

## Association between iron deficiency anaemia and ischemic stroke with a focus on the incidence, clinical presentation and treatment outcome in Adults: Research protocol

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### Abstract

**Background:** The evidence encompassing the correlation between iron status and the risk of ischaemic stroke is conflicting. Iron deficiency anaemia is an unusual aetiology of ischaemic stroke in adults. Despite having reports on the association between iron deficiency anaemia and stroke, little research is undertaken on a large scale to explore the association of iron deficiency anaemia with stroke and its treatment outcomes.

**Aims and objectives:** The overall aim of the study is to assess the association between iron deficiency anaemia and ischemic stroke, to examine the incidence of iron deficiency anaemia in patients with ischemic stroke, their clinical presentation and treatment outcomes, assess the health-related quality of life and capture the lived experiences of the stroke survivors.

**Methods:** This is a mixed method study with a quantitative and qualitative component. This study has two parts. Part 1 is a quantitative component with retrospective chart review. Part 2 is a prospective exploratory design with a quantitative and a qualitative component. The health-related quality of life of the stroke survivors will be assessed using questionnaire and their lived experiences will be captured using semi structured interview as a patient reported outcome.

**Result:** It is expected that the successful completion of this study will provide some evidence on the association between iron deficiency anaemia and ischaemic stroke.

**Conclusion:** This study will be beneficial to add to the existing knowledge on the aetiology of stroke and to fill the gap on the current knowledge on the association between iron deficiency anaemia and ischaemic stroke. If iron deficiency anaemia can be established as a risk factor for stroke in adults, many major cerebrovascular events can be prevented.

**Keywords:** Iron deficiency anaemia; Ischaemic stroke; IDA; Stroke.

**Abbreviations:** IDA: Iron deficiency anaemia; TIA: Transient Ischaemic Attack; LHID: Longitudinal Health Insurance Database; HRQoL: Health Related Quality of Life; OPD: Outpatients Department; VAS: Visual Analogue Scale; RCSI: Royal College of Surgeons in Ireland.

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## Introduction

Though the incidence of stroke is more common in adults over 65 years, almost 25% of stroke is reported in adults less than 65 years of age [1]. The most common aetiologies of strokes include prolonged hypertension, cardio-embolic disease, haematologic disorders, connective tissue disorders, substance abuse etc. However, the aetiology of stroke is undetermined in almost 30% of cases in young adults [1]. A case-control study conducted by Maguire et al [2] reported iron deficiency anaemia (IDA) as aetiology for almost 50% of stroke in paediatric population. A small number of case studies also reported IDA as an underlying cause for stroke in young adults.

The association between IDA and stroke was first reported by Alexander in 1983 [3]. Later, Bruggers et al [4] reported transient ischemic attacks (TIA) in an adolescent with history of a severe iron-deficiency. Shahar and Sadeh [5] reported a case of a 67-year-old man with haemoglobin 5.6 g/dl, who presented with generalised fatigue and non-fluent expressive aphasia. Symptoms resolved with blood transfusion. It was also reported that whenever his haemoglobin dropped below 5 g/dl, he developed aphasia that always resolved with blood transfusion. Shahar and Sadeh also reported a similar case of a 60-year-old woman who presented with anaemia-induced hemiparesis [5]. The neurological signs gradually disappeared with blood transfusion [5]. Akins et al described three women with severe IDA and thrombocytosis secondary to menorrhagia who developed carotid artery thrombi [6]. Years later Keung & Owen reported a case of fatal cerebral infarct in a 48-year-old woman secondary to IDA [7]. Mehta et al reported hypoxia-induced stroke secondary to IDA in a 47-year-old female [8]. Similarly, Caglayan et al described the case of a 41-year-old female admitted with transient numbness and weakness of the left and right upper and lower extremities with underlying anaemia [9].

Gopalratnam et al [1] reported IDA as a possible cause for stroke in a young adult aged who presented with severe anaemia (haemoglobin of 5.8 mg/dl). IDA has been associated with idiopathic intracranial hypertension [10], venous sinus thrombosis [11], and ischemic stroke [12]. An Asian study undertaken in Pakistan reported a significant association between anaemia and severity of stroke [13]. The largest study on this topic was conducted in Taiwan by Chang et al [14]. Data for this study were retrieved from the “Longitudinal Health Insurance Database (LHID2000) from January 1, 2003-December 31, 2011, involving 51,093 subjects. This study reported significant association between IDA and ischemic stroke. This study lacks treatment information for the IDA patients. Also, there is possibility of surveillance bias. Anaemia accounts for 8.8% of the global health burden [15] and IDA accounts for 50% of anaemia worldwide.

Despite having reports on the association between IDA and stroke, little research is undertaken on a large scale to explore the association of IDA with stroke and its treatment outcomes. This study aims

to better understand the association of IDA and ischemic stroke using retrospective cohort study and the Health-related quality of life (HRQoL) and lived experiences of the stroke survivors using prospective exploratory design with a qualitative and quantitative component.

## Research Protocol

### Research questions

This study has three primary research questions?

- What is the association between Iron deficiency anaemia (IDA) and ischemic stroke?
- What difference does the presence of IDA makes in the incidence, clinical presentation and treatment outcome in adults with ischemic stroke?
- How does IDA and ischemic stroke affect the health-related quality of life (HRQoL) of the stroke survivors and their lived experience?

### Aims and objectives

**Aim:** The overall aim of the study is to assess the association between IDA and ischemic stroke, to examine the incidence of IDA in patients with ischemic stroke, their clinical presentation and treatment outcomes, assess the HRQoL and capture the lived experiences of the stroke survivors.

### Objectives

1. Undertake a systematic review and explore the available literature to gain knowledge on the association between IDA and stroke.
2. To identify the incidence of IDA in patients with ischemic stroke.
3. To assess the duration, prognosis, management, and outcome of patients admitted with ischaemic stroke.
4. To assess the HRQoL and lived experience of the patients with stroke as a patient reported outcome.
5. Describe the findings of the individual strands and converge the findings from the quantitative and qualitative strands using a data triangulation approach.

### Study design

This will be a mixed method design with a quantitative component and a qualitative component. This study has two parts. Part one is a quantitative component with retrospective chart review. Part two is a prospective exploratory design with a qualitative and quantitative component to assess the HRQoL of the stroke survivors using EQ-5D-5L questionnaire and to capture their lived experiences using semi

structured interview.

**Part 1:** Association between IDA & stroke treatment outcomes.

This component is a retrospective cohort study to assess the incidence of IDA in patients with stroke and to assess the effects of IDA on stroke treatment outcomes. Patients' data will be collected from their medical records retrospectively by maintaining their anonymity and confidentiality. No identifying data will be collected from the medical records. So, consent will not be obtained in part 1 of the study.

**Part 2: HRQoL & lived experience**

Part 2 will be an exploratory design and includes prospective recruitment of patients with history of ischaemic stroke for at least one year. All patients admitted to Connolly hospital with ischaemic stroke, who have had their first stroke episode at least one year prior to their outpatients (OPD) appointment, will be invited to participate in the study. Eligible participants will be recruited while attending the stroke clinic for follow up. Informed consent will be obtained from the participants. (Participant consent form is included in Appendix 1). To assess the participant's IDA status, participant's clinical status during the acute stage of stroke and their health status one year post stroke, the researcher will do a retrospective chart review of all participants recruited to Part 2 of the study. The participants recruited for Part 2 of the study will complete the EQ-5D-5L questionnaire to assess their HRQoL and a selection of that group (participants with IDA, anaemia with other causes and participants with no anaemia) will attend the semi structured interview. They will be interviewed to collect data on their lived experience and how the stroke has affected their HRQoL.

**Study setting**

The study will be based in Connolly Hospital Blanchardstown.

**Population and sampling**

In the proposed study, the "target population" will be patients with an acute ischaemic stroke who were admitted to Connolly Hospital.

**In Part 1 of the study,** the "sample population" will be all patients aged 18 years and above admitted and discharged from Connolly Hospital between January 2018 and December 2020 with acute ischaemic stroke and not having a previous history of stroke.

**In Part 2 of the study,** the "sample population" will be adult patients with clinically diagnosed first time ischaemic stroke for more than one year.

**Sample size**

Sample size was calculated based on the proportion of the prevalence of IDA in general adult population Vs. prevalence of IDA in stroke patients, as advised by the statistician. Based on the available litera-

ture, the prevalence of IDA in general adult population is 0.7%-1.39% [16]. For sample size calculation the lower range of the prevalence of IDA in general adult population was considered (0.7%). Choi et al (2013) identified that the prevalence of IDA is 3.9% in population with acute ischemic stroke [17]. Considering these factors along with Type 1 error 5% and power 80% the minimum sample size required for this study is 341. Preliminary analysis shows that incidence of IDA is lower in the IDA group. So, a detailed incidence analysis based on the document history of IDA as well as the clinical co relation with blood values will be carried out. This will be discussed and finalised with the clinical supervisor. The possible implications of low number of events will be outlined in the discussion of thesis.

## **Eligibility criteria**

### **Inclusion criteria for part 1 of the study**

- Patients  $\geq 18$  years of age.
- Patients diagnosed with first time ischemic stroke.
- Connolly Hospital inpatient between January 2018 and December 2020.

### **Exclusion criteria for Part 1 of the study.**

- Patients  $< 18$  years of age.
- Patients with previous history of stroke.
- Patients diagnosed with TIA.

### **Inclusion criteria for part 2 of the study.**

- Stroke survivors  $\geq 18$  years of age.
- First time clinically diagnosed ischaemic stroke.
- At least one year post stroke.
- Independent life before stroke.
- Patients who are willing and able to consent for themselves.
- Stroke survivors who speak English.

### **Exclusion criteria for part 2 of the study.**

- Stroke survivors  $< 18$  years of age.
- Patients with TIA, previous history of stroke.

- Less than one year post stroke.
- Functional dependence before stroke.
- Patients who are unwilling or unable to consent for themselves.
- Stroke survivors who do not speak English.

## **Variables**

The variables selected for this study are based on the Irish National Audit of Stroke, National Report (2019). Variables refer to the data which is extracted from the medical records. The variables that are going to decide on the study outcomes (e.g., clinical variables and variables that affect the stroke prognosis) will be categorised as dependent variables or outcome variables. All other variables will be categorised as independent variables (e.g., sociodemographic and behaviour related variables).

## **Primary outcome**

- Incidence of stroke
- Severity of stroke
- Functional Dependence
- Length of hospital stay
- Discharge Destination
- Clinical Fatality rate

## **Secondary outcomes**

- Health related Quality of life (HRQoL)
- Lived experiences of the stroke survivors

## **Recruitment**

Patients who meet the inclusion/exclusion criteria will be eligible for recruitment into the study. The researcher will engage the medical records manager to support the retrospective data extraction and a suitably qualified gatekeeper to identify participants and issue the Participant Information Leaflet (Appendix 2).

## **Data Collection Methods**

In **Part 1** of the study, the data related all stroke patients admitted to Connolly Hospital from January

2018 and December 2020 will be collected retrospectively from the patient's medical records and Connolly hospital Stroke register ensuring anonymity and confidentiality of the patients.

Part 2 of the study has a quantitative and a qualitative component. To assess the HRQoL, patients with history of ischaemic stroke for at least one year will be given the EQ-5D-5L generic questionnaire to complete. EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). EQ-5D-5L is a standardised measure of health status to provide a simple generic measure of health for economic appraisal [18] (EQ-5D-5L tool is included in this document as Appendix 3).

Also, a semi structured interview lasting for 20 minutes will be carried out on patients with history of stroke for one year or more to evaluate their lived experience and how stroke has affected their quality of life. The interview will be audio recorded and transcribed verbatim.

After collecting the data, the researcher will verify same for any inaccurate or missing data while writing, reading, entering the system, or processing the computer data (data cleaning). For easy interpretation and analysis, the collected data will be summarised and tabulated. If any data is found missing or inaccurate, the researcher will review the patient's medical records again to collect same. All data that are unable to find will be considered as missing and will be reported in the findings of the study as missing.

To ensure the confidentiality of the participants and the records, caution will be taken while storing or disposing the data. The consent forms and key codes will be stored separately and will be kept locked in filing cabinet in Connolly Hospital where no one else can access and all electronic data will be uploaded to a dedicated password protected study folder on the Royal College of Surgeons (RCSI) secure data storage. The data will be kept for five years after completion of the study. When disposing the data, the paper records will be destroyed. Same will be witnessed, shredded and recycled. Electronic records will be deleted. The researcher will ensure there are no identifying marks anywhere in the data.

### **Data analysis of the mixed method study**

STATA will be used for the statistical analyses of the quantitative data collected. Descriptive data analysis will be carried out at the baseline. Chi-square tests and independent-sample t-tests will be performed to compare the categorical data and interval data respectively. Regression analysis will be used to assess the independent association between IDA and the treatment outcomes in patients with stroke. Univariate regression analysis will be performed to assess the association of each independent variable with the dependent variables. The IDA status and all the independent variables with significant association in the univariate analyses with a p-value of 0.2 will be considered in the final model. This model will help to identify the independent association of IDA on stroke treatment outcomes after controlling for all the potential confounding variable.

Analysis of the qualitative data will be done using a thematic analysis described by Braun and Clarke [19]. To converge the findings of the quantitative and qualitative strands, a data triangulation approach will



be used. This will help to generate a meta inference regarding quality of life of patients with stroke.

## Declarations

**Funding:** None. This is a self-funded study.

**Conflict of interest:** None

**Ethics approval:** Researcher has obtained ethics approval from Connolly hospital ethics committee (Study CHB 004/22) and Royal College of Surgeons in Ireland (RCSI) ethics committee (ID: 212611378).

**Insurance:** RCSI researcher indemnity/insurance cover is in place.

**Data protection impact assessment:** Data Protection Impact Assessment has taken place and is approved by the Data Protection Officer.

**Dissemination:** Periodic reporting of the study progress and final report will be submitted to RCSI. The findings from this study will be presented at national and international stroke conferences. The study will be published in peer-reviewed journals and authorship according to RCSI School of Nursing Publication Policy.

**Acknowledgements:** None

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**Manuscript Information:** Received: June 27, 2023; Accepted: July 27, 2023; Published: July 31, 2023

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**Citation:** Manoj P, Derwin R, Dolan E, Moore Z, Patton D, O'Connor, Nugent T, et al. Association between iron deficiency anaemia and ischemic stroke with a focus on the incidence, clinical presentation and treatment outcome in adults: Research protocol. *Open J Clin Med Case Rep*. 2023; 2082.

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