceland constitutes a unique observation [9]. Considered as a quasi-experiment, it is consistent with the high prevalence and incidence of PD among the Faroe Islanders and Greenland Inuit [10,11]. Since PD shares protein deposits with multiple system atrophy, Lewy body disease (LBD) and AD, BP infection in genetically susceptible young individuals was proposed as an environmental driver for late-life neurodegenerations. We know of no reported epidemiological links between infection by *E. coli* and risk of synucleinopathies, and would therefore be grateful for the authors' comments on the potential usefulness of BP as an experimentally alternative agent to *E. coli*.

Driver 7 is related to the invariant ratio of the incidence of sporadic versus genetic cases of CNDD. The ratio, defined by the proportion of incident disease corresponding to familial forms, tends to increase due to the progressive improvement in the identification of such mutations, and may reach 25% in selected CNDD. Complementary data supporting the relevance of driver 7 for this study are: (a) the ecologic relationship between sporadic and genetic forms, interpreted as a footprint of a causal link between genetic and sporadic forms of CNDD. Ontogenically speaking, sporadic neurodegenerative disease forms might be considered secondary to genetic forms in terms of cases and biochemical similarity [12]. In a prior article, we proposed that the most relevant field of knowledge for assessment of the role of vectors in sporadic neurodegeneration might be transfer of pathological genetic sequences from the human host to bacteria as a part of the adaptation process, followed by xeno-templating between bacterial and host proteins [13]. As an example of the first potential process we selected that of *E. coli*, as more than 17% of its genetic material is the result of horizontally transferred protein-coding DNA [14]. Human coexistence with commensal or pathogenic bacteria might have led to the interaction between aggregated bacterial proteins and aggregation-prone sequences

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from the susceptible host. We hypothesized that seeding of naturally occurring protein fibrils from bacteria, such as curli from *E. coli*, might be the biological mechanism underlying infection as a causal factor of diverse late-life CNDD. Since inflammation appears to be a key element that facilitates templating, the role of *E. coli* might be mediated by gastrointestinal infections at a young age, more frequent in rural environments and linked to poverty. Such elements, underlying measures of educational level or cognitive reserve, constitute risk indicators of PD and AD [2]. A relevant question is whether the experimental *E. coli* strain [1] has similar genetic characteristics to those possibly present several decades ago when the pathological process of human synucleinopathies might have been initiated.

Most bacterial infections do not leave cross-time persistent footprints. Hence, the use of epidemiologic criteria for causal research on neurodegenerative or other conformational disorders is problematic. Seeding of naturally occurring protein, either directly or conveyed by *E. coli* [1,15] BP or other amyloid-bearing pathogens, might be hypothesized as a biological pluripotential mechanism underlying infection as a causal factor of PD, AD and diverse late-life neurodegenerative disorders.

To summarize, the Chen et al. [1] study validates single components of the driver model of CNDD. Conversely, experimental approaches similar to that reported by Chen et al. [1] might achieve or increase external validity using young rats infected by *E. coli* or BP. Targeted developments inspired by epidemiologic findings may further mimic the human biological process and increase the value of laboratory approaches for identification of therapies. BP strains circulating before the mid-1950s and found to be acting on survivors at the present time may guarantee the absence of genetic changes due to vaccination. Infection by human-adapted agents exhibiting natural protein fibrils might well constitute a plausible trigger mechanism for neurodegenerative disorders and other proteinopathies.

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