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EDITORIAL

From guidelines to practice: an INNN protocol for CSF tap test assessment

De la guía a la práctica clínica: un protocolo del INNN para la prueba de punción lumbar

*Óscar Esquivel-Zapata[1], Juan C. Delgado-Uriarte[2], Juan C. López-Hernández[3], Ramiro Ruíz-García[4], Mayela Rodríguez-Violante[1], and Raúl Medina-Rioja[4]**

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Introduction

Normal pressure hydrocephalus (NPH), first described by Hakim and Adams in 1965, is characterized by gait impairment, cognitive decline, and urinary dysfunction associated with ventriculomegaly despite normal cerebrospinal fluid (CSF) pressure. Since its description, several diagnostic tests have been developed to support diagnosis and predict shunt responsiveness. Among these, the CSF tap test remains the most widely used preoperative assessment.[1,2]

Recently, the International Parkinson and Movement Disorder Society NPH Study Group published the first systematic effort to standardize the large-volume CSF tap test. Although this initiative provides practical recommendations, external validation remains limited.[3] Based on these recommendations and our institutional experience at the Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez (INNN), a national tertiary referral center in Mexico, we adapted and implemented a standardized assessment sheet for patients undergoing a CSF tap test. Given the considerable heterogeneity that persists in routine practice in patient selection, CSF volume removal, timing of post-tap assessments, outcome measures, and the definition of a positive response, this institutional initiative is intended to standardize the performance and documentation of the procedure, support clinical decision-making, and promote homogeneous data collection for quality improvement and future research (Supplementary material 1).

As clinical experience continues to evolve, further refinement of evaluation protocols may improve the predictive accuracy and clinical utility of the CSF tap test. In this editorial, we describe the institutional implementation of current recommendations at the INNN through a standardized protocol for conducting, documenting, and interpreting the CSF tap test in patients with suspected NPH.

Who is the right candidate?

In routine clinical practice, it is uncommon to encounter patients who fulfill all three components of the classic Hakim triad. The complete Hakim triad is present in only a subset of patients, with gait impairment being the most common manifestation, followed by cognitive impairment and urinary dysfunction. Considerable heterogeneity in symptom characterization complicates clinical classification.[4,5]

At our institution, candidates for the tap test are patients presenting with gait impairment – such as

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broad-based gait, reduced stride length, shuffling gait, impaired tandem gait, bradykinesia, or hypokinesia – together with cognitive impairment and/or urinary dysfunction, neuroimaging findings suggestive of NPH, and exclusion of alternative diagnoses.

How do we do it?

The primary objective of the CSF tap test is to identify measurable motor changes following the removal of a large volume of CSF. The target CSF volume is 40-50 mL. If this volume cannot be safely obtained because of patient discomfort, cessation of CSF flow, or technical limitations, the maximum volume removed is recorded and interpreted together with the clinical response. Opening pressure, closing pressure, and CSF volume are documented for procedural quality control but are not used independently to define a positive test.

Assessments are performed immediately before lumbar puncture, approximately 3 h afterward, and again at 24 h. Although no universally accepted timing for post-tap evaluations has been established, these intervals were selected to balance clinical feasibility with evidence that improvement may begin within 30-90 min after CSF removal and may persist or become more evident over the following 12-24 h. When no improvement is observed, repeated assessments over the following week may be considered. Delayed or prolonged responses suggest that mechanisms beyond transient reductions in CSF volume may contribute to clinical improvement.[6,7]

What do we measure?

In routine clinical practice, the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are practical and validated tools that can be used to monitor cognitive changes after CSF drainage. Changes in MMSE or MoCA scores following the procedure have been associated with cognitive improvement and may help support clinical decision-making.[8] Cognitive assessment is performed at baseline and repeated 24 h after CSF removal. In contrast to gait, cognitive changes are generally less immediate and often require several hours to become clinically apparent; therefore, cognitive reassessment is performed only at 24 h in our protocol.

Gait assessment remains a cornerstone of evaluation. The Timed Up and Go (TUG) test is among the most extensively studied and clinically relevant measures in NPH. Patients are instructed to rise from a standard chair (seat height 44-47 cm), walk 3 m at a comfortable pace, turn around, return to the chair, and sit down. Routine walking aids may be used when necessary; however, patients are instructed not to use their arms to assist with standing. No physical assistance should be provided during the test. The total completion time is recorded using a stopwatch.[9]

The 10-m Walk Test provides a complementary measure of gait performance. Patients walk a total distance of 14 m, consisting of 2 m for acceleration, 10 m for timed assessment, and 2 m for deceleration. Walking speed, time, and number of steps are recorded and compared across evaluations.[3]

Next steps

A positive tap test is generally defined by the presence of one or more of the following findings:[3,5,9]

- An increase of at least 3 points on the MMSE
- An improvement in the TUG test, defined as either a ≥ 10% reduction in completion time or an absolute decrease of ≥ 5 s
- A reduction of ≥ 25% in the time required to complete the 10-m walk test.

Patients demonstrating a positive response, together with compatible clinical and neuroimaging findings, should be referred for neurosurgical evaluation and consideration of ventriculoperitoneal or lumboperitoneal shunt placement.

Conclusion

This assessment tool represents our institutional implementation of current recommendations to standardize the performance and documentation of the CSF Tap Test at a national tertiary referral center while promoting homogeneous data collection for clinical practice, quality improvement, and future research. It is intended to complement, rather than replace, established instruments such as the iNPH Scale.[10]

Although this protocol has not undergone prospective or multicenter validation, it reflects current institutional practice based on the best available evidence. Future studies should evaluate its reproducibility and generalizability.

Author contribution statement

Ó. Esquivel-Zapata, J.C. Delgado-Uriarte, and R. Medina-Rioja: conceptualization, methodology, writing original draft. J.C. López-Hernández, R. Ruíz-García, R. Medina-Rioja, and M. Rodríguez-Violante: writing- review and editing.

Supplementary data

Supplementary data is available at DOI: 10.24875/ANC.26000035. This data is provided by the corresponding author and is published online for the benefit of the reader. The content of the supplementary data is the sole responsibility of the authors.

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ORIGINAL ARTICLE

Bioinformatic analysis of genes associated with protective factors in Alzheimer's disease

Análisis bioinformático de genes asociados a factores protectores en la enfermedad de Alzheimer

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Abstract

Background: *Alzheimer's disease (AD) is a multifactorial neurodegenerative pathology characterized by the accumulation of β-amyloid, neuroinflammation, and synaptic deterioration. While researchers have identified numerous risk genes, they have also studied genetic variants with potential neuroprotective effects less extensively.* **Objectives:** *To analyze genes with potentially protective functions against AD using a bioinformatics approach to identify molecular pathways associated with neuroprotective mechanisms.* **Methods:** *We selected 15 candidate genes from a systematic review of scientific literature on PubMed between 2017 and 2024. Subsequently, the ShinyGO v8.01 tool was used to perform functional enrichment analysis and identify relevant metabolic and signaling pathways.* **Results:** *Pathways associated with cholesterol metabolism, neurotrophin signaling, and the NF-κB pathway were identified. Genes such as APOE ε2, KL, and ABCA1 are involved in moving fats around and controlling inflammation, whereas REST, BDNF, and DLGAP2 are linked to how brain connections change and how the body responds to stress.* **Conclusions:** *The results suggest that the analyzed genes are involved in key mechanisms linked to the progression of AD. Their study could contribute to the design of therapeutic strategies focused on neuroprotection.*

Keywords: *Alzheimer's disease. Bioinformatic. Neuroprotector. Neurodegenerative.*

Resumen

Antecedentes: *La enfermedad de Alzheimer (EA) es una patología neurodegenerativa multifactorial caracterizada por la acumulación de β-amiloide, neuroinflamación y deterioro sináptico. Aunque se han identificado numerosos genes de riesgo, también existen variantes genéticas con posibles efectos neuroprotectores que han sido menos estudiadas.* **Objetivo:** *Analizar genes con funciones potencialmente protectoras frente a la EA mediante un enfoque bioinformático, con el fin de identificar rutas moleculares asociadas a mecanismos neuroprotectores.* **Método:** *Se seleccionaron 15 genes candidatos a partir de una revisión sistemática de la literatura científica en PubMed entre 2017 y 2024. Posteriormente, se empleó la herramienta ShinyGO v8.01 para realizar el análisis de enriquecimiento funcional y la identificación de rutas metabólicas y de señalización relevantes.* **Resultados:** *Se identificaron rutas asociadas al metabolismo del colesterol, señalización por neurotrofinas y vía del NF-κB. Genes como APOE ε2, KL y ABCA1 mostraron implicación en el transporte lipídico y la modulación inflamatoria, mientras que REST, BDNF y DLGAP2 se asociaron a la plasticidad sináptica y la respuesta al estrés oxidativo.* **Conclusiones:** *Los resultados sugieren que los genes analizados participan en mecanismos clave vinculados con la progresión de la EA. Su estudio podría contribuir al diseño de estrategias terapéuticas enfocadas en la neuroprotección.*

Palabras clave: *Alzheimer. Bioinformática. Neuroprotector. Neurodegenerativo.*

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Introduction

Alzheimer's disease (AD) is a disease associated with a neurodegenerative and progressive disorder, which is mainly characterized by the development of dementia. In addition, patients exhibit cognitive decline that can affect a person's independence and functionality[1].

The development of AD is complex and multifactorial, as there are numerous mechanisms related to the disease, including neuroinflammatory pathways involving small proteins such as cytokines and chemokines[2].

The neuroinflammatory processes related to AD development are closely linked to risk genes. For example, the *APOE* ε4 variant is a cholesterol transport protein and has been described as a primary risk factor for patients carrying it in AD; patients with one copy of the gene represent 3-4 times the risk, whereas two copies increase it by 10-15 times compared to the APOE3 allele[3-5].

Some research has demonstrated mutations in the amyloid precursor protein (*APP*) gene in families with a history of early-onset AD; these mutations affect the generation and propensity for β-amyloid plaque aggregation. Another version linked to a higher chance of getting AD is the *TREM2* gene, which has a change in the receptor gene that activates myeloid cells[6,7].

In the past 3 years, human genetic studies have suggested risk modifiers that mitigate or increase the risk of AD[8].

It is known that genes can protect against neurodegenerative diseases by reducing neuropathological burden, improving the inflammatory response to normal levels of pathology, and strengthening the biological and cognitive foundation to delay the onset of signs and symptoms. The mutant human *APP* and presenilin-1 substantially protect against AD development by reducing nitric oxide synthase expression. A rare version of *APP* (A672T) helps protect against problems by lowering the production of harmful proteins and slightly reducing the clumping of Aβ (β-amyloid)[9].

Recent studies have investigated the loss of *REST* activation, which significantly accelerates the deposition and formation of Aβ and increases the abnormal accumulation of tau protein[10,11].

In this research, we will analyze, through bioinformatics, various genes associated with the protection against the development of AD, and possible precision therapeutic strategies will be described through the analyzed biological pathways.

Objective

This study aims to investigate several genes associated with protective factors that affect biological processes related to the development of AD through bioinformatics methods.

Methodology

A comprehensive search was performed in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) to discover genes previously reported to have a potential protective impact against AD.

This manuscript was written following the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guideline, which was created as part of the EQUATOR initiative (www.equator-network.org). The guidelines were followed to ensure transparency in the development and validation of the predictive model.

The gene selection was based on a comprehensive review of peer-reviewed literature published between 2017 and 2024, using targeted search terms related to neuroprotection, AD genetics, and the molecular pathways implicated in the disorder. The final panel of 15 genes was curated from robust evidence indexed in PubMed, ensuring the inclusion of candidates with well-documented neuroprotective roles and established involvement in molecular mechanisms associated with AD. This focused approach was designed to prioritize genes with the strongest and most reproducible associations to enhance the biological relevance and interpretability of the subsequent analyses.

Fifteen genes of significant relevance in scientific literature were identified due to this search: *APP, APOE, KL, CASP7, ABCA1, SORL1, RAB10, PICALM, REST, PLCG2, TREML2, TMEM106B, BDNF, DLGAP2*, and *MS4A1*.

A bioinformatic study was performed utilizing the web application ShinyGO v8.01 (http://bioinformatics.sdstate.edu/go/), which facilitates the discovery of enriched metabolic pathways and biological processes within a specified list of genes. The gene names were input into the platform, and functional enrichment analysis was conducted to identify metabolic and cellular signaling pathways associated with neuroprotection in AD.

The analysis encompassed the assessment of the statistical significance of the identified paths, taking into account three primary criteria: (1) fold enrichment, quantifying the ratio of observed to expected gene frequency within a specific metabolic pathway; (2) the

p-value, assessing the statistical significance of the correlation between a gene and a biological pathway; and (3) the false discovery rate (FDR), employed to reduce the likelihood of false positives in the findings.

The acquired data were illustrated in pathway enrichment graphs and gene interaction diagrams, facilitating the visualization of the functional relationships between the selected genes and essential biological processes in AD. This study did not require ethics committee permission, as it relied on bioinformatics data from publicly available sources accessible to the scientific community, addressing ethical considerations and repeatability. All applied methodologies guarantee the study's repeatability.

The STRING v12.0 platform (search tool for the retrieval of interacting genes/proteins; https://string-db.org/) was utilized for protein-protein interaction (PPI) study. This platform is extensively utilized in bioinformatics for the analysis of functional protein networks. A compilation of genes previously identified for their significance in the pathogenesis of AD was provided, encompassing *APP, APOE, SORL1, PICALM, BDNF, CASP7, REST, TREM2, RAB10, TMEM106B, MS4A1, KL, ABCA1, PLCG2,* and *DLGAP2*.

The analysis was set with a confidence threshold of 0.7 (high confidence) to prioritize interactions substantiated by robust experimental and bibliographic evidence. The organism *Homo sapiens* was designated as the biological reference, incorporating interactions based on experimental evidence, co-expression, knowledge databases, bioinformatic predictions, and scientific text mining. The nodes exhibiting the highest connectivity (degree) were examined for their potential regulatory roles in cellular and molecular processes related to neurodegeneration, encompassing amyloid processing, lipid metabolism, neuroinflammation, and synaptic plasticity.

Results

A descriptive table was generated highlighting the primary properties and functions of the selected genes of interest concerning AD. Table 1 presents an analysis of 15 genes, detailing their biological activity associated with AD and the scholarly references substantiating their involvement in the condition. The findings indicate that numerous genes are implicated in critical pathways of AD development. Specifically, genes, including APP, *APOE*, and *SORL1*, play a role in controlling β-amyloid peptide metabolism, a crucial element in developing senile plaques associated with the disease. Additional genes, including *ABCA1, KL, and PLCG2*, are involved in lipid metabolism and regulating the inflammatory response, processes linked to the advancement of AD.

Furthermore, genes that confer neuroprotection through regulating neural plasticity and synapses, including *BDNF, REST*, and *DLGAP2*, were associated with the maintenance of cognitive function. Genes associated with apoptosis and tau protein stability, including *CASP7, TREML2*, and *TMEM106B*, were identified, with their alterations potentially contributing to the neuronal degeneration observed in AD. The results indicate the variety of biological pathways associated with these genes and their potential influence on the risk and course of the disease. The data from this table establishes a basis for subsequent studies focused on formulating therapeutic options informed by understanding genetic variables linked to AD.

The bioinformatic analysis conducted with the ShinyGO 8.1 tool identified multiple metabolic pathways and signaling pathways significantly enriched in genes associated with protective factors in AD. One of the most critical pathways, cholesterol metabolism, had the highest increase in gene involvement (59.8) with a p = 0.034, and it included two genes. This pathway is of particular interest due to its participation in cell membrane formation and lipid homeostasis, key elements in the pathogenesis of AD (Table 2).

Another relevant pathway is apoptosis in multiple species, which showed a fold enrichment of 47.7 and a p = 1.3E-01. This result emphasizes the importance of regulating programmed cell death in neurodegeneration. Likewise, the interconversion of pentoses and gluconates, along with ABC transporters, highlights their possible role in energy metabolism in transporting lipids and toxins, as they also showed significant enrichments (43.6 and 33.9, respectively).

Regarding the signaling pathways, VEGF and neurotrophins showed considerable enrichment (25.9 and 25.6, respectively). These pathways are involved in neurogenesis, brain plasticity processes, and critical neuronal protection aspects. Furthermore, the NF-κB signaling and longevity pathways had scores of 14.7 and 17.1, respectively, indicating that they play a role in controlling inflammation and how cells age.

Finally, the identification of AD as a pathway with significant enrichment (10.3) is noteworthy, reaffirming the relevance of the analyzed genes in the etiology of this condition. The pathways linked to neurodegeneration in several diseases also showed significant enrichment (9.6), emphasizing the complicated and connected

Table 1. Genes associated with neuroprotective functions and pathophysiological processes in Alzheimer's disease

Genes	Biological activity in Alzheimer's disease	References
APP	It is a glycoprotein that plays an essential role in maintaining neuronal homeostasis as signaling, neuronal development, and intracellular transport.	21
APOE	It emphasizes the pathogenesis of AD through the accumulation of amyloid-β peptide and neurofibrillary tangles. APOE ε2 is associated with mild neuropathological changes in AD.	8,22
KL	The α-Klotho protein participates in the aging processes due to the biological changes in the tissues. The α-Klotho protein participates in the aging processes due to the biological changes in the tissues. In addition, it inhibits inflammatory pathways such as NF-κB and -TGF-β that contribute to the development of EA.	23,24
CASP7	They play a central role in the regulation of cellular apoptosis. This process is linked to the neuropathology of AD, including the caspase cleavage of *APP* and tau.	25,26
ABCA1	It transfers intracellular free cholesterol and phospholipids to *APOA-1* to generate nascent high-density lipoprotein particles and enhances the lipid-binding properties of *APOE4*.	27,28
SORL1	It retains *APP* in early endosomes, which helps contribute to the degradation pathways of the endosomal and recycling pathways in neurons. The progressive loss of *SORL1* induces a specific reduction of neurons in *APOE*.	29,30
RAB10	It performs polarization processes in neurons, dendritic arborization, and anterograde transport of vesicles along the axon.	31,32
PICALM	Facilitate the removal of Aβ from the brain through enhanced translocation across the blood-brain barrier and uncouple the presence of *APOE ε4* from its detrimental effects on endocytosis.	33,34
MS4A1	It is expressed in the membrane of precursor and mature B cells, but its expression is lost in plasma cells.	34
DLGAP2	It is a critical component in the postsynaptic density that participates in regulating synaptic function and the morphology of dendritic spines. The reduction of *DLGAP2* is associated with faster cognitive decline, linked to the development of AD and neurological diseases.	35,36
BDNF	It participates in properly developing and maintaining dopaminergic, GABAergic, cholinergic, and serotonergic neurons. Some polymorphisms in the gene may increase the risk of developing neuropsychiatric disorders.	37,38
REST	They are master regulators in the processes of neuronal plasticity, and they also provide robust protection to neurons against oxidative stress and the toxicity of β-amyloid protein.	39,40
PLCG2	It is an enzyme selectively expressed in microglia and plays a fundamental role in the immune response within the pathogenesis of AD. In addition, it is specifically induced in microglia associated with amyloid plaques, suggesting its involvement in the modulation of inflammation and the clearance of β-amyloid.	41,42
TREML2	Some *TREML2* variants are involved in the levels of hyperphosphorylated tau at threonine 181 and total tau in cerebrospinal fluid and the volumes of brain structures related to AD.	43
TMEM106B	Its deletion in mouse models accelerated cognitive decline, paralysis, tau accumulation, and neurodegeneration, aligning transcriptional patterns with those observed in Alzheimer's patients. It also plays a neuroprotective role, and its loss exacerbates the consequences of tau pathology.	44,45

nature of the harmful processes in different neurodegenerative diseases (Table 2).

The enrichment analysis conducted with ShinyGO indicated that only the cholesterol metabolism pathway achieved substantial statistical significance ($p < 0.05$) following multiple testing correction by the Benjamini–Hochberg method (FDR < 0.05). The remaining pathways exhibited p-values beyond 0.05; hence, they ought to be regarded as exploratory trends rather than definitive connections.

The pathway enrichment analysis conducted with ShinyGO 8.1 discovered numerous critical biological pathways associated with regulating processes in AD. Cholesterol metabolism exhibited the highest fold enrichment, approximately 60, as illustrated in figure 1. This discovery highlights the substantial role of lipid metabolism in the development of AD. Additional pertinent pathways encompass apoptosis across many species and the interconversion of pentoses and glucuronates, which exhibited significant fold enrichment,

Table 2. Enrichment of molecular pathways associated with genes implicated in Alzheimer's disease

Enrichment	Number of genes	Gene pathways	Folded enrichment	Genes	Pathways
3.4E-02	2	51	59.8	*ABCA1, APOE*	Cholesterol metabolism
1.3E-01	1	32	47.7	*CASP7*	Apoptosis in multiple species
1.3E-01	1	35	43.6	*KL*	Interconversion of pentoses and glucuronates
1.3E-01	1	45	33.9	*ABCA1*	ABC Carriers
1.3E-01	1	59	25.9	*PLCG2*	VEGF signaling pathway
5.7E-02	2	119	25.6	*PLCG2, BDNF*	Neurotrophin signaling pathway
1.3E-01	1	73	20.9	*PLCG2*	Metabolism of inositol phosphates
1.3E-01	1	79	19.3	*PLCG2*	Resistance to EGFR tyrosine kinase inhibitors
1.3E-01	1	84	18.2	*PLCG2*	ErbB signaling pathway
1.3E-01	1	89	17.1	*KL*	Longevity regulation pathway
1.3E-01	1	97	15.7	*PLCG2*	Phosphatidylinositol signaling system
1.3E-01	1	104	14.7	*PLCG2*	NF-κB signaling pathway
1.1E-01	2	214	14.3	*ABCA1, CASP7*	Lipids and atherosclerosis
1.3E-01	1	109	14	*PLCG2*	HIF-1 signaling pathway
1.1E-01	2	235	13	*PLCG2, BDNF*	Ras signaling pathway
1.3E-01	1	121	12.6	*RAB10*	AMPK signaling pathway
1.3E-01	1	124	12.3	*PLCG2*	Platelet activation
1.3E-01	1	126	12.1	*PLCG2*	Differentiation of osteoclast
5.7E-02	3	384	11.9	*APOE, APP, CASP7*	Alzheimer's disease
5.7E-02	3	476	9.6	*APP, BDNF, CASP7*	Neurodegeneration pathways in multiple diseases

signifying an essential function in cell cycle regulation and energy metabolism. The pathways associated with VEGF signaling and neurotrophins demonstrated considerable enrichment, indicating their roles in angiogenesis and neural plasticity.

Furthermore, significant involvement in the pathways of resistance to EGFR tyrosine kinase inhibitors and NF-κB signaling, essential for inflammation and cellular regulation, was noted. The differentiation of osteoclasts and neurodegenerative pathways in various disorders was an additional focal point, highlighting their significance in advancing neurodegeneration. Figure 1 illustrates the number of genes associated with each pathway and the statistical significance of the results, quantified by the -log(FDR) parameter. This investigation offers an extensive overview of the biochemical pathways likely implicated in AD, emphasizing the intricacy of the molecular interactions involved in the condition. This investigation provides a detailed examination of the biochemical pathways likely implicated in AD, emphasizing the intricacy of the molecular interactions involved in the condition.

The functional enrichment analysis conducted using the ShinyGO v8.01 program generated a network of significant biological pathways associated with genes that may contribute to neuroprotection in AD. In this network, the nodes symbolize metabolic and signaling pathways, whereas the edges denote functional connections among shared genes. The data indicate that "Alzheimer's disease," "cholesterol metabolism," and "pathways of neurodegeneration-multiple diseases" occupy a pivotal position in the network, implying a significant density of linkages with other biological pathways.

Protective genes concurrently affect various pathophysiological pathways associated with AD (Fig. 2). The

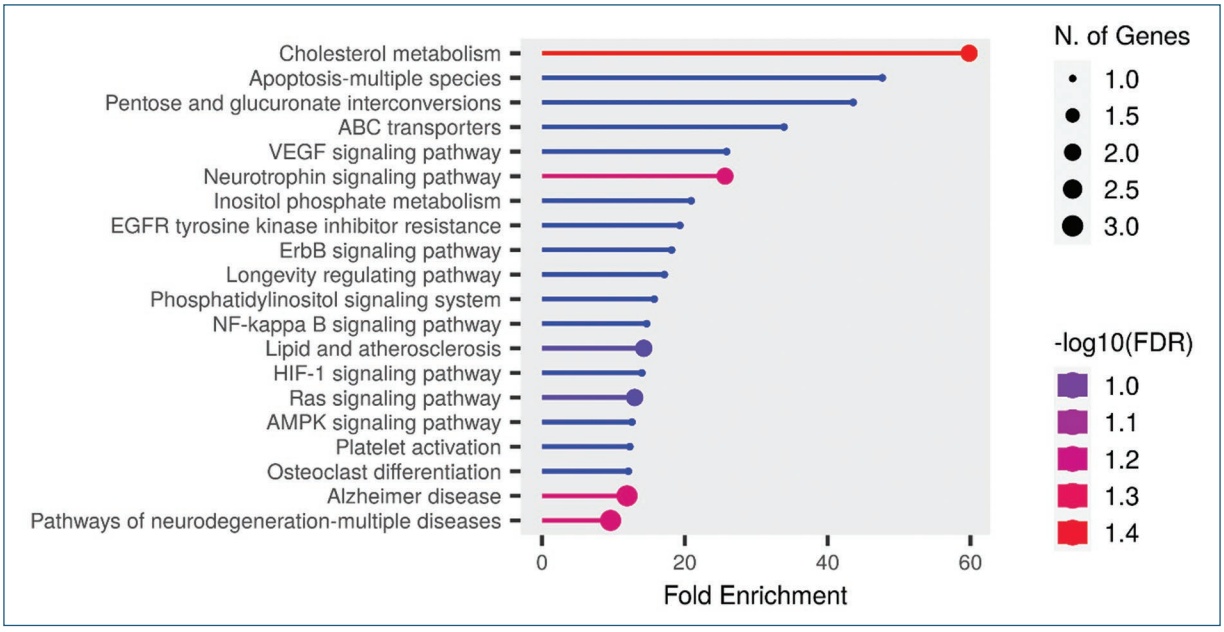

Figure 1. Analysis of biological pathway enrichment using ShinyGO 8.1. The most significant pathways are shown based on their fold enrichment, number of involved genes, and statistical significance (-log false discovery rate).

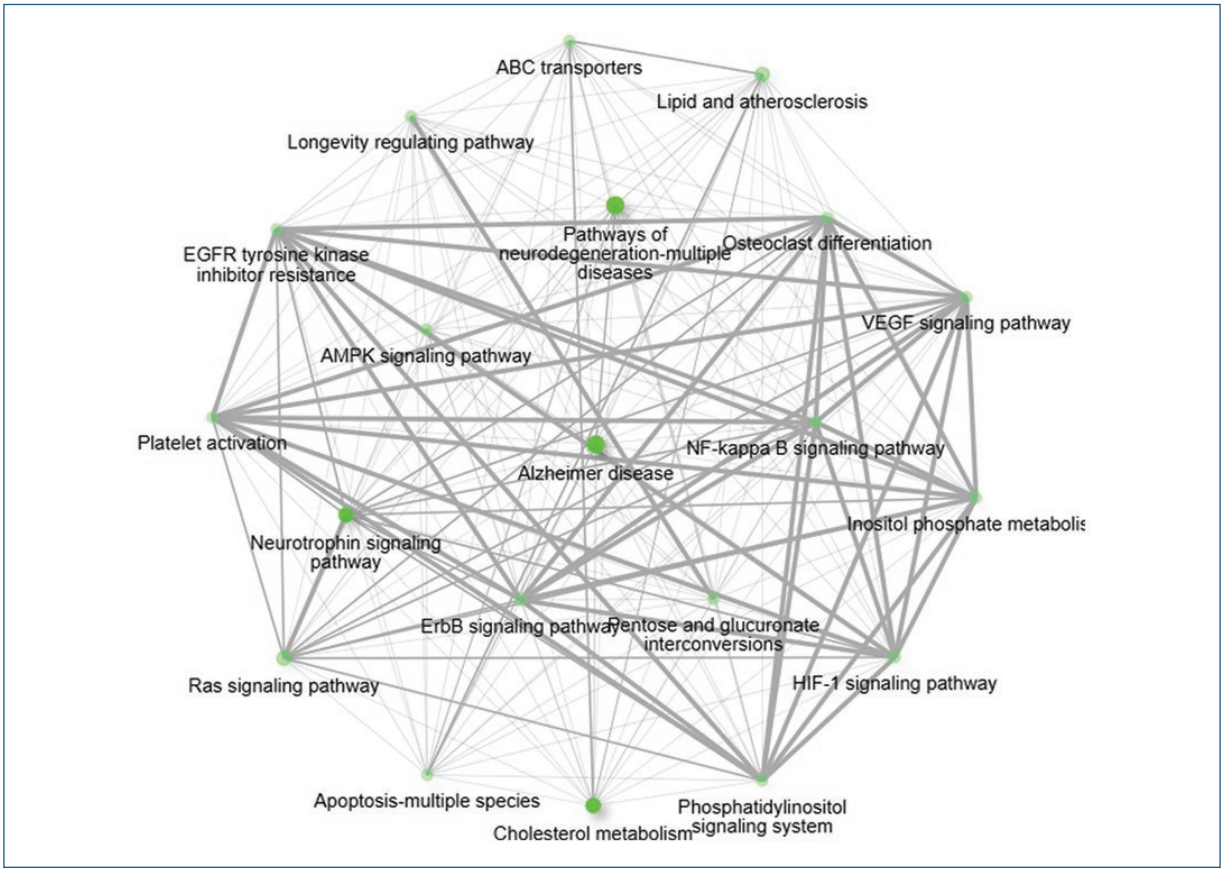

Figure 2. The network of biological pathways is significantly enriched by genes associated with Alzheimer's disease.

Table 3. Enrichment analysis of the 15 candidate genes using DAVID. Significant terms (q < 0.05) include plasma membrane, perinuclear region of cytoplasm, extracellular exosome, and synaptic vesicle, supporting roles in lipid transport and synaptic regulation

Category	Term	Count	List total (LT)	Population hits (PH)	Population total (PT)	%	p	Benjamini
GOTERM_CC_DIRECT	Plasma membrane	13	15	5597	20795	86.7	7.4E-6	8.9E-4
GOTERM_CC_DIRECT	Perinuclear región of cytoplasm	6	15	750	20795	40.0	9.2E-5	3.7E-3
GOTERM_BP_DIRECT	Endosomal transport	3	15	69	19478	20.0	1.1E-3	1.8E-1
GOTERM_CC_DIRECT	Extracellular exosome	7	15	2242	20795	46.7	2.2E-3	2.6E-2
FOTERM_CC_DIRECT	Synaptic vesicule	3	15	126	20795	20.0	3.2E-3	3.4E-2
REACTOME_PATHWAY	Signal transduction	8	13	2628	11494	53.3	8.5E-3	8.1E-1
GOTERM_CC_DIRECT	Membrane raft	3	15	211	20795	20.0	8.6E-3	6.9E-2
GOTERM_CC_DIRECT	Membrane	9	15	5415	20795	60.0	1.3E-2	9.3E-2
UP_KW_CELLULAR_ COMPONENT	Membrane	12	15	8353	18049	80.0	1.5E-2	8.1E-2
GOTERM_MF_DIRECT	Small GTPase binding	3	15	293	19253	20.0	1.9E-2	3.8E-1
GOTERM_MF_DIRECT	Protein binding	14	15	13690	19253	93.3	5.6E-2	7.1E-1
UP_SEQ_FEATURE	COMPBIAS: acidic residues	5	15	2242	20675	33.3	5.7E-2	1.0E0
UP_SEQ_FEATURE	COMPBIAS: polar residues	8	15	5942	20675	53.3	7.6E-2	1.0E0
KEGG_PATHWAY	Pathways of neurodegeneration - multiple diseases	3	10	483	8534	20.0	8.8E-2	1.0E0
UP_KW_PTM	Phosphoprotein	12	15	8435	14316	80.0	1.1E-1	5.2E-1
GOTERM_CC_DIRECT	Intracellular membrane - bounded organelle	3	15	1022	20795	20.0	1.5E.1	6.0E-1
UP_SEQ_FEATURE	REGION: Disordered	11	15	13820	20795	73.3	4.8E-1	1.0E0
UP_KW_DISEASE	Disease Variant	8	10	3955	4859	53.3	7.7E-1	1.0E0
GOTERM_CC_DIRECT	Nucleoplasm	3	15	4107	20795	20.0	8.0E-1	1.0E0
UP_KW_PTM	Acetylation	3	15	3515	14316	20.0	8.9E-1	1.0E0

cholesterol metabolism pathway, exhibiting the highest fold enrichment (59.8), is a prominent pathway within the network. Genes such as *APOE* and *ABCA1* substantiate the implication, recognized for their involvement in cerebral lipid homeostasis and the regulation of β-amyloid buildup. This pathway is closely associated with others concerning lipid transport ("ABC transporters") and vascular disorders ("Lipid and atherosclerosis"), illustrating the interconnection between general metabolism and cerebral degeneration. Similarly, the neurotrophin signaling system and the NF-κB pathway are significant pathways intricately linked to inflammatory, neurogenic, and synaptic processes.

The pathways are influenced by genes such as *BDNF*, *PLCG2*, and *REST*, which regulate neural plasticity, microglial immunological response, and resistance to oxidative stress. Other prominently highlighted pathways encompass "Apoptosis-multiple species," "Longevity regulating pathway," "Ras signaling pathway," and "Inositol

Table 4. Pathway enrichment using reactome and KEGG. Only cholesterol metabolism remains significant after false discovery rate correction ($q < 0.05$); other pathways are reported as exploratory trends

Annotation cluster 1	Enrichment score: 2.69	Count	p	Benjamini
GOTERM_CC_DIRECT	Golgi apparatus	6	6.0E-4	1.7E-2
GOTERM_CC_DIRECT	Early endosome	4	1.1E-3	1.9E-2
GOTERM_BP_DIRECT	Receptor-mediated endocytosis	3	1.3E-3	1.8E-1
GOTERM_MF_DIRECT	Amyloid-beta binding	3	1.7E-3	9.9E-2
GOTERM_CC_DIRECT	Neuronal cell body	3	2.5E-2	1.3E-1
Annotation cluster 2	**Enrichment score: 2.44**	**Count**	**p**	**Bejamini**
UP_KW_CELLULAR_COMPONENT	Endosome	6	1.3E-4	2.5E-3
GOTERM_CC_DIRECT	Golgi apparatus	6	6.0E-4	1.7E-2
GOTERM_BP_DIRECT	Cholesterol metabolic process	3	1.8E-3	1.8E-1
GOTERM_MF_DIRECT	Signaling receptor binding	3	3.1E-2	4.6E-1
GOTERM_BP_DIRECT	G Protein-coupled receptor signaling pathway	3	1.4E-1	1.0E0
Annotation cluster 3	**Enrichment score: 1.88**	**Count**	**p**	**Benjamini**
GOTERM_CC_DIRECT	Endosome	5	4.2E-5	2.5E-3
UP_KW_CELLULAR_COMPONENT	Endosome	6	1.3E-4	2.5E-3
UP_KW_DISEASE	Alzheimer disease	3	5.7E-4	6.3E-3
GOTERM_CC_DIRECT	Golgi apparatus	6	6.0E-4	1.7E-2
GOTERM_CC_DIRECT	Cell surface	5	7.9E-4	1.7E-2
GOTERM_CC_DIRECT	Early endosome	4	1.1E-3	1.9E-2
UP_KW_DISEASE	Amyloidosis	3	1.6E-3	8.6E-3
GOTERM_BP_DIRECT	Axonogenesis	3	2.3E-3	1.8E-1
GOTERM_CC_DIRECT	Recycling endosome	3	3.9E-3	3.6E-2
UP_KW_BIOLOGICAL_PROCESS	Endocytosis	3	5.4E-3	8.6E-2
UP_KW_DISEASE	Neurodegeneration	5	5.7E-3	2.1E-2
REACTOME_PATHWAY	Amyloid fiber formation	3	6.0E-3	8.1E-1
UP_KW_PTM	Lipoprotein	5	1.2E-2	2.0E-1
GOTERM_CC_DIRECT	Lysosome	3	1.9E-2	1.0E-1
UP_KW_CELLULAR_COMPONENT	Cyroplasmatic vesicle	4	1.9E-2	8.1E-1
UP_KW_CELLULAR_COMPONENT	Golgi apparatus	4	3.9E-2	1.1E-1
REACTOME_PATHWAY	Vesicle-mediated transport	4	3.9E-2	8.1E-1
UP_KW_BIOLOGICAL_PROCESS	Transport	5	9.5E-2	3.0E-1
REACTOME_PATHWAY	Membrane trafficking	3	1.4E-1	1.0E0
GOTERM_CC_DIRECT	Endoplasmic reticulum membrane	3	1.9E-1	6.8E-1
GOTERM_CC_DIRECT	Endoplasmic reticulum	3	2.0E-1	6.8E-1
UP_KW_PTM	Ubl conjugation	5	2.8E-1	6.4E-1
UP_KW_CELLULAR_COMPONENT	Endoplasmic reticulum	3	3.0E-1	6.4E-1
REACTOME_PATHWAY	Metabolism of proteins	4	4.0E-1	1.0E0
REACTOME_PATHWAY	Post-translational protein modification	3	4.9E-1	1.0E0
UP_KW_PTM	Isopeptide bond	3	5.7E-1	1.0E0

(Continues)

Table 4. Pathway enrichment using reactome and KEGG. Only cholesterol metabolism remains significant after false discovery rate correction (q < 0.05); other pathways are reported as exploratory trends *(continued)*

Annotation cluster 4	Enrichment score: 1.84	Count	p	Bejamini
GOTERM_MF_DIRECT	Low-density lipoprotein particle receptor binding	3	1.6E-4	1.8E-2
GOTERM_CC_DIRECT	Golgi apparatus	6	6.0E-4	1.7E-2
GOTERM_CC_DIRECT	Early endosome	4	1.1E-3	1.9E-2
GOTERM_BP_DIRECT	Negative regulation of gene expression	4	1.3E-3	1.8E-1
REACTOME_PATHWAY	Vesicle-mediated transport	4	3.9E-2	8.1E-1
GOTERM_BP_DIRECT	Positive regulation of DNA-templated transcription	3	9.1E-2	8.0E-1
GOTERM_MF_DIRECT	Identical protein binding	4	1.3E-1	1.0E0
UP_KW_DOMAIN	Coiled coil	3	6.4E-1	1.0E0
GOTERM_CC_DIRECT	Nucleus	5	6.5E-1	1.0E0
Annotation cluster 5	**Enrichment score: 1.72**	**Count**	**p**	**Bejamini**
GOTERM_CC_DIRECT	Extracellular space	7	8.3E-4	1.7E-2
GOTERM_CC_DIRECT	Endoplasmic reticulum lumen	3	1.9E-2	1.0E-1
UP_KW_CELLULAR_COMPONENT	Secreted	6	2.1E-2	8.1E-2
GOTERM_CC_DIRECT	Dendrite	3	3.8E-2	1.8E-1
GOTERM_CC_DIRECT	Extracellular region	4	2.0E-1	6.8E-1
Annotation cluster 6	**Enrichment score: 1.54**	**Count**	**p**	**Benjamini**
REACTOME_PATHWAY	Signaling by receptor tyrosine kinases	4	1.6E-2	8.1E-1
REACTOME_PATHWAY	PIP3 Activates AKT signaling	3	3.0E-2	8.1E-1
REACTOME_PATHWAY	Disease	6	3.7E-2	8.1E-1
REACTOME_PATHWAY	Intracellular signaling by sencond messengers	3	3.9E-2	8.1E-1
Annotation cluster 7	**Enrichment score: 1.12**	**Count**	**p**	**Bejamini**
UP_KW_CELLULAR_COMPONENT	Cell Membrane	9	5.9E-3	5.6E-2
UP_SEQ_FEATURE	TRANSMEM: Helical	8	5.0E-2	1.0E0
UP_SEQ_FEATURE	CARBOHYD: N-Linked (GlcNAc…) Asparagine	7	5.9E-2	1.0E0
UP_KW_DOMAIN	Signal	7	8.0E-2	3.9E-1
UP_KW_DOMAIN	Transmembrane helix	8	1.0E-1	3.9E-1
UP_KW_DOMAIN	Transmembrane	8	1.1E-1	3.9E-1
UP_SEQ_FEATURE	TOPO_DOM: Cytoplasmic	6	1.1E-1	1.0E0
UP_SEQ_FEATURE	TOPO_DOM: Extracellular	5	1.4E-1	1.0E0
UP_KW_PTM	Glycoprotein	8	1.6E-1	5.2E-1
UP_KW_PTM	Disulfide bond	7	1.6E-1	5.2E-1
Annotation cluster 8	**Enrichment score: 0.92**	**Count**	**p**	**Bejamini**
REACTOME_PATHWAY	Disease	6	3.7E-2	8.1E-1
GOTERM_BP_DIRECT	Positive regulation of gene expression	3	4.7E-2	5.7E-1
REACTOME_PATHWAY	Infectious disease	3	3.2E-1	1.0E0
GOTERM_CC_DIRECT	Cytoplasm	6	3.8E-1	1.0E0

(Continues)

Table 4. Pathway enrichment using reactome and KEGG. Only cholesterol metabolism remains significant after false discovery rate correction (q < 0.05); other pathways are reported as exploratory trends *(continued)*

Annotation cluster 9	Enrichment score: 0.7	Count	p	Benjamini
UP_KW_MOLECULAR_FUNCTION	Hydrolase	5	5.7E-2	5.8E-1
REACTOME_PATHWAY	Innate immune system	3	3.4E-1	1.0E0
REACTOME_PATHWAY	Immune system	4	4.0E-1	1.0E0
Annotation cluster 10	**Enrichment score: 0.68**	**Count**	**p**	**Benjamini**
UP_KW_CELLULAR_COMPONENT	Cytoplasmic vesicle	4	1.9E-2	8.1E-2
UP_KW_CELLULAR_COMPONENT	Golgi apparatus	4	3.9E-2	1.1E-1
GOTERM_CC_DIRECT	Cytosol	7	1.6E-1	6.2E-1
UP_KW_PTM	Ubl Conjugation	5	2.8E-1	6.4E-1
GOTERM_CC_DIRECT	Nucleus	5	6.5E-1	1.0E0
UP_KW_CELLULAR_COMPONENT	Cytoplasm	4	8.8E-1	1.0E0
UP_KW_CELLULAR_COMPONENT	Nucleus	4	8.9E-1	1.0E0
Annotation cluster 11	**Enrichment score: 0.65**	**Count**	**p**	**Benjamini**
REACTOME_PATHWAY	Signaling by receptor tyrosine kinases	4	1.6E-2	8.1E-1
GOTERM_CC_DIRECT	Cytoplasm	6	3.8E-1	1.0E0
REACTOME_PATHWAY	Generic transcription pathway	3	3.9E-1	1.0E0
REACTOME_PATHWAY	RNA Polymerase II Transcription	3	4.4E-1	1.0E0
REACTOME_PATHWAY	Gene Expression (Transcription)	3	5.2E-1	1.0E0
Annotation cluster 12	**Enrichment score: 0.61**	**Count**	**p**	**Benjamini**
KEGG_PATHWAY	Alzheimer disease	3	6.1E-2	1.0E0
GOTERM_CC_DIRECT	Cytoplasm	6	3.8E-1	1.0E0
GOTERM_CC_DRECT	Nucleus	5	6.5E-1	1.0E0
Annotation cluster 13	**Enrichment score: 0.5**	**Count**	**p**	**Benjamini**
UP_KW_BIOLOGICAL_PROCESS	Lipid metabolism	3	1.4E-1	3.7E-1
UP_KW_DOMAIN	Repeat	6	3.2E-1	8.9E-1
REACTOME_PATHWAY	Metabolism	3	7.0E-1	1.0E0

phosphate metabolism," which establish a functional framework connecting intracellular signaling, programmed cell death, and the regulation of neuronal survival.

The AD pathway is significantly interconnected with signaling pathways, including VEGF, ErbB, and HIF-1, which are implicated in angiogenesis, cellular stress, and hypoxia. This functional network underscores the intricacy and interconnection of the molecular pathways that govern genetic neuroprotection in AD. Identifying these pathways provides a thorough understanding of the biological mechanisms that may be medically targeted to postpone or avert cognitive decline.

Cross-validation utilizing DAVID and Reactome corroborated the participation of the chosen genes in cellular and molecular processes intimately associated with neuroprotection. Enrichment analysis demonstrated a notable correlation with plasma membrane constituents (13 genes, $p = 7.4 \times 10^{-6}$; Benjamini-Hochberg FDR = 8.9×10^{-4}), the perinuclear region of the cytoplasm (6 genes, $p = 9.2 \times 10^{-5}$; Benjamini-Hochberg FDR = 3.7×10^{-3}), and extracellular exosomes (7 genes, $p = 2.2 \times 10^{-3}$; Benjamini-Hochberg FDR = 2.6×10^{-2}). Furthermore, an enrichment in

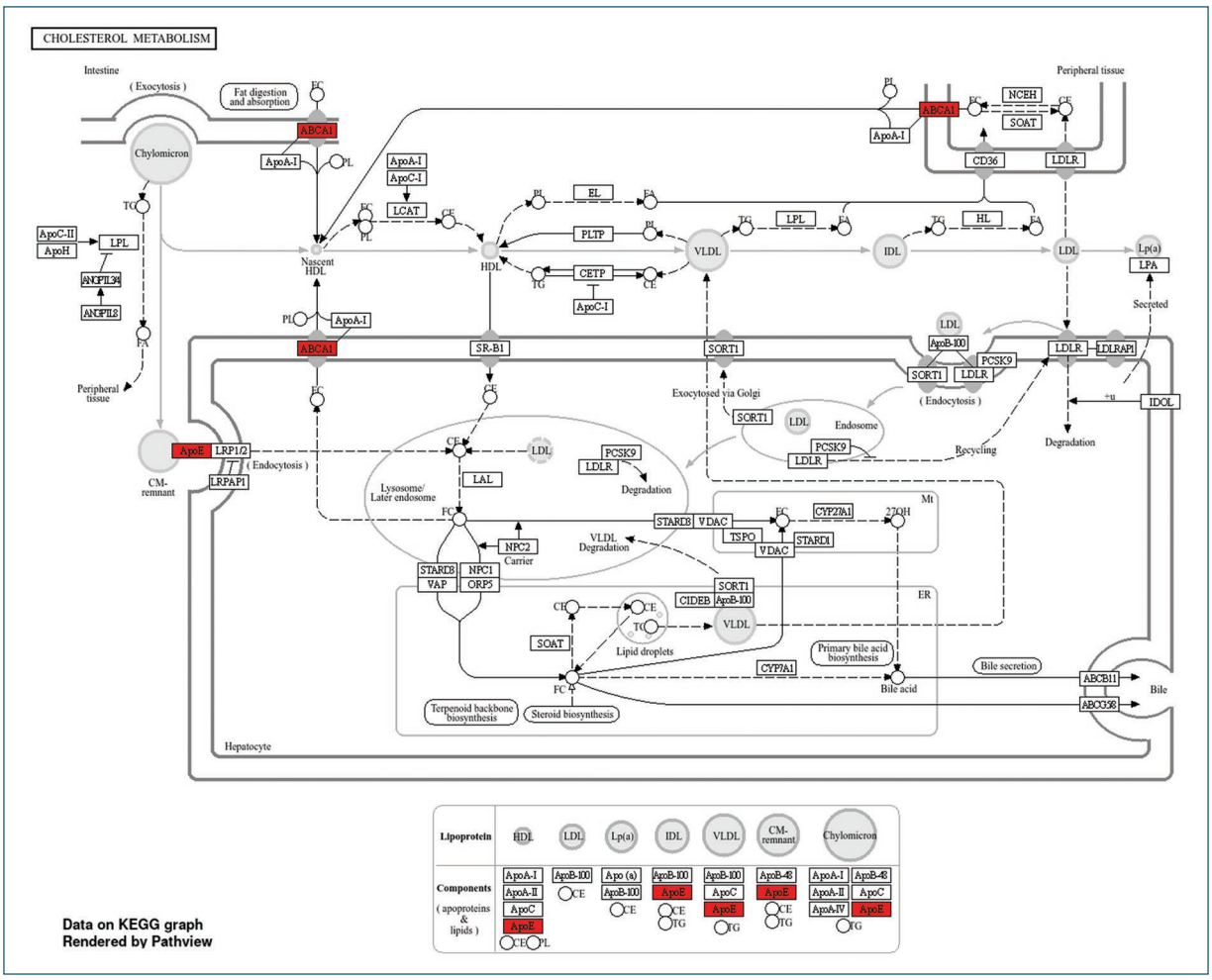

Figure 3. Cholesterol metabolic pathway highlighting genes associated with protection against Alzheimer's disease.

synaptic vesicles was detected (3 genes, $p = 3.2 \times 10^{-3}$; Benjamini FDR = 3.4×10^{-2}) (Tables 3 and 4).

DAVID found neurodegeneration-related signaling pathways, including numerous disease pathways (*KEGG, APP–APOE–ABCA1*; $p = 8.8 \times 10^{-2}$), aligning with prior findings from ShinyGO, although it did not achieve significance post-FDR correction. These findings strengthen the association between the examined genes and essential cellular mechanisms, especially those pertaining to lipid transport, intercellular communication, and synaptic plasticity (Table 3).

Cholesterol metabolism and its implications in AD

Cholesterol metabolism is a meticulously regulated process encompassing its absorption, transport, storage, and excretion across many bodily tissues. Figure 3 depicts the cholesterol metabolic pathway according to the KEGG database, highlighting the primary transport and processing processes in the colon, liver, and peripheral organs. During intestinal absorption, dietary cholesterol is integrated into chylomicrons, which are then conveyed through the systemic circulation.

The *ABCA1* protein is essential for synthesizing nascent high-density lipoproteins by enabling the transfer of cholesterol to Apolipoprotein A-I (ApoA-I). Lipoproteins, when entering into circulation, experience several alterations facilitated by proteins such as LCAT, CETP, and PLTP, which govern the transfer of cholesterol among distinct lipid compartments. Cholesterol conveyed by low-density lipoproteins (LDL) is absorbed by peripheral tissues and the liver through the LDL receptor, facilitating its internalization and recycling.

Lysosomal hydrolysis facilitated by LAL in the liver enables cholesterol mobilization for metabolic

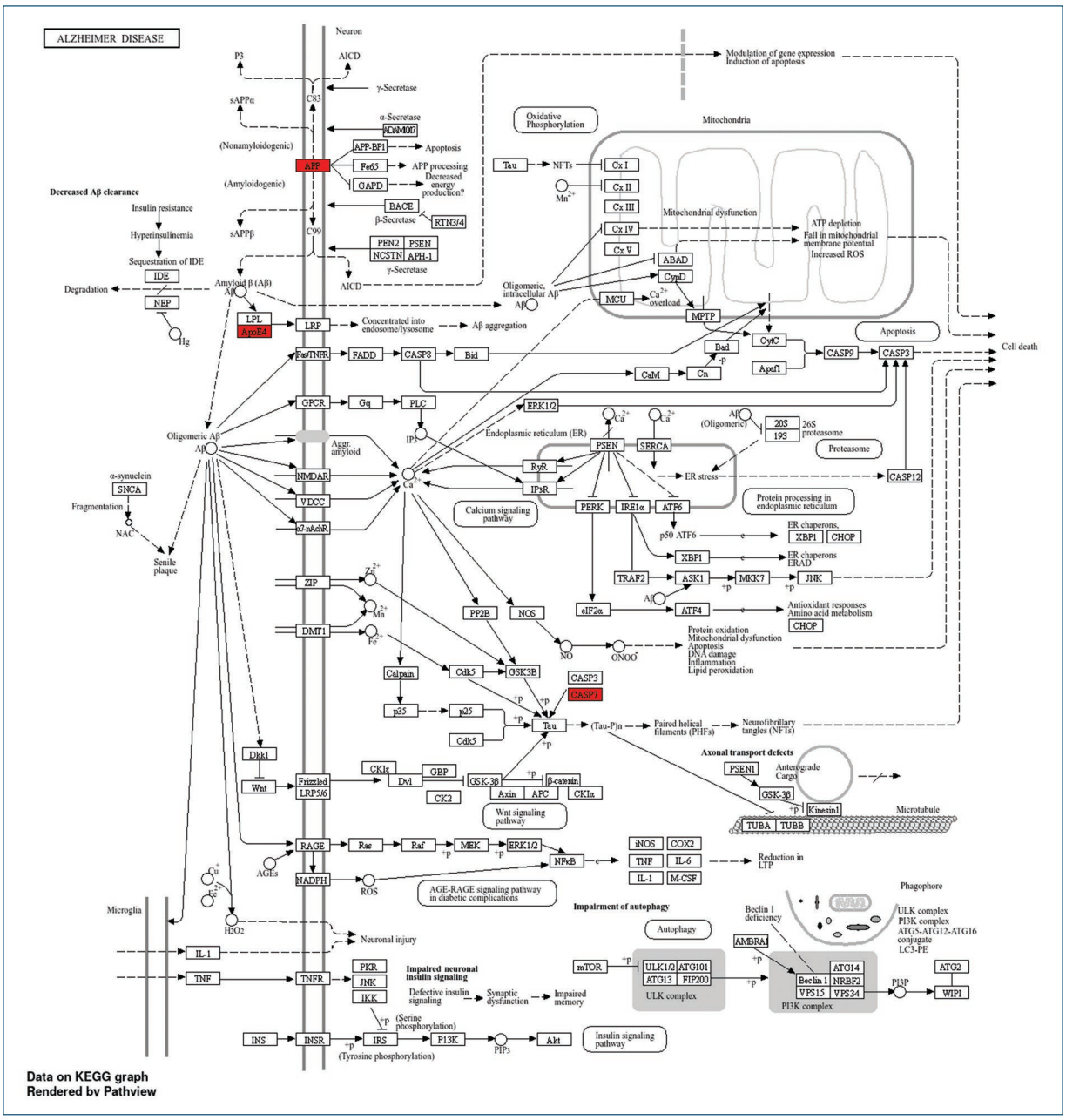

Figure 4. Molecular pathway of Alzheimer's disease highlighting protective genes identified in the bioinformatics analysis.

processes, including steroid biosynthesis and bile acid generation. Moreover, transport proteins such as ABCG5/ABCG8 promote cholesterol excretion into bile, serving as a crucial mechanism for its removal.

Numerous elements depicted in the picture, including ApoE, ApoC-I, and ApoB-100, have been associated with the modulation of cholesterol metabolism and its connection to neurodegenerative disorders, particularly AD. Variants in the *APOE* gene have been thoroughly investigated for their influence on β-amyloid buildup and the functionality of the blood-brain barrier. The bioinformatics study of these genes can yield pertinent information regarding the protective variables that influence the likelihood of developing AD.

Molecular processes implicated in AD

Figure 4 illustrates the molecular route of AD per the KEGG database, emphasizing the primary detrimental processes associated with β-amyloid (Aβ) accumulation, mitochondrial dysfunction, cell signaling

abnormalities, and neuronal apoptosis. The primary event in the advancement of AD is the generation and accumulation of Aβ peptides, resulting from the aberrant processing of the *APP*.

In the illustration, *APP* is cleaved by secretases (β-secretase and γ-secretase), producing deleterious fragments that aggregate into tiny clusters and form plaques extracellularly. The reduction in Aβ clearance, facilitated by insulin resistance and hyperinsulinemia, exacerbates disease progression. The accumulation of Aβ initiates many signaling pathways that influence cellular homeostasis. Calcium signaling pathways (CaMKII, IP3R) and endoplasmic reticulum stress (PERK, ATF4) are activated, resulting in synaptic dysfunction and neuronal demise.

The mitochondria play a crucial role in the condition, as oxidative stress and dysfunction in oxidative phosphorylation result in increased reactive oxygen species, which damage nerve cells and induce their apoptosis. A critical mechanism involves the increased phosphorylation of the Tau protein (MAPT), forming neurofibrillary tangles and compromising neuronal integrity. The graphic illustrates the relationship between the signaling pathway of the kinase GSK3β, which facilitates the addition of phosphate groups to tau, and other detrimental mechanisms affecting neurons, such as autophagy dysfunction and inflammation induced by activated microglia.

Several genes depicted in the image (*APOE, LPL, GSK3β, CASP3*) have been thoroughly investigated for their influence on advancing AD. Specifically, *APOE* facilitates the clearance of Aβ, and the APOE4 variant is associated with an increased risk of developing the disease. The bioinformatic study of these genes aids in identifying potential protective factors and biological processes that may be crucial for developing targeted treatment options.

Protein-protein

STRING's network analysis revealed a highly linked relationship among the assessed genes/proteins. The APP serves as the pivotal element of the network, forming strong connections with essential proteins such as *APOE, SORL1, PICALM, BDNF*, and *CASP7*. This interconnectedness underscores its vital function in amyloid metabolism, the preservation of synaptic homeostasis, and processes associated with neuronal stress (Fig. 5).

Interactions were depicted by color-coded linkages based on the available evidence: Green (interactions obtained from *in vitro* or *in vivo* studies). Blue (co-expression across many transcriptome datasets). Black (co-occurrence in scientific literature). Yellow signifies forecasts obtained from text mining. Purple/Pink (associations documented in integrated interaction databases).

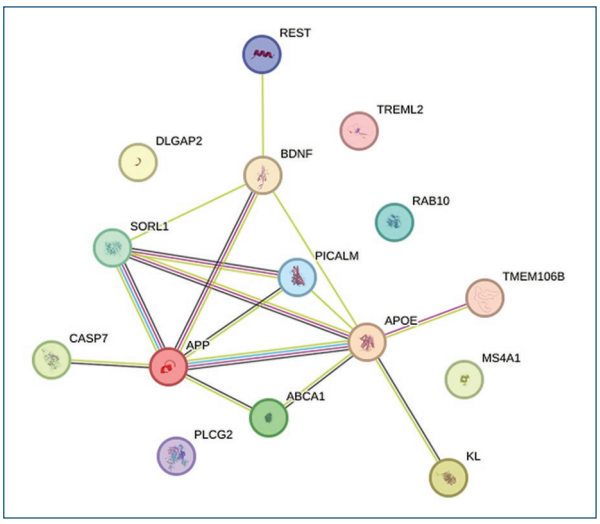

Figure 5. Protein-protein interaction network generated in STRING, reflecting its key role in amyloid processing and neurodegeneration.

Proteins, including *REST, TMEM106B, TREM2, KL*, and *MS4A1*, were found at the network's periphery; although possessing fewer direct connections, they play roles in neuroprotection, inflammatory response control, lipid metabolism, and synaptic function. These data indicate that, while not central nodes, these proteins function as modulators within the pathways related to AD.

The PPI study conducted on the STRING platform revealed a network of 15 nodes, each representing proteins linked to the pathogenesis of AD, interconnected by 15 edges denoting direct functional relationships. The mean connectivity degree was 2, indicating a moderate interconnectivity among the nodes, with central proteins such as *APP* and *APOE* displaying a greater number of connections and functioning as primary hubs within the network. The mean local clustering coefficient (0.535) signifies a coherent architecture wherein several nodes exhibit shared contacts and establish functional subnetworks, illustrating interrelated molecular activities. Moreover, the observation of 15 interactions, in contrast to the anticipated number of edges (4), substantiates a level of connection that exceeds what would be predicted from random

occurrence. The PPI enrichment value ($p = 5.37 \times 10^{-6}$) substantiates this evidence, indicating a statistically significant enrichment of interactions and implying that the examined proteins are collaboratively involved in crucial biological pathways associated with amyloid metabolism, synaptic regulation, and the neurodegenerative processes typical of AD.

Discussion

The results of the current bioinformatics research indicate that multiple genes may serve as protective factors in AD, influencing critical processes, including lipid metabolism, synaptic plasticity, neuroinflammation, and neuronal survival. Through computational methods, significant metabolic and signaling pathways that link these genes to disease and protective mechanisms were identified, aiding in formulating novel treatment strategies for AD.

The enrichment analysis revealed that only the cholesterol metabolism pathway exhibited robust statistical significance after multiple testing corrections, reinforcing its role in cerebral lipid regulation and neuroprotective mechanisms. The other pathways, although biologically plausible, should be considered exploratory hypotheses that require validation in experimental models and larger cohorts.

The cross-validation outcomes using DAVID and Reactome enhance and reinforce the preliminary results from ShinyGO. The observed enrichment in the plasma membrane and external exosomes indicates that the examined genes play an active role in regulating lipid and protein transport, which are essential for neuronal homeostasis and the prevention of β-amyloid buildup. This discovery aligns with recent findings emphasizing the function of extracellular vesicles in the removal of protein aggregates and the modulation of neuroinflammation. The correlation with synaptic vesicles substantiates the concept that variations such as *BDNF* and *DLGAP2* affect synaptic plasticity and cognitive resilience, as indicated in recent studies on genetic protective factors against AD development[12]. Despite the neurodegeneration pathway across various diseases not achieving statistical significance post-FDR correction, its consistent identification by multiple tools (ShinyGO and DAVID) indicates substantial biological relevance, consistent with literature associating genes such as *APOE* and *ABCA1* with cholesterol metabolism and the modulation of the inflammatory response[13].

This research possesses considerable limitations. Gene selection derived from literature produced between 2017 and 2024 may engender selection bias by omitting less-explored genes. The bioinformatic analysis was predominantly performed using ShinyGO, with additional support from DAVID and Reactome, excluding other platforms, which may constrain the comprehensiveness of the results. This analysis is solely computational and based on a restricted gene list; hence, experimental validation and subsequent integrative studies are necessary to verify and enhance the findings. Considering these constraints, the analysis establishes a robust basis for subsequent research that integrates experimental validations and comprehensive omics methodologies.

The *APOE* ε2 allele is the sole discovered mutation that reduces the chance of acquiring AD. A study including patients homozygous for *APOE* ε2 revealed a reduced accumulation of senile plaques and superior cognitive ability relative to other genotypes, despite advanced age[14].

Furthermore, the *ABCA1* transporter enhances the lipidation of *APOE*, hence promoting the clearance of β-amyloid. Lafranco et al. (2020) revealed that the activation of *ABCA1* with nuclear agonists markedly diminished amyloid deposition and neuroinflammation in animal models[15].

BDNF (brain-derived neurotrophic factor) regulates synaptic modulation and neuronal aging, playing a crucial role in synaptic plasticity and memory. Polymorphisms in *BDNF* are correlated with reduced hippocampus volume and an increased risk of AD[16]. Aerobic exercise interventions have been associated with elevated blood *BDNF* levels and cognitive enhancements in older people with mild impairment.

Furthermore, our bioinformatics study has recognized *REST*, a transcriptional repressor that modulates genes linked to oxidative stress and death, as neuroprotective in aging. Lu et al. (2014) established that *REST* is lacking in the brains of individuals with AD, while present in cognitively intact adults. Lam et al. (2023) have noted that *REST* regulates genes associated with autophagy and neuronal survival in human *in vitro* models[17].

The α-Klotho (KL) protein modulates brain lifespan and neurodegenerative resistance as a marker for longevity and neuroprotection. Chen et al. (2023) discovered that individuals possessing the KL-VS haplotype exhibited reduced levels of tau and amyloid in cerebrospinal fluid and enhanced episodic memory, even in the presence of *APOE* ε4 alleles[18]. This underscores the

concept that beneficial genetic modification might mitigate high-risk factors.

The *PLCG2* gene has recently been acknowledged for its dual function in modulating microglia through immunoregulation and neuronal homeostasis. The polymorphism p.P522R is linked to decreased inflammation and improved regulation of Aβ deposition[19]. Similarly, *TMEM106B*, which plays a role in lysosomal trafficking and protein homeostasis, seems to mitigate synaptic damage and tau buildup, as evidenced by research utilizing animal models of AD and frontotemporal lobar degeneration[20].

The PPI network analysis conducted in STRING indicates that *APP* functions as a core node, forming significant connections with *APOE, SORL1, PICALM,* and *BDNF*, thereby affirming its crucial role in amyloid metabolism, vesicular trafficking, and neural plasticity. This outcome aligns with prior research emphasizing APP as a pivotal regulator in amyloid plaque development and in mechanisms contributing to synaptic dysfunction and neurodegeneration.

The statistically significant network enrichment ($p = 5.37 \times 10^{-6}$) and the local clustering coefficient (0.535) indicate substantial functional cohesion, suggesting that the examined proteins operate within interconnected networks that govern processes associated with neuronal homeostasis, the inflammatory response, and lipid metabolism. These connections underscore the intricacy of the biological pathways linked to the disease and imply that modifications in these nodes may exacerbate the destructive cascades of AD. Similarly, distinct modular subnetworks with defined activities have been identified: proteins include *APOE*, *ABCA1*, and *SORL1* involved with lipid metabolism; *CASP7*, connected to apoptosis control; and molecules such as *REST, TREM2*, and *MS4A1*, pertinent to neuroprotective and inflammatory mechanisms. This network analysis method not only corroborates previously documented material but also reveals new avenues for examining peripheral nodes, such as *KL* and *TMEM106B*, whose functions in synaptic regulation and neuronal resilience necessitate additional experimental inquiry.

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Conclusion

This bioinformatics analysis identified a group of genes that may confer protective effects against AD, incorporating functional evidence regarding their roles in critical biological pathways, including cholesterol metabolism, synaptic plasticity, neurogenesis, inflammatory signaling, and the regulation of cellular longevity. Genes include *APOE ε2, KL, ABCA1, PLCG2*, and *REST*, which serve as essential regulators of mechanisms that mitigate the etiology of AD by diminishing β-amyloid buildup, maintaining neuronal integrity, and modulating the immunological response in the central nervous system. The results underscore the necessity of evaluating risk genes and those that provide resilience or biological resistance to cognitive decline. This method offers a more thorough understanding of the clinical heterogeneity of AD and presents prospects for developing therapeutic strategies centered on gene manipulation and precision medicine. Subsequent scientific and clinical investigations must confirm the functional significance of these genes in biological models and human cohorts to establish their efficacy as prognostic biomarkers or neuroprotective treatment targets.

Overall, these data underscore the pivotal role of lipid metabolism, especially cholesterol, in neuroprotection against AD. The exploratory nature of this bioinformatics research and the modest statistical significance of the discovered pathways highlight the necessity for supplementary investigations with cross-validation and biological models to reinforce these relationships.

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Authors' contribution

All authors contributed equally to the study's conceptualization, data collection, formal analysis, investigation, and methodological development. Likewise, they actively participated in the supervision, validation of results, data visualization, and manuscript writing, including preparing the original draft, its critical review, and the final editing.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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ORIGINAL ARTICLE

Mild cognitive impairment and dementia in early-onset Parkinson's disease: a comparative study across disease duration

Deterioro cognitivo leve y demencia en la enfermedad de Parkinson de inicio temprano: un estudio comparativo según la duración de la enfermedad

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Abstract

Background: *Few studies have analyzed the frequency of Parkinson's disease (PD) associated mild cognitive impairment (PD-MCI) or dementia (PD-D), and its association with disease duration in the specific population of early-onset PD (EOPD).* **Objectives:** *To describe and compare the frequency of PD-MCI and PD-D in patients with EOPD with short-, mid-, and long-disease duration.* **Methods:** *Data from 168 individuals with EOPD who were categorized as having short (1-8 years, n = 44), mid (9-16 years, n = 88), and long disease durations (> 16 years, n = 36) were examined. Disease duration was defined as years from the onset of the first cardinal PD motor symptoms (self-reported and described in the clinical record) to the time of assessment. Patients in each disease duration group were classified according to whether they had normal cognition, PD-MCI, PD-D, and with cognitive impairment + severe depression. Cognitive performance on all tests and the frequency of cognitive statuses were compared between groups.* **Results:** *With the exception of the clock drawing test, no significant between-group differences were found in cognitive performance. There were no differences between the groups in terms of the frequency of normal cognition, PD-MCI, or PD-D.* **Conclusions:** *In our sample of patients with EOPD, no differences in cognitive performance or frequency of PD-MCI or PD-D were found between disease duration groups. These findings could indicate that MCI in EOPD remains stable and that PD-D is rare in patients under 70 years despite long disease duration, although further longitudinal studies should be carried out.*

Keywords: *Parkinson's disease. Mild cognitive impairment. Dementia. Cognition. Neuropsychological tests. Nervous system diseases.*

Resumen

Antecedentes: *Pocos estudios han analizado la frecuencia de deterioro cognitivo leve (DCL) y demencia asociados a la enfermedad de Parkinson (EP) y su relación con la duración de la enfermedad en la EP de inicio temprano (EPIT).* **Objetivo:** *Describir y comparar la frecuencia de DCL y demencia en pacientes con EPIT que presentan corta, media y larga evolución de la enfermedad.* **Método:** *Se analizaron datos de 168 individuos con EPIT, clasificados según la duración de la*

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enfermedad: corta (1-8 años, n = 44), media (9-16 años, n = 88) y larga (> 16 años, n = 36). La duración de la enfermedad se definió como el número de años entre el primer síntoma motor cardinal de EP (autorreportado y descrito en el expediente clínico) y el momento de la evaluación. Los pacientes se clasificaron con cognición normal, DCL, demencia y deterioro cognitivo + depresión grave. El rendimiento cognitivo en las pruebas y la frecuencia de los estados cognitivos se compararon entre los grupos. **Resultados:** *No hubo diferencias significativas entre los grupos en el rendimiento cognitivo, excepto en la prueba de dibujo del reloj. Tampoco hubo diferencias en los distintos estados cognitivos.* **Conclusiones:** *En los pacientes con EPIT, no hubo diferencias en el rendimiento cognitivo ni en la frecuencia de DCL entre los grupos según la duración de la enfermedad. Estos hallazgos podrían indicar que el DCL se mantiene estable y que la demencia es infrecuente en pacientes menores de 70 años a pesar de una larga evolución de la enfermedad; no obstante, se deberán llevar a cabo estudios longitudinales para confirmar el hallazgo.*

Palabras clave: *Enfermedad de Parkinson. Deterioro cognitivo leve. Demencia. Cognición. Pruebas neuropsicológicas. Enfermedades del sistema nervioso.*

Introduction

Early-onset Parkinson's disease (EOPD) is defined as Parkinson's disease (PD) with an onset of motor symptoms before 50 years and represents 3-7% of overall PD cases[1]. Cognitive decline has been recognized as a common non-motor symptom of PD[2]. Nevertheless, previous studies only conceptualized major forms of cognitive dysfunction (i.e., dementia) and based diagnosis on clinical criteria not specifically adapted to the cognitive profile of PD[3]; therefore, minor forms of cognitive decline could go unnoticed. Such concepts influenced the first studies in the 1980s, 1990s, and early 2000s describing cognitive characteristics of EOPD, concluding that EOPD was not associated with (major) cognitive decline[4-6]. Reports that address the cognitive profile specific to EOPD are scarce and with heterogeneous results. For example, Caccappolo et al.[7] reported that the EOPD sample assessed, regardless of genetic mutation status (specifically whether participants presented a parkin mutation or not), showed normal cognitive function. In contrast, a previous study by Hietanen and Teräväinen[8] found that patients with EOPD scored lower than an age-matched control group on tasks that involved visuoconstructive abilities, visual attention, and memory.

Over the past few decades, extensive research has identified the various types of cognitive dysfunction associated with PD. In 2007, specific criteria for the diagnosis of PD-associated dementia (PD-D) were published[9], followed in 2012 by the PD-associated mild cognitive impairment (PD-MCI) diagnostic criteria[10], reporting a prevalence of 30% and 19-38%, respectively. More recently, a similar frequency of PD-MCI in EOPD has been reported[11]. PD-MCI refers to a degree of cognitive decline that is not normal for someone of that age, but where functional activities are essentially normal. Moreover, it is associated with an increased risk of developing dementia[12]. A study found that 27% of patients with PD-MCI at the time of PD diagnosis developed PD-D, in comparison to 1% of patients without MCI in a 3-year follow-up[13]. Similarly, another study found that 62% of patients initially classified with PD-MCI developed dementia in 4 years[14]. It is important to highlight that studies specifically addressing PD-MCI in EOPD are scarce, and, to our knowledge, no studies have analyzed the progression from PD-MCI to PD-D or the variables associated with different degrees of cognitive decline in this population.

The factors most strongly associated with PD-MCI in the general PD population are increasing age, disease duration, and the severity of motor symptoms[12]. A cumulative prevalence of over 80% has been reported for PD-D after 20 years of disease duration[15], with an increasing prevalence also related to age and disease duration[16]. For example, Aarsland et al.[17] reported an association between age at baseline and the risk of developing PD-D, despite finding no effect of age at symptom onset. Similarly, Williams-Gray et al.[18] found that age was a predictor of subsequent dementia. They also reported that the incidence of dementia increased with disease duration in a cohort with a 10-year follow-up.

To the best of our knowledge, few studies have analyzed the frequency of PD-MCI and its association with disease duration and age in the specific population of individuals with EOPD. Therefore, the aim of this study was to examine the frequency of PD-MCI and PD-D in patients with EOPD and short-, mid-, or long-term disease durations. Based on the reviewed literature, we hypothesized that the frequency of PD-MCI and possibly PD-D would increase with disease duration.

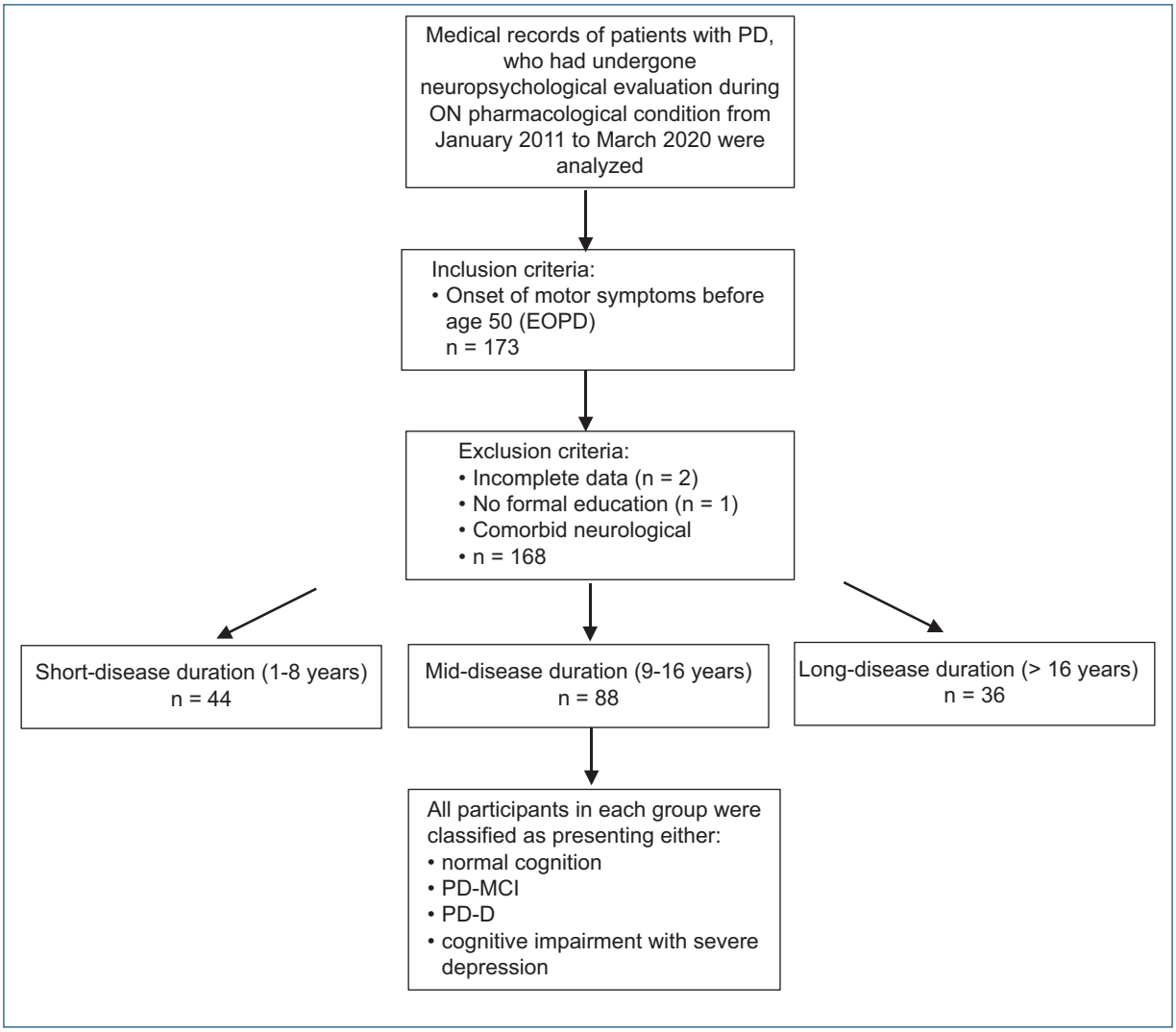

Figure 1. Participant selection flowchart.

Materials and methods

This study was conducted in accordance with the STROBE statement guidelines for reporting observational studies.

Participants

The present report is a retrospective study that analyzed existing data of 168 patients with EOPD assessed between January 2011 and March 2020 in the Movement Disorders Clinic at the Specialties' Hospital in Centro Médico Nacional Siglo XXI, a national public health referral center for PD in Mexico City. In accordance with recent consensus, we refer to EOPD as cases with onset of motor symptoms before the age of 50[1].

The protocol was evaluated and approved by the Research and Ethics Committee of the Centro Médico Nacional Siglo XXI hospital. The data included in this manuscript were obtained in compliance with regulations of the Centro Médico Nacional Siglo XXI, registration no. R-2021-3601-051. Research was completed in accordance with Helsinki Declaration. All participants signed an informed consent form for participation in the study and for the publication of the data.

The diagnosis of PD was established according to the UK Brain Bank Criteria[19]. Exclusion criteria included comorbid neurological conditions, significant uncorrected visual or hearing impairments, and low educational attainment (< 6 years). Patients with incomplete records or assessments were also excluded. Figure 1 shows the participant selection flow. All clinical and

neuropsychological assessments were performed during ON pharmacological condition.

Motor assessment

Clinical assessment was performed by a movement disorder specialist and included the motor subscale from the Unified PD Rating Scale III[20] and Hoehn and Yahr staging[21]. Disease duration was calculated as years since the onset of cardinal motor symptoms. Levodopa equivalent daily doses were calculated according to the standard formula[22].

Neuropsychological assessment

All neuropsychological assessments were completed in one or two consecutive sessions. Patients completed a battery of neuropsychological tests to evaluate the following domains: attention/working memory, memory, language, visuospatial, and executive function, as suggested by the International Movement Disorder Society[10]. All neuropsychological tests included normative data corrected for age and education level, except for the clock drawing test, for which the correction criteria and cut-off scores established by Cacho et al.[23] were used. Table 1 provides information on the tests and normative data used to assess each domain. In addition, the vocabulary subtest from the Wechsler Adult Intelligence Scale-Third Edition[24] was used as an indicator of premorbid intelligence level. The Spanish adaptation[25] of the beck depression inventory (BDI)[26] was used to evaluate depressive symptoms. Further information on the neuropsychological assessment protocol can be found in Seubert-Ravelo et al.[11].

Classification of cognitive status, diagnosis of PD-MCI or PD-D

Patients in each disease-duration group were classified into one of the following four categories according to their cognitive characteristics: (1) Normal cognition, patients whose scores on all cognitive tests were within the normal range or those who scored below -1 standard deviation (SD) on one or more tests but did not fulfill the diagnostic criteria for PD-MCI; (2) PD-MCI; (3) PD-D; and (4) cognitive impairment + severe depression, patients who fulfilled the cognitive (number and severity of affected cognitive tests) and functional affectation (no significant impairment) criteria for PD-MCI but could not receive a formal diagnosis due to the presence of severe depressive symptoms which may have contributed to cognitive impairment.

Table 1. Neuropsychological assessment instruments used to evaluate cognition in the early-onset Parkinson's disease sample

Domain	Subtest
Attention/ working memory	Digit span backward[a]
	Digit span forward[a]
	Stroop color word test interference[b]
Memory	Word list learning immediate and delayed recall[c]
	Prose: immediate and delayed recall[a]
Language	Similarities[a]
	Naming[a]
Visuospatial function	Clock copying[d]
	Block design[a]
Executive function	Wisconsin card sorting teste (Heaton et al., 1997)
	Category and letter fluency[c]
	Clock drawing[d]

[a]Programa Integrado de Exploración Neuropsicológica Test Barcelona[37], Mexican standardization norms by Villa-Rodríguez[38].
[b]Stroop Color Word Tests[39], Mexican standardization norms by Rivera et al.[40]
[c]Neuropsi Atención y Memoria[41]. The test's manual's norms were used.
[d]10-point correction criteria by Cacho et al.[23].
[e]Wisconsin Card Sorting Test[42]. The test's manual's norms were used.

The PD-MCI or PD-D diagnosis was obtained using the movement disorder society criteria for PD-MCI[10] and PD-D[9]. In both cases, a cutoff of either two SD below the mean or the 10th percentile, depending on the normative information provided by each test, was used to distinguish between normal and impaired cognition. Considering the findings of Goldman et al.[27] regarding the optimal sensitivity and specificity, a two SD cut-off was used. Information on daily life functioning, which is essential for distinguishing between PD-MCI and PD-D, was obtained through semi-structured interviews with the patients and a close relative. For further information on the diagnostic algorithm, please refer to Seubert-Ravelo et al.[11]. As major depression is an exclusion criterion for PD-MCI and PD-D according to the MDS diagnostic criteria, patients with severe depressive symptoms (BDI ≥ 30) were excluded from the subsequent analysis used to determine the frequency of PD-MCI and PD-D. The initial diagnosis of PD-MCI or PD-D was made by the trained neuropsychologist who conducted the assessment. All diagnoses and assignments to cognitive status groups were subsequently reviewed by another trained researcher, in accordance with the aforementioned criteria for the purposes of this study.

Disease duration groups

The symptoms and progression of PD can be classified according to many criteria[28], and there is currently no consensus on which cut-off to use when referring to early, short-, mid-, or long-disease duration. For example, short duration has been described as < 2 or 3.5 years of disease duration, while advanced PD has been described as having a mean disease duration of approximately 10 years[29,30]. Nonetheless, this classification does not fully apply to EOPD, as patients with disease onset before their 50s have been reported to exhibit slower progression in certain aspects of the condition[31], and can be expected to survive with the disease for 20-40 years or more. Therefore, considering the absence of criteria to classify the duration of EOPD and the wide range of disease duration among our patients, we divided our sample into three groups for the purposes of this study and data analysis: short disease duration (1-8 years), mid disease duration (9-16 years), and long disease duration (> 16 years).

Statistical analyses

Missing data on certain tests due to random circumstances was present in a minority of cases (< 10% per variable). As such cases were rare, statistical analyses were performed using pairwise deletion.

The data did not meet the assumptions required for parametric statistics, including differences in group sizes and the lack of normal distribution for most variables, as determined by Shapiro-Wilk tests. Therefore, Kruskal-Wallis tests were used to assess whether performance in tests within each cognitive domain differed between the three disease duration groups (Table 1). Due to the significant age differences between groups, standardized scores, which are adjusted for age and education, were used for all comparisons, and significance was defined as $p < 0.05$. To reduce the probability of Type-1 errors arising from multiple comparisons, a Bonferroni correction was applied ($p < 0.002$). Follow-up pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons[32]. Adjusted p values are presented for the *post hoc* tests.

All cases were independently reviewed to determine their cognitive status, categorized as normal cognition, PD-MCI, PD-D, or cognitive impairment + severe depression. Frequencies were obtained for each cognitive status category (short, mid, and long). A two-way contingency table was used to calculate X^2 test values.

Results

A total of 168 patients with EOPD were included in the study: of these, 44 had short-duration disease, 88 had mid-duration disease, and 36 had long-duration disease. Table 2 shows the sociodemographic and clinical characteristics of the groups. The groups were homogeneous regarding variables relevant to cognitive performance, such as years of formal education, premorbid intelligence, and depressive symptomatology. As was expected, given the nature of the study, differences were found regarding age at assessment. *Post hoc* analysis revealed statistically significant differences in age between the short- and mid-disease duration groups ($p \leq 0.0005$), the short- and long-disease duration groups ($p < 0.0005$), and the mid- and long-disease duration groups ($p < 0.0005$). Statistical differences were also found in the age at disease onset. However, the *post hoc* analysis only revealed differences between the groups with short- and long-disease duration ($p = 0.039$).

There were no significant differences in cognitive performance between disease duration groups in any of the tests within the five cognitive domains except for the Stroop test (interference condition) and the clock drawing test (free drawing condition; Table 3). However, following Bonferroni correction ($p < 0.002$), only the differences observed in the clock-drawing test remained significant: specifically between the long- and mid- disease duration groups ($p = 0.002$) and between the long- and short-disease duration groups ($p = 0.002$).

Patients across the three disease duration groups exhibited similar frequencies of the different cognitive statuses, with approximately half of the participants in each group showing normal cognition, around 40% presenting with PD-MCI, and notably, no participants presenting with PD-D. A minority of cases (one case in both the short- and mid- disease duration groups) could not receive a formal cognitive diagnosis due to the presence of severe depressive symptomatology (Fig. 2). Contingency table analysis showed no statistically significant between-group differences in the frequency of normal cognition, PD-MCI, or cognitive impairment with severe depression ($p = 0.994$). As no cases of PD-D were identified, frequencies were not statistically compared.

The results indicate that cognitive ability and the proportion of PD-MCI do not vary significantly across disease duration groups. More specifically, neither PD-MCI nor PD-D became more frequent as disease duration increased in our EOPD sample, which included individuals under the age of 72.

Table 2. Sociodemographic and clinical characteristics of EOPD patients with short-, mid-, and long-disease durations

Variable	EOPD disease duration groups			
	Short (1-8 year) n = 44	Mid (9-16 year) n = 88	Long (> 16 year) n = 36	Kruskall-Wallis
	Median (range) / %			χ^2 (p)
Age at assessment	48 (27-58)	54 (37-65)	62 (45-72)	45.38 (0.0005)
Education (years)[a]	13 (4-24)	12 (2-18)	11 (5-22)	2.02 (0.365)
WAIS-III Vocabulary[b]	10 (6-18)	10 (6-15)	9 (6-13)	3.41 (0.181)
Sex (male)	65.9	70.5	72.2	0.431 (0.806)
Age at disease onset	43 (20-50)	42 (28-50)	39.5 (15-50)	6.41 (0.041)
Disease duration (years)	6 (1-8)	12 (9-16)	21 (17-40)	138.92 (0.0005)
LEDD	1075 (0-4200)	1187.5 (500-4350)	1200 (625-1960)	5.07 (0.079)
UPDRS III[c]	26 (12-90)	29 (7-72)	28.5 (14-77)	0.462 (.794)
Hoehn and Yahr	2 (1-3)	2 (1-4)	2.5 (1-4)	5.43 (0.066)
I	2.6	1.3	0	
II	66.7	49.4	50.0	
III	30.8	43	36.7	
IV	0	6.3	13.3	
BDI	7.5 (0-34)	9 (0-41)	9 (0-35)	0.126 (.939)

[a]Education is measured in years of formal education starting in primary school.
[b]Estimated intelligence is based on the standardized score obtained in the Vocabulary Subtest of the Wechsler Adult Intelligence Scale III (mean = 10, standard deviation = 3).
[c]All UPDRS III scores were obtained in the on-medication state.
BDI: beck depression inventory; LEED: levodopa equivalent daily doses; UPDRS III: unified parkinson's disease rating scale

Discussion

This study aimed to describe and compare the cognitive performance and the frequency of different degrees of cognitive impairment in patients with EOPD at different stages of the disease (short-, mid-, and long-disease durations). Our results show no significant differences in cognitive performance across all tests belonging to the five assessed cognitive domains (attention/working memory, memory, language, visuospatial, and executive function) between the three disease duration groups, except for the clock drawing test, in which significant differences were found between the long-disease duration and the other two groups. In addition, no between-group differences were found in the frequency of PD-MCI, which was present in 43-45% of participants in each group. No participants with PD-D were identified. Only one participant in each of the short- and mid-disease duration groups could not be formally diagnosed as having PD-MCI due to the presence of severe depressive symptoms.

Our study found that different disease duration groups only significantly differed in their performance in one test, the clock drawing test free drawing condition. Nonetheless, it is important to note that the median scores of all three groups are not clinically significant; that is, they are above the cut-off score indicating cognitive decline[23]. It is important to note that the clock drawings test was the only test without age-corrected normative data. Although analyses performed by Cacho et al.[23] found no influence of age on performance in either test condition, other evidence suggests that older age is associated with lower scores within the normal range, particularly in the free drawing condition, which demands higher levels of executive function[33]. Therefore, it is possible that significant between-group differences and noticeable differences in the proportion of patients with scores below the cutoff indicative of altered performance may be related to the lack of age-adjusted norms.

Despite the initial assumption that cognition remains normal in most patients with EOPD[4-6], our work supports the idea that patients with EOPD may exhibit cognitive deficiencies, with a frequency of PD-MCI similar to that reported in late-onset PD[10]. Specifically, we found that 43% of individuals in our sample with EOPD presented PD-MCI in the first years of the disease. This finding is consistent

Table 3. Comparison of cognitive performance in neuropsychological tests and frequency of MCI between short-, mid-, and long-disease duration groups

Cognitive process	Short (1-8 year) n = 44	Mid (9-16 year) n = 88	Long (> 16 year) n = 36	Kruskall-Wallis
Subtest	Median (range)	Median (range)	Median (range)	$\chi 2$ (p)
Attention/working memory				
Digit span forward	60 (10-90)	80 (9-95)	80 (9-95)	0.161 (0.923)
Digit span backward	60 (9-95)	60 (9-95)	60 (9-95)	2.123 (0.346)
Stroop interference	40 (5-95)	30 (5-95)	40 (5-95)	6.563 (0.038)
Memory				
Immediate prose recall -free	20 (9-90)	10 (9-95)	25 (9-90)	2.284 (0.319)
Immediate prose recall -cued	30 (9-90)	20 (9-95)	35 (9-90)	1.576 (0.455)
Delayed prose recall- free	50 (9-95)	50 (9-95)	55 (9-95)	0.850 (0.654)
Delayed prose recall-cued	60 (10-95)	70 (9-95)	60 (9-95)	1.367 (0.505)
Average word list learning curve[a]	10 (4-14)	9 (2-16)	8 (4-16)	0.427 (0.808)
Delayed word list recall[a]	9 (4-16)	9 (4-15)	9 (3-13)	0.197 (0.906)
Language				
Similarities	40 (9-95)	50 (9-95)	45 (9-90)	0.469 (0.791)
Naming	95 (10-95)	95 (9-95)	95 (95-95)	1.869 (0.393)
Visuospatial				
Clock copying[b]	10 (6-10)	9.5 (5-10)	9.5 (6-10)	2.054 (0.358)
Block design	20 (9-95)	30 (9-95)	20 (9-95)	1.185 (0.553)
Executive				
Category fluency[a]	9 (4-15)	9 (3-16)	9 (1-13)	0.990 (0.610)
Letter fluency[a]	8.5 (1-10)	8.5 (1-19)	8 (3-16)	2.876 (0.237)
Clock drawing[b]	38 (1-78)	8.5 (3-10)	7.2 (3-10)	13.822 (0.001*)
WCST perseverative errors[c]		42 (20-80)	44.5 (26-71)	5.218 (0.074)

Participants with cognitive impairment and severe depressive symptoms were excluded from the analysis. MCI: mild cognitive impairment. All comparisons were performed using standardized scores. If not otherwise indicated, mean scores represent percentiles.
*Differences significant after Bonferroni correction ($p < 0.002$).
[a]Standardized scores represent scale scores (mean 10, standard deviation [SD] 3).
[b]The clock drawing test is scored on a 1-10 scale. Scores < 7 are considered indicative of cognitive decline in the free-drawing condition, and scores < 9 are considered indicative of cognitive decline in the copying condition.
[c]Standardized scores represent T scores (mean 50, SD 10).

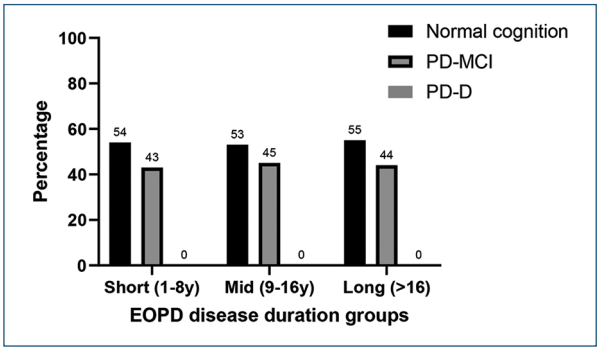

Figure 2. Frequency of normal cognition and mild cognitive impairment between short-, mid-, and long-disease duration groups.

with previous studies reporting that 32-41% of individuals with recently diagnosed PD show cognitive impairment. Nonetheless, in contrast with studies of other populations with PD, our results suggest that in EOPD, the proportion of individuals with cognitive impairment is similar across different disease duration groups, even among those with 16 years or more of disease progression.

Increasing age and disease duration have been associated with the presence of both PD-MCI and PD-D[12,16]. Based on these findings, an increased frequency of PD-MCI and PD-D could be expected in the group with a longer duration of PD in our study. Contrary to this idea, the cognitive ability and frequency of PD-MCI were similar in the three EOPD groups, and no participants presented PD-D regardless of the disease duration, even after over nine and 16 years. These results suggest that disease duration alone is not a relevant factor in the development of PD-MCI or the conversion to PD-D in EOPD, as has been reported in late-onset PD[34]. Other studies have suggested that age, rather than disease duration, is a more significant risk factor for the development of major cognitive decline[6,29]. Aarsland et al.[17] studied a sample of PD patients with a mean age at disease onset of 73.5 ± 9.3 years, and concluded that age at baseline rather than disease

duration was the main factor associated with PD-D. Another study conducted on patients with PD with a median age of 71.8 years, also found that those in the older age group (over 72) were at significantly higher risk of developing dementia[35]. In addition, other age-related pathologies (e.g., vascular changes, cerebral amyloid angiopathy, and Alzheimer's disease) likely interact with PD pathology in determining the rate of cognitive decline, which may explain why older people with PD are at a higher risk of PD-dementia[36]. It is important to note that the mean/median age of participants in the studies described is over 10 years older than the median age of our long-disease duration group (our oldest group on average), which could explain why despite most of our participants having over 12 years of disease duration, we did not find cases of PD-D. That is, it is possible that our sample has not reached the age threshold at which said variable becomes a relevant predictor of major cognitive decline. The absence of cases involving PD-D in our sample is consistent with one of the first papers describing the cognitive characteristics of patients with EOPD, which stated that the incidence of dementia is negligible in patients with EOPD under the age of 65[5].

Such results suggest that in EOPD, the incidence of PD-MCI is not related to disease duration, and in patients < 72, age does not seem to be a determining factor either. Although PD-MCI was common even in the short-disease duration group, its frequency or the presence of PD-D was not higher in longer disease duration groups, which raises the question of whether PD-MCI in patients under 72 has a progressive nature in EOPD and whether it predicts the onset of PD-D in the mid-term, as has been reported in late-onset PD-D.

The results of our study may have several clinical implications. First, the prevalent idea that cognitive decline is nonexistent in EOPD could begin to shift toward the recognition that PD-MCI is as common in EOPD as in late-onset PD. Moreover, it is well recognized that patients with EOPD face the disease at an age when family, work, and social demands are high, and their ability to respond effectively to these demands may be negatively affected by the presence of MCI. Clinicians should make a concerted effort to assess the presence of PD-MCI and its potential impact on patients' lives. Second, although PD-MCI appears to remain stable over many years in EOPD patients, this should be viewed as an opportunity to implement intervention strategies – such as non-pharmacological approaches – to prevent or reduce the risk of major cognitive decline as the patient ages.

Our study had several limitations. One of these was that it involved a clinical sample, which can influence the characteristics of the patients assessed. The main limitation was the lack of a longitudinal follow-up, which meant that we were unable to determine how our patients' cognitive status progressed over time. In addition, genetic testing was not available for our study, meaning we were unable to analyze possible genetic factors related to the cognitive characteristics of our sample. Finally, there is no consensus on how to classify patients with EOPD as short-, mid-, and long-disease duration, and cutoffs used in other late-onset PD studies do not apply to our population, which limits our ability to compare our results to those of other studies. Nevertheless, the cut-offs used enabled us to compare cognitive status across a wide range of disease durations.

Conclusion

Our study found no significant differences in cognitive performance or PD-MCI frequency of in patients with EOPD with short, mid, and long disease durations. Moreover, there were no cases of PD-D, even in the group with over 16 years of disease progression. The frequency of PD-MCI in EOPD is similar to that reported in late-onset PD and seems to remain stable as years of disease progression increase. Further longitudinal studies in the EOPD population are needed to clarify this; additionally, the impact of monogenic forms of EOPD and the presence of common polymorphisms related to cognition in PD should be further longitudinally studied in samples with EOPD. Furthermore, establishing an international consensus related to the classification of disease duration in EOPD would benefit future research.

Author's contributions

A.N. Seubert-Ravelo: conceptualization, data curation, formal analysis, funding acquisition, writing – original draft, writing – review and editing. M.G. Yáñez-Téllez: conceptualization, funding acquisition, methodology, supervision, writing – original draft, writing – review and editing. G.A. Neri-Nani: conceptualization, methodology, writing – original draft, writing – review and editing. A. Calderón-Vallejo: project administration, methodology, supervision, writing – original draft, writing – review and editing. J. Moreno-Villagómez: data curation, formal analysis, writing – original draft, writing – review and editing. M. Ortega-Luyando: data curation, formal analysis, writing – original draft, writing – review and editing.

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Conflicts of interest

The authors report there are no competing interests to declare.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Post SARS-CoV-2 sequelae in healthcare personnel of a non-COVID institution in Mexico City

Secuelas tras SARS-CoV-2 en personal de salud de una institución no COVID en la Ciudad de México

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Abstract

Background: *COVID-19 is a disease caused by SARS-CoV-2, a highly contagious virus belonging to the Coronaviridae family. It is transmitted from person to person through the air. The clinical presentation ranges from mild to severe can be fatal. Worldwide, 10-20% of people who recover from the acute phase may continue to experience symptoms for a longer period.* **Objectives:** *To estimate the prevalence of post-SARS-CoV-2 sequelae in staff of a tertiary healthcare institution, five years after the beginning of the pandemic, and to describe the types of sequelae by sex and year of onset according to the different infection episodes.* **Methods:** *A cross-sectional study was conducted based on self-administered surveys. The study population consisted of 179 participants. Sequelae were evaluated in relation to the different infection episodes.* **Results:** *A peak in health impact on staff was observed during 2022 (37%). 59.2% of the population presented some type of sequelae; the majority (95%) experienced some sequelae after the first episode of infection. The most prevalent sequelae were neuro logical and state of mind (66.4%), musculoskeletal (51.5%), and respiratory (36.6%), with a predominance in females ($p \leq 0.05$).* **Conclusions:** *The obtained results are similar to those reported in previous studies. The most prevalent sequelae were neurological and persisted throughout the study period, primarily in women.*

Keywords: *SARS-CoV-2. COVID-19. Sequelae. Healthcare workers. Post-acute symptoms.*

Resumen

Antecedentes: *La COVID-19, es una enfermedad causada por el SARS-CoV-2, virus contagioso de rápida transmisión perteneciente a la familia Coronaviridae. Se transmite de persona a persona por vía aérea. El cuadro clínico varía de leve a severo, pudiendo ocasionar la muerte. En el mundo el 10-20% de las personas que se recuperan del cuadro agudo pueden persistir con síntomas por más tiempo.* **Objetivo:** *Estimar la prevalencia de secuelas post SARS-CoV-2 en el personal de una Institución de Salud de tercer nivel de atención, después de 5 años del inicio de la pandemia, y describir los tipos de secuelas por sexo y año de aparición de acuerdo con los diferentes episodios de infección.* **Método:** *Se realizó un estudio transversal basado en encuestas autoaplicadas. La población de estudio fue de 179 participantes. Se evaluaron las secuelas con relación a los diferentes episodios de infección.* **Resultados:** *Se observó un pico máximo de afectación sanitaria en el personal durante el año 2022 (37%). El 59.2% de la población presentó algún tipo de secuela; la mayoría (95%) presentó alguna secuela posterior al primer episodio de infección. Las secuelas más prevalentes fueron las neurológicas y del estado mental (66.4%), musculoesqueléticas (51.5%) y respiratorias (36.6%), con predominio en el sexo femenino ($p \leq 0.05$).* **Conclusión:** *Los resultados obtenidos son similares a los reportados en estudios previos. Las secuelas más prevalentes fueron las neurológicas y permanecen a lo largo del periodo de estudio, principalmente en mujeres.*

Palabras clave: *SARS-Cov-2. COVID-19. Secuelas. Personal de salud. Síntomas postagudos.*

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Introduction

In March 2020, the World Health Organization declared COVID-19, caused by SARS-CoV-2, a pandemic. SARS-CoV-2 is a highly contagious, rapidly transmitted virus belonging to the coronavirus family. This pandemic has been considered one of the worst health crises in history.[1]

Infected individuals can transmit the virus through the air when coughing, talking, or sneezing, as well as through direct contact. The incubation period for COVID-19 is up to 14 days. Clinical signs vary from person to person, with symptoms that may include fever, headache, adynamia, GI, neurological, and respiratory symptoms, the latter being the most characteristic manifestations of the disease and potentially progressing to severe acute respiratory syndrome type 2, thereby increasing the risk of death. Extrapulmonary manifestations can affect different systems, including the cardiovascular, haematological, renal, neurological, gastrointestinal, dermatological, and ophthalmological systems.[1] Nevertheless, up to 40% of cases are asymptomatic.[2] Most patients have a favourable course with symptomatic treatment.[3] However, between 10 and 20% of those who recover from the acute phase continue to experience symptoms thereafter.[4] In Mexico, according to the 2020 National Health and Nutrition Survey, the prevalence of COVID-19 sequelae at 1 year was estimated at 15.7%.[5] Although the epidemiological and pathogenic characteristics, as well as the complications of the acute phase of the disease, have been extensively described, both short- and long-term sequelae continue to be reported.[6-11]

In Mexico City, several health care institutions were converted into COVID hospitals during the pandemic to provide exclusive care for individuals with suspected or confirmed COVID-19. However, staff working at institutions that were not converted were not exempt from the risk of contracting COVID-19, as many patients attending for other conditions were subsequently found to be carriers of the virus.

Therefore, the aim of this study was to estimate the prevalence of sequelae following SARS-CoV-2 infection among staff at a tertiary-level non-COVID healthcare institution from the beginning of the pandemic until June 2025, and to describe the distribution of the types of sequelae according to sex and year of onset in relation to the different episodes of infection.

Methods

We conducted a cross-sectional study using self-administered printed questionnaires completed by health care staff at the Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez 5 years after the first case of COVID-19 was reported worldwide. Considering that the institution had a workforce of 1,500 employees, an expected prevalence of 15 ± 10% variability, a 95% confidence level, and statistical power of 80%, a minimum sample size of 161 questionnaires was estimated. A total of 179 questionnaires were ultimately included.

Because some staff remained at home during the pandemic because they were considered to belong to a high-risk population, the questionnaire was administered only to staff at the institution who had experienced at least one episode of COVID-19 (Supplementary material 1) and who had worked between January 2020 and June 2025. This selection was performed by directly questioning the participants, although no record of this procedure is available.

The information was anonymous and participation was voluntary. The variables analysed included sociodemographic characteristics, past medical history of other diseases, number of infections, year of each infection, duration of illness, principal signs and symptoms, treatment received, personal aspects and areas of life affected by the disease, presence of sequelae and the time at which they appeared after infection, and treatment received for the sequelae. Information was also collected on COVID-19 vaccination history and the presence of sequelae following vaccination.

According to former studies,[1,4,7,10,11] the sequelae were grouped into several categories: respiratory, metabolic, musculoskeletal, gynaecological, GI, dermatological, cardiovascular, mental health, neurological, and genitourinary disorders. Only cases reporting the presence of some type of sequela were analysed.

The information obtained was entered into a database for subsequent statistical analysis using SPSS v. 26. Simple frequencies and measures of central tendency and dispersion were calculated. The information was analysed according to the different episodes of infection experienced by the institution's staff. Proportions and means were compared, and $p \leq 0.05$ was considered statistically significant.

This study complies with the international STROBE guidelines.

Results

Of the 179 completed questionnaires, 59 (33%) were from men, 108 (60.4%) from women, and 12 (6.7%) did not report their sex. The mean age was 45 years, with SD, 12, a minimum age of 23 years, and a maximum age of 72 years. The mean age was 46 years in women and 43 years in men, with SD, 11 in both groups.

When the number of times each participant had COVID-19 was analysed, 89 (49.7%) had been infected only once, 65 (36.3%) twice, 18 (10.1%) 3 times, and 7 (3.9%) 4 times. The mean number of infections per participant was 2, with a minimum of 1 and a maximum of 2.

Regarding the year of infection, 66 (36.9%) participants experienced their first infection in 2022, 59 (33%) in 2020, and 36 (20.1%) in 2021. Among those who experienced a 2nd infection, most occurred in 2022, with 31 cases (34.4%), followed by 24 cases (26.7%) in both 2021 and 2023. Among those who experienced a 3rd or 4th infection, most episodes occurred in 2023. The remaining distribution of infections by year is shown in figure 1.

The main symptoms during the different episodes of infection were muscle pain, headache, and fever. However, muscle pain predominated during the first episode (73.7%), headache during the 2nd (67.8%), odynophagia during the 3rd (60%), and muscle pain and headache during the 4th (57.1%). The remaining distribution of symptoms is shown in table 1.

On average, the first episode of infection lasted 10 days, with SD, 12.27, a minimum of 2 days, and a maximum of 120 days. The mean durations of the 2nd, 3rd, and 4th infections were 7.91, 9.40, and 6.1 days, respectively. No statistically significant difference was found between the mean durations of the different episodes.

Of all participants, 176 (98.3%) received some form of treatment for the infection; of these, 151 (85.8%) reported receiving analgesics, 55 (31.2%) antihistamines, 41 (23.3%) antibiotics, 12 (6.8%) oxygen via nasal cannula, 10 (5.7%) vitamins, 9 (5.1%) steroids, 4 (2.3%) anticoagulants, 4 (2.3%) antitussives, 3 (1.7%) required intubation, and 1 (0.6%) received ivermectin.

Of the 179 participants who developed COVID-19, 106 (59.2%) reported some type of sequela; however, among those who became infected after their index episode, 101 (56.4%) reported sequelae. Of the 90 participants who experienced a 2nd episode, 47 (52.2%) developed sequelae, and of the 7 who experienced a 4th episode, 4 (57.1%) developed sequelae. The difference in the proportion of sequelae between the different episodes of infection was statistically significant ($p < 0.001$).

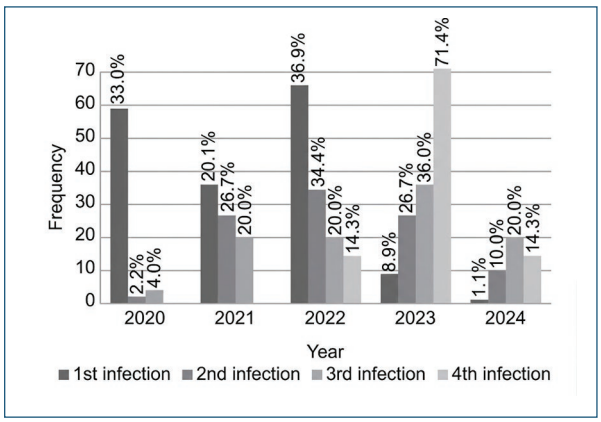

Figure 1. Year of occurrence of the different episodes of SARS-CoV-2 infection.

The most common types of sequelae after the index episode of infection were musculoskeletal (51.5%), respiratory (36.6%), and mental health-related (34.7%). For the remaining episodes, respiratory sequelae were the most frequent, occurring in 44.7%, 60%, and 100% of cases after the 2nd, 3rd, and 4th episodes, respectively. The remaining sequelae by episode are detailed in table 2.

When sequelae were compared according to sex, regardless of the episode of infection, prevalence was higher among women, at 66.9%, compared with 25.4% among men ($p \leq 0.05$). When the types of sequelae were analysed in both groups, no statistically significant differences were found between them (Table 3).

Among participants with sequelae, 53 (63.8%) had a past medical history of at least 1 comorbidity, the most common being obesity (30.2%), hypertension (26.4%), and type 2 diabetes (20.8%); the remaining distribution is shown in figure 2.

Discussion

This study describes the prevalence and distribution of sequelae following SARS-CoV-2 infection among staff at a tertiary-level non-COVID health care institution 5 years after the beginning of the COVID-19 pandemic. Most of the study population with COVID-19 were women (60.4%), which may be related to the higher number of women who developed COVID-19 within health care institutions in Mexico according to the Comprehensive COVID-19 Report in Mexico.[12] This

Table 1. Symptoms by COVID-19 episode among workers at the Instituto Nacional de Neurología y Neurocirugía

Symptoms	Episodes of infection							
	1st episode (n = 179)		2nd episode (n = 90)		3rd episode (n = 25)		4th episode (n = 7)	
	n	%	n	%	n	%	n	%
Muscle pain	132	73.7	53	58.9	13	52.0	4	57.1
Headache	115	64.2	61	67.8	11	44.0	4	57.1
Fever	113	63.1	42	46.7	13	52.0	3	42.9
Rhinorrhoea	102	57.0	48	53.3	11	44.0	1	14.3
Cough	100	55.9	50	55.6	13	52.0	2	28.6
Odynophagia	99	55.3	53	58.9	15	60.0	2	28.6
Chills	98	54.7	41	45.6	8	32.0	2	28.6
Anosmia	73	40.8	16	17.8	3	12.0	0	0.0
Dysgeusia	62	34.6	19	21.1	4	16.0	1	14.3
Red or irritated eyes	58	32.4	31	34.4	7	28.0	2	28.6
General malaise	54	30.2	32	35.6	8	32.0	2	28.6
Chest pain	51	28.5	21	23.3	5	20.0	3	42.9
Dyspnoea	38	21.2	11	12.2	2	8.0	1	14.3
Diarrhoea	35	19.6	8	8.9	2	8.0	1	14.3
Irritability	25	14.0	17	18.9	1	4.0	1	14.3
Tachypnoea	20	11.2	4	4.4	1	4.0	2	28.6
Abdominal pain	16	8.9	10	11.1	0	0.0	0	0.0
Vomiting	9	5.0	2	2.2	0	0.0	0	0.0
Asymptomatic	4	2.2	1	1.1	2	8.0	1	14.3
Cyanosis of the skin and mucous membranes	1	0.6	1	1.1	0	0.0	1	14.3

Episode sample sizes: 1st episode, n = 179; 2nd episode, n = 90; 3rd episode, n = 25; 4th episode, n = 7.

may be related to the fact that women constitute the majority of employees in health care institutions compared with men, as female nursing staff outnumber those in any other professional group.

The mean age was 45 years, corresponding to the productive stage of life, as expected for health care workers, who were among the groups actively working during the COVID-19 pandemic.

The presence of obesity, hypertension, and diabetes as the principal comorbidities may reflect the diseases that are prevalent in the Mexican population.[13]

More than 50% of participants were infected only once, and the percentage of those who experienced a 2nd or subsequent infection decreased thereafter. This may be because vaccination of health care staff began towards the end of the first year of the pandemic. Conversely, the fact that most infections occurred in 2022 rather than at the beginning of the pandemic may be because workers and the general population relaxed public health and protective measures. This was the year in which routine working life resumed and exposure increased; furthermore, the circulating variant that year was Omicron, considered one of the most transmissible variants, although associated with less severe disease.[14,15] The symptoms observed, such as muscle pain, headache, fever, rhinorrhoea, and cough, are those generally prevalent among patients with COVID-19, as reported in most studies and reports worldwide,[12,16,17] particularly in uncomplicated outpatient cases receiving symptomatic treatment.

Table 2. COVID-19 sequelae among workers at the Instituto Nacional de Neurología y Neurocirugía

Sequelae	Episodes of infection							
	1st episode (n = 101)		2nd episode (n = 47)		3rd episode (n = 10)		4th episode (n = 4)	
	n	%	n	%	n	%	n	%
Musculoskeletal disorders (general malaise, osteoarthritis, myalgia, joint pain, fatigue)	52	51.5	17	36.2	4	40.0	2	50.0
Respiratory disorders (dyspnoea, cough, odynophagia, recurrent colds)	37	36.5	21	44.7	6	60.0	4	100.0
Mental health disorders (cognitive impairment, amnesia, bradypsychia, inattention, bradylalia, insomnia, anxiety, depression, emotional lability)	35	34.7	13	27.7	1	10.0	1	25.0
Neurological disorders (sensory disturbances of smell and taste, headaches-migraines, sensory disturbances such as neuropathy or paraesthesia, vertigo, dizziness)	32	31.7	9	19.1	2	20.0	0	0.0
Cardiovascular disorders (tachycardia, arrhythmia, hypertension, myocarditis)	7	6.9	2	4.3	0	0.0	0	0.0
Gynaecological disorders (oligomenorrhoea, dysmenorrhoea)	2	2.0	2	4.3	0	0.0	0	0.0
GI disorders (nausea, vomiting, stomach pain)	1	1.0	1	2.1	0	0.0	0	0.0
Dermatological disorders (alopecia, dermatitis)	2	2.0	0	0.0	0	0.0	0	0.0
Metabolic disorders (hyperglycaemia, changes in body weight)	4	4.0	0	0.0	0	0.0	0	0.0
Genitourinary disorders (prostatitis)	0	0.0	1	2.1	0	0.0	0	0.0

Table 3. Post-COVID-19 sequelae among workers at the Instituto Nacional de Neurología y Neurocirugía, by sex

Sequelae	Male (n = 27)		Female (n = 71)		p
	n	%	n	%	
Musculoskeletal disorders (general malaise, osteoarthritis, myalgia, joint pain, fatigue)	17	63.0	48	67.6	NS
Respiratory disorders (dyspnoea, cough, odynophagia, recurrent colds)	12	44.4	44	62.0	NS
Mental health disorders (cognitive impairment, amnesia, bradypsychia, inattention, bradylalia, insomnia, anxiety, depression, emotional lability)	10	37.0	33	46.5	NS
Neurological disorders (sensory disturbances of smell and taste, headaches, sensory disturbances such as neuropathy or paraesthesia, vertigo, dizziness)	10	37.0	29	40.8	NS
Cardiovascular disorders (tachycardia, arrhythmia, hypertension, myocarditis)	2	7.4	2	2.8	NS
Gynaecological disorders (oligomenorrhoea, dysmenorrhoea)	-	-	3	4.2	NS
GI disorders (nausea, vomiting, stomach pain)	1	3.7	1	1.4	NS
Dermatological disorders (alopecia, dermatitis)	-	-	2	2.8	NS
Metabolic disorders (hyperglycaemia, changes in body weight)	1	3.7	4	5.6	NS
Genitourinary disorders (prostatitis)	1	3.7	-	-	NS

NS: not significant.

The symptoms during the acute phase lasted an average of 10 days, regardless of the episode. The duration range for the first infection (2-120 days) contrasted with that of subsequent infections, which was considerably shorter, possibly because of greater immunity or receipt of at least one vaccine dose. The

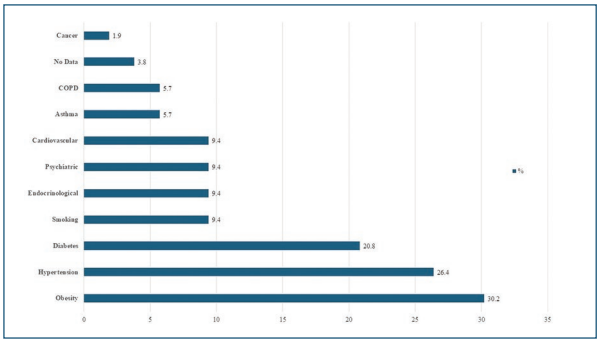

Figure 2. Pre-existing diseases among workers who developed sequelae after COVID-19. COPD: chronic obstructive pulmonary disease.

fact that symptoms persisted for an average of 1 week may be related to the characteristic course of the acute phase of the disease, during which fever, headache, and general malaise are the most common symptoms, as reported in most publications, which clearly indicate that these symptoms generally last less than 10 days.[18]

Regarding disease management, almost 100% of cases received symptomatic treatment only, reflecting the fact that these were uncomplicated cases, with few participants requiring oxygen or antibiotic therapy because of a complication.

Although most of the study population did not require extensive therapeutic management and did not experience major complications during episodes of infection, the prevalence of sequelae in the study population was considerably high (59.2%). The presence of sequelae decreased with subsequent episodes of infection, which may reflect greater immunity or, alternatively, insufficient time having elapsed after the most recent episodes for sequelae to develop. Nevertheless, the latter explanation appears unlikely because most reported sequelae developed within 1 month of disease onset or within the first 3 months, consistent with previous studies reporting that most sequelae appeared within the first 3 months.[6,8,9]

Although the reported sequelae were diverse, the most prevalent were musculoskeletal, respiratory, mental health, and neurological sequelae. However, if mental health and neurological disorders are grouped into a single category, as in other studies,[10,11] and renamed neuropsychiatric sequelae, they would rank first, with a prevalence of 66.4%, which is higher than the 60% prevalence of neuropsychiatric manifestations reported by Chau et al.[8] in 2024.

The sequelae were very similar in both sexes, but there was a marked predominance among women (66.9%), possibly because of a mechanism associated with the immune system, as reported by Arnold et al.[19] in 2022.

The prevalence of sequelae decreased year by year ($p \leq 0.05$). Cai et al.[10] reported in 2024 that this may be explained by individual vulnerability, existing medical conditions, comorbidities, immune system alterations, and genetic predisposition. Nevertheless, we consider that pre-existing comorbidity had little influence in the present study because its prevalence among the institution's staff was low. However, sequelae were clearly more prevalent among women, regardless of the episode of infection, with neurological and musculoskeletal sequelae predominating. This may be related to hormonal factors, as oestrogens in women have been shown to modulate and regulate brain functions such as memory, behaviour, and cognition within the central nervous system, with a greater number of neuropsychiatric and neurodegenerative abnormalities occurring when oestrogen levels decline,[20] as occurs during the climacteric period and menopause,[21] and our study population fell within this age range. Alternatively, this finding may also reflect the fact that women outnumber men among staff working in healthcare institutions. In addition, it is important to note that women generally undertake multiple roles involving work, household responsibilities, and childcare, potentially resulting in emotional overload and a greater predisposition to develop these types of conditions.

Study limitations

Certain limitations inherent to the study design should be considered when interpreting the results. First, this was a non-randomised sample because of the retrospective design of the questionnaire-based study, creating a risk of information bias that could lead to underestimation or overestimation of the frequency and intensity of the events investigated. Second, the data collection questionnaire was developed by the authors specifically for this study and has not been validated or previously applied in other studies. Finally, unlike studies such as that of Núñez-Cortés et al.,[3] the assessment of sequelae was subjective because it was based on participants' self-reports rather than a formal clinical evaluation; nevertheless, the information provided by participants cannot be disregarded because it is consistent with that reported in the literature.

Conclusions

During the period analysed, the largest proportion of staff developed COVID-19 in 2022 (37%). Most staff became ill only once, and the main symptoms were muscle pain, headache, and fever. The mean duration of acute illness was 10 days, and most participants reported receiving symptomatic treatment only. A total of 59.2% reported sequelae within the 3 months following the first infection, with some persisting even 3 years after the episode. The principal sequelae were neurological, musculoskeletal, and respiratory.

Although much of the information presented here is consistent with that reported in the literature, it is important to emphasise that sequelae in this population persisted for several years, with a greater prevalence after the first episode of infection than after subsequent episodes.

Of note, the study population comprised health care-sector workers. Thus, unlike the general population, this group was among the first to receive vaccination against SARS-CoV-2, and it is possible that some sequelae may have been related to administration of the vaccine rather than to the disease *per se*, or may have resulted from an interaction between the two. However, other types of studies would be required to clarify this issue.

Authors' contributions

All authors contributed equally to the production of this article, in accordance with the CRediT taxonomy.

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Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors followed the protocols of their healthcare centre/institution for access to medical record data. Informed consent was obtained from the patients, and approval was obtained from the Ethics Committee. The recommendations of the SAGER guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

Supplementary data

Supplementary data is available at DOI: 10.24875/ANC.25000043. This data is provided by the corresponding author and are published online for the benefit of the reader. The content of the supplementary material is the sole responsibility of the authors.

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EVIDENCE SYNTHESIS

Artificial neural networks in psychiatry. Overview and applications

Redes neuronales artificiales en psiquiatría. Generalidades y aplicaciones

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Abstract

Since its early days, artificial intelligence (AI) has found fertile ground for application in the medical domain, perhaps due to the way events are modeled and approached, and the openness of healthcare professionals. The key has always been to provide practical solutions to problems of interest; over time, trending algorithms and tools have been applied. This article provides an overview of how the evolution of AI, some historic details, differences between "machine learning" and "deep learning", the concept of artificial neural networks, and their application in medicine, specifically in psychiatry. Today, the medical domain is once again at the forefront due to the new challenges being addressed with deep learning tools. Its use has disrupted several sub-fields, including psychiatry.

Keywords: *Artificial intelligence. Neural networks. Psychiatry. Deep learning. Medicine.*

Resumen

Desde sus primeros tiempos, la inteligencia artificial ha encontrado un campo fértil de aplicación en el dominio médico; quizá por la forma en que se modelan y abordan eventos, y por la apertura del personal sanitario. Lo importante es que ha ayudado a resolver de manera práctica problemas de interés; según la época, se han aplicado algoritmos de tendencia. El objetivo del presente artículo es describir de manera sintetizada la evolución de la inteligencia artificial, algunos detalles históricos, las diferencias entre aprendizaje automático y profundo, el concepto de redes neuronales y su aplicación en medicina, particularmente en psiquiatría. Hoy, de nuevo el dominio médico vuelve a estar en el punto de mira por los retos y las situaciones que se están abordando mediante aprendizaje profundo. Su uso ha impactado de manera disruptiva en sus diversas áreas, incluyendo la psiquiatría.

Palabras clave: *Inteligencia artificial. Redes neuronales. Psiquiatría. Aprendizaje profundo. Medicina.*

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Introduction

Real-world events, regardless of the field, can be more surprising and challenging than a person might expect. They may seem implausible compared to anything that can be imagined or invented in fiction. Today, this reflection takes on new meaning in light of the rapid technological development we are experiencing. Artificial intelligence (AI), the internet of things, big data, robots, and smart devices have completely reshaped human life. What seemed like science fiction decades ago – machines that learn, systems that anticipate decisions – is now part of the present. These advances have a profound impact on key sectors such as finance, industry, commerce, tourism, entertainment, and, increasingly, medicine.

It is interesting to note that many of these scenarios had already been imagined by writers from different eras and cultures, who approached AI from a fictional perspective. These ideas were viewed with amazement or skepticism, but today, thanks to scientific and technological progress, they have taken concrete form. What was once narrative speculation is now real tools with practical applications, proving that, indeed, reality can be more surprising than fiction. Figure 1 shows a timeline with a non-exhaustive selection of literary works that have addressed concepts related to what is now known as AI.

In the health sciences, especially in medicine, AI has generated significant benefits. Various specialties, such as hematology, genetics, oncology, cardiology, imaging, psychiatry, and surgery, have experienced remarkable advances, especially with the use of artificial neural networks (ANNs). Its impact has been key in diagnosis, prognosis, and risk prediction, as well as in the development of pharmacological and non-pharmacological treatments, improving hospital management and decision-making.

The objective of this article was to provide a concise description of the evolution of AI, the field of learning, the concept of machine learning (ML), deep learning, as well as neural networks and their application in medicine, particularly in the specialty of psychiatry.

Methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Abstract guidelines were used for the abstract section; apart from that, no international guidelines were used, as this is a narrative review. By its nature, this type of study does not follow a standardized protocol, as it is based on the selection, analysis, and critical integration of existing literature on the subject. A computerized search for information was conducted in the electronic databases Scopus, Web of Science, PubMed, and Google Scholar. The recommended search terms in Medical Subject Headings were AI, neural networks, psychiatry, deep learning, and medicine. The qualitative selection criteria were: original articles, reviews, meta-analyses, or editorials in English, works with scientific methodology, with well-defined and specific contributions, and content in line with the main topic. Works in other languages, not peer-reviewed, from predatory journals, and with approaches different from those established in the objectives were excluded. The Boolean operators NOT, OR, and AND were used in the search. The authors of this project selected a total of 84 references from all the material reviewed, based on their relevance and group consensus.

AI: history and definitions

AI is a branch of computer science dedicated to solving problems that require human intelligence, such as learning, image recognition, and perception. Its goal is to create self-learning systems that give meaning to data and, consequently, apply this knowledge to solving new problems[1]. Since the 1940s, methods have been developed to replicate human cognitive functions such as reasoning, analysis, and creativity using machines. With the advancement of computer science, these efforts laid the foundation for AI[2]. Although Turing did not coin the term "Artificial Intelligence," his work was fundamental to its development. In 1950, he proposed what is now known as the "Test," a test to evaluate whether a machine can exhibit intelligent behavior indistinguishable from that of a human being[1]. Another key contribution came in 1952 from Ashby, who introduced fundamental concepts about adaptive behavior and self-regulating systems, with an impact on biology, AI, and robotics[3]. The term "Artificial Intelligence" was coined in 1956 by John-McCarthy, who defined it as "the science and engineering of making intelligent machines, especially intelligent computer programs;[4]" Shortly thereafter, together with Minsky, he founded the AI Laboratory at MIT[5]. In 1958, Frank Rosenblatt developed the perceptron, an ANN model capable of solving complex problems and making predictions based on data, laying the foundation for the development of neural networks and deep learning[6]. In the late 1960s, Minsky published the theory of perceptrons, single-layer neural networks. They highlighted their limitations in modeling

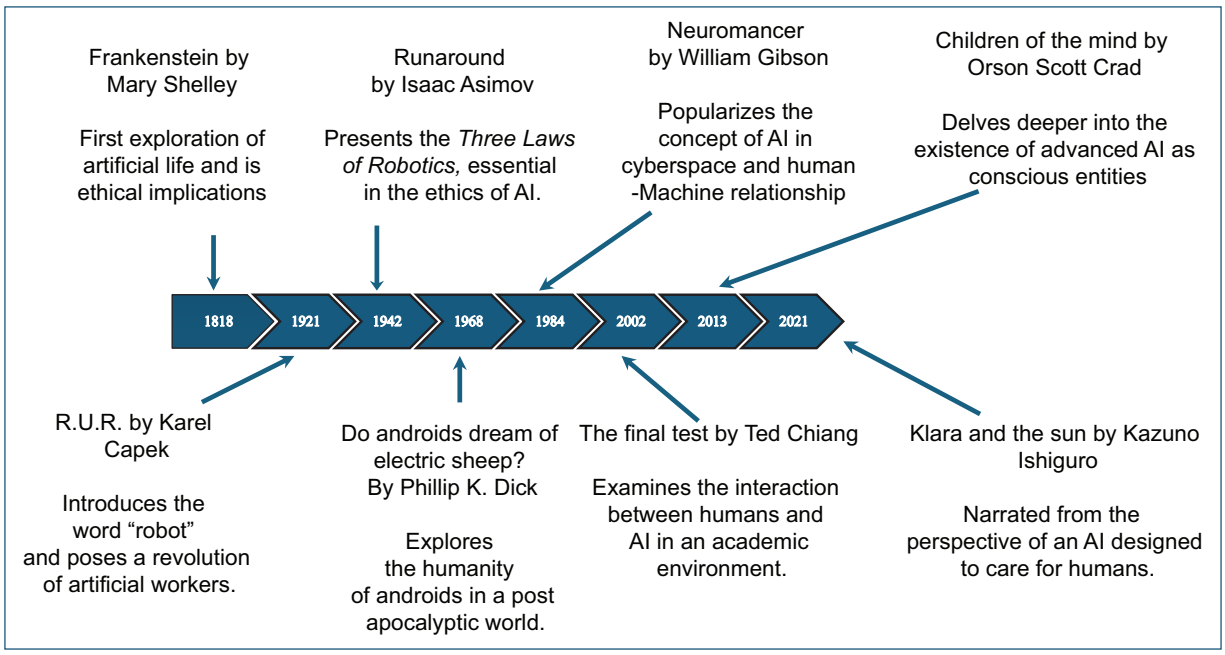

Figure 1. Timeline of literature with content related to artificial intelligence.

complex relationships in data[6], which drove the development of multilayer networks. The authors' observations, coupled with a lack of progress, researcher discouragement, and reduced funding, contributed to the phenomenon known as the "AI winter" in the 1970s[7]. Despite these limitations, advances were made in hardware systems between 1957 and 1974, increasing storage and processing capacity[8]. During this period, scientists made progress in the development of ML algorithms, defined as techniques that enable systems to learn automatically from data without being explicitly programmed for a specific task[9]. In the early 1980s, the development of mathematical algorithms optimized the development of AI[10]. Rumelhart and Hopfield demonstrated that computers could learn from experience using deep learning techniques[11]. In 1982, Hopfield introduced recurrent neural networks (RNNs)[12], while the backpropagation algorithm developed by Werbos[13] it became established as a key method for training neural networks.

Between 1995 and 2000, AI made key advances, such as IBM''s Deep Blue supercomputer[14]. In 1996, a semi-autonomous car traveled 4,501 km from coast to coast in the United States[15]. In 2016, Google launched GNMT, a multilingual machine translation system that uses deep neural networks (DNNs)[16]. In 2019, the GPT-2 model, developed by OpenAI, appeared, capable of generating coherent texts, answering questions, and producing summaries[17]. Since May 2024, OpenAI''s main multimodal model has been GPT-4[18], which offers more natural and accurate responses in different formats and styles. At present, there is a wide variety of AI-based tools designed to meet diverse needs and applications. Some of these tools are available for free, such as OpenAI's GPT-3 Playground[19], image recognition tools such as Google Vision AI, and data analysis platforms such as Google Colab[20]. However, there are also paid options that offer more advanced capabilities, such as Microsoft Azure AI[21] and OpenAI''s GPT-4 model.

AI is advancing rapidly, allowing machines to learn and make autonomous decisions, something that was unthinkable just a few years ago[22]. Technological advances, big data, and deep learning, together with analytical tools applied to voice and image recognition, have revolutionized everyday life[23]. AI is now a broad field that has evolved thanks to contributions from various disciplines, as shown in table 1[23-32]. Disciplines have contributed to the development of AI. The literature shows that there is no single definition of AI; different authors have proposed various concepts over time, as summarized in table 2[33-40].

ML and deep learning

ML and deep learning are essential forms of computational learning, with their own methodologies and

Table 1. Disciplines that have contributed to the development of artificial intelligence

Disciplines	Contribution
Mathematics	Statistics and probability theories have favored the development of machine learning algorithms[24].
Philosophy	Has contributed to debates on the nature of mind, reasoning, consciousness, and the possibility of building thinking machines[25].
Neuroscience	It has enabled us to understand how humans perceive, think, and learn, and has guided the development of systems that attempt to replicate these processes[26].
Computer science	It has been involved in the development of algorithms and systems capable of performing various tasks[27].
Cognitive psychology	By studying how people perceive, remember, and make decisions, it has developed models of information processing[28].
Learning and Memory	Classical and operant conditioning have enabled the development of machine learning algorithms[29].
Linguistics	Has contributed in "training" the machines into learning and generating language[30].
Economy and game theory	Has influenced the development algorithms for decision making in situations of uncertainty and competitive environments[31].
Electrical and electronics engineering	Allowed for the development of specialized hardware, and has contributed in the creation of robots and autonomous systems[32].

Table 2. Concepts of artificial intelligence from different authors

Author and year	Definition
Bellman, 1978[33]	The automation of activities associated with human thought.
Charniak, 1985[34]	The study of mental faculties through the use of computational models.
Hagueland, 1985[35]	Machines with minds, in a complete and literal sense.
Rich and Knight, 1991[36]	How to make computers perform actions that, for the moment, humans are better at.
Winston, 1992[37]	The study of computers that perceive, reason, and act.
Nilsson, 1998[38]	AI is concerned with intelligent behavior in artifacts.
Poole, 1998[39]	It is the study of the design of intelligent agents.
Kurzweil, 1999[40]	The art of creating machines that perform functions that require intelligence.

applications that enable computers to process information and act autonomously based on data[41].

ML: types and applications

Also known as ML, it is a field of AI that encompasses a wide range of techniques that enable computers to learn from previously integrated information[42]. ML algorithms are logical sequences that enable computers to identify patterns, predict outcomes, and act without explicit programming. This allows computers to learn and improve their performance over time[43]. ML involves the use of various types of algorithms, the most common being supervised learning, unsupervised learning, and reinforcement learning[44]. Supervised learning involves training a model with labeled data, allowing the algorithm to learn how to relate inputs to the correct outputs. Its goal is to predict results for new data. It is applied in tasks such as spam detection, image recognition, opinion analysis, personalized recommendations, and disease identification[45]. Unsupervised learning, on the other hand, trains models with unlabeled data, allowing hidden patterns and structures to be discovered without prior human intervention. It is applied in clustering tasks, identifying elements with similar characteristics. In medicine, it helps to understand diseases, optimize treatments, and personalize patient care[46]. Reinforcement learning allows the algorithm to act through trial and error, receiving rewards or punishments based on its actions. Its goal is to maximize rewards over time. It is applied in robotics, autonomous vehicles, video games, medical diagnostics, and personalized treatment recommendations[47]. As can be seen, ML has had a major impact on sectors such as healthcare, finance, and marketing, and will continue to evolve and expand as technology advances.

Deep learning and architectures

Deep learning is a subfield of ML that uses multilayer ANNs to analyze complex data. Inspired by the human brain, these networks learn representations at different levels of abstraction, improving their performance in tasks such as image recognition, natural language processing, and autonomous driving. In addition, they can work with supervised and unsupervised data, adapting to various applications[48]. Thanks to its ability to learn

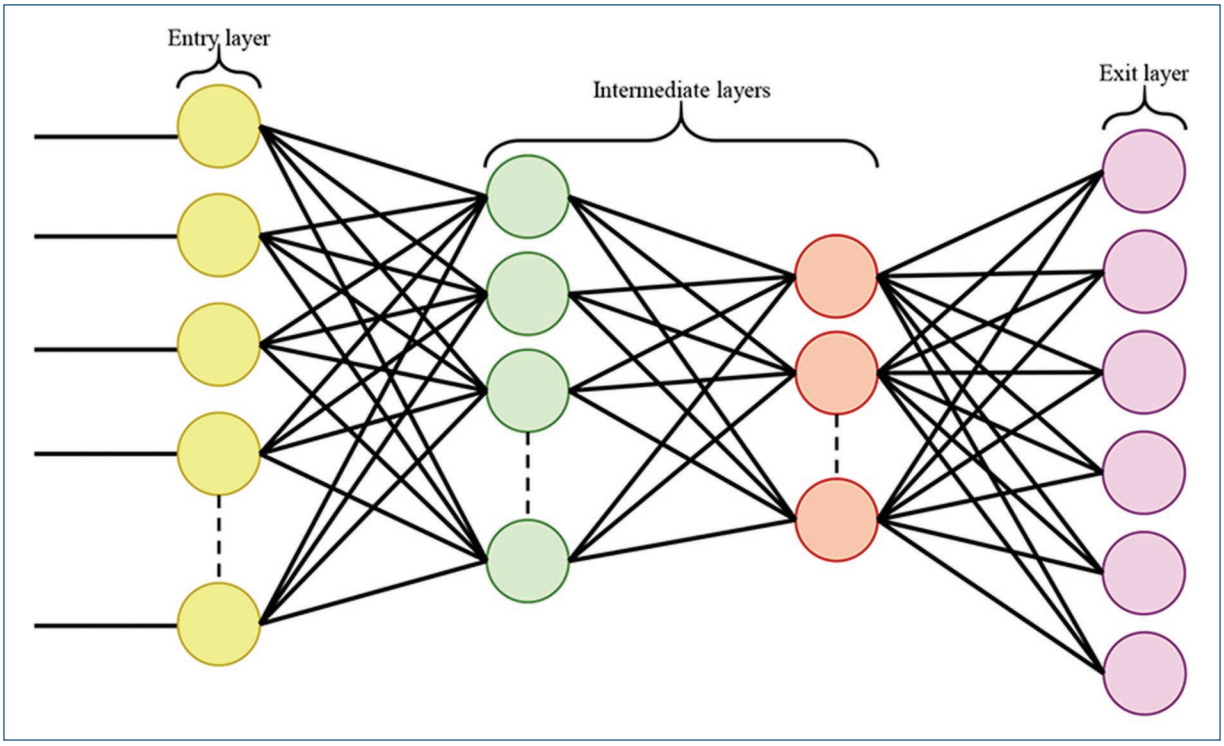

Figure 2. Artificial neural network.

from large volumes of data, deep learning is key in Big Data applications. It is used in image recognition and classification, scene analysis, and surveillance. It also facilitates language comprehension and generation, enabling chatbots, machine translation, voice commands, behavior analysis, and medical diagnostics using images and electronic records[49].

Neural networks

At present, a key component of AI is ANNs, inspired by biological neurons, which process and organize information in a similar way to the human brain and learn from the data they receive[50]. This comparison is illustrated in figure 2. An ANN is composed of nodes called artificial neurons, which receive information from external sources or other neurons, process that data, and generate outputs to feed other neurons or produce a final response[51]. Unlike traditional computer systems, which follow algorithmic instructions, neural networks offer an approach based on learning and adaptation[52]. They have a complex structure formed by interconnected neurons that model functions or distributions between data sets. Generally, an ANN has three layers: input, hidden (intermediate), and output. The neurons in the input layer receive data that is transmitted through connections called synapses, with parameters called weights, to the following layers. More complex networks may have multiple additional layers to improve processing[53]. It is important to note that neural network models are linked to learning algorithms or rules. These models improve by adjusting parameters, modifying connection weights, or changing the structure of neurons and their connectivity. ANNs are defined by three types of parameters: (a) the interconnection between different layers of neurons, (b) the learning process to update the interconnection weights, and (c) the activation function that converts the weighted inputs of a neuron into its output activation. Knowledge in a neural network is represented by the weights of its connections. For the network to learn from the data, a learning rule is applied that adjusts these weights according to the data[54]. In 2020, DNNs, convolutional neural networks (CNNs), and RNNs reached remarkable maturity, improving image recognition and machine translation and expanding the scope of AI[55]. In 2021, these networks were integrated into consumer devices such as smartphones and virtual assistants, improving personalization and user experience. In 2022, generative adversarial networks (GANs) stood out for generating autonomous content, such as

images and music, opening up new possibilities in creation and simulation. In 2023, ANNs advanced in fields such as medicine and biotechnology, facilitating more accurate diagnoses and the development of new drugs. The evolution of ANNs in recent years has shown significant advances, with applications ranging from personalization in consumer devices to important progress in areas of high-precision engineering and medicine.

Typical applications of neural networks

Currently, ANNs are used in various areas, especially where there is little systematic information and it is necessary to process large amounts of imprecise data to obtain concrete results[53]. Some examples include image recognition, voice recognition, pattern recognition, speech synthesis, complex process control, economic forecasting, early warning systems, time series analysis, and biometric systems, among others. ANNs have demonstrated great potential for innovation in multiple disciplines. In medicine, where the demand for advances is constant, their application has produced promising and reliable results, especially in diagnosis and treatment.

Neural networks in medicine

Medicine is marked by key milestones, such as Louis Pasteur's germ theory, William Osler's educational model, evidence-based medicine, human genome sequencing, and, more recently, AI. These advances show that the development of medicine is continuous and with no end in sight[56]. Currently, ANNs are widely used for medical applications in a wide variety of specialties[57], although many authors have also used them for clinical and basic research purposes. At present, their applicability as a support for Big Data stands out, as health information is growing exponentially due to the wide range of diseases in the population[58]. Challenges in the structure and administration of the health sector have been addressed with the support of AI, especially through ANNs, which help solve operational, administrative, financial, and resource management problems[59].

General medical and psychiatric applications

Below are some relevant applications in which ANNs have shown great potential[60,61].

- Medical diagnosis: they identify diseases from images such as X-rays or magnetic resonance imaging (MRIs). CNNs detect patterns with high accuracy in cases such as breast cancer or Alzheimer's disease
- Risk prediction and prognosis: they model risks and the progression of diseases such as diabetes and hypertension by analyzing large volumes of clinical data
- Personalized medicine: they allow treatments to be tailored to genetic profiles and biomarkers, especially in oncology, improving clinical outcomes
- Natural language processing: they analyze clinical records and medical literature to optimize data management and improve medical communication
- Surgical support: they assist in surgical procedures using computer vision, providing real-time support and reducing operational risks.

Types of neural networks used in medicine

In the literature, various authors stand out in their work for the type of DNN they use. Among the most relevant are:

- CNNs: Especially useful in interpreting medical images. They improve the accuracy of image segmentation, facilitating the diagnosis of diseases such as cancer and heart disease[60].
- RNNs: Ideal for analyzing sequential data from medical records and electrocardiograms. They are efficient in predicting adverse cardiac events by recognizing temporal patterns[61].
- GANs: Useful for generating artificial images for medical training and simulation. They improve the clinical training of residents by creating realistic images for diagnostic practice[60].

Neural networks in psychiatry

Computational paradigms for brain and mental health research have seen significant advances in recent years. These developments are largely due to the emergence of new technologies such as ANNs[62]. Recent advances have been made in sensors and mobile health technologies applied to mental health, as well as in advanced bioinformatics methods, tools, and techniques used in modeling and inference. One paradigm that stands out for its speed, adaptability, and reliability in the study of mental illness is ML[63]. Its development has enabled its application in different areas of psychiatry, promising better diagnosis and treatment. In this field, ML has made it possible to analyze large volumes of clinical and behavioral data to identify patterns associated with various mental

disorders. It has been used in the early diagnosis of autism by evaluating social interactions and movement patterns in infants and adolescents[64]. Likewise, by analyzing behavior and language, ANNs help predict suicidal or self-harming behavior, facilitating timely preventive interventions[65]. Their ability to process large amounts of information allows them to identify warning signs that might go unnoticed in traditional assessments. ANNs are capable of processing complex brain images from MRI, positron emission tomography (PET), and electroencephalograms[66]. This facilitates the identification of biomarkers associated with different mental disorders, improving diagnostic accuracy and understanding of the neurobiological basis of these conditions. However, there are still some problems to be solved, such as the lack of comparative studies that establish benchmarks for the performance of supervised learning and deep learning in neuroimaging studies[67]. By its very nature, the analysis of prosody and proxemics could greatly benefit from the association of biomarkers with depressive states using ANNs[68].

In addition to these advances, ANNs have emerged as powerful tools for modeling the high-dimensionality and non-linear nature of psychiatric data. Architectures such as deep feedback networks and multilayer perceptrons have demonstrated better performance in classification and prediction tasks compared to traditional statistical models, especially in disorders characterized by heterogeneous clinical presentations. ANNs are capable of automatically learning hierarchical representations of features from raw data, reducing dependence on manually designed features[69]. This capability is particularly relevant in psychiatry, where symptoms often overlap across diagnostic categories. By integrating multimodal data, deep learning models contribute to a more dimensional and biologically informed understanding of mental disorders, aligning with contemporary transdiagnostic frameworks.

Despite these promising applications, several methodological and conceptual challenges limit the widespread clinical adoption of ANNs in psychiatry. A recurring concern is the "black box" nature of many deep learning models; non-interpretable (black box) methods can lead to unintended, inappropriate use and unfair clinical decisions[70]. This lack of transparency raises ethical and legal questions, particularly when the model's results may influence diagnostic or therapeutic decisions. Furthermore, many studies rely on relatively small and homogeneous datasets, which can lead to overfitting and poor generalization across populations. A recent article (Sun et al.) emphasized the need for rigorous external validation, standardized reporting, and the development of comprehensive and interpretable AI, integrating it with domain knowledge and closing the interpretability gap to promote trust and wider adoption of AI[70]. Addressing these issues is essential to ensure that ANNs evolve from experimental tools to reliable components of psychiatric practice.

On the other hand, GANs have become increasingly relevant in the field of neuroscience, mainly through their applications in neuroimaging-based research, where data scarcity and heterogeneity are persistent challenges. GANs are generative models that can "generate realistic data with a probabilistic model by learning distributions from real samples," enabling the synthesis of high-quality, biologically plausible brain images[71]. In psychiatric research, this capability has been particularly useful for data augmentation, cross-site harmonization, and cross-modality synthesis, such as generating PET images from MRI data. In this way, GANs facilitate the study of psychiatric disorders characterized by diffuse and heterogeneous neurobiological alterations, mood disorders, and neurodevelopmental conditions[71]. These approaches not only improve the robustness of models but also support the identification of latent disease patterns that may contribute to a more nuanced understanding of psychiatric phenotypes.

Although the integration of Big Data allows ANNs to offer personalized treatment options by identifying specific symptomatic patterns in psychiatry, there is still a gap in access to this type of data due to ethical and legal issues, as is the case in several subdomains of medicine, which has slowed down several ANN applications. As in other medical specialties, different types of ANNs could also be applied in psychiatry if the data were available, such as convolutional and RNNs for the diagnosis of various types of mental disorders, the prediction and prognosis of psychiatric diseases, and applications for the treatment and monitoring of behaviors and behaviors. However, challenges related to data standardization, interoperability, informed consent, and algorithmic bias remain critical barriers. Addressing these limitations is essential to enable the responsible translation of ANN-based tools into psychiatric care.

Ethical and implementation challenges in medicine

ANNs have demonstrated enormous potential in modern medicine, from diagnosing diseases to predicting clinical risk. However, as these tools become increasingly integrated into healthcare systems,

Table 3. Glossary of terms

Term	Abbreviation	Concept
Artificial Intelligence	AI	It is a technology that allows computers and machines to simulate human learning, understanding, problem-solving, and decision making[76].
Machine Learning	ML	It is the process by which computers use neural networks to recognize patterns and improve their ability to identify them[77].
Artificial Neural Networks	ANN	It is a machine learning model that stacks simple neurons in layers and learns pattern recognition weights and biases from the data to assign inputs to outputs[78].
Deep Neural Networks	DNN	Type of artificial neural network with multiple hidden layers, which makes them more complex and consumes more resources compared to conventional neural networks[79].
Convolutional Neural Networks	CNN	Deep learning neural network designed to process structured data arrays, such as images[80].
Recurrent Neural Networks	RNN	They are distinguished by their "memory," as they take information from previous inputs to influence the current input and output[81].
Generative Antagonist Network	GAN	They are based on unsupervised learning algorithms. This means that the network trains itself without a human having previously given it a goal[82].
Perceptron	/	It is a simple model of a biological neuron used in an artificial neural network[83].
Big Data	/	Extremely large data sets that cannot be easily managed or analyzed with traditional processing tools[84].

significant challenges arise that must be addressed to ensure their responsible and effective use:

- Interpretability and explainability. Although they are powerful tools in medical diagnosis and analysis, their internal workings are opaque. This lack of explainability poses a challenge, especially in an environment such as medicine, where decisions must be justified. If a model recommends a treatment without an understandable reason, professionals may hesitate to accept it, limiting its clinical usefulness. To address this problem, techniques such as LIME, SHAP, and Grad-CAM have been developed to help visualize which variables influence the network's decision. However, these techniques still require advanced computational expertise. Improving interpretability in an accessible way is crucial for these technologies to be truly useful in everyday medical practice[72].
- Ethics, privacy, and security. Its use involves working with enormous amounts of sensitive data: images, medical records, genetic information, among others. If this data is leaked or misused, it can seriously affect patient privacy. Furthermore, if algorithms are trained with biased data, they can generate discriminatory diagnoses or treatments. Given these risks, it is essential to establish ethical and legal frameworks that regulate the development and use of AI in healthcare. Robust cybersecurity systems are also required to protect data, as well as mechanisms to audit models for potential flaws or unfair decisions[73,74].
- Rigorous clinical validation. Many neural network models achieve impressive levels of accuracy in controlled environments. However, transferring them to a hospital with real patients is a completely different challenge. Variables such as data quality, demographic differences, and conditions of use affect their performance. Models must be validated in multiple clinical contexts before they can be officially adopted. This process should include testing with different populations and medical centers to ensure that the model is safe, reliable, and useful in daily practice[75].
- Acceptance by medical staff. Although this technology is advancing rapidly, its adoption depends largely on healthcare professionals. Many doctors may be wary of systems they do not understand or perceive as a threat to their professional judgment. For them, diagnosis is not just a calculation, but a comprehensive interpretation based on years of experience. Encouraging acceptance involves providing understandable tools and specific training. ANNs should be presented as assistants that reinforce clinical practice, not as substitutes for medical expertise. Only then will they be integrated harmoniously and ethically into the healthcare system.

Conclusions

ANN applications are widespread in various real-world and scientific domains. The medical field, in particular, has benefited from various applications that have made great strides in several subdomains. The use of ANNs in psychiatry has opened up new possibilities for diagnosis, prognosis, and treatment of mental disorders. Their ability to process large volumes of clinical, behavioral, and neurobiological data allows them to identify complex patterns that may go unnoticed in traditional assessments performed by highly specialized physicians. In particular, CNNs have proven useful in neuroimaging analysis, while recurrent networks and hybrid models have been highly effective in language processing to predict risky behaviors. Despite these advances, significant challenges remain, such as the need to improve model interpretability, reduce data bias, and ensure privacy and confidentiality in the handling of sensitive information, a problem that has slowed its application in multiple ways. Comparative studies are needed to define the effectiveness of deep learning in psychiatry, with the collaboration of specialists from other medical fields. The future of ANNs in mental health will depend on their integration with other AI tools that explain, interpret, and validate clinical results, enabling more accurate and personalized medical assessments (Table 3).

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CASE REPORT

Choreiform movements associated with the use of extracorporeal circulation in an adult patient undergoing cardiac surgery: case report

Movimientos coreiformes asociados a uso de circulación extracorpórea en paciente adulto sometido a cirugía cardiaca: reporte de caso

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Abstract

Chorea or choreiform movements associated with prolonged extracorporeal circulation time are more commonly observed in children, with only a limited number of cases reported in adults. These movements are characterized by fluid, random, and contorted motions that may affect the face, neck, or limbs, typically appearing within 3 to 12 days following cardiac surgery. Although the exact etiology remains unclear, the symptoms are believed to be secondary to focal lesions in the basal ganglia. Currently, there is no specific treatment for this condition, and management is primarily symptomatic. We present the case of a 68-year-old male who developed choreiform movements in his right lower limb three days after undergoing aortic valve replacement surgery.

Keywords: *Choreiform movements. Extracorporeal circulation. Cardiac surgery. Case report.*

Resumen

La corea o movimientos coreiformes asociados al tiempo prolongado de circulación extracorpórea es más común en niños, siendo limitados los casos presentados en adultos. Se manifiestan como movimientos de contorsión fluidos y aleatorios que pueden afectar la cara, el cuello o las extremidades con aparición dentro de los primeros 3 a 12 días posterior a la cirugía cardiaca. Actualmente las causas no están claras, los síntomas podrían ser secundarios a lesiones focales a nivel de los núcleos de la base. No existe un tratamiento específico para esta afección, este solo va dirigido a la sintomatología. Presentamos el caso de un paciente de sexo masculino de 68 años de edad quien inició con movimientos coreiformes en miembro inferior derecho tres días posterior a cirugía cardiaca de recambio valvular aórtico.

Palabras clave: *Movimientos coreiformes. Circulación extracorpórea. Cirugía cardiaca. Reporte de caso.*

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Introduction

The presence of chorea or choreiform movements following cardiac surgery has been described mainly as a complication in the pediatric population. In adults, it is a rare entity, also known as post-pump chorea[1].

During surgery, cardiopulmonary support is used to divert blood flow to a circuit external to the body to maintain circulation and systemic perfusion[2]. This method, known as cardiopulmonary bypass (CPB), is accompanied by aortic cross-clamping and deep hypothermia (temperature < 25 °C) to stop cardiac blood flow during the intervention[3]. Prolonged exposure to these factors has been associated with the development of choreiform movements in the postoperative period[1,3].

Although the causes of this neurological complication remain unclear, it has been proposed that it could be due to focal lesions in the basal ganglia. One proposed hypothesis is hypoxic-ischemic in origin, suggesting a decrease in intraoperative blood flow. Another hypothesis explains that the damage is a consequence of mechanical trauma to erythrocytes during CPB, and more recently it has been attributed to a mechanism related to neuroinflammation[4-6].

Symptoms generally appear within the first 3 to 12 days after cardiac surgery and are characterized by twisting, fluid, and random movements that may affect the face, neck, or extremities[3,7]. In most cases they are transient and reversible, showing improvement or complete resolution within weeks or months.

The lack of specific biomarkers makes establishing an accurate diagnosis challenging, and metabolic causes such as hyperglycemia and hydroelectrolytic disorders related to magnesium must be ruled out, as well as Sydenham chorea within the differential diagnosis[6,8].

Currently, there is no specific treatment, and therapy is directed only at symptom management. Recent studies suggest the use of steroids, while in other reported cases haloperidol and tetrabenazine have been used[4,9,10]; however, when movements are refractory to treatment, deep brain stimulation has been employed, resulting in a reduction of symptoms[11].

With the aim of expanding knowledge about neurological sequelae following cardiovascular surgery and providing a basis for future research to clarify its cause and treatment, we present the case of a 68-year-old male patient who developed choreiform movements in the right lower limb 3 days after aortic valve replacement cardiac surgery.

Method

This manuscript was prepared following the recommendations of the SAGER and EQUATOR guidelines to ensure transparency, ethical integrity, and quality in the presentation of the clinical case. A literature search was performed in the following databases: PubMed, ScienceDirect, and Google Scholar, where 10 articles reporting cases of choreiform movements related to cardiovascular surgical procedures were identified.

Case presentation

A 68-year-old man presented with choreiform movements in the right lower limb 3 days after a second cardiac surgery for aortic valve replacement. Relevant pathological history included hypertension diagnosed 3 months earlier and treated medically. In February 2024, the patient underwent cardiac surgery due to severe aortic failure, during which a 21-mm biological valve was implanted; 3 months later, the findings made were consistent with infectious endocarditis, requiring reintervention. During this 2nd surgical act, aortic valve replacement was performed with implantation of a 21-mm mechanical valve, and multiple vegetations due to prosthetic valve endocarditis caused by *Staphylococcus epidermidis* were identified. Surgery was performed under balanced general anesthesia with mild hypothermia, maintaining a body temperature of 32-34 °C. The CPB time was 216 minutes and the aortic cross-clamping time, 173 minutes; the procedure concluded without immediate peri- or postoperative complications. Three days after surgery, the patient developed choreiform movements in the right lower limb, characterized by twisting movements that increased with voluntary movement and stress (Supplementary video 1), decreased during sleep, and could be slightly suppressed voluntarily, causing limitation for standing and walking. Additionally, physical examination revealed hyperreflexia of the affected extremity, with preserved strength and sensation and no other motor abnormalities. Computed tomography was requested on the 6th day, revealing no significant alterations (Fig. 1). Magnetic resonance imaging was not performed due to the stainless-steel material used in the sternotomy. Laboratory studies included complete blood count, renal function tests, blood chemistry, and liver function tests, none of which showed significant changes. The use of neuroleptics or other dopaminergic blockers was also ruled out. Physical therapy was initiated on day 2 after symptom onset, aimed at functional recovery of standing and

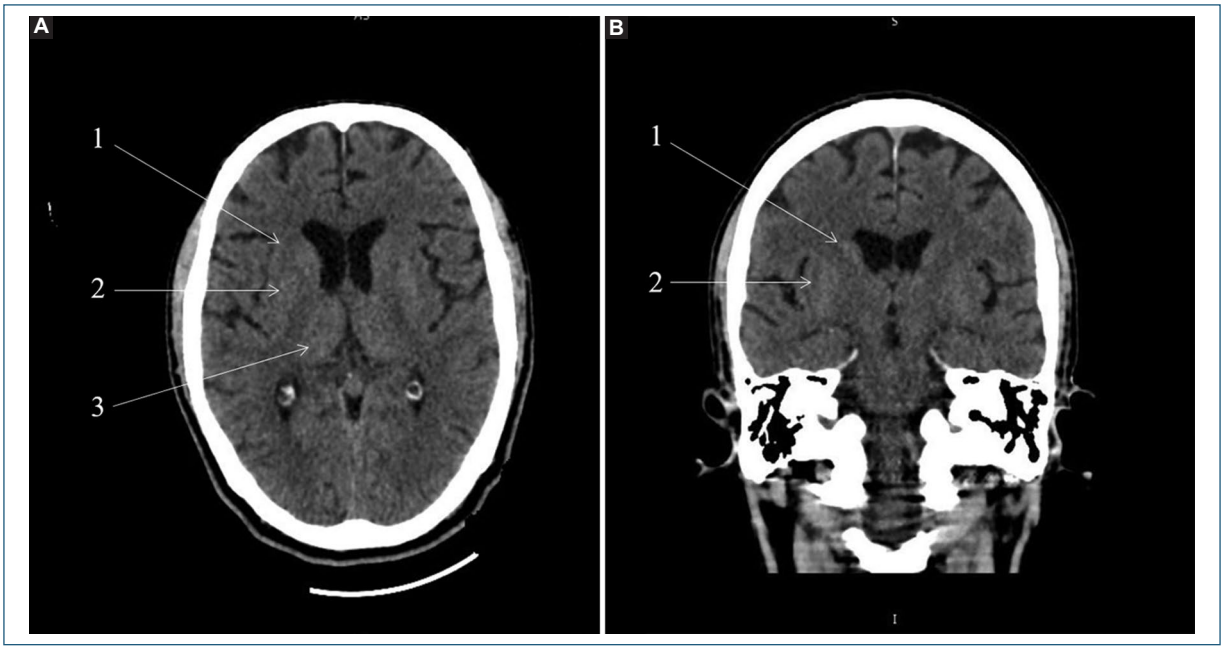

Figure 1. A: brain computed tomography in axial section at the level of the basal ganglia showing no relevant lesions in 1) caudate nucleus, 2) lentiform nucleus, or 3) thalamus. **B:** brain computed tomography in coronal section at the level of the basal ganglia showing no relevant lesions in 1) caudate nucleus or 2) lentiform nucleus.

ambulation. Pharmacological treatment was started day 8 with haloperidol 5 mg every 8 hours and was discontinued 3 days later due to improvement in the movements (Supplementary video 2).

Discussion

CPB-related chorea is a rare complication in adults and occurs more frequently in children undergoing "open-heart surgeries". The underlying mechanisms remain unknown; however, the duration of aortic cross-clamping, CPB time, and deep hypothermia have been considered risk factors[4].

The first reports of chorea in children were recorded around the 1960s, while cases in adults began to be documented from the 2000s onward[12]. To date, 19 cases in adults related to major heart procedures have been reported, such as pulmonary endarterectomy, aortic aneurysm dissection, and most frequently aortic valve replacement[4].

Iqbal et al. (2024) presented a case of generalized chorea initially suspected to be encephalopathy, which progressed to abnormal frontal chorea-ballism movements involving the buccolingual, axial, and appendicular regions. They explained that the possible cause could be related to a primary or systemic neuroinflammatory mechanism resulting from increased proinflammatory cytokines in the bloodstream following CPB use, hypoxia, and immunosuppression associated with the use of a bovine valve[6,12].

A systematic review described 11 cases in which other neurological signs were present, such as agitation, cognitive deficit, and speech disturbances, together with generalized choreiform movements. This study supports the hypothesis of reduced blood flow during CPB as the cause of lesions observed in the basal ganglia in imaging studies; however, not all reported cases showed abnormalities on magnetic resonance imaging[4].

Unlike the previously described cases, our patient presented focal choreiform movements in the right lower limb with the characteristics described above, making it an atypical sign[13].

Within the differential diagnosis, Sydenham chorea—the most common cause in children, mainly following infection by group A beta-hemolytic streptococcus (GABHS)—was ruled out[7], as well as other less frequent causes such as hyperglycemia and hypomagnesemia[14,15]. A limitation of the present case is that, in the absence of magnetic resonance imaging, a structural lesion as the cause of chorea cannot be excluded.

The most relevant factor for the development of choreiform movements in this case was the prolonged CPB time and aortic cross-clamping, which were nearly twice the average duration. Some studies report an

average CPB time between 90 and 130 minutes, whereas a period longer than 150 minutes of aortic cross-clamping has been associated with a higher risk of adverse effects[16].

Of note, unlike other studies in which only pharmacological treatment was provided, this case was complemented with physiotherapeutic intervention aimed at functional recovery, highlighting the importance of multidisciplinary management.

Conclusions

Chorea or choreiform movements in adults are a very rare diagnostic entity that should be considered in patients undergoing cardiac surgery with a history of prolonged CPB time. Although no specific treatment currently exists, lack of recognition of this condition may negatively affect patient prognosis by limiting functionality, quality of life, and clinical evolution. Therefore, timely multidisciplinary management should be provided, as well as further studies to determine its cause and early interventions. In this context, greater documentation and systematic reporting of cases in the adult population are emphasized, which will enrich the scientific literature and optimize clinical decision-making in similar scenarios.

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Author contributions

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Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality, informed consent, and ethical approval. The authors followed their institution's confidentiality protocols, obtained informed consent from the patients, and received approval from the Ethics Committee. The recommendations of the SAGER guidelines were followed according to the nature of the study.

Statement on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

Supplementary data

Supplementary data is available at DOI: 10.24875/ANC.25000036. These data are provided by the corresponding author and are published online for the benefit of readers. The content of the supplementary material is the sole responsibility of the authors.

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