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RESEARCH ARTICLE

OBSERVATIONAL STUDY ON SILENT CEREBRAL INFARCT IN CHILDREN OF SICKLE CELL DISEASE IN ASSOCIATION WITH RISK FACTORS

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Abstract

Aim and Objectives: To find out the presence of silent cerebral infracts (SCI) among sickle cell diseased children and to identify risk factors and correlate risk factors with silent cerebral infracts in sickle cell diseased children.. Settings, Design.

Methods and Materials: The children who came to paediatrics department of maharaja institute of medical sciences, with confirmed haemoglobin electrophoresis findings of sickle cell disease in steady-state are subjected to T2 weighted MRI scan of the brain using Philips ingenia CX 1.5Tesla MRI machine.

Results: out of 50 children with sickle cell disease ,18(36%) children have silent cerebral infarct and it was observed that the lower hemoglobin concentration, Lower RBC count, Lower Serum Ferritin, and elevated WBC count were considered to be the potential risk factors for Silent cerebral infarcts in Sickle cell disease.

Conclusion : Patients with risk factors for silent cerebral infarcts should be evaluated for cerebrovascular disease. If evidence of the presence of SCI, consideration must be given to therapeutic intervention.

Introduction:-

Sickle cell disease (SCD) is a haematological disorder, Autosomal Recessive (AR) characterized by haemolytic anemia, Vaso-occlusive episodes and gradually leading to progressive multi-organ failure. Worldwide estimation of 3,12,000 neonates with this disorder are born yearly[1]. SCD is due to defective substitution of a single nucleotide, wherein glutamic acid, a polar amino acid in position six of a β-globin gene is replaced by valine, a non -polar amino acid. This mutation results in the formation of defective haemoglobin called sickle cell haemoglobin(HbS).[2] When exposed to low oxygen saturation, HbS erythrocytes alter their shape to sickle or crescent form, become more rigid and, are more prone to haemolysis. Subsequently, these sickle cells upon interaction with leukocytes and endothelium of blood vessels leading to occlusion and vasculopathy, resulting in many acute and chronic complications of the disease, including cerebrovascular disease[3,4]. One of the most common neurological complications in children with SCD is the formation of silent cerebral infarcts (SCIs), also called silent strokes.[5–7]In comparison to clinically evident overt strokes, SCI's will not cause any apparent focal neurological manifestations, can be detected on screening with help of neuroimaging techniques[8,9]. Although SCI's will not cause any significant motor or sensory defects, their persistence can lead to significant morbidity, and there lies the increased risk of strokes in the future.[10–13]Both computed tomography (CT) scans and magnetic resonance imaging (MRI) scans will

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show visibility of SCI as focal lesions. Detection is better by MRI.[14]. Long-term blood transfusions were given for stroke prevention in children having abnormal transcranial Doppler (>200msec). Chronic blood transfusions will reduce the ongoing risk of recurrent infarction according to SIT trial, this benefit was incomplete because of infarct recurrence seen in some children who underwent frequent transfusion therapy [15.] .The incidence of SCD is relatively high in and around the district of Vizianagaram, Andhra Pradesh. There are no significant studies reported from this part of Andhra Pradesh state on silent cerebral infarct(SCI) in sickle cell disease(SCD). We investigated children with SCD for the presence of SCI, identify associated risk factors by doing work up in MIMS Hospital, Nellimarla Village, Vizianagaram.

Materials and Methods:-

This was Prospective Observational Study was conducted in the Department of Pediatrics at Maharaja Institute of Medical Sciences (MIMS), Nellimarla, Vizianagaram on 50 Sickle cell disease children of age group 5-14years, during January- 2020 to June- 2021 (18 Months).

Children with sickle cell disease of HbSS, HbSC, HbS beta-thalassemia in a steady-state visit to pediatric department are included and History of any episode of stroke in the past, more than six transfusions per year, Presence of comorbidity and parent refusal for consent were excluded. Parents of children who fulfil the above eligibility criteria were invited to participate in the study. An information sheet providing the details of the study was provided. Enrolment was be done after obtaining written informed consent from parents/guardians. Approval of the institutional ethics committee was taken before the start of this study. Children presented with anaemia in the age group of 5 – 14 years are evaluated for the presence of SCD. Detailed information related to the geographical area, symptoms, signs of sickle cell disease is recorded. Baseline systolic blood pressure was recorded for all the children. Laboratory workup which includes hemogram, Hb electrophoresis, and other relevant investigations are carried out. The children with confirmed haemoglobin electrophoresis findings of sickle cell disease in steady-state are subjected to T2 weighted MRI scan of the brain using Philips ingenia CX 1.5Tesla MRI machine. The opinion of the Neuroradiology Department of MIMS hospital, Vizianagaram was taken regarding the identification of silent cerebral infarcts. Children showing silent cerebral infarct (SCI) more than 3millimetres (> 3mm) in two different planes (coronary, sagittal) are included in the study, and the presence of risk factors is investigated.

Results and Observations:-

Table 1: basic demographic data

	YES	NO
SCI	18(36%)	32(64%)
5 – 9	5(27.8%)	14(43.8%)
10 – 14	13(72.2%)	18(56.3%)
SCA	10(55.2%)	22(67.75%)
SCA AND THALSSEMIA	5(27.78%)	5(15.63%)
SCD	3(16.67%)	5(15.63%)
BLOOD TRANSFUSION <1	3(16.67%)	21 (65.63%)
BLOOD TRANSFUSION 2-3	14(17.78%)	5 (15.63%)
BLOOD TRANSFUSION 4-5	1(5.56%)	6 (18.75%)
HYDROXYUREA	18(100%)	32(100%)

Table 2:- Lab investigations.

	Minimum	Maximum	Mean SD	Median
Hb	5.50	10.80	3.46 ± 0.98	3.7
RBC	1.40	5.20	13916.00 ± 5375.05	12000
WBC	7300	22100	3.41 ± 1.29	3.5
Platelet	0.50	5.60	1.86 ± 1.91	1.4
Reticulocyte count %	0.20	9.0	105.70 ± 55.32	90.5
Serum Iron	35	210	288.44 ± 50.76	287
TIBC	172	389	38.17 ± 21.63	37.31
% Iron saturation	10.39	95.39	207.66 ± 26.05	211.645
Transferrin	143	251	213.84 ± 147.58	198
Serum Ferritin	58.90	1000	3.46 ± 0.98	3.7

Table 3:- Relation Of Lab Parameters With Sickle Cell Disease.

	Yes	No	P value
Hb Mean ± SD	7.33 ± 0.79	8.87 ± 0.57	<0.0001*
Platelet Mean ± SD	3.61 ± 1.67	3.29 ± 1.01	0.40
WBC Count Mean ± SD	17122.22 ± 5020.61	12112.50 ± 4745.23	0.001*
SBP Mean ± SD	95.44 ± 4.98	93.75 ± 4.42	0.23
RBC	3.81 ± 0.63	2.84 ± 0.18	<0.0001*
retic%	2.10 ± 2.35	1.43 ± 2.47	0.35
Sr.iron	103.69 ± 49.20	109.28 ± 49.22	0.70
TIBC	280.94 ± 40.14	301.78 ± 40.77	0.08
%iron saturation	37.52 ± 17.80	39.33 ± 17.72	0.73
Transferrin	203.34 ± 26.20	215.34 ± 26.63	0.13
Ferritin	192.10 ± 85.86	252.50 ± 85.47	0.02*

In cases of SCI, it was HB 7.33 ± 0.79 and in cases of no SCI it was found to be 8.87 ± 0.57 and the difference was found to be statistically significant. The mean WBC count in cases of SCI was observed to be 1.71±5.02 and in

cases of no SCI the mean WBC count was found to be 1.21±4.74 and the difference between the mean WBC values was found to be statistically significant. Mean RBC in cases of SCI was observed to be 3.81 ± 0.63 and in cases of no SCI it was found to be 2.84 ± 0.18 and the difference was found to be statistically significant. The overall mean serum ferritin was observed to be 213.84 ± 147.58, Mean Serum Ferritin was 192.10 ± 85.86 in cases of SCI and cases of no SCI mean S. ferritin was 252.50 ± 85.47 and the difference was found to be statistically significant.

Discussion:-

Casella et al[9] in The Silent Cerebral Infarct Trial (SIT Trial)[16,17] gave definition for SCI, an MRI lesion showing at least 3 mm measurement in greatest linear dimension and T2-weighted images showing visibility in at least two planes. The SIT Trial definition does not include any prior episodes of seizures and no current focal neurologic deficit concerning the anatomic zone of the presumed SCI. Thus, participants could have a clinical neurological examination, for example, related to peripheral neuropathy, but would still meet the criteria according to definition of SCI that the location of the infarct would not show any neurological deficit. In the present study, silent infarct was found in 36% of the study participants. In the study done by **DeBraun RM et al.**[5] prevalence of SCI was found to be 30.8% and correlates with our study.

For SCA patients who underwent chronic transfusions, one of the important therapeutic goals is to maintain the total hemoglobin concentration to be high enough to suppress endogenous erythropoiesis of sickle cells . [(97)]In cases with the SCI majority requiring 2-3 episodes of blood transfusions per year, there was a significant difference in the requirement of blood transfusions per year in cases of SCI when compared to non-SCI cases. In the study conducted by **DeBraun RM et al**[5]**,** SCI children requiring frequent blood transfusions and the blood transfusion on time help to decrease complications . Hydroxyurea has proven efficacy in numerous clinical trials as a disease-modifying treatment modality in sickle cell anemia (SCA) patients but is currently under-used in clinical practice. In the study conducted at present, there was no significant difference in the duration of hydroxyurea in cases with and without SCI. In the study conducted by **De Baun MR et al.**[5]**,** they have concluded that there was no difference in the occurrence of SCI in cases of SCA by the usage of hydroxyurea therapy. Positive family history was seen in 88.88% of the cases of SCI and there was no significant difference in the positive family history in cases of SCI and non-SCI cases but positive family history should be considered as a potential risk factor for SCI while assessing the cases of SCA. The present study findings were in support with the findings made by **Roberts L et al.**[18] where they concluded that familial role has minor effect as supported by twin studies, but they have emphasized upon the incidence of SCI to be considered more when the familial history of Triple vessel disease (TVD) is observed in the siblings.

Lab investigations:

In my study, Hb ranged from 5.5-10.8mg/dl and the mean HB was observed to be 3.46 ± 0.98.

In cases of SCI, it was 7.33 ± 0.79 and in cases of no SCI it was found to be 8.87 ± 0.57 and the difference was found to be statistically significant. In the study done by **DeBraun RM et al.**[5] the mean Hb was found to be **7.95** ± 1.06 in cases of SCI and 8.25 ± 1.10 g/dl in cases of Non-SCI. the difference in the mean Hb values was found to be statistically significant across the groups and these findings are compatible with the present study.In my study, RBC values ranged between 1.40 to 5.20 and the mean was found to be 3.41 ± 1.29. Mean RBC in cases of SCI was observed to be 3.81 ± 0.63 and in cases of no SCI it was found to be 2.84 ± 0.18 and the difference was found to be statistically significant. In the study conducted by El-Hazmi MA et al[101], it was observed that the mean RBC values did not show any significant difference across the groups in cases of SCI and normal cases and this observation was not compatible with the present study.In my study, WBC ranged between 7300 to 22100 and the mean WBC count in cases of SCI was observed to be 1.71±5.02 and in cases of no SCI the mean WBC count was found to be 1.21±4.74 and the difference between the mean WBC values was found to be statistically significant .In the sntudy conducted by **Villella A et al.**[19]**.** it was observed that the mean WBC when lower correlates more with SCI in cases with SCA. There was no statistical difference in the mean values of platelet count is observed across the groups with SCI and non-SCI. The overall reticulocyte count in my study was observed to be 1.05 ± 0.55 and Mean reticulocyte % in cases of SCI was found to be 2.10 ± 2.35. there was no statistical difference in the mean values observed across the groups with SCI and non-SCI. The overall mean of serum iron was observed to be 105.7± 55.32 and the Mean serum Iron observed in cases of Sci was 103.69 ± 49.20. There was no statistical difference in the mean values observed across the groups with SCI and non-SCI. The overall mean TBIC in my study was found to be 288.17 ± 50.76 and the mean TBIC in cases of SCI was 280.94 ± 40.14. There was no statistical difference in the mean values observed across the groups with SCI and non-SCI.

The overall mean iron saturation was found to be 38.16 ± 21.63 and in cases of SCI the mean iron saturation was found to be 37.52±17.80. There was no statistical difference in the mean values observed across the groups with SCI and non-SCI. The overall mean transferrin was found to be 207.66 ± 26.0 and the Mean transferrin in cases of SCI was found to be 203.34 ± 26.20. The overall mean serum ferritin was observed to be 213.84 ± 147.58, Mean Serum Ferritin was 192.10 ± 85.86 in cases of SCI and in cases of no SCI mean Ferritin was 252.50 ± 85.47 and the difference was found to be statistically significant. In cases of SCI mean SBP was found to be 95.44 ± 4.98mm Hg and in no SCI cases the mean SBP was found to be 93.75 ± 4.42 and the difference was found to be statistically not significant. In the study conducted by **DeBraun RM et al.**[5]**,** the mean SBP was found to be 108.0 ± 11.5 mm Hg and they have also observed that there was a statistically significant difference in the groups with SCI and without SCI. the mean SBP observed in the SCI group was comparatively higher and this finding did not agree with the present study. In the study conducted by **Villella A et al.**[19]**,** they have observed that the odds ratio of SCI in cases of SCA was 1.73 when the SBP was >112mm Hg and they have also stated that the higher SBP could be considered as the potential risk factor for the cases of SCI in cases of SCA and this was not compatible with the present study.

Conclusions:-

1) In my study, silent infarct was found in 36% of the study participants and it was observed that the lower hemoglobin concentration, Lower RBC count, Lower Serum Ferritin, and elevated WBC count were considered to be the potential risk factors for Silent cerebral infarcts in Sickle cell disease.

2) Patients with risk factors for silent cerebral infarcts should be evaluated for cerebrovascular disease. If evidence of the presence of SCI, consideration must be given to therapeutic intervention.

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