

<https://doi.org/10.48047/AFJBS.6.16.2024.1245-1263>



African Journal of Biological Sciences

Journal homepage: <http://www.afjbs.com>



Research Paper

Open Access

Understanding Alzheimer's Disease: Risk Factors And Symptoms In Oran Province

Behar Ahmed Abbou Abdellah^{1*}, Fizazi Anissa², Hadbi Mohammed³, Ziouane Karima⁴, Belhadj Amina², Amrani Laouni¹, Kharoubi Omar¹, Sahraoui Tewfik².

¹Laboratory of Experimental Biotoxicology, Biodepollution and Phytoremediation, Faculty of Life and Natural Sciences, University Oran1 ABB, Oran 31000, Algeria.

²Biology of Development and Differentiation Laboratory, Department of Biology, Faculty of Natural and Life Science University of Oran1, Algeria.

³Neurology Department, University Hospital Center (CHU), Oran, Algeria.

⁴Medical Neurology Consultation Department, University Hospital Center (EHU) of Oran, 1st November 1954, Oran, Algeria.

Corresponding author: Behar Ahmed Abbou Abdellah, +213793630077 behar.ahmedabbouabdellah@edu.univ-oran1.dz

Article Info

Volume 6, Issue 16, December 2024

Received: 02 October 2024

Accepted: 20 November 2024

Published: 12 December 2024

[doi: 10.48047/AFJBS.6.16.2024.1245-1263](https://doi.org/10.48047/AFJBS.6.16.2024.1245-1263)

ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by neurocognitive disorders such as memory deterioration. Its frequency increases with the aging of the population,

We examined the clinical characteristics and risk factors associated with AD in Oran Province.

This is a retrospective study carried out at the Department of Medical Neurology Consultation, University Hospital Center (EHU) of Oran, 1st November 1954, and the Neurology Department, University Hospital Center (CHU) of Oran. On medical records of 5,360 patients, from February 2013 to November 2024. These data were processed by Microsoft Excel2016.

The clinical profile of the 5,360 patients with AD, aged 45 to 96 years, both sexes with various comorbidities (hypertension in 53.17% of cases, diabetes in 48.19% and obesity in 28.13% of cases, etc.) which constitute risk factors. The most frequent clinical complaints were memory problems (69.00%), depression (54.50%), agnosia (47%), as well as behavior disorders (43.50%), aphasia (30.20%), stress (26.70%), appetite disorders (26.50%) and sleep disorders (22%).

Additionally, we performed a cognitive assessment using the Mini Mental State Examination (MMSE) to study the distribution of cognitive impairment among the patients.

The existence of several risk factors, and the different symptoms that show the presence of this dementia.

Keywords: Alzheimer disease (AD); Epidemiology; Environmental Factors; Risk Factors; Symptoms; MMSE.

© 2024 Behar Ahmed Abbou Abdellah, This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the central nervous system characterized by neuropathological and neurochemical alterations, which can lead to death. **(Salmès & Derouesné, 2009).**

It is one of the most diagnosed forms of dementia in older adults. Its frequency increases with the aging of the population, making it one of the leading causes of death among the elderly. **(Garre-Olmo et al., 2009).**

This condition is associated with gradual alterations as well as the destruction of brain tissue. It is characterized by major neurocognitive disorders, distinguished by the deterioration of memory, reflexes, recognition of objects and people, and a loss of the ability to orient in time and space. There are also psychological and behavioral symptoms, such as mental confusion and depression, which often progress to a deterioration of intellectual faculties. **(El-Kadmiri et al., 2013).**

The increasing life expectancy of the population elevates the risk of developing this disease. Therefore, age is considered a risk factor, as well as sex and countless comorbidities that can have an impact on this disease. **(Boustani et al., 2003).** In Algeria, nearly 100,000 people are affected by Alzheimer's disease. However, there is a notable lack of data and studies on Alzheimer's disease in this country. **(WHO, 2015).**

In this context, we carried out a study to examine the clinical characteristics and risk factors associated with Alzheimer's disease within the municipalities of Oran Province.

Materials and methods

This study was conducted in the Department of Medical Neurology Consultation at the University Hospital Center (EHU), 1st November 1954, and the Neurology Department at the University Hospital Center (CHU). Prior to initiating the study, authorization was obtained from the relevant departments to proceed with the archival consultation.

Based on medical records, this was a retrospective study involving 5,360 patients between February 2013 and November 2024. Among these patients, 2,243 were men and 3,117 were women, aged 45 to 96 years.

Inclusion Criteria: The study included patients with accessible medical records, covering demographic data, medical history, and symptoms. Factors considered included sex, age, chronic diseases (e.g., diabetes, hypertension), history of head trauma, obesity and hereditary medical conditions. The most frequently reported symptoms were memory loss, depression, aphasia, agnosia, spatiotemporal disorientation, disturbances in sleep and appetite, behavioral changes, and stress. The Mini-Mental State Examination (MMSE) was used as a cognitive screening tool to assess the mental status of the study participants.

Exclusion criteria: Patients with unusable medical records were excluded, particularly those diagnosed with conditions unrelated to the study focus.

Data Collection: The data were collected from hospital archives, focusing on the medical records of hospitalized patients. For each patient, data were gathered from the following sources:

- **Medical Records:** diagnostic reports, discharge summaries, symptom documentation and treatment plans.
- **Biological Evaluations:** Laboratory tests and imaging results were reviewed to assess relevant biological markers and diagnostic findings.

Ethical Considerations: All data were collected and analyzed while ensuring the confidentiality and anonymity of the patients.

Data Analysis: Statistical analysis was performed using Microsoft Excel 2016. Descriptive statistics, including frequencies and percentages, were used to summarize patient demographics, clinical characteristics, and symptom profiles. No inferential statistical tests were conducted, as the study aimed to provide an overview of the patient population based on medical record data.

Results

The average age of the patients was 73.28 ± 0.78 years. A significant majority of cases (88.08%) occurred in individuals aged 60 to 85, while younger patients represented only 3.35% of the total cases (**Figure1**).

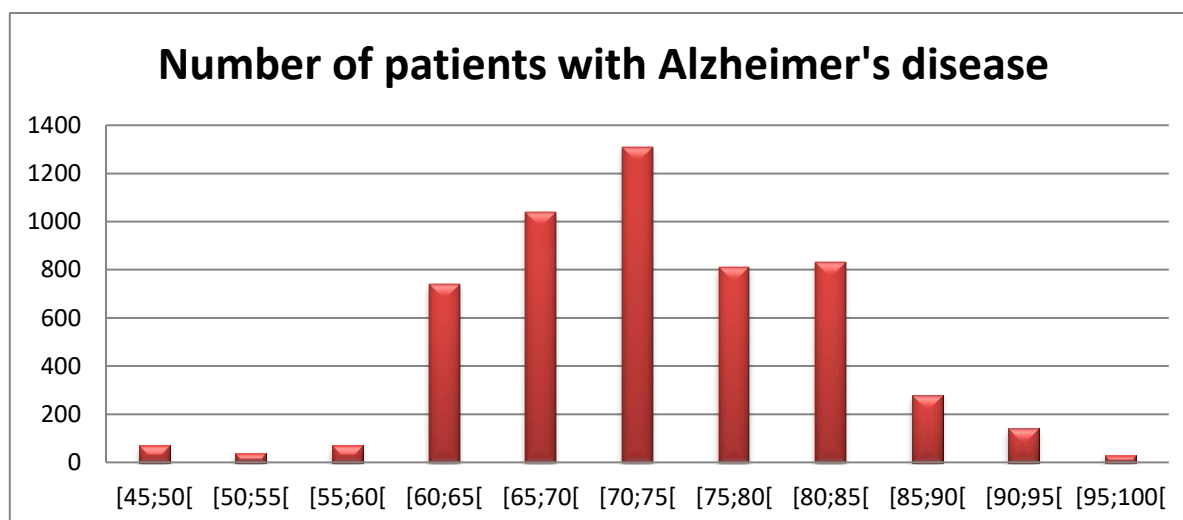


Figure 1. Representation of the distribution of patients with AD by age.

Based on gender, 58.02% of the patients were women (**Figure2**).

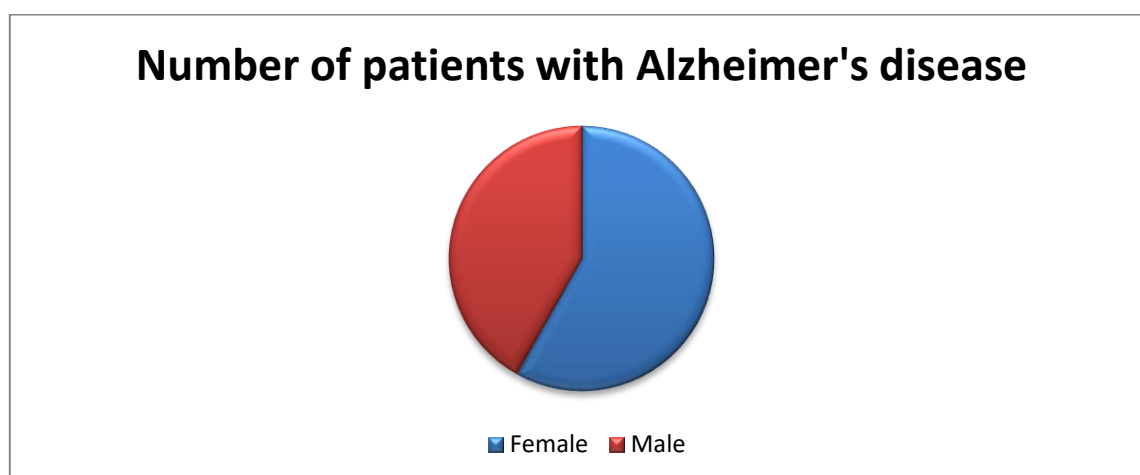


Figure 2. Representation of the distribution of patients with AD by gender.

Numerous comorbidities were observed in the infected patients, with the most common being hypertension (53.17%), diabetes (48.19%)(**Figure3**), and obesity (28.13%). Other conditions included cranial trauma (17.94%), heart disease (13.62%) and thyroid disorders (18.23%)(**Table1**).

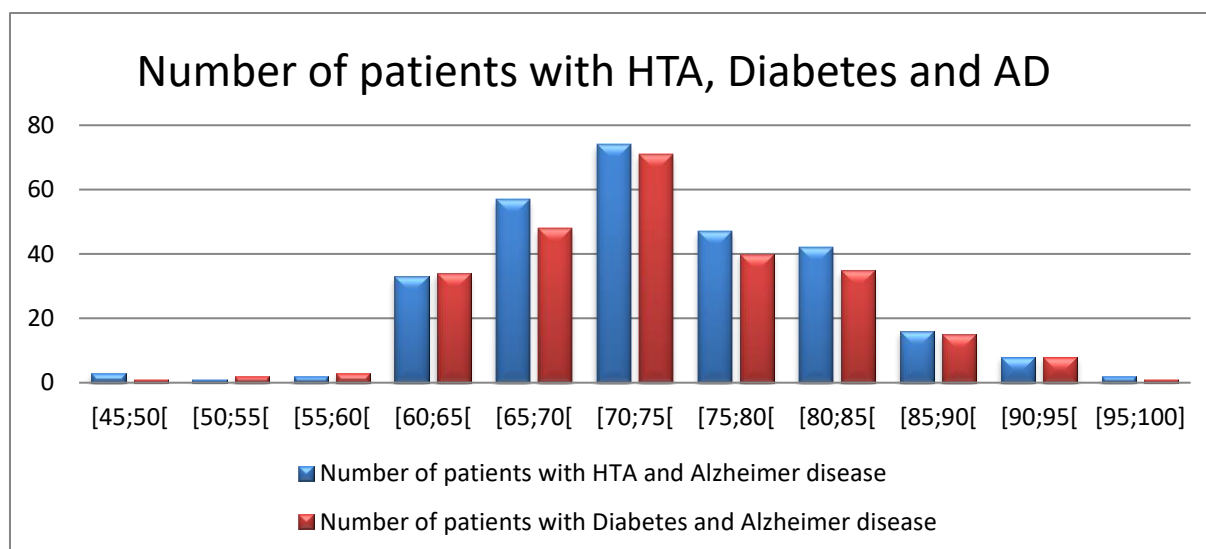


Figure 3. Representation of the distribution of patients with AD HTA and Diabetes by age.

Table 1. Representation of the distribution of different risk factors (hypertension, diabetes, obesity, head trauma, heart disease and thyroid) in patients with AD.

Risk Factors		Number of patients suffering from AD and another risk factor	Percentage of patients suffering from AD and another risk factor
AGE	[45 ; 50]	70	1.30%
	[50 ; 55]	40	0.76%
	[55 ; 60]	70	1.30%
	[60 ; 65]	740	13.80%
	[65 ; 70]	1040	19.40%
	[70 ; 75]	1310	24.44%
	[75 ; 80]	810	15.11%
	[80 ; 85]	830	15.49%
	[85 ; 90]	280	5.22%
	[90 ; 95]	140	2.61%
	[95 ; 100]	30	0.56%
GENDER	Female	3117	58.02%
	Male	2243	41.98%
HTA		2852	53.17%
DIABETES		2583	48.19%
OBESITY		1508	28.13%
CRANIAL TRAUMA		962	17.94%
HEART DISEASE		730	13.62%
THYROID		977	18.23%

We also observed the clinical features, with memory problems being the most prevalent, affecting 69.00% of patients (Table2).

Table 2. Representation of the distribution of AD symptoms in the studied population.

SYMPTOMS	Number of patients	Percentage of patients
MEMORY PROBLEMS	3700	69.0%
DEPRESSION	2920	54.5%
APPETITE DISORDER	1420	26.5%
SLEEP DISORDER	1180	22.0%
APHASIA	1620	30.2%
STRESS	1430	26.7%
SPATIO-TEMPORAL DISORIENTATION	1810	33.8%
AGNOSI	2520	47.0%
BEHAVIOR DISORDER	2330	43.5%

The census of Alzheimer's cases in the Oran region yielded the following results (**Figure4**).

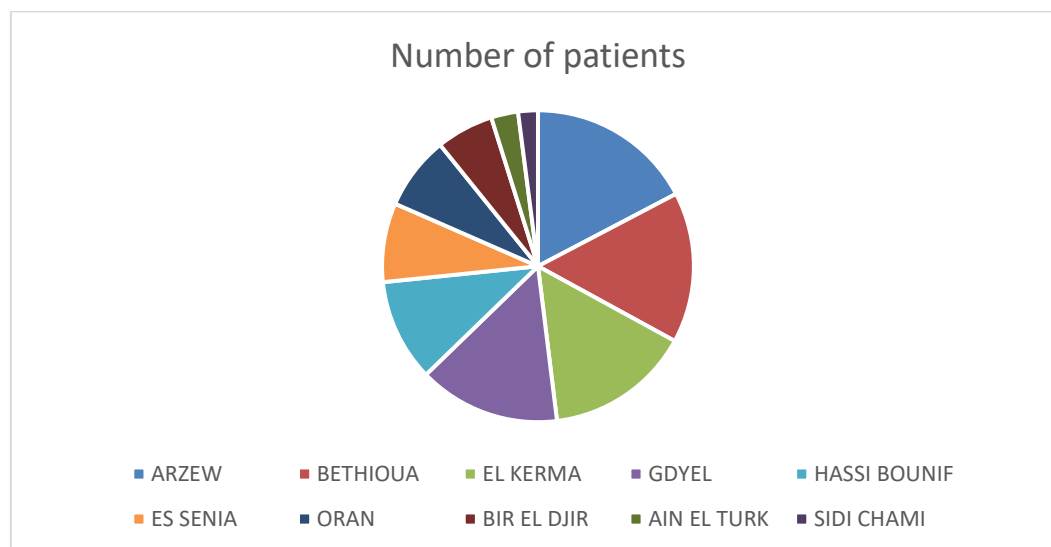


Figure 4. Representation of the distribution of patients with AD across the municipalities of the Oran.

A cognitive assessment was also performed using the Mini Mental State Examination (Table3).

Table 3. Distribution of MMSE Scores Among Patients.

Category	MMSE Score Range	Number of Patients	Percentage (%)
Mild Cognitive Impairment	18-23	2432	45.38%
Moderate Cognitive Impairment	oct-17	1851	34.54%
Severe Cognitive Impairment	<10	1077	20.08%
Total	-	5360	100%

Discussion

Risk factors

Age

Alzheimer's disease (AD) is a neurodegenerative disorder affecting elderly individuals. Figure 1 illustrates data from a sample of 5,360 patients. Age was the most prominent risk factor.

A Canadian study found a decreasing age of AD patients, which contrasts with our findings **(Helmer et al., 2006)**. **Niu et al., (2017)** showed that the proportion of elderly individuals in a prospective study in Europe increases with age, reaching 22.53% among those over 85 years.

AD could represent an accelerated form of normal aging, characterized by severe neuronal synapse loss and pathological changes. For instance, the excessive accumulation of senile plaques in elderly individuals may cause early AD cases **(Rossor & Mountjoy, 1986)**. Moreover, the early appearance of neurofibrillary tangles in the locus coeruleus may contribute to AD, potentially triggering memory loss **(Guillozet et al., 2003)**.

Sex

Our study aligns with others showing that women are more affected by AD than men, despite men's shorter life expectancy.

Studies reporting identical prevalence rates in both sexes are less common **(Hebert et al., 2001)**. Data analysis considering sex and education level indicates a higher incidence of AD among women **(Letenneur et al., 1999)**.

This predominance may be linked to hormonal factors, such as estrogen deficiency and genetic factors **(Niu et al., 2017)**.

Other risk factors

HTA

Hypertension is common in individuals over 60 years old. Studies have linked middle-aged hypertension (40 to 64 years) with AD neuropathology, including brain atrophy, senile plaques, and neurofibrillary degeneration (**Hebert et al., 2001**). A Canadian study also reported high rates of chronic diseases among these patients (**Letenneur et al., 1999**). Elevated systolic blood pressure (>160 mmHg) is associated with reduced brain weight and more hippocampal senile plaques, while elevated diastolic blood pressure (>95 mmHg) is linked to neurofibrillary degeneration, supporting the connection between hypertension and Alzheimer's (**Tzourio et al., 1999**).

Diabetes

It was associated with a high risk of AD (Type3 Diabetes), especially with elevated blood sugar levels over the past five years. A Canadian study found that chronic diseases like diabetes increase the risk of AD and cardiovascular diseases (**Wallace, 2014**). In a study of 5,180 individuals over 60, diabetes was associated with hippocampal atrophy, insulin resistance, and AD risk. Another study suggests that there is a risk of developing AD even in individuals with high insulin levels, without having diabetes (**den-Heijer et al., 2003**).

There is an association between hyperinsulinemia, hyperglycemia, and AD due to insulin resistance, which leads to senile plaque accumulation and TAU protein hyperphosphorylation (**Rasgon et al., 2011**). Research on women revealed that insulin plays a central role in the brain's metabolism of A β , with high C-peptide levels in non-diabetic being linked to a higher AD risk (**Stewart et al., 2005**).

Obese

Many studies show an association between AD and BMI. Weight loss and a BMI <18.5 have been linked to an increased risk of dementia (**Stewart et al., 2005**), while a high BMI, for example, in a study conducted in Sweden among 290 women, shows an association between obesity and a smaller hippocampal volume (**Gustafson et al., 2004**). The metabolic changes associated with obesity can damage the nervous system, leading to neuronal death by altering neuronal plasticity.

Cranial traumas

Mazon et al., (2017) has highlighted the existence of a relationship between head traumas and the risk of developing AD.

Athletes can suffer head traumas which increase the risk of developing AD. A study has found similarities between head trauma and AD symptoms, such as neurofibrillary degeneration, the accumulation of amyloid precursor protein (APP) in neuronal cell bodies, which increases the expression of A β (**Gentleman et al., 1993**), and excessive phosphorylation of Tau proteins.

Heart disease

Many studies have explored the relationship between Alzheimer's and cardiovascular conditions, including its link to coronary artery disease (**de la Torre, 2006**) and heart failure (**Beeri et al., 2006**). Autopsy studies have concluded a relationship between the density of neuropathological brain lesions and AD.

A Swedish study involving 1,301 elderly subjects found an association between heart failure and AD (**Qiu et al., 2006**). It is essential to note that brain health is directly affected by heart health, as the brain consumes a large amount of oxygen (**Mergenthaler et al., 2013**). Several factors can help reduce the risk of developing dementia, such as physical activity and a healthy diet (**Barberger-Gateau et al., 2007**).

Thyroid disorders

Alterations in the endocrine system are increasingly linked to AD: high levels of cortisol (**Hogervorst et al., 2004**) and primarily thyroid hormone, a powerful neuroregulator of the central nervous system, being responsible for cognitive alterations (**Asher, 1949**).

Several studies have been conducted on this subject, yielding various results. Some have found no association between TSH levels and AD, while others have shown that high TSH levels are associated with a positive diagnosis of dementia in elderly subjects (**Kuriakose & Xiao, 2020**). However, in a study conducted in Rotterdam, after more than five years of observation, found no association between the two (**de Jong et al., 2006**).

Clinical features

Memory disorders (amnesia)

Amnesic disorders, which involve difficulty in memorizing current facts or retrieving memories (**Table 2**), are generally the first signs of AD (**Rigaud, 2001**).

There are different types of memory; short-term memory (STM) for limited-duration data retention; encompassing working memory, the first to be disturbed in AD (**Baddeley et al., 1986**); and long-term memory (LTM), retaining data for a lifetime, it is composed of:

- ✓ Explicit memory, includes episodic memory (the most vulnerable), which stores personal information and is affected early in AD, causing spatiotemporal disorientation (Adam, 2006), and semantic memory, which is the memory of words and is disrupted early in AD.
- ✓ Implicit memory, this remains preserved in AD.

Numerous studies have focused on episodic memory to understand the progression of AD (**Perry et al., 2003**).

Depression

AD is accompanied by depression (with an unpleasant feeling of fear, sadness, pessimism). Depression was present in 54.50% of the entire population studied. Many hypotheses have been proposed to explain this; brain imaging studies have found that depression generates hypoperfusion in the frontal regions (Chi et al., 2014) and a high rate of senile plaques and neurofibrillary tangles (**Förstl et al., 1992**).

Appetite disorders

Regarding nutritional imbalance, it was present in 26.50% of all patients. Several studies have shown that weight loss due to appetite disorders is widespread in Alzheimer's patients. Another study conducted by White et al. has shown that AD is the only predictive factor for weight loss. Furthermore, some studies have shown that weight loss could increase the mortality rate in patients with AD (**White et al., 1996**).

Sleep disorders

Circadian disorders were found in 22.00% of Alzheimer's patients (Table 2). Researchers have demonstrated a relationship between the severity of these disorders and AD (**Bliwise et al., 1995**), highlighting that these disorders appear from the moderate stages of AD and are accompanied by aggression (**Moran et al., 2005**). Studies on sleep abnormalities indicate

severe cognitive disorders that worsen over time, potentially causing memory issues. This is explained by the presence of monoamine oxidase A in patients suffering from sleep disorders associated with AD (**Bliwise, 2002**).

Language disorders (Aphasia)

30.20% of Alzheimer's patients suffer from aphasia, which has three variants: Wernicke's aphasia, Broca's aphasia, and a variant characterized by difficulties in finding the words (**Macoir et al., 2014**). Over time, patients speak less, experience difficulties naming objects, and understanding verbal language. In severe stages, they may become mute or have restricted communication (**Cardebat et al., 1995**). Studies show that while patients struggle with conversation, they communicate better with their spouses than alone. Regarding gestural and eye communication, these remain preserved (**Bayles et al., 1987**).

Stress

Stress affects 26.70% of Alzheimer's patients (**Table 2**). Many studies highlight the impact of stress on neurodegenerative and cardiovascular diseases (**Bayles et al., 1987**). Studies show that an excess of circulating glucocorticoids due to chronic stress is associated with an increase in A β , and TAU protein phosphorylation in the hippocampus and prefrontal cortex, impairing memory (**Crestani, 2017**). Neuroinflammation in the hippocampus due to stress increases pro-inflammatory cytokines, causing temporary working memory loss (**McKim et al., 2016**). Whether these cognitive effects are temporary or permanent depends on the duration of exposure. The adverse effects of stress are intensified during periods of vulnerability, such as childhood brain development or aging-related degeneration (**Lupien et al., 2009**). This produces structural changes in the brain that increase the risk of developing AD.

Spatial-temporal disorientation

The patient progressively loses their ability to orient in space. This disorientation is divided into three stages. At the first two stages, the inability to memorize new information and forgetfulness set in. In the last stage, spatial-temporal abilities are greatly affected.

From birth, children begin their cognitive development, which includes the evolution of memory and the acquisition of spatial-temporal orientation. Spatial-temporal disorientation is a common symptom observed in 33.80% of all patients (**Table 2**). Patients progressively lose their ability to orient themselves in space. This disorientation is divided into three stages: the

first two stages are marked by an inability to memorize new information, and the final stage, where spatial-temporal abilities are significantly impaired (**Ylieff, 1995**).

Agnosia (Recognition disorders)

The patient may also experience frequent mood changes. Among patients who suffer from this symptom, aggression is often present among these patients, manifesting as verbal and gestural violence.

Moreover, wandering behaviors are common: the patient can no longer find their bearings (**Teri, 1997**).

Agnosia is present in 47.00% of all patients. These disorders represent an inability to identify messages from the environment and can manifest in various forms:

- Tactile disorder: The patient cannot identify what they are touching.
- Auditory disorder: They cannot identify sounds.
- Visual disorder: They cannot recognize faces or objects.
- Olfactory disorder.

Agnosia can progress to the point where the patient can no longer recognize themselves (asomatognosia). Behavioral disorders affect 43.50% of patients. These include the loss of the ability to perform tasks learned during childhood, such as writing or swallowing, which often leads to a loss of autonomy. Wandering behaviors are frequently observed, as patients lose their sense of orientation (**Teri, 1997**).

The distribution of patients within the province of Oran

The distribution of AD cases within the province of Oran highlights a higher prevalence in certain municipalities (**Figure4**).

The Arzew Hub: Located in the eastern part of Oran, it includes the municipalities of Arzew and Bethioua. These areas have experienced significant demographic growth, which has led to the establishment of industrial platforms at the expense of agricultural lands. This industrialization has led to a high concentration of petrochemical complexes and other production units, such as helium, nitrogen, and liquid fertilizers. Consequently, air and water pollution have become significant issues. Heavy metals prevalent in this area have been linked

to an increased risk of AD by contributing to amyloid pathology (González-Domínguez et al.,2014).

El Kerma: Air pollution caused by fine particles, which can accumulate in the brain, has been identified as a potential risk factor for AD

Gdyel: 15% of Alzheimer's patients seek consultations in this region, making it a significant urban and industrial area. This municipality faces severe pollution issues, threatening plant and animal life and contributing to cardiovascular and cerebrovascular diseases. Research has shown that air pollution increases inflammatory markers and beta-amyloid levels in individuals living in polluted areas (**Calderón-Garcidueñas et al., 2004**), and impacts cognitive decline (**Weuve et al., 2011**).

Low Pollution Areas: Es Senia, Oran, and Bir El Djir have low levels of air pollution, which decreases the risk of neurodegenerative diseases.

Ain El Turk and Sidi Chami: a low rate of Alzheimer's patients is found. However, these two regions are characterized by the presence of nitrogen and phosphorus-based pollutants.

Cognitive Assessment Using the Mini Mental State Examination (MMSE)

The MMSE evaluates cognitive functions including memory, attention, language and visuospatial abilities. It also classifies patients according to the severity of cognitive impairment and the progression of AD, which is crucial for intervention.

In our study, the MMSE scores of 5,360 patients were classified into three categories:

- Mild cognitive impairment (18-23): 45.38% of patients have minimal deficits and are at an early stage, allowing for early intervention.
- Moderate cognitive impairment (10-17): 34.54% (1851 individuals) show significant deficits in memory and daily living activities.
- Severe cognitive impairment (<10): 20.08% require intensive care and tailored therapeutic interventions due to severe functional dependence.

These results align with existing literature, which highlights a mild prevalence of these impairments in populations at risk of AD. A meta-analysis by **Zhao et al. (2022)** demonstrated that moderate and severe stages represent over 54% of patients receiving clinical evaluations, confirming the MMSE's utility in assessing the severity of cognitive impairment.

A study showed that MMES scores below 17 are strongly linked to severe functional dependence (Garre-Olmo et al., 2015).

Conclusion

In the study conducted on AD patients in Oran, several risk factors were identified. Advanced age, gender, high blood pressure, diabetes, obesity, and head injuries emerged as the most significant contributors to cognitive decline and dementia. Cholesterol levels and thyroid disorders were also noted as risk factors.

Clinically, memory disorders predominated, often accompanied by spatial-temporal disorientation. Depression was another common symptom, along with appetite, sleep disturbances, aphasia, and agnosia. Behavioral disorders, including stress and aggression, were also observed.

As perspectives, early detection and intervention strategies should be prioritized to delay disease progression and improve patient outcomes. Additionally, further research into managing risk factors and developing targeted interventions is essential to reduce the prevalence and impact of AD.

References

- Adam, S. (2006). Le fonctionnement de la mémoire épisodique dans la maladie d'Alzheimer. *In Actualités sur les démences: aspects cliniques et neuropsychologiques*. 135–165.
- ASHER, R. (1949). Myxoedematous madness. *Br Med J*. 2, 555–562. DOI: 10.1136/bmj.2.4627.555.

Baddeley, A., Logie, R., Bressi, S., Della Sala, S. and Spinnler, H. (1986). Dementia and working memory. *The Quarterly Journal of Experimental Psychology Section A*. **38**, 603–618.

Barberger-Gateau, P., Raffaitin, C., Letenneur, L., Berr, C., Tzourio, C., Dartigues, J.F. and Alpérocitch, A. (2007). Dietary patterns and risk of dementia. *Neurology*. **69**, 1921–1930. DOI: 10.1212/01.wnl.0000278116.37320.52.

Bayles, K.A., Kaszniak, A.W. and Tomoeda, C.K. (1987). Communication and cognition in normal aging and dementia. College-Hill Press/Little, Brown & Co.

Beeri, M.S., Rapp, M., Silverman, J.M., Scgmeidler, J., Grossman, H.T., Fallon, J.T., Purohit, D.P., Perl, D.P., Siddiqui, A., Lesser, G., Rosendorff, C. and Haroutunian, V. (2006). Coronary artery dis-ease is associated with Alzheimer disease neuropathology in APOE4 carriers. *Neurology*. **66**, 1399–1404. DOI: 10.1212/01.wnl.0000210447.19748.0b.

Bliwise, D.L., Hughes, M., McMahon, P.M. and Kutner, N. (1995). Observed Sleep/Wakefulness and Severity of Dementia in an Alzheimer's Disease Special Care Unit. *J Gerontol A Biol Sci Med Sci*. **50A**, M303–M306. DOI: 10.1093/gerona/50a.6.m303.

Bliwise, D.L. (2002). Sleep apnea, APOE4 and Alzheimer's disease 20 years and counting?. *J Psychosom Res*. **53**, 539–546.

Boustani, M., Peterson, B., Hanson, L., Harris, R. and Lohr, K.N. (2003). Screening for Dementia in Primary Care: A Summary of the Evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. **138**, 927. DOI: 10.7326/0003-4819-138-11-200306030-00015.

Calderón-Garcidueñas, L., Reed, W., Maronpot, R.R., Henriquez-Roldan, C., Delgado-Chavez, R., Calderon-Garciduenas, A., Dragustinovis, I., Franco-Lira, M., Aragon-Flores, M., Solt, A.C., Altenburg, M., Torres-Jardon, R. and Swenberg, J.A. (2004). Brain Inflammation and Alzheimer's-Like Pathology in Individuals Exposed to Severe Air Pollution. *Toxicol Pathol*. **32**, 650–658. DOI: 10.1080/0192623049052023.

Cardebat, D., Aithamon, B. and Puel, M. (1995). Les troubles du langage dans les démences de type Alzheimer. *Neuropsychologie*. **213–223**.

Chi, S., Yu, J.T., Tan, M.S. and Tan, L. (2014). Depression in Alzheimer's disease: epidemiology, mechanisms, and management. *Journal of Alzheimer's disease*. **42**, 739–755.

Crestani, C.C. (2017). Adolescent vulnerability to cardiovascular consequences of chronic emotional stress: Review and perspectives for future research. *Neuroscience & Biobehavioral Reviews*. **74**, 466–475. DOI: 10.1016/j.neubiorev.2016.03.027.

De Jong, F.J., den Heijer, T., Visser, T.J., de Rijke, Y.B., Drexhage, H.A., Hofman, A. and Breteler, M.M.B. (2006). Thyroid Hormones, Dementia, and Atrophy of the Medial Temporal Lobe. *The Journal of Clinical Endocrinology & Metabolism*. **91**, 2569–2573. DOI: 10.1210/jc.2006-0449.

De la Torre, J.C. (2006). How do heart disease and stroke become risk factors for Alzheimer's disease?. *Neurol Res*. **28**, 637–644. DOI: 10.1179/016164106x130362.

Den-Heijer, T., Vermeer, S.E., Van Dijk, E.J., Prins, N.D., Koudstaal, P.J., Hofman, A. and Breteler, M.M.B. (2003). Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia*. **46**, 1604–10. DOI: 10.1007/s00125-003-1235-0.

El-Kadmiri, N., Hamzi, K., El Moutawakil, B., Slassi, I. and Nadifi, S. (2013). Les aspects génétiques de la maladie d'Alzheimer. *Pathologie Biologie*. **61**, 228–238. DOI: 10.1016/j.patbio.2013.04.001.

Förstl, H., Burns, A., Luthert, P., Cairns, N., Lantos, P. and Levy, R. (1992). Clinical and neuro-pathological correlates of depression in Alzheimer's disease. *Psychol Med*. **22**, 877–884. DOI: 10.1017/s0033291700038459.

Garre-Olmo, J., Flaqué, M., Gich, J., Pulido, T.O., Turbau, J., Vallmajo, N., Viñas, M., Lopez-Pousa, Secundi. And Registry of Dementia of Girona Study Group. (2009). A clinical registry of dementia based on the principle of epidemiological surveillance. *BMC Neurology*. **9**, :1–9.

Garre-Olmo, J., Vilalta-Franch, J., Calvo-Perxas, L., Monserrat-Vila, S., Lopez-Pousa, S. and CoDep-AD Study Group. (2015). Dependence scale for Alzheimer's disease: relationship with other clinical indicators and psychometric properties. *Journal of Geriatric Psychiatry and Neurology*. **28**(2), 117-125.

Gentleman, S.M., Nash, M.J., Sweeting, C.J., Graham, D.I. and. Roberts, G.W. (1993). B-Amyloid precursor protein (β APP) as a marker for axonal injury after head injury. *Neurosci Lett*. **160**, 139–144. DOI: 10.1016/0304-3940(93)90398-5.

González-Domínguez, R., García-Barrera, T. and Gómez-Ariza, J.L. (2014). Homeostasis of metals in the progression of Alzheimer's disease. *BioMetals*. **27**, 539–549. DOI: 10.1007/s10534-014-9728-5.

Guillozet, A.L., Weintraub, S., Mash, D.C. and Mesulam, M.M. (2003). Neurofibrillary Tangles, Amyloid, and Memory in Aging and Mild Cognitive Impairment. *Arch Neurol*. **60**, 729. DOI: 10.1001/archneur.60.5.729.

Gustafson, D., Lissner, L., Bengtsson, C., Björkelund, C. and Skoog, I. (2004). A 24-year follow-up of body mass index and cerebral atrophy. *Neurology*. **63**, 1876–1881. DOI: 10.1212/01.wnl.0000141850.47773.5f.

Hebert, L.E., Scherr, P.A., McCann, J.J., Beckett, L.A. and Evans, D.A. (2001). Is the Risk of Developing Alzheimer's Disease Greater for Women than for Men?. *Am J Epidemiol*. **153**, 132–136. DOI: 10.1093/aje/153.2.132.

Helmer, C., Pasquier, F. and Dartigues, J.F. (2006). Épidémiologie de la maladie d'Alzheimer et des syndromes apparentés. *Médecine/sciences*. **22**, 288–296. DOI: 10.1051/medsci/2006223288.

Hogervorst, E., Bandelow, S., Combrinck, M. and Smith, A.D. (2004). Low free testosterone is an independent risk factor for Alzheimer's disease. *Exp Gerontol*. **39**, 1633–1639. DOI: 10.1016/j.exger.2004.06.019.

Kuriakose, D. and Xiao, Z. (2020). Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives. *Int J Mol Sci*. **21**, 7609. DOI: 10.3390/ijms21207609.

Letenneur, L., Gilleron, V., Commenges, D., Helmer, C., Orgogozo, J.M. and Dartigues, J.F. (1999). Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. *J Neurol Neurosurg Psychiatry*. **66**, 177–183. DOI: 10.1136/jnnp.66.2.177.

Lupien, S.J., McEwen, B.S., Gunnar, M.R. and Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci*. **10**, 434–445.

Macoir, J., Monetta, L. and Wilson, M. (2014). Les troubles du langage dans les principales formes de démence et dans les aphasies primaires progressives: mise à jour à la lumière des nouveaux critères diagnostiques. *Geriatr Psychol Neuropsychiatr Vieil*. **12**, 199–208.

Mazon, J.N., de Mello, A.H., Ferreira, G.K. and Rezin, G.T. (2017). The impact of obesity on neurodegenerative diseases. *Life Sci.* **182**, 22–28. DOI: 10.1016/j.lfs.2017.06.002.

McKim, D.B., Niraula, A., Tarr, A.J., Wohleb, E.S., Sheridan, J.F. and Godbout, J.P. (2016). Neuroinflammatory Dynamics Underlie Memory Impairments after Repeated Social Defeat. *J Neurosci.* **36**, 2590–2604. DOI: 10.1523/JNEUROSCI.2394-15.2016.

Mergenthaler, P., Lindauer, U., Dienel, G.A. and Meisel, A. (2013). Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends Neurosci.* **36**, 587–597.

MORAN, M., LYNCH, C., WALSH, C., COEN, R., COAKLEY, D. and LAWLOR, B. (2005). Sleep disturbance in mild to moderate Alzheimer's disease. *Sleep Med.* **6**, 347–352. DOI: 10.1016/j.sleep.2004.12.005.

Niu, H., Álvarez-Álvarez, I., Guil-lén-Grima, F. and Aguinaga-Ontoso, I. (2017). Prevalence and incidence of Alzheimer's disease in Europe: A me-ta-analysis. *Neurología (English Edition).* **32**, 523–532. DOI: 10.1016/j.nrleng.2016.02.009.

Organisation mondiale de la santé (World Health Organization- WHO). Maladie d'Alzheimer : 35 millions de personnes atteintes dans le monde, don't 100.000 en Algérie. 2015.

Perry, G., Castellani, R.J., Smith, M.A., Harris, P.L.R., Kubat, Z., Ghanbari, K., Jones, P.K., Cordone, G., Tabaton, M., Woloizin, B. and Ghanbari, H. (2003). Oxidative damage in the olfactory system in Alzheimer's disease. *Acta Neuropathol.* **106**:552–556.

Qiu, C., Winblad, B., Marengoni, A., Klarin, I., Fastbom, J. and Fratiglioni, L. (2006). Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med.* **166**, 1003–08.

Rasgon, N.L., Kenna, H.A., Wroolie, T.E., Kelley, R., Silverman, D., Brooks, J., Williams, K.E., Powers, B.N. and Reiss, A. et al. (2011). Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. *Neurobiol Aging.* **32**, 1942–1948.

Rigaud, A.S. (2001). Symptômes de la maladie d'Alzheimer : point de vue du médecin. *Gérontologie et société.* **24**, 139–150. DOI: 10.3917/gs.097.0139.

Rossor, M. and Mountjoy, C.Q. (1986). Post-Mortem Neurochemical Changes in Alzheimer's Disease Compared With Normal Ageing. *Canadian Journal of Neurological Sciences*. 3, 499–502. DOI: 10.1017/s0317167100037203.

Selmès, J. and Derouesné, P.C. (2009). La maladie d'Alzheimer pour les nuls. *Revue Francophone des Laboratoires*. 411, 17. DOI: 10.1016/s1773-035x(09)72548-1.

Stewart, R., Masaki, K., Xue, Q.L., Peila, R., Petrovitch, H., White, L.R. and Launer, L.J. (2005). A 32-Year Prospective Study of Change in Body Weight and Incident Dementia. *Arch Neurol*. 62, 55. DOI: 10.1001/archneur.62.1.55.

Teri, L. (1997). Behavior and caregiver burden: behavioral problems in patients with Alzheimer disease and its association with caregiver distress. *Alzheimer Dis Assoc Disord*. 11, S35-8.

Tzourio, C., Dufouil, C., Ducimetière, P. and Alpérovitch, A. (1999). Cognitive decline in individuals with high blood pressure. *Neurology*. 53, 1948. DOI: 10.1212/wnl.53.9.1948.

Wallace, S.E. (2014). Inuit health: selected findings from the 2012 Aboriginal Peoples Survey. *Statistics Canada*.

Weuve, J., Puett, R.C., Schwartz, J., Yanosky, J.D., Laden, F. and Grodstein, F. (2011). EXPOSURE TO PARTICULATE AIR POLLUTION AND COGNITIVE DECLINE IN OLDER WOMEN. *ISEE Conference Abstracts*. DOI: 10.1289/isee.2011.00543.

White, H., Pieper, C., Schmader, K. and Fillenbaum, G. (1996). Weight Change in Alzheimer's Disease. *J Am Geriatr Soc*. 44, 265–272. DOI: 10.1111/j.1532-5415.1996.tb00912.x.

Ylief, M. (1995). Analyse et traitement des déficits de l'autonomie dans les états démentiels de la vieillesse. Thèse de Doctorat, Université de Liège.

Zhao, X., Huang, X., Cai, Y., Cao, T. and Wan, Q. (2022). The relative effectiveness of different combination modes for exercise and cognitive training on cognitive function in people with mild cognitive impairment of Alzheimer's disease: A network meta-analysis. *Aging & Mental Health*. 26(12), 2328-2338.