www.jmscr.igmpublication.org
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v7i1.128

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Legg –calve –perthes disease: Thrombophilia

Authors
Dr Kiran Kumar.Vokkerla[1], Dr Raghavendra Chidrawar[2]
[1]Assistant Professor, Dept. of Orthopaedics, Government Medical College, Nizamabad, Telangana State
Email: *kiranvokkerla@gmail.com*, mobile no: 99590 43987
[2]Senior Resident, Dept. of, Orthopaedics, Government Medical College, Nizamabad, Telangana State
Email: *ragz0000@gmail.com*
Corresponding Author
Dr Raghavendra Chidrawar
Email: *ragz0000@gmail.com*, Mobile no: 98499 98347

Abstract
Legg-calve Perthes Disease was an idiopathic osteonecrosis of developing femoral head complicated by pain and disability of hip joint. This study evaluated the changes in thrombotic protein in patients with LCPD. This study includes 10 Perthes disease were diagnosed based on symptoms, radiographic and clinical evaluation. These were compared with 10 controls of same age and sex. The mean age of effected population was 7.84±2.97 year. The male versus female population ratio was 2.33. In these 6 patients were belongs to Herring classification as C and 7 patients belongs to Catterall grade IV. In our study there is a highly significant difference in the values of FVIII between patients and controls. Effected boys significantly differ than girls. Low antithrombin levels would enhance thrombosis which was noted significantly. There were no significant differences in the values for protein C between patients and controls in our study. Protein S values and fibrinogen levels were also normal in our patients. The tests for sickle cell, Paroxysmal nocturnal haemoglobinuria were negative in both the patients and controls.
Keywords- *Legg-calve Perthes Disease, thrombophilia, herring classification, Catterall grade.*

Introduction

Perthes' disease was diagnosed based on both radiological and clinical features. Clinical features were hip pain, referred pain to the knee, limp and limitation of movement in association with radiological features of avascular necrosis of the capital femoral epiphysis. Legg-Calve-Perthes disease (LCPD) is osteonecrosis of the femoral head epiphysis. It is 4 times more common among boys and bilateral involvement occurs in 8–24% of cases. The reported annual incidence varies between 0.45 and 21 cases/100,000 children. The disease is usually diagnosed among children <15 years of age, with a peak onset between 5 and 8 years of age.[1] There is delayed skeletal maturation and impaired growth. In addition to congenital abnormalities, LCPD is associated with greater risk of cardiovascular diseases and diseases of the blood.[1,2] These patients may have several congenital abnormalities such as congenital heart disease, Goldenhar syndrome, haemophilia, renal disease, Down syndrome, epilepsy and

scoliosis. These patients may have several congenital abnormalities such as congenital heart disease, Goldenhar syndrome, haemophilia, renal disease, Down syndrome, epilepsy and scoliosis.[2]

These patients have a 70% higher risk of cardiovascular diseases. Of all cardiovascular diseases, hypertension and ischaemic heart disease have been more common. These patients have a 40% higher risk of diseases of blood including nutritional, haemolytic and aplastic anaemia, purpura and other haemorrhagic conditions[1].

These patients also have increased risk of coagulation defects such as thrombophilia, activated protein C resistance, protein S deficiency and antiphospholipid antibody syndrome[3,4]. These are hypercoagulable states and patients may benefit from anticoagulant thromboprophylaxis.

The natural history of the disease and pathological changes in the femoral head have been studied extensively[5,6]. The most widely accepted cause of the disease is one or a series of interruptions of the blood supply to the femoral head[7,8]. Amongst the causes of these interruptions of the blood flow, thrombophilic disorders have been suggested as a causative factor by several authors[3,4,9,10]. Some studies have correlated the findings of thrombophilic disorders in Legg-Calvé-Perthes disease with the severity of the disease[11]. This study aims at To evaluate prothrombotic tendencies among children with Perthes' disease.

Materials and Methods

The study was conducted at Government medical college, Nizamabad during the period from June 2015 to May 2018. This study includes 200 patients which were divided in two groups. The group C consist of 10 members of controls and group D consist of 100 members. Patients diagnosed based on clinical and X-ray criteria with LCP were recruited at the clinical orthopaedics outpatient facility of the hospital. Matching age, sex, height and weight children were selected as controls.

We collected data on the age, sex, address, height and weight, family history of disease, trauma and fever, as well as coexisting disease. Radiographs were taken for all the effected children based on radiographs they were classified. This was done as described earlier. The Caterall classification gauging the extent of femoral head involvement was used and group III and IV disease was classified as severe involvement. Herring's classification was used to assess the lateral pillar and Herring C was classified as severe disease.[5,6].

In all cases blood collected after a 12 hour fast in the morning to reduce the effect of circadian rhythms on the levels of factors. The samples were drawn for both the DNA based tests and the thrombotic work up at the same time. Informed consent was taken from the parents at the outpatient department. Prothrombin and Partial thromboplastin time, Fibrinogen, Factor VIII, and APCR, Protein C and Antithrombin were estimated. Protein S was evaluated using an ELISA kit sourced from Dako (Denmark). Sickle cell and paroxysmal nocturnal haemoglobinuria was evaluated. All these were evaluated at standard specific laboratories.

Statistical analysis

The Fisher's exact test was used for categorical variables and the students t-test for normal and Mann-Whitney U test for the non normal continuous variables. All values are expressed as the mean ± Standard Dev (continuous variables) or as a percentage of the group they were derived from (categorical variables). All p values of ≤ 0.05 were considered to indicate statistical significance.

Results

This prospective case control study was conducted at government medical college, Nizamabad during the period June 2015 to May 2018 after obtaining permission from the hospital ethics committee, at department of orthopaedics. This includes 10 diseased patients and 10 controls of similar age, height and weight. The demographic parameters were shown in table 1 and clinical findings were shown in table2. In two cases patients were suffering with fever and 2 cases had history of trauma. Three of our patients had a history of transient synovitis of the hip.

Table 1: Demographic data

Parameter	Control	Disease
Age (years)	7.36±3.73	7.84±2.97
Sex (M/F)	7/3	6/4
Height (cms)	123.3±6.2	124.8±7.9
Weight (kgs)	26.4±8.7	25.9±9.5

Activated protein C values are calculated using the gold standard, as the time taken by a person with a homozygous mutation of Factor V Leiden mutation in the test. These two variables are interconnected as the FVL mutation is the commonest cause for APRC.

Table 2: Thrombophilia Clinical findings

Parameters	Control	Disease
Protein C	119 ±10.6	113.6±14.3
Protein S total	88.4±15.5	87.7±10.8
Free Protein S	78.5±20.6	94.4±23.9
Anti Thrombin	128.8±13.9	110.7±15.8
Sickle cell	Negative	Negative
Paroxysmal Nocturnal Hemoglobinuria	Negative	Negative
Fibrinogen	230.5±30.6	251.6±32.4
Factor VIII	110.7±20.7	180.5±25.4
APCR (Activated protein C resistance)	2.73±0.86	1.98±0.95

In our study 10 patients, were classified using radiographs by two different classification systems.

Table 3: Classification of Perthes Disease Patients

Herrings Classification	No of patients
Herrings A	2
Herrings B	2
Herrings C	6
Caterall grading	
Catterall I	1
Catterall II	1
Catterall III	1
Catterall IV	7

Head at risk signs

Gage Sign was positive 6 cases, one was in healing stage. Lateral extrusion was noticed in 6 seven cases only.

Six of our cases had a horizontal growth plate on X-rays. All those cases who had a horizontal growth plate also had lateral extrusion. Metaphyseal cysts were observed in eight cases suggesting that there was severe involvement of the epiphysis.

Discussion

The aetiology of Legg-Calvé-Perthes disease is still a matter of lively debate. The pathophysiology still remain unclear[5,6,11] in some studies, inherited thrombophilia has been suggested as a potential cause of the disease[1,3,4].

Hall and Barker reported that the average annual incidence was 10.2 per 100,000 in boys aged14 years and under and 2.2 in girls.[12] Pillai et al in reported that in 40 children with Perthes' disease from South West Scotlan. The mean annual incidence of Perthes' disease was 15.39 per 100,000 children aged 0 to 14 years[13].

They have shown that this disease occurs in the western region of India, in the coastal belt, with an incidence of 4.4/100,000/year. The male:female ratio as reported by Chacko et al was 2.58:1 and the age at onset of disease was 10 years[14] Joseph et al noted that about 50% of their cases had severe disease[15]

In our study 10 patients were radiographically and clinically diagnosed as LCPD patients. The male to female ratio was 2.33:1, the mean age was 7 years, and children were effected from an age of 3 years to six years.. Our results were in consistent with other results[12-16].

In Perthes' disease, the femoral head is susceptible to insult by a thrombotic phenomenon more than any other site because of its peculiar blood supply and its temporal change in the growing child. Below 5 years, the blood supply of the femoral head is almost entirely derived from the transphyseal and the lateral epiphyseal vessels. At around five years, the physeal vessels undergo attrition and the supply is derived mainly from the lateral epiphyseal vessels, except for a minor contribution from the medial metaphyseal vessels. From five to nine years, the head is at risk as only the lateral epiphyseal vessels contribute any blood supply of significance. At nine years, the vessels of the ligamentum teres begin to grow and provide a significant contribution near skeletal maturity. At skeletal maturity, the physeal plate disappears and there is an additional intramedullary supply to the head of the femur.

Coagulation parameters were studied by Monen et al[17] 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. They 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.

In a study by Liu et al[18], The disease/control ratios showed 26 proteins were significantly differentially expressed (all $p < 0.05$). Including higher abundances of complement factor H (1.44), complement C4-B (1.45), isocitrate dehydrogenase [NAD] subunit alpha (2.7) alpha-1-acid glycoprotein 1 (1.87), heptoglobin (1.53) and Ig lambda-2 chain C regions (1.46), and lower levels of apolipoprotein E (0.50), apolipoprotein F (0.60), apolipoprotein C-III (0.69), S100-A8 (0.73), S100-A9 (0.75) and prothrombin (0.77) in LCPD than in controls. The alpha-1-acid glycoprotein 1 and haptoglobin increases, and apolipoprotein E and S100-A8 decreases were confirmed by western blot. The complement and coagulation cascades, and abnormal lipid metabolism may be involved in the pathogenesis of LCPD.

Balasa et al[19] study Thrombophilia has been identified as a potential etiologic factor in Legg-Calve-Perthes disease. The factor-V Leiden mutation was more common in the patients (8 of 72) than in the controls. A high level of anticardiolipin antibodies (IgG and/or IgM) was found in nineteen of the seventy-two patients.

The serum immunoglobulin levels in Perthes' disease was examined by Joseph et al and he found that there were significant increases in IgG and IgM were seen In Indian children with Perthes' disease in both boys and girls as compared to age and sex matched controls[20].

Inherited tendency to hypercoagulability has been suggested as a cause of vascular thrombosis resulting in Legg-Calvé-Perthes disease. An investigation of the most common inherited risk factor for hypercoagulability - the mutation in the V-factor gene[21]

Woratanarat P et al[22] in their metaanalysis aimed to systematically review the association between genetic determinants of hypercoagulability (Factor V Leiden, prothrombin II, and methylenetetra-hydrofolate reductase; MTHFR) and Perthes disease. The mean age range of 6.1-14.7 years. The prevalence of the minor allele in controls was 0. and 0.105 for factor V Leiden, prothrombin II, and MTHFR, respectively. The factor V Leiden allele increased the risk of Perthes with a pooled OR of 3.10 .The factor V Leiden mutation is significantly related to Perthes disease, and its screening in at-risk children might be useful in the future.

In a study by Vosmaer A et al[23] one hundred and sixty-nine consecutive patients who had been diagnosed with Legg-Calvé-Perthes disease at two centers in Rotterdam, the Netherlands, when they were between 1.5 and 13.5 years of age. The incidence of Legg-Calvé-Perthes disease was increased in the presence of the factor V Leiden mutation in the presence of the prothrombin G20210A mutation in association with elevated levels of factor VIII (>150 IU/dL) and in association with protein S deficiency (<67 U/dL). Neither high levels of fibrinogen (>4.0 g/L) nor protein C deficiency (< or =55 U/dL) had an apparent effect on the risk of Legg-Calvé-Perthes disease. Overall, males had a 2.4 times higher risk of than females.

This study has tried to look at thrombophilia, a major contributory factor in Perthes' disease. In our study there is a highly significant difference in the values of Factor VIII between patients and controls. Effected boys significantly differ than girls. Since Factor VIII gene is coded on the X chromosome, we are able to postulate that a male predominance is probably based on an X linked genetic abnormality. This could then explain the high boy:girl ratio recorded in all studies. Antithrombin is a factor which inhibits the action of thrombin on fibrinogen-thus preventing clot formation. Low antithrombin

levels would enhance thrombosis which was noted significantly.

Though the activated protein C resistance is the commonest cause and the factor V Leiden the commonest mutation discovered to cause thrombosis in the western population, there were no significant differences in the values for protein C between patients and controls in our study. Protein S Values were also normal in our patients. The tests for sickle cell, Paroxysmal nocturnal haemoglob-inuria were negative in both the patients and controls. The fibrinogen levels were also within normal levels.

This indicates that there may be a wide variation in the causes leading to thrombosis in different populations and that each population needs to be investigated separately.

References

1. Hailer YD, Montgomery SM, Ekbom A, Nilsson OS, Bahmanyar S. Legg-Calve-Perthes disease and risks for cardiovascular diseases and blood diseases. Pediatrics 2010;125:e1308-15.
2. Hall DJ, Harrison MH, Burwell RG. Congenital abnormalities and Perthes' disease. Clinical evidence that children with Perthes' disease may have a major congenital defect. J Bone Joint Surg Br 1979;61:18-25.
3. Glueck CJ, Glueck HI, Greenfield D, Freiberg R, Kahn A, Hamer T, *et al.* Protein C and S deficiency, thrombophilia, and hypofibrinolysis: Pathophysiologic causes of Legg-Perthes disease. Pediatr Res 1994;35 (4 Pt 1):383-8.
4. Glueck CJ, Brandt G, Gruppo R, Crawford A, Roy D, Tracy T, *et al.* Resistance to activated protein C and Legg-Perthes disease. Clin Orthop Relat Res 1997;338:139-52.
5. Catterall A. The natural history of Perthes' disease. *J Bone Joint Surg* 1971; 53-B : 37-53.
6. 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.
7. Thomas DP, Morgan G, Tayton K. Perthes' disease and the relevance of thrombophilia. *J Bone Joint Surg* 1999 ;81-B : 691-695.
8. Weinstein SL. Perthes disease. *Curr Orthop* 1998 ; 2 :181-188.
9. Eldridge J, Dilley A, Austin H, el-Jamil M, Wolstein L, Doris J et al. The role of protein C, Protein S, and resistance to activated protein C in Legg-Perthesdisease. Pediatrics. 2001;107:1329-34.
10. Gruppo R, Glueck CJ, Wall E, Roy D, Wang P. Legg-Perthes disease in three siblings, two heterozygous and one homozygous for the factor V Leiden mutation.J Pediatr Orthop. 1998;132:855-8.
11. 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.
12. Hall AJ, Barker DJP. Perthes' disease in Yorkshire. J Bone Joint Surg [Br].1989;71-B(2):229-33.
13. Pillai A., Atiya S., Costigan PS. The incidence of Perthes' disease in Southwest Scotland. J Bone Joint Surg [Br]. 2005;87-B:1531-5.
14. Chacko V, Joseph B., Seetharam B. Perthes' Disease in South India. Clin Orthop 1986;209: 95-99.
15. Joseph B., Chacko V, Rao BS, Hall AJ. The Epidemiology of Perthes Disease in South India. Internat J Epidem. 1988;17(3):603-7.
16. Joseph B, Varghese G, Mulpuri K, Rao KLN, Nair SN. Natural Evolution of Perthes' Disease: A Study of 610 Children under 12 Years of Age ar Disease Onset. J Pediatr Orthop. 2003;23:590-600.
17. Moens P, Defoort K, Vancampenhout A, Peerlinck K, Fabry G.Thrombophilia and Legg-Calvé-Perthes disease: is it a causative factor and does it affect the severity of the disease? Acta Orthop Belg. 2007 Oct;73 (5):612-7.

18. Liu R, Fan L, Yin L, Wang K, Miao W, Song Q, Dang X, Gao H, Bai C. Comparative study of serum proteomes in Legg-Calve-Perthes disease. BMC Musculoskelet Disord. 2015 Oct 5;16:281. doi: 10.1186/s12891-015-0730-z
19. Balasa VV, Gruppo RA, Glueck CJ, Wang P, Roy DR, Wall EJ et al. Legg-Calvé- Perthes disease and thrombophilia. J Bone Joint Surg Am. 2004;86:2642-7.
20. Joseph B. Serum immunoglobulin in Perthes' disease. J Bone Joint Surg [Br] .1991;73; 509-10.
21. Lia Lira Olivier Sanders, Manuel Bomfim Braga Júnior, César Wagner Montenegro Cima, Rosa Maria Salani Mota, Maria Inês de M. C. Pardini, Sílvia Helena Barem Rabenhorst. Leiden's v-factor in Legg-calvé-perthes disease. Acta Ortop Bras. 2009; 17(2):40-2
22. Woratanarat P[1], Thaveeratitharm C, Woratanarat T, Angsanuntsukh C, Attia J, Thakkinstian A. Meta-analysis of hypercoagulability genetic polymorphisms in Perthes disease. J Orthop Res. 2014 Jan;32(1):1-7. doi: 10.1002/jor.22473. Epub 2013 Aug 27.
23. Vosmaer A[1], Pereira RR, Koenderman JS, Rosendaal FR, Cannegieter SC. Coagulation abnormalities in Legg-Calvé-Perthes disease. J Bone Joint Surg Am. 2010 Jan;92(1):121-8. doi: 10.2106/JBJS.I.00157.