v. 4, n. 72, 2024

International Journal of Health Science

ON THE ASSOCIATION OF ANEMIA IN PATIENTS WITH PREVIOUS NEUROLOGICAL PATHOLOGIES

Luiza Caffarate Sarturi
Franciscan University – UFN
Santa Maria – state of Rio Grande do Sul
ORCID: 0000-0003-4675-5647

Vinicius Freitas Pedron
Franciscan University – UFN
Santa Maria – state of Rio Grande do Sul
ORCID: 0000-0002-9097-7960

Maria Elizabeth Bonorino Bortolanza
Franciscan University – UFN
Santa Maria – state of Rio Grande do Sul
ORCID: 0009-0001-9116-1533

João Francisco Pozzebon Dotto
Franciscan University – UFN
Santa Maria – state of Rio Grande do Sul
ORCID: 0009-0008-7798-7479

Lillian Cocco
Franciscan University – UFN
Santa Maria – state of Rio Grande do Sul
ORCID: 0009-0004-7947-0036

Gisre Merg Saraiva
Franciscan University – UFN
Santa Maria – state of Rio Grande do Sul
ORCID: 0009-0006-3999-2862

Pedro Caffarate Sarturi
Franciscan University – UFN
Santa Maria – state of Rio Grande do Sul
ORCID: 0009-0006-2123-5337

Juliana Silveira
Franciscan University – UFN
Santa Maria – state of Rio Grande do Sul
ORCID: 0000-0001-7469-2482

Abstract: Anemia is characterized by a decrease in the hemoglobin mass in an individual, laboratory-reported as below 12 g/dL. This pathological condition is considered the main disorder among diseases of the hematologic system, affecting approximately 33% of the world's population. Anemia, regardless of its etiology, causes, among several symptoms, fatigue, weakness, and reduced cognitive function. Iron, in addition to being part of erythropoiesis, is essential for several brain cellular processes, including neurotransmitter synthesis, mitochondrial function, and neuronal myelination. It remains unclear to what extent hemoglobin levels are directly responsible for the increased risk of neurological deficits (e.g., by reduced tissue oxygenation), or whether the associations can be explained by underlying or concomitant vascular and metabolic alterations, mainly involving iron, folate, and vitamin B12. This study aimed to evaluate the prevalence of anemia in patients with previous neurological diseases, including dementia syndromes, ischemic stroke (CVA), epilepsy, and Parkinson's disease. This was a quantitative, descriptive, retrospective, documentary, population-based, or epidemiological study based on information collected from medical records at the Neurology outpatient clinic of Hospital Casa de Saúde (HCS) through a questionnaire formulated for this purpose. After data collection, quantitative, statistical, and descriptive analysis was performed. There was no correlation between the neurological diseases studied and anemia, according to Pearson's correlations. Although there was no relationship between the pathologies studied, the need for future research is highlighted given the potential interaction between anemia and neurological manifestations.

Keywords: Anemia. Dementia. Epilepsy. Ischemic CVA. Parkinson's.

INTRODUCTION

Anemia, a prevalent and multifactorial clinical condition, significantly impacts the quality of life of affected individuals. Regardless of its origin, it is the main disorder among hematological diseases, affecting 32.9% of the global population (DE SANTIS, 2019; MCLEAN, 2009; UNICEF, 2004). As reduced hemoglobin levels represent a global health challenge, affecting 1.6 billion people globally, the prevalence of anemia ranges from approximately 10% after age 65 in Europe and the Americas to up to 45% in nations in Africa and Southeast Asia (WOLTERS, 2019).

The primary symptoms associated with anemia include fatigue, weakness, changes in the skin and mucous membranes, reduced cognitive function, decreased growth, and drowsiness, among others, making the condition often nonspecific. Although, unquestionably, adequate brain function depends on essential nutrients for erythropoiesis, such as vitamin B12 and iron (Fe2), the association between anemia and neurological diseases remains partially understood (WOLTERS, 2019). For this reason, hematological evaluation emerges as an important measure for all patients presenting nonspecific symptoms, as well as for those who, even asymptomatic, have a clinical condition susceptible to the adverse effects of anemia (FABIAN, 2007).

Considering the long-term and, in some cases, silent consequences of anemia, the World Health Organization (WHO) and the Pan American Health Organization (PAHO) have established as a priority the commitment to combat this condition throughout the American continent (FABIAN, 2007). With a notable relationship of 34% increased probability of patients with anemia developing some type of dementia, it becomes imperative to explore this relationship in more depth (WOLTERS, 2019).

LITERATURE REVIEW

ANEMIA

Anemia is a pathological condition in which there is a decrease in erythrocyte mass (DE SANTIS, 2019), demonstrated in the laboratory as hemoglobin less than 12 g/dL in the general population (UFRJ, 2022). The reference value of hemoglobin for the diagnosis of anemia should be individualized according to age, sex (13 and 12 g/dL for men and women, respectively), and skin color (ROSENFELD, 2019). The prevalence of anemia varies from 10% after 65 years of age in Europe and the Americas to 45% in countries in Africa and Southeast Asia (WOLTERS, 2019). Recent data indicate in Brazil a prevalence of anemia of up to 50% in children aged 6 to 60 months, 15 to 30% in pregnant women, 20% in women of childbearing age, and 20% in adolescents (FABIAN, 2007).

Anemia é definida como uma condição patológica em que ocorre diminuição da massa eritrocitária (DE SANTIS, 2019), demonstrada laboratorialmente como uma hemoglobina menor que 12 g/dl na população em geral (UFRJ, 2022). Sabe-se hoje que o valor de referência da hemoglobina para diagnóstico de anemia deve ser individualizado conforme idade, sexo (13 e 12 g/dL para homens e mulheres, respectivamente) e cor da pele (ROSENFELD, 2019). A prevalência de anemia varia de 10% após os 65 anos na Europa e nas Américas até 45% em países da África e do Sudeste Asiático (WOLTERS, 2019). Dados recentes apontam no Brasil prevalências de anemia de até 50% em crianças de 6 a 60 meses, 15 a 30% em gestantes, 20% em mulheres em idade fértil e 20% em adolescentes (FABIAN, 2007).

Regardless of the etiology, anemic syndrome presents common symptoms, including fatigue, weakness, skin and mucous membrane changes, reduced cognitive

International Journal of Health Science ISSN 2764-0159 DOI https://doi.org/10.22533/at.ed.1594722402084

function, growth retardation, and drowsiness (BUENO, 2006). The reduction in hemoglobin concentration compromises oxygen transport to all tissues, reducing work capacity, physical performance, and resistance to fatigue in anemic people (FABIAN, 2007). We must take into account that anemia, in many situations, is an insidious disease with long-term repercussions, including neurological changes such as dementia (DOMINGUES, 2021; ZAGO et al, 2013).

Once anemia is identified, it is essential to classify it in order to establish its cause in order to treat it. There are several classifications to guide its etiological investigation, one of the most important classifications is based on the functioning of the bone marrow, which divides anemias into hyperproliferative and hypoproliferative, the latter being more prevalent and of greater relevance in clinical practice (DE SANTIS, 2019). This classification is based on the number of reticulocytes and the functioning of the bone marrow. In addition, anemias can be classified according to the morphology and amount of pigment in the red blood cells as microcytic and hypochromic, normocytic and normochromic, or macrocytic (DE SANTIS, 2019; UFRJ, 2022).

HYPOPROLIFERATIVE ANEMIA

The hypoproliferative classification is defined by the reduced number of reticulocytes (immature red blood cells), and, therefore, it is concluded that the bone marrow has low activity and impaired reticulocyte synthesis. Iron deficiency, megaloblastic, and anemia of chronic disease are included in this classification (DE SANTIS, 2019; UFRJ, 2022; ZAGO et al, 2013, MONTEIRO, 2019).

Iron deficiency anemia

Iron deficiency anemia is the most prevalent type of anemia, affecting more than one billion people worldwide (DE SANTIS, 2019). Most of it is microcytic and hypochromic and is characterized by a reduction in hemoglobin levels due to a deficiency in the body's iron stores. Iron is necessary for the production of the heme group that makes up the four globin chains responsible for forming hemoglobin. The most common signs and symptoms of iron deficiency anemia are brittle nails, angular cheilitis, fatigue, and blue sclera (SANT'ANNA, 2021; ZAGO et al, 2013).

Iron deficiency can occur due to excessive blood loss, decreased absorption in the gastrointestinal tract, or increased demand (SANT'ANNA, 2021; ZAGO et al, 2013). Deficiency due to lack of intake of this metal is not common, except in children on a diet restricted to milk for long periods (DE SANTIS, 2019). Considering that renal and gastrointestinal tract (GIT) excretion is not part of iron metabolism in a normal individual, as is the case with other ions, iron deficiency anemia in adults is due to excessive blood loss such as increased menstrual bleeding or bleeding from the GIT. In short, iron deficiency anemia results from some underlying clinical condition that should be investigated (SANT'ANNA, 2021; ZAGO et al, 2013; DE SANTIS, 2019).

Anemia of Chronic Disease

Anemia of chronic disease, also called inflammatory anemia, is the second most prevalent type of anemia. It can be microcytic and hypochromic or normocytic and normochromic (DE SANTIS, 2019). This is a hematologic response to a systemic insult, such as inflammatory diseases, subacute infections, or neoplasms (ZAGO et al, 2013).

Its pathophysiology includes 3 main mechanisms: a relative iron deficiency since

the increase in inflammatory cytokines blocks iron transport; suppression of erythropoiesis; and reduced red blood cell survival. The symptoms of this type of anemia are more related to the underlying disease than the anemia (ZAGO et al, 2013; DE SANTIS, 2019).

The diagnosis of this type of anemia is often difficult due to its concomitant deficiency of some element necessary for erythropoiesis, excessive bleeding, or the fact that the inflammatory phenomenon is not evident. In ideal situations, the treatment of this pathology is based on compensating for the underlying disease (DE SANTIS, 2019).

Megaloblastic anemia

In addition to inflammatory and iron deficiency anemias, megaloblastic anemia is also common in the world population. This anemia is characterized by reduced hemoglobin levels and macrocytosis, where red blood cells have an average size larger than normal.

This type of anemia is characterized by megaloblastosis, which means an increase in red blood cells due to a deficiency in DNA synthesis. There are two major etiologies for this type of anemia, namely vitamin B12 deficiency and folic acid deficiency. Among these etiologies, megaloblastic anemia due to vitamin B12 deficiency often causes reversible dementia as one of its main symptoms, in addition to paresthesias and proprioceptive disorders. The treatment of this hematological condition is done by replenishing the deficiency causing the drop in hemoglobin

HYPERPROLIFERATIVE ANEMIA

Hyperproliferative anemias are those in which there is reticulocytosis in the blood count, that is, the number of reticulocytes is increased. This means that the bone marrow is suitable and, as a compensation mechanism, there is an increase in erythropoiesis due to increased peripheral hemolysis. Sickle cell anemia and hemolytic anemias are within this classification (FAILACE, 2009).

Sickle Cell Anemia

Sickle cell anemia is an inherited genetic disease characterized by a mutation in the hemoglobin gene, resulting in the production of an abnormal form of hemoglobin, known as hemoglobin S (HbS). This condition mainly affects individuals of African origin, although it can also occur in people of other ethnic origins, including Mediterranean, Arab, Indian, and Latin American people (ANVISA, 2022; SENA & TOSTES, 2023). Estimates indicate that around 300,000 to 400,000 children are born annually with sickle cell anemia worldwide; this estimate is 70,000 to 100,000 in Brazil (SPSP, 2023).

The most common symptoms include pain crises (known as vaso-occlusive crises), hemolytic anemia, fatigue, jaundice, frequent infections, delayed growth and development in children, and complications such as ischemic stroke, splenic infarction, acute chest syndrome, and lower limb ulcers. The main pathophysiology of these complications is vaso-occlusive crises (ANVISA, 2022; SENA & TOSTES, 2023).

NEUROLOGICAL DISEASES

Neurological diseases affect approximately 30% of the Brazilian population, and this prevalence increases with aging (Ministério da Saúde, 2022). However, the pathophysiology of different neurological diseases is complex and may be correlated with erythropoiesis

factors, such as iron and vitamin B12. Therefore, some neurological diseases may be developed or aggravated by other pathologies, such as hematological diseases.

Many of the anemia groups mentioned above produce, in addition to the classic symptoms, neurological symptoms, such as reversible dementia. In megaloblastic anemia, for example, caused by vitamin B12 deficiency, neurological changes occur, including paresthesias, proprioception, and cognition disorders. Both brain function, neurotransmitter synthesis, and erythropoiesis depend on iron and vitamin B12 for proper functioning (NETO, 2008; WOLTERS, 2019).

As for the direct effects of this relationship, reduced oxygenation can lead to hypoxia and subsequent inflammation with deleterious effects on neurons. The close correlation of hemoglobin with cerebral blood flow supports the notion of a compensatory mechanism that maintains cerebral oxygen supply and may be crucial in cases of impaired oxygen extraction and failures in autoregulatory mechanisms in cerebral small vessel disease. Brain imaging findings suggest that white matter structure connectivity, cerebral perfusion, and microhemorrhages may act as pathophysiological substrates in these associations (WOLTERS, 2019).

Iron is essential for several brain cellular processes including neurotransmitter synthesis, mitochondrial function, and neuronal myelination. However, the central question that has not been elucidated is to what extent hemoglobin levels are directly responsible for this increased risk (e.g., reduced tissue oxygenation), or whether the associations can be explained by underlying or concomitant vascular and metabolic changes, mainly involving iron, folate and vitamin B12 (WOLTERS, 2019).

DEMENTIA

Brazil is undergoing a demographic transition due to the decrease in birth and mortality rates associated with the increase in life expectancy, therefore the Brazilian population, in general, is aging (SANTOS, 2020). In Brazil, in 2022, there were approximately 32.1 million people aged 60 or over and 2 million people living with some dementia syndrome (Ministério da Saúde, 2023; Ministério dos Direitos Humanos e da Cidadania, 2023). Due to the aging of the Brazilian population in general, chronic non-communicable diseases (NCDs), including dementia, are standing out as a public health challenge (SANTOS, 2020).

Dementia is a syndrome characterized by a progressive deficit in cognitive function, mainly memory loss, being intense enough to cause interference in social, occupational, and self-care activities (GALLUCCI, 2005; LEAL, 2022). In the etiological investigation, one should try to differentiate reversible dementia, which would include vitamin B12 deficiency, thyroid disease, and neurosyphilis, from irreversible or neurodegenerative dementias (LEAL, 2022). There are several known causes of irreversible dementia; the most common is Alzheimer's disease (AD) (50 to 70% of cases, according to TALMELLI et al.) and dementia with vascular causes (approximately 45% of cases, according to BOOF et al.).

Even with few studies on the association of anemia and cognitive decline, low hemoglobin is an important risk factor for the development of dementia and cognitive decline. Regarding the pathophysiology of this association, it is probably due to low cerebral oxygenation for a sustained period or that low hemoglobin causes a silent cerebral accident, such as a small ischemic CVA or a transient ischemic attack (TIA), leading to deleterious effects on neurons and, ultimately, cognitive decline (PETERS, 2008).

Anemia is associated with up to a 34% increased risk of developing dementia and 41% for AD (WOLTERS, 2019). In addition, anemia can be a factor in worsening the outcome of patients with a previous diagnosis of AD - worsening of neurocognitive symptoms in the presence of anemia. Given that there is currently no curative therapy available for Alzheimer's disease dementia, identifying modifiable risk factors is crucial for preventive and therapeutic interventions to delay the onset of cognitive decline (JIANG, 2021).

EPILEPSY

Epilepsy is among the 4 most common neurological diseases in the world, affecting approximately 50 million people of all ages (LEAL, 2022, WHO, 2019). It is 2 to 3 times more common in people with sickle cell anemia (PADDA, 2021).

It is a chronic disease characterized by recurrent epileptic seizures, which are brief episodes of involuntary movements that can involve the entire body (generalized) or a part of it (focal), sometimes accompanied by loss of consciousness and sphincter control (WHO, 2019). Its etiology is classified as structural, genetic, metabolic, infectious, immune, and unknown, and they can coexist (LEAL, 2022; ILAE, 2017).

Febrile seizures are one of the risk factors for developing epilepsy, occurring mainly in children aged 6 to 60 months (MACHADO, 2018). Iron deficiency anemia increases the risk of febrile seizures in children, probably because it is an essential factor for growth and development (PADDA, 2021). In addition to anemia contributing to the emergence of febrile seizures in children, low hemoglobin is one of the several adverse effects caused by anticonvulsant drugs that must be investigated and managed appropriately to reduce patient risks and symptoms (PADDA, 2021).

ISCHEMIC STROKE (iCVA)

iCVA is one of the main causes of mortality and morbidity in the world. Due to the demographic transition of developing countries, the aging of the general population, and the lack of control of the main risk factors (hypertension, DM, and dyslipidemia), there is an increase in the incidence and prevalence of this pathology. It is defined as a sudden episode of cognitive, sensory, and/or motor changes due to focal or global disturbance of brain function of an ischemic vascular nature (LEAL, 2022; Ministério da Saúde, 2013).

Defining the etiology of iCVA is extremely important to direct treatment and secondary prevention. The etiologies of iCVA are cryptogenic, cardioembolic, and atherothrombotic, among others less common (LEAL, 2022). In children, the main cause of ischemic stroke is sickle cell anemia (SANT'ANNA, 2018). Anemia has been associated as a prothrombotic factor that leads to a state of hypercoagulability and, therefore, leads to an increased possibility of thrombus formation, thus increasing the chance of developing iCVA (ELIAS, 2004; CORREIA, 2021). This occurs mainly in young women with iron deficiency anemia caused by intense bleeding mainly of gynecological origin (ELIAS, 2004; CORREIA, 2021).

PARKINSON'S DISEASE

Parkinson's disease is the second most prevalent neurodegenerative disease in the world, affecting approximately 2% of people over the age of 65 (LEAL, 2022; WERNECK, 2010). A progressive, idiopathic neurodegenerative disease diagnosed by two of the following criteria: bradykinesia, resting tremor, cogwheel rigidity, and postural instability, with bradykinesia being obligate (LEAL, 2022).

Regarding pathophysiology, Parkinson's disease is caused by changes in the

dopaminergic, noradrenergic, serotonergic, and cholinergic systems (WERNECK, 2010). Its pathological markers include the loss of dopaminergic neurons in the substantia nigra and the accumulation of mutated α-synuclein in the cerebral cortex, brainstem, and spinal cord (WERNECK, 2010).

The hypothesis that iron deficiency anemia is related to Parkinson's disease is still being studied and has not been fully proven. However, some animal studies have shown dopaminergic degeneration in iron deficiency states, which in theory is related to the disease studied. In addition, the main hypotheses for the relationship between anemia and Parkinson's disease are that low hemoglobin and low iron concentrations cause systemic inflammation and oxidative stress (MAMATEO-SÁNEZ, 2020). Since Parkinson's disease is currently incurable and degenerative, the intervention process is necessary, complex, and multidisciplinary, aiming at the best possible coexistence of the patient with the disease (SILVA & CARVALHO, 2019).

METHODOLOGY

RESEARCH DESIGN

This study was a quantitative, descriptive, retrospective, documentary, population-based, or epidemiological study based on information collected from medical records at the Neurology outpatient clinic of Hospital Casa de Saúde (HCS). After data collection, quantitative, statistical, and descriptive analyses were performed.

RESEARCH SUBJECTS AND LOCATION

The research subjects were patients at the Neurology outpatient clinic who consulted between March and December 2023. The study was carried out in a medium-sized, tertiary hospital, which only serves the Unified Health System (SUS), located in the municipality of Santa Maria, state of Rio Grande do Sul.

DATA ANALYSIS

For sociodemographic characterization, a descriptive analysis of the data of the study participants was performed, with categorical variables presented as percentages and quantitative variables as means and standard deviations. The chi-square test was applied to analyze the association between the variables of neurological diagnosis and anemia. IBM SPSS Version 25 was used as a computational tool for statistical analysis of the data.

ETHICAL PROCEDURES

This project was submitted to and approved by Plataforma Brasil under the Certificate of Presentation for Ethical Appreciation (CAAE) number 74152223.9.0000.5306, in addition to having been evaluated and accepted by the Research Ethics Committee (CEP) of UFN. The evaluations and data collection only began after approval by these two committees. The non-disclosure agreement is included in the appendices.

RESULTS

Between March and December 2023, there were 269 consultations at the HCS neurology outpatient clinic, with a total of 114 patients. Each of these patients returned for consultation at least once, with some returning 2 to 3 times, justifying the higher number of consultations than the number of patients per se.

As for demographic characteristics, 59% of patients are female, while 41% are male, with an average age of 60 years (± 16.8 years), ranging from 18 to 94 years, as listed in Table 1. As indicated in Figure 1, the age distribution among neurological diseases was uniform and without statistical variation.

Descriptive parameters	Total	Gender	
		Male	Female
N	114	47 (41%)	67 (59%)
Age	60 (±16.8)	61.6 (±16)	58.3 (±17.3)

Table 1: Descriptive data on age and sample values per gender.

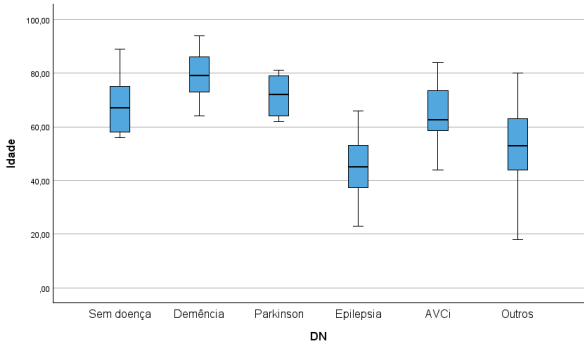

Figure 1: Average age by neurological disease.

Thirty-five (31%) patients had anemia, that is, hemoglobin less than 12 g/dL. These patients were classified according to the morphology and amount of pigment in the red blood cells and, therefore divided into macrocytic; normocytic, and normochromic anemia; microcytic, and hypochromic anemia. Thus, they presented a distribution of 2 (6%), 28 (80%), and 5 (14%), respectively, shown in Table 2.

Sample Values	Type of anemia		
	Macrocytic	Normo/Normo	Micro/Hypo
N = 35	2 (6%)	28 (80%)	5 (14%)

Table 2: Descriptive data on types of anemia.

Referente aos 35 pacientes com anemia, 31 deles (88,6%) apresentavam Hb entre 9 e 12 g/dl, 3 (8,6%) entre 7 e 8,9 g/dl e 1 paciente (2,8%) apresentava Hb menor ou igual a 6,9 g/dl. Sendo assim, a maioria dos pacientes apresentavam anemia leve (Table 3).

Sample Values	Values of Hemoglobin (Hb)		
	9-12 g/dL	7-8,9 g/dL	≤ 6,9 g/dL
N = 35	31 (88.6)	3 (8.6%)	1 (2.8%)

Table 3: Descriptive data of patients according to Hb value.

Seeking to clarify the etiology of anemia in these patients, 23 (65.7%) of the cases did not have detailed records in the medical records about the investigation performed, specifying which laboratory tests were requested to elucidate its cause, as shown in Table 4. Only 12 (34.3%) patients had anemia with an established etiology, of which 5 (14.2%) of these cases were due to iron deficiency, 3 (8.6%) to chronic kidney disease, 2 (5.7%) to chronic disease or inflammatory anemia, 1 (2.9%) to B12 hypovitaminosis, and 1 (2.9%) to side effects of medications.

Only 1 (0.9%) patient out of the 114 patients surveyed and 35 patients with diagnosed anemia was referred for follow-up with a hematologist. Low hemoglobin was not the reason for the referral, but rather a previous diagnosis of Antiphospholipid Syndrome (APS).

Regarding the neurological diseases surveyed, 20 (17.5%) patients were diagnosed with iCVA, 19 (16.7%) had epilepsy, 17 (14.9%) had some type of dementia, and 6 (5.3%) patients had Parkinson's, as presented in Table 5. Forty-two (36.8%) patients fell into the classification of other neurological diseases such as essential tremor and migraine. Furthermore, 10 (8.8%) patients did not meet the criteria for any neurological disease; all had some significant cognitive complaint, with the diagnostic hypotheses being mild cognitive impairment (MCI) and mood changes.

Analyzing the causes of dementia, of the 22 patients diagnosed with dementia, 7 (31.8%) had Alzheimer's dementia, 1 (4.5%) had dementia with Lewy bodies, 6 (27.2%) had vascular dementia, 3 (13.7%) had dementia

Sample Values	Etiology					
	Determined					No investigation
	Iron deficiency	CKD	CD/IA	B12 deficiency	Effect of medications	
N = 35	5 (14.2%)	3 (8.6%)	2 (5.7%)	1 (2.9%)	1 (2.9%)	23 (65.7%)

Table 4: Descriptive data according to anemia etiology.

Sample values	Neurological disease				
	iCVA	Epilepsy	Dementia	Parkinson's	Others
N = 114	20 (17.5%)	19 (16.7%)	17 (14.9%)	6 (5.3%)	42 (36.8%)

Table 5: Descriptive data on neurological diseases.

Sample values	Causas de Demência					Other Main diagnosis
	Alzheimer's disease	Lewy's disease	Vascular	B12 deficiency	Other underlying disease	Parkinson's
N = 22	7 (31.8%)	1 (4.5%)	6 (27.2%)	3 (13.7%)	2 (9.1%)	3 (13.7%)

Table 6: Descriptive data on the causes of dementia.

due to vitamin B12 deficiency, and 2 (9.1%) patients had dementia due to other underlying diseases, such as frontotemporal dementia and anemia (Table 6). In addition, another 3 (13.7%) patients had dementia associated with Parkinson's disease, their main diagnosis (Table 6).

In the descriptive analysis, of the 20 patients with iCVA, 8 (40%) had anemia; of the 19 patients with epilepsy, 4 (21.1%) were anemic; of the 17 patients with some type of dementia, 9 (52.9%) had hemoglobin below 12 g/dL; of the 6 patients with Parkinson's, 2 (33.3%) had anemia; of the 42 patients diagnosed with other neurological diseases, 9 (21.4%) were anemic; and finally, of the 10 patients without criteria for neurological disease but with cognitive complaints, 3 (30%) had anemia, as listed in Table 7.

Parameters		Anemia	
		Absent	Present
Neurological diseases	No disease	7 (6.1%)	3 (2.6%)
	Dementia	8 (7%)	9 (7.9%)
	Parkinson's	4 (3.5%)	2 (1.8%)
	Epilepsy	15 (13.2%)	4 (3.5%)
	iCVA	12 (10.5%)	8 (7%)
	Others	33 (29%)	9 (7.9%)
Total = 114		79 (69.3%)	35 (30.7%)

Table 7: Relationship between neurological diseases and the presence of anemia.

The chi-square test was applied to correlate the presence of anemia with neurological diseases, revealing no statistically significant association (p=0.198).

DISCUSSION

Anemia has been the subject of considerable research due to its potential impact on the progression of neurological diseases. Epidemiological studies have already corroborated the relationship between anemia and previous neurological pathologies. For example, the meta-analysis conducted by Melèndez-Flores et al. in 2023 exposed a trend of increased incidence of Parkinson's disease

in people with anemia and highlighted the need for further studies on the association of these pathologies. Similarly, a retrospective cohort study in 2023 conducted by Chen et. al. revealed a consistent association between moderate anemia and increased risk of CVA.

The estimated percentage of anemia according to the 2013 Global Burden of Disease study was 27% in the world population, which does not differ significantly from the results obtained in this study, which showed a prevalence of anemia of 31% in the population studied (KASSEBAUM, 2016).

According to the cross-sectional study that included more than 8,000 patients, led by Machado et al in 2019, anemia classified as normocytic and normochromic has the highest prevalence, 56%, followed by microcytic and hypochromic anemia, 21.4%, and macrocytic anemia, 10.2%. In this study, we obtained results from the equivalent classification, but in different percentages, which can be attributed to the small sample size.

The investigation of the etiology of anemia was one of the limitations of this study. There was no detailed information on the tests requested in most (65.7%) medical records, thus, it was not possible to analyze whether the investigation was complete and adequate to conclude this etiological diagnosis. Of these 65.7%, only 1 medical record recorded that the patient was referred for a hematology consultation. However, all patients are advised to seek clinical follow-up with a general practitioner at the basic health unit, given the bureaucratic limitation that prevents adequate referral by interconsultation to other specialists at the HCS. Therefore, it is essential to investigate the etiology of the patient's anemia due to its great systemic repercussions. Even with the low number of patients with a determined etiology, iron deficiency anemia was the most prevalent, corroborating the data presented by De Santis in 2019.

The prevalence of dementia causes was assessed in this study and we observed that Alzheimer's disease is the most common, with 31.8%, followed by vascular dementia, with 27.2% of patients. These data are corroborated by Souza *et al*., who evaluated more than 700 patients between 2008 and 2015, and reported that Alzheimer's disease was the most prevalent, affecting 48.9% of patients, followed by vascular dementia, affecting 11.3% of patients.

Although the mechanisms underlying the association between anemia and previous neurological pathologies are not yet fully understood, evidence suggests some possible pathophysiological pathways. For example, Fabian (FABIAN, 2007) highlighted the role of cerebral hypoxia induced by anemia. Furthermore, according to Bragagnolo *et al*., systemic inflammation associated with iron deficiency and iron deficiency anemia may play a role in the progression of neurodegenerative diseases, such as Parkinson's disease, through neuroinflammatory mechanisms.

This study aimed to fill this gap in knowledge by examining the association between anemia and previous neurological pathologies in a representative sample of patients. Although the literature shows that there is a relationship between these two entities, this study did not obtain the same results.

The limitation of the present study was mainly the low number of patients, the high number of patients classified as "other" in neurological diseases, and the non-uniformity of sample values between each variable studied. Due to the small sample size, it was necessary to reduce the number of variables, further limiting the statistical analysis. Therefore, further research is required with a larger sample size and greater uniformity between the variables.

CONCLUSION

In summary, there is no significant correlation between the neurological diseases studied, namely dementia, epilepsy, iCVA, and Parkinson's disease with anemia, according to Pearson's correlations. Nevertheless, it is necessary to conduct new studies with larger sample sizes, quantitative hemoglobin parameters, and more variables of neurological disorders, given the limitations of this study.

However, considering the potential relationship between neurological diseases and anemia, multidisciplinary approaches that integrate care from these two major areas are necessary to optimize clinical and functional results in this complex population.

Understanding these relevant interactions can guide clinical practice and direct future research in the development of more effective therapeutic strategies focused on the needs of each patient.

REFERENCES

ANVISA. **Manual de diagnóstico e tratamento de doenças falciformes,** 2022. Disponível em: https://bvsms.saude.gov.br/bvs/publicacoes/anvisa/diagnostico.pdf. Acesso em: 22 mar. 2023.

BOFF, Mario S.; SEKYIA, Felipe S.; BOTTINO, Cássio M., C. **Prevalence of dementia among Brazilian population: systematic review**. Revista de Medicina, v. 94, n. 3, p.154-161, 2015. Disponível em: http://dx.doi.org/10.11606/issn.1679-9836.v94i3p154-161. Acesso em: 08 jun. 2023.

BRAGAGNOLO, J. G.; MARRONE, L. C. P. **A influência do metabolismo do ferro na Doença de Parkinson: revisão de literatura**. Revista da AMRIGS, v. 65, n. 2, pg. 21-26, 2021. Disponível em: https://efaidnbmnnnibpcajpcglclefindmkaj/https://docs.bvsalud.org/biblioref/2022/04/1367545/ar-26661.pdf. Acesso em 02 de mar. 2024.

BUENO, Milena. **Prevalência e fatores associados à anemia entre crianças atendidas em creches públicas de São Paulo**. Revista Brasileira de Epidemiologia,n. 9, v. 4, p. 462-470, 2006.

CHEN, H.; HO, T.; KUO, Y.; CHIEN, J. **Association between Anemia Severity and Ischemic Stroke Incidence: A Retrospective Cohort Study**. International Journal of Environmental Research and Public Health, v. 20, n. 5, pg. 2-11, 2023. Disponível em: https//efaidnbmnnnibpcajpcglclefindmkaj/file:///C:/Users/pedro/Downloads/ijerph-20-03849-v2.pdf. Acesso em 01 de mar. 2024.

CORREIA, Ana C. C. **Trombos Associados a Anemia Ferropenica como causa de AVC isquêmico: revisão sistemática de literatura**. Faculdade de Medicina de Lisboa, 2021. Disponível em: https://repositorio.ul.pt/bitstream/10451/51230/1/AnaCCorreia.pdf. Acesso em: 25 nov. 2023.

DE SANTIS, GC. **Anemia: definição, epidemiologia, fisiopatologia, classificação e tratamento**. Revista USP, v. 52, n. 2, p. 131-140, 2019.

DE SOUZA, R. K. M. et. al. **Prevalência de demência em pacientes atendidos em um hospital privado no sul do Brasil**. Einstein, v. 18, pg. 1-7, 2020. Disponível em: https://efaidnbmnnnibpcajpcglclefindmkaj/https://www.scielo.br/j/eins/a/VBNwrZvwx4s9w8Jcd4jdBtg/?lang=pt&format=pdf. Acesso em 03 de mar. 2024.

DOMINGUES, N.T. **Anemia: causas, consequências e prevenção.** Sociedade de Pediatria de São Paulo, São Paulo, 29 nov. 2021. Disponível em: https://www.spsp.org.br/2021/11/29/anemia-causas-consequencias-e-prevencao/. Acesso em: 17 maio 2022.

ELIAS, Merrill F. et al. **Framingham Stroke Risk Profile and Lowered Cognitive Performance**. Stroke, v. 35, n. 2, p.404-409, 2004. Disponível em: https://www.ahajournals.org/doi/10.1161/01.STR.27.5.1002. Acesso em: 25 set. 2023.

FABIAN, Cristina. **Prevalência de anemia e fatores associados em mulheres adultas residentes em São Leopoldo, Rio Grande do Sul, Brasil**. Cadernos de Saúde Publica, n.23, v. 5, p. 1199-1205, 2007.

GALLUCCI NETO, José; TAMELINI, Melissa Garcia; FORLENZA, Orestes Vicente. **Diagnóstico diferencial das demências**. Archives Of Clinical Psychiatry, São Paulo, v. 5, n. 32, p. 119-130, 2005. Disponível em: https://www.scielo.br/j/rpc/a/vDWWPRwcxyLdXzvSqy5NSSx. Acesso em: 12 nov. 2023.

ILAE. **International League Against Epilepsy Classification of the Epilepsies**, 2017. Disponível em: https://efaidnbmnnnibpcajpcglclefindmkaj/https://www.ilae.org/files/ilaeGuideline/ClassificationEpilepsies-Scheffer2017-Brazil.pdf. Acesso em 03 de mar. 2024.

KASSEBAUM, N. J. **The Global Burden of Anemia**. Hematology/Oncology Clinics of North America, v. 30, n. 2, pg. 247-308, 2016. Disponível em: https://www.sciencedirect.com/science/article/abs/pii/S0889858815001896?via%3Dihub. Acesso em 02 de mar. 2024.

LEAL, André, G. **Tratado de neurologia clínica e cirúrgica 1ª edição**. Academia Brasileira de Neurocirurgia, 2022.

MACHADO, I. E.; MALTA, D. C.; BACAL, N. S.; ROSENFELD, L. G. M. **Prevalência de anemia em adultos e idosos brasileiros**. Revista Brasileira de Epidemiologia, v. 22, n. 2, pg. 7-21, 2019. Disponível em: https://efaidnbmnnnibpcajpcglclefindmkaj/https://www.scielo.br/j/rbepid/a/q47JnZ8YGgcqbN8gNDyQNJL/?format=pdf&lang=pt. Acesso em 02 de mar. 2024.

MACHADO, Mayara R.; CARMO, André L. S.; ANTONIUK, Sérgio A. **Febrile seizure in childhood: A review of the main concepts**. Sociedade Brasileira de Pediatria, v. 8, p. 113-117, 2018. Disponível em: https://residenciapediatrica.com.br/detalhes/336/crise%20febril%20na%20infancia-%20uma%20revisao%20dos%20principais%20conceitos#:~:text=Em%20um%20estudo%20britânico%2C%20após,convulsões%20focais%2C%20de%2029%25. Acesso em: 14 out. 2023.

MATEO-SÁNEZ, Henry A. et al. **Preservación de la fertilidad en una paciente con teratoma bilateral. Reporte de un caso y revisión de la literatura**. Cirugía y Cirujanos, [S.I], v. 88, n. 92, p. 1-6, 2020. Publicidad Permanyer, SLU. http://dx.doi.org/10.24875/ciru.20000480. Disponível em: https://doi.org/10.24875/ciru.20000480. Acesso em: 19 jun. 2023.

MCLEAN, E**. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005**. Public Health Nutrition, n. 12, v. 4, p. 444-454, 2009

MELÉNDEZ-FLORES, J. D. et. al. **Association of anemia with Parkinson's disease: a systematic review with meta-analysis of epidemiological studies**. Revista Mexicana de Neurologia, n. 24, v. 1, pg. 19-28, 2023. Disponível em: https://mhnlakgilnojmhinhkckjpncpbhabphi/pages/pdf/web/viewer.html?file=https%3A%2F%2Fwww.scielo.org.mx%2Fpdf%2Frmn%2Fv24n1%2F2604-6180-rmn-24-1-19.pdf. Acesso em 03 de mar. 2024.

MINISTÉRIO DA SAÚDE. **Diretrizes de Atenção à Reabilitação da Pessoa com Acidente Vascular Cerebral**. 2013. Disponível em: https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_atencao_reabilitacao_acidente_vascular_cerebral.pdf. Acesso em: 26 maio 2023.

MINISTÉRIO DA SAÚDE. **Ministério da Saúde debate Primeiro Relatório Nacional sobre a Demência,** 2022. Disponível em: https://www.gov.br/saude/pt-br/assuntos/noticias/2022/setembro/ministerio-da-saude-debate-primeiro-relatorio-nacional-sobre-a-demencia-nesta-quarta-21. Acesso em: 24 maio 2023.

MINISTÉRIO DOS DIREITOS HUMANOS E DA CIDADANIA. **Brasileiros com 60 anos ou mais superam 32 milhões de pessoas; MDHC reforça importância do cuidado e respeito com essa faixa etária**. 2023. Disponível em: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwitp5_-8-KDAxVcgGEGHdwODX8QFnoECAkQAw&url=https%3A%2F%2Fwww.gov.br%2Fmdh%2Fpt-br%2Fassuntos%2Fnoticias%2F2023%2Foutubro%2Fbrasileiros-com-60-anos-ou-mais-superam-32-milhoes-de-pessoas-mdhc-reforca-importancia-do-cuidado-e-respeito-com-essa-faixa-etaria%23%3A~%3Atext%3DDe%2520acordo%2520com%2520os%2520dados%2Canunciados%2520na%2520%25C3%25BAltima%2520PNAD%252Dcont%25C3%25ADnua.&usg=AOvVaw11VD0HsMP8Ih1jpo93qclt&opi=89978449. Acesso em 27 dez, 2023.

MONTEIRO, M. **Anemia megaloblástica: revisão de literatura**. Edição nº11. São Paulo: Revista Saúde em Foco, 2019.

NETO, João. **Manifestações neurológicas da anemia perniciosa**. Revista Brasileira de Hematologia e Hemoterapia, n. 30, v. 2, p. 162-166, 2008.

PADDA, Jaskamal, et al. **Association of anemia with epilepsy and antiepileptic drugs**. Cureus, n. 13, v. 11, 2021. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8653853/#REF14. Acesso em 13 nov. 2023.

PETERS, Ruth et al. **Haemoglobin, anaemia, dementia and cognitive decline in the elderly, a systematic review**. BMC Geriatrics, n. 8, v. 18, p.1-6, 2008.

ROSENFELD, Luiz G. et al. **Valores de referência para exames laboratoriais de hemograma da população adulta brasileira: pesquisa nacional de saúde**. Revista Brasileira de Epidemiologia, [S.L.], v. 22, n. 2, p. 01-13, 2019.

SANT'ANA, Lívia. **Anemia ferropriva: fisiopatologia e fatores de risco**. Whitebook, São Paulo, 22 dez. 2021. Disponível em: https://pebmed.com.br/anemia-ferropriva-fisiopatologia-e-fatores-de-risco/. Acesso em: 17 maio 2022.

SANT'ANNA, Lívia P. **Doença falciforme no Brasil: principal causa de morte são as infecções**. 2018. Disponível em: https://pebmed.com.br/doenca-falciforme-no-brasil/. Acesso em: 21 maio 2021.

SANTOS, Camila de Souza dos; BESSA, Thaíssa Araujo de; XAVIER, André Junqueira. **Fatores associados à demência em idosos**. Ciência & Saúde Coletiva, v. 25, n. 2, p. 603-611, 2020.

SENA, Tais S.; TOSTES, Meire A. **Manejo da Crise Dolorosa na Doença Falciforme**. Revista Baiana de Pediatria, Salvador, Ba, v. 5, n. 1, p.63-66, set. 2011. Disponível em: http://www.sobape.com.br/revistas/Revista-baiana-de-pediatria-vol-5-n-1-2011%20ISSN%201806-7085.pdf. Acesso em: 15 out. 2023.

SILVA, Thaiane P.; CARVALHO, Claudia R. A. **Doença de Parkinson: o tratamento terapêutico ocupacional na perspectiva dos profissionais e dos idosos**. Cadernos Brasileiros de Terapia Ocupacional, São Carlos, v. 27, n. 2, p. 331-344, 2019. Disponível em: https://www.scielo.br/j/cadbto/a/svqsc36yy5sHYqMBsdzHWZy/?lang=pt&format=pdf. Acesso em: 04 jun. 2023.

SOCIEDADE DE PEDIATRIA DE SÃO PAULO. **Dia Mundial de Conscientização da Anemia Falciforme**, 2023. Disponível em: https://www.spsp.org.br/dia-mundial-de-conscientizacao-da-anemia-falciforme/#:~:text=Nascem%20aproximadamente%20por%20ano%20300.000,refletindo%20a%20sua%20heterogeneidade%20étnica. Acesso em 20 de jan. de 2024.

TALMELLI, Luana Flávia da Silva et al. **Doença de Alzheimer: declínio funcional e estágio da demência.** Acta Paulista de Enfermagem, São Paulo, v. 5, n. 26, p. 219-225, 31 jul. 2013. Disponível em: https://www.scielo.br/j/ape/a/6QYKZNFvLPCq9Vp3vKqRPGC/?lang=pt. Acesso em: 17 maio 2023.

UFRJ (Rio de Janeiro). **Anemias**. Disponível em: http://www.me.ufrj.br/images/pdfs/protocolos/obstetricia/anemias.pdf. Acesso em: 17 maio 2022.

UNICEF. **Focusing on anaemia: towards an integrated approach for effective anaemia control**. World Health Organization, 2004 Disponível em: https://cdn.who.int/media/docs/default-source/nutritionlibrary/focusing-on-anaemia_970a28fe-a055-4e63-b3ba-11be7b940b16.pdf?sfvrsn=9ab36bdb_6&download=true. Acessado em: 17 maio 2022.

WERNECK, Antonio L. S. **Doença de Parkinson: Etiopatogenia, Clínica e Terapêutica**. Revista Hospital Universitário Pedro Ernesto, Rio de Janeiro, v. 9, n. 1, p.9-19, 2010. Disponível em: https://www.e-publicacoes.uerj.br/revistahupe/article/download/9026/6922/0. Acesso em: 19 nov. 2023.

WOLTERS, Frank J. **Hemoglobin and anemia in relation to dementia risk and accompanying changes on brain MRI**. Neurology, n. 93, v. 9, p. 917-926, 2019.

WORLD HEALTH ORGANIZATION. **Epilepsy**. 2019. Disponível em: https://www.who.int/news-room/fact-sheets/detail/epilepsy. Acesso em: 29 out. 2023.

ZAGO, Marco Antonio; FALCÃO, Roberto Passetto; PASQUINI, Ricardo. **Tratado de hematologia**. Journal of Alzheimer's Disease, n, 83, v, 3, p. 1187-1198 2021.