



Considerations on the Lifespan from Diagnosis to Death in Alzheimer's Disease

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Authors' contributions

This work was carried out in collaboration between both authors. Author GC designed the study, wrote the protocol, analyzed the data, discussed the results and managed the conclusions. Author OLC managed the literature searches and references, wrote the first draft of the manuscript and synthesized the data into figures and tables. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Evolution of Alzheimer's disease from the onset of dementia to death is estimated by different authors as lasting between a few months and 21 years.

Objective: To verify whether there is an explanation for this dispersion of evolution of cases, starting only from clinical information.

Methods: A number of 75 cases of patients dead between 01. Jan. 2011 and 31. Dec. 2012 were analyzed. Data on deaths was collected from the County's Statistics Institute; other information was collected from patient charts.

Results: Gender, onset age, co-morbidities and treatment do not influence the dispersion of cases. Dispersion started at less than one month from diagnosis and ended 11.42 years after diagnosis. At the age of 65, a boom in incidence of dementia symptoms as a stage of the disease was recorded. Dispersion of cases was divided into 3 evolution groups: the majority between 0-3 years, followed by 3-6 years and 6-11.42 years, as a Gaussian curve.

Conclusions:

1. The age of 64-65 may be considered a high risk age and it should be monitored accordingly.
2. The question of how just was Kraepelin's disjunction into pre-senile and senile dementias arises.

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In terms of evolution, according to dispersion, there are versions of the same disease or different diseases in pathogenesis depth, but similar in symptomatology.

Keywords: Alzheimer's disease; lifespan from diagnosis to death; dispersion of remaining lifespan; evolution of disease.

1. INTRODUCTION

“What characterizes the end of the 19th century is not so much the victory of science as the victory of method over science”, Nietzsche said in 1888 [1].

The discovery of the scientific method by the ancient Greeks was, according to history, the second greatest discovery of humanity. But the ancient Greeks' method was a method of thinking. It systematized thinking without limiting it. Rediscovering the scientific method in research has led to a technical and scientific boom, witnessed by Nietzsche, who had the genius to foresee its direction. But, as human nature is predisposed to exaggeration, even carried to the distortion of truth, even in the case of science, a situation in which things need to be reconsidered has been reached. It is undoubted that the rigor and the formality of the scientific speech have been and still remain a great benefit, but today methodology overwhelms science and sometimes it slows it down. This fact narrows the logic of the researcher to a punctual space. And, any obvious result of research, any proof, in case of evidence based medicine, is the result of a question, which is the fruit of an idea. That is why, besides the logical action in the punctual space of the definite research theme, it is useful for the tangible, the result of research, the equivalent of an experimental fact, to represent the starting point of an extended logical approach of the generality of the topic, allowing the contextualization of the results of the research within the general topic. Overall thinking can be just as creative as research or an experiment can. Using a metaphoric, yet intuitive analogy, overall thinking allows a long range perspective like a road lit by the high beam of a car's headlights, going far into the distance but not revealing the holes in the road ahead. Methodological thinking, encased in punctual research space is like a low beam, revealing all the holes in the road. Just as Dugas [2] said, it means overcoming the „empirics that see merely facts”, or accessing the supplement of what he called „the superiority of the theoretician is able to predict the results of a test”. Combining the two perspectives may lead to an enhanced

benefit of search through research, or experiment and associated overall thinking. In the light of these ideas, a plan researching the aspects of the evolution span of Alzheimer's disease from the diagnosis of dementia to death has been designed.

The definition of lifespan for the cases diagnosed with Alzheimer's disease in the stage with dementia symptoms is difficult because duration is measuring length and it implies two fixed points. The day of death is certain, but what about the onset date? There are three possibilities: a). To establish the onset as the time when the first symptoms of dementia occur, yet nobody could precisely pinpoint this moment in time. b). The date of the first clinical diagnosis of Alzheimer's disease with symptoms of dementia. c). The date when all information markers that substantiate the diagnosis in addition to clinical information are collected. Out of the three possibilities, the date of the first clinical diagnosis is the most realistic from several points of view. As for the lifespan of these patients, bearing in mind that the incidence and the prevalence of the disease increases with age and that there are great differences of lifespan after diagnosis, the first question to answer is whether *the patients' lifespan depends on the age at which the state of dementia occurs*. Also, knowing the difference of incidence and prevalence regarding genders, the second question to answer is whether *lifespan is influenced by gender*. At the age at which Alzheimer's disease is diagnosed in the stage with dementia symptoms, the frequency of consuming, and also acute diseases is high, so that the third question on the list is whether *comorbid diseases might be responsible for the difference in lifespan of the patients*. Last but not least, no case evolves naturally after diagnosis, so the fourth question being asked is whether *treatment influences the patients' different lifespan dispersions*. Here are four fundamental questions that the clinician has to answer. In scientific literature, the average lifespan of these cases was assessed as ranging from a few months to over 21 years [3-16]. The stake of knowing the factors influencing this lifespan is immense because if, at the age of 65, one gets

the diagnosis of Alzheimer's disease and has 3-4 months left to live, the situation is dramatic, but if they have 21 years more to live, up to 86 years of age, then the situation is different. If knowing the factors influencing this lifespan allowed us to influence them, then, a serious matter of this disease would be solved. This is the aim of this paper.

2. AIMS

To obtain the answers to the questions mentioned above from studying a lot of patients who were diagnosed with, and treated for Alzheimer's disease in a clinic in Romania.

3. MATERIALS AND METHODS

Data on deaths between 1st January 2011 and 31 December 2012 of people having suffered from Alzheimer's disease in Bihor County in Romania was collected from the County's Statistics Institute. Afterwards, the cases having the exact date of clinical diagnosis written down in patient charts, and treated with donepezil and memantine (as nonspecific medication is variable) were picked from the Clinic's archive. The inclusion criteria were also the exclusion criteria. In addition, we regarded as an exclusion criterion the presence of an acute disease as cause of death: Pneumonias, strokes, etc. The data selected were: Age at the time of clinical diagnosis, lifespan from diagnosis to death, gender and co-morbidities. Data processing and analysis was performed using the SPSS Statistics Software, version 17. 0.

4. RESULTS

The resulting lot consisted of 75 patients: 52 women and 23 men, a Female/Male ratio of 2.4. Cases were grouped by age when diagnosed and by gender.

Results were as follows: (Tables 1, 2, 3, Figs. 1, and 2).

The first thing to be noticed, though unsought, is that the majority of cases (95.65% of men and 88.46% of women, $P = .04$) were diagnosed with Alzheimer's disease in the stage with dementia symptoms starting with the age of 65, age at which an incidence boom occurs. The conclusion is that the age group of 60-64 years represents a growing evolution risk in the pre-dementia stage. The second aspect to be noticed, first to be sought, however, is that all cases are distributed by lifespan from diagnosis, regardless of the age of symptomatology onset, between 0.08 years (less than a month) and 11 years and 5 months (11.42 years). The cases of onset before the age of 65 are situated within these limits. The answer to the second question is nuanced, in the sense that after the age of 60 the margins narrow according to the lifespan of the general population, but the age group of people with dementia symptoms onset does not influence the wide dispersion of the survival of patients diagnosed between 40 and 80 years of age. The age of diagnosis does not say anything about the evolution speed towards exitus for each case.

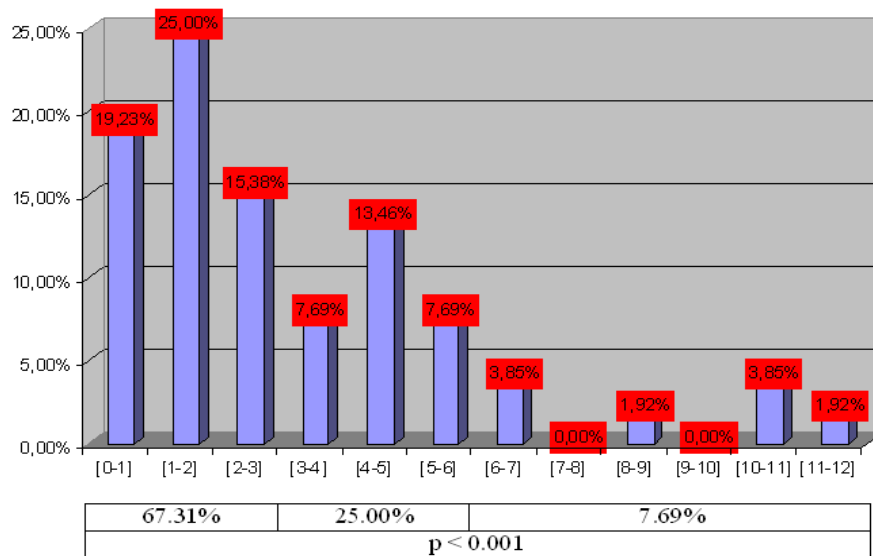


Fig. 1. The evolution span (in years) from diagnosis to death in women

Table 1. Average evolution span and limits from diagnosis to death, on age groups (in years) for women

Onset age	40 - 44	50 - 54	55 - 59	60 - 64	65 - 69	70 - 74	75 - 79	80 - 84	85 - 89
Number of cases	1	0	4	1	6	12	14	12	2
Average evolution span and limits	4	-	5,75	6	3,83	4	1,93	2,08	2,5
			1 - 10,16		0,16 - 11,42	0,58 - 10,25	0,08 - 6,75	0,33 - 4,75	1,92 - 2,66
Average evolution span	5,50				2,78				
Total number of cases with onset over 65 y/o					88,46%				

Table 2. Average evolution span and limits from diagnosis to death, on age groups (in years) for men

Onset age	40 - 44	45 - 49	50 - 54	55 - 59	60 - 64	65 - 69	70 - 74	75 - 79	80 - 84	85 - 89
Number of cases	0	0	0	1	0	4	5	10	3	0
Average evolution span and limits	-	-	-	1	-	5,25	1,6	3,2	1,67	-
						2,58 - 7,25	0,33 - 2,92	0,42 - 10,08	0,42 - 4,08	
Average evolution span	1,00					3,00				
Total number of cases with onset over 65 y/o						95,65%				

Table 3. Dispersion of co-morbidities on years of survival (cardiovascular diseases like ischemic cardiopathy, cardiac arrhythmias, high blood pressure and other non-cardiovascular diseases) in percentages from the total lot

Survival years	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	>11
Percentage of cases with AD from total	20	22,7	19,7	8,0	12,0	6,7	2,7	1,3	1,3	0	4	1,3
Percentage of cases with cardiovascular diseases	19,7	20	19	7	11	5	2	1,3	1,3	0	3	1,3
Percentage of cases with non cardiovascular diseases	20	22	19	8	12	6	2,7	1,3	1,3	0	4	1,3

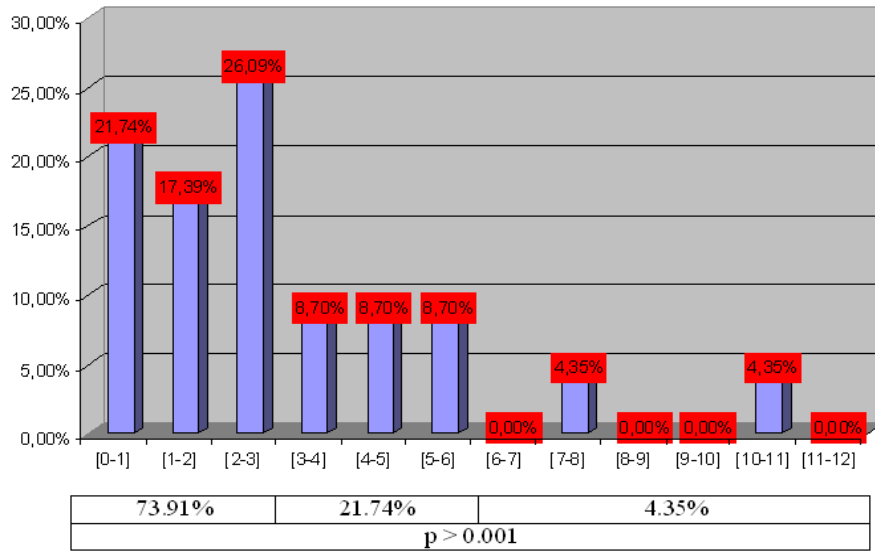


Fig. 2. The evolution span (in years) from diagnosis to death on age groups in men

The picture for both men and women is similar. The differences between evolution span groups are statistically insignificant ($P = .08$), both between those of the same gender, up to the age of 80, as well as for the same evolution span groups for the two genders.

Therefore, the answer to the second question is that gender does not influence the dispersion of evolution from diagnosis to death. But, what we immediately notice regarding both genders is the three lifespan groups: a group in which death occurs within three years from diagnosis, where most of the cases are comprised (59,61% Female, 65,22% Male), the second group in which death occurs between 3 and 6 years from diagnosis (26,7% Female, 26,1% Male), and the third group with death occurring between 6 and 11.42 years from diagnosis (13,69 Female, 8,68% Male). Mathematically, the difference between the three lifespan groups is highly significant ($P < 0.001$).

Data obtained is interesting if corroborated with data from scientific literature regarding sensitivity and sensibility of the biomarkers proposed for Alzheimer's disease [17,18], which, according to some authors, narrow up to 70% of cases, leaving out 20-30 % of the cases not subscribing to the general rule from this point of view. Given the relatively small size of the researched lot, we cannot interpret this aspect further. Even if we considered the age at which diagnosis was made, the tolerance degree of the population, early or delayed visits to the doctor, the

dispersion of cases over such a long period of time cannot be explained, as this is a homogenous population who is well aware of the financial advantages of the Alzheimer's disease diagnosis in the stages with dementia symptoms.

The differences in presence of co-morbidities (Table 3 above) are not significant ($P = 0.08-0.21$). De factum, almost every case had another diagnosis in addition to Alzheimer's disease. Therefore, the answer to the third question is simple and negative. The co-morbidities cannot explain the dispersion of the lifespan from diagnosis to death. As the specific treatment is identical, the fourth question is answered similarly. Although the treatment has an undeniable positive effect, it alone does not influence the dispersion of cases on lifespan.

5. DISCUSSION AND CONCLUSION

Referring strictly to the punctual space of the topic in discussion, three conclusions can be drawn. First of all, the most obvious aspect is the age barrier of 65 when there is an incidence and prevalence boom of the disease. From the public health point of view this implies a continuous screening of the general population (clinically and through biomarkers, yearly) at the age of 64, in order to identify the disease in a pre-dementia stage, when treatment can block or even reverse the pathogenic evolution of the disease, at least for some of the cases. Secondly, the four questions stated can be answered. None of the parameters that can be clinically followed

influences the different evolution speeds of the cases towards death from the diagnosis of Alzheimer's disease with symptoms of dementia.

Third of all, the tendency of grouping the cases by three different evolution speeds towards exitus can be noticed, speeds grouping the cases in three evolution spans: 0-3 years, 3-6 years and over 6 years. But the research data allows a logical extension at the level of the general topic of which the subtopic in discussion is part.

Generally, one's opinion of things depends on the accessibility to their intimacy. Actually, every discovery defines the limit we have reached in penetrating into the intimacy of things, limit which is referred to by metaphysics as the horizon of the transcendent subject, or, more technically, the front of knowledge horizon, which is in continuous expansion. One perfects one's models of representing reality, or creates new models designed to correspond to a specific series of similar events, according to the dynamics of the horizon mentioned above. A disease is a specific series of similar cases. An explanatory model has the quality of enabling the understanding of both the series of specific things and the constitutive elements of the series. In addition, it must allow for predictions, including on the evolution of the series and of each constitutive element. The ratio between the representation model and the series of things is a binary system. When the model of understanding does not cover the specific series, or when the model is not sufficient, or incorrect, or the series is not entirely specific, it can overlap with other series, even with personal variants forming subseries with a tendency of independent specificity. The current model of understanding Alzheimer's disease allows for a systemic articulation of genetic, metabolic, neurochemical, neuroanatomical and clinical data conferring its credibility. Yet, it does not allow any logical and coherent possibility to make prediction about the evolution of the cases, as seen in previous research. Therefore, the representation model is not to blame. The flaw must be searched in the purity of the series, in the absence of the complete similarity of the cases. A question can be asked: wasn't the Kraepelian disjunction between presenile and senile dementia fairer? Dementia as a syndrome occurs in at least 77 neurological diseases, so the dementia syndrome is totally non-specific. The main biomarkers of what is labeled as Alzheimer's disease are also non-specific. Are there, in the

depth of things, pathogenic variants which lead to preclinical and clinical similar results?

To sum up, according to this research and the data in literature [16,17], there is a question mark about the unity and homogeneity of cases labeled as Alzheimer's disease in the stage with dementia symptoms. Are there more variants of the same disease, or even independent, rare diseases which lie under the same unique diagnostic label?

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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