ORIGINAL ARTICLE

Lupus Anticoagulant Positivity in Diabetes With Retinal Vascular Disease

Dash S[a], Dash RJ[b], Gupta A[c]

Departments of [a]Haematology, [b]Endocrinology , and [c]Ophthalmology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

To investigate whether lupus anticoagulant (LA) positivity, a frequently associated factor in a variety of thromboembolic events, might be relevant to the pathogenesis of retinal vascular disease in diabetes mellitus.

Materials and Methods: Eighty-five diabetic patients (44 type 1 and 41 type 2) were examined for total blood counts, screening coagulogram and LA.

Results: LA was positive in 20.5% of patients with type 1 diabetes and in 33.3% with patients of type 1 diabetes and retinopathy, whereas, LA was positive in only 7.3% of patients with type 2 diabetes and in 6.4% of them with retinopathy.

Conclusion: These findings suggest that LA positivity might be considered as an additional risk factor in the pathogenesis of microvascular disease in type 1 diabetes.

Key Words: Lupus anticoagulant, Retinopathy, Type 1 diabetes, Type 2 diabetes

Introduction

Diabetic retinopathy is the most common microvascular complication in diabetes, which can lead to severe visual loss.[1,2] The pathogenetic mechanisms involved in the onset and progression of retinopathy are poorly understood. Several risk factors have been identified. A number of studies indicate that a hypercoagulable state is present in diabetes, especially so in type1 diabetes with retinopathy.[3] Vascular damage and disturbed endothelial function seem to occur early in the course of diabetic retinopathy, converting the endothelial surface from thromboresistant to a thrombogenic surface.[4,5] Immunological mechanisms may also play a role through deposition of immune complex material.[6] Auto antibodies to endothelial antigens could be responsible for initiating vascular injury,[7] and, could thus be a marker for endothelial dysfunction.

Lupus anticoagulant (LA) is an antiphospholipid antibody frequently associated with thromboembolic events, e.g. miscarriage, SLE and diabetic vascular disease such as nephropathy, and retinal occlusive vasculopathies,[8-12] mediated by an LA induced endothelial dysfunction.[8,9] Guisti et al,[13] found increased incidence of retinopathy, in diabetic patients positive for LA suggesting LA, positivity as an additional risk factor in the pathogenesis of microangiopathy in diabetes.

Correspondence:. Sumitra Dash, Department of Haematology, PGIMER, Chandigarh-160012, India
E-mail: sumitradash2001@yahoo.com

The present study was designed to examine whether LA positivity is associated with an increased prevalence of retinopathy in patients with diabetes in India.

Materials and Methods

A total of 85 patients with diabetes mellitus (DM), 44 with type 1, and 41 with type 2, classified according to the National Diabetes Data Group criteria[14] were studied. They included 64 males (27 with type 1, 37 with type 2) and 21 females (17 with type1, 4 with type 2). Those with good glycaemic control (HbA1c<7%) and no hypertension (>140/90), hypertriglyceridaemia (fasting triglyceride >1.9 mmol/L), or hypercholesterolaemia (total cholesterol >5.6 mmol/L) were included. Most patients were on multiple injections of subcutaneous insulin (Isophane insulin alone or mixed with soluble insulin 70/30), with or without additional drugs such as metformin, and/or glitazone. All patients were non-smokers and had not taken any drugs known to affect hemostasis for at least 4 weeks before the study.

Retinopathy was assessed by clinical examination by a consultant ophthalmologist, fundus photography and fluorescein angiography. Diabetic retinopathy was categorized into proliferative (PDR) and non-proliferative (NPDR) types, as per ADA guidelines.[15] Complete blood counts including platelet counts were performed in an automated hematology cell counter. Plasma samples were examined for prothrombin time (PT) and activated partial thromboplastin time (APTT). LA was diagnosed according to the criteria of the International Society of Hemostasis and Thrombosis.[16]

Detection of LA

Blood drawn by clean venipuncture was collected in plastic tubes containing 105 mmol/L buffered citrate solution in a 1:9 proportion. After centrifugation at 4000g for 20 minutes at 4°C, platelet-poor plasma was used immediately for coagulation assays. The following coagulation tests were used for the laboratory detection of LA: Kaolin-clotting time (KCT), confirmed by dilute Russels Viper Venom time (dRVVT). Normal values were obtained from the normal pooled plasma for the day of test. All tests were performed on the patient's plasma and normal pool plasma. Mixing studies were evaluated by the ratio of clotting time mixture: clotting time of normal pool, for KCT index and dRVVT index. A positive result was indicated by a ratio greater than 1.0 in both KCT and dRVVT.

Results

Of the 85 plasma samples, 12 were LA - positive (14.1%). LA positivity was higher in type 1 DM (20.5%) than in type 2 (7.3%). The results are shown in Table 1.

Type 1 diabetes

There were 44 patients in this group. Their age ranged from 7.5 to 38 years with a median of 17 years. Retinopathy was present in 9 cases (20.5%, proliferative in 2 and non-proliferative in 7). LA was positive in 3 of them (33.3%). Of the 35 without retinopathy, 6 were positive for LA (17.1%). Thus in type 1 DM, LA was positive in 9 of the 44 cases (20.5%). Conversely retinopathy was present in 33.3% of the LA -posiitivee patients, but only in 18.7% of the LA-negative patients.

Type 2 diabetes

There were 41 patients in this group. Their age ranged from 22 years to 74 years with a median of 52 years. Retinopathy was present in 31 (85.5%, proliferative in 15, and non proliferative in 16). Of these, only 2 were

Table 1. Lupus anticoagulant (LA) positivity in patients with type 1 and type 2 diabetes with or without retinopathy

Diabetics	Total no. of cases (%)	Retinopathy present (%)	Retinopathy absent (%)
Type 1	44 (100)	9 (20.5)	35 (79.5)
LA –positive	9 (20.5)	3 (33.3)	6 (17.1)
Type 2	41 (100)	31 (75.6)	10 (24.4)
LA –positive	3 (7.3)	2 (6.4)	1 (10.0)
Type1 versus type 2 (ratio)	1 : 1	1 : 3.7	3.2 : 1
LA positivity in type 1 vs. type 2	2.9 : 1	5.2 : 1	1.7 : 1

positive for LA (6.4%). Of the 10 patients who did not have retinopathy, one was LA-positive (10%). Overall LA positivity in type 2 DM was 3 (7.3%) only. Since only three patients were LA positive, no comparison of occurrence of retinopathy was considered between LA-positive and LA-negative cases.

Though retinopathy was around 4 times more common in type 2 diabetes patients than in type 1, LA positivity was more frequent (around 3 times) in type 1, more so (around 5 times) in type 1 patients with retinopathy. Retinopathy was also more common in LA positive type 1, than in LA negative type 1. We did not find any significant difference for gender ratio, duration of diabetes, platelet counts, or degree of retinopathy among the patients with or without LA in both type 1 and type 2 cases.

Discussion

Lupus anticoagulant is frequently associated with thromboembolic events including diabetic nephropathy, macroangiopathy and retinal occlusive vasculopathy.[7-11] Lupus anticoagulant is a subgroup of antiphospholipid antibodies, and consists of a heterogenous group of IgM and IgG autoantibodies against protein/phospholipid complexes. The lupus anticoagulant is characterized by a paradoxical phenomenon of a thrombotic tendency in vivo, despite prolongation of phospholipid dependent coagulation assays in vitro. The LA dependent pathophysiologic mechanisms causing thrombophilia seem to be multifunctional including impaired anticoagulant activity of activated protein C. LA also induces endothelial cell dysfunction,[8,9,17] and in diabetes mellitus, there are many reports that extensively document the presence of a remarkable endothelium-related dysfunction of the coagulant and anticoagulant pathways.[18,19]

The present study shows that the presence of LA in type 1 DM is not infrequent. The prevalence is even higher in type 1 diabetics who already have retinopathy, although no comparison could be drawn as to the occurrence of LA between proliferative and non-proliferative retinopathy as the numbers were small. Our prevalence of 33.3% is less than the 60% reported by Guisti et al.[13] This could be due to the smaller number (20.5%) of type 1 patients with retinopathy in our study

group, while retinopathy was documented in 30% of cases in their study.

The precise role played by LA in retinopathy in type 1 diabetes is speculative. In view of increasing evidence of immune abnormalities in the pathogenesis of type 1 diabetes, and the possible role of LA in endothelial dysfunction, LA positivity should be considered as an additional risk factor. To clarify and support this issue, studies in larger multiethnic patient groups are necessary, not only to reach a better understanding of the pathogenesis of diabetic retinopathy but also to prevent its onset and/or progression, with appropriate treatment.

References

1. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol. 1984 Apr;102 (4):527-32.
2. Klein R, Klein BE, Moss SE. Epidemiology of proliferative diabetic retinopathy. Diabetes Care. 1992 Dec;15 (12):1875-91.
3. Fuller JH, Keen H, Jarrett RJ, Omer T, Meade TW, Chakrabarti R, et al. Haemostatic variables associated with diabetes and its complications. Br Med J. 1979 Oct 20;2 (6196):964-6.
4. Haefliger IO, Meyer P, Flammer J, Luscher TF. The vascular endothelium as a regulator of the ocular circulation: a new concept in ophthalmology? Surv Ophthalmol. 1994 Sep-Oct;39 (2):123-32.
5. Kohner EM, Patel V, Rassam SM. Role of blood flow and impaired autoregulation in the pathogenesis of diabetic retinopathy. Diabetes. 1995 Jun;44 (6):603-7.
6. Andreani D. Malignant microangiopathy. Diabetologia. 1980 Mar;18 (3):255.
7. Jones DB, Wallace R, Frier BM. Vascular endothelial cell antibodies in diabetic patients. Association with diabetic retinopathy. Diabetes Care. 1992 Apr;15 (4):552-5.
8. Lechner K, Pabinger-Fasching I. Lupus anticoagulants and thrombosis. A study of 25 cases and review of the literature. Haemostasis. 1985;15 (4): 254-62.
9. Triplett DA. Obstetrical complications associated with antiphospholipid antibodies. In: Coulama BC, Faulk WP, McIntyre JA, ed. Immunological Obstetrics. New York: WW Norton; 1992. p. 377-403.
10. Montehermoso A, Cervera R, Font J, Ramos-Casals M, Garcia-carrasco M, Formiga F, et al. Association of antiphospholipid antibodies with retinal vascular disease in systemic lupus erythematosus. Semin Arthritis Rheum. 1999 Apr;28 (5):326-32.
11. Galtier-Dereure F, Biron C, Vies M, Bourgeois V, Schved JF, Bringer J. Vascular complications of diabetes mellitus: what role for phospholipid-binding antibodies? Lupus. 1998;7 (7):469-74.
12. Wiechens B, Schroder JO, Potzsch B, Rochels R. Primary antiphospholipid antibody syndrome and retinal occlusive vasculopathy. Am J Ophthalmol. 1997 Jun;123 (6):848-50.
13. Giusti C, Schiaffini R, Bosco D, Ciampalini P, Pantaleo A, Vingolo EM, et al. Lupus anticoagulant positivity in insulin dependent diabetic patients: an additional risk factor in the pathogenesis of diabetic retinopathy? Br J Ophthalmol. 2000 May;84 (5):531-3.
14. National Diabetes Data Group. Classification of diabetes mellitus and other categories of glucose intolerance. Diabetes. 1970; 28:1039-57.
15. American Diabetes Association. Diabetes Care 2000; 23 (suppl).
16. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost. 1995 Oct; 74 (4): 1185-90.
17. Meroni PL, Papa ND, Beltrami B, Tincani A, Balestrieri G, Krilis SA. Modulation of endothelial cell function by antiphospholipid antibodies. Lupus. 1996 Oct;5 (5):448-50.
18. Dash S. Alterations in haemorrheological and coagulation parameters in Diabetes. In: Dash RJ, editor. New Vistas in type 2 Diabetes; 2000. p.61-72.
19. Lorenzi M, Cagliero E. Pathobiology of endothelial and other vascular cells in diabetes mellitus. Call for data. Diabetes. 1991 Jun;40 (6):653-9.