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ORIGINAL STUDY

Thrombophilia and Legg-Calvé-Perthes disease : Is it a causative factor and does it affect the severity of the disease ?

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Coagulation parameters were studied in a population of 118 children with Perthes disease in order to determine the possible role of thrombophilia as a causative factor for the disease and to determine if thrombophilia could affect its course.
We found 27 children presenting one or more coagulation disorders.
The statistical analysis concurs with previous findings of a relationship between Legg-Calvé-Perthes disease and an increased liability to thrombosis ; however, no significant effect of thrombophilia on the severity of the disease could be demonstrated.

Keywords : Legg Calvé Perthes disease ; thrombophilia ; severity of disease.

INTRODUCTION

Legg-Calvé-Perthes disease is a paediatric hip condition with an incidence from 1 in 1,200 to 1 in 12,000 live births. The incidence varies with the geographic area studied, being very high in South-East Wales for instance. The typical patient is a 5 to 7-year-old boy (male to female ratio of 3 to 5:1). The disease causes variable amounts of disability in these young children.

The natural history of the disease and pathological changes in the femoral head have been studied extensively (*3,4,17,18*). The aetiological mechanisms, though, are still under debate. The most widely accepted cause of the disease is one or a series of interruptions of the blood supply to the femoral head (*20,24*). Amongst the causes of these interruptions of the blood flow, thrombophilic disorders have been suggested as a causative factor by several authors (*2,5-12*). Recent studies however have questioned these findings (*13,16,21,23*). Few studies have correlated the findings of thrombophilic disorders in Legg-Calvé-Perthes disease with the severity of the disease (*16*).

We have analysed our population of Legg-Calvé-Perthes patients for coagulation anomalies and correlated our results with the severity of the disease by using validated radiological classification systems.

MATERIALS AND METHODS

A population of 118 children with Perthes disease who were treated at the Orthopaedic Department of the

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University Hospitals of Leuven between 1995 and 2000 was studied. There were 97 boys and 21 girls (male to female ratio of 4.62:1). All the children were Caucasian. The mean age at the time of the study was 9 years for the boys (range : 2 to 37) and 9.5 years for the girls (range : 3 to 19).

Blood samples were obtained at least 6 months after an acute event and after an established diagnosis of Legg-Calvé-Perthes disease. A series of coagulation tests were performed : prothrombin time (PT), accelerated prothrombin time (aPTT), fibrinogen. Specific thrombophilic factors antithrombin, Protein C, Protein S, Resistance to Activated Protein C (APC resistance), Factor II mutation (Prothrombin G20210A mutation), elevated Factor VIII activity and Homocystein levels were determined by established laboratory techniques at the Department of Bleeding and Vascular Disorders of the University Hospitals of Leuven. Specific cut-off values were used, considering the age-related change in the levels of some of these coagulation tests *(19)*.

Radiographic studies were retrieved from the patient's files. Radiographs were retrieved for 116 of the 118 patients. A review of the radiological file was performed using the Catterall *(4)* and Herring *(5)* classifications. Where applicable, a Stulberg *(6)* classification was determined. The latter classification could only be used in a mature stage of the disease, where a sufficient amount of remodelling had been reached. Also, the outcome of this Stulberg classification is altered by the treatments that each particular patient received. The Stulberg classification has been determined in 104 patients.

An age-matched control population of 51 children was established. These 51 children attended the paediatric outpatient clinics for unrelated conditions.

Since APC resistance and prothrombin G20210A are age-independent, previously established control groups were used as controls (158 blood donors for APC resistance and 100 hospital staff members for prothrombin G20210A).

After collection of the data a statistical analysis was performed to determine whether our population of Legg-Calvé-Perthes patients had a higher incidence of abnormal thrombophilic laboratory findings than our control population. Secondly, a query was made to establish whether Legg-Calvé-Perthes patients with a thrombophilic anomaly have a more severe disease pattern, as indicated by a higher ranking in the different classification systems described, than the Legg-Calvé-Perthes patients without a coagulation anomaly.

RESULTS

Of the 118 children with an established diagnosis of Legg-Calvé-Perthes disease, 27 (22.88%) had one or more abnormal coagulation tests (table I). Two of these patients had two abnormal values : one patient had an increased resistance to Activated Protein C combined with a Factor II mutation ; the second patient had an elevated Homocystein level combined with an elevated Factor VIII level. In the control population, 7 coagulation anomalies (13.7%) were seen. In both populations there were no abnormal values for PT, aPTT and Fibrinogen.

The results of the laboratory screening of the Legg-Calvé-Perthes population and of the control population are given in tables II, III and IV.

The 116 patients of the Legg-Calvé-Perthes population of which the radiographs were retrieved

Table I. — Coagulation anomalies in the Legg-Calvé-Perthes population studied

Test	*N studied*	*N positive*	*% positive*
Antithrombin	118	1	0.8
Protein C	118	2	1.69
Protein S	118	3	2.5
APC resistance	118	7	5.9
Factor II mutation	109	9	8.26
Factor VIII elevated	118	1	0.8
Homocystein	118	4	3.4
Total	118	27	22.89%

Table II. — Coagulation anomalies in the paediatric control population studied

Test	*N studied*	*N positive*	*% positive*
Antithrombin	51	0	0
Protein C	51	1	1.96
Protein S	51	3	5.9
APC resistance	51	1	1.96
Factor II mutation > 150%	42	0	0
Factor VIII elevated	51	1	1.96
Homocystein	51	1	1.96
Total	51	7	13.7%

Table III. — Specific control populations for APC resistance and Factor II mutation

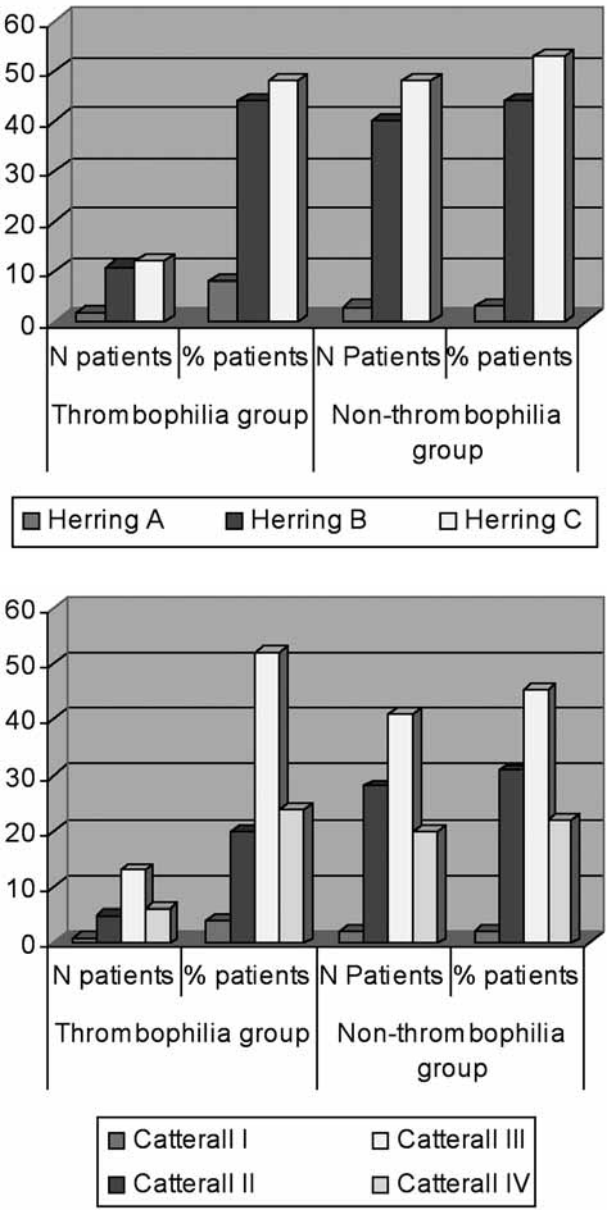
Test	*N studied*	*N positive*	*% positive*
APC resistance	158	1	0.63
Factor II mutation	158	1	0.63

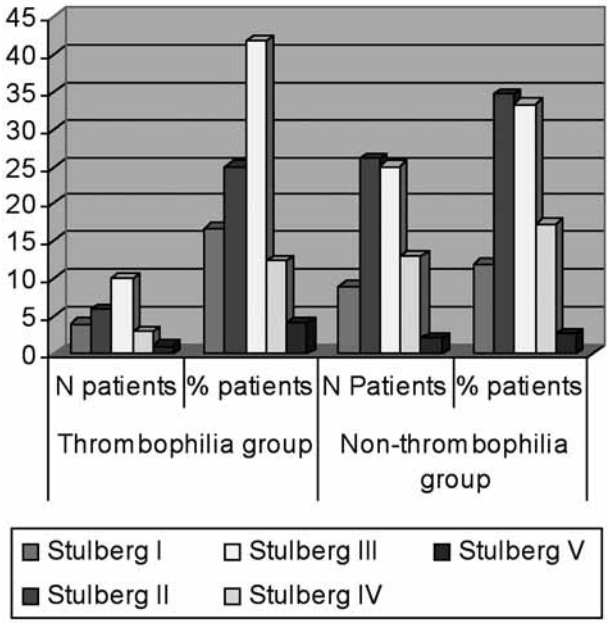
were divided into a group without coagulation anomalies (91 patients) and a group with one or more coagulation anomalies (25 patients). For each patient in both groups, a Herring and Catterall classification score was determined. In the group without a coagulation anomaly, a Stulberg classification score could be determined in 80 cases ; in the group with a coagulation anomaly, this Stulberg classification score could be determined in 24 patients. The results of these classification scores are given in tables V, VI and VII, and in figures 1, 2 and 3.

Statistical analysis

Both populations (Legg-Calvé-Perthes and the paediatric control populations) were age-matched, yielding a p-value of 0.034 using a parametric Mann-Whitney U test.

When considering all coagulation anomalies as a group, there was no statistically significant difference in incidence of coagulation anomalies in both populations ($p = 0.2921$ using Fisher's Exact test). When considering all tested coagulation anomalies separately, there also was no statistically significant





Figs. 1, 2 and 3. — Herring, Catterall and Stulberg classifications in both the thrombophilia and non-thrombophilia groups.

Table IV. — Herring classification of the Legg-Calvé-Perthes patients

	Thrombophilia group		*Non-thrombophilia group*	
	N patients	*% patients*	*N Patients*	*% patients*
Herring A	2	8	3	3.3
Herring B	11	44	40	43.96
Herring C	12	48	48	52.75

Table V. — Catterall-classification of the Legg-Calvé-Perthes patients

	Thrombophilia group		*Non-thrombophilia group*	
	N patients	*% patients*	*N Patients*	*% patients*
Catterall I	1	4	2	2.2
Catterall II	5	20	28	30.77
Catterall III	13	52	41	45.05
Catterall IV	6	24	20	21.98

Table VI. — Stulberg-classification of the Legg-Calvé-Perthes patients

	Thrombophilia group		*Non-thrombophilia group*	
	N patients	*% patients*	*N Patients*	*% patients*
Stulberg I	4	16.7	9	12
Stulberg II	6	25	26	34.7
Stulberg III	10	41.7	25	33.3
Stulberg IV	3	12.5	13	17.3
Stulberg V	1	4.2	2	2.7

Table VII. — Statistical analysis of each coagulation anomaly separately using Fisher's Exact test

Test	*p-value*
Antithrombin	1.0000
Protein C	1.0000
Protein S	1.0000
APC resistance using paediatric controls	0.4376
APC resistance using specific controls	0.0120
Factor II mutation using paediatric controls	0.1133
Factor II mutation using specific controls	0.0133
Factor VIII elevated	0.5137
Homocystein	1.0000

difference between both populations. The p values for all tests are given in table VIII.

However, when using the specific control populations for Resistance to Activated Protein C and Factor II mutation, statistical analysis yielded a significantly higher incidence of these two coagulation anomalies in the Legg-Calvé-Perthes group ($p = 0.0120$ for Resistance to Activated Protein C and $p = 0.0133$ for Factor II mutation, using Fisher's Exact test).

When considering the severity of the disease in the groups of Legg-Calvé-Perthes patients with and without coagulation anomalies, a statistical analysis was made using the *Chi-Square* test. No statistically significant difference was found in the three classification systems studied. The p values for these tests are given in table IX.

DISCUSSION

The aetiology of Legg-Calvé-Perthes disease is still a matter of lively debate. The pathophysiologys remain unclear *(3,4,14,15)*. Recent papers suggested a congenital deficiency in several plasma proteins involved in coagulation *(2,5-12)*. To our knowledge, there is only one paper in the English literature that made a correlation with the severity of the disease *(16)*. In that paper, a group of 64 Legg-Calvé-Perthes patients was studied. We have made a similar analysis of our population of

Table VIII. — Statistical analysis of the difference in classification between the thrombophilia and non-thrombophilia groups in the Legg-Calvé-Perthes population studied

Classification	*p-value*
Herring	0.5793
Catterall	0.7327
Stulberg	0.8120

118 patients, using three different and validated classification systems.

Our patients had low levels of the various coagulation proteins in approximately 23%, using paediatric cut off values. The question remains whether these values are indeed low, or whether they are simply indicative of an immature blood clotting system (*1*).

No statistically significant difference has been found when comparing our Legg-Calvé-Perthes population to a normal age-matched paediatric population, when considering the different coagulation tests as a whole or every test separately. However, using two larger control populations for Resistance to Activated Protein C and Factor II mutation, there is a statistically significant higher incidence in the Legg-Calvé-Perthes group. This concurs with previous papers, pinpointing thrombophilia as a causative factor in Legg-Calvé-Perthes disease. In our study, only Resistance to Activated Protein C and Factor II mutation had a significantly higher incidence.

No statistically significant difference could be demonstrated when comparing the Legg-Calvé-Perthes patients with and without coagulation anomalies, considering the severity of the disease by using three radiological classification systems (*4,19,22*). As already mentioned, the Stulberg classification is altered by the treatment the patient received previously. Therefore this classification is of lesser value in predicting the course of the disease itself.

In conclusion, our study concurs with previous findings of a relationship between Legg-Calvé-Perthes disease and an increased liability to thrombosis ; however, no significant effect of thrombophilia on the severity of the disease could be demonstrated.

REFERENCES

1. **Andrew M, Vegh P, Johnston M *et al.*** Maturation of the hemostatic system during childhood. *Blood* 1992 ; 80 : 1998-2005.
2. **Arruda VR, Belangero WD, Ozelo MC *et al.*** Inherited risk factors for thrombophilia among children with Legg-Calvé-Perthes disease. *J Pediatr Orthop* 1999 ; 19 : 84-87.
3. **Barker DJP, Dixon E, Taylor JF.** Perthes' disease of the hip in three regions of England. *J Bone Joint Surg* 1978 ; 60-B : 478-480.
4. **Catterall A.** The natural history of Perthes' disease. *J Bone Joint Surg* 1971 ; 53-B : 37-53.
5. **De Stefano V, Finazzi G, Mannucci PM.** Inherited thrombophilia : pathogenesis, clinical syndromes, and management. *Blood* 1996 ; 87 : 3531-3544.
6. **Dilley A, Eldridge J, Austin H *et al.*** The role of resistance to activated protein C, protein S deficiency and protein C deficiency in Legg-Perthes disease. *Thromb Haemost* 1997 ; suppl : 1- 843. abstract 23.
7. **Eldridge J, Dilley A, Austin H *et al.*** The role of protein C, protein S, and resistance to activated protein C in Legg-Perthes disease. *Pediatrics* 2001 ; 107 : 1329-1334.
8. **Gallistl S, Reitinger T, Linhart W *et al.*** The role of inherited thrombotic disorders in the etiology of Legg-Calvé-Perthes disease. *J Pediatr Orthop* 1999 ; 19 : 82-83.
9. **Glueck CJ, Brandt G, Gruppo R *et al.*** Resistance to activated protein C and Legg-Perthes disease. *Clin Orthop* 1997 ; 338 : 139-152.
10. **Glueck CJ, Crawford A, Roy D *et al.*** Association of antithrombotic factor deficiencies and hypofibrinolysis with Legg-Perthes disease. *J Bone Joint Surg* 1996 ; 78-A : 3-14.
11. **Glueck CJ, Glueck HI, Greenfeeld D *et al.*** Protein C and S deficiency, thrombophilia and hypofibrinolysis : pathophysiologic causes of Legg-Perthes disease. *Pediatr Res* 1994 ; 35 : 383-388.
12. **Glueck CJ, Glueck HI, Welch M *et al.*** Familial idiopathic osteonecrosis mediated by familial hypofibrinolysis with high levels of plasminogen activator inhibitor. *Thromb Haemost* 1994 ; 71 : 195-198.
13. **Hayek S, Kenet G, Lubetsky A *et al.*** Does thrombophilia play an aetiological role in Legg-Calvé-Perthes disease ? *J Bone Joint Surg* 1999 ; 81-B : 686-690.
14. **Herring JA, Williams JJ, Neustadt JN *et al.*** Evolution of femoral head deformity during the healing phase of Legg-Calvé-Perthes' disease. *J Pediatr Orthop* 1993 ; 13 : 41-45.
15. **Herring JA.** Management of Perthes' disease. *J Pediatr Orthop* 1996 ; 16 : 1-2.
16. **Kealey W, Mayne E, McDonald W *et al.*** The role of coagulation anomalies in the development of Perthes' disease. *J Bone Joint Surg* 2000 ; 82-B : 744-746.
17. **Molly MK, MacMahon B.** Incidence of Perthes disease (osteochondritis deformans). *N Engl J Med* 1966 ; 275 : 988-990.

18. Norlin R, Hammerby S, Tkaczuk H. The natural history of Perthes' disease. *Int Orthop* 1991 ; 15 : 13-16.
19. Ritterbusch JF, Shantharam SJ, Gelinas C. Comparison of lateral pillar classification and Catterall classification of Legg-Perthes' disease. *J Pediatr Orthop* 1993 ; 13 : 200-202.
20. Sanchis M, Zahir A, Freeman MAR. Experimental stimulation of the blood supply to the capital epiphysis in the puppy. *J Bone Joint Surg* 1973 ; 55-A : 335-342.
21. Sirvent N, Fisher F, El Hayek T *et al.* Absence of congenital prethrombotic disorders in children with Legg-Perthes disease. *J Pediatr Orthop* (*B*) 2000 ; 9 : 24-27.
22. Stulberg D, Cooperman D, Wallenstein R. The natural history of Legg-Calvé-Perthes. *J Bone Joint Surg* 1981 ; 63-A : 1095-1108.
23. Thomas DP, Morgan G, Tayton K. Perthes' disease and the relevance of thrombophilia. *J Bone Joint Surg* 1999 ; 81-B : 691-695.
24. Weinstein SL. Perthes disease. *Curr Orthop* 1998 ; 2 : 181-188.