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A STUDY OF ANTICARDIOLIPIN ANTIBODIES IN CHILDHOOD TUBERCULOUS MENINGITIS

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ABSTRACT

Tuberculosis remains a major public health issue of considerable magnitude all over the world. In recent times, there has been a resurgence of tuberculosis in both developing and developed countries for various reasons. There are many reasons and factors that have drawn attention of investigators on role of anticardiolipin antibodies in causation and severity of intracranial stroke in many diseases. A total of 19 children suffering from tuberculous meningitis (diagnosed on the basis of diagnostic criteria)[2] and 12 children suffering from nonmeningitic tuberculosis admitted in Institute of child Health, Niloufer hospital, Hyderabad between June 2004- December 2004 were included in this study. The prevalence of anticardiolipin antibodies was very high in cases of childhood tuberculous meningitis. The more severe form of tuberculous meningitis is associated with high levels of anticardiolipin antibodies.

Key words: Tuberculous meningitis, Anticardiolipin antibodies, Intracranial stroke.

INTRODUCTION

Tuberculosis remains a major public health issue of considerable magnitude all over the world. In recent times, there has been a resurgence of tuberculosis in both developing and developed countries for various reasons. Tuberculous involvement of the central nervous system (CNS) is an important and serious type of extra pulmonary manifestation. It has been estimated that approximately 10% of all patients with tuberculosis have CNS disease [1].

While many children suffer from primary tuberculosis, only a few go on to develop tuberculous meningitis. There are many reasons and factors that have drawn attention of investigators on role of anticardiolipin antibodies in causation and severity of intracranial stroke in many diseases. Since the stroke is a well known feature in tuberculous meningitis, this study attempts to find a relationship of anticardiolipin antibodies to development of intracranial ischemic lesions in childhood tuberculous meningitis.

The mean age of the study group with aCL positive is 4.33 and with a CL negative is 4.31 as compared to 5.05 of control group. There were 5 males and 6 females in study group with aCL positive and 7 male 1 female with aCL negative as compared to 6 female in control group.

MATERIAL AND METHODS

It is a prospective case study.

A total of 19 children suffering from tuberculous meningitis (diagnosed on the basis of diagnostic criteria)[2] and 12 children suffering from nonmeningitic tuberculosis admitted in Institute of Child Health, Niloufer hospital, Hyderabad between June 2004- December 2004 were included in this study.

Inclusion Criteria

1. A child between 3 month to 12 years of age, presenting with a sudden onset of neurological dysfunction due to a vascular cause and persisting for > 24 hours and later diagnosed to be suffering from tuberculous meningitis.

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The criteria for diagnosing TBM is based on Ahuja et al [2].

2. All children suffering from nonmeningitic tuberculosis.

Exclusion criteria

1. Neonates or children less than 3-4 months.
2. Postical paralysis in the absence of infarct or hemorrhage on radioimaging, traumatic stroke and hemorrhage in a brain tumor.
3. Sequelae.

Departmental ethics committee approval was obtained. Informed consent was taken from the parents. Once the child was enrolled in the study a detailed relevant history, clinical examination and appropriate investigations were done. 5ml of venous blood was drawn under strict aseptic precautions and obtained in a vacutainer and sent for analysis of anticardiolipin antibodies-IgG and IgM.

Quantitative determination of autoantibodies against cardiolipin was done using ENZYME Linked Immuno sorbent Assay (ELISA).

Statistical Analysis

The results were analysed using Pearson's chi square test. A p value of > 0.05 was considered to be statistically not significant.

P value <0.05 was considered to be statistically significant, p value <0.0001 was considered very highly significant.

RESULTS

19 children with recent onset of neurological deficit and diagnosed to be suffering from TBM formed the study group. 12 children suffering from non-meningitic tuberculosis mostly with pulmonary lesions were included in control group. Both the groups were evaluated for the presence of anticardiolipin (aCL) antibodies.

In study group 11 were found to be aCL antibody positive and 8 negative whereas in control group none of them found to be aCL antibodies positive.

Table 1. The demographic details of both the groups

Group		Anticardiolipin antibodies		Total
		IgG, IgM and IgG& IgM	Negative	
Study	Age <1 Year	1		1
Study	1-5 Years	8	4	12
	6-10Year		4	4
	>10Years	2		2
	Total	11	8	19
Control	Age <1Year		2	2
	1-5Years		3	3
	6-10Year		5	5
	>10Years		2	2
	Total		12	12

The mean age of the study group with aCL positive is 4.33 and with aCL negative is 4.31 as compared to 5.05 of control group. The statistical analysis revealed that there is significance between study group and control group with a P value 0.045.

Table 2. Sex wise distribution of subjects

Group		**Anticardiolipin antibodies**			
			IgG, IgM and IgG& IgM	**Negative**	**Total**
Study	SEX	Male	5	7	12
		Female	6	1	7
		Total	11	8	19
Control	SEX	Male		6	6
		Female		6	6
		Total		12	12

There were 5 males and 6 females in study group with aCL positive and 7 male 1 female with aCL negative as compared to 6 female in control group. The statistical analysis revealed that there is no significant difference between study group and control group.

Table 3. Distribution of subjects according to duration of illness

Group	Anticardiolipin antibodies			
		IgG, IgM and IgG& IgM	Negative	Total
TBM	Duration of illness > = 14days	11	8	19
	Total	11	8	19
Control	Duration of Illness UPTO 7days		1	1
	7-14days		7	7
	>=14days		4	4
	Total		12	12

Details about the relationship between duration of illness and aCL antibodies positive and negative in study and control group are summarized in table 3 and figure 3.

In study group all of them presented with duration of illness more than 14 days where as in control group they presented with variable duration of illness i.e.7 with 7-14 days, 4 with > 14 days and 1 with less than 7 days. There is no statistical significant association between the study group and control group relating to duration of illness.

Table 4. Distribution of subjects according to nutritional status

Group	Anticardiolipin antibodies			
		IgG, IgM and IgG & IgM	Negative	Total
study	Nutrition status N	2	2	4
	1	1	3	4
	2	4	1	5
	3	3	1	4
	4	1	1	2
	Total	11	8	19
Control	Nutrition status N		3	3
	1		5	5
	2		3	3
	3		1	1
	Total		12	12

Details about relationship between malnutrition and aC1 antibodies positive and negative in study and control group are summarized in table 4 and figure 4.

In study group, out of 11 positive cases 2 were found normal, 1 was grade I malnourished, 4 were grade II malnourished, 3 were grade III malnourished and 1 was grade IV malnourished, whereas in a CL negative cases 2 were normal, 3 were grade I malnourished, 1 were grade II malnourished, 1 were III malnourished and 1 were grade IV malnourished. In control group 3 were normal, 5 were grade I malnourished, 3 were grade II malnourished and 1 were grade III malnourished. Malnutrition was graded according to IAP Classification. There was no statistical significant association between malnutrition in study group and control group.

Table 5. Distribution of subjects according to stages of TBM and Lung TB

Group		Anticardiolipin antibodies				
TBM	Stages TBM (Stage I) TBM (Stage II TBM(Stage III)	IgG	IgM 3	IgG & IgM 2	Negative 2 5 1	Total 2 11 6
	Total	1	6	4	8	19
Control	Diagnosis Lung TB				12	12
	Total					

The details about the relationship between types of aCL positively and negativity between study group and control group were summarized in table 5 and figure 5.

In study group, out of 11 aCL positive cases, 6 were positive for IgM antibodies, 4 were positive for both IgG and IgM antibodies and 1 was positive for IgG antibody where as in control group all are negative for aCL antibodies.

Out of 6 IgM antibodies, 3 each belongs to stage II and stage III TBM respectively, out of 4 IgG and IgM antibodies 2 each belongs to stage II and stage III TBM and 1 IgG antibody belongs to stage IITBM. There is no statistical significance between the two groups.

DISCUSSION

In this study, the study group consisted of 19 children with tuberculous meningitis and 12 with non-meningitic tuberculosis as a control. There were 12 boys and 7 girls in the study group with a mean age of 4.32. The mean age of children with aCL antibodies positive is 4.33 which has been found to be statistically significant with p value of 0.045 i.e. aCL antibodies are more common in 1-5 year age children suffering from TBM. Out of 19 children, 11(57.9%) had positive aCL antibodies, of which 6(54.5%) had IgM type, 4 (36.4%) had IgG and IgM type and 1 has IgG (9%) type of antibodies. In the control group none of them was positive for aCL antibodies.

Pilarska E, observed 60% of the children with ischemic stroke in his study to be positive for antiphospholipid antibodies [3].

Cojocaru M et al, found that in ischemic stroke patients IgM aCL antibodies is positive in 58%, IgG-IgM aCL antibodies in 43% and IgG aCL in 36% respectively [4].

Ejaz Ahmed et a1 studied on the role of anticardiolipin antibodies in stroke as an independent risk factor that out of 123 cases 14(11.4%) were positive for IgM aCL antibodies. So, they concluded that aCL are associated with future stroke but do not contribute independent risk factors [5].

All these studies had results that are consistent with our findings but none of them is related to tuberculous meningitis because they are studies in other causes of strokes and not in tuberculous meningitis. So, our study is the first study to relate childhood tuberculous meningitis and anticardiolipin antibodies. Very few studies have been done in children but none of them were related to tuberculous meningitis.

In our study out of 11 children positive for aCL antibodies, no case belongs to stage I TBM. Stage II TBM 6 (54.5%) was positive out of 11 cases where as in stage III TBM 5(83.3%) was positive out of 6 cases for aCL antibodies.

These findings suggest that children with more neurological damage showed increase in aCL antibodies.

TBM (Stage 1)
TBM (stage II)-54.5%
TBM (stage III)-83.3%

Czlonkowska a. found in his study that antiphospholipid antibody (lupus anticoagulant and anticardiolipin antibodies) is strongly linked to immune mediated thromboembolic events in the pathogenesis of cerebrovascular disease [6].

In our study we restricted ourselves to anticardiolipin antibodies only. Therefore whether there was any relation of lupus anticoagulant in such cases who stroke requires further investigations.

Brey RL et al found in their study that interaction between antiphospholipid antibodies and central nervous system cellular elements rather than antiphospholipid antibodies associated thrombosis seem to be a more plausible mechanism for cerebral diseases [7].

Grunebaum L et al in their study found that phospholipid binding antibodies in autoimmune pathogenesis is high, immunological disorders can be a high possibility, but it is not established whether they possess its own pathogenic potential or appears as a secondary response following cellular alteration known to be thrombogenic [8].

Feldmann E and Levine SR studied mechanism of antiphospholipid antibodies in cerebrovascular disease and found that antiphospholipid antibodies interact withB2 Glycoprotein and impairs coagulation mechanism and also associated with immune mediated prothrombotic state [9].

In this context of suggestion of immunological basis of causation of thrombotic phenomenon in stroke, it may be mentioned here that tuberculosis has delayed hypersensitivity as contributing to its pathogenesis and endarteritis predisposing to ischemic changes secondary to thrombosis in these terminal vessels. Therefore, whether any modifications of this immunological process will help to improve the morbidity and possibly mortality in TBM? We suggest it needs serious consideration.

CONCLUSION

1. The prevalence of anticardiolipin antibodies was very high in cases of childhood tuberculous meningitis.
2. The more severe form of tuberculous meningitis is associated with high levels of anticardiolipin antibodies.
3. The cause and effect relationship between levels of anticardiolipin antibodies and more severe forms of tuberculous meningitis has to be established, though we propose that it is the presence of anticardiolipin antibodies that predisposes to greater severity of disease.
4. The role of presence of any other antiphospholipid antibodies particularly lupus anticoagulant need to be studied.

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