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RESEARCH ARTICLE

CORRELATION BETWEEN CEREBRAL VENOUS SINUS THROMBOSIS AND SERUM HOMOCYSTEINE LEVELS IN A TERTIARY CARE HOSPITAL, INDIA A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Objective: To study correlation between Cerebral Venous Sinus Thrombosis and Serum Homocysteine levels.

Patients and Methods: 76 patients having Cerebral Venous Thrombosis were admitted to our hospital from September 2017 to September 2019. In each patient fasting serum homocysteine levels and serum B12 levels were taken and analyzed. Every patient was subjected to a detailed clinical history and neurological examination. In each patient fasting serum homocysteine levels and serum B12 levels were done. The serum homocysteine levels were done by kinetic biochemistry using R1 and R 2 reagents. The serum B12 levels were done by using ELISA Technique. On the basis of serum homocysteine levels, the patients were divided into 4 categories: Normal Level, Mild Hyperhomocysteinemia, Moderate Hyperhomocysteinemia and Severe Hyperhomocysteinemia. On the basis of serum B12 levels, the patients were again divided into 4 categories: Severe Deficiency, Mild Deficiency, Normal range and High levels.

Conclusion: Hyperhomocysteinemia could be a risk factor accounting for Cerebral Venous Sinus Thrombosis. The results of this study have shown that homocysteine levels were significantly higher in CVST patients and serum hyperhomocysteinemia is one of the risk factor in the etiology of Cerebral Venous Sinus Thrombosis patients. Though, Serum B12 levels showed no correlation in patients of CVST. Thus, Serum homocysteine estimation needs to be sent from emergency department of all patients with diagnosis of Cerebral Venous Sinus Thrombosis.

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Introduction:-

Cerebral Venous Sinus Thrombosis (CVST) is the presence of thrombus in the dural venous sinuses. It is a distinctive cause of cerebrovascular disease in young adults. Clinical manifestations of CVST are very variable and depend on the site and extent of thrombosis. Clinical features include headache, thunderclap headache, blurred vision, altered sensorium, raised intracranial pressures leading to cranial nerve palsies with focal neurodeficit and seizures. The diagnosis of CVST requires high index of suspicion because of its varied presentation. Neuroimaging is the corner stone in the diagnosis of CVST^[1].

Hypercoagulable states associated with puerperium as well as infectious diseases are believed to be the major causes in the third world ^[2,3,4]. Coagulation abnormalities, particularly associated with an increased gain-of-function mutations in the genes encoding factor V (factor V Leiden) and prothrombin^[5] are associated with an increased risk of cerebral vein thrombosis^[6,7,8].

Epidemiological studies have suggested that even mild hyperhomocysteinemia (hyper- Hcy) is associated with occlusive arterial vascular disease^[9] and venous thromboembolism^[10-15]. Little information about the role of homocysteine in CVST is available. High plasma concentrations of homocysteine and low plasma folate levels were associated with an increased risk of CVT in the population in with low socioeconomic conditions and deficient nutritional status^[16].

Thrombosis of the cranial venous sinuses and the cerebral cortical veins can lead to a distinct cerebrovascular disorder, which unlike arterial stroke, most often affects even young adults and children. The disorder can occur de novo as the first manifestation or can overlap on another existing clinical problem. In either case it is always multifactorial and is variable in each patient. Each component of the Virchow's triad (endothelial damage, stasis and hypercoagulability of blood) may in turn have several contributory factors or causes to produce the final manifestation of CVST^[17].

The common conditions with tendency for thrombosis (thrombophilic states) to be routinely looked for are dehydration, hyperhomocysteinemia, unusual postures in travel or sleep, prolonged immobilization, surgery or trauma, pregnancy or puerperium, polycythemia, thrombocytosis, obesity, diabetes, oral contraceptive pills, hormone replacement therapies, smoking, congestive cardiac failure, dyslipidemia, atherosclerosis and malignancies^[17,18].

It is also an observation that in many patients with CVST, nutritional deficiencies and lifestyle issues are more important basic etiological factors in pathogenesis. Deficiency of folic acid, vitamin B6 and vitamin B12 is the most common cause of hyperhomocysteinemia, rather than other inherited causes of it^[19].

Need for the study:

Despite the epidemiological evidence for the relationship between Hyperhomocysteinemia and venous thrombosis, little is known about its pathophysiology. Role of vitamin B12 deficiency with hyperhomocysteinemia and CVST in Indian population is also not very well established. Epidemiological studies have suggested that hyperhomocysteinemia is associated with atherosclerotic arterial disease and venous thromboembolism. Role with cerebral venous sinus thrombosis is less clear. In India one of the studies carried out in Bangalore (South India) concluded that hyperhomocysteinemia is a risk marker for Indian patients with CVST. Though many studies have not been carried out in the central and northern zone of India.

Aims And Objectives:-

Aim:

To find out the relation of serum homocysteine and serum B12 levels in patients of cerebral venous thrombosis.

Objectives:-

1. To find out the correlation of Vitamin B12 with Hyperhomocysteinemia in patients of cerebral venous thrombosis.
2. To find out the incidence of cerebral venous thrombosis patients according to age, sex, existing comorbidities and incidence according to seasonal variation.

Background and pathophysiology:

Cerebral Venous Sinus Thrombosis (Cvt): The syndrome of intracranial venous and sinus thrombosis termed as cerebral venous sinus thrombosis (CVST) is a distinctive cause of cerebrovascular disease in the young. Magnetic

resonance imaging and magnetic resonance angiography are the best diagnostic methods for diagnosis of CVST and heparin is the first-line of treatment. The Dural sinuses that are most frequently thrombosed are the superior sagittal sinus, the lateral sinus (transverse sinus and sigmoid sinus), and cavernous sinus. Less frequently affected are the straight sinus and the vein of Galen. Still rarely smaller cortical veins may be the primary site of thrombus formation without evidence of thrombus in the major sinuses or the thrombus in the major sinus would have resolved by the time the patient comes to clinical attention. This is one reason for the misdiagnosis in CT and MRI. Occlusion of a venous sinus and/or cortical vein is usually caused by a partial thrombus or an extrinsic compression that subsequently progresses to complete occlusion^[20]. Once the sinus is occluded, thrombus may extend to the cerebral cortical veins draining into that sinus (Figure 1). Thrombosis and complete occlusion results in cortical venous infarction, with petechial haemorrhages or overt haemorrhagic infarction^[20]. Normally, the CSF is transported from the cerebral ventricle through the subarachnoid spaces at the base and surface of the brain to the arachnoid villi, where it is absorbed and drained into the venous sinuses^[21]. Thrombosis of these venous sinuses leads to impaired absorption of CSF and, consequently, increased intracranial pressure. Pathological examination shows enlarged, swollen veins, oedema, ischemic neuronal damage, and petechial haemorrhages, which can merge and become large hematomas^[20,21].

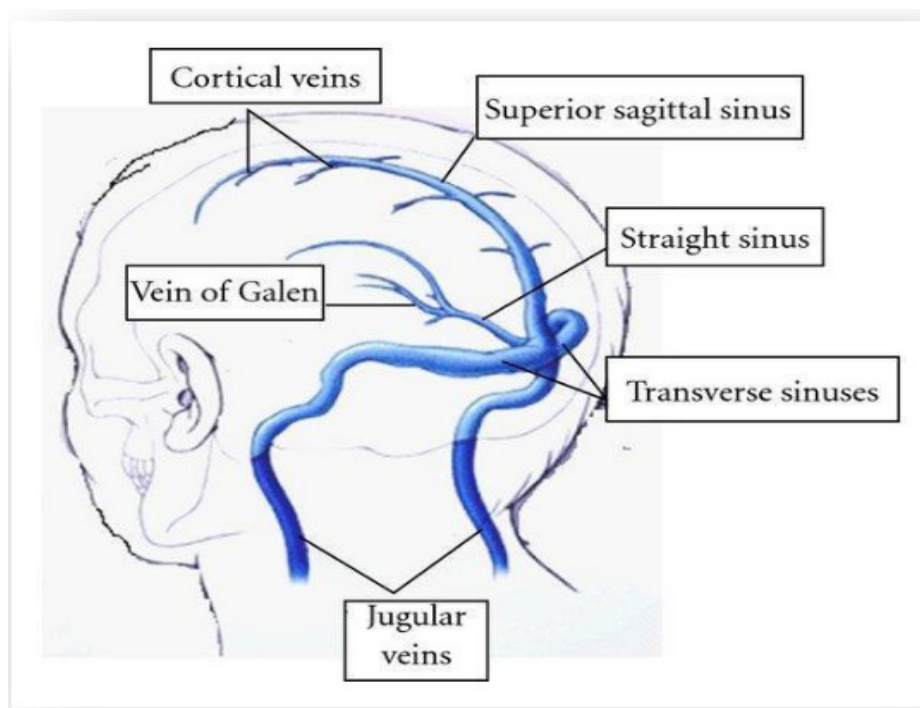


Figure 1:- Major Cerebral Venous Sinuses And Their Tributaries.

Homocysteine:

History And Structure: Homocysteine has been under a lot of speculation since its discovery in 1932. Its chemical properties showed a similarity to cysteine hence the name homocysteine. The heating of the amino acid methionine with sulphuric acid led to this amino acid of interest. The importance of this discovery cannot be emphasized without alluding to the 1955 Nobel Prize in Chemistry, awarded to Vincent du Vigneaud for his work on biochemically important sulphur compounds, especially for the first synthesis of a polypeptide hormone^[22].

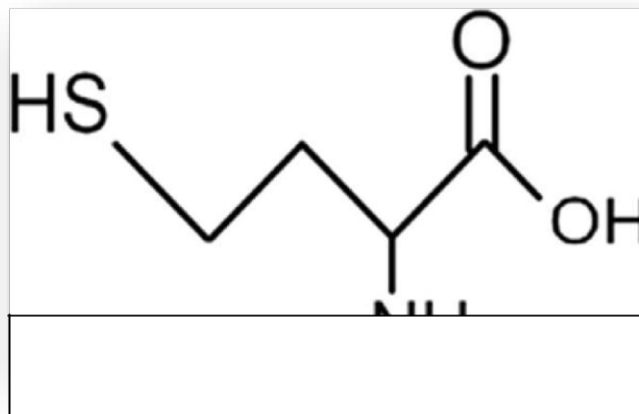


Figure 2:- Homocysteine Chemical Structure.

Vitamin b12:

Structure: Vitamin B12, also known as cobalamin, is a water-soluble vitamin that is involved in the metabolism of every cell of the human body: it is a cofactor in DNA synthesis, and in both fatty acid and amino acid metabolism.[24] It is particularly important in the normal functioning of the nervous system via its role in the synthesis of myelin^[25,26] and in the maturation of developing red blood cells in the bone marrow^[27] Vitamin B12 is one of eight B vitamins; it is the largest and most structurally complex vitamin. It consists of a class of chemically related compounds (vitamers), all of which show physiological activity. It contains the biochemically rare element cobalt (chemical symbol Co) positioned in the center of a corrin ring.

Pathogenesis Of Hyperhomocysteinemia:

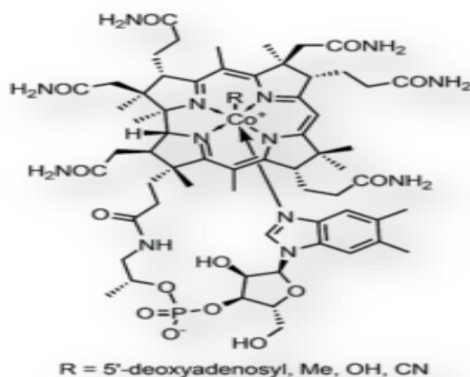


Figure 3:- Chemical Structure Vitamine B12.

Homocysteine (Hcy) is a sulfhydryl amino acid compound that is generated from protein breakdown and the essential amino acid methionine as it is metabolized to cysteine. Hcy can be metabolized by two major pathways [Figure 4]. When methionine is in excess, Hcy is directed to the transulphuration pathway, where it is irreversibly sulfoconjugated to cysteine by cystathionine B-synthase with vitamin B6 as a cofactor. Hcy is also remethylated in a methionine-conserving pathway. This process requires methionine synthase, vitamin B12 as a cofactor, and methyltetrahydrofolate as a cosubstrate. The methionine conserving pathway requires folic acid and methyltetrahydrofolatereductase (MTHFR). There is a strong inverse correlation of plasma Hcy with plasma folate concentration. In contrast to folate, serum vitamin B12 or vitamin B6 levels show only a weak correlation with plasma Hcy. Deficiencies in any of these above enzymes, folic acid, or the cofactors may lead to some degree of hyperhomocysteinemia. Homocysteine is toxic to vascular endothelium, can potentiate the oxidation of low density lipoprotein cholesterol and promote thrombosis^[22].

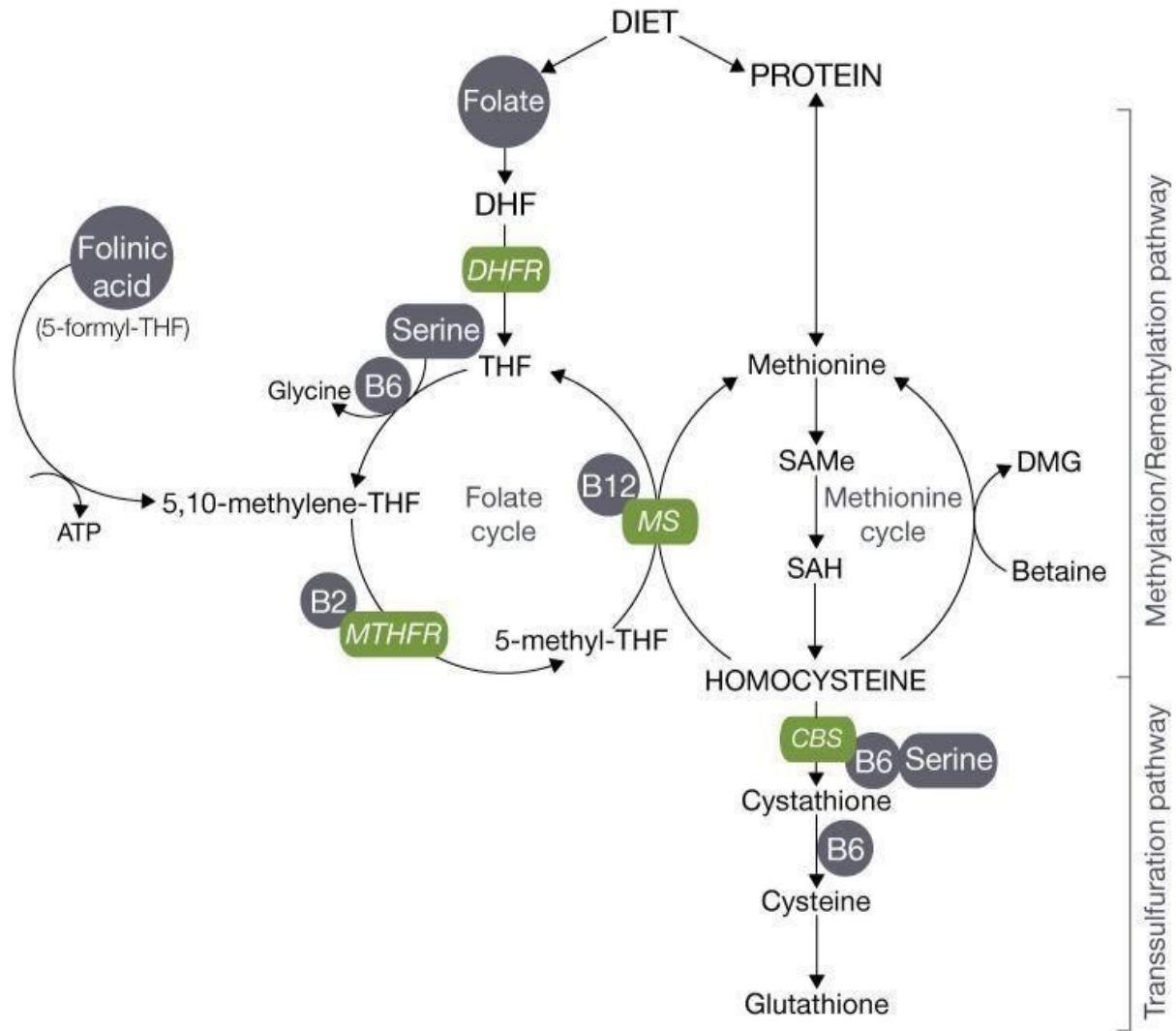


Figure 4:-Homocysteine Metabolism.

Hyperhomocysteinemia:

Hyperhomocysteinemia is defined as a medical condition characterized by an abnormally high level (above 15 $\mu\text{mol/L}$) of homocysteine in the blood [28]. Total concentration of homocysteine in plasma of healthy humans (fasting) is low and its level is between 5.0 and

15.0µmol/L when assessed with the use of HPLC, or 5.0-12.0µmol/l when immunoassay methods are used [29]. When the level is between 15-30 µmol/L it is classified as moderate, 30-100 µmol/L is considered intermediate and a value 100-189 µmol/L is classified as severe hyperhomocysteinemia^[30].

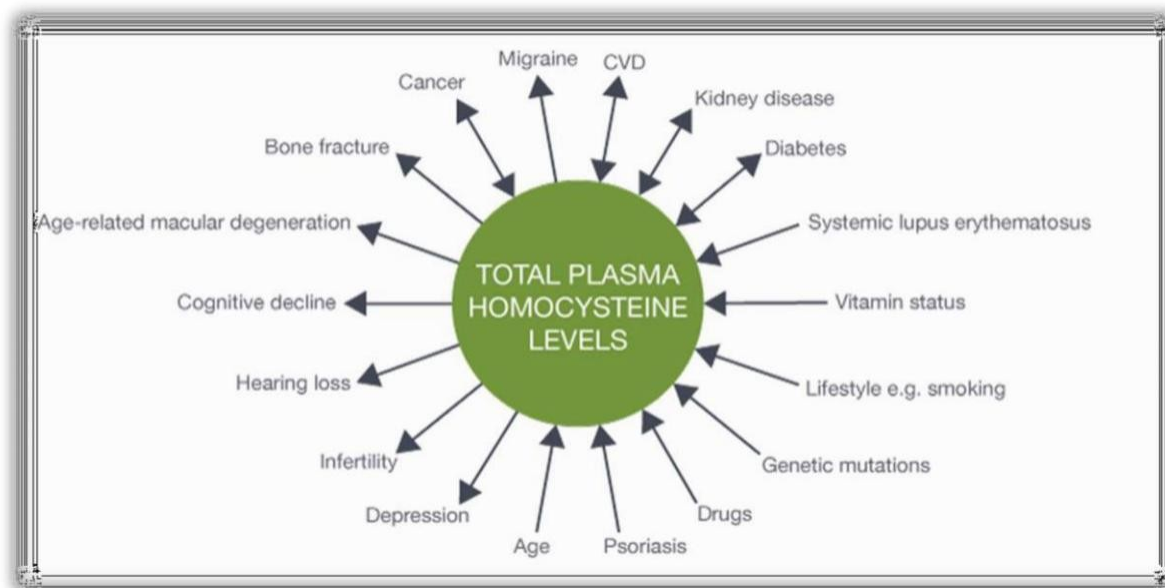


Figure 5:- Cause And Implication Of High Homocysteine Level.

Hyperhomocysteinemia can also arise from nutritional deficiencies of folate, vitamin B₆, and vitamin B₁₂^[31]. Several diseases such as renal and thyroid dysfunction, cancer, psoriasis, and diabetes as well as various drugs, alcohol, tobacco, coffee, older age and menopause, are believed to be associated with moderately elevated homocysteine concentrations^[23]. Plasma homocysteine concentrations can be increased by various drugs and diseases that interfere with folate, vitamin B₆, and B₁₂ metabolism, hence an abnormal homocysteine concentration may have a probable use as a diagnostic aid for some of these conditions^[30].

Vitamin b12 deficiency:

Vitamin B₁₂ deficiency can potentially cause severe and irreversible damage, especially to the brain and nervous system^[26,31]. At levels only slightly lower than normal, a range of symptoms such as fatigue, lethargy, difficulty walking (staggering balance problems)^[33] depression, poor memory, breathlessness, headaches, and pale skin, among others, may be experienced. The intracellular concentrations of vitamin B₁₂ can be inferred through the total plasma concentration of homocysteine, which can be converted to methionine through an enzymatic reaction that uses 5methyltetrahydrofolate as the methyl donor group. Consequently, the plasma concentration of homocysteine falls as the intracellular concentration of vitamin B₁₂ rises. The active metabolite of vitamin B₁₂ is required for the methylation of homocysteine in the production of methionine, which is involved in a number of biochemical processes including the monoamine neurotransmitters metabolism. Thus, a deficiency in vitamin B₁₂ may impact the production and function of those neurotransmitters^[34]. Thus, Vitamin B12 levels are further classified as into Normal range 190-900 pg/ml, mild deficiency 100-189 pg/ml, severe deficiency < 100pg/ml.

Literature Review:-

Cerebral vein thrombosis is a relatively rare but severe thrombotic manifestation with the potential to cause disability, and the tendency to recur^[35]. High plasma levels of total homocysteine (tHcy) result from the interaction between genetic and acquired determinants^[36]. The deficiencies of vitamins such as folic acid, pyridoxine and cobalamin, are involved in the metabolic pathways of homocysteine. Among genetic determinants, a homozygous substitution of cytosine by thymine at position 677 of the gene encoding for methylenetetrahydrofolatereductase (MTHFR) causes a 50% reduction in the activity of this enzyme and is associated with mild to moderate hyperhomocysteinemia in individuals with inadequate dietary intake of folic acid^[37]. Vitamin supplementation with folic acid, pyridoxine, and cobalamin lowers the plasma levels of tHcy in most cases^[38]. Therefore, if hyperhomocysteinemia is associated with cerebral vein thrombosis; vitamin therapy has the potential to decrease the risk of recurrence.

A study conducted by **VenkataPinnelliBharatkumar** et al in 185 patients with aseptic CVT concluded that hyperhomocysteinemia is a risk marker for Indian patients with aseptic CVT^[39]. This study was carried out in Bangalore, India which has separate demography as compared to our study population.

A study by **Makoto Takemaru** et al in 16 patients with CVT in 5 year study concluded that the disease more commonly occurred in older males and prevalence of hyperhomocysteinemia as a risk factor was high and the main underlying disorder was folate and Vitamin B12 deficiencies^[40]. This study was conducted in Japan over a period of 5 years having only 16 patients, this makes it bit insignificant as the study population was very low.

A study by **Ida Martenelli** et al in 121 patients with first episode of CVT was conducted and concluded that hyperhomocysteinemia is associated with a 4- fold increased risk of cerebral venous thrombosis and its correlation with vitamins to reduce the risk of the disease was not clearly demonstrated^[41]. This study was conducted in Italy which has different demography as compared to our study population.

Carlos Cantu et al in his study with 45 patients of CVT concluded that high plasma concentration of homocysteine and low plasma folate levels were associated with increased risk of CVT in which population of low socioeconomic status and deficient nutritional status contributed to relatively high incidence^[42].

This study was conducted in Mexico having only 45 patients, this makes it bit insignificant as the study population was low.

A study conducted by **Jana Himerova** et al in 65 patients of Venous Thromboembolism [VTE] and concluded that hyperhomocysteinemia might be the risk factor for recurrent VTE and homocysteine levels can be lowered by vitamin supplementation especially folic acid and Vitamin B12^[43]. This study was conducted in patients having venous thromboembolism and not in patients having cerebral venous sinus thrombosis.

In a case study by **MdEnayet Husain** et al in a 35 year old male with CVT concluded that the case had moderately elevated homocysteine level and other investigations done to search for etiology were normal and the patient did not have other risk factors for CVT. Thus, Hyperhomocysteinemia in CVT can contribute as an independent risk factor^[44]. This was a case study, so it is bit insignificant to conclude anything on the basis of just a case study.

In another case study, conducted by **Soumyabrata Roy Chaudhuri** et al, in a 38 year old female without any comorbidities and other risk factors, was found to have CVST had elevated levels of serum homocysteine, which might be the risk factor of CVST^[45]. This was a case study, so it becomes inconclusive on the basis of a case study.

A study conducted by **Manasi Harale** et al in 50 patients of Cerebral Venous Sinus Thrombosis patients and concluded that Vitamin B12 levels in CVST patients are lower and if Vit B12 levels are low, homocysteine levels are high. Hyperhomocysteinemia may not be always associated with low B12 level but is associated with CVST^[46]. This study was conducted in Pune which has different demography as compared to our study population.

Materials and Methods:-

Study Site:

Study was conducted at RAMKRISHNA CARE HOSPITAL, RAIPUR.

Study Population:

Patients having Cerebral Venous Sinus Thrombosis.

Study Design:

Two Years of observation study.

Sample Size:

76 patients of Cerebral Venous Thrombosis.

Study Question:

What is the co-relation of serum homocysteine levels and serum B12 in patients of Cerebral Venous Sinus Thrombosis.

Patients of Cerebral Venous thrombosis who were admitted to Ramkrishna Care Hospital, Raipur, were included in this study. We are taking sample size of 76 patients of Cerebral Venous Thrombosis from September 2017 to September 2019 for fasting homocysteine and serum B12 level. Every patient was subjected to a detailed clinical history and neurological examination. In each patient fasting serum homocysteine levels and serum B12 levels were done. The serum homocysteine levels were done by kinetic biochemistry using R1 and R 2 reagents. The serum B12 levels were

done by using ELISA Technique. On the basis of serum homocysteine levels, the patients were divided into 4 categories: Normal Level, Mild Hyperhomocysteinemia, Moderate Hyperhomocysteinemia and Severe Hyperhomocysteinemia.

1. Normal Levels : 4 -15 nmol/L.
2. Mild Hyperhomocysteinemia: 15 – 30 nmol/L
3. Moderate Hyperhomocysteinemia : 30 – 100 nmol/L
4. Severe Hyperhomocysteinemia : >100 nmol/L

On the basis of serum B12 levels, the patients were again divided into 4 categories: Severe Deficiency, Mild Deficiency, Normal range and High levels.

1. Severe Deficiency: <100 pg/ml
2. Mild Deficiency: 100-189 pg/ml
3. Normal Range: 190-900 pg/ml
4. High levels: >900 pg/ml

Statistical analysis:

Continuous data will be summarized as Mean $\pm$ SD (Standard Deviation) while Discrete (categorical) in number and percentage.

Quantitative data will be analyzed by, mean, SD, T TEST....

Qualitative data will be analyzed by percentage, Chi square test, Fisher exact test, Statistical significance
 $P > 0.05$ is not significant

$P < 0.05$ is significant

$P < 0.01$ is highly significant

Statistics software SPSS 16.0

Randomization by computer generated random numbers.

From previous study conducted by Ida Martenelli et al

$P =$ Incidence of **Hyperhomocysteinemia in CVT patients** = 27% = 0.27 1.96 = z value for 5% confidence level
 level = precision = 10%

Cochran formula for descriptive analysis

$$\text{Minimum Sample Size} = N = \frac{1.96^2 * p * (1-p)}{e^2} = (3.8416 * 0.27 * 0.73) / (0.10)^2 = 76$$

Minimum sample size = 76

Does the study require any investigation to be conducted on patients?

YES

Has the ethical clearance been obtained from your institution?

YES (COPY ENCLOSED)

Inclusion & exclusion criteria:

Inclusion Criteria:

All the patients of Cerebral Venous Sinus Thrombosis.

Exclusion Criteria:

Patients having CVA and other neurological diseases.

Observation:-

In this study a total of 76 Cerebral Venous Sinus Thrombosis patients were taken in the span of two years from September 2017 to September 2019. All the patients were examined and necessary supportive investigations such as

fasting serum homocysteine levels and serum B12 levels were sent. MRI Brain and MR Venogram were done. Data obtained from these patients were compared with prior studies of similar objectives.

Table 1:- Age distribution.

Age group	N	%
11-20	3	3.95
21-30	28	36.84
31-40	26	34.21
41-50	14	18.42
51-60	2	2.63
>60	3	3.95
Total	76	100

Chart 1:-Age distribution

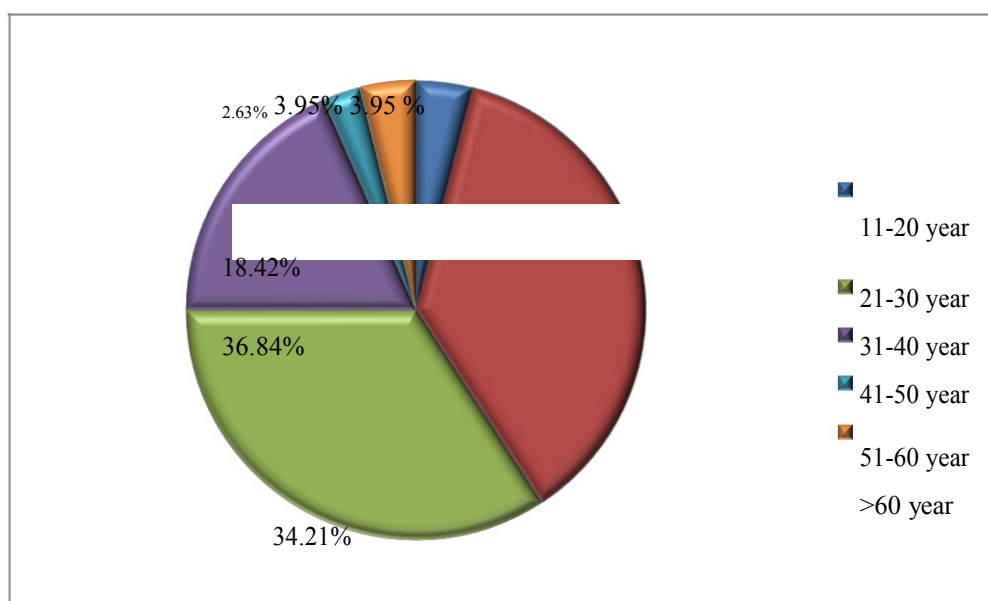


Table 1 and Chart 1 shows that out of 76 patients of CVST only 3 patients,

3.95% of patients were of age group 11yrs to 20 years, 28 patients, 36.84% of patients were of age group 21 to 30 years, 26 patients, 34.21% of patients were of age group 31 to 40 years, 14 patients, 18.42% of patients were of age group 41 to 50 years, 2 patients, 2.63% of patients were of age group 51 to 60 years and 3 patients, 3.95% of patients were of age group >60 years of age.

Table 2:-Gender distribution.

Gender	N	%
Male	46	60.53
Female	30	39.47
Total	76	100

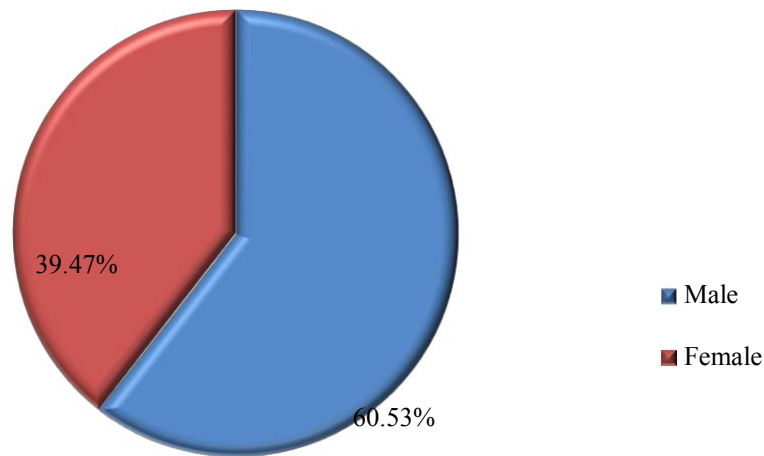
Chart 2:-Gender Distribution

Table 2 and Chart 2 shows that out of 76 patients of CVST 46 patients, 60.53% of patients were male and 30 patients, 39.47% of patients were female.

Table 3:- Serum Homocysteine levels

Homocysteine Level	N	%
Normal (<15)	24	31.58
Moderate (15-30)	16	21.05
Intermediate (30-100)	36	47.37
Severe (>100)	0	0
Total	76	100

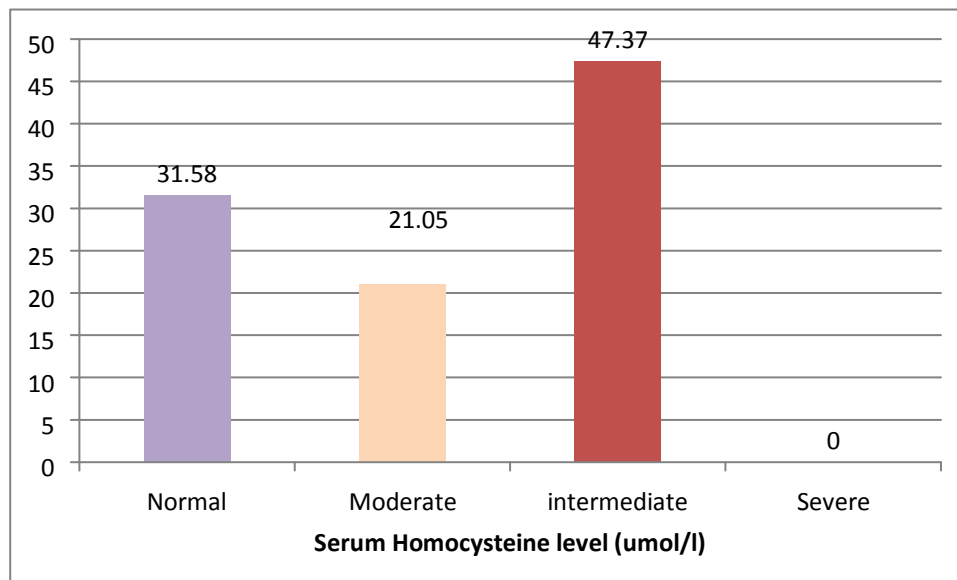
Chart 3:- Serum Homocysteine Levels.

Table 3 and Chart 3 shows that out of 76 patients of CVST 24 patients, 31.58% of patients had normal serum homocysteine levels, 16 patients, 21.05% of patients had moderate hyperhomocysteinemia and 36 patients, 47.37% of patients had intermediate hyperhomocysteinemia and no patients had severe hyperhomocysteinemia.

Table 4:- Serum B12 Levels.

Homocysteine Level	N	%
Normal (<15)	24	31.58
Moderate (15-30)	16	21.05
Intermediate (30-100)	36	47.37
Severe (>100)	0	0
Total	76	100

Serum B12 Level (pg/ml)
CHART 4: SERUM B12 LEVELS

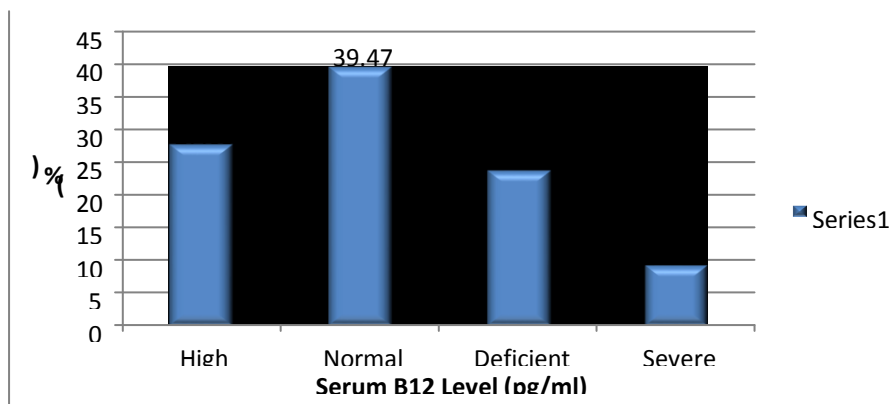


Table 4 and Chart 4 shows that out of 76 patients of CVST 21 patients, 27.63% of patients had high levels of serum B12, 30 patients, 39.47% of patients had normal serum B12 levels, 18 patients, 23.68% of patients had mild deficiency of serum B12 and 7 patients, 9.21% of patients had severe deficiency of serum Vitamin B12.

Table 5:- Comorbidities.

Comorbidity	N	%
HTN+DM2	18	23.68
HTN	12	15.79
DM2	3	3.95
NONE	43	56.58
Total	76	100

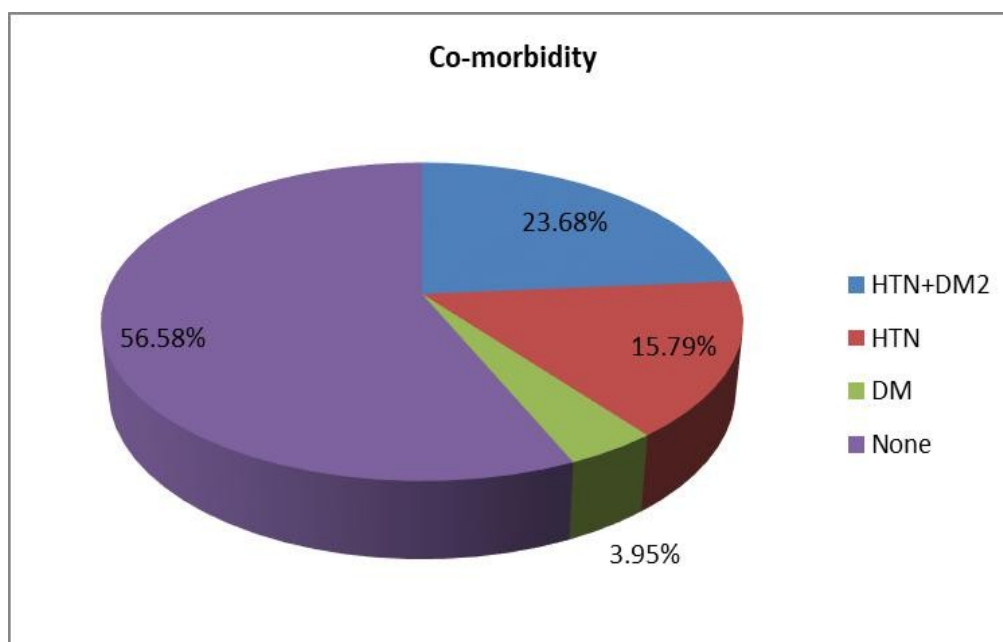
Chart 5:- Comorbidities.

Table 5 and Chart 5 shows that 18 patients out of patients, 23.68% of patients suffered from hypertension (HTN) and diabetes mellitus type 2 (DM2); 12 patients out of 76 patients, 15.79% of patients were only having HTN, 3 patients out of 76 patients 3.95% of patients were only having DM2 and 43 patients out of 76 patients, 56.58% of patients had no comorbidities.

Table 6:- Month Of Admission.

M/O	N	%
Admission		
January	6	7.89
March	3	3.95
April	11	14.47
May	10	13.16
June	8	10.53
July	5	6.58
August	8	10.53
September	10	13.16
October	2	2.63
November	8	10.53
December	5	6.58

Total	76	100

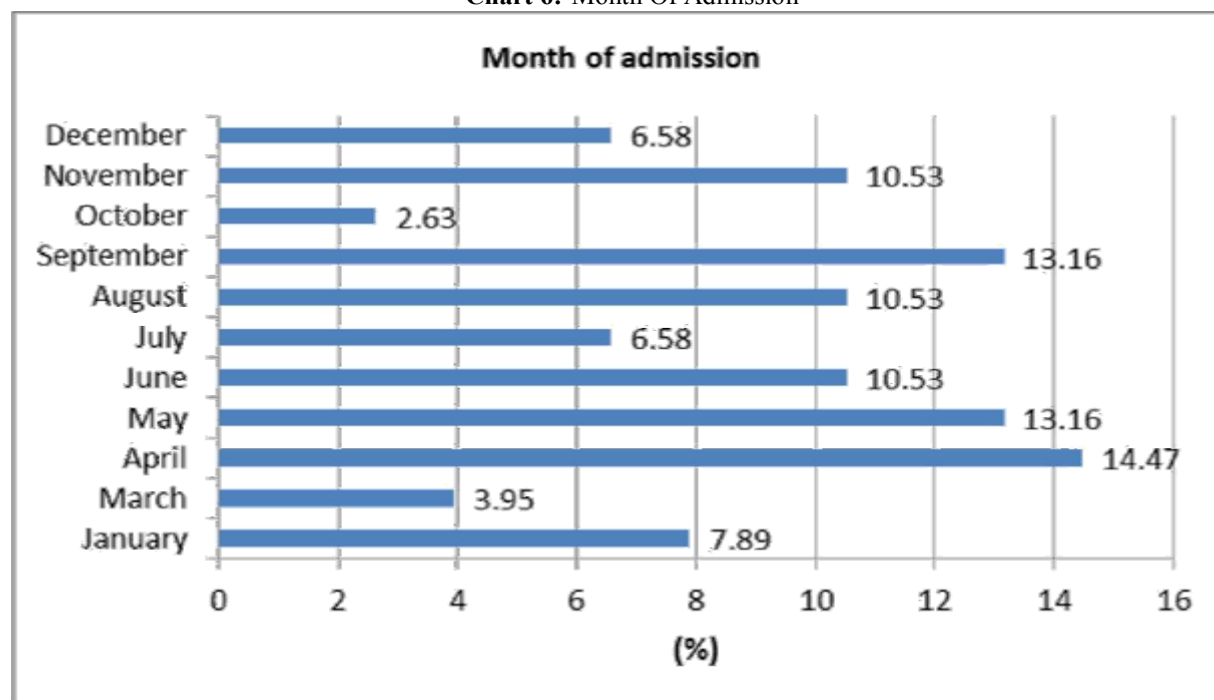
Chart 6:-Month Of Admission

Table 6 and Chart 6 shows that 6 patients of CVST out of 76 patients, 7.89% of patients were admitted in the month of January; 3 patients out of 76 patients,

3.95% of patients were admitted in the month of March; 11 patients out of 76 patients, 14.47% of patients were admitted in month of April; 10 patients out of 76 patients; 13.16% of patients were admitted in month of May; 8 patients out of 76 patients, 10.53% of patients were admitted in month of June; 5 patients out 76 patients; 6.58 % of patients were admitted in month of July; 8 patients out of 76 patients, 10.53% of patients were admitted in month of August; 10 patients out of 76 patients, 13.16% patients were admitted in month of September; only 2 patients out of 76 patients, 2.63% of patients were admitted in month of October; 8 patients out of 76 patients, 10.53% of patients were admitted in month of November and only 5 patients out of 76 patients, 6.58% of patients were admitted in month of December.

Table 7:-MRI Findings.

MRI FINDINGS	N	%
Right transverse & sigmoid sinus	27	35.53
Left transverse & sigmoid sinus	42	55.26
Inferior Sagittal & right Sinuses	3	3.95
Inferior Sagittal & left Sinuses	3	3.95
B/L transverse & sigmoid sinuses	1	1.32
Total	76	100

Chart 7:- MRI Findings.

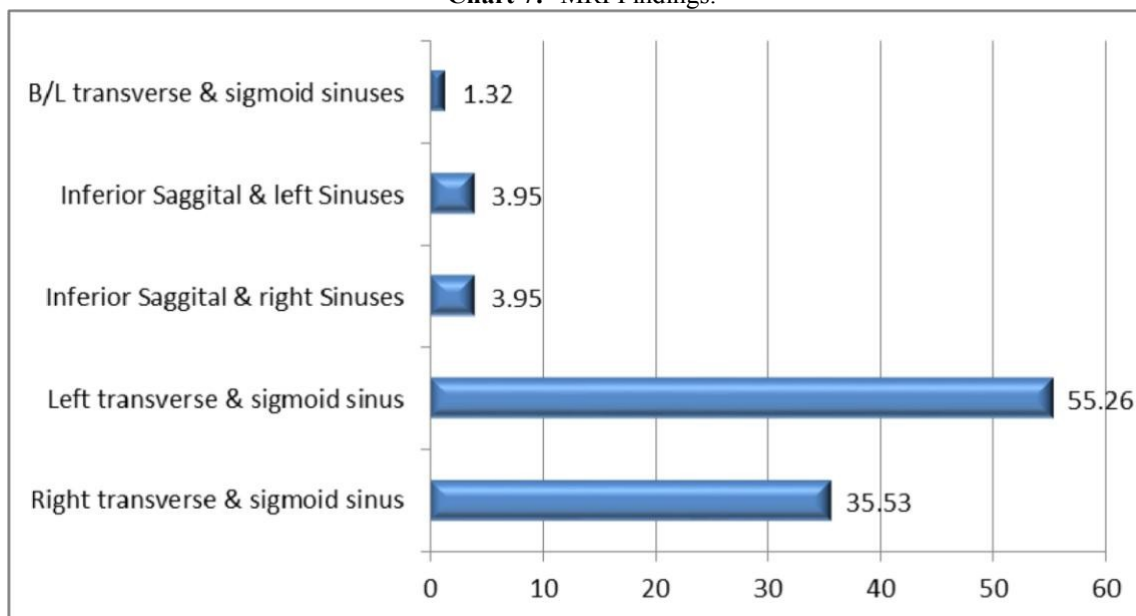


Table 7 and Chart 7 shows that 27 out of 76 patients, 35.33% of patients had Right transverse and Sigmoid sinus thrombosis; 42 patients out of 76 patients, 55.26% of patients had Left transverse and Sigmoid sinus thrombosis; 3 patients out of 76 patients, 3.95% Inferior sagittal and left transverse sinus thrombosis and 3 patients out of 76 patients, 3.95% of patients had inferior sagittal and right transverse sinus thrombosis and only 1 patient out of 76 patients, 1.32% of patients had Bilateral transverse and sigmoid sinus thrombosis.

Table 8:- Age Distribution.

Age Group	Male		Female		Total	
	N	%	N	%	N	%
11-20	1	2.17	2	6.67	3	3.95
21-30	17	36.96	11	36.67	28	36.84
31-40	16	34.78	10	33.33	26	34.21
41-50	9	19.57	5	16.67	14	18.42
51-60	2	4.35	0	0	2	2.63
>60	1	2.17	2	6.67	3	3.95

P=0.95 NS

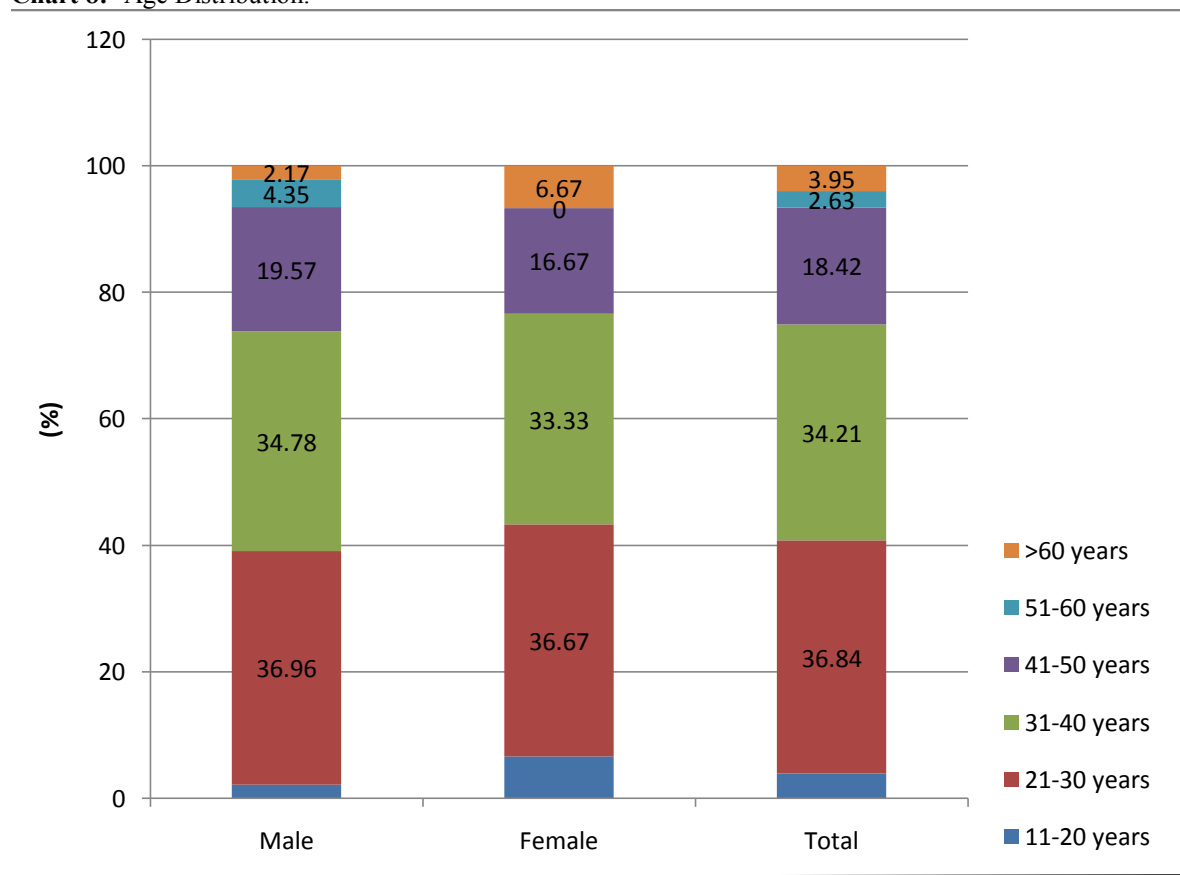
Chart 8:- Age Distribution.

Table 8 and Chart 8 shows that there was only 1 patient of age group 11-20 years, 17 patients were of age group 21-30 years, 16 patients were of age group 31-40 years, 9 patients were of age group 41-50 years, 2 patients were of age group 51-60 years and 1 patient was of age group of more than 60 years. In females 2 patients were of age group of 11-20 years, 11 patients were of age group 21-30 years, 10 patients were of age group 31-40 years, 5 patients were of age group 41-50 years and 2 patients were of age group more than 60 years.

Table 8 and Chart 8 shows that there was only 1 patient of age group 11-20 years, 17 patients were of age group 21-30 years, 16 patients were of age group 31-40 years, 9 patients were of age group 41-50 years, 2 patients were of age group 51-60 years and 1 patient was of age group of more than 60 years. In females 2 patients were of age group of 11-20 years, 11 patients were of age group 21-30 years, 10 patients were of age group 31-40 years, 5 patients were of age group 41-50 years and 2 patients were of age group more than 60 years.

Table 8 and Chart 8 shows no statistically significant difference of age distribution between males and females (p Value: 0.95)

Table 9:- Mean Age.

Age in years	Male	Female	Total
Mean	33.97	34.85	34.5
SD	13.05	10.81	11.67

P value	0.75 NS		

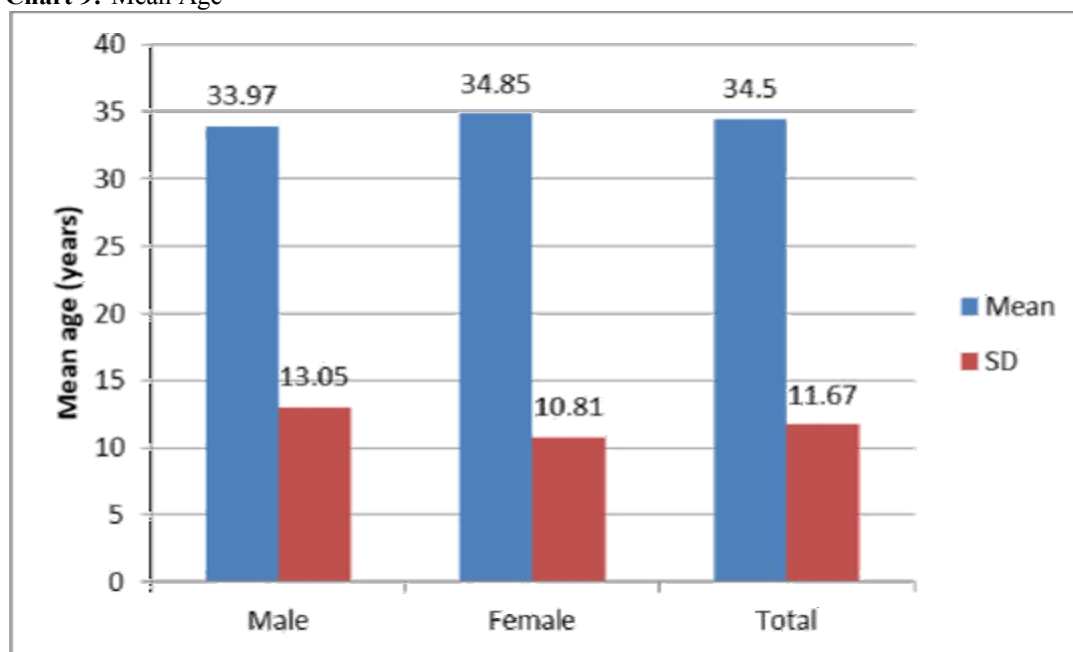
Chart 9:-Mean Age

Table 9 and Chart 9 shows that the mean age was 33.97 ± 13.05 in males and 34.85 ± 10.81 in females. The difference in mean age in two groups was found to be statistically not significant. (p Value 0.75).

Table 10:- Serum Homocysteine Levels.

Homocysteine	Male	Female	Total
Mean	26.3	30.07	28.58
SD	18.79	17.06	17.74
P value	0.37 NS		

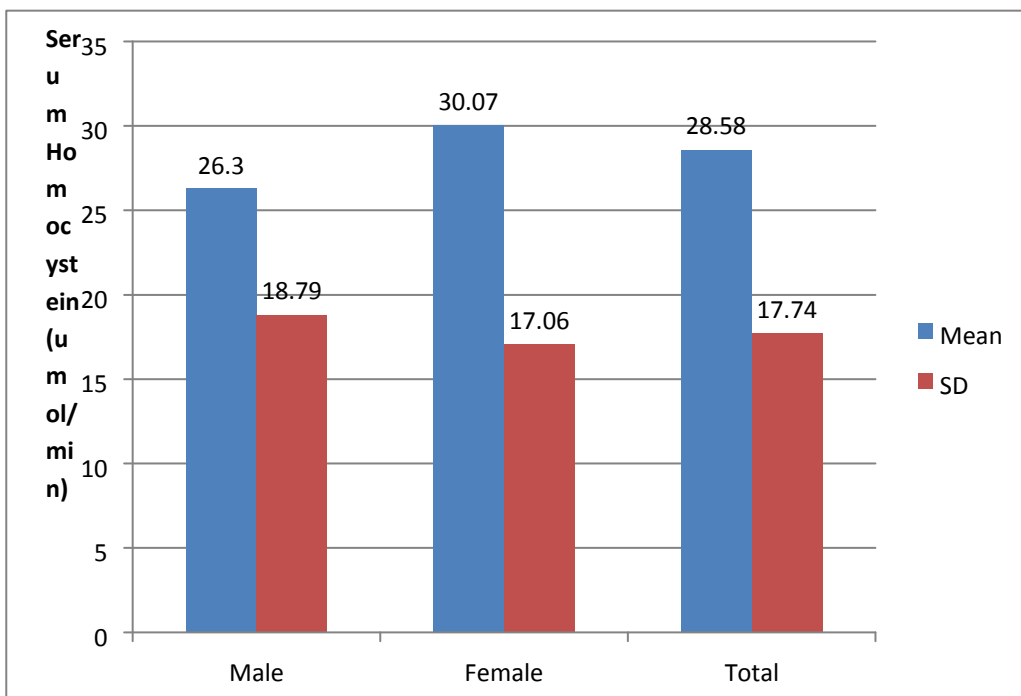
Chart 10:- Serum Homocysteine Levels.

Table 10 and Chart 10 shows that mean Serum Homocysteine levels in males were 26.3 ± 18.79 and in females were 30.07 ± 17.06 . The difference in mean Serum Homocysteine levels in males and females is statistically not significant (p Value 0.37).

Table 11:- Correlation of Serum Homocysteine With Age.

Age in years	Homocysteine level				Total
	Normal	Moderate	Intermediate	Severe	
11-20	3(100%)	0(0%)	0(0%)		3(100%)
21-30	6(21.43%)	7(25%)	15(53.57%)		28(100%)
31-40	8(30.77%)	5(19.23%)	13(50%)		26(100%)
41-50	4(28.57%)	3(21.43%)	7(50%)		14(100%)
51-60	1(50%)	0(0%)	1(50%)		2(100%)
>60	2(66.67%)	1(33.33%)			3(100%)
P value=0.32 NS					

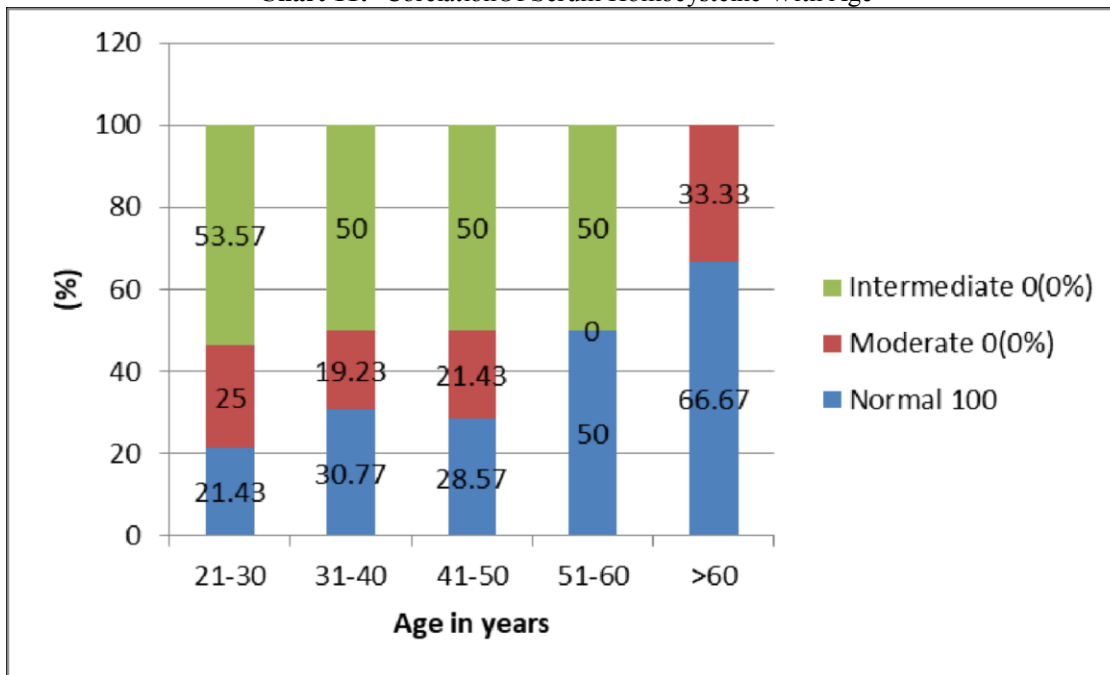
Chart 11:- CorrelationOf Serum Homocysteine With Age

Table 11 and Chart 11 shows that out of 76 patients 3 patients were of age group 11-20 years and had normal serum homocysteine levels. 28 patients were of age group 21-30 years out of which 6 patients had normal levels of serum homocysteine, 7 patients had moderate levels of serum homocysteine and 15 patients had intermediate levels of serum homocysteine. 26 patients were of age group 31-40 years out of which 8 patients had normal levels of serum homocysteine, 5 patients had moderate levels of serum homocysteine and 13 patients had intermediate levels of serum homocysteine. 14 patients were of age group 41-50 years out of which 4 patients had normal levels of serum homocysteine, 3 patients had moderate levels of serum homocysteine and 7 patients had intermediate levels of serum homocysteine.

2 patients were of age group 51-60 years out of which 1 patient had normal levels of serum homocysteine and 1 patient had intermediate levels of serum homocysteine.

3 patients were of age group more than 60 years out of which 2 patients had normal levels of serum homocysteine and 1 patient had moderate levels of serum homocysteine.

The correlation between serum homocysteine and age group is statistically not significant (p Value: 0.32)

Table 12:- CorrelationBetween Serum Homocysteine And Gender.

Gender	Homocysteine levels				Total
	Normal	Moderate	Intermediate	Severe	
Male	12(26.09%)	12(26.09%)	22(47.83%)	0(0%)	46(100%)
Female	12(40%)	4(13.33%)	14(46.67%)	0(0%)	30(100%)
P value=0.28 NS					

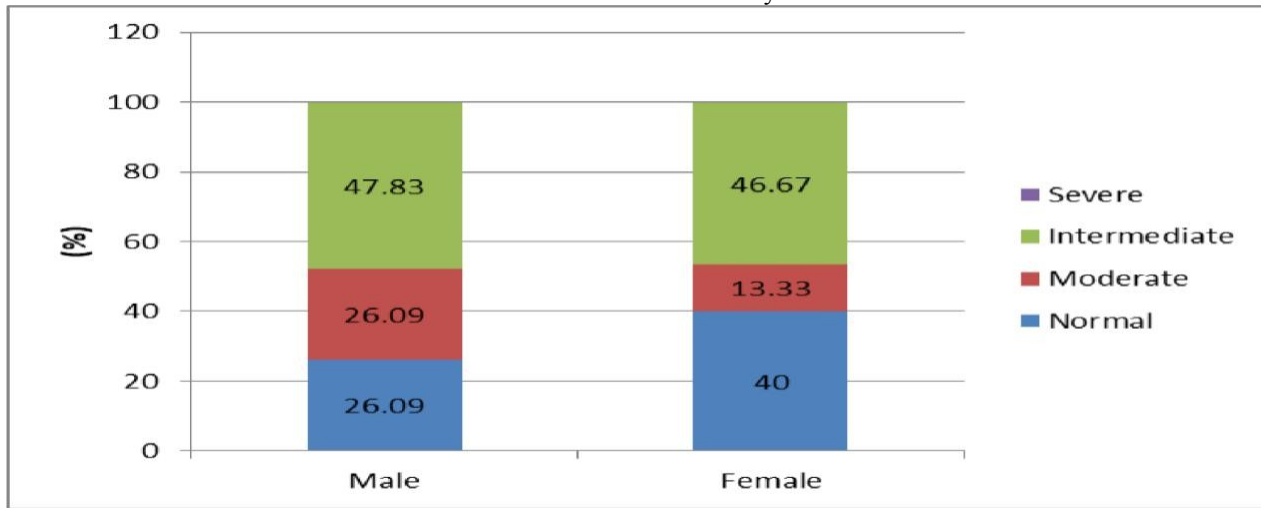
Chart 12:- CorrelationBetween Serum Homocysteine And Gender.

Table 12 and Chart 12 shows that out of 76 patients, 46 patients were males out of which 12 patients had normal serum homocysteine levels, 12 patients had moderate serum homocysteine levels and 22 patients had intermediate serum homocysteine levels.

30 patients were females out of which 12 patients had normal serum homocysteine levels, 4 patients had moderate levels of serum homocysteine levels and 14 patients had intermediate levels of serum homocysteine.

The correlation between serum homocysteine levels and gender is statistically not significant (p Value: 0.28).

Table 13:- CorrelationOf Serum B12 Levels And Age.

	Serum B12				
Age in years	High	Normal	Mild Deficient	Severe Deficient	Total
11-20	1(33.33%)	2(66.67%)	0(0%)	0(0%)	3(100%)
21-30	7(25%)	13(46.43%)	7(25%)	1(3.57%)	28(100%)
31-40	9(34.62%)	7(26.92%)	8(30.77%)	2(7.69%)	26(100%)
41-50	2(14.29%)	6(42.86%)	2(14.29%)	4(28.57%)	14(100%)
51-60	1(50%)	1(50%)	0(0%)	0(0%)	2(100%)
>60	1(33.33%)	1(33.33%)	1(33.33%)	(0%)	3(100%)
P value	0.52 NS				

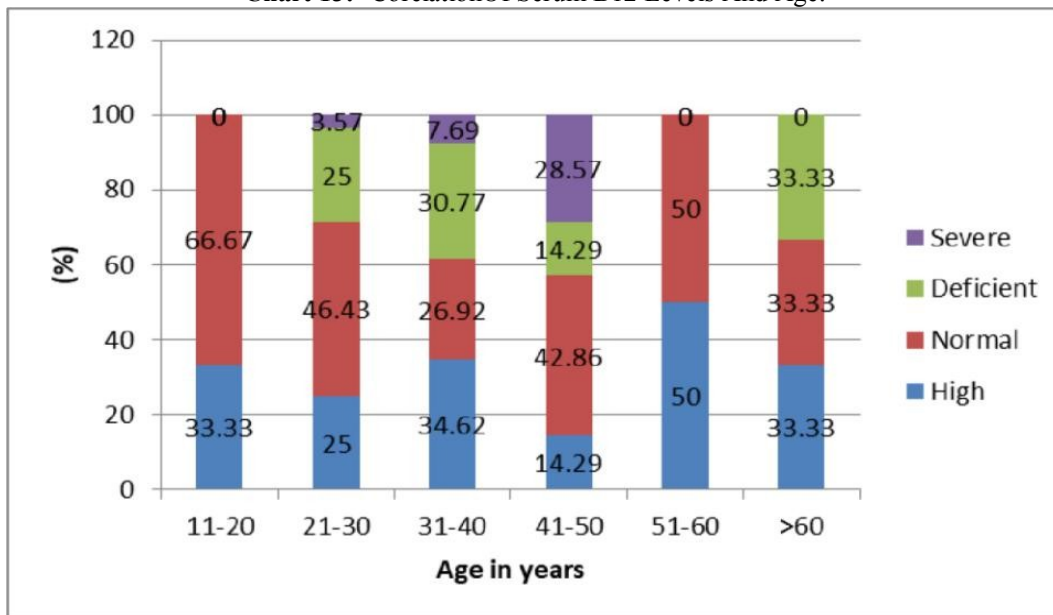
Chart 13:- CorrelationOf Serum B12 Levels And Age.

Table 13 and Chart 13 shows that out of 76 patients 3 patients were of age group 11-20 years, out of which 1 patient had high levels of serum B12 and 2 patients had normal levels of serum B12.

28 patients were of age group 21-30 years, out of which 7 patients had high levels of serum B12, 13 patients had normal levels, 7 patients had mild deficiency and 1 patient had severe deficiency of serum B12 levels.

26 patients were of age group 31-40 years, out of which 9 patients had high levels of serum B12, 7 patients had normal levels, 8 patients had mild deficiency and 2 patients had severe deficiency of serum B12 levels.

14 patients were of age group 41-50 years, out of which 2 patients had high levels of serum B12, 6 patients had normal levels, 2 patients had mild deficiency and 4 patients had severe deficiency of serum B12.

patients were of age group 51-60 years, out of which 1 patient had high levels of serum B12 and 1 patient had normal levels of serum B12.

patients were of age group more than 60 years, out of which 1 patient had high levels of serum B12, 1 patient had normal levels and 1 patient had mild deficiency of serum B12 levels.

The correlation between serum B12 levels and age is statistically not significant (p Value: 0.52).

Table 14:- CorrelationBetween Serum B12 Levels And Gender.

	Serum B12				
	High	Normal	Mild Deficient	Severe Deficient	Total
Gender					
Male	18(39.13%)	16(34.78%)	8(17.39%)	4(8.7%)	46(100%)
Female	3(10%)	14(46.67%)	10(33.33%)	3(10%)	30(100%)
P value	0.041 S				

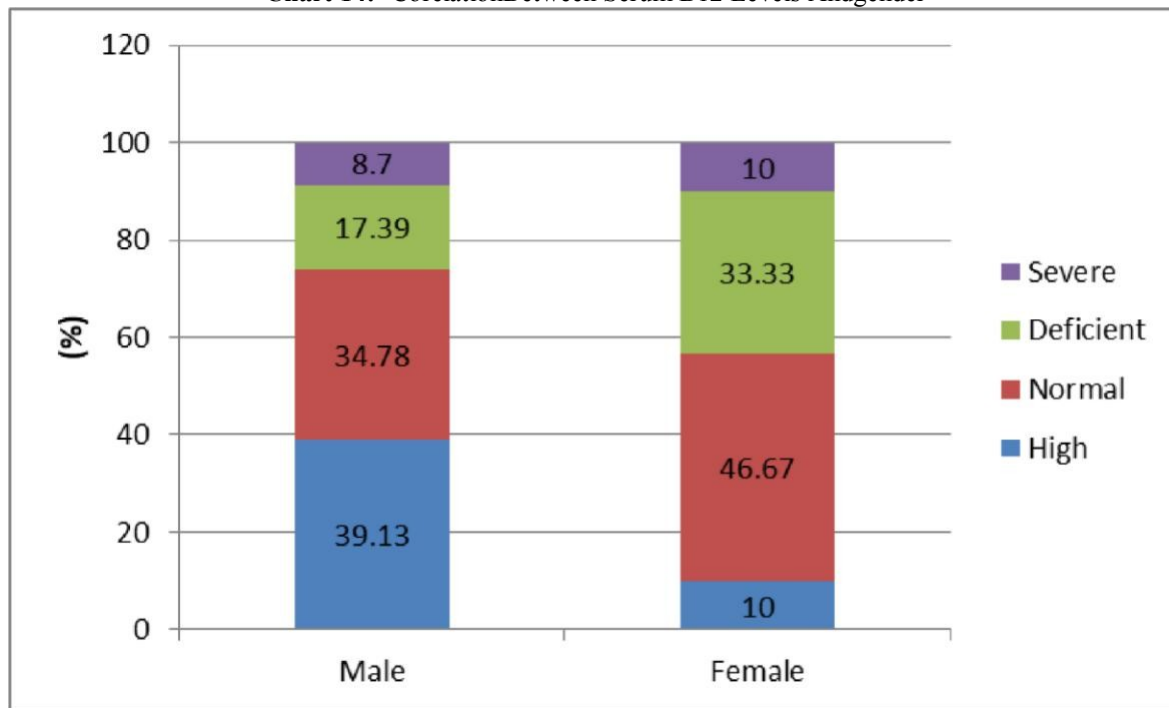
Chart 14:- Correlation Between Serum B12 Levels And gender

Table 14 and Chart 14 shows that out of 76 patients 46 patients were males out of which 18 patients had high levels of serum B12, 16 patients had normal levels, 8 patients had mild deficiency and 4 patients had severe deficiency of serum B12 levels.

30 patients were females out of which 3 patients had high levels of serum B12, 14 patients had normal levels, 10 patients had mild deficiency, 3 patients had severe deficiency of serum B12 levels.

The correlation between serum B12 levels and gender is statistically significant (p Value 0.41).

Discussion:-

Results:-

This observational comparative study was done at RamkrishnaCare Hospital, Raipur, from September 2017 to September 2019 and involved 76 patients of Cerebral Venous Sinus Thrombosis. With the help of clinical evaluation and detailed investigations we had determined hyperhomocysteinemia is the risk factor for Cerebral Venous Sinus Thrombosis. 68.42% patients were found to have high homocysteine level either mild or intermediate. Data obtained from these patients were analyzed and the results were compared with prior studies of similar objectives. We also found in our study that most common age group of presentation with CVST are 21-40 years :71.05% (21-30 years : 36.84% & 31-40 years : 34.21%) with a slight male (60.53%) prevalence in comparison to female (39.47%). In 56.58% of patients no associated comorbidity was found in the study population. Based on the MRI findings, most commonly affected are left transverse & sigmoid sinuses (55.26%) followed by right transverse sinus & sigmoid sinuses (35.53%). No statistical significance could be derived between serum homocysteine or vitamin B12 levels and age or gender of the patients.

Correlation between Serum Homocysteine levels and Cerebral Venous Sinus Thrombosis:

In the present study of 76 patients of CVST, 52 patients had hyperhomocysteinemia, out of which 16 patients had moderate hyperhomocysteinemia, 36 patients had intermediate hyperhomocysteinemia and 24 patients had normal levels of serum homocysteine. The mean of serum homocysteine levels was 28.58 ± 17.74 (Normal- 24, Moderate- 16, Intermediate-36, Severe - 0).

In a similar study conducted by **ManasiHarale et al** (46) on 50 patients, 35 patients were found to have elevated serum homocysteine levels. According to the published literature, hyperhomocysteinemia is an important cause of hypercoagulopathy and increases risk of CVST by 4 folds. Therefore, it would be

prudent to include homocysteine levels in initial prothrombotic workup for unprovoked venous thrombosis.

In a similar study conducted by **Carlos Cantu et al** (16) on 45 patients of CVST, concluded that high plasma concentrations of homocysteine were associated with an increased risk of Cerebral Venous Thrombosis.

Correlation between Serum B12 levels and Cerebral Venous Sinus: Thrombosis:

In the present study of 76 patients of CVST, 18 patients had mild deficiency, 07 patients had severe deficiency, 30 patients had normal levels and 21 patients had high level of Serum B12. The mean of Serum B12 levels was

824.9±430.8. In a similar study conducted by **Manasi Harale et al** (46), there was no correlation between vitamin B12 levels in CVST patients. The study stated that if vitamin B12 levels are low, homocystine levels tend to be high but hyperhomocysteinemia may not always be associated with low vitamin B12 levels. In the study conducted by **Carlos Cantu et al** (16), concluded that low folate and vitamin B12 levels were associated with an increased risk of CVT in the population in which low socioeconomic and deficient nutritional status may contribute to its relatively high incidence.

In our study population we did not find any co-relation of CVST with renal disease, smoking and oral contraceptive use. Though we would like to do multi-centric study in one zone or whole of India, in longer period of time to find these co-relation. We should include detailed drug history and personal history in emergency department, after our initial workup.

Limitations:

Any correlation between Vitamin B12 deficiency and CVST or hyperhomocysteinemia could not be drawn from this study as patients included in the study group were already receiving vitamin B12 supplementations.

This study was done only in one tertiary centre of Raipur and to find out the prevalence and correlation of hyperhomocysteinemia in a particular zone we need larger population in longer period of time.

Conclusion:-

In conclusion, hyperhomocysteinemia could be a risk factor accounting for Cerebral Venous Sinus Thrombosis. The results of this study have shown that homocysteine levels were significant in CVST patients and serum hyperhomocysteinemia is a risk factor in the etiology of Cerebral Venous Sinus Thrombosis patients.

Thus, Serum homocysteine estimation in emergency department of all patients of Cerebral Venous Sinus Thrombosis and periodically in yearly follow up should be recommended. Hyperhomocysteinemia when discovered should be treated with supplements and suitable vitamins.

Nevertheless, these statements need further confirmation with more elaborate trials. It is necessary to perform larger scale based prospective and interventional studies to clarify the independent risk of homocysteine in patients of Cerebral Venous Sinus Thrombosis.

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