

Aging as Emerging Disease? Considerations from the Ontopathogenic Model

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Keywords

Aging; Emerging disease; Ontopathogenic model

Summary

The article presents the discussion of situation concerning interrelationship of aging and disease, citing both the opinions in favor and against the idea of considering aging as disease and concluding, on the basis of our own investigations and literature review, about poor chances for reinforcing this idea in near future. In contrast, life-course epidemiology of age-related disorders and studies in the framework of DOHaD concept need continuous attention and support from biomedical community.

The question about interrelationship of aging and disease is not new. Usually, pathologic aging is separated from biological one [1]. On the other hand, the aging without any detectable disease, i.e. so called "successful aging" may be present in not more than 20% of the whole human population [2]. Obviously, it means that pathologic aging is predominating.

However, just recently the situation began to change in this regard, with some trend to polarization of opinions and ideas. In fact, several researchers appeal to consider aging as poly-systemic syndrome [3], whereas others suggest, at least, to promote the investigations of relationship between the aging and disease in the framework of geroscience, i.e. something intermediate between biogerontology and geriatrics [4].

As a matter of fact, the discussion about aging and disease depends on their definitions. For some time already we support the definition of aging as a process that results in augment of morbidity and mortality with age. In many cases only mortality is considered, but as pathologic aging is predominant (see above), we find it quite adequate to include morbidity (evaluated by the number of hospital admissions) in the definition of aging.

Since 2005 we are studying epidemiologic indices in Southern region of Brazil by means of retrieving the data from Brazilian national database called DataSus. Just recently we began to perform also some international comparisons, at least with the populations of Argentina and Chile (see discussion in [5]). These investigations have allowed for conclusion about the absence of evidence in favor of unique general scheme of aging [6]. In fact, there exists considerable heterogeneity in age-related patterns of various diseases, together with significant gender differences, both in morbidity and mortality. For example, affective disorders and schizophrenia, cholecystitis and peptic ulcer are the diseases of middle-age categories, in contrast with the components and consequences of metabolic syndrome, like arterial hypertension, diabetes mellitus and myocardial infarction, more characteristic to the period of senescence. Moreover, calculating the female fraction of morbidity and mortality in various age categories has allowed for suggestion about accelerated aging in females, at least with the onset of menopause [7].

In the framework of DOHaD paradigm, we have offered to use the terms "ontopathogeny" and "ontopathogenic model" [8,9]. Ontopathogeny means pathogeny that occupies the great part or even the whole ontogeny, from pre- and postnatal development to adult state, continuing to middle age and senescence, whereas ontopathogenic model is theoretical construct we are elaborating for the promotion of life-course epidemiology and related areas of research. These terms are novel, but are based on the pioneering works of the epidemiologist David J.P. Barker and his colleagues [10] in Southampton (UK), with subsequent investigations all over the world, including studies on experimental models of laboratory animals and providing essential corroboration for the so called "Barker's hypothesis" [11]. Historically, our first contribution to the concept of DOHAD was evaluation of body and organ growth retardation after neonatal administration of dexamethasone to rats [12]. But since many studies have suggested glucocorticoids to be the mediators and targets of developmental programming/imprinting and embedding [13], we are currently investigating the role of stress hormones and proteins in pathogeny of various groups of disorders [14,15].

Our own epidemiologic studies have suggested the possibility of periodization of postnatal ontogeny on the basis of age-related patterns of morbidity and mortality [16]. Another opportunity for such periodization was employed by us earlier, using linearized plots of somatic growth [17]. Moreover, later on we have offered the hypothesis of

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metamorphosis-like phenomenon, indicating the essential role of juvenile (as compared with pubertal) transition, considered to be the principal transition from development to aging (see discussion in [18]). This conclusion was based also on evaluation of age-related dynamics of mortality in humans, with a minimum at the age of 9-10 years, at least in Brazilian population.

Returning to discussion of relationship between the aging and disease, obviously it is not a good idea to consider aging as disease, since it means that already from prepubertal phase all humans may be considered as patients, what is surely not appropriate. On the other hand, the boundaries between the norm and pathology are frequently not clear-cut, so it was possible already to introduce a concept of premorbid state or pre-disease, like pre-hypertension, pre-diabetes, etc. [19]. It is interesting that another theoretical construct, of allostatic load and overload, perfectly utilizes the concept of pre-disease and subclinical alterations, in contrast with clinically evident, manifest pathology [20].

Recently Valery M. Novoselov, a chief of Gerontology Section in Moscow Society of Naturalists (MOIP) has initiated a discussion about the relationship between the aging and disease [21]. It is interesting that although the majority of experts having taken part in this discussion were against considering the aging as disease, at least one of them was in favor of such idea. This situation reflects partially the reality of modern society, where some people become "biohackers", trying to escape from the universal law of biological aging or at least, to postpone its action.

In this regard, recently we have evaluated the situation with anti-aging medicine [22], affirming that at least in Brazil the researchers in gerontology and geriatrics became in strict opposition to this new area. Such opposition may be caused by professional competition, as revealed also in discussions on the interrelationship of aging and disease.

And finally, it is important to evaluate the position of World Health Organization (WHO), as referred to future transition from the present, 10th version of International Classification of Disease (ICD-10) to 11th version (ICD-11). We have estimated, if during the last two decades the code designating senility in ICD-10 was really used for confirming morbidity and mortality in the most southern Brazilian state of Rio Grande do Sul (RS), using DataSus epidemiologic indices. As a matter of fact, during the years 1998-2018 this code was used only 18 times, i.e. less than once per year for designating morbidity, as evaluated by hospital admissions. However, senility was indicated as a cause of mortality much more frequently (Table 1). Nevertheless, even in the oldest age category (> 80 years) the mortality because of senility was attributed in less than 1% of all cases. When evaluating the data of morbidity and mortality together, it appears that physicians don't like to designate senility for justifying hospital admissions and on the other hand, they use this code as mortality cause only minimally, when it is not possible to find other, more frequent pathologies, including cardiovascular disorders, diabetes mellitus, cancer, etc.

It means that perhaps, it will be not easy to modify the present situation by changing the characteristics of senility codification in ICD-11. Moreover, it seems almost impossible to consider aging as emerging disease, in spite of the opinions of some researchers and interested persons like "biohackers" behind them. Of course, this is not a reason to stop or slow the investigations in gerontology and geriatrics, life-course epidemiology and related areas. Really, there

are many problems also in evaluating comorbidity and polymorbidity, as referred to present-day ICD-10 and future ICD-11. In addition, from our point of view, the DOHaD paradigm needs continuous support and promotion, including not only the ontopathogenic model mentioned above, but also the emerging phylopathogenic model [23], with multi- and intergenerational transfer of the risk for at least some pathologies. But this question surely deserves separate publication, since it might discuss, among other things, the evolutionary aspects of aging and disease.

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Age category, years	Cases of mortality	Relative mortality, per cent
50-59	8	0.004
60-69	36	0.01
70-79	293	0.08
≥ 80	3602	0.9

Table 1: Absolute and relative mortality because of senility in the population of Brazilian state of RS for both genders together during the years 1996-2016 (retrieved from DataSus)

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