Revista Mexicana de
Neurociencia

Academia Mexicana de Neurología, A.C.

Publicación oficial de la Academia Mexicana de Neurología A.C.

VOLUME 24 - NUMBER 1 / January-February 2023 – ISSN: 2604-6180

www.revmexneurociencia.com

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EDITORIAL

The growing evidence of neurodegenerative diseases risk factors

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The increasing rate of dementia prevalence represents a menace to the world health system and our society. At present, there are 55 million people living with dementia and this number will increase to 78 million by 2030[1]. Age, certain genes, and family history represent the main non-modifiable risk factors for dementia development[2]. Nevertheless, there are many modifiable elements that could play a potential role for dementia prevention[3].

The 2020 report of the Lancet commission on dementia prevention added three "new" risk factors for dementia (excessive alcohol consumption, head injury, and air pollution) to their prior report from 2017 that included the following nine factors: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and infrequent social contact[4]. Further, there are several reports finding other associated factors with dementia, these risk factors include severe mental illness (not only depression)[5], fibromyalgia[6], gut microbiota dysfunction[7], and among others.

Despite Alzheimer's disease (AD) is the most common type of dementia and the risk factors described above are also described precisely for AD[8]; it is important to recall that "dementia" is an umbrella term that is often used to describe neurodegenerative (or non-neurodegenerative) diseases of different etiologies. One potential next step to better characterize risk factors in specific neurodegenerative diseases is the development of studies differentiating risk factors for specific neurodegenerative etiologies. Let's take Parkinson's disease (PD) as an example, this is a complex disease that typically starts with motor and neuropsychiatric clinical manifestations but is frequently accompanied by dementia as the disease progresses[9]. Interestingly, there are risk factors described for PD that are "exclusive" for this neurodegenerative disorder such as the exposure to pesticides[10]. Furthermore, people with an established diagnosis of bipolar disorder (odds ratio, 3.35; 95% CI, 2.00–5.60; I^2 = 92%)[11] or schizophrenia (odds ratio, 4.63 95% CI, 1.76–12.19; $p < 0.01$)[12] have an increased risk for developing PD. Interestingly, diabetes, which is one of the 12 risk factors described by the Lancet commission on dementia prevention, was identified as a component that could play a role on delaying PD onset in a sample of Mexican patients with PD. For more details of this study, please see the article by Cervantes-Arriaga et al. published in the current issue.

Given the health emergency of the recent pandemic, different studies were developed to describe the outcomes in patients affected by COVID-19. One of the frequently observed consequences in this population is different neurological manifestations[13]. A cross-sectional study identified an increased risk of cognitive decline, specifically in executive function in patients with COVID-19 and a history of hospitalization compared with outpatients[14]. In this issue, Anaya-Escamilla et al. described the likely role of COVID-19 and diabetes mellitus in the development of cognitive decline.

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Date of reception: 01-12-2022
Date of acceptance: 12-12-2022
DOI: 10.24875/RMN.M22000093

Available online: 16-01-2023
Rev Mex Neuroci. 2023;24(1):1-2
www.revmexneurociencia.com

A great effort in terms of dementia risk factors recognition is ongoing. Disclosure of this information needs to become greater and be spread among the medical and non-medical communities, especially in low-income developing countries where the prevalence of dementia will rise in the following years.

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Revista Mexicana de Neurociencia

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ORIGINAL ARTICLE

Type 2 diabetes mellitus as a determinant factor for the age of Parkinson's disease onset

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Abstract

Objective: *This study aims to identify whether type 2 diabetes mellitus (T2DM) impacts the age of Parkinson's disease (PD) onset.* **Methods:** *Consecutive people living with PD (PwP) with 2-4 years of disease duration were included and categorized according to the presence of T2DM. A 2:1 ratio randomization from the non-DM sample was performed. T2DM diagnosis was defined by a positive personal history of T2DM recorded in the medical files or reported by the subject, or the use of a hypoglycemic drug for glycemic control. A clinical assessment including the Movement Disorder Society Unified Parkinson's disease rating scale and the Hoehn and Yahr was performed by a movement disorders specialist.* **Results:** *One hundred and twenty-four non-T2DM PwP and 62 PwP with T2DM (PD-DM) were included in the study. No statistically significant differences between groups were found in motor and non-motor scores nor in disease duration. The mean age of the whole sample was 63.4 ± 11.9 years, with a mean PD duration of 3.4 ± 0.8 years. In the PD-DM group, the mean duration of T2DM was 12.4 ± 6.8 years, and T2DM was diagnosed 9.2 ± 6.8 years before the PD onset. The PD-DM group had an older age of PD onset (5.9 ± 1.6 year, p < 0.001).* **Conclusions:** *Patients with PD-DM had an older age at PD onset, suggesting a potential T2DM role in delaying the age of disease onset.*

Keywords: *Parkinson disease. Type 2 diabetes mellitus. Age of onset. Risk factors.*

Diabetes mellitus *tipo 2 como factor determinante de la edad de aparición de la enfermedad de Parkinson*

Resumen

Introducción: *Se ha demostrado previamente una relación entre la enfermedad de Parkinson (EP) y la diabetes* mellitus *tipo 2 (DM2). La DM2 en personas con EP se asocia con un curso más agresivo de la enfermedad. Este estudio tiene como objetivo identificar si la DM2 tiene un impacto en la edad de inicio de la EP.* **Métodos:** *Se incluyeron consecutivamente personas con enfermedad de EP (PCP) con una duración de entre dos y cuatro años y se clasificaron según la presencia de DM2. Se realizó una aleatorización de proporción 2:1 de la muestra No DM2. La evaluación clínica fue realizada por un especialista en trastornos del movimiento.* **Resultados:** *Se incluyeron un total de 124 PCP no diabéticas y 62 PCP con DM2 (EP-DM).*

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Date of reception: 04-07-2022
Date of acceptance: 04-10-2022
DOI: 10.24875/RMN.22000048

Available online: 16-01-2023
Rev Mex Neuroci.
2023;24(1):3-7

No se encontraron diferencias estadísticamente significativas en las puntuaciones motoras y no motoras ni en la duración de la enfermedad entre los grupos. El grupo EP-DM tuvo una mayor edad de inicio de la EP (5.9 ± 1.6 años, p < 0.001) en comparación con el grupo No DM. **Conclusión:** *Los pacientes con EP-DM tenían una edad más avanzada al inicio de la EP, lo que sugiere un papel potencial de la DM2 en el retraso de la edad de inicio de la EP.*

Palabras clave: *Enfermedad de Parkinson. Diabetes* mellitus *tipo 2. Edad de inicio. Factores de riesgo.*

Introduction

Parkinson's disease (PD) is the second most crucial neurodegenerative disease worldwide. Globally, nearly 10 million persons live with PD, and its prevalence is expected to increase in the upcoming years[1].

Since the seventies, the relationship between impaired glucose metabolism, elevated insulin levels, and PD has been studied in cellular, animal, and human models. Thus, suggesting a link between PD and type 2 diabetes mellitus (T2DM)[2]. Clinical evidence shows that T2DM in people living with PD (PwP) is associated with a more aggressive disease course[3,4]. In addition, in such cases with T2DM diagnosed before PD, PwP had more significant impairment in consequent motor symptoms[5]. Furthermore, persons with PD-DM have an earlier presentation of motor complications[6].

Studies reporting the relationship between PD and T2DM are vast. However, evidence is scarce when addressing the effect of T2DM onset on the age of PD onset. This study aims to identify whether T2DM contributes to a different age of PD onset.

Methods

An observational, cross-sectional, and analytical study was carried out. The study protocol was approved by the Institutional Review Board and by the Local Ethics Committee (121/19). All participants gave their written Informed Consent.

Consecutive PwP attending the Movement Disorders Clinic at the National Institute of Neurology and Neurosurgery in Mexico City from 2018 to 2020 was recruited. The International Parkinson and Movement Disorders Society clinical criteria were used for diagnosing PD[7]. Only patients with a disease duration between 2 and 4 years were included. This range was selected based on the disease progression model proposed by Holford et al.,[8] allowing to study the disease when a more predictable progression was expected, and symptom overlap between the two conditions was less problematic.

T2DM diagnosis was defined by at least one of the following: a positive personal history of T2DM recorded in the medical files, a previous diagnosis reported by the subject, or the use of a hypoglycemic drug for glycemic control. The age of T2DM onset was determined as recorded in the medical files or as reported by the subject.

Patients with incomplete demographic or clinical data were excluded from the study. A 2:1 ratio randomization from the non-DM sample was performed. This randomization aimed to reduce the risk of errors resulting from comparing groups with highly unequal sample sizes, especially when parametric assumptions were violated. Unequal sample sizes can lead to unequal variances between samples which affect the assumption of equal variance in some statistical tests, thus increasing the risk for Type 1 error as well as loss of statistical power[9]. On the other hand, increasing the control-to-case ratio in unmatched case-control settings, results in a gain of statistical power until a ratio of 1:4 and then stabilizes thereafter[10]; in our study, samples were matched according to a disease duration between 2 and 4 years, thus a matching ratio higher than 2:1 may still have substantial power loss given that T2DM was rare (< 15%) in an under-lying cohort[11].

The age of PD onset represented the age when each subject perceived their first motor symptom. For clinical assessment, a movement disorders specialist evaluated motor symptoms. The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was employed for assessing non-motor experiences of daily living (Part I), motor experiences of daily living (Part II), motor evaluation (Part III), and motor complications (Part IV)[12]. The Hoehn and Yahr (HY) stages were used to classify PD as mild (stages 1 and 2), moderate (stage 3), and severe (stages 4 and 5).

414 PwP were initially recruited. Seventy-six subjects were categorized as PD-DM, 14 of which were excluded due to T2DM diagnosis after PD onset. Consequently, a total of 62 PD-DM participants were incorporated into the analyses.

From the remaining 338 non-DM PD subjects, 124 were randomly assigned to match a 2:1 ratio, as described above. For the randomization, the function Random Sample of Cases from SPSS was used (Data

> Select Cases > Random Sample of Cases). Description of sociodemographic data was done with measures of central tendency (modes, medians, and means) and dispersion ranges (standard deviations and variances). For the inferential analyses, the tests used were as follows. The Pearson's and Spearman's coefficients were used to determine correlations. Comparisons of quantitative variables were performed using independent samples Student's t-test, Welch's t-test (unequal variances), or Mann-Whitney test, as needed. The Chi-square test and Fisher's test were used when comparing qualitative variables. $p < 0.05$ was considered for statistical significance. The statistical package SPSSv25.0 was used.

Results

Overall, 186 PwP (54.3% male) were analyzed. The mean age of the whole sample was 63.4 ± 11.9 years, with a mean PD duration of 3.4 ± 0.8 years. In the PD-DM group, the mean duration of T2DM was 12.4 ± 6.8 years, and T2DM was diagnosed 9.2 ± 6.8 years before the PD onset. No statistical differences in demographic and clinical variables between included and excluded subjects were found.

Regarding T2DM therapy, metformin was the most commonly used treatment (74%), both as monotherapy or as an add-on to glibenclamide (11%). In addition, 14% of the subjects were on a premixed insulin regimen.

Table 1 compares the main variables between the non-DM and the PD-DM groups. In summary, subjects in the PD-DM group were older (mean difference 5.7 ± 1.8, 95% CI: 2.2-9.3 years) and had an older age of onset (mean difference 5.9 ± 1.6, 95% CI: 2.7-9.0 years) in comparison to the non-DM group. No statistically significant differences between groups were found in motor and non-motor scores or disease duration. A statistically significant but weakly positive correlation was found between the T2DM course and the age of PD onset ($rs = 0.27$, $p = 0.03$).

Table 1. Comparisons of the main variables among the PD non-DM group and the PD-DM group

Variables	PD non-DM group (n = 124)	PD-DM group (n = 62)	p-value
Male, n (%)*	68 (54.8)	33 (53.2)	0.84
Age**	61.3 ± 13.5	67.5 ± 8.9	< 0.001
Body mass index	26.6 ± 4.6	27.9 ± 4.1	0.08
Age of PD onset**	58 ± 13.5	64.2 ± 8.8	< 0.001
PD duration**	3.4 ± 0.8	3.3 ± 0.7	0.25
MDS-UPDRS**			
Part I	8.7 ± 6.0	9.6 ± 5.6	0.18
Part II	10.5 ± 7.9	11.3 ± 8.1	0.46
Part III	28.7 ± 14.3	29.4 ± 13.5	0.48
Part IV	1.1 ± 2.7	1.0 ± 2.7	0.78
MDS-UPDRS total	41.6 ± 21.8	43.4 ± 20.6	0.42
Hoehn and Yahr, n (%)*			
Mild (1-2)	86 (69.4)	41 (66.1)	0.66
Moderate (3)	33 (26.6)	19 (30.6)	0.56
Severe (4-5)	5 (4)	2 (3.2)	0.78

PD non-DM, Parkinson's disease without diabetes mellitus type 2; PD-DM, Parkinson's disease and diabetes mellitus type 2; MDS-UPDRS, movement disorders society-unified Parkinson disease rating scale.
*Chi-square test.
**Mann–Whitney test.

Discussion

A link between PD and insulin resistance has been formerly described, suggesting a common neurodegenerative pathway[13]. Animal models have demonstrated that hyperglycemia inhibits dopaminergic neuron activity and lessens levels of extracellular dopamine[14].

On the other hand, T2DM drugs such as glucagon-like peptide-1 receptor (GLP-1R) agonists, thiazolidinediones, and dipeptidyl-peptidase 4 (DPP4) inhibitors have been proposed as potential neuroprotectors or disease modification therapies in PD based on epidemiological studies and *in vitro* models[15].

Epidemiological studies had reported T2DM as a risk factor or a protective factor for PD, depending on the study design. Prospective studies have shown an increased risk for PD[16], while case-control studies (retrospective) describe a protective role[17].

In this study, the age of PD onset was older in the DM-PD group, which may suggest a neuroprotective role in a certain stage of the pathogenesis of the T2DM. This finding was unexpected due to the substantial evidence suggesting hyperglycemia and insulin resistance as a catalyst of mitochondrial dysfunction, oxidative stress, and inflammation leading to neurodegeneration[18].

A recent meta-analysis on T2DM as a determinant of PD risk and progression failed to find age as a relevant factor. Interestingly, only one of the seven cohort studies included in the meta-analysis T2DM was required to be developed before PD, with the remaining studies also including incident T2DM cases. Age was not investigated in the two case-control studies analyzed[19].

A possible factor that could be responsible for the older age at the PD onset in the PD-DM group could

be the hypoglycemic treatment. In our cohort, the most used therapy was metformin. Metformin has shown a neuroprotective role in several neurodegenerative diseases, as well as in PD[20]. Metformin may have a potential role in almost every aspect of PD physiopathology, resulting in a possible protective factor for the development of PD[21].

In the present study, neither motor nor HY differences were found. The fact that our groups were controlled by a rather short PD progression may explain these findings.

Several limitations can be listed. First, subjects on the PD-DM were older. Arguably, the age difference might create a bias translating into the age of PD onset. While this cannot be ruled out, the PD duration in both groups is similar. Therefore, subjects in the PD-DM did not have a longer follow-up due to a longer PD duration leading to a bigger chance of developing diabetes. Age-matching between groups using the whole sample before randomization was attempted and was not feasible. Second, no biomarkers such as insulin or HbA1c were collected. In consequence, the relationship between insulin metabolism or glycemic control and its implication in the age of PD onset could not be appraised. Third, the fact that three-quarters of the PD-DM group were on metformin and that there were no patients on GLP-1R agonists, thiazolidinediones, or DPP4 inhibitors does not allow to address the possible effect of drug treatment on the age of PD onset. Finally, due to the study, design recall bias is expected.

Furthermore, the comorbidity burden of T2DM may include other conditions that have been associated with the risk of developing PD. For instance, it has been reported that the use of statins in the context of dyslipidemia decreases the risk of PD[22], as well as the use of beta-blockers commonly used to treat hypertension[23]. Other commonly sees metabolic disturbance seen in metabolic syndrome is in serum uric acid levels; low uric acid has been associated with morbidity, severity progression, non-motor symptoms, and motor complications of PD[24]. Due to the study design, these potential confounders or effect modifiers were not assessed and future studies must also consider them.

Likewise, considering that T2DM is one of the most common illnesses among our population, as well as the increasing prevalence of PD worldwide, additional longitudinal research should be conducted to determine if this phenomenon on age of PD onset might be attributed to T2DM metabolic pathogenesis, but also taking into account the role of T2DM treatment and glycemic control periodical measurements. In the future, these could provide valuable information that would furthermore help prevent or delay PD onset.

Conclusion

Patients with DM-PD had an older age at PD onset, suggesting a potential T2DM role in delaying the PD age of onset. Further, research should be conducted to identify if this phenomenon can be attributed to T2DM metabolic pathogenesis but also to T2DM treatment and glycemic control.

Funding

None.

Conflict of interests

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Incidence of congenital malformations of the central nervous system in newborns in Chiapas, Mexico, and associated factors

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Abstract

Introduction: *Malformations of the central nervous system (CNS), the type of congenital defect second only to cardiac malformations, cause infant disability and mortality.* **Objective:** *The aim of the study was to evaluate the incidence of congenital malformations of the CNS in newborns treated at a regional public hospital in Southern Mexico and explore the associated factors.* **Methods:** *This descriptive study included 113 newborns with CNS malformations. A specific diagnosis was provided and information was obtained from the parents in relation to age, schooling, occupation, prenatal control, intake of folic acid, and exposure to pesticides. A database was created in the statistical program Epi Info version 3.4.3 to carry out univariate and bivariate analyses using the Chi-square test, with significance considered at $p < 0.05$.* **Results:** *The most frequent malformations were hydrocephalus (45.1%), Arnold-Chiari (32.7%), and encephalocele (8.0%). Of the 113 newborns herein examined, a greater percentage of congenital malformations was found when the first pregnancy took place in mothers 12-19 versus over 19 years of age (78.8% vs. 21.2%, respectively; $p < 0.05$). Furthermore, 40.2% of mothers were exposed to insecticides and 39.8% to herbicides and/or fungicides before or during pregnancy. Only 15.4% of the mothers consumed folic acid during the first trimester of pregnancy.* **Conclusion:** *The incidence of congenital abnormalities of the CNS in newborns is a serious problem, perhaps associated with exposure of the mother to pesticides and a deficient intake of folic acid. Therefore, it is necessary to strengthen prenatal care and health literacy to help reduce the occurrence of these disorders.*

Keywords: *Congenital malformations. Risk factors. Central nervous system. Folic acid. Pesticides.*

Incidencia de malformaciones congénitas del sistema nervioso central y factores asociados en recién nacidos de Chiapas, México

Resumen

Introducción: *Las malformaciones congénitas del sistema nervioso central (SNC) son el segundo defecto congénito más común después de las malformaciones cardiacas y pueden asociarse a mortalidad y discapacidad infantil.* **Objetivo:** *estudiar la incidencia de las principales malformaciones congénitas del SNC y factores asociados en recién nacidos atendidos en un hospital público de segundo nivel en Tuxtla Gutiérrez, Chiapas.* **Métodos:** *estudio descriptivo, que incluyó a 113 recién nacidos con malformaciones del SNC. Se precisó el diagnóstico, se obtuvo información de los padres: edad, escolaridad, ocupación, control prenatal, ingesta de ácido fólico, exposición a plaguicidas. Se integró una base de datos en el programa*

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Dater of reception: 24-08-2022
Date of acceptance: 08-11-2022
DOI: 10.24875/RMN.22000067

Available online: 16-01-2023
Rev Mex Neuroci. 2023;24(1):8-12
www.revmexneurociencia.com

estadístico Epi Info versión 3.4.3, se realizó un análisis univariado y bivariado mediante la prueba chi cuadrada y un valor p < 0.05 se consideró un resultado significativo. **Resultados:** *las malformaciones más frecuentes fueron: hidrocefalia (45.1%), Arnold-Chiari (32.7%) y encefalocele (8.0%). El porcentaje de casos fue más elevado (78.8%) en madres cuyo primer embarazo fue entre los 13 y 20 años (p < 0.05). El 40.2% de las madres durante el embarazo estuvieron expuestas a insecticidas y 39.8% a herbicidas y fungicidas. Únicamente el 15.4% de las madres consumieron ácido fólico durante el primer trimestre del embarazo.* **Conclusión:** *es grave y preocupante la alta incidencia de anormalidades congénitas del SNC, lo cual podrían estar asociado con la exposición de plaguicidas y deficiencias en la ingesta de ácido fólico. Consecuentemente se necesita fortalecer la atención prenatal y la alfabetización en salud para coadyuvar en la disminución de estos padecimientos.*

Palabras clave: *Malformaciones congénitas. Sistema nervioso central. Ácido fólico. Plaguicidas.*

Introduction

Central nervous system (CNS) anomalies appear to be the most common systemic congenital anomalies, with an incidence of about 1%[1-3]. In low-income countries, 17-70% of neonatal deaths resulting from birth defects are attributed to neural tube defects (NTDs)[4]. Unfortunately, the information available on birth defects in Latin America is scarce and fragmented, indicating inadequate epidemiological surveillance. This information is a vital element for the proper monitoring and evaluation of the impact of prevention and intervention programs. Hence, the ability to adequately assess efforts aimed at reducing the incidence of NTDs in the total births per year (~11 million) is hindered[5].

Moreover, the etiology and mechanisms of fetal CNS abnormalities are still poorly understood. One report has estimated that ~40% of pathogenic factors may be genetic and environmental[6]. As an example of the environmental factor, human exposure to pesticides takes place by direct contact with sprayed crops, through consumption of residues in food and water, and during or after indoor/outdoor application[7]. Various studies have found an association between exposure to organophosphates during fetal development and early childhood and adverse neurodevelopmental effects[8-10].

Regarding the preventative strategies to diminish CNS anomalies, various clinical trials have evidenced the importance of periconceptional folic acid intake to reduce the occurrence of NTDs in newborns[11]. According to long-term surveillance of NTDs in countries that have successfully implemented fortification (e.g., the United States, Canada, Costa Rica, South Africa, and Chile) and data from a supplementation program in China, folic acid intervention strategies can apparently decrease the incidence rate of NTDs to as low as 5-6 cases per 10,000 pregnancies[12-14]. However, epidemiological surveillance of NTDs and other birth defects is still limited worldwide[15]. The objective of the current contribution was to evaluate the annual incidence (2014) of congenital abnormalities of the CNS in newborns treated at a regional second-level public hospital in Tuxtla Gutiérrez, Chiapas, Mexico, and explore some factors that may be associated with this serious problem.

Materials and methods

During 2014, a descriptive study of a population of 113 newborns was carried out in a second-level hospital, the Regional Public Hospital "Dr. Rafael Pascacio Gamboa", in the City of Tuxtla Gutiérrez, the State of Chiapas, Mexico. The diagnosis of each case with a congenital abnormality of the CNS was made by a certified neurosurgeon (the main author of the current report). A questionnaire was developed to explore diverse factors possibly associated with the incidence of NTDs. The sociodemographic factors included the age and education of the parents as well as the type of maternal prenatal control. An evaluation was also made of the maternal intake of folic acid (the dose and whether it began in the periconceptional stage or the first or second trimester of pregnancy) and maternal exposure to distinct types of pesticides (insecticides, herbicides, and fungicides). The questionnaire, expressly elaborated for this investigation, consisted of concrete, closed-ended, and categorical questions accompanied by mutually exclusive response options. Before its application to study participants, a pilot study was conducted with a sample of 25 mothers to test the validity and reliability of the different sections of questions (data not shown). Hence, the final version of the instrument was understandable and coherent.

This research was authorized by the Institutional Research Committee and also by its Bioethics Committee. Care was taken to maintain the anonymity of the participants.

Once the information was collected, a database was created in the statistical program Epi Info version 3.4.3. For each type of variable, a univariate descriptive analysis was carried out to calculate the average and the corresponding percentage. With such information, the general characteristics of the sample could be identified

relative to each variable. Subsequently, a bivariate analysis was conducted to reveal the extent of the correlation between the sociodemographic and independent variables, using Pearson's Chi-square statistic and considering significance at $p < 0.05$.

Results

The results included in the present study were 113 newborns with a diagnosis of congenital malformations of the CNS, of which 55 were boys (48.6%) and 58 girls (51.4%). The diagnosis with the greatest incidence was hydrocephalus, with 51 cases (45.1%), followed by Arnold-Chiari malformation and encephalocele with 37 and 9 patients (32.7% and 8.0%), respectively (Table 1).

The number and percentage of congenital malformations of the CNS in the newborns under study were analyzed in relation to each of the sociodemographic variables of the fathers and mothers (Table 2). A significant association was found between most of the sociodemographic variables of the parents of the newborns (age of each parent during the pregnancy, educational level of the father, and the type of prenatal care) and the existence of a congenital malformation of the CNS. The exception was the lack of relation with the educational level of the mother.

Although the majority of both parents was over 19 years old, the mothers 12-19 years of age during the first trimester of pregnancy corresponded to 78.8% of the newborns with congenital malformations of the CNS. Likewise, the majority of parents had over 6 years of schooling and prenatal control attended by a doctor, but the ones without these characteristics presented the highest percentage (71.7%) of newborns with congenital malformations of the CNS (Table 2).

The number and percentage of mothers of newborns with a congenital abnormality of the CNS were classified with respect to the time at which folic acid intake began (Table 3). Folic acid supplements were consumed by 77 of the 113 mothers interviewed (68.1%). However, 41 of these mothers (36.2%) started taking this treatment during the second trimester of pregnancy, while 17 (15.4%) did so during the first trimester. Only six of the mothers (5%) took folic acid supplements during the 3 months before pregnancy (Table 3).

Positive substance dependence (alcoholism and/or smoking) was manifested in 99 fathers (87.6%) and 21 mothers (18.6%). On the other hand, 34 mothers (30.4%) were exposed to insecticides before pregnancy and 46 (40.2%) during pregnancy. Likewise, 45 mothers had contact with herbicides and one with fungicides (a total of 39.8%) (data not shown).

Table 1. Distribution of the type of congenital defect of the CNS in the newborns under study

Diagnosis	n (%)
Hydrocephalus	51 (45.1)
Arnold Chiari malformation	37 (32.7)
Encephalocele	9 (8.0)
Anencephaly	4 (3.5)
Lipomeningocele	4 (3.5)
Hydroanencephaly	2 (1.8)
Meningocele	2 (1.8)
Total	113 (100.0)

n: the number of each malformation found.

Table 2. Analysis of the sociodemographic variables of the fathers and mothers of newborns with congenital abnormalities of the central nervous system

Variable	Number (%)	χ^2; p
Age of the mother (years)		
12-19	32 (28.3)	20.2; 0.0003
≥ 20	81 (71.7)	
Age of the father (years)		
12-19	9 (8.0)	35.2; 0.0001
≥ 20	104 (92.0)	
Age of the mother (years) during her first pregnancy		
12-19	89 (78.8)	21.2; 0.0001
≥ 20	24 (21.2)	
Years of schooling: Father		
≤ 5 years	49 (43.4)	3.98; 0.04598
≥ 6 years	64 (56.6)	
Years of schooling: Mother		
≤ 5 years	62 (54.9)	2.14; 0.14335
≥ 6 years	51 (45.1)	
Type of prenatal control		
Doctor	48 (71.7)	55.84; 0.0000
Mixed	12 (17.9)	
Midwife	7 (10.4)	

A significant association (Chi-squared test (χ^2); $p < 0.05$) between congenital defects and the sociodemographic variables is indicated in bold type.

Discussion

The high number (113 cases) of congenital malformations of the CNS detected in the present study is

Table 3. Distribution of mothers according to intake of folic acid supplements

Time at which folic acid intake began	n (%)
Over 3 months before pregnancy	6 (5.0)
0-3 months before pregnancy	8 (7.0)
During the 3rd trimester	17 (15.4)
During the 1st trimester	41 (36.2)
During the 2nd trimester	5 (4.4)
Total	77 (68%)

n: the number of cases.

alarming. The current data contrast sharply with that found in the report of the epidemiological surveillance system of neural tube and craniofacial defects (SVEDTN/DCF) for 2020 in relation to the State of Chiapas, which identified only 45 cases, corresponding to an incidence of 33.3 cases per 100,000 newborns[16]. This could be due to certain failures in the compilation of information by the national health system.

One of the strengths of the present study was the timely diagnosis of the 113 newborns encountered in daily medical practice in a second-level hospital, which demonstrates the feasibility of planning and executing observational research in similar clinical scenarios to provide key insights that can improve healthcare.

The most frequent diagnoses, in descending order, were hydrocephalus, Arnold-Chiari malformation, and encephalocele. According to the SVEDTN/DCF, hydrocephalus was one of the most frequent malformations in 2020 at the national level as well, followed by microcephaly and ODD[17]. Similar findings have been described in other Latin American countries, especially in Colombia, where hydrocephalus was one of the most frequent congenital anomalies[18-21].

Another similarity with national reports became apparent when analyzing the proportion of congenital abnormalities in regard to the gender of the children. In the present study, congenital malformations of the CNS were disproportionately concentrated among female versus male newborns (58% vs. 42%, respectively)[22]. Likewise, the SVEDTN/DCF figures indicate that abnormalities at the national level were greater in female than male newborns in 2012 (51% vs. 46%, respectively)[22], a trend also observed in 2020[16].

On the other hand, the proportion of cases was higher in children when the first pregnancy of their mother had taken place from 12 to 19 versus over 19 years of age (78.8% vs. 21.2%, respectively). In contrast, the greatest percentage of congenital abnormalities at the national level was in newborns from mothers from 20 to 24 year old, followed by those between 15 and 19 years of age[16]. This difference is probably associated with the high incidence of teenage pregnancies registered in the State of Chiapas[23].

Concerning the capacity of folic acid intake to reduce NTDs, the timing of folic acid consumption is critical, being most effective when it begins during the periconceptional period (as of at least 1 month before pregnancy) and continuing to the end of the first trimester[24-26]. Unfortunately, the practice of most mothers in the current sample was not consistent with the aforementioned indications. Only 7.8% of the mothers started taking folic acid supplements 3 months before pregnancy, while 15.4% and 36.2% did so during the first and second trimester of pregnancy, respectively. Hence, the majority of mothers who gave birth to a child with a CNS abnormality had an inadequate consumption of this food supplement, which is probably related, at least in part, to deficiencies in the application of existing prenatal care programs of the Secretary of Health in Mexico. Consequently, it is essential to strengthen the application of these programs and at the same time promote health literacy.

Moreover, the considerable percentage of mothers presently evaluated who were exposed to pesticides (40.2%), herbicides, and fungicides (39.8%) during pregnancy points to toxicity as a possible cause of congenital malformations of the CNS. A study carried out in Paraguay found the following factors to be associated with this type of malformation: Living next to fumigated fields (OR = 2.5; p = 0.02) or < 1 km away from these (OR = 2.7; p = 0.008), the storage of pesticides at home (OR = 15.4; p = 0.003), and direct or accidental contact with pesticides (OR = 3.2, CI = 95%; p = 0.04)[27].

The main weakness of the current contribution is the lack of information about the specific pesticide to which the mothers were exposed and the degree of exposure or the quantity of the toxic substance in the blood of the mother or the newborn. However, this weakness creates an opportunity for the future research in rural and urban areas, with the aim of gaining further insights into the hypotheses herein posed.

CNS malformations are a complex group of disorders that are being increasingly studied and diagnosed. Unfortunately, developing countries like Mexico face a complex reality for early diagnosis and follow-up of such malformations. The limited implementation of health programs due to the lack of government funding likely

constitutes a key element involved in the slow progress of prevention[28], early diagnosis, and health education. Several articles have emphasized the importance of prenatal care for the application of new strategies (e.g., fetal ultrasonography, fetal magnetic resonance imaging, and amniocentesis with advanced genetic techniques) to achieve an early diagnosis of these abnormalities[29].

In conclusion, the alarmingly high number of congenital malformations of the CNS presently found in newborns in Chiapas could be associated with exposure to pesticides and/or a deficient folic acid intake. It is necessary to strengthen prenatal care and health literacy programs to contribute to the reduction of such disorders.

Funding

None.

Conflict of interests

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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REVIEW ARTICLE

COVID-19 and diabetes mellitus in cognitive impairment: an undrawn relationship

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Abstract

Cognitive impairment is a potential short- and long-term disease consequence of COVID-19 virus, the exact mechanism is still in debate. One of their potential linking is with diabetes. Diabetes and COVID-19 infection have possible multiple common mechanisms that could ensue cognitive impairment as pulmonary microthrombi (silent hypoxia); endothelial dysfunction; cerebral vascular injury oxidative stress; renin-angiotensin-aldosterone system; and galectine and interferon responses. In addition, histological markers as amyloid AB plaques and neurofibrillary tangle of Tau protein are common in both pathologies. Despite of this evidence, diabetes mellitus and COVID-19 in cognitive impairment are establishing a bright light in terms of neurological progress. This article describes the relationship between diabetes mellitus and COVID-19 as potential cause of cognitive impairment.

Keywords: *COVID-19. Diabetes mellitus. Cognitive dysfunction. Inflammation. Amyloid.*

COVID-19 y diabetes mellitus *en el deterioro cognitivo: una relación no trazada*

Resumen

El deterioro cognitivo es una probable consecuencia a corto y largo plazo de la enfermedad por COVID-19 cuyo mecanismo preciso aún está en discusión. Una de sus causas factibles es la diabetes. La infección por COVID-19 y la diabetes tienen múltiples posibles mecanismos comunes que podrían precipitar el deterioro cognitivo como son los micro-trombos pulmonares (hipoxia silenciosa); la disfunción endotelial; la lesión vascular cerebral inducida por estrés oxidativo; el sistema renina-angiotensina-aldosterona y la respuesta al interferón y galectina. Además, los marcadores histológicos como son las placas amiloides AB y los ovillos neurofibrilares de la proteína tau que son frecuentes en ambas patologías. A pesar de esta evidencia, la diabetes mellitus *y el COVID-19 en contexto de deterioro cognitivo están dictando futuros caminos en términos de progreso neurológico. Este artículo describe la relación entre la diabetes* mellitus *y el COVID-19 como causa potencial de deterioro cognitivo.*

Palabras clave: *COVID-19. Diabetes* mellitus*. Disfunción cognitiva. Inflamación. Amiloide.*

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Date of reception: 07-06-2022
Date of acceptance: 25-09-2022
DOI: 10.24875/RMN.22000039

Available online: 16-01-2023
Rev Mex Neuroci. 2023;24(1):13-18
www.revmexneurociencia.com

Introduction

Since December 2019, when the first case of COVID-19 pneumonia was reported, the world became aware of a new challenge yet to be completely unfold. In March 11 2020, the World Health Organization (WHO) declared COVID-19 as pandemic[1]. During its evolution, multiple complications have been noted. Importantly, these morbid sequelae appear to affect patients with previous comorbidities, such as diabetes mellitus (DM). Furthermore, cognitive impairment has recently been described as a potential short- and long-term disease consequence of COVID-19 virus. Diabetes and COVID-19 infection have multiple common mechanisms that could ensue cognitive impairment instatement or worsening[2]. Therefore, in this paper, we aim to address the possible and suggested physiopathological mechanisms in a bi-dimensional relationship between COVID-19 and diabetes mellitus that lead to cognitive impairment.

Approximately 10% of patients with COVID-19 infection have DM. A Chinese meta-analysis, which included 1527 patients, observed a DM prevalence of 9.7% on infected cases. Furthermore, those with diabetes and hypertension had a two-fold increase in severity or ICU requirement.[3] Several other detrimental associations between COVID-19 and DM have been noted. A glycated hemoglobin of > 9% increased by 60% the risk of hospitalization and severity progression in pneumonia[4]. On the other hand, mortality increased 3 times in patients with history of DM who developed severe acute respiratory syndrome[5].

On the other hand, brain fog has been recently described in COVID-19 survivors, mainly attributed to endothelial dysfunction and inflammation. Both are mainstays on DM pathophysiology and together may lead to further complications. For example, disturbed function of T-cells and elevated levels of interleukin-6 (IL-6) appear in both. Covid-19 may lead to a cytokine storm, where IL-6 is one of the main inflammatory agents; also, liberation of catecholamine and steroids, higher hyperglycemia, is associated to worse outcomes[6,7]. Novel inflammatory mechanisms in the COVID-diabetes relationship and how they affect cognitive impairment will be described further.

Relationship between diabetes mellitus and cognition. What we know

Regarding the relationship between DM and cognitive impairment, it should be noted that the two main histological markers for this are amyloid AB plaques and neurofibrillary tangle of Tau protein. The amyloid precursor protein (APP) passes through several cuts during its processing. The first is given by the alpha-secretase; the second, by the beta-secretase (BACE); and the third, by gamma-secretase. The latter is encoded by presenilin 1 and 2 associated with hereditary AD. Factors such as oxidative stress and mitochondrial dysfunction overly activate BACE in the amyloid cascade with amyloid AB as the final product. The deposit of amyloid plaques leads to subsequent chronic inflammation and generation of advanced glycosylation products with increased oxidative stress, thus generating a vicious circle by stimulating BACE again.

Theories involve insulin or diabetes mellitus type 3. AB amyloid is enzymatically de-graded by certain enzymes including the insulin-degrading enzyme[8]. The AB peptide that is not removed by the insulin degrading enzyme will form Ab oligomers that later lead to amyloid plaques. Hyperphosphorylation of tau protein and amyloid ab plaques promotes neuroinflammation and the creation of oxygen reactants or peroxides. As previously mentioned, oxidative stress caused by these reactants will promote BACE function[9,10].

There is evidence that insulin can be produced by certain neurons, such as those in the olfactory bulb and the hippocampal gyrus in smaller quantities, than the pancreas. Chronic hyperinsulinemia due to inflammation decreases the insulin receptors in the blood–brain barrier with a consequent decrease in insulin levels in the CNS[9,10]. The pathophysiology occurs as follows: insulin and AB peptide, before the formation of the amyloid AB plaque, compete for the insulin receptor on the neuronal surface. When insulin resistance exists, the affinity for the receptor is lost, and so AB peptide takes its place. The insulin-degrading enzyme, which removes both AB peptide and insulin, consequently acts on the insulin erroneously. The insulin will be degraded and the AB peptide will bind to the insulin receptor[9,10]. Therefore, blocking the insulin receptors will not activate the second messenger system. This leads to hyperphosphorylation of the Tau protein, with instability of the microtubules and aggregation into neurofibrillary tangles[9,10]. These deleterious mechanisms could begin when a glycated hemoglobin (HbA1c) is higher than 8%, an association with cognitive impairment has been drawn[11].

DM generates multiple micro and macrovascular complications. These arise from advanced glycation end-products, oxidative stress, and inflammation. Some abnormalities that will be of interest in this paper are hypercoagulability and endothelial damage. Endothelial and capillary dysfunction is one of the main mechanisms for brain damage in

DM. Endothelial dysfunction could be described as an irregular response to endothelial vasodilators and lower flow response in consequence. The exposition of proteins to high glucose leads to chronic accumulation of advanced glycation end products. These are oxidants that may potentiate oxidative stress and compromise vascular activation[12,13].

The main mechanisms involved in cognitive impairment development in DM and COVID-19 are pulmonary microthrombi (silent hypoxia); endothelial dysfunction; cerebral vascular injury; oxidative stress; renin-angiotensin-aldosterone system; and galectine and interferon responses. Other theories are available such as cerebral hypoperfusion or COVID-19 encephalitis; however, these do not involve DM as a main factor. As we dive into the concepts, first, a relationship between lungs and brain by direct and indirect mechanisms will be established as is important to understand its outcomes (Fig. 1).

Pulmonary microthrombi (silent hypoxia)

Both, DM and COVID-19, predispose to thrombi formation by generating a hypercoagulable environment. Platelet hyper reactivity, inflammation, renin-angiotensin-aldosterone system (RAS) over-activation, and factors related to sepsis are some of the disturbed pathways for induced coagulation[14]. COVID-19 creates clots and shunts all over the lungs, and this has shown to be 9 times more prevalent in COVID-19 than other infections such as Influenza AH1N1[15].

Alveolar capillary microthrombi could form during the acute disease, which could damage gas exchange, and later on, when oxygen is insufficient and required in the brain, it could predispose to cognitive impairment. Normally, gas exchange or oxygen uptake is regulated to meet specific levels by maintaining blood flow and the rate of oxygen exchange in the alveoli. Microthrombi may limit the permeable surface for gas exchange; therefore, the time necessary for this process needs to increase to avoid hypoxia. In other words, with less functional surface, transit time increases to compensate this loss. As we know, the brain is a high-level consumption organ and relatively sensitive to change. This pathophysiological process could be of no acute clinical relevance in infected patients, principally in the young, but, in the future, brain damage could be boosted. This mechanism is called silent hypoxia. However, in the elderly and more commonly in patients with established dementia, it could worsen previous cognitive symptoms. In summary, transit time increases due to high permeability in alveoli causing hypoxia that could cause a "brain fog" either now or in the future[16,17].

Endothelial dysfunction

Very closely related to thrombi formation, endothelial dysfunction completes the full circle in cognitive impairment development. Integrating the basis to maintain blood flow in cerebral strokes, additional mechanisms need to activate when brain oxygen is lacking. When a threshold is reached by hypoxia, vasodilatation occurs to increase blood oxygen availability and maintain flow. This step occurs both in brain and lungs. DM develops microvascular damage over the years and inhibits a full transition to vessel vasodilatation. Other comorbidities such as dyslipidemia or tobacco history also worsen endothelial dysfunction. A partial compensatory mechanism could led to loss of cognitive functions over time, as oxygen blood extraction is impaired[16,17]. In fact, patients with mild cognitive impairment and Alzheimer's disease have shown abnormal cerebral microvascular flows when compared to controls[18].

Brain oxygen uptake is not the only way that endothelial dysfunction could cause decline particular regions and cognitive impairment. Compromised neurotransmission and secondary inflammation go along with acute or chronic hypoxia. Impaired neurotransmission is an important cognitive impairment contributor. Enzymes associated with neurotransmitter synthesis are oxygen dependent. Tyrosine hydroxylase and dopamine-B-hydroylase require oxygen for their catalytic activity to synthetize dopamine, serotonin, and norepinephrine, respectively. As in sleep apneas, hypoxia by COVID-19 may interfere with rate-limit enzymes and impair cognition[19].

Cerebrovascular injury

COVID-19 infection has shown neurotropic characteristics. Brain vasculature damage and thrombi formation are due to multiple causes. As for now, virus direct brain damage or endothelial brain cell targeting is suspected; however, other mechanisms proposed seem to also contribute to cognitive impairment[20]. SARS-COV-2 virus binds by its spike protein to the angiotensin converting enzyme receptor (ACE2) located at endothelial and glial cells. Furthermore, there is evidence that supports olfactory bulb nerve invasion[21].

Brain damage is caused by numerous interrelated and connected effects. Similarly, as alveoli capillary microthrombi, subcortical white matter microcirculation is subject to vascular lesions characterized by small subcortical ischemic and hemorrhagic injury[22]. Brain inflammation caused by multiple paths such as hypoxia, oxidative stress, vascular injury, infection, innate immune response or microglial response, and amyloid aggregates,

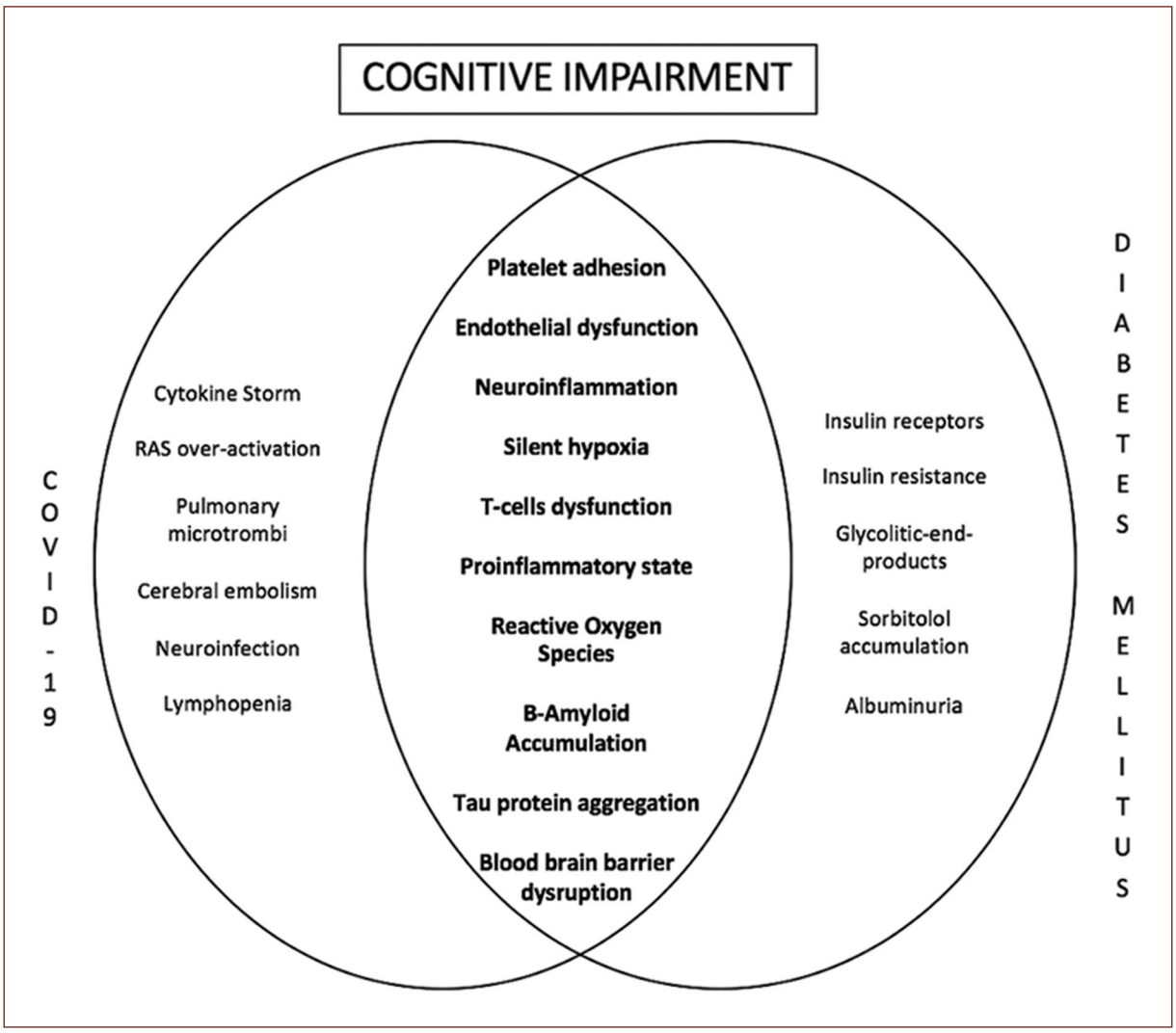

Figure 1. Cognitive impairment mechanisms in COVID-19 and diabetes mellitus.

among others, compromise the blood–brain barrier (BBB) structure. As a vicious circle, BBB leakage increases hypoxia and inflammation, with neuronal death as consequence[17]. Hippocampal structures are one of the main areas affected by inflammation, hypoxia, and neurotropic virus. CA-1 and CA-3 areas present neuronal loss after COVID infection in animal models[23].

Diabetes mellitus-COVID-19-cognition

Some interesting specificities support a relationship between DM, COVID-19, and cognition. Related to the already mentioned injury routes, RAS is dysregulated. DM increases angiotensin II levels. Remarkably, COVID-19 infection also increases angiotensin II levels. Although angiotension II is increased, SARS-COV-2 virus blocks its activity by binding to its receptor first; leading to deleterious effects. RAS disruption leads not only to vasoconstriction but also to inflammation, snowballing endothelial dysfunction, oxidative stress, and cerebral injury[24]. Of note, ACE2 in Alzheimer's disease patients is overexpressed, but its activity is reduced[25,26]. This theorizes a higher brain entry for SARS-COV-2, as more receptors are available, but with serious deleterious effects as vasoconstriction is highly reasonable.

Another synergic compromised activity is immune response in specific proteins such as galectine, interferon, and amyloid. Chronic inflammation in diabetes stimulates the expression of immune modulators such as IL-6 and galectine-9, a β-galactoside binding protein with polarizing effects. Considered as a damage-associated molecular pattern, it has shown to improve chemotaxis, cell adhesion, and

apoptosis in T-helper cells among others[27]. In the brain, it facilitated myelin repair and oligodendrocyte activity[28]. However; recently in COVID-19, galectin has been described as a therapy target, as its "beneficial" effects could prompt cytokine storm and enhance immune reaction[29]. Galectins are also considered inducers of amyloid oligomerization[30].

β-Amyloid-42 (Aβ42), one of the main proteins involve in AD pathology, has shown antipathogenic properties, as Aβ42 oligomers form fibrils to enclose microbes and activate microglial cells[31]. This response has been demonstrated for diverse viruses such as hepatitis, herpes, and zoster virus[32]. Aβ42 mediates the expression of interferon genes, in particular the amyloid-stimulated type I interferon (A-IFN). These cytokines increase the inflammatory response to virus and induce complement cascade activation[33]. On the other hand; DM and hyperglycemia accelerate the expression of interferon regulatory factor 5 (IRF5), as it is glucose sensitive. IRF5 was investigated in the influenza A infection. DM, COVID-19, and amyloid may synergize by stimulating a highly inflammatory environment[34].

In relationship with cognitive impairment, multiple mechanisms have already been shown to increase its risk[35]. IL-6 is inversely correlated to cognitive performance in such as the Mini-mental test, and hippocampal volumes[36]. Interferon levels are higher accordingly to a greater Braak score in patients with AD[37]. At last, it is also important to remember the association between DM, insulin, and amyloid, previously described. The olfactory bulb has the highest concentration of insulin and insulin receptors in the brain. The study of ACE2 expression in insulin sensitive tissues began as a search for an explanation of smell loss, a characteristic COVID-19 symptom. Now, as SARS-COV-2 invades the olfactory bulb, a dysregulation of insulin signaling begins[38]. The previously proposed connection between DM and cognition exacerbates. Therefore, secondary to insulin resistance due to DM, insulin-degrading enzyme is unable to remove increased Aβ42 aggregates as innate pathogen response. This promotes greater neuroinflammation, higher oxidative stress, increased BACE function, and most importantly tau protein aggregation into neurofibrillary tangles[9].

At last, a vicious cycle has been suggested. A newly described hypothesis between SARS-COV-2 and DM proposes the expression of ACE2 receptor on pancreatic islets. ACE2 is an important mechanism in the homeostasis of pancreatic B-cell survival and also maintains insulin resistance at its minimum. Therefore, COVID-19 infection leads to an inflammatory state, where persistent hyperglycemia and elevated insulin resistance due to downregulation of ACE2 receptors are created[39,40]. These hypotheses could add another step into the predisposition of developing dementia.

From clinical perspective, severe COVID-19 cases are at higher risk of developing cognitive decline according to 1 year follow-up in Wuhan, China population, intriguingly this population reported higher number of comorbidities compare to non-severe cases, such as diabetes, hypertension, stroke, coronary heart disease, and chronic obstructive pulmonary disease[41]. In addition, from electronic health records in US population, individuals with COVID-19 were in increased risk for new diagnosis of Alzheimer's disease in 12 months after infection[42]. These suggest that comorbidities such as diabetes mellitus may synergize with COVID-19, predispose to cognitive impairment and later to dementia.

In neurocognitive studies, some authors have described executive function, attention, and memory impaired by COVID-19[43-45], which is most likely a vascular dementia pattern, this correlates with silent hypoxia, endothelial dysfunction, and cerebrovascular injury mechanisms; nevertheless, anatomical hippocampal changes are reported in COVID-19 patients and hippocampal and Aβ42 inflammation play a major role in Alzheimer's disease as we described in the previous sections[46].

We suggest that COVID-19 predispose cognitive impairment specially in severe cases and studies show Alzheimer's disease and/or Vascular dementia progression. We hypothesize that infection itself through neuroinflammation, endothelial dysfunction, silent hypoxia, pro-inflammatory state, and reactive oxygen species, predisposes a vascular dementia at the beginning, in case of diabetes mellitus, these pathways could be precipitated, thereafter β-amyloid accumulation and tau protein aggregation begins making patients susceptible to develop Alzheimer's disease, or according to infectious hypothesis of Alzheimer disease COVID-19 triggers this process[47].

Conclusion

The silent access of SARS-COV-2 into the brain could predispose to neurodegenerative disease in many ways. Many questions are still unsolved. Although, many answers, such as the inflammatory response, are currently being elucidated, some like the synergistic effect of diabetes mellitus and COVID-19 in cognitive impairment are establishing a bright light in terms of neurological progress.

Acknowledgment

Ninive Vargas De la Peña for assistance with reviewing and revising the manuscript for grammar and syntax.

Funding

None.

Conflict of interests

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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REVIEW ARTICLE

Association of anemia with Parkinson's disease: a systematic review with meta-analysis of epidemiological studies

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Abstract

Background: *As more risk factors are identified for Parkinson's disease (PD), attention has increased toward hematological disorders, as studies have found increased eryptosis, a process characterized by increased erythrocyte apoptosis, in PD patients. We aimed to synthesize scientific evidence assessing the effect of anemia on future PD incidence.* **Material and methods:** *A systematic review was conducted on multiple electronic databases. Any study that assessed the effect or association between presence of anemia and future PD in a longitudinal manner was considered for inclusion.* **Results:** *Five of the 5525 articles met inclusion criteria; three retrospective cohort studies and two case–control studies. Anemia exposure definition varied among studies. Four of the five studies observed an increased risk for PD; pooled analysis showed a non-significantly increased risk for PD in the cohorts (RR = 1.10; 95% CI = 0.08-15.84) and case–control studies (RR = 1.44; 95% CI = 0.04-52.47). However, heterogeneity among studies was high (I^2 = 97, $p < 0.01$ and I^2 = 85, $p < 0.01$, respectively).* **Conclusion:** *There are few clinical studies on the association of anemia and PD, despite growing preclinical evidence on their connection. In this review, a tendency toward an increased risk for PD in anemic population was observed, with further research needed to reach a definite conclusion.*

Keywords: *Parkinson disease. Anemia. Iron. Gender. Risk factors*

Asociación de la anemia con la enfermedad de Parkinson: una revisión sistemática con meta-análisis de estudios epidemiológicos

Resumen

Antecedentes: *Reciente ha aumentado la atención hacia los trastornos hematológicos en pacientes con Enfermedad de Parkinson, ya que los estudios han encontrado un aumento de la eriptosis, un proceso caracterizado por un aumento de la apoptosis de los eritrocitos, en estos pacientes. Nuestro objetivo fue sintetizar la evidencia científica que evalúa el efecto de la anemia en la incidencia futura de la EP.* ***Material y métodos:*** *Se realizó una revisión sistemática en múltiples bases de datos electrónicas. Se consideró para la inclusión cualquier estudio que evaluara la asociación entre la presencia de anemia y la EP futura de forma longitudinal.* ***Resultados:*** *Cinco de los 5525 artículos cumplieron con los criterios de inclusión;*

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Date of reception: 21-07-2022
Date of acceptance: 21-09-2022
DOI: 10.24875/RMN.22000059

Available online: 16-01-2023
Rev Mex Neuroci. 2023;24(1):19-28
www.revmexneurociencia.com

tres estudios de cohortes retrospectivos y dos estudios de casos y controles. La definición de exposición a la anemia varió entre los estudios. Cuatro de los cinco estudios observaron un mayor riesgo de EP. El análisis combinado mostró un aumento no significativo del riesgo de EP en las cohortes (RR = 1.10; IC del 95 % = 0.08-15.84) y estudios de casos y controles (RR = 1.44; IC del 95 % = 0.04-52.47). Sin embargo, la heterogeneidad entre los estudios fue alta (I2 = 97, p < 0.01 e I2 = 85, p < 0.01, respectivamente). ***Conclusión:*** *Existen pocos estudios clínicos sobre la asociación de anemia y EP, a pesar de la creciente evidencia preclínica sobre su conexión. En esta revisión, se observó una tendencia hacia un mayor riesgo de EP en la población anémica.*

Palabras clave: *Enfermedad de Parkinson. Anemia. Hierro. Género. Factores de riesgo*

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease among human population[1-3]. Characteristic symptomatology involves bradykinesia, tremor, rigidity, and common motor symptoms. With an age increasing prevalence, it affects over 1% of the population over 60 years old[4].

Although risk factors for PD are not yet fully understood, more of them have been identified during the past decade. The importance of identifying more risk factors relies on prevention of PD and on raising focus on new mechanisms involved in its pathogenesis that could help obtain a better understanding of the disease and propose new treatment alternatives.

Among newly described risk factors, focus on the link between PD and hematologic disorders has risen, more specifically on the relation between iron deficiency anemia and future PD incidence. As PD, the prevalence of anemia increases as a function of age after the 5th decade[5], and more than 10% of older adults suffer from this affection[6].

Iron deposition on the substantia nigra of the brain is a hallmark of PD[7,8], conversely, the previous evidence has suggested that PD is associated with lower serum iron levels when compared to healthy controls[9,10]. Studies on animals have shown dopaminergic neurodegeneration in iron deficiency states[11], where, on the contrary, other evidences have implied that elevated iron levels lead to reactive oxygen species (ROS) production, which produce further cellular damage and death[12]. The above-mentioned statements suggest that iron dysregulation plays a role in PD pathogenesis. A study proposed linking iron excess and mitochondria to PD pathogenesis[13,14], as its dysfunction has long been implied in the mechanisms of the disease. This suggests that iron level balance is important for adequate brain function as iron is necessary for mitochondria biogenesis[15].

In addition to the previously mentioned, a study observed erythrocytes of 30 PD patients and observed changes in their morphology, hypothesizing that the inflammatory signaling molecules involved in PD pathophysiology may affect the hematology system of these patients, which could be used as potential prognostic or diagnostic indicator[16]. It is important to remark that iron-deficiency and anemia are different events; however, the former could be a possible pathway for the relation of the latter with PD. Two clinical trials have already studied the efficacy, safety, and tolerability of erythropoietin on patients with PD[17,18]; nevertheless, further studies are needed to corroborate these results.

Some clinical studies evaluating the association between presence of anemia and risk for further PD incidence have been published; however, results have been inconsistent, and no solid conclusion has been reached. Therefore, to further clarify this topic, we performed a systematic review to summarize the available evidence on clinical studies evaluating the relation between anemia and PD.

Material and methods

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. A previous protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42020150456.

Eligibility criteria

Prospective or retrospective cohorts and case–control studies performed on humans that directly compared the incidence of PD in anemic population (according to the World Health Organization criteria; hemoglobin [Hb] levels < 12 g/dL in women and < 13 g/dL in men[19]) versus non-anemic population or evaluated the association between both conditions.

Information sources

A systematic search strategy using a combination of keywords and MesH terms regarding the population, intervention, comparison, and outcomes of interest was

developed by an experienced librarian, along with the main researchers of the study. This search was performed in MEDLINE, Scopus, EMBASE, Web of Science, and the COCHRANE Central Register for Clinical Trials (CCRCT). The time lapse considered for our search was from each database inception date until March 2020. In addition, an update was made in November 2021 (see Supplementary Material for search strategy).

Study selection

This process was conducted by four reviewers and included a title/abstract and a full-text screening phase. Before each phase, a pilot study was conducted to ensure adequate inter-rater agreement. Any disagreement that appeared in the tile/abstract phase was passed on to the full-text phase, where disagreements were resolved by consensus or involvement of another reviewer. After concluding each phase, kappa index was calculated to ensure inter-rater reliability (> 0.7). Articles that were included by the reviewers in the full-text phase were included for qualitative analysis.

Data collection process

Data extraction from studies fulfilling validity criteria was conducted using a template form to standardize extraction. The data extracted were as followed: study identification data (author, year of publication, place of study conduction, and study design), population identification (baseline characteristics), and description of intervention and study outcomes (incidence rates for PD in anemic and non-anemic population, and for potential confounding variables adjusted). This process was performed by two researchers in an independent and duplicate manner, where any disagreement was resolved by intervention of a third reviewer. A final version of the data form was approved by all researchers.

Quality assessment in individual studies

Three reviewers working independently and in duplicate assessed the methodological quality of each study included in the review using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies and Case–Control Studies[20]. This scale evaluates three domains: selection, comparability, and outcome. For our study, a maximum of eight stars was considered as maximum score for Cohort Studies, whereas a maximum of nine stars for case–control studies, indicating this greater quality. Concerning cohort studies, the last question of the "Outcome" section with regard to the adequacy of follow-up did not apply to the included studies due to their retrospective nature.

Outcomes' measure

A qualitative synthesis is provided, where the characteristics and findings from each study are explained and summarized. Categorical data were reported as frequency and percentage, whereas numeric data as mean and standard deviation. Incidence of PD was reported for each group divided by sex and/or in total population when available. Risk of developing PD is reported in total anemic population or/and divided by sex as unadjusted hazard ratios (HR) with their respective confidence intervals (95% C.I.). HR for PD adjusted for confounders was also reported when available.

Statistical analysis

When enough data were available (more than one study reporting on the outcome), random effect meta-analysis was performed to estimate exposure's effect on PD incidence. $p < 0.10$ for the test of heterogeneity across studies and > 50% for the measure of inconsistency (I^2) was considered as high heterogeneity. The primary analysis used an inverse-weighted variance random-effect meta-analysis to account for the uncertainty in the location of the mean of different effects between studies. When events were evaluated, we used a modified Mantel-Haenszel meta-analysis with Peto's method. Meta-analyses were performed using R (Version 4.0).

Results

Initially, database search identified 4153 references. Of these, 4136 studies were excluded, because they did not meet the inclusion criteria. Subsequently, 17 full-text articles were reviewed for possible eligibility and 13 were excluded for different reasons, mainly as they did not assess the intervention of interest. At the update, from March 2020 to November 2021, data search identified 1097 references, and 1093 were excluded at the abstract screening. Afterward, four full-text articles were assessed, and three of them were excluded for being duplicated. Finally, five studies met the inclusion criteria and were included in our final qualitative synthesis; three of them were retrospective cohorts; and two were case–control studies[21-25].

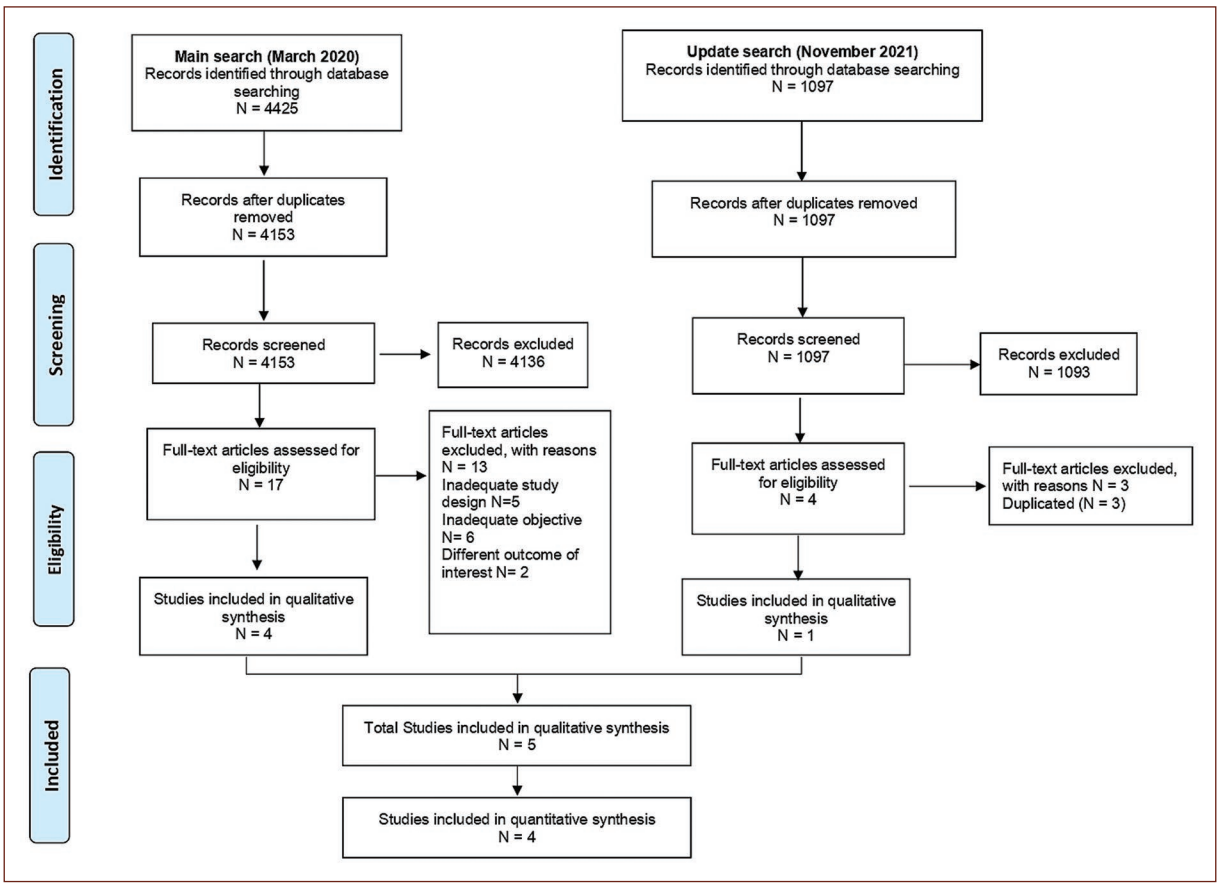

Figure 1. Flowchart of the number of identified and included studies.

The complete study selection process is depicted in Figure 1.

Study characteristics

Three retrospective cohorts were included; all of them retrieved their data from healthcare databases in Israel, Korea, and Taiwan and compared PD incidence between anemic population and a control group. Mean follow-up varied between across them, ranging from 5.0 to 8.8 years and mean age of the studied population ranged between the fifth and sixth decade. Only one cohort (Rozani et al.) had an almost balanced population based on gender (47.4% men and 52.6% female). Two case-control studies were included; both compared anemia diagnoses between a group of patients with PD and a group of matched healthy controls; one retrieved its data from a previous epidemiological project from US, while the other employed a Korean national healthcare cohort. From the five studies, two of them reported patient comorbidities such as hypertension, diabetes mellitus, and hyperlipidemia (Table 1).

Incidence and risk of Parkinson disease

Risk for PD among anemic population

Cho et al. and Hong et al. both reported an adjusted multivariate analysis assessing PD risk among population who had a diagnosis of anemia, the former reported a decreased PD risk among this population (HR = 0.89 95% CI = 0.81-0.99), whereas contrasting results were reported on the latter (HR = 1.36 95% CI = 1.22-1.52). Rozani et al. analysis was stratified by gender; therefore, general PD risk was not reported (Table 2a). Moreover, in the case–control study performed by Savica et al., greater odds for having a diagnosis of anemia were associated with the presence of PD when compared to healthy controls (unadjusted OR = 2.00, 95% CI = 1.31-3.06). This was supported in the study by Kim et al., with an adjusted OR for the total population of 1.09, 95% CI = 1.01-1.18 (Table 2b).

Table 1. Baseline characteristics of included studies: (a) cohort studies and (b) case-control studies

A. Cohort studies									NOS score
Author, year	Country	Population number	Follow-up (years)	Age (mean, SD)	Female (n, %)	Hypertension (n, %)	Diabetes Mellitus (n, %)	Hyperlipidemia (n, %)	
Rozani et al., 2019	Israel	474,129*	8.8 ± 3.6	Male: 48.7 (9.3) Female: 47.7 (9.7)	249,181 (52.6)	NR	NR	NR	8
Cho et al., 2020	Korea	AN: 217,086 CO: 2,024,033	5.0	AN: 59.6 (9.4) CO: 57.17 (7.2)	AN: 129,962 (59.9) CO: 699,075 (34.6)	AN: 72,438 (33.4) CO: 704,394 (34.8)	AN: 25,174 (11.6) CO: 247,706 (12.3)	AN: 40,984 (18.9) CO: 468,511 (23.2)	8
Hong et al., 2016	Taiwan	AN: 86,334 CO: 86,334	6.6	AN: 56.4 (11.5) CO: 56.4 (11.5)	AN: 65,526 (75) CO: 65,526 (75)	AN: 26,018 (30.1) CO: 26,036 (30.2)	AN: 13,362 (15.5) CO: 26,037 (30.2)	AN: 17,994 (20.8) CO: 18,001 (20.9)	8

B. Case-control studies						
Author, year	Country	Population number	Age (mean, range) (years)	Female (n, %)	Median duration of enrollment (years)	NOS score
Savica et al., 2009	United States of America	Cases: 196 Controls: 196	71 (41-97)	75 (38.3)*	38	8
Kim et al., 2021	Korea	Cases: 5844 Controls: 23,376	NR	3094 (52.9)	13	8

*Total population; AN: anemic population, CO: control population; NR: not reported; NOS: Newcastle-Ottawa scale.

Gender stratified risk for PD

In their unadjusted analysis, both Rozani et al. and Cho et al. found a greater risk for PD among male population with diagnosis of anemia (HR = 1.19 95% CI = 1.04-1.37; HR = 1.57 95% CI = 1.37-1.79); however, in their adjusted analysis, Cho et al. found no associated risk for PD among them (HR = 0.88 95% CI = 0.77-1.02). Rozani et al. did not report an adjusted analysis. Regarding female population with diagnosis of anemia, no higher risk of PD incidence was observed in neither of these studies (Table 2).

Subgroup analysis

To perform the subgroup analysis, the cohorts and case-controls studies were pooled in a separate way. In the cohort studies, the pooled relative risk of anemia and PD was 1.10; 95% CI = 0.08-15.84, and it is presented in figure 2a. On the other hand, the pooled OR of the case–control studies was 1.44; 95% CI = 0.04-52.47 (Fig. 2b). High heterogeneity was observed among included studies.

Certainty of evidence

All studies, both cohort and case-control, were classified as high-quality studies according to Newcastle-Ottawa Quality Assessment Scale (Table 1).

Discussion

In this systematic review, we aimed to assess the currently available clinical evidence which evaluated a possible association between a diagnosis of anemia and PD. We found three retrospective cohorts that reported PD risk associated to presence of anemia and two case-control studies that reported odds of having anemia when PD was present. Among the two cohorts who reported PD risk among general population with

Table 2. Parkinson's disease incidence among included studies: (a) cohort studies and (b) Case-control studies

A. Cohort studies									
Author, year	**PD incidence in male group**	**HR (95% CI)**	**aHR (95% CI)**	**PD incidence in female group**	**HR (95% CI)**	**aHR (95% CI)**	**PD incidence in total population**	**HR (95% CI)**	**aHR (95% CI)**
Rozani et al., 2019	AN: 1.2%Ω CO: 0.6%Ω	1.19 (1.04-1.37)	NR	AN: 0.3%Ω CO: 0.4%Ω	1.02 (0.95-1.09)	NR	NR	NR	NR
Cho et al., 2020	AN: 236 (0.3%) CO: 2,258 (0.2%)	1.57 (1.37-1.79)	0.88 (0.77-1.02)	AN: 219 (0.1%) CO: 1,131 (0.1%)	1.04 (0.91-1.21)	0.91 (0.78-1.05)	AN: 455 (0.2%) CO: 3,389 (0.16%)	1.24 (1.13-1.37)	0.89 (0.81-0.99)
Hong et al., 2016	NR	NR	NR	NR	NR	NR	NR	NR	1.36 (1.22-1.52)

B. Case-control studies						
Author, year	**Incidence of anemia in cases**	**Incidence of anemia in controls**	**OR total population (95% CI)**	**OR (95% CI) in male group**	**OR (95% CI) in female group**	**aOR total population (95% CI)**
Savica et al., 2009	86 (43.9%)	54 (27.6%)	2.00 (1.31-3.06)	1.52 (0.88-2.64)	2.91 (1.47-5.77)	2.17 (1.40-3.37)* 1.74 (1.02-2.97)**
Kim et al., 2021	1090 (18.7%)	3944 (16.9%)	1.13 (1.05-1.23)	< 70 years: 1.44 (1.22-1.70) > 70 years: 1.14 (0.97-1.34)	< 70 years: 1.05 (0.92-1.21) > 70 years: 1.04 (0.90-1.20)	1.09 (1.01-1.18)***

HR: Hazard ratio, 95% CI: 95% confidence interval, aHR: adjusted Hazard ratio, NR: not reported, Ωabsolute incidence not reported.
OR: odds ratio, 95% CI: 95% confidence interval, aOR: adjusted odds ratio.
*adjusted for smoking.
**adjusted for pesticide exposure.
***adjusted for obesity, smoking, blood glucose, head trauma and alcohol exposure.

anemia diagnosis, results were contrasting. Furthermore, when analyzed by gender, unadjusted analyses revealed higher risk for PD among male anemic population; however, the only adjusted analysis, which was reported by Cho et al. did not support this finding. No higher risk for PD was observed among female anemic population. In the case–control studies, individuals with PD had higher odds of having diagnosed anemia than patients without PD diagnosis[21,25]. Overall, the pooled relative risk observed in the included studies suggested a not significant increased risk for PD in anemic populations.

Analyzing the implications of the included studies, two cohorts and one case-control study proposed anemia to be a prodromal marker for PD. This, as it is acknowledged that this disease begins years before dopaminergic degeneration in the substantia nigra[26]. Thus, the presence of anemia may be originated by the inflammatory, oxidative stress changes in the prodromal stages of PD[27,28]. Moreover, we suggest a bidirectional model, in which anemic conditions might further contribute to PD related to oxidative stress, inflammation, and iron dysregulation. Nonetheless, when considering the study by Cho et al., the authors concluded a protective effect of anemia in future PD incidence, contradicting the conclusions of the other studies. However, one important aspect that must be considered to interpret these conclusions is the definition of exposure in these included studies.

The previously mentioned is rather important as most studies define the exposure (presence of anemia) in heterogeneous ways (Table 3). Rozani et al. calculated the mean annual hemoglobin levels of each included individual, with a mean number of hemoglobin tests of

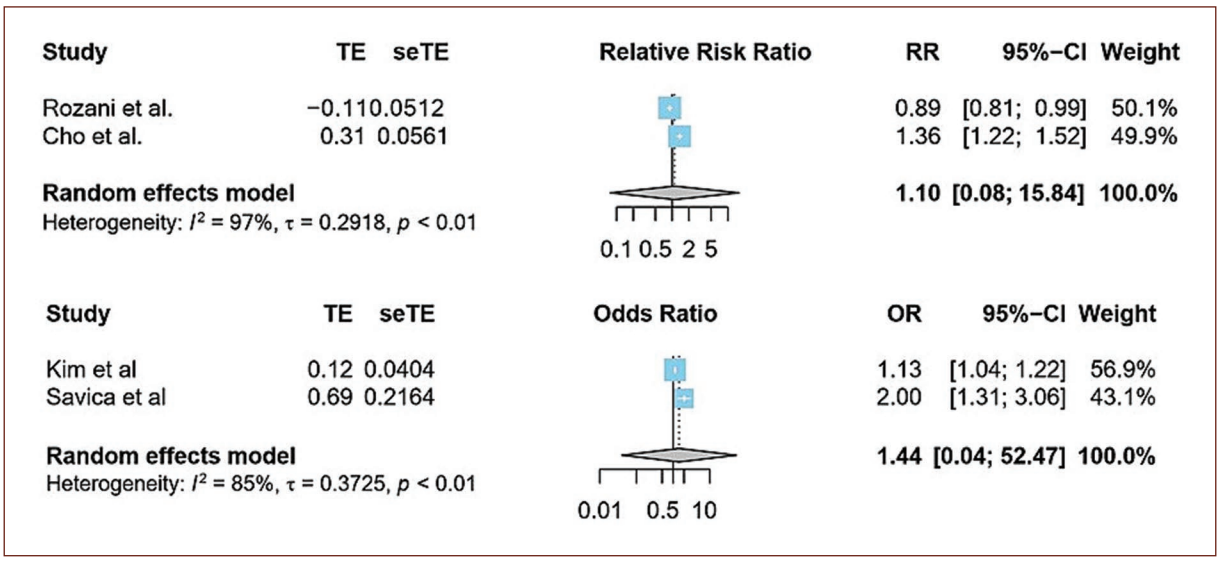

Figure 2. A: forrest plot displaying risk ratios and 95% confidence intervals of developing Parkinson's disease in anemic versus non-anemic population in cohort studies. **B:** forrest plot displaying pooled odds ratio of previous anemia exposure and Parkinson's disease risk in case-control studies.

Table 3. Definition of anemia exposure for each included study

Study	Anemia definition
Cho et al. 2020	One-time result at baseline (Hb < 13g/dL M, < 12 g/dL W)
Rozani et al. 2019	Mean annual Hb classified as anemia (Hb < 13g/dL M, <12 g/dL W)
Hong et al. 2016	At least two diagnostic claims for anemia or iron supplementary medication in a 7-year period.
Savica et al. 2009	1) A diagnosis of anemia ever mentioned in medical records or, 2) Hb < 13 g/dL M, < 12 g/dL W persisting over a 6-week period to exclude acute blood related anemia.
Kim et al. 2021	The most recent hemoglobin concentration before the diagnosis of PD (index date), Hb < 13 g/dL in M and < 12 g/dL in W

Hb: hemoglobin, M: men, W: women.

6 ± 3 per individual during the entire follow-up, where if the mean of one annual Hb measurement was below the threshold for anemia, exposure was considered positive. Moreover, Hong et al. required at least two diagnostic claims for anemia or iron supplementary therapy during a time lapse of 7 years. Savica et al. study required a diagnosis of anemia ever mentioned, or hemoglobin levels under anemic values according to the World Health Organization persisting over a 6-week period to exclude blood loss related values. Compared to these exposure criteria, Cho et al. and Kim et al. used a one-time hemoglobin result under anemic conditions to define anemia, which raises questions on the validity of the exposure's effect on the measured outcome, as a one-time reported result might not reflect its actual effect. In this manner, the former studies, which reported an increased risk for PD incidence and used multiple hemoglobin or diagnostic claims, might reflect better the exposure's effect on the measured outcome. However, a limitation that must be highlighted in the study by Rozani et al. is the lack of adjustment for confounding variables, as the other cohort studies and case–control studies did perform. This is important as PD is influenced by various factors that have been observed in meta-analysis and observational studies such as diabetes mellitus, hypertension, pesticide exposure, and smoking[29-32].

PD clinical characteristics, progression and risk factors follow sex-specific differences[33]. As an example, in this review, we found that Savica et al. reported anemia to be more associated to PD among female population, whereas lifestyle and occupational risk factors were more related to the disease in male population[34]. As PD, anemia also has gender-dependent differences as its prevalence is higher among female population[35,36]; nonetheless, no increased risk for PD was observed for female anemic population in neither of our included cohort studies. Whether gender-related differences are present in the

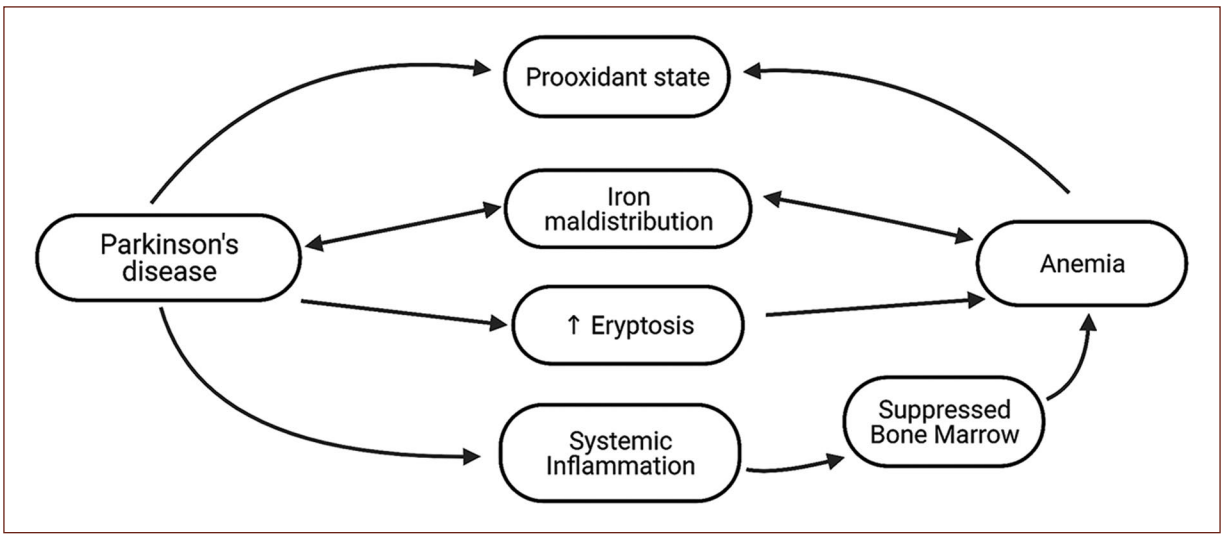

Figure 3. Diagram of the potential mechanisms in the association of anemia and Parkinson's disease.

relation of anemia and future PD incidence is a non-clarified issue to date. In this review, no conclusive evidence regarding the abovementioned was reached.

The possible pathological pathways that may explain anemia association with PD are inflammation, oxidative stress, and iron metabolism (Fig. 3). The previous evidence has assessed hemoglobin and iron levels on patients with PD, showing inconsistent results, as some studies have shown hemoglobin levels to decreases as PD progresses, but others exhibited no difference in neither hemoglobin nor iron levels compared to controls[37-39]. Nonetheless, as systemic inflammation has been recognized to contribute to PD pathogenesis[40], and inflammatory cytokines have been shown to suppress bone marrow and inhibit erythropoietin-induced erythrocyte maturation[41], this could possibly explain the low red blood cell count and its relation with future PD.

Considering oxidative stress, some evidence has shown that red blood cells of PD patients lack superoxide dismutase, an enzyme responsible for counteracting oxidative stress, and are as a result susceptible to stress-induced damage[42,43]. Regarding iron-deficiency anemia, a study showed that patients with this condition have a higher oxidant and a lower antioxidant activity compared to controls, which normalizes to control levels after iron treatment[44]. In addition, a review described the pro-oxidant shift that occurs in anemic conditions, which is further worsened by a weakened antioxidant capacity in this environment[45]. Thus, anemia might contribute to the oxidant conditions that are needed for PD pathogenesis, whereas red blood cells' changes in PD patients might support eryptosis[16], showing a hypothetical bidirectional association.

Considering the oxidant properties of iron[46] and that its deposition in the substantia nigra has been observed in PD patients[7], its metabolism could be another element in the relationship between anemia and future PD incidence. Contrary to the hypothesis that arises when considering the oxidant properties of iron, where anemia and low serum iron levels should apparently contribute to a decreased risk for PD, evidence has shown that increased levels of serum iron were associated with a reduced risk for future PD[9,47]. The latter could be supported considering that iron is a cofactor for the enzyme L-tyrosine hydroxylase, which is responsible for dopamine synthesis[48]. Animal models of iron deficiency have shown altered dopamine metabolism and function[49,50], which could explain the protective effect of increase serum iron levels on PD incidence. Moreover, an iron maldistribution process could also explain the increased deposition in substantia nigra but the low serum iron levels[51], which might affect erythropoiesis, exhibiting a possible link between anemia and PD incidence.

Finally, another element linking both pathologies is red cell distribution width (RDW), which is commonly increased in iron-deficiency anemia as sign of anisocytosis[52]. A study showed patients with PD have increased RDW levels compared to controls, whereas another correlated RDW to PD progression[53,54]. The former compared hemoglobin and white blood count to controls, and no difference except RDW was shown. Although RDW has been shown to be an inflammatory marker[55,56], its increase

in PD patients could be related to an iron maldistribution process and could demonstrate that patients with PD experience disruption in erythrocyte cell line, possibly linking iron metabolism, and PD.

This study has some limitations. The high heterogeneity of the pooled studies limits the interpretation of the pooled analysis. Moreover, available evidence regarding our research questions was scarce and this could seriously limit our findings. Another consideration is that patients with decreases in hemoglobin values not reaching anemic WHO cutoffs might have inflammatory and iron maldistribution processes that might contribute to PD and could not be evaluated.

Conclusion

A non-significantly increased pooled risk for PD was observed in the included cohort and case–control studies. The pathophysiological mechanisms related to iron maldistribution, oxidative stress, and systemic inflammation might explain this observed tendency. Prospective studies with various hemoglobin measurements under anemic values during follow-up and control of confounding variables are needed to corroborate and further confirm the idea of anemia as prodromal marker of PD.

Funding

None.

Conflict of interests

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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