Pathogenesis of senile diabetes

The first time in 1898, Bernhard Von Naunyn distinguished three types of DM: the juvenile, the senile and the organic ones in his book entitled “Der Diabetes Mellitus”. Since then the distinction of various types of DM had been maintained on the basis of the clinical characteristics and the age of the patients even in the international classifications until 1979, when the National Diabetes Data Group (NDDG) proposed a classification of DM according to the aetiology. This classification was confirmed in 1985 by the WHO Study Group, establishing two main forms of DM, namely the type 1 (DMT1) and type 2 (DMT2).

Today it is difficult to support the existence of an aetiological specificity of the senile DM. As a matter of fact, although there are a large number of publications on the various pathogenetic, clinical and therapeutical aspects of the senile DM, age is not even considered as a factor in the actually accepted classifications.

In reality, the ageing phenomena plays an important role in the evolution of DM at both the biological and epidemiological levels. The prevalence of DM in the elderly population is on the rise continuously with considerable differences in various nations or ethnic groups, its global prevalence is an estimated 20 per cent of the population.

On the basis of the age at onset, we divided the DMT2 in the elderly (>65 yr of age) in two forms: DM of long duration (the onset was before the age of 60 yr), and DM of late onset, called senile DM (manifesting after the age of 65 yr).

The prevalence found in the elderly population (65-84 yr) by the Italian Longitudinal Study on Aging (ILSA) was 15.1 per cent. The proportion of the subjects with senile DM reached 44.7 per cent. With advancing age, the mortality rate of the subjects with DM of long duration and those of senile DM progressively increased reaching 99.7 per cent in the centenarians studied by the Italian Multicenter Study on Centenarians (IMUSCE).

Numerous genealogical studies established that the DMT2 can be considered as hereditary-familiar disease of recessive character with variable prevalence. The late onset senile DM, if considered uniformly as the DMT2 of adults, has been indicated as a hereditary condition of late expression.

Recently Grant and colleagues have identified the first time an association between the susceptibility for DMT2 and common variants of the gene of the T-cell factor-7-like-2 (TCF7L2). This was followed by a large number of publications and congressual presentations demonstrating that (i) the TCF7L2 is really associated with the susceptibility for DMT2; (ii) the population risk of DMT2 is estimated about 10-25 per cent; (iii) other variants inside the gene may result in even higher risks; (iv) the TCF7L2 is present in both sexes, in various ethnic groups and in all ages; and (v) the variants of TCF7L2 are not associated with DMT1, MODY and with the neonatal DM.

Up to now 18 genetic loci have been identified which are significantly associated with the DMT2. One can assume that an even higher number of genetic variations will be identified in association with DMT2. The great significance of the genetic factors determining the DMT2 is evident.

The presence of an increased progressive prevalence of late onset DM in advanced age (senile DM) stimulates evaluations of the possibilities that the related genetic variations may represent a late expression.

The pathogenesis of the senile DM is complex, and one has to recognize a multifactorial character
of genetic correlation with the onset of DMT2 and of ageing. We have to understand the complexity of definition of the significance of the numerous genetic components determining the DM and its complications in the adults and in the elderlies. In order to understand the importance of distinguishing the DM of long duration and the senile DM, one has to underline the clinical, therapeutic and comportament differences between these two types of DM. In the first case, there is a diabetic subject who knows already the problems of this disease when he/she becomes older, i.e., he/she does not have any particular difficulty in the management of this disease. In the second case, we see an older person who becomes diabetic at a later age and has to manage the complex problems among the conditions of the elderly.

The genetic component of senile DM may be characterized by the interaction of the genetic variations being responsible for the susceptibility for DM, and those accounting longevity. This is complicated by a number of complex interactions of genetic, epigenetic, and environmental factors. Many genes/polymorphisms gave negative results, while others showed a positive association with human longevity and a sometimes-positive association with unsuccessful ageing (myocardial infarction, Alzheimer’s disease, and DMT2). Of particular importance are also the genes involved in inflammation (IL-1 cluster, IL-6, IL-10, TNF-alpha, TGF-beta, TLR-4, PPARgamma), insulin/IGF-1 signaling pathways and lipid metabolism (apolipoproteins, CETP, PON1), and oxidative stress [p53, p66(shc)].

The common denominator between DM and ageing is the atherosclerosis, multifactorial environmental processes, and the life style, i.e., a particular significance is attributed to the anatomo-pathological lesions of the pancreas described by ourselves as follows: in the non-diabetic elderly subjects there are no significant pancreatic lesions, the Langerhans islands (LI) remain intact in 90.5 per cent, and the arterioles are not altered in 67 per cent of the cases. In cases of DM in medium age and of recent onset, the LI remain intact and show no arteriolar lesions. In senile DM of recent onset (diagnosed < 6 yr ago), one can find a macroangiopathic damage of the arterioles and frequently encounter LIIs of reduced dimensions with poor cellular content and signs of fibrosis.

In the cases of senile DM persisting >10 yr, one can notice arteriolar LI damages, hyalinosis and amiloidosis, with a progressive substitution with fibers, up to a manifest fibrosis. In these cases one cannot find intact LI.

In the elderly subjects with DM of early onset (< 60 yr of age), the anatomo-pathological findings are similar to those in the cases of senile DM manifesting for over 10 years. These data document the interaction between the ageing process and the duration of DM.

The modifiable risk factors, such as visceral obesity, hypertension, dyslipidaemias, trombophilia, inflammations, smoking, bad alimentation, missing physical activity, unhealthy lifestyle, etc., may interfere with the evlution of the disease and in determination of the chronic-degenerative complications of the elderly diabetics. A majority of these factors are influenced by separate and autonomous genetic processes (Fig.).

In conclusion, the pathogenesis of DMT2 is correlated with structural genetic defects, associated with the common genetic variations, giving rise to the susceptibility of the subjects for this type of DM. The factors seem to influence the biosynthesis and secretion of insulin and glucagon. Taking into account the clinical, therapeutic and behavioural peculiarities, the senile DM may be considered as an autonomous nosographic entity. It is a multifactorial genetic condition, in which genes responsible for the susceptibility for DM and for the aging process are involved. The latter ones are characterized by the intervention of “longevity genes” representing some antagonistic factors toward the genes of ageing.

In addition, the intervention of the modifiable risk factors is also important, since these may disrupt the
homeostatic equilibrium, influencing the development of the DM and its chronic-degenerative complications. This aspect of DM is of particular importance today, because this is the only preventive way against the DM and its complications. Yet, in spite of the extensive research and valuable results, we may have to wait for some years before see the genetic map(s) of DMT2, and even more of senile DM.

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