

Clinical Profile of Cerebral Venous Thrombosis in Correlation with Anticardiolipin Antibody Titre

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ABSTRACT

BACKGROUND

Anticardiolipin antibodies (aCL) have been recognized as an independent risk factor for an increased risk of thrombosis. The aim of our study was to assess the prevalence of aCL antibodies in patients with CVT (Cerebral Venous Thrombosis) and correlate clinical profile of CVT with anticardiolipin antibody titre.

METHODS

Forty-two patients with CVT diagnosed by neuroimaging were investigated for the presence of aCL. We compared the clinical profile of ACL antibody positive and negative group.

RESULTS

Anticardiolipin antibodies were detected in 30.9 % of CVT patients. In anticardiolipin antibody negative group, mean age was 26.76 ± 8.49 years, compared to positive group in which mean age was 32.00 ± 10.88 years which was statistically not significant. In our study, mean leukocyte count was low among aCL positive group compared to negative group (8396 ± 2694.8 vs. 10472.41 ± 3353.5), which was statistically not significant. Both positive and negative groups were comparable with respect to other clinical findings.

CONCLUSIONS

Anticardiolipin antibodies (aCL) have been recognized as an independent risk factor for an increased risk of thrombosis. Its presence in patients with CVT requires lifelong anticoagulation to prevent recurrence. So all patients of CVT need to be evaluated for the presence of anticardiolipin antibodies.

KEYWORDS

Cerebral Venous Thrombosis, CVT, Anticardiolipin Antibodies

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BACKGROUND

Cerebral venous thrombosis can present with headache, papilloedema, seizures, focal deficits, coma and even death. CVT is characterized pathologically by haemorrhagic infarction and is more common than previously thought.¹ approximately 20 – 35 % of cases have no identifiable aetiology. So the search for etiological factors remains a challenge for the treating physician.

Antiphospholipid (aPL) antibodies are part of a heterogeneous group of circulating serum polyclonal immunoglobulins (IgG, IgM, IgA or mixed) that bind negatively charged or neutral phospholipid components of cell membrane and cause increased tendency to venous or arterial thrombosis.²

Of all the antiphospholipid antibodies the anticardiolipin (aCL) antibodies and the lupus anticoagulant (LA) are the most extensively studied.^{3,4}

Antibodies against phospholipids other than cardiolipin have been less studied and characterized than aCL antibodies. These include mainly anionic moieties such as phosphatidylserine and phosphatidylinositol and occasionally neutral phospholipids such as phosphatidyl ethanolamine. Also data accumulated over the last few years

Identified β 2-glycoprotein I (β 2-GPI; also named apolipoprotein H) as a necessary plasma cofactor to bind cardiolipin in vitro on ELISA plates.^{5,6} Cerebral venous thrombosis is a rare disorder having a relatively high mortality (10 % - 15 %).^{7,8}

Study by Juan R. Carhuapoma et al⁹, has shown that aCL may be an important factor contributing to development of CVT even in the presence of other potential aetiologies or risk factors. Onset of aCL positive CVT occurs at a relatively young age and with relatively more extensive superficial and deep cerebral venous system involvement than aCL negative CVT.

In Christopher. R et al study¹⁰, it was shown that anticardiolipin antibodies were detected in 22.6 % of CVT pts. Headache (87 %) and seizures (71 %) were the common presenting symptoms. The only significant laboratory finding in the aCL positive group was thrombocytopenia which was seen in 28.6 % and was not seen in aCL negative patients ($p < 0.001$).

In study by M. Saadatnia et al¹¹ aCL was detected in 20 % of patients. Low death rate in aCL positive CVT patients is probably because of the more superficial sinus or veins involvement in this group. In this study clinical and demographic characteristic were similar in the aPL positive and the aPL-negative group. However, aCL-positive group was commonly associated with seizure, infarct, superficial veins and sinus involvement and the use of OCP.

In study by S Chandrashekhara et al¹² high titres of aCL IgG was seen in 14.29 % of CVT patients. In study by E. M. Wysokinska et al¹³ Anticardiolipin antibodies were positive in 17 % of patients with CVT. So far various studies indicated that aCL-positive patients were commonly young females. Among the 20 aCL-positive CVT patients described in literature since 1985, 75 % were women and the mean age of patients was 28 years.

Objectives

1. To assess the prevalence of anticardiolipin antibodies in patients with CVT.
2. To correlate clinical profile of CVT with anticardiolipin antibody titre.

METHODS

CVT patients attending Victoria Hospital and Bowring and Lady Curzon Hospital attached to Bangalore Medical College and Research Institute were included in the study after obtaining proper informed consent and clearance from institutional Ethical Committee. After reviewing the admission data of CVT patients in our hospital in the previous 2 years; a time duration of 2 years was set and all patients coming with the diagnosis of CVT were evaluated as prospective study subjects. At the end of study, sample size was 42.

The diagnosis of CVT was based on cranial computerized tomography (CT) or Magnetic Resonance Imaging (MRI) or MR venography in the presence of an appropriate clinical picture. Patients developing CVT secondary to head, facial, or neurosurgical infections, trauma and neurosurgical procedures were not included in the study. Particular attention was paid to predisposing factors like anaemia, history of abortions, puerperium, use of oral contraceptives and history of previous thrombotic events. It is a prospective cross-sectional study.

The following investigations were done after obtaining the informed consent.

1. Complete haemogram,
2. ANA,
3. VDRL,
4. Liver function tests,
5. Renal function tests,
6. Anticardiolipin antibody titre-IgM and IgG (Test was done using freesias kit manufactured by Dr. Fenning Biomed GmbH. Cut off values for positive result was taken as for IgM > 10 MPL Units, for IgG > 12 GPL Units.).
7. CT Brain or MRI or MR angiography OR MR venography of brain anticardiolipin antibody titre-IgM and IgG

Statistical Analysis

In the present study descriptive statistical analysis has been done. Continuous measurements are presented as Mean $\pm$ SD (Min-Max) and categorical measurements are presented as Number (%).

Significance is assessed at 5 % level of significance. Student t test has been used to find the significance of study parameters on continuous scale between two groups on metric parameters.

Chi-square / Fisher Exact test has been used to find the significance of study parameters on categorical scale between the two groups. 95 % confidence interval has been computed to find the significant features. Confidence interval with lower limit more than 50 % is associated with statistical significance.

The Statistical software namely SPSS Ver. 23 was used for the analysis of the data. Microsoft word and Excel were used to generate tables.

RESULTS

In our study the most common age group was 21 - 30 years (57.1 %).

Age in Years	Number of Patients	%
18 - 20	7	16.7
21 - 30	24	57.1
31 - 40	7	16.7
41 - 50	2	4.8
> 50	2	4.8
Total	42	100.0
Mean $\pm$ SD: 28.38 $\pm$ 9.48		
Gender		
Male	13	31.0
Female	29	69.0
Total	42	100.0

Table 1. Age and Gender Distribution

In our study 69 % of patients were females, 31 % were males. In our study 8 patients (27.6) had history of abortion out of 29 female patients. In our study 13 patients belonged to puerperal CVT. In our study 44.8 % of female patients had history of puerperium. Mean duration of puerperium was 18.44 $\pm$ 7.99.

Clinical Profile	No. of Patients (n = 42)	%	95 % CI
1. H / O OCP Use	1	2.4	0.4 - 12.32
2. H / O DVT	1	2.4	0.4 - 12.32
3. H / O CVT	1	2.4	0.4 - 12.32
4. H / O PIH	2	4.8	1.32 - 15.79
5. Headache	38	90.5	77.93 - 96.23
6. Vomiting	33	78.6	64.06 - 88.29
7. Visual Disturbances	11	26.2	15.30 - 41.07
8. Loss of Consciousness	21	50.0	35.53 - 64.47
9. Seizures	30	71.4	56.43 - 82.83
10. Motor Weakness	17	40.5	27.04 - 55.54
11. Pallor	33	78.6	64.06 - 88.29
12. Papilledema	12	28.6	17.17 - 43.57
13. Speech Disorder	5	11.9	5.19 - 25.00
14. Cranial Nerve Palsies	11	26.2	15.30 - 41.07

Table 2. Clinical Profile of Patients

In our study headache was the most common symptom seen in 90.5 % of patients, followed by vomiting in 78.6 %, seizures in 71.4 %, loss of consciousness in 50 %, motor weakness in 40.5 %. Visual disturbances were seen in 26.2 % of patients. On examination most common finding was pallor seen in 78.6 % of patients, followed by papilloedema in 28.6 %, cranial nerve palsies in 26.2 %. Speech disturbances were present in 11.9 % of patients.

In our study anaemia was present in 85.7 % of patients. Leucocytosis was present in 28.6 % of patients. All of them had neutrophilic leucocytosis. None of the patient had leukopenia. ESR was elevated in 85.7 %. Thrombocytosis was seen in 7.1 %. None of the patients had thrombocytopenia. ANA test was positive in 7.1 %.

IgM anticardiolipin antibodies were positive in 30.9 % of patients. IgG anticardiolipin antibodies were positive in 9.5 % of patients but all of them were also positive for IgM anticardiolipin antibodies. Out of 13 positive patients, 4 had low positive titer (< 20 MPL Units) and 9 were moderately

positive (21 to 60 MPL Units). None of them had high titer. All the 4 patients had moderately high titer for IgG (21 to 100 GPL Units).

Investigations	Criteria	Number of Patients (n=42)	%	95 % CI
Haemoglobin (g/dl)	Male > 12; Female > 11	6	14.3	6.72 - 27.64
	Male < 12; Female < 11	36	85.7	72.16 - 93.28
Total count	< 4000	0	0.0	-
	4000 - 11000	30	71.4	56.43 - 82.83
Neutrophils	> 11000	12	28.6	17.17 - 43.57
	< 70	29	69.1	53.97 - 80.93
Lymphocytes	> 70	13	30.9	19.07 - 46.03
	< 50	42	100.0	91.62 - 100.0
ESR	> 50	0	0.0	-
	Male < 20; Female < 15	6	14.3	6.72 - 27.84
Platelet count	Male > 20; Female > 15	36	85.7	72.16 - 93.26
	< 1.5	0	0.0	-
LFT	1.5 - 4.0	39	92.9	80.99 - 97.54
	> 4.0	3	7.1	2.46 - 19.61
RFT	Normal	42	100.0	91.62 - 100.0
	Abnormal	0	0.0	-
ANA	Normal	42	100.0	91.62 - 100.0
	Abnormal	0	0.0	-
IgM aCL MPL Units	Negative	39	92.9	80.9 - 97.54
	Positive	3	7.1	2.46 - 19.01
IgG aCL GPL Units	< 10	29	69.1	53.97 - 80.93
	> 10	13	30.9	19.07 - 46.03
	< 12	38	90.4	77.93 - 96.23
	> 12	4	9.5	3.77 - 22.07

Table 3. Laboratory Findings

Variables	IgM Levels MPL Units < 10 (n = 29)	IgM Levels MPL Units > 10 (n = 13)	P Value
Age in Years; Mean $\pm$ SD	26.76 $\pm$ 8.49	32.00 $\pm$ 10.88	0.098 +
Male; No (%)	9 (31.0 %)	4 (30.8 %)	1.000
Female; No (%)	20 (68.9 %)	9 (69.2 %)	1.000
H / O OCP Use; No (%)	1 (3.4 %)	0	1.000
H / O DVT; No (%)	0	1 (7.7 %)	0.310
H / O CVT; No (%)	1 (3.4 %)	0	1.000
H / O PIH; No (%)	1 (3.4 %)	1 (7.7 %)	1.000
Headache; No (%)	27 (93.1 %)	11 (84.6 %)	0.576
Vomiting; No (%)	25 (86.2 %)	8 (61.5 %)	0.107
Visual Disturbances; No (%)	8 (27.6 %)	3 (23.1 %)	1.000
Loss of Consciousness; No (%)	13 (44.8 %)	8 (61.5 %)	0.317
Seizures; No (%)	20 (68.9 %)	10 (76.9 %)	0.722
Motor Weakness; No (%)	12 (41.4 %)	5 (38.5 %)	1.000
Pallor; No (%)	23 (79.3 %)	10 (76.9 %)	1.000
Papilledema; No (%)	9 (31.1 %)	3 (23.1 %)	0.722
Speech Disorder; No (%)	4 (13.8 %)	1 (7.7 %)	1.000
Cranial Nerve Palsies; No (%)	9 (31.0 %)	2 (15.4 %)	0.453
Anaemia; No (%)	22 (75.9 %)	11 (84.6 %)	0.695
Haemoglobin; Mean $\pm$ SD	10.11 $\pm$ 3.33	8.71 $\pm$ 2.41	0.181
Total Count; Mean $\pm$ SD	10472.41 $\pm$ 3353.5	8396.2 $\pm$ 2694.8	0.057
Platelet Count; Mean $\pm$ SD	2.99 $\pm$ 1.24	2.62 $\pm$ 0.62	0.313

Table 4. Comparison of Study Variables According to IgM Levels

In our study most common radiological finding was haemorrhagic infarct seen in 59.5 %. Most common sinus involved was SSS (Sick Sinus Syndrome) in 52.4 %, followed by transverse sinus in 42.9 %, straight sinus in 19.1 %, sigmoid sinus in 9.5 %. Empty delta sign was positive in 30.9 % of patients. Venous infarct was present in 16.7 % of patients.

In anticardiolipin antibody negative group mean age was 26.76 $\pm$ 8.49 years, compared to positive group 32.00 $\pm$ 10.88 years which was statistically not significant. There was no sex difference among aCL positive and negative group. Headache and vomiting were more common among aCL negative group compared to positive group though it was not statistically significant. Loss of consciousness and seizures were more common among aCL positive group compared to

negative group though it was not statistically significant. In our study mean leukocyte count was low among aCL positive group compared to negative group (8396.2 ± 2694.8 vs. 10472.41 ± 3353.5), which was not statistically significant. Mean haemoglobin was low among aCL positive group compared to negative group (8.71 ± 2.41 vs. 10.11 ± 3.33 g / dl), which was statistically not significant.

Radiological Findings	IgM levels MPL Units		P Value
	< 10 (n=29)	> 10 (n=13)	
1. Haemorrhagic infarct	16 (55.2%)	10(76.9%)	0.303
2. SSS	17(58.6%)	5(38.5%)	0.320
3. Transverse sinus	15(51.7%)	4(30.8%)	0.317
4. Empty delta sign	11(37.9%)	3(23.1%)	0.485
5. Straight sinus	7(24.1%)	1(7.7%)	0.398
6. Infarct	5(17.2%)	2(15.4%)	1.000
7. Sigmoid sinus	3(10.3%)	2(15.4%)	0.637
8. Vein of Labbe	-	1(7.7%)	0.310
9. Cord sign	1(3.4%)	0	1.000

Table 5. Comparison of Radiological Findings According to IgM Levels

Though haemorrhagic infarct was more among aCL antibody positive group (76.9 % vs 55.2 %) it was not statistically significant. Other radiological findings were comparable among the two groups.

Patients Characteristic	Our study	Christopher et al ¹⁰	Pillai L V et al ¹⁴	Cantu C et al ⁸ (Puerperal CVT)	Cantu C et al ⁸ (Non-Puerperal CVT)
Age	28.38 ± 9.48	27.55 ± 8.37	32.27 ± 11.8	26	36
Sex					
Male %	31	16	59		28
Female %	69	84	41	100	72
Abortion %	27.6	30.8	-	-	-
Puerperium %	44.8	64.5	23.1	-	-
Duration -days	18.44 ± 7.99	16.4 ± 7.1			
Headache	90.5	87	82	88	69.5
Vomiting	78.6	-	-	-	-
Seizures	71.4	71	56.2	59.7	63
Loss of consciousness	50	-	40.6	62.6	58.6
Motor weakness	40.5	-	56.3	77.6	71.7
Papilledema	28.6	-	26.6	40.2	52.1
Cranial nerve palsies	26.2	-	32.8	-	-
Speech disorders	11.9			25.3	21.7
Anaemia	85.7	-	-	64.1	26
Leucocytosis	28.6	-	-	35.8	43.4
↑ ESR	85.7	-	-	55.3	29.2
Thrombocytosis	7.1	-	-	2.9	13.0
Anticardiolipin antibodies positive %	30.9	22.6	25	-	-

Table 6. Comparison with Other Studies

DISCUSSION

Age Distribution

In our study mean age was 28.38 ± 9.48 years. In anticardiolipin antibody negative group mean age was 26.76 ± 8.49 years, compared to positive group in which mean age was 32.00 ± 10.88 years which was not statistically significant.

In a study by Christopher et al the patients mean age was 27.55 ± 8.37 years¹⁰. Although the aCL-positive patients tended to be younger, this was not statistically significant.

In a study by Carlos Cantu et al⁸ the mean age of patients was 26 years in puerperal CVT (range, 16 to 44 years) and 36 years among non-puerperal CVT (range, 15 to 77 years).

In a study by Lalitha V Pillai et al the patients mean age was 32.27 years.¹⁴

In a study by M. Saadatnia et al¹¹ mean age of aPL positive patients was 35 ± 6.89 years compared to negative group in which mean age was 30.56 ± 1.76 years.

Sex Distribution

In our study 69 % of patients were females and 31 % were males. There was no sex difference among aCL positive and negative group. In a study by Christopher et al¹⁰ 84 % of patients were females and 16 % were males. The aCL-positive patients were all women, and 64.5 % were puerperal period CVT. In a study by Lalitha V Pillai et al¹⁴ among 64 patients, 59 % were males and 41 % were females.

Abortion

In our study 27.6 % of female patients had history of abortion. There was no significant difference between aCL positive and negative group. In a study by Christopher et al 30.8 % of patients had history of abortion.¹⁰ Abortions were more frequent in aCL-positive group although it did not have any statistical significance.

Puerperium

In our study 44.8 % of female patients had history of puerperium. Mean duration of puerperium was 18.44 ± 7.99 . In a study by Christopher et al¹⁰ 64.5 % of patients had history of puerperium. The mean duration between delivery and presentation was 16.4 ± 7.1 days. In a study by Lalitha V Pillai et al¹⁴ history of puerperium was present in 23.1 %.

Clinical Features

In our study headache was the most common symptom seen in 90.5 % of patients, followed by vomiting in 78.6 %, seizures in 71.4 %, loss of consciousness in 50 % and motor weakness in 40.5 %. Visual disturbance was seen 26.2 % of patients. In contrast to other studies in our study use of oral contraceptive pills was seen in only one patient (2.4 %). Headache and vomiting were more common among aCL negative group compared to positive group though it was not statistically significant.

Loss of consciousness and seizures were more common among aCL positive group compared to negative group though it was not statistically significant. On examination most common finding was pallor seen in 78.6 % of patients, followed by papilledema in 28.6 %, cranial nerve palsies in 26.2 %. Speech disturbances were present in 11.9 % of patients.

In a study by Christopher et al¹⁰ headache was seen in 87 % and seizures was seen in 71 % as the presenting symptom. In a study by Lalitha V Pillai et al, in 82.8 % of the cases headache was the presenting symptom. The combination of headache and seizures was seen in 42 % of the cases.

Combination of headache, drowsiness and seizures were seen in 23.4 of the patients. In their study seizures were seen in 56.2 %, loss of consciousness in 40.6 %, hemiplegia in 56.3 % and cranial nerve palsies in 32.8 %. Visual disturbances and papilloedema was present in 26.6 %.

In a study by Carlos Cantu et al⁸ headache was the most common symptom, seen in 88 % among puerperal CVT, 69.5 % among non-puerperal CVT. Among CVT associated with pregnancy and puerperium focal signs were present in 79.1 %, aphasia was seen in 25.3 %, disorders of consciousness in 62.6 %, seizures 59.7 %, papilledema was present in 40.2 %.

In a study by Christopher et al¹⁰ both the aCL positive group and the aCL negative group were similar with respect to clinical, demographic and risk factor profile.

In a study by M. Saadatnia et al¹¹ clinical and demographic characteristics were similar in the aPL positive and the aPL-negative group. However, aCL-positive group was commonly associated with seizure, infarct, superficial veins and sinus involvement and the use of OCP.

Laboratory Findings

In our study anaemia was present in 85.7 %. Leucocytosis was present in 28.6 %. All of them had neutrophilic leucocytosis. None of the patient had leucopenia. ESR was elevated in 85.7 %. Thrombocytosis was seen in 7.1 %. None of the patients had thrombocytopenia.

In our study mean leukocyte count was low among aCL positive group compared to negative group (8396.2 ± 2694.8 vs 10472.41 ± 3353.5), which was not statistically significant. Mean haemoglobin was low among aCL positive group compared to negative group (8.71 ± 2.41 vs. 10.11 ± 3.33), which was statistically not significant. IgM anticardiolipin antibodies were positive in 30.9 %. IgG anticardiolipin antibodies were positive in 9.5 % but all of them were also positive for IgM anticardiolipin antibodies.

In a study by Christopher et al¹⁰ aCL antibodies was positive in 22.6 % patients which was significant compared to the control group. 5 of the 7 patients with aCL had elevated titres of IgG and IgM antibodies and 2 of the 7 had only IgG antibodies. Only CVT patients had moderately elevated levels of either IgG or IgM antibodies. The only significant laboratory finding in the aCL positive group was thrombocytopenia which was seen in 28.6 % and was not seen in aCL negative patients ($p < 0.001$).

In study by M. Saadatnia et al 11 aCL was detected in 20 % of patients. In study by S Chandrashekhara et al 12 high titers of aCL IgG was seen in 14.29 % patients.

In study by EM Wysokinska et al 13 Anticardiolipin antibodies were positive in 17 % of patients with CVT.

In our study most common radiological finding was haemorrhagic infarct seen in 64.3 %. Most common sinus involved was SSS in 47.6 %, followed by transverse sinus in 40.4 %, straight sinus in 19.1 %, sigmoid sinus in 9.5 %.

Empty delta sign was positive in 28.6 % of patients. Venous infarct was present in 19.1 % of patients. Though haemorrhagic infarct was more among aCL antibody positive group (76.9 % vs. 55.2 %) it was not statistically significant. Other radiological findings were comparable among the two groups.

In a study by Christopher et al¹⁰ both aCL antibody positive and negative group had similar CT findings.

CONCLUSIONS

Anticardiolipin antibodies (aCL) have been recognized as an independent risk factor for an increased risk of thrombosis. Its presence in patients with CVT requires lifelong anticoagulation to prevent recurrence. In our study, anticardiolipin antibodies were positive in 30.9 % of patients. However, quantitative estimation of serum IgM anticardiolipin antibodies titer did not show any significant impact on clinical and laboratory parameters. So, all patients of CVT should be evaluated for presence of anticardiolipin antibodies.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

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