

Original Article

Relationship between Cerebral Vein Thrombosis and Non-Anticardiolipin Antiphospholipid Antibodies

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ABSTRACT

Background: Anticardiolipin antibody(aCL)has been recognized as a marker for increased risk of Cerebral Vein Thrombosis (CVT). However, there are only rare reports on CVT associated with other antibodies against different phospholipids such as phosphatidyl inositol, phosphatidyl serine, phosphatidic acid and beta 2 glycoprotein I. In this study, we studied the presence of these antiphospholipid antibodies (aPL), demographic and clinical characteristics in 30 patients with CVT.

Methods: After diagnosis of CVT in 30 patients with MRI, we measured the titer of aCL and aPL (IgM and IgG) in all cases. The titers of IgG and IgM type of aPL and aCL were estimated in the sera.

Results: Anticardiolipin antibody was solely detected in 20% (n=6) and aCL and other aPL in 23.3% (n=7) of patients, indicating one patient positive for other aPL but not for aCL (non-aCL). Although the aPL positive group did not differ from the aPL-negative group from the stand point of clinical and demographic characteristics, yet seizure, infarct, superficial veins and sinus involvement and the use of OCP were seen more frequently in aPL-positive group

Conclusion: Our findings suggest that in addition to aCL, other antiphospholipid antibodies may be an associated condition that plays a role in the pathogenesis of CVT. The presence of aPL in CVT patients is probably associated with more superficial sinus or veins involvement and as a result death rate was lower in aPL- positive group. Further investigations are necessary to establish this hypothesis.

Keywords: Cerebral Vein Thrombosis, antiphospholipid antibody, anticardiolipin

Antiphospholipids antibodies (aPL) are part of a heterogeneous group of circulating serum polyclonal immunoglobulins (IgG, IgM, IgA or mixed) that bind negatively charged or neutral phospholipids components of cell membranes and cause increased tendency to venous or arterial thrombosis¹.

The two most extensively studied aPL are the anticardiolipin (aCL) and the lupus anticoagulant (LA)^{2, 3}. Antibodies against phospholipids other than cardiolipin have been less studied and characterized than aCL. These include mainly anionic moieties such as phosphatidylserine and

phosphatidylinositol and occasionally neutral phospholipids such as phosphatidylethanolamine. 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^{4, 5}.

Cerebral vein thrombosis (CVT) is a rare disorder having a relatively high mortality (10% - 15%)^{6,7}. With the advent of MRI and MR angiography and digital subtraction angiography, the prevalence and natural history of CVT are being refined⁸⁻¹⁰.

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Risk factors for CVT include systemic noninfectious conditions such as pregnancy and puerperium, hyperviscosity syndromes, Behçet's disease, coagulopathies including activated protein C resistance, factor V Leiden mutation¹¹⁻¹³ and collagen vascular diseases¹⁴⁻¹⁶. The presence of aPL (aCL or LA) has been suggested as a risk factor for CVT¹⁷⁻²², however there are only rare reports on CVT associated with non-cardiolipin antiphospholipids (non-aCL aPL) and anti- β_2 -GPI antibodies and there is little information on the prevalence of these antibodies in patients with CVT in Iran. In this study, the presence of aCL, non-aCL aPL, demographic, clinical and radiological features in CVT patients were investigated.

Materials and Methods

Thirty patients with CVT admitted in neurology ward, Al-Zahra hospital, Isfahan Medical University, between May 2000 and March 2002 were studied prospectively. The diagnosis of CVT was made by the presence of an appropriate clinical picture supported by cranial computerized tomography (CT), Magnetic Resonance Imaging (MRI) and MR venography. Patients with CVT directly related to head, facial, or neurosurgical infections, trauma and neurosurgical procedures were excluded from the study. In addition to CT, MRI and MR angiography, MR venography and all routine and related specific investigations like hemogram, platelet count, activated partial thromboplastin time (aPTT), prothrombin time, chest X-ray, electrocardiogram, liver function and renal function tests, anti-nuclear antibody (ANA), VDRL, were done. We systematically collected demographic, epidemiological, clinical, radiological, laboratory, treatment and outcome data. We paid particular attention to predisposing factors relevant to cerebral arterial ischemia and venous thrombosis, like anemia, history of abortions, Puerperium and use of oral contraceptives (OCP), history of previous thrombotic events, topography of involved cerebral venous structures, and laboratory evidence of

inflammatory or autoimmune conditions. aCL and non-aCL aPL (Anti-phosphatidylinositol, Antiphosphatidic acid, Antiphosphatidylserine and Anti- β_2 -GPI antibodies) titers were measured by enzyme linked immunosorbent assay (ORG515 and ORG529 kits, Orgentec Diagnostica, Germany). aCL titers > 7 MPL or >10 GPL units (ORG515 kit-microplate is coated with cardiolipin and β_2 -GPI) and aPL levels (aCL or non-aCL aPL) >10 MPL or GPL units (ORG529 kit-microplate is coated with cardiolipin, Phosphatidylinositol, Phosphatidic acid, Phosphatidylserine and β_2 -GPI) were considered positive. aPTT was routinely tested on admission. Patients with prolonged aPTT in the absence of anticoagulation therapy were screened for LA. Data were subsequently analyzed. ACL titers were categorized into low positive (10-20 MPL or GPL), moderately positive (21-60 MPL or 21-100 GPL), and highly positive (>60 MPL or 100 GPL) following the interpretations of the APASS group²³. Statistical analysis of the data was done by Fischer's exact test and Student t-test. A P value < 0.05 was considered as statistically significant.

Results

The demographic characteristics, clinical signs and symptoms, topography of involved cerebral venous structures, and laboratory data of the CVT patients with and without aPL are shown in table 1. The aPL-positive patients' demographic and prominent clinical features are shown in table 2. Although the results were not statistically significant, infarct, seizure and superficial sinus involvement in aPL-positive patients were seen more. aCL was detected in 20% (n=6) of patients and aCL or non-aCL in 23.3% (n=7) indicating only 1 case positive for non-aCL aPL. While IgM rose in all cases of aCL-positive patients, IgG increased only in one case and in one patient positive for non-aCL; both IgM and IgG titers were elevated. Only patients with CVT had moderately elevated titers of either IgG or IgM antibodies. A low positive titer of IgM or IgG antibodies was observed in 5 aPL-positive patients

(71%) while two patients had moderate titers of IgM type antibodies. Very high titers were not observed in any group. No patients had positive antinuclear antibodies or a prolonged aPTT. None of the subjects had any evidence of systemic lupus erythematosus or related autoimmune disorders. All patients were treated with intravenous heparin sulfate.

Discussion

Previous studies showed the association of CVT and aCL^{12, 18, 20, 24-27}. aCL antibodies have been reported in 5% to 22.6% of CVT patients^{12, 26, 27}. In this study, aCL-positive and aCL with non-aCL aPL-positive patients formed 20% and 23.3% of the cases respectively. In many studies, it was shown that patients with clinical (and other laboratory) manifestations of the antiphospholipid syndrome may occasionally have persistently negative conventional assays for LA and aCL but positive for antibodies directed against other phospholipids. These include mainly anionic moieties such as phosphatidylserine and phosphatidylinositol and occasionally neutral phospholipid such as phosphatidylethanolamine²⁸⁻³³. Preliminary data also suggest that antibodies directed against phosphatidylserine may be more specifically associated with ischemic stroke³⁴. Also anti- β_2 -GPI antibodies were shown to be more specific for thrombosis than conventional aCL³⁵⁻³⁷ and can occasionally be the only positive assay associated with the antiphospholipid syndrome^{38, 39}. As a result both ELISA kits used in this study were coated with β_2 -GPI.

There are few reports on non-aCL aPL and CVT. However, nearly one quarter of arterial cerebral thrombosis patients with negative immunoreactivity to aCL demonstrated positive immunoreactivity specific to non-aCL aPL⁴⁰. In this study 3% of patients were aCL-negative but non-aCL aPL-positive. Because of small sample size, the results do not seem to be conclusive, yet it presumes that in addition to arterial thrombosis, CVT patients should also be evaluated for non-aCL aPL antibodies and

only assessing aCL and LA in young patients with stroke (arterial or venous) may lead to underestimating the potential prevalence of aPL-Protein. A further large study is needed to confirm this idea.

In addition to aPL, other causes of coagulopathic disorders such as OCP use and puerperium were seen in 4 of 5 of our women aPL-positive patients (80%). Carhuapoma et al⁴¹ also reported coexistence of risk factors such as OCP use, Puerperium or pregnancy in 75% of patients. Many other studies also showed coexistence of risk factors such as pregnancy, OCP use, Puerperium and hereditary coagulopathy (protein S or C deficiency, factor V leiden) in patients with peripheral venous thrombosis or CVT with increased frequency^{12, 25, 42-46}. It seems that the coexisting risk factors in different countries may be of different types. For example in this study in Iran the most associated condition with aPL was OCP use while in Christopher et al's study in India, it was puerperium. OCP use and puerperium were not significant in both groups; hence, the pathogenesis of CVT is multifactorial.

Since all Characteristics of aPL- positive and negative groups were non significant, the results are not conclusive due to small sample size. However seizure, infarct and superficial veins and sinus involvements in aPL-positive patients were more frequently observed.

In contrast to Carhuapoma et al⁴¹ sagittal and lateral sinuses were involved more frequently in aPL-positive group but deep cerebral veins thromboses were seen more in aPL - negatives. It seems that existence of aPL causes more involvement of superficial sinus and vein.

Similar to the study by Carhuapoma et al⁴¹, in this study, death was less in aPL-positive group. It is explained with more involvement of deep vein thrombosis that was accompanied with loss of consciousness and poorer prognosis in aPL-negative patients.

Infarct, similar to Carhuapoma et al⁴¹ was higher but all infarcts were superficial and caused the development of seizure in aPL- positive group.

Previous deep vein thrombosis in the two groups was observed, largely due to hereditary coagulopathies in aCL – negative patients which were not investigated in our study.

In the present study, IgM aCL or non-aCL aPL levels increased in all patients and only 2 patients showed elevation of IgG type. This is in agreement with the Christopher et al²⁶ study in which 5 of 7 patients had rising of IgM type and in contrast to Carhuapoma et al⁴¹ series who showed that only 2 of 8 patients were positive for IgM type of aCL. As a result it seems that in developing countries like Iran and India IgM types of aPL antibodies are detected in higher percentage of CVT patients than in developed countries²⁶. This may be due to more infection and toxic exposures in these countries. Further studies are needed to confirm this theory.

In conclusion our study suggests that aPL (aCL or non-aCL aPL) may be an associated condition or risk factor for CVT. IgM type of such antibodies were seen more in developing countries probably due to more toxin exposure or infection. Seizure, superficial venous infarct and superficial venous and sinus involvement were seen in higher percentage in the aPL–positive group but because of small sample size the results do not seem to be conclusive. Death in aPL – positive group was seen less. A large, prospective study is suggested to determine the significance of both aCL and non- aCL aPL in the context of CVT as a risk factor and to identify the prognosis and clinical features of these antibodies in CVT.

Table 1. Characteristics and demographic data of the aPL-negative and aPL-positive CVT patients. Values are mean \pm SD or percentage where applicable.

		aPL	
		Positive	Negative
Age (years)(Mean+/-SD)		35 \pm 6.89	30.56 \pm 1.76
Sex	Male	28.5%	21.7%
	Female	71.4%	78.2%
Seizure		57.1%	52.1%
Venous infarct veins involvement		71.4%	60.8%
Involved sinus	Sagital	85.7%	73.9%
	Lateral	42.8%	30.4%
Deep veins involvement		0	17.3%
Abortion		25%(female)	17.3%
Deep veins thrombosis		14.2%	8.6%
Oral contraceptive		60%(female)	44.4%(female)
Puerperium		20%(female)	5% (female)
Death (acute phase)		0	13%

No statistically significant differences between the two groups.

Table 2. Characteristics of aPL – positive patients with CVT

	Case number						
	1	2	3	4	5	6	7
Age	22	27	27	32	40	43	74
Sex	Female	Female	Female	Female	Male	Male	Male
aCL titer (IgM type)	13	15	22	11	NA	11	48
aCL titer (IgG type)	ND	ND	11	ND	ND	ND	ND
aPL titer (IgM type)	12	12	15	10	14	10	40
aPL titer (IgG type)	10	ND	ND	ND	ND	ND	ND
Headache	+	+	+	+	+	+	+
Motor or sensory signs	-	-	-	+	+	+	+
Seizures	+	-	+	-	+	-	+
Visual signs	+	+	+	+	+	+	+
Depressed consciousness	+	-	+	-	+	-	+
Associated conditions	Puerperium DVT	OCP	Pancyto- penia	OCP	OCP Abortion	Opiate Addiction	Thrombo- cytopenia
Thrombus location	SSS, CV	Let TS	SSS, CV	SSS	SSS both TS CV	SSS CV	SSS Left TS CV

NA: not available, ND: not detectable, OCP: oral contraceptive pill use, DVT: deep vein thrombosis, SSS: superior sagittal sinus, CV: cortical vein, TS: transverse sinus,

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