SHORT REPORT OPEN ACCESS

Iron Deficiency Anemia and Ischemic Stroke in Young Adults

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ABSTRACT

Background: Iron deficiency anemia (IDA) is the most common cause of anemia and is linked to higher arterial stroke risk in children, but its effect in adults remains unclear.

Methods: We performed a retrospective study examining the prevalence of IDA in young adults with and without ischemic stroke.

Results: We found that the prevalence of IDA was five times higher in patients with ischemic stroke than those without stroke (5% vs. 1.05%).

Conclusion: IDA independently increased the odds of an ischemic stroke by 39% ($p < 0.001$). Given the global burden of IDA, effective screening strategies are necessary.

1 | Introduction

Iron deficiency anemia (IDA) is the most common cause of anemia worldwide [1, 2]. It disproportionately affects younger women and children [3] and is often undertreated and under-recognized [1]. IDA is often identified only after the individual presents with clinical features of fatigue or neurological symptoms such as lack of concentration, dizziness, or restless leg syndrome [2]. Although these symptoms are associated with some morbidity, a more serious complication associated with untreated IDA has been venous and arterial thrombosis [4, 5]. Numerous case reports and retrospective studies report that adults with IDA are prone to venous thrombosis. This association persists regardless of the presence or absence of thrombocytosis [4]. In children, IDA is also associated with ischemic stroke [6]. Indeed, in one study, children with stroke were 10 times more likely to have iron deficiency, suggesting IDA as a risk factor for stroke in children [6]. Case reports have described a similar association with IDA and ischemic stroke in young adults. The individuals affected tend to be younger, have little or no evidence of atherosclerotic disease, and lack the usual risk factors of smoking, dyslipidemia, hypertension, and atrial fibrillation [7, 8]. However, large studies examining this association are lacking.

It is currently estimated that 10–15% of all strokes occur in adults aged 18–50 years (herein referred to as young adults) [9], and this group has also a high prevalence of IDA [1]. There is a paucity of data that explores the association between IDA and stroke in young adults. This study is in response to this knowledge gap. We used a large health service database to elucidate the prevalence

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of IDA among individuals younger than 50 years of age who were presented with a first-time ischemic stroke.

2 | Methods

To determine the association of iron deficiency with ischemic stroke, we queried a national database (Explorys Inc, Cleveland, OH, USA), an aggregate of electronic health record data from over 300 hospitals across the United States. Further details on the database can be found in the Supporting Information.

Patients with and without a history of ischemic stroke of ages 15–50 years were identified using SNOMED (Systematized Nomenclature of Medicine) code (43250400) between May 1999 and March 2018. Within both cohorts, patients with antecedent IDA were identified. Antecedent IDA was defined as a diagnosis of IDA within a year prior to the event. An event was defined as the index date of first-time diagnosis of stroke, whereas in those without stroke it was defined as a day of any encounter with healthcare. We specifically selected the age group under 50 years of age as IDA in older subjects is often an initial presentation of gastrointestinal malignancy. Given diagnosis of cancer could be a potential confounder, we specifically selected those with ischemic stroke under the age of 50 years.

Subjects who had a diagnosis of first-time ischemic stroke were defined as cases (from here on referred to as group A) and those without ischemic stroke were defined as controls (from here on referred to as group B). We recorded prevalence rates of IDA in both groups. We specifically investigated those who had a diagnosis of IDA prior to the stroke as antithrombotic agents used to treat stroke could contribute to IDA. We excluded patients with known diagnosis of thrombocytosis, malignancy, atrial fibrillation, antiphospholipid syndrome, previous history of stroke, pregnancy, hemoglobinopathies including sickle cell trait, use of combined oral contraceptives, thrombophilia, obesity, and use of anticoagulants in 1 year prior to onset of stroke. In addition, demographic information, such as age and gender along with risk factors for stroke (had to be present prior to ischemic stroke) such as diabetes, dyslipidemia, smoking, and hypertension was extracted and compared between adults with and without stroke. A list of SNOMED terms used in the study is summarized in Table S1. Studies utilizing this database are considered IRB-exempt at the University Hospital Cleveland Medical Center. These same criteria were used to identify the control group except for the absence of stroke. For studying schema, please see Figure S1.

Descriptive statistics using proportion and frequencies were used to summarize the baseline characteristics of the overall study cohort. Proportions were compared using the chi-squared test. A logistic regression model was used to identify variables that correlated strongly with stroke. In addition, the effect modification of IDA, on incident stroke by baseline risk factors such as smoking, presence of diabetes, hypertension, dyslipidemia, age, race, and gender, was evaluated by including an interaction term in the original regression model. p values less than 0.05 were considered significant. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS, version 21, IBM Corp., Armonk, NY, USA).

3 | Results and Discussion

A total of 21,802,239 individuals with and without ischemic stroke between the age of 15–49 years were identified. Of these, 36,989 patients had a first-time diagnosis of ischemic stroke. In this group (group A), 1880 (5.1%) subjects had a diagnosis of antecedent IDA. A total of 21,765,250 subjects of age 15–49 years had no history of ischemic stroke (from here on referred to as group B). In group B, 241,110 subjects were identified with a first-time diagnosis of IDA (1.10%). There was a fivefold difference in the prevalence rates of IDA among individuals in groups A and B.

The baseline characteristics of groups A and B are presented in Table 1. Group A had a higher proportion of all the comorbidities such as essential hypertension, diabetes, dyslipidemia, smoking, and obesity compared to group B. In multivariable analysis, when adjusted for age, gender, race, and other risk factors, the risk of stroke was significantly higher among those with antecedent IDA (Table 2). In fact, IDA was associated with 39% increased odds of stroke independently of all the described risk factors for stroke (Table S1). In summary, young adults presenting with an ischemic stroke were more likely to have antecedent IDA.

Although multiple studies have explored the association of IDA and thrombotic events in children, our study was the first to explore its role in ischemic stroke in a young adult population, that is, most susceptible to IDA. We show that there is a 39% increase in the odds ratio for stroke in those with antecedent IDA ($p < 0.001$). Similar results were also reported in a nationwide study done in Taiwan [7]. While these odds may be modest, the high prevalence of IDA in the USA and worldwide may magnify this effect, making IDA-related stroke a public health concern. Also, IDA-associated ischemic stroke appeared to be independent of atherosclerotic risk factors. Finally, we detected a significant statistical interaction with IDA, age, and non-Caucasian race on ischemic stroke ($p < 0.05$). This suggests that African American adults aged 20–39 years had a higher likelihood of ischemic stroke than Caucasian adults aged 40–50 years with IDA (Table S2). It is plausible that the younger cohort had fewer regular healthcare visits for medical risk factor management, and lack of access to a nutritious diet which could lead to increased atherosclerotic risk factors and IDA [3].

Mechanistically, in addition to decreased red blood cell deformability [10], IDA increases hypoxia-inducible factors and endothelial P-selectin expression and results in larger venous and arterial thrombus size in mice with induced iron deficiency [11, 12]. IDA also downregulates Kruppel-like factor-2 (KLF-2), a critical transcription factor involved in neutrophil activation, and augments the risk of thrombosis in myeloproliferative neoplasms [13]. Finally, transferrin upregulation (the main transporter of iron) may increase the risk of ischemic stroke in general population but may be protective in conditions like Chuvash polycythemia by neutralizing toxic nonbound iron and reducing neutrophil activation [12, 14, 15]. These observations suggest that IDA independently leads to a hypercoagulable state via several mechanisms.

A major strength of our study is the use of a large healthcare database that provides real-world data regarding IDA and

TABLE 1 | Clinical characteristics of patients under 50 years of age with and without ischemic stroke.

Patient characteristics	Patients with stroke $n = 36,980$ (%)	Patients without stroke $n = 21,765,250$ (%)	*p* value
Age range in years (%)			
20–24	1210 (3)	2,995,380 (14)	< 0.0001
25–29	2180 (6)	3,717,090 (17)	< 0.0001
30–34	3450 (9)	3,896,510 (18)	< 0.0001
35–39	5700 (15)	3,931,940 (18)	< 0.0001
40–44	9050 (24)	3,572,680 (16)	< 0.0001
45–49	15,660 (42)	3,760,590 (17)	< 0.0001
Gender			
Male (%)	16,510 (45)	9,557,170 (44)	0.0001
Female (%)	20,470 (55)	12,156,680 (56)	< 0.0001
Race			
Caucasian (%)	23,350 (64%)	11,577,700 (53)	< 0.0001
African-American (%)	9090 (25)	2,613,220 (12)	< 0.0001
Asian (%)	630 (2)	408,020 (2)	1.0000
Comorbidities			
IDA (%)	1880 (5.10)	241,110 (1.10%)	< 0.0001
Essential hypertension (%)	20,220 (55)	1,487,470 (7)	< 0.0001
Dyslipidemia (%)	5450 (15)	338,850 (2)	< 0.0001
Smoking (%)	14,080 (38)	2,216,110 (10)	< 0.0001
Diabetes (%)	9150 (25)	601,470 (3)	< 0.0001
Coronary artery disease(%)	3920 (11)	65,000 (0)	< 0.0001

TABLE 2 | Multivariable analysis of risk factors associated with increased odds of stroke.

Patient characteristics	OR	2.5th-ile	97.5th-ile	*p* value
IDA	1.389	1.333	1.447	< 0.001
Age (≥40 years vs. 20–39 years)	1.814	1.779	1.849	< 0.001
Gender (female vs. male)	1.037	1.019	1.055	< 0.001
Race (non-Caucasian vs. Caucasian)	1.199	1.178	1.221	< 0.001
Diabetes	1.493	1.462	1.524	< 0.001
Hypertension	3.242	3.176	3.309	< 0.001
Dyslipidemia	2.286	2.241	2.333	< 0.001
Smoking	1.965	1.931	2.000	< 0.001

ischemic stroke. The prevalence of IDA in the overall population in this study (1.11%) is lower than previously reported 5% [1], this probably reflects the underdiagnoses and underreporting of IDA in the real world. Our data are also less likely to be confounded by the presence of malignancy or the use of thrombotic agents, as these were deliberately excluded. A major limitation of this study is that it is retrospective in nature. We were unable to ascertain ferritin values for every participant or include those with latent iron deficiency. Given the underreporting noted in the study, it is likely that these represent true cases of IDA. In addition, we were unable to exclude participants with inflammatory conditions, a potential confounder for thrombosis, due to their heterogeneity in presentation and severity. Our study was also not designed to evaluate the effects of socioeconomic risk factors on the effects of treatment and mortality related to IDA and stroke. Finally, we were not able to assess the effect of iron deficiency without anemia on stroke which remains a subject of future studies.

In summary, we demonstrate an association between antecedent IDA and ischemic stroke in young adults. Given the high prevalence of IDA in this population, an effective screening strategy is urgently needed to diminish its subsequent complications.

Author Contributions

JG and LN designed the study. JG was responsible for data collection. SAK did the statistical analysis. JG wrote the manuscript, and LN was responsible for critical revision.

Ethics Statement

This project was considered IRB-exempt per University Hospital Cleveland Medical Center.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data can be requested via a third-party vendor—EXPLORYS, Inc.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.