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Original Research Article

RISK FACTORS OF STROKE AMONG CHILDREN WITH SICKLE CELL ANAEMIA A CASE CONTROL STUDY

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Abstract

Background: Sickle cell anemia and disease is the common burden of western Odisha. Cerebrovascular disease, particularly stroke, is one of the most severe clinical complications associated with sickle cell disease and is a significant cause of morbidity in both children and adults. Hense predicting the risk of stroke by searching the most common risk factors associated with SCD with stroke may decrease the morbidity and mortality due to stroke. **Materials and Methods:** we conducted a case control study in department of pediatrics, VIMSAR, Burla from November 2019 to September 2021 a retrospective study after institutional ethics committee approval.we had included 74 subjects as per predefined inclusion and exclusion criteria .cases were defined as HPLC confirmed cases of sickle cell anemia and disease and had a stroke and controls are HPLC confirmed cases of SCD/SCA and without any history of stroke and socio demographic variables like increasing age , gender ,socioeconomic status and clinical history variables like Number of hospitalizations, frequency of anemia,ACS ,VOC ,frequency of BT and laboratory variables like Hb, RC, MCV,MCH,MCHC,WBC, and HPLC variables like HbA2 , HbF, HbS are studied and analyzed in both groups. **Results:** Out of total 2263 sickle cell patients visited to pediatric OPD& IPD , VIMSAR, BURLA.Total 37 patients were had stroke and remaing doesn't had stroke and among cases variables like socio demographic variables like increasing age , male gender 44 (59.5%) ,socioeconomic status and clinical history variables like family history of stroke ((48.48%) increased Number of hospitalizations 6-10 27(73.0%) , increased frequency of anemia ,ACS 23(62.2%) ,increased VOC > 5 28(75.7%) , increased frequency of BT 8-10 33 (89.2%) and laboratory variables like decreasesed Hb, increased RC(%) , MCV,MCH,MCHC, increased WBC are clinically and statistically significant and HPLC variables like HbA2 , HbF, HbS are clinically significant but statistically insignificant. **Conclusion:** The absence of uniformity and standardization in the definition of distinct CVD events (ischemic stroke, TIA, hemorrhagic stroke, silent infarcts, vascular stenosis detected by MRA, and moya-moya disease) makes the interpretation and comparison of study results difficult and is probably a major factor that explains the controversies.

INTRODUCTION

Stroke is a well-recognised complication of homozygous sickle cell anaemia (SCA; haemoglobin SS-HbSS) and also occurs in compound heterozygotes, e.g., those with HbSC disease and HbSβthalassaemia (HbSβthal).[1] Sickle cell anaemia (SCA) is the most common cause of childhood stroke, occurring with the highest frequency before the age of 6 years.[2] Despite the relative frequency of stroke in SCA, few predictors of risk exist. Anaemia, leucocytosis, hypertension, silent infarction, and history of acute chest syndrome are well-documented risk factors for ischaemic stroke in SCA. Recent data suggest that

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other environmental and genetic factors, many unrelated to SCA, influence the development of cerebrovascular disease.[3]

There are data on the epidemiology of stroke in SCD from cohort studies, records of patients enrolled in healthcare provision, discharge data from hospitalisations and treatment trials. A major difficulty is the lack of information about diagnostic criteria for inclusion.[4] Earlier studies used definitions which were not necessarily standardised and, although more recent studies have included neuroimaging, as well as using the World Health Organisation definition of stroke, there is little evidence of neurological or neuroradiological over-reading or of the inclusion/exclusion criteria applied.[5] In fact, there is a wide differential of focal and generalised vascular and non-vascular pathologies, often distinguished using acute MR techniques, with important management implications.[6]

Acute neurological symptoms and signs are common in SCD and, as well as stroke, include transient ischaemic attack (TIA), headaches, seizures and coma.[7] Altered mental status with or without reduced level of consciousness, headache, seizures, visual loss or focal signs can occur in numerous contexts, including infection, acute chest syndrome (ACS), acute anaemia, after surgery, transfusion or immunosuppression and apparently spontaneously.[8] For example, in one large series of patients with SCD and ACS, 3% of patients had neurological symptoms at presentation, and these symptoms developed in a further 7–10% as a complication of ACS.[9]

MATERIALS AND METHODS

This is a Unmatched Case Control Study was conducted in Veer Surendra Sai Institute of Medical Sciences and Research, Burla.

The study settings were at the IPD and OPD of Department of Paediatrics and the Sickle Cell Institute of VIMSAR, Burla with Global positioning as follows.

Sickle cell anemia children HbSS attending our OPD / IPD for any cause.

Inclusion Criteria

1. All Sickle cell homozygous HPLC diagnosed children
2. Sickle cell patients diagnosed as stroke.
3. With age group below 14 years.
4. Either gender.

Exclusion Criteria not required

Automated high performance liquid chromatography (HPLC)

HPLC has four advantages over electrophoresis in diagnosing sickle disorders.

1. The analyzers are automated and thus utilize less time and permit Processing of large batches.
2. Very small samples (5pl) are sufficient for analysis; this is especially needful for pediatric patients.
3. Quantification of normal and variant hemoglobin is available on every sample.
4. A provisional identification of large proportion of variant hemoglobin can be made.

Data Analysis and Interpretation

Data collected from the study was processed, checked for internal errors, internal and external validation was done using n Master Version 2.0 software and SPSS v 25 software. Data was analyzed and the result was interpreted.

RESULTS

Table 1: showing that out of total 74 homozygous sickle subjects significant proportion of study population are in the age group of 7-10 years 37 (50.0%) followed by 1-6 years of age 26(35.1%) and mostly males children 44 (59.5%).

Table 1: Sociodemographic profile of the study participants

	Overall (N=74)
Age	
1-6 yrs	26 (35.1%)
7-10 yrs	37 (50.0%)
10-14 yrs	11 (14.9%)
Sex	
Male	44 (59.5%)
Female	30 (40.5%)

Table 2: Baseline Sociodemographic and Clinical Charecterestics of Study Population Mean

Charecterestics	**Mean (SD)**
Age (years)	6.75(3.07)
Weight (kilograms)	18.71(5.29)
Height(centimeters)	96.24(13.68)
Number of blood transfusions	6.74(2.21)
Number of hospitalisations	6.837(1.81)
Number of acute chest syndrome	0.36(0.48)
Number of vaso occlusive crisis	5.337(2.50)
Reticulocyte count (%)	5.83(3.188)
Hemoglobin(g/dl)	6.20(1.41)
Packed cell volume (%)	42.97(2.82)
Mean corpuscular volume (fl)	35.59(8.37)

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Mean corpuscular hemoglobin (pg)	34.28(4.24)
Mean corpuscular hemoglobin concentration (g/dl)	35.94(8.13)
Total platelet count (lakhs)	1.96(0.42)
HbS(%)	67.14(11.2)
HbF(%)	5.1(2.46)
HBA2(%)	1.86(0.48)
White blood cell count /mm^3	12529.8(4976.3)

Table 2 Shows mean and standard deviation of the baseline clinical charecterestics of study population both cases and controls.

Table 3: Comparison of hematological variables of the study participants between two groups

	Case (N=37)	Control (N=37)	Total (N=74)	P value
BP				0.16
70-90	14 (37.8%)	20 (54.1%)	34 (45.9%)	
>91	23 (62.2%)	17 (45.9%)	40 (54.1%)	
MRA				**<0.001**
ACA	7 (18.9%)	0 (0.0%)	7 (9.5%)	
MCA	26 (70.3%)	0 (0.0%)	26 (35.1%)	
N	0 (0.0%)	37 (100.0%)	37 (50.0%)	
PCA	4 (10.8%)	0 (0.0%)	4 (5.4%)	
RC				**<0.001**
<5%	6 (16.2%)	27 (73.0%)	33 (44.6%)	
>5%	31 (83.8%)	10 (27.0%)	41 (55.4%)	
Hb				**<0.001**
<6	30 (81.1%)	5 (13.5%)	35 (47.3%)	
>6	7 (18.9%)	32 (86.5%)	39 (52.7%)	
PCV				**0.02**
<35	22 (59.5%)	12 (32.4%)	34 (45.9%)	
>35	15 (40.5%)	25 (67.6%)	40 (54.1%)	
MCV				0.79
<50	2 (5.4%)	1 (2.7%)	3 (4.1%)	
50-75	22 (59.5%)	24 (64.9%)	46 (62.2%)	
76-90	13 (35.1%)	12 (32.4%)	25 (33.8%)	
MCH				**<0.001**
<35	9 (24.3%)	27 (73.0%)	36 (48.6%)	
>35	28 (75.7%)	10 (27.0%)	38 (51.4%)	
MCHC				**<0.001**
<35	8 (21.6%)	31 (83.8%)	39 (52.7%)	
>35	29 (78.4%)	6 (16.2%)	35 (47.3%)	
TPC				1
1-2.5	20 (54.1%)	20 (54.1%)	40 (54.1%)	
2.6-3.5	15 (40.5%)	15 (40.5%)	30 (40.5%)	
>3.5	2 (5.4%)	2 (5.4%)	4 (5.4%)	
WBC				**<0.001**
<10,000	10 (27.0%)	27 (73.0%)	37 (50.0%)	
>10,000	27 (73.0%)	10 (27.0%)	37 (50.0%)	

Table 4: Baseline Socio Demographic and Clinical Variables in Cases and Controls with Mean and P- Value

Variables	**Sickle cell disease with stroke (n=37)**	**Sickle cell disease without stroke (n=37)**	**Pvalue**
Age (years)	7.24 (2.58)	6.27(3.42)	<0.001
Weight (kilograms)	19.9(4.63)	17.4(5.67)	0.016
Height(centimeters)	99.9(13.9)	92.5(12.5)	0.97
Number of blood transfusions	8.35(1.2)	5.13(1.78)	<0.001
Number of hospitalisations	7.48(1.07)	6.18(2.15)	<0.001
Number of acute chest syndrome	0.62(0.49)	0.108(0.3)	<0.001
Number of vaso occlusive crisis	6.54(2.19)	4.13(2.22)	<0.001
Reticulocyte count (%)	7.54(2.84)	4.13(2.56)	<0.001
Hemoglobin(g/dl)	4.729(1.938)	7.67(2.10)	<0.001
Packed cell volume (%)	39.75(12.78)	46.18(10.6)	0.02
Mean corpuscular volume (fl)	32.13(7.39)	39.05(7.93)	0.79
Mean corpuscular hemoglobin (pg)	33.02(7.18)	35.54(14.64)	<0.001
Mean corpuscular hemoglobin concentration (g/dl)	33.16(7.18)	38.72(8.16)	<0.001
Total platelet count (lakhs)	1.95(0.4)	1.97(0.399)	1
HbS(%)	67.29(10.85)	67(11.68)	0.87
HbF(%)	5.37(2.37)	4.83(2.56)	0.82
HBA2(%)	1.84(0.53)	1.87(0.42)	0.81
White blood cell count /mm3	12931.9(4948.68)	12127.7(5039.2)	<0.001

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Table 4: shows mean and standard deviation of various variables among both cases and controls showing age ,number of blood transfusions, number of vaso occlusive crisis,and reticulocyte count ,hemoglobin,packed cell volume and MCV,MCH,MCHC and WBC count showing significance.

Table 5: Association of Number of blood transfusions and stroke

Study groups	≤4	Number of Blood transfusion (5-7)	10-Aug	Pvalue
SCD with stroke n=37	0	4 (10.8%)	33 (89.2%)	<0.001
SCD without stroke n=37	20(54.05%)	14 (37.8%)	3 (8.1%)	

Table 5. shows frequency of blood transfusion among study population showing total 36 subjects received 8-10 (48.6%) blood transfusions among 74 patients and 18 (24.3%) received 5-7 blood transfusions and 20 subjects (27.02%) blood transfusions .Increased frequency of blood transfusions was observed in cases than controls and it is also significant with Pvalue <0.001.

DISCUSSION

The study involved 74 cases of sickle cell disease and of which 44 (59.5%) were male and 30 (40.5%) were females .Male to Female ratio 1.46:1. With male preponderance 44 (59.5%). But studies done by Domingos.[10] and Sarnaik et.[11] showed little female preponderance than male this may be due to little more male preponderance may be due to different geographical areas and different study populations.

The prevalence of stroke in children with sickle cell anemia is 3.75%.[12] .Risk of stroke is highest during first decade of life, drops in second decade and rises again from the beginning of third decade .

STOP data study by Hsu et al.[13], cohort study by Rees et al.[14], BABY HUG DATA by Pavlakis et al.[15], cross sectional studies by Cox et al.[16] all these studies reported that steady low level haemoglobin associated with increased risk of stroke but none mentioned about the mean low value of haemoglobin value .

Kirkham et al.[17] a cohort study among homozygous sickle cell children shows increased haemoglobin levels are associated with increased risk. Kwiatkowski et al.[18] shown that increased Hb is also a protective factor for stroke.

In our study we found that among cases the mean haemoglobin was 4.729(±1.938) and among controls it was 7.67 (±2.10) showing less haemoglobin in cases than controls which is supported by the above studies . which was significant with P value of < 0.001.

Cohort study conducted by Meier et al.[19] & cross sectional study done by silva et al.[20] & cohort study conducted by Belisario et al.[21] & cohort study conducted by Bernaudina et al 22 shown that increased recticulocyte count % associated significantly with stroke in SCD children .

In our study also we found that more increased reticulocyte was observed in cases than in controls. reticulocytosis (>5%) with P value <0.001 has significantly associated with stroke in SCD. among subjects with reticulocyte count >5% 41 ,31 (75.6%) had stroke & 10 (24.3%) are without stroke.

Cohort study conducted by Lagunju et al.[23] & cohort study conducted by Adams et al.[24] shown that decreased hematocrit is associated with increased risk of stroke . And cohort study conducted by Miller et al 25 shown that increased hematocrit is associated with increased risk of stroke In our study we found mean value of Hematocrit was 39.75 (12.78) among cases and ampng controls it was 46.18 (10.6) both of which are within the normal reference range . but lower hematocrit values were observed in cases than the controls.

CONCLUSION

In our study we found that clinical history findings like increasing age , and family history of sickle cell anemia ,and acute chest syndrome increased frequency of blood transfusions and vaso-occlusive crisis, hopsitalisations , blood transfusions are associated with significant increases in risk of stroke. And laboratory findings like decreased steady state hemoglobin level, and increased steady reticulocyte count % and increased MCH,MCHC and increased WBC count are associated significantly with increased stroke risk. And when comes to sickling history and HPLC parameters of study subjects values of HbS% , HbF%,HbA2% was not associated significantly statistically.

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