Original Article

Relationship between Cerebral Vein Thrombosis and Non-Anticardiolipin Antiphospholipid Antibodies

M. Saadatnia MD*, M. Etemadifar MD, S. Haghighi MD***, V. Shaigannejad MD****, M. Tajmir riahi MD*****

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 thrombosis[1].

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 ß$_2$-glycoprotein I (ß$_2$-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 refined[8-10].

*Resident, Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran
**Associate Professor, Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran
***Cardiovascular Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
****Assistant Professor, Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran
*****Resident of Cardiology, Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
Correspondence to: Dr Mohammad Saadatnia, Al-Zahra Medical Center, Isfahan, Iran.

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 mutation[11-13] and collagen vascular diseases[14-16]. The presence of aPL (aCL or LA) has been suggested as a risk factor for CVT[17-22], however there are only rare reports on CVT associated with non-cardiolipin antiphospholipids (non-aCL aPL) and anti–$ß_2$-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–$ß_2$-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 $ß_2$-GPI) and aPL levels (aCL or non-aCL aPL) >10 MPL or GPL units (ORG529 kit-microplate is coated with cardiolipin, Phosphatidylinositol, Phospha- tidicacid, Phosphatidylserine and $ß_2$-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 group[23]. 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 phosphatidylethanolamine[28-33]. Preliminary data also suggest that antibodies directed against phosphatidylserine may be more specifically associated with ischemic stroke[34]. Also anti–$ß_2$-GPI antibodies were shown to be more specific for thrombosis than conventional aCL[35-37] 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 $ß_2$-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 aPL[40]. 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 al[41] 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 purperium 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 al[41] sagital 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 al [41], 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 al [41] 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 al[26] study in which 5 of 7 patients had rising of IgM type and in contrast to Carhuapoma et al[41] 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 countries[26].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 ± SD or percentage where applicable.

		aPL	
		Positive	Negative
Age (years)(Mean+/-SD)		35 ± 6.89	30.56 ± 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 sagital sinus, CV: cortical vein, TS: transverse sinus,

References:

1. Levine SR, Brey RL, Joseph CL, Havstad S. Risk of recurrent thromboembolic events in patients with focal cerebral ischemia and antiphospholipid antibodies. Stroke 1992; (2 Suppl): I29-32.
2. Alarcon-Segovia D. Clinical manifestations of the antiphospholipid syndrome. J Rheumatol.1992; 19: 1778–81.
3. The Antiphospholipid Antibodies in Stroke Study Group. Clinical and laboratory findings in patients with antiphospholipid antibodies and cerebral ischemia. Stroke 1990; 21: 1268–73.
4. McNeil HP, Simpson RJ, Chesterman CN, Krilis SA. Antiphospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation: ß$_2$ glycoprotein I (apolipoprotein H). Proc Natl Acad Sci U S A. 1990; 87: 4120–24.
5. Galli M, Comfurius P, Maassen C, Hemker HC, de Baets MH, Van Breda-Vriesman PJ, et al. Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. Lancet 1990; 335:1544–47.
6. Bousser MG, Chiras J, Bories J, Castaigne P. Cerebral venous thrombosis: a review of 38 cases. Stroke 1985; 16: 199–213.
7. Preter M, Tzourio C, Ameri A, Bousser MG. Long term prognosis in cerebral venous thrombosis: follow-up of 77 patients. Stroke 1996; 27: 243–46.
8. Isensee Ch, Reul J, Thron A. Magnetic resonance imaging of thrombosed dural sinuses. Stroke 1994; 25: 29–34.
9. Tsai FY, Wang AM, Matovich VB, Lavin M, Berberian B, Simonson TM, et al. MR staging of acute dural sinus thrombosis: correlation with venous pressure measurements and implications for treatment and prognosis. AJNR Am J Neuroradiol 1995; 16: 1021–29.
10. Vogl TJ, Bergman C, Villringer A, Einhaupl K, Lissner J, Felix R. Dural sinus thrombosis: value of venous MR angiography for diagnosis and follow-up. AJR Am J Roentgenol 1994; 162: 1191–98.
11. Zuber M, Toulon P, Marnet L, Mas J-L. Factor V Leiden mutation in cerebral venous thrombosis. Stroke 1996; 27: 1721–23.

12. Deschiens M-A, Conard J, Horellou MH, Ameri A, Preter M, Chedru F, et al. Coagulation studies, factor V Leiden, and anticardiolipin antibodies in 40 cases of cerebral venous thrombosis. Stroke 1996; 27: 1724–30.
13. Dulli D, Luzzio C, Willliams EC, Schutta HS. Cerebral venous thrombosis and activated protein C resistance. Stroke 1996; 27: 1731–33.
14. Ameri A, Bousser MG. Cerebral venous thrombosis. Neurol Clin 1992; 10: 87–111.
15. Bousser MG, Barnett HJM. Cerebral venous thrombosis. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM, editors. Stroke: Pathophysiology, Diagnosis, and Management. New York: Churchill Livingstone; 1992. p. 517–37.
16. Lefkowitz D. Cortical thrombophlebitis and sinusvenous disease. In: Vinken PJ, Bruyn GW, Klawans HL, Toole JP. Handbook of Clinical Neurology. New York: Elsevier Science Publishers BV; 1989. p. 395–423.
17. Vidaihet M, Piette JC, Wechsler B, Bousser MG, Brunet P. Cerebral venous thrombosis in systemic lupus erythematosus. Stroke 1990; 21: 1226–31.
18. Levine SR, Kieran S, Puzio K, Feit H, Patel SC, Welch KA. Cerebral venous thrombosis with lupus anticoagulants: report of two cases. Stroke 1987; 18: 801–4.
19. Provenzale JM, Loganbill HA. Dural sinus thrombosis and venous infarction associated with antiphospholipid antibodies: MR findings. J Comput Assist Tomogr 1994; 18: 719–23.
20. Mokri B, Jack CR Jr, Petty GW. Pseudotumor syndrome associated with cerebral venous sinus occlusion and antiphospholipid antibodies. Stroke 1993; 24: 469–72.
21. Khoo KBK, Long FL, Tuck RR, Allen RJ, Tymms KE. Cerebral venous sinus thrombosis associated with the primary antiphospholipid syndrome: resolution with local thrombolytic therapy. Med J Aust 1995; 162: 30–32.
22. Boggild MD, Sedhev RV, Fraser D, Heron JR. Cerebral venous sinus thrombosis and antiphospholipid antibodies. Postgrad Med 1995; 71: 487–89.
23. The Antiphospholipid Antibodies in Stroke Study Group. Anticardiolipins antibodies are an independent risk factor for first ischaemic stroke. Neurology 1993; 43: 2069-72.
24. Kesler A, Pomeranz IS, Huberman M, Novis B, Kott E. Cerebral venous thrombosis and chronic active hepatitis as part of the antiphospholipid syndrome. Postgrad Med J1996; 72: 690–92.
25. Ricchieri GL, Pizzolato G, Fabri M, Patrassi G, Sartori MT. Cerebral and vein thrombosis, transient protein S deficiency, and anticardiolipin antibodies. Am J Hematol 1996; 52: 69–70.
26. Christopher R, Nagaraja D, Dixit NS, Narayanan CP. Anticardiolipin antibodies: a study in cerebral venous thrombosis. Acta Neurol Scand 1999; 99: 121-4.
27. Daif A, Awada A, Al-Rejeh S et al. Cerebral venous thrombosis in adults: a study of 40 cases from Saudi Arabia. Stroke 1995; 26: 1193-5.
28. Triplett DA, Brandt JT, Musgrave KA, Orr CA. The relationship between lupus anticoagulants and antibodies to phospholipid. JAMA 1988; 259: 550–54.
29. Toschi V, Motta A, Castelli C, Gibelli S, Cimminiello C, Molaro GL, et al. Prevalence and clinical significance of antiphospholipid antibodies to noncardiolipin antigens in systemic lupus erythematosus. Haemostasis 1993; 23: 275–83.
30. Laroche P, Berard M, Rouquette AM, Desgruelle C, Boffa MC. Advantage of using both anionic and zwitterionic antigens for the detection of antiphospholipid antibodies. Am J Clin Pathol 1996; 106: 549–54.
31. López-Soto A, Carvera R, Font J, Bové A, Reverter JC, Muñoz FJ, et al. Distribution and clinical significance of antibodies to cardiolipin, phosphatidic acid, phosphatidylinositol and phosphatidylserine in systemic lupus erythematosus: prospective analysis of a series of 92 patients. Clin Exp Rheumatol 1997; 15: 143–49.
32. Berard M, Chantome R, Marcelli A, Boffa MC. Antiphosphatidylethanolamine antibodies as the only antiphospholipid antibodies, I: association with thrombosis and vascular cutaneous diseases. J Rheumatol 1996; 23: 1369–74.
33. Falcón CR, Hoffer AM, Carreras LO. Antiphosphatidylinositol antibodies as markers of the antiphospholipid syndrome. Thromb Haemost 1990; 63: 321–22.
34. Turhim S, Rand JH, Goldbold JH, Weinberger J, Horowitz DR, Goldman M. Elevated antiphosphatidyl serine antibodies are a risk factor for ischemic stroke. Neurology 1999 22; 53: 1523-7.
35. El-Kadi HS, Keil LB, DeBari VA. Analytical and clinical relationships between human IgG autoantibodies to $ß_2$-glycoprotein I and anticardiolipin antibodies. J Rheumatol. 1995; 22: 2233–37.
36. Roubey RAS, Maldonado MA, Byrd SN. Comparison of an enzyme-linked immunosorbent assay for antibodies to $ß_2$-glycoprotein I and a conventional anticardiolipin immunoassay. Arthritis Rheum 1996; 39: 1606–7.
37. Sanmarco M, Soler C, Christides C, Raoult D, Weiller PJ, Gerolami V, et al. Prevalence and clinical significance of IgG isotype anti-$ß_2$-glycoprotein I antibodies in antiphospholipid syndrome: a comparative study with anticardiolipin antibodies. J Lab Clin Med 1997; 129: 499–506.
38. Cabral AR, Amigo MC, Cabiedes J, Alarcón-Seovia D. The antiphospholipid/cofactor syndromes: a primary variant with antibodies to $ß_2$-glycoprotein I but no antibodies detectable in standard antiphospholipid assays. Am J Med 1996; 101: 472–81.

39. Guérin V, Couchouron A, Vergnes C, Parrens E, Vernhes JP, Constans J, et al. Antiphospholipid syndromes with anti-human ß$_2$-glycoprotein I antibodies despite negative reactivity in conventional aPL and LA assays. Thromb Haemost 1997; 77: 1037–38.
40. Toschi V, Motta A, Castelli C, Paracchini ML, Zerbi D, Gibelli A. High prevalence of antiphosphatidylinositol antibodies in young patients with cerebral ischemia of undetermined cause. Stroke 1998; 29: 1759–64.
41. Carhuapoma JR, Mitsias P, Levine SR. Cerebral venous thrombosis and anticardiolipin antibodies. Stroke 1997; 28: 2363–9.
42. Koeleman B, Reitsma PH, Allart CF, Bertina RM. Activated protein C resistance as an additional risk factor for thrombosis in protein C-deficient families. Blood 1994; 84: 1031–35.
43. Van Boven HH, Reitsma PH, Rosendaal FR, Bayston TA, Chowdhury V, Bauer KA. Factor V Leiden (FV R506Q) in families with inherited antithrombin deficiency. Thromb Haemost1996; 75: 417–21.
44. Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet 1994; 344: 1453–57.
45. Vermylen J, Blockmans D, Spitz B, Deckmyn H. Thrombosis and immune disorders. Clin Haematol 1986; 15:393–412.
46. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. N Engl J Med 1998; 338: 1793–97.