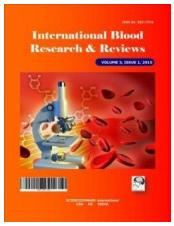

International Blood Research & Reviews
4(1): 1-5, 2015, Article no.IBRR.18154
ISSN: 2321–7219

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Cerebrovascular Disease in Children with Sickle Cell Disease: Is There Any Need for Iron Therapy?

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Authors' contributions

This work was carried out in collaboration between both authors. Author IOG designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors IOG and AIF managed the literature searches, analyses of the study. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IBRR/2015/18154
Editor(s):
(1) Ricardo Forastiero, Department of Hematology, Favaloro University, Argentina.
Reviewers:
(1) Anonymous, Ain Shams University, Egypt.
(2) Anonymous, University of Benin Teaching Hospital, Nigeria.
(3) Adrià Arboix, Department of Neurology, University of Barcelona, Spain.
Complete Peer review History: http://sciencedomain.org/review-history/10145

Original Research Article

Received 7th April 2015
Accepted 29th June 2015
Published 13th July 2015

ABSTRACT

Background: Iron deficiency is a common problem affecting children world-wide. It has been recognized to have an association with stroke. The aim of this study was to evaluate the prevalence of iron deficiency anaemia among children with sickle cell anaemia with cerebrovascular accident and the need for iron therapy.
Materials and Methods: All cases of cerebrovascular disease in children with sickle cell anaemia presenting in the department of Paediatrics of the University of Teaching Hospital were prospectively investigated for serum ferritin, haemoglobin, and MCV, MCHC and blood film.
Results: A total of 152 children with sickle cell disease were seen during this period. One hundred and forty nine had HbSS genotype while 3 had HbSC genotype. Cerebrovascular disease was diagnosed in 7 patients giving a prevalence rate of 4.6%. Of these, 2(28.6%) had low serum ferritin levels (P=0.09) with hypochromia and microcytosis.
Conclusion: Iron deficiency anaemia is not uncommon among sickle cell patients with cerebrovascular disease. There is need for elaborate iron study in these patients so as to identify at risk cases and institute prompt treatment.

Keywords: Cerebrovascular disease; sickle cell anaemia; iron deficiency.

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1. INTRODUCTION

Sickle cell disease (SCD) is one of the commonest but preventable inherited diseases [1]. It affects all races of the world; it affects the people of tropical Africa, Mediterranean Sea, Middle East and South India [1]. It has contributed considerably to the high childhood mortality rate.

Nigeria has an estimated population of 150 million with annual growth rate of 3.2%. The current figure of people in Nigeria with this disease is not known since the majority born in rural community do not survive childhood and for lack of proper statistics. However, estimates of about 2.3% of the Nigerian population suffer from sickle cell disorder and about 25% of Nigerians are healthy carriers of the abnormal haemoglobin gene [2].

Clinically evident cerebrovascular disease (CVD) is a devastating complication of sickle cell anaemia (SCA) that affects from 6 to 12 percent of patients [3-5]. Cerebrovascular diseases are very rare in persons with Hb SC disease. In children under age 10 years, the most common cause of CVD is cerebral infarction. Ischemic stroke typically presents with signs and symptoms of hemiparesis or monoparesis, hemianesthesia, visual field deficits, aphasia, cranial nerve palsies, or acute change in behaviour. Although recovery occasionally is complete, intellectual, motor, and sensory impairments are typical sequelae. Intracranial haemorrhage becomes increasingly more common with advancing age. In haemorrhagic CVD, more generalized phenomena such as coma, headache, and seizures occur. Recurrent CVD causes progressively greater impairment and increased likelihood of mortality. Factors such as low haemoglobin levels, increased systolic blood pressure, transient ischaemic attack, acute chest syndrome and male gender are linked to a higher risk of silent cerebral infarcts (SCIs), or silent strokes, in children with SCA [3].

Despite the reasonable speculation that a decrease in haemoglobin might possibly compromise the oxygen-carrying ability of the blood flow and subsequently increase the risk of cerebrovascular or cardiovascular diseases, the relationship between the iron deficiency anaemia (IDA) and the stroke was seldom studied [6]. In 1983, Alexander et al. [7] first reported that a patient developing a right hemiparesis and aphasia was found to have underlying IDA and marked thrombocytosis [7]. A few years later, another brain infarction cases were reported and thought to have resulted from the thrombocytosis secondary to the IDA [8,9]. Despite these peculiar cases, the relative importance of IDA seems to have been overlooked as most researchers have chosen to focus on sickle cell anaemia. Even after the publication of Framingham study [10] which seemingly implicated haematocrit as an important risk factor for some cardiovascular diseases, the possible relationships between the IDA and the stroke were still yet to be investigated through a large scaled study [11]. Given this, the study aims to evaluate the association of IDA and CVD in children with sickle cell disease.

2. MATERIALS AND METHODS

This was a prospective study of all children with sickle cell disease who presented in the Department of Paediatrics of the University of Port Harcourt Teaching Hospital (UPTH) with cerebrovascular disease from February 2014 to February 2015. Information obtained from the patients such as age, gender, age at diagnosis of sickle cell disease, episodes of cerebrovascular disease, mode of treatment, CT scan findings, full blood count, film report, serum ferritin, mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration (MCHC) were entered and analysed with SPSS version 22.0.

Haematologic test were performed using Abbott Cell Dyn Ruby analyzer (Abbott Diagnotic, Abbott, IL, USA).The ferritin test was performed by using the Chemiluminescent Microparticle Immunoassay (CMIA) method.

Diagnosis of sickle cell disease was made by haemoglobin electrophoresis. Cerebrovascular disease (CVD) was defined as sudden loss of speech, weakness, or paralysis of one side of the body. Confirmation of CVD was made by brain CT scan.

Iron-deficiency anemia was defined as a packed cell volume level of <33%, mean corpuscular volume <85fL, and serum ferritin level <7ng/ml.

Differences among clinical outcomes were analyzed by the Student's t test. A p-value<0.05 was considered statistically significant.

Ethical approval was from the Ethical Committee of UPTH.

3. RESULTS

A total of 152 children with sickle cell disease were seen during the study period (See Table 1). There were 83(54.6%) males and 69(45.4%) females. One hundred and forty nine (98.0%) had HbSS genotype while 3(2.0%) had HbSC genotype. Patient ages varied from 0.8 to 16 years with a mean of 7.34±3.56 years. CVD was diagnosed in 7 patients giving a prevalence rate of 4.6%. The mean age at diagnosis of cerebrovascular disease was 6.7±2.4 years. Of the 7 patients who had stroke, 2 had more than one episode of stroke, giving a 28.6% recurrence rate. None of children below 2 years had a stroke. The highest cases of CVD were seen between the ages of 2 and 10 years. The neurological symptoms observed were weakness of limbs 5(71.4%), Speech disturbances 4(42.9%) Seizure 3(42.9%), Coma 2(28.6%), confusion 1(14.3%).Computed Tomography (in 4 of the 7 children) showed cortical infarction (n=3) and Right middle cerebral artery infarction (n=1), Left middle cerebral infarction (n=1). None of children with CVD received antiplatelet therapy. Serum ferritin level was low in 2(28.6%) [P=<0.05] patients. The Mean packed cell volume (PCV) of the study group was 17±1.5 (range 15-20). PCV was below 21% in all the cases of CVD.

4. DISCUSSION

Children less than 2 years of age had the lowest incidence of CVD suggesting that there may be a protective mechanism functioning in early life or that, in SCD, the pathology responsible for CVD develops over time. However, we found the incidence of CVD to be higher in the 2 to 10 years of age. This finding suggests that a subset of patients may have additional risk factors for early stroke.

Children who have suffered a CVD in the past have a high risk of having another stroke. SCD children have a 67 percent risk of recurrence with CVD recurring up to nine months apart [12].The recurrence rate for CVD in this study was 28.6%. This is much lower than had been recorded in previous studies [13,14].This was because our patients were already on preventive transfusion program and hydroxyuria which explains the lower recurrence rate noted.

Anaemia in SCD is a reflection of overall severity of SCD. Haematologic disorders are the most frequent cause of ischaemic stroke of unusual cause [15]. Most of children with CVD in our study had severe anaemia. Severe anaemia may create an added risk for CVD. It has been suggested that the increased cerebral blood flow and flow velocity associated with chronic anaemia cause flow disturbances that may lead to cerebrovascular damage [16].

Table 1. Age Distribution of 152 Children with Sickle Cell Disease

Age(Years)	Frequency	Percentage
<1	9	6.0
1-<5	54	35.5
5-<10	66	43.4
>10	23	15.1

Table 2. Age Distribution of the 7 SCA with CVD

Age(Years)	Frequency	Percentage
<2	0	0
2-<5	2	28.6
5-<10	4	57.1
>10	1	14.3

SCA=Sickle Cell Anaemia; CVD=Cerebrovascular Disease

Table 3. PCV of the 7 SCA Children with CVD

PCV	Frequency	Percentage
10-<15	1	14.3
15-<20	5	71.4
21-25	1	14.3

Table 4. Haematological Parameters of Children with CVD

Factors	Mean value (SD) without iron deficiency	Mean value(SD) with iron deficiency	P-value
Serum ferritin (ng/ml)	13.2(3.4)	3.2(2.1)	<0.05
MCV (fl)	89(2.3)	75(1.4)	<0.05
MCHC (%)	35(3.1)	29(1.3)	>0.05
MCH (pcg)	21.3	21.3(2.4)	>0.05
Microcytosis (no.)	0	2	
Hypochromia (no.)	0	2	

MCV=Mean Corpuscular Volume; MCHC=Mean Corpuscular Haemoglobin Concentration; MCH= Mean Corpuscular Haemoglobin

Iron deficiency anaemia (IDA) is the most common cause of anaemia, affecting roughly two billion people worldwide [14]. It can cause low energy, weakness, frequent infections, dizziness, and can affect appetite, cognitive and motor development in the young [14]. Though normally not thought of as a life threatening condition, a number of studies have found that iron deficiency anemia may increase risk of ischaemic CVD [10]. We found a 28.6% prevalence rate of iron deficiency among our patients with cerebro-vascular disease. Three mechanisms to explain an association between IDA and childhood ischemic stroke have been suggested: a hyper-coagulable state directly related to iron deficiency and/or anemia; thrombocytosis secondary to IDA; and anaemic hypoxia, whereby a mismatch between oxygen supply and end-artery oxygen demand leads to ischemia and infarction [17]. Several reports have already indirectly suggested iron deficiency anaemia as a risk factor for CVD [18-20]. Mount et al. report a series of four young children with ischemic stroke underlying with significant IDA [21]. Remarkably, several reports have revealed that in children populations the IDA seems to contribute to the development of the stroke [22-24]. Maguire et al. conducted the first case-control study to investi-gate whether IDA is associated with stroke in young children [25].The authors found that children with IDA accounted for more than half of all stroke cases in children without an underlying medical illness, which suggests that IDA is a significant risk factor for stroke in otherwise healthy young children.

5. CONCLUSION

Iron deficiency anaemia is not uncommon among sickle cell patients with cerebrovascular disease. There is need for elaborate iron study in these patients so as to identify at risk cases and institute prompt treatment. Supplementation therapy for iron deficiency may be an important strategy to prevent cerebrovascular disease.

CONSENT

A written consent was obtained from parents.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/10145