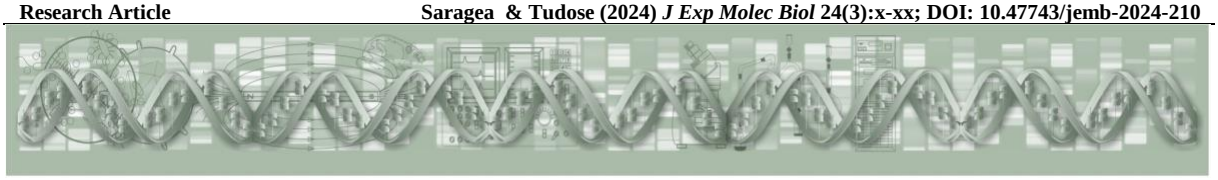

ALZHEIMER'S DISEASE AS A MULTIFACTORIAL NEURODEGENERATIVE PATHOLOGY - A COHORT STUDY

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Abstract

Situated within the broad spectrum of neurodegenerative disorders, Alzheimer's disease (AD) is known for its complexity, heterogeneity, multiple genetic mutations, epigenetic and biochemical modifications, and irreversible progression from early stages characterized by deficits in the ability to encode and store new information to subsequent progressive cognitive, functional, and behavioral decline. **Objective:** The conducted study aimed to compile conclusive statistics, identify genetic factors, and correlate them with environmental ones, thus highlighting the importance of developing evaluation programs and early introduction of medication to decelerate the progression of neurodegenerative processes. **Materials and methods:** The analytical, observational, retrospective study was conducted on an extended cohort of 2277 patients admitted with chronic neurological diseases to the Neurology Department of "Dr. Iacob Czihac" Clinical Military Emergency Hospital Iași from January 1, 2022, to December 31, 2023. Among these, 219 patients were diagnosed with AD at various stages. Forty-three cases exhibiting genetic predisposition (19.63%) were selected and thoroughly analyzed based on medical records. **Results:** The study emphasizes the significant position of AD among chronic neurological diseases. Although the majority do not present hereditary antecedents (80.36%), predisposing conditions, environmental factors, stress, and the region of residence play fundamental roles in the disease's determinism. It is observed that individuals in the 60-70 age category (71.23%) from urban areas (63.01%), especially females (63.47%), have a higher probability of developing AD. Maternally transmitted AD prevalence was 58.13%, while paternally inherited AD accounted for 32.55%, with only 4 cases having antecedents on both lines (9.30%). **Conclusion:** Unequivocally characterized by a vast etiology, AD is a multifactorial disorder resulting from the bilateral interaction and continuous corroboration of genetic and environmental factors.

Keywords: Alzheimer, Neurodegeneration, Multifactorial, Dementia, Hereditary

Introduction

Initially described in 1906 by the pathologist and psychiatrist Alois Alzheimer as a "disease of forgetting," the eponymous condition is first recognized by short-term memory impairment, followed by a progressive decline in cognitive, functional, and behavioral abilities. The disease involves deterioration in reasoning, memory, and visual perception, along with difficulties in focusing attention and maintaining social interactions. As the disease advances to moderate or severe stages, patients may experience symptoms such as agitation, delusional thoughts, anxiety, depression, irritability, apathy, hallucinations, delirium, and insomnia (Burns

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et al., 2002; Hippius & Neundörfer, 2003; Maurer et al., 1997; Soria Lopez et al., 2019; Szalontay, 2014; Szalontay et al., 2005).

Situated within the broad spectrum of neurodegenerative disorders, AD is recognized for its heterogeneity, underlying hypotheses, numerous genetic mutations, epigenetic and biochemical alterations, and irreversible progression from early stages characterized by deficits in the ability to encode and store new information to subsequent progressive cognitive, functional, and behavioral decline in advanced, terminal stages. It is unequivocally characterized by a vast etiology, including cerebral atrophy associated with neurotrophin depletion, mitochondrial dysfunction, and the accumulation of senile plaques and intraneuronal neurofibrillary tangles as a result of autosomal dominant mutations (APP, PSEN1, PSEN2) or the presence of allelic variants (APOE4, SORT1, MAPT, APOJ).

As one of the major causative factors of progressive, irreversible dementia, the pathogenesis of AD is predominantly attributed to the presence of intracellular neurofibrillary tangles, composed of hyperphosphorylated tau protein, and dense or diffuse extracellular β-amyloid ("senile") plaques within the limbic and cortical areas. AD is classified as a neurodegenerative disorder primarily driven by protein misfolding, where conformational changes are induced by a combination of genetic and non-genetic factors, including physiological, biological, demographic, behavioral, pathological, and environmental influences. The principal mechanism underlying the disease is the hyperphosphorylation, aberrant polymerization, and processing of normal soluble proteins (Tiwari et al., 2019).

AD is characterized by a complex and extensive etiology, attributable to both genetic and environmental factors. Genetic mutations on chromosomes 14, 1, 19, and 21 play significant roles, with autosomal-dominant inheritance patterns being common—AD often follows a monogenic inheritance model for chromosomes 21, 14, and 1. In addition to genetic predispositions, the disease may be induced by exposure to toxic substances (such as aluminum, pesticides, and organic compounds), infectious agents (including herpes virus and lentiviruses), and cranio-cerebral trauma. The development of amyloid plaques, cerebrovascular amyloidosis, and cerebrovascular accidents, particularly in mixed forms, also contributes to the pathogenesis of AD. Moreover, several pathological mechanisms are implicated in the progression of AD, including acute-phase inflammatory responses, the formation of amyloid plaques and neurofibrillary tangles of protein tau, and significant deficits in choline acetyltransferase and acetylcholine, leading to marked neurochemical and cholinergic deficiencies. Structural and cytoskeletal impairments in mitochondria—key organelles responsible for oxidative phosphorylation and energy release—resulting from neurofibrillary accumulations, as well as metabolic lesions, the proliferation of apolipoprotein E4, and imbalances in neurotransmitters such as norepinephrine, dopamine, and serotonin, can all initiate and exacerbate the neurodegenerative processes associated with AD (Masters et al., 2015; Szalontay, 2014; Szalontay et al., 2005).

This study is driven by the pressing need to deepen our understanding of the underlying mechanisms of AD, a neurodegenerative disorder with a profound impact on global public health. Current treatment options remain limited and are not curative, highlighting the urgent need for novel therapeutic approaches. The increasing prevalence of AD, along with its significant social and economic consequences underscores the importance of advancing research in this area.

The purpose of the retrospective study was to establish conclusive statistics and to identify/observe both genetic and non-genetic factors. It encompasses individuals admitted to the Neurology Department of the "Dr. Iacob Czihac" Clinical Military Emergency Hospital in Iași over a two-year period (from January 1, 2022, to December 31, 2023).

With the continuous global aging of the population (corresponding to an increase in life expectancy), scientific research has increasingly focused on identifying the factors that

contribute to the onset of AD, a neurodegenerative disease, as well as elucidating its underlying mechanisms and exploring potential treatment options. The rising incidence and mortality rates further underscore the importance of these investigative efforts (Gustavsson et al., 2023; Li et al., 2022).

Although there are no effective methods to halt the progression of AD, which remains irreversible and progressive with variable rates of decline, published studies demonstrate that up to one-third of dementia cases could potentially be prevented or the onset delayed by understanding controllable risk factors. This involves meticulous population monitoring and screening, the identification of genetic and non-genetic determinants, and the systematic, comprehensive reporting of epidemiological trends, all of which are essential components in addressing this intricate, multifaceted, and evolving process (Gao & Liu, 2021; Gauthier et al., 2016; GBD 2019 Dementia Forecasting Collaborators, 2019; GBD 2019 Diseases and Injuries Collaborators, 2020; GBD 2019 Risk Factors Collaborators, 2020; Gustavsson et al., 2023; Li et al., 2022; Livingston et al., 2020).

Materials and Methods

Characterization of the study cohorts

The retrospective study includes individuals who were admitted to the Neurology Department of the "Dr. Iacob Czihac" Clinical Military Emergency Hospital in Iași between January 1, 2022, and December 31, 2023.

Patients were selected according to their diagnoses, specifically targeting cases of chronic neurological disorders, with a particular emphasis on AD, from the hospital's databases. The selection focused on individuals who exhibited a familial genetic predisposition to neurodegenerative diseases.

During the years 2022 and 2023, a total of 2277 individuals with chronic neurological conditions were admitted, 219 of whom were diagnosed with AD. For the purpose of the genetic study, 43 cases exhibiting genetic predisposition were selected, and their medical records were analyzed: 25 cases with maternal inheritance, 14 cases with paternal inheritance, and 4 cases with a history of neurodegenerative conditions (AD) in both maternal and paternal lines.

In 2022, out of the 121 patients admitted with AD, only 22 individuals were identified with varying degrees of genetic predisposition, distributed as follows: 13 cases with maternal inheritance, 7 cases with paternal inheritance, and 2 cases where both parents had previously been diagnosed with AD. In 2023, in Iași, of the 98 patients with AD, only 21 had genetic predisposition, including 12 cases with antecedents on the mother's side, 7 cases with antecedents on the father's side, and 2 cases where the genetic predisposition or history was traced through both the maternal and paternal lineages.

Thus, the study cohort for the year 2022 included 1265 patients with various forms of chronic neurological disorders, whereas in 2023, a smaller number of 1012 individuals were admitted. Among the 1265 patients hospitalized in 2022, a final diagnosis of AD was established in 121 cases at various stages. Over the subsequent 12 months (i.e., in 2023), 98 individuals with AD were identified out of a total of 1012 patients admitted (at their first hospitalization). The prevalence of AD diagnosis in 2022 was 9.5652%, a trend that continued into the following year, with a prevalence of 9.6837%. The study thus highlights that AD holds a significant position among chronic neurological disorders, with 9.6179% of patients admitted with chronic neurological conditions being diagnosed with early-onset, late-onset, atypical, mixed, or unspecified AD over the two-year period.

Methods applied to conduct the research

The methodology comprised a comprehensive analysis of medical records, including the results of supplementary investigations, cognitive assessments, and general clinical examinations, as well as neurological, psychiatric, and neuropsychological evaluations. This process also involved the extraction of relevant, pertinent information. The medical data recorded in the patients' electronic files were processed, and the inclusion criteria comprised hospitalized patients who had been diagnosed with AD. The overarching objective of this study was to generate conclusive statistical insights. The relevant data for this retrospective study were graphically illustrated and tabulated to enhance the visualization of the observations derived from the analyzed information.

Results and discussions

The observational, analytical, retrospective study includes individuals admitted to the Neurology Department of the "Dr. Iacob Czihac" Clinical Military Emergency Hospital in Iași between January 1, 2022, and December 31, 2023, as of the date of their last admission (Figure 1).

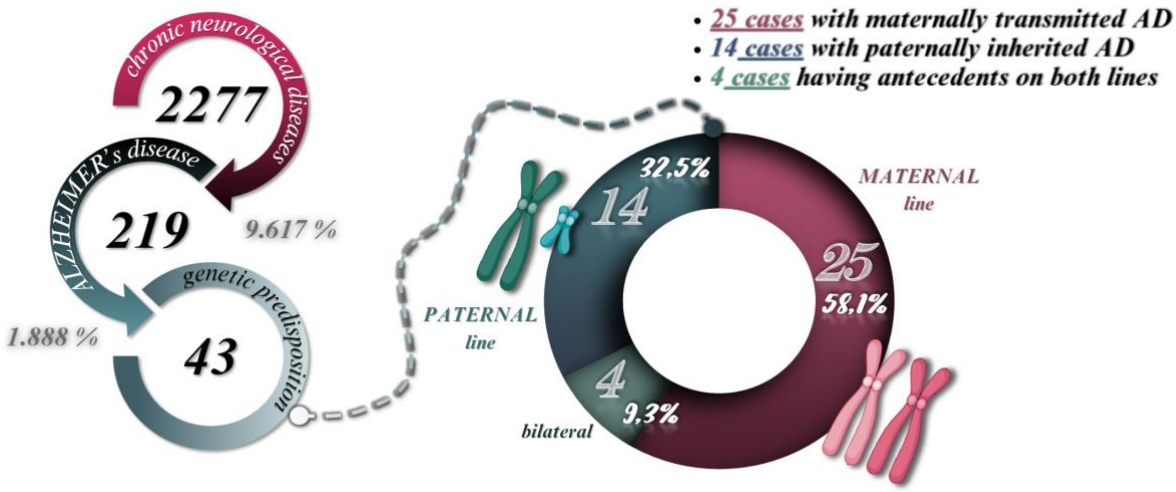

Figure 1. The numerical distribution of the cohort from Iași according to diagnosis and the hereditary lineage involved in the genetic susceptibility transmission process

During the two-year period, a total of 2277 individuals with chronic neurological conditions were admitted. In 2022, 1265 cases were recorded, whereas in 2023, only 1012 cases were documented. This observation indicates a slight decrease in the number of newly diagnosed and hospitalized patients (a difference of 253 cases) between the two years during which the statistical data were collected (Table 1).

Table 1. Patients admitted with chronic neurological conditions-"Dr. Iacob Czihac" Clinical Military Emergency Hospital Iași-2022 and 2023

	Total number of patients with chronic neurological conditions	Total number of patients with AD	Without genetic / familial predisposition	With genetic or familial predisposition	Familial history of AD on:		
					mother's side of the family	father's side of the family	both sides of the family
2022	1265	121	99	22	13	7	2
2023	1012	98	77	21	12	7	2
TOTAL	**2277**	**219**	**176**	**43**	**25**	**14**	**4**
Percentage of the total number of patients (2,277)		9,6179 %	7,7294 %	1,8884 %	1,09 %	0,61 %	0,17 %
Percentage of the total number of patients with AD (219)			80,3652 %	19,6347 %	11,4155 %	6,3926 %	1,8264 %
Percentage of the total number of patients with genetic predisposition (43)					58,1395 %	32,558 1%	9,3023 %

Among the total of 2277 patients admitted with chronic neurological conditions (at the onset of their illnesses), 219 were diagnosed with AD (121 patients in 2022 and 98 patients in 2023). In accordance with the inclusion criteria outlined in the preceding section, 43 individuals exhibiting genetic predisposition were selected, and their medical records were thoroughly analyzed. Upon analyzing the medical records and focusing on individuals with familial predisposition, it was determined that the genetic predisposition was inherited as follows: 25 cases through the mother's side of the family, 14 cases through the father's side of the family, and in the remaining 4 cases, both parents were diagnosed with the same neurodegenerative disorder (AD) (Figure 1, Figure 2, Table 1).

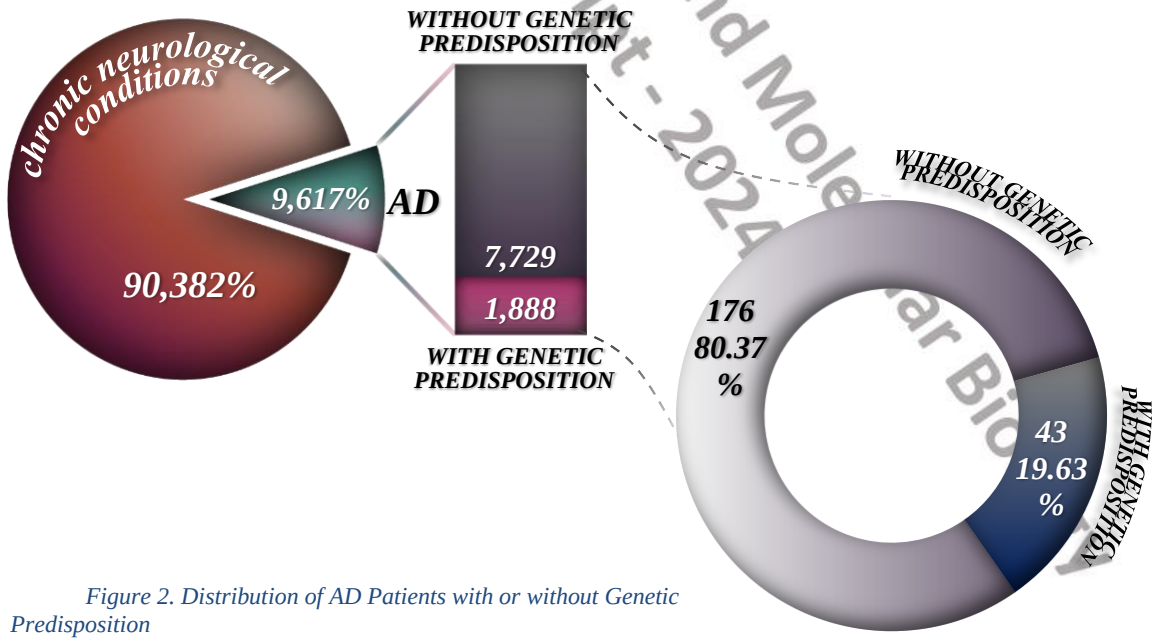

Figure 2. Distribution of AD Patients with or without Genetic Predisposition

Epidemiological Analysis

The study emphasizes the significant position of AD among chronic neurological diseases. Analyzing the data, it is observed that 2058 patients, representing a percentage of 90.382%, were diagnosed with other chronic neurological conditions, including various forms of dementia, whereas only 9.61% were diagnosed with AD (219 patients) (Figure 2). From an etiological perspective, dementias are a heterogeneous group of systemic or neurological conditions affecting the central nervous system, including forms such as AD, mixed dementias (AD associated with cerebrovascular disease or with Lewy bodies), vascular dementias, α-synucleinopathies (Lewy bodies and dementia associated with Parkinson's disease), as well as inflammatory, infectious, metabolic, and neoplastic diseases.

Demographic and Physiological Risk Factors

▪ **Gender distribution of patients diagnosed with AD**

The analysis of medical records reveals that out of the 219 patients diagnosed with AD at various stages, 139 were female (63.47%), while the remaining 80 individuals were male (36.52%) (Table 2).

Table 2. Gender Distribution Based on the Year of AD Diagnosis

	Total number of patients with chronic neurological conditions	Total number of patients with AD	Women	Men
2022	1265	121	78	43
2023	1012	98	61	37
TOTAL	**2277**	**219**	**139**	**80**

The breakdown of this patient cohort across the two years yields the following observations: in 2022, out of the total 121 patients diagnosed with AD, 78 were women (64.46%) and 43 were men (35.53%). In contrast, in 2023, among the 98 patients with AD, there were 61 women (62.24%) and only 37 men (37.75%) (Table 2).

Consequently, a higher incidence is observed among females (63.47% of the diagnosed AD cases), a trend also supported by globally published statistics. The female sex is considered a physiological risk factor for AD. The disparity in sex distribution in favor of females becomes increasingly pronounced as the incidence rate escalates (Figure 3).

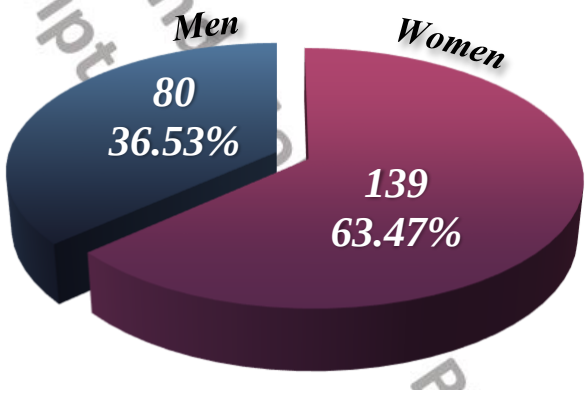

Figure 3. Physiological risk factors: distribution by sex of patients admitted between January 1, 2022, and December 31, 2023

▪ **Age distribution of patients diagnosed with AD**

The distribution across age groups is fundamentally associated with risk factors involved in the etiology of this progressive condition, characterized by minor or major neurocognitive disturbances (Stănescu, 2015; Szalontay, 2014) (Table 3).

Table 3. The distribution by age of patients diagnosed with AD

AGE	*No. of CASES*	*DIAGNOSIS*
< 60 years	***20***	AD - presenile dementia
60-70 years	***156***	AD
> 70 years	***43***	AD - senile dementia

The analysis of the interdependence between the age of onset or diagnosis and the type of AD reveals that, in most cases, the disease is detected after the manifestation of specific symptoms (including significant impairment of memory, visual perception, language, attention, reasoning, communication, and behavior) during the seventh decade of life (60-70 years: 71.23%) (Figure 4). This statistical finding aligns with the data available in the scientific literature.

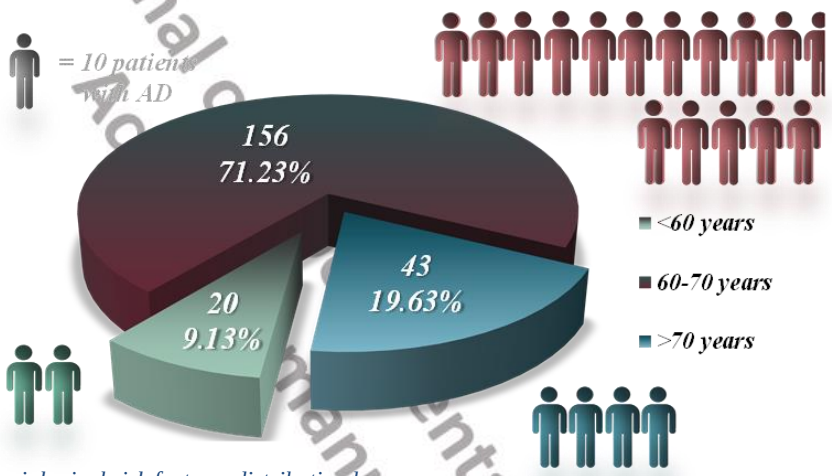

Figure 4. Physiological risk factors: distribution by age groups

Pathological, Behavioral, and Physiological Risk Factors

The analysis of pathological factors was conducted based on their heightened risk of developing AD. Within the high-risk group, 153 individuals with predisposing conditions such as obesity, hypertension, hypercholesterolemia, type 2 diabetes, and previously identified cranio-cerebral trauma, 34 individuals subjected to daily stress, 62 cases of chronic alcoholism, 61 smokers, 29 with aluminium exposure, 38 patients exposed to pesticides, and 16 with exposure to organic solvents were selected (Figure 5).

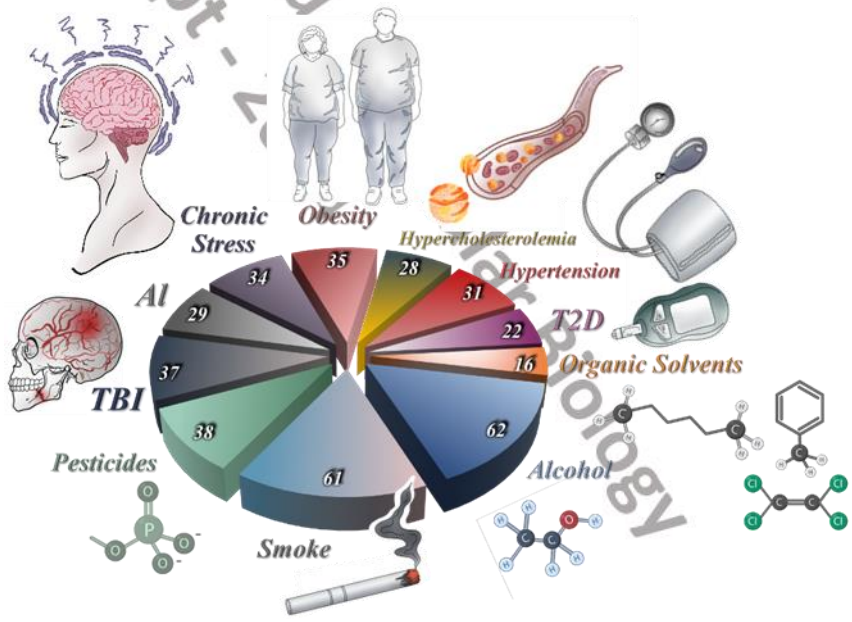

Figure 5. Numerical distribution of individuals exposed to environmental risk factors

Environmental Risk Factors

The study conducted in Iași reveals a notable predominance of AD diagnoses among individuals from urban areas (Table 4), with approximately 63% of the cases, corresponding to 138 patients, originating from these environments. Conversely, only 81 cases, representing 36.98%, were identified in patients from rural areas (Figure 6).

Table 4. Distribution by area and year of admission

	Urban areas	***Rural areas***
2022	69	52
2023	69	29
TOTAL	138	81

In both years, the number of patients admitted from urban environments remained constant (69 patients). In contrast, a decline in the diagnosis of AD among patients from rural areas was noted (Figure 7). The lower number of patients from rural areas, especially in the case of early dementia diagnosis (and the higher prevalence of individuals from urban areas), is attributed in this case to the lower level of medical education and proactive decision-making in rural settings.

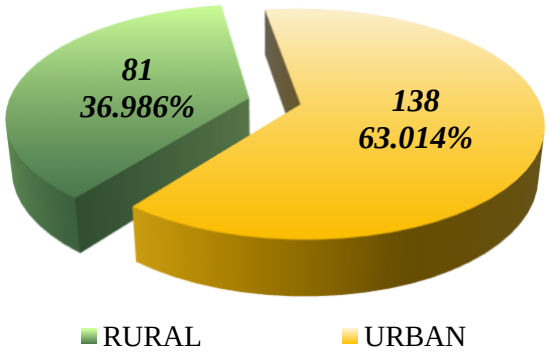

Figure 6. The distribution according to the place of residence of patients diagnosed with AD

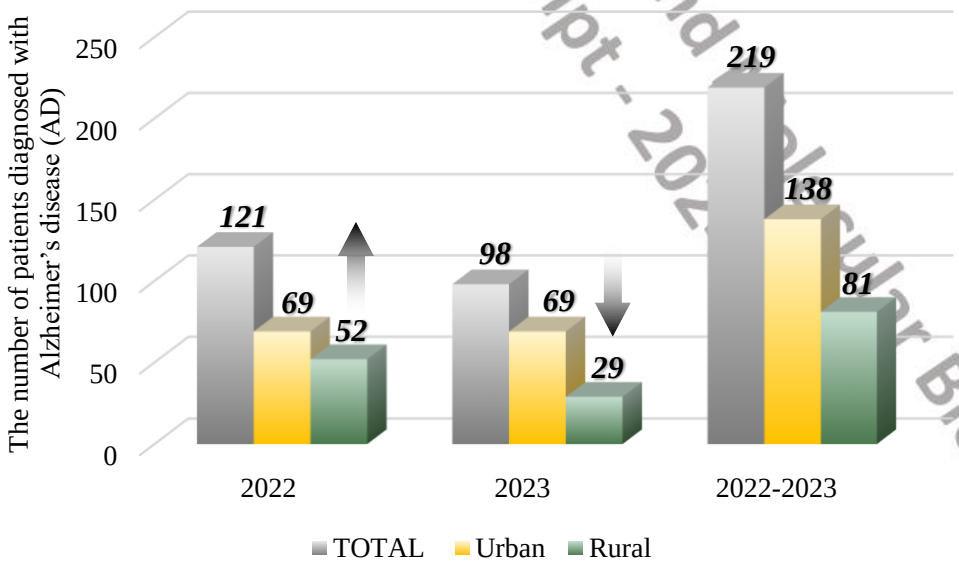

Figure 7. Numerical distribution of patients based on place of residence

Genetic Factors in the Pathogenesis of AD

The analysis of patient cohorts reveals that genetic predisposition contributed to the development of AD in 43 patients (Figure 8): 22 in 2022 and 21 in 2023 (Table 1). However, the risk levels varied depending on the number of relatives previously diagnosed with AD.

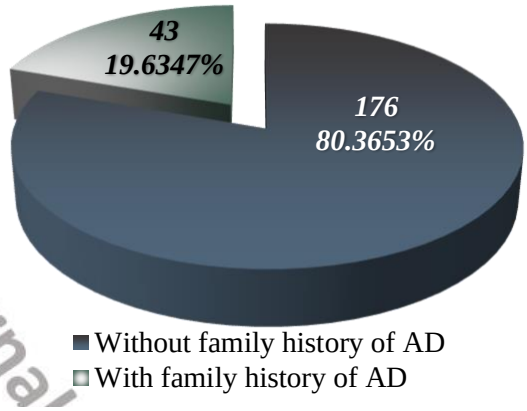

Figure 8. Distribution of Patients Based on Familial Predisposition

Following a detailed examination of the 43 patients with genetic predisposition (Figure 9), it was determined that:

- 4.65% of individuals (2 cases) had only second- or third-degree relatives affected by AD: one patient had a grandparent diagnosed with AD, while the other had an uncle affected by neurodegenerative processes.
- 51.16% of individuals (22 cases) had only one parent previously diagnosed with AD (prior to the genetic consultation and hospitalization).
- 25.58% of individuals (11 cases) had both a parent and a second-, third-, or fourth-degree relative affected by AD: 2 individuals had a fourth-degree relative (a cousin), 2 had a third-degree relative (an aunt or uncle), and 7 had a second-degree relative (a sibling or grandparent).
- The remaining 8 cases had either both parents diagnosed with AD or one parent and at least two second- or third-degree relatives with AD (increased risk).

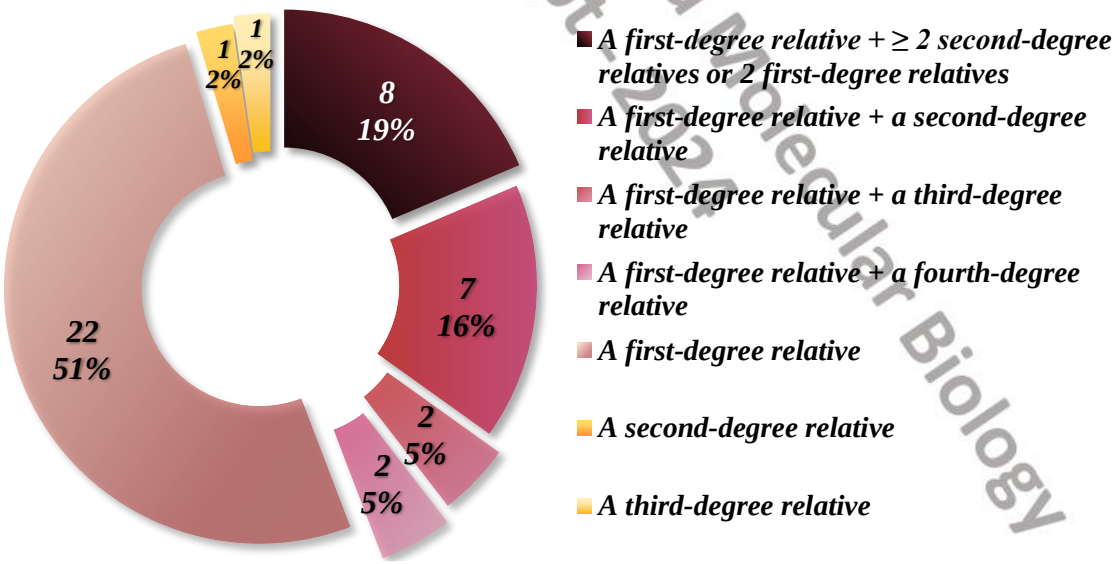

Figure 9.Distribution of patients based on the number of relatives diagnosed with AD

Calculation of Recurrence Risk

In the case of AD, genetic factors are represented by multiple risk genes with minor but additive effects, which collectively contribute to the susceptibility to the disease. The number of these genes is highly variable. Thus, multifactorial determinism involves a complex, continuous interaction between environmental and hereditary components with polygenic influences (the presence of multiple risk genes). In some cases, neurodegenerative processes are triggered in susceptible individuals by exposure to certain environmental factors, leading to the onset of the disease and its specific symptoms.

Reaching and surpassing the risk threshold is dependent on the number of mutant genes and the allelic variants possessed or inherited by an individual. The assessment of genetic risk in AD is calculated similarly to general risks, in accordance with the values specified in the recurrence risk tables for multifactorial diseases (Table 5).

Table 5. Recurrence Risks in Multifactorial Diseases: AD is associated with a frequency of 0.5% and a heritability of 60% (Smith, 1972; cited in Covic et al., 2004).

Disease Frequency in Population (%)	***Heritability (%)***	***No. of parents diagnosed with AD***								
		0			***1***			***2***		
		No. of siblings diagnosed with AD								
		0	***1***	***2***	***0***	***1***	***2***	***0***	***1***	***2***
1.0	***80***	0.9	6.7	14.6	8.5	18.7	27.9	40.3	45.9	50.6
	60	1.0	4.9	10.6	5.7	12.3	19.2	21.7	28.3	34.1
	40	1.0	3.3	6.5	3.5	7.0	12	9.7	14.1	18.7
0.5	***80***	0.5	5.1	12.3	6.2	15.5	24.3	37.6	43.2	47.9
	60	***0.5***	***3.4***	***8.4***	***3.8***	***9.5***	***15.8***	***18.1***	***24.4***	***30.0***
	40	0.5	2.1	4.5	2.2	4.9	8.3	7.0	10.8	14.9
0.1	***80***	0.1	2.6	8.4	2.9	9.8	17.6	30.4	36.7	41.2
	60	0.1	1.5	4.6	1.5	5.0	9.6	11.5	17.1	22.2
	40	0.1	0.7	0.7	0.7	2.2	4.2	3.6	6.0	8.7

An important objective of the study was to calculate the recurrence risk (a procedure conducted in accordance with the information provided by empirical risk tables for multifactorial diseases - population frequency of approximately 0.5% and a heritability of 60%), which was estimated to be empirical, between 2-4% (Table 6) for the majority of the studied cases without affected relatives (out of the total 219 patients admitted and diagnosed with AD in 2022 and 2023, 176 had no family history of AD).

Table 6. Risk of recurrence for the studied cases

No. of relatives diagnosed with AD	Year	No. of patients	Recurrence risk	Risk level	Genetic cause
Without family history of AD	2023	77	***2%***	empirical	mutagenesis
	2022	99			
	TOTAL	***176***			
A third-degree relative (uncle)	2022	***1***	***2-3.4%***	very low	genealogical / genetic transmission
A second-degree relative (grandparent)	2022	***1***	***3.4%***	low	

A first-degree relative (parent)	2023	10	***3.8%***	minimal / slight
	2022	12		
	TOTAL	***22***		
A first-degree relative (mother/father) + a fourth-degree relative (cousin)	2022	***2***	***3.8-9.5%***	moderate
A first-degree relative (mother/father) and a third-degree relative (aunt/uncle)	2022	***2***	***3.8-9.5%***	
A first-degree relative (parent) and a second-degree relative (sibling/grandparent)	2023	5	***9.5%***	
	2022	2		
	TOTAL	***7***		
A first-degree relative (parent) and at least two second-degree or third-degree relatives or Both parents (first-degree relatives)	2023	6	***18%***	high / very high
	2022	2		
	TOTAL	***8***		

The study reveals that there is a high risk of developing AD for patients with both parents affected by AD or for those who have one first-degree relative along with at least two second-degree or third-degree relatives with AD. This highlights the critical importance of genetic counseling and monitoring throughout an individual's life, including premarital, prenatal, and postnatal stages.

In the context of providing genetic counseling to patients from families with a history of chronic neurological conditions such as AD, prophylaxis primarily involves the implementation of programs for testing, early evaluation, and identification of both genetic and non-genetic risk factors, as well as individual predispositions and associated diseases that may exacerbate the vulnerabilities earlier. Additionally, it entails providing genetic counseling in accordance with the established protocols and specific guidelines for this complex medical procedure.

The process of providing genetic counseling and recommendations is grounded in the analysis of families or individuals, considering their level of education, training, and ability to comprehend the concepts presented. This includes defining and explaining anatomical processes and terminology. Additionally, the medical counselor must respect the individual's religious and ethical beliefs while addressing the specific characteristics of the identified condition (AD), including its severity and progression rates.

Conclusions

The purpose of the conducted study was to compile conclusive statistics, identify genetic factors, and correlate them with environmental ones, highlighting the importance of developing evaluation programs and early introduction of medication to decelerate the progression of neurodegenerative processes.

The analysis of the cohort emphasized the necessity to investigate known genetic mutations and to identify all genetic and biochemical alterations that may increase an individual's susceptibility to develop AD over the course of life. The familial predisposition can

lead to the irreversible progression of cognitive decline and the eventual loss of one's identity. Additionally, the study highlights the significance of exploring the complex interactions between genetic, physiological, demographic, and environmental factors that may insidiously trigger the inherited vulnerabilities. All the extensive familial investigations should be followed by the formulation and delivery of informed genetic counseling and recommendations.

The retrospective study conducted on patients admitted to the Neurology Department of the "Dr. Iacob Czihac" Clinical Military Emergency Hospital Iași highlights that AD occupies a significant position among chronic neurological disorders. Although the majority of patients do not present hereditary antecedents, predisposing diseases, environmental and behavioral factors, stress, as well as the region of residence, play fundamental roles in the onset of the disease. It is observed that individuals in the 60-70 age category, from urban areas, especially females, have a higher probability of developing AD.

In conclusion, with the global increase in incidence, prevalence, and mortality rates, focusing on identifying genetic and non-genetic factors involved in the development of neurodegenerative diseases, along with advancing research to create modern personalized therapies, is essential to counter these adverse trends. In this context, the medicine of the future is envisioned as both preventive and personalized.

Unequivocally characterized by a vast etiology, through cerebral atrophy associated with neurotrophin depletion, mitochondrial dysfunction, accumulation of neurofibrillary tangles, and senile plaques following the appearance of allelic variants (APOE4, MAPT, APOJ, SORT1) or dominant autosomal mutations (PSEN1/2, APP), AD is a multifactorial disorder resulting from the bilateral interaction between genetic and environmental factors or solely one of them. However, the transition from vulnerability to the actual disease is achieved through the continuous corroboration of these two major classes of factors.

Acknowledgments: -

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