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Review Article

Clinical and genetic characteristics of Legg-Calve-Perthes disease

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ABSTRACT

Legg-Calve-Perthes disease (LCPD) is a known childhood form of idiopathic femoral head osteonecrosis. It is characterized by a sequence of events involving the capital femoral epiphysis. The disease process is associated with the disruption of the blood supply to the femoral head. In most cases, LCPD appears in a sporadic form. Occurrences of cases in families have also been reported, with some families having more than two affected individuals. The disease etiology is still unknown, however, various factors have been considered for the pathogenesis of LCPD, including very low body weight or short stature at birth, maternal smoking, and second-hand smoke exposure. Interaction of multiple environmental and genetic factors has also been postulated as an underlying player in the development of the disorder. Hypercoagulability may have a major role in LCPD development. Families segregating LCPD largely demonstrate autosomal dominant inheritance. Variants in coagulations genes (Factor 5 and Factor 2) and collagen encoding gene (*COL2A1*) have been linked to the disease. However, our knowledge of the LCPD pathogenic factors is limited. A better understanding of the association between LCPD and causative factors, for example, the role of hypercoagulability in osteonecrosis development, might lead to the development of improved treatments, to shorten the acute phase of the disease during childhood as well as to possibly reduce the long-term effects of osteoarthritis in adulthood. Detection of large-effect variants underlying LCPD may help in offering extended screening for all first-degree family members. In this review, we would like to discuss the etiological factors underlying LCPD with special emphasis on the role of coagulation factors and mutations in the genes encoding those coagulation factors.

Keywords: Perthes' disease, Legg-Calve-Perthes disease, Factor 5 Leiden, *COL2A1*, Osteonecrosis

INTRODUCTION

Legg-Calve-Perthes disease (LCPD) or coxa plana is an idiopathic avascular necrosis (AVN) of the femoral head epiphysis that occurs during childhood. It was first described independently in 1910 by Georg Perthes', Arthur Legg, and Jacques Calvé.[1] LCPD is characterized by hip pain, restricted mobility, reduced physical activity, and disability typically leading to gait disturbance.[2]

It usually occurs in 3–12 years old children. The highest occurrence is at 5–7 years.[3] This condition is 4 times more common in boys.[4] LCPD is bilateral in 10–20% of affected cases. The incidence of LCPD varies in different geographical regions. Overall, analysis of data from 16 countries has shown that the incidence of the disease ranges from 0.2 per 100,000 to 19.1 per

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100,000.[2,5] A single study has reported a highest incidence of 29.0 per 100,000 individuals in the Faroe Islands of Denmark.[6] It has also been observed that children from families of low socioeconomic status may have high incidence and are, therefore, disproportionately affected.[2,7]

Key events in the development of LCPD can be divided into four distinct phases, including (a) subchondral fracture, (b) fragmentation, (c) re-ossification, and (d) healing with residual deformity. The first stage of this condition is characterized by a temporary disruption of the femoral capital epiphysis blood supply leading to infarction of subchondral cortical bone and capital epiphysis. As a result, growth of the ossific nucleus ceases and the infracted bone dies. This stage is termed necrosis.[8] Over time fragmentation takes place. In this process, the dead bone is reabsorbed, and new bone is formed.[9] In the re-ossification phase, the femoral head eventually heals, and the femoral epiphysis re-establishes due to the osteoblastic activity. However, during this process, the re-ossified femoral head may get enlarged or flattened, and deformity can develop due to reshaping because of weight bearing pressure on the weakened epiphysis during growth. This stage is called remodeling. Remodeling typically leads to disturbance in gait, mobility restriction, pain, and reduction in physical activity.[3,10,11]

The aim of this review article is to discuss the etiological factors underlying LCPD with special emphasis on the role of coagulation factors and mutations in the genes encoding those coagulation factors.

ETIOLOGY OF LCPD

The exact cause of LCPD is not known. A large nationwide Swedish study found an association between suboptimal birth characteristics and breech presentation during delivery with the development of LCPD.[12] A strong correlation has also been described with maternal smoking as well as exposure to second-hand smoke.[13-15] Moreover, high rates of obesity and hypertension were also identified in a group of children having LCPD.[16]

The cause of the LCPD is largely unknown, though, many experimental and clinical studies provide support to the idea that the temporary disruption of the blood supply to the femoral head is a key event in the pathogenesis of the disease. Various diagnostic tools including selective angiography,[17] bone scintigraphy,[18] perfusion magnetic resonance imaging (MRI),[19] and the biopsy studies[20] from the early stages of the disease show clear indication of disruption of perfusion and bone damage consistent with AVN. The underlying cause may be disruption of supply of blood to the femoral epiphysis due to trauma, coagulopathy, or the use of steroids. Disruption of blood supply might be due to either thrombophilia (an increased tendency for thrombus formation) or hypofibrinolysis (a reduced ability for thrombolysis). The two processes have been suggested to play an essential role in the pathogenesis of osteonecrosis.[21-24] This is supported by the fact that thrombophilia and some forms of coagulopathy are present in approximately 50% and 75% of the LCPD patients, respectively.[25]

Some authors refer to the injury and initial bone collapse as the cause of LCPD. Others have proposed intravascular thrombosis as a causative mechanism.[26] Recently, congenital growth hormone deficiency has also been associated with LCPD.[27]

PATHOBIOLOGY OF THE LCPD

The difficulty in getting clinical specimens from patients with LCPD is the key issue in understanding the pathophysiology of this condition. The current knowledge of the LCP disease process is based on the review of a histopathological findings of six femoral heads, a few reports of isolated necropsy, and findings from some surgical biopsies.[20,28-32] Briefly, the pathological process affects mainly the bony epiphysis, physis, and metaphysis with the covering articular cartilage. The articular cartilage changes include increased thickness in its deep layer with necrosis of the chondrocytes, cessation of the endochondral bone formation, a clear separation of articular cartilage from the subchondral bone, invasion of the cartilage by blood vessels, and new accessory ossification. In the epiphyseal bone, the necrosis of the marrow space and the trabecular bone, compression fracture of trabeculae, invasion of the fibro-vascular granulation tissue, necrotic bone resorption, and thickened trabeculae due to new bone formation have been reported. The physeal changes can often be seen in the anterior part of the femoral head, with focal areas of growth cartilage extending into the metaphysis. Premature growth arrest of the growth plate is seen only in 30% of LCPD patients, suggesting that the growth plate continues to function in the majority of the patients. Changes in metaphysis are usually observed during the initial stages of the disease.[32]

DIAGNOSIS OF LCPD

Imaging (radiographs and MRI) is used to diagnose LCPD. Recently, non-invasive magnetic resonance angiography has been shown to provide clear images of the epiphyseal blood supply of the femoral head in LCPD patients.[33] However, early radiographs can be normal. Imaging studies of the initial stages of the disease show epiphyseal cartilage hypertrophy, changes in the epiphysis, and subchondral fracture. In advanced stages of LCPD, flattening of the femoral head, fragmentation, and healing are evident in radiographs. In addition, MRI shows decreased femoral head perfusion and bone marrow changes.[3]

MANAGEMENT OF LCPD

The main goal of the management for LCPD is to manage pain and symptoms.[34] Moreover, the aim is to promote self-healing of the femoral head with minimal deformity and restoration of the hip range of motion.[34] This is achieved by maintaining the optimum local environment in and around the hip joint.[35,36] Repair and resorption take place, leading to remodeling and femoral head deformation.[9] Once children start to recover with the femoral head remodeling, symptomatic improvement may be observed in the hip joints.

Non-surgical, as well as surgical intervention, is required to manage the LCPD. Non-surgical management is preferred over surgical options. This type of management typically suffices in children with bone age below 6 years.[37] Almost 90% of physicians refer LCPD children for physical therapy[38] with the aim to maintain hip joint mobility. The evidence base for this type of management is limited.[39] Non-surgical management options include orthosis, physical therapy such as stretching and strengthening regimes, walking aids, activity modification, or watchful waiting.[40,41] The selection of the type of non-surgical interventions is totally dependent on the treating physician. However, robust evidence regarding which kind of intervention is most effective for treating children with LCPD is lacking.[37,39] In a few cases, the hip deformity is severe and surgical containment may be necessary. Operative treatment is performed based on age, severity, and type of deformity. It can be femoral or pelvic osteotomies, varus or valgus femoral osteotomies, shelf procedure, hip arthroscopy, or hip arthrodiastasis.[42] In many cases, surgical intervention is usually considered after skeletal maturity in late adolescence.[43] Clinical guidelines for the management of LCPD are absent and currently, no standardized approach is there for selecting the right treatment.

GENETICS OF LCPD

LCPD is a complex disease, and the interaction of multiple environmental and genetic factors may play a role in the development of the disease. LCPD-associated factors include deprivation, the abnormal clotting mechanism, smoke exposure, and genetic predisposition.[4,44,45] Although most LCPD cases are isolated, multiple cases in families have also been reported, with some families having more than two affected individuals.[46-48] Several reports of siblings with similar features of disease have also been published.[49,50] Moreover, a study has shown the incidence of 2.5% in first-degree relatives of LCPD index cases.[51] This incidence of LCPD in relatives is much higher (35 times) than that in the general population. These studies raise the possibility of a strong genetic component in the etiology of LCPD. Furthermore, the occurrence of LCPD-like hip changes in a few inherited dysplasias of the skeleton, such as trichorhinophalangeal syndrome[52-54] and Floating-Harbor syndrome,[55] also suggests the presence of major genetic defects underlying LCPD. In the succeeding section, genetic factors associated with the pathogenesis of LCPD will be discussed.

COAGULATION FACTORS AND LCPD

AVN develops, at least in part, as the end result of partially and temporarily disrupted blood flow to the femoral head.[22-24,45,56,57] Defects in coagulation factors have been considered as one of the possible causes of the impaired supply of blood to the femoral epiphysis.[58] The thrombophilia-based hypothesis (thrombophilia followed by thrombotic venous occlusion of the femoral head) of LCPD is based on the notion that thrombosis selectively blocks the femoral head venous outflow, leading to increased intraosseous pressure, and subsequent AVN. Several studies have investigated coagulation abnormalities in LCPD patients. In a case–control study on the correlation between LCPD and coagulation defects, 19 patients out of 44 patients were found to have a protein-C deficiency and four patients out of 44 patients were found to have a protein-S deficiency.[56] Three fourths of the study patients had coagulation abnormalities. A high risk of LCPD is statistically significant with decreasing levels of protein C and a high risk of LCPD is nearly significant with decreasing levels of protein S was found.[22] Therefore, it was concluded that the thrombophilic state due to abnormalities of the coagulation system plays a role in the LCPD.[22]

While some studies have found an increased rate of abnormalities of coagulation in the patients with LCPD,[21,22,56,59,60] others have not found any association at all.[61-64] The discrepancy might be due to some confounding factors, including a small sample size in some studies, the retrospective study design, use of suboptimal controls, and non-standardized range of laboratory values for coagulation factor level. As far as prospective studies are concerned, a random series of 50 consecutive LCPD patients did not show a difference in the prevalence of antithrombin III, protein-S, or protein-C deficiencies between the group of LCPD patients and the estimated frequency of disease in the population.[65] Recently a Cincinnati case–control study with 72 non-selected, consecutive LCPD patients and 197 healthy controls failed to find an increase in the prevalence of antithrombin-III, protein-S, and protein-C deficiencies.[66] Nevertheless, the Cincinnati study did find an increased prevalence of factor-V Leiden and anticardiolipin antibodies (IgG and IgM) in LCPD patients.

Mutations in genes involved in coagulation, including factor V Leiden (*F5;* OMIM 612309), prothrombin II (*F2;* OMIM 176930), and methylenetetrahydrofolate reductase (*MTHFR;* OMIM 607093) have the tendency to cause vascular

occlusion. Below, studies describing mutations in *F5*, *F2,* and *COL2A1* (OMIM 120140) genes and their association with the LCPD will be discussed.

F5 variants in LCPD

A correlation between thrombophilia (hypercoagulability or a prothrombotic state) and hypofibrinolysis (a decreased capacity to dissolve a blood clot) and AVN of the hip in adults have been reported[21,26] followed by detection of associations of the *F5* gene (1q24.2) polymorphism (c.G1691A) and LCPD.[26,44,45,56] The same variant (c.G1691A) was found with high incidence in children with LCPD than in the general population.[59] Data from 12 case–control studies, a meta-analysis consisting of 824 cases and 2033 controls, suggests that the *F5* variant might increase the odds of LCPD around 3 times. In such cases, the *F5* mutant allele may explain around 3% of the cases of LCPD in childhood.[67] In a larger case–control study from the Netherlands, a higher prevalence of the *F5* mutation was also observed.[25] Similarly, in another study, *F5* variant was found more common in the patients than in the healthy individuals.[66] Moreover, a homozygous mutation in *F5* has been associated with a more severe form of LCPD.[60] However, another case–control study from Israel failed to establish an association between *F5* mutations and the LCPD.[57] Moreover, in terms of a prospective study, a random series of 50 consecutive LCPD patients did not show any difference in *F5* mutation between the study group and the estimated population frequency.[65]

As far as families are concerned, the rate of LCPD is quite variable in the multi-generation transmission of *F5* mutation. Out of 11 members of a family, with a heterozygous *F5* variant (c.G1691A), only one was found to have LCPD features. LCPD was found in three out of ten members of another family, with either heterozygous or homozygous *F5* variant (c.G1691A).[21] A large study has concluded that *F5* variant is statistically significantly related to LCPD and screening of *F5* mutation in those children who are at-risk of LCPD might be useful in the future.[67]

Prothrombin gene (F2) variants in LCPD

A common genetic variant (c.G20210A) in the 3' UTR (untranslated region) of the prothrombin gene (*F2*; 11p11.2) is responsible for the high expression of the *F2* gene product. This variant has been found as the most prevalent predisposing genetic factor for elevated plasma prothrombin levels and consequently causes an increase in venous thrombosis.[68] In a larger case–control study from the Netherlands, a higher prevalence of the *F2* mutation (c.G20210A) was observed.[25] However, multiple studies failed to replicate these findings. For instance, a German study did not identify a high rate of *F2* variants in LCPD cases in comparison to the natural incidence.[69] Similarly, studies in other populations failed to find any association between *F2* variants and LCPD.[64,66,70]

Type II collagen gene *(COL2A1)* variants and LCPD

Linkage analysis in three families, segregating idiopathic osteonecrosis in an autosomal dominant pattern, identified a 15cM interval on chromosome 12q13.6. Sequencing the potential candidate genes in the region detected a nonsynonymous variant (c.3665G>A; p.Gly1170Ser) in the *COL2A1* gene in all 23 affected individuals of two families. In a third family, a different missense variant (c.2306G>A; p.Gly717Ser) was identified in the same gene.[71] The variant (c.3665G>A; p.Gly1170Ser) in the *COL2A1* gene was also identified in a large Japanese family segregating autosomal dominant LCPD.[72] The Japanese family has multiple affected individuals, and the phenotypic expressivity of the disease was variable. *COL2A1* mutations leading to helical glycine substitutions (p.Gly393Ser) have also been described in association with LCPD in other populations.[73] For instance, a Saudi family with multiple affected individuals has also been reported with *COL2A1* mutation.[74] A heterozygous variant (c.1888 G>A, p. Gly630Ser) in exon 29 of a *COL2A1* has also been identified in a large four-generation Chinese family segregating LCPD.[75] In this study, 45 individuals from a four-generation pedigree were studied. Usually, individuals with *COL2A1* mutations exhibit characteristic clinical features such as a small jaw, cleft palate, flat midface, and visual or hearing impairment. However, in the above-described families, patients demonstrate a rare finding in which the disease is restricted to hip development, and features usually associated with *COL2A1* mutations were missing.[76]

COL2A1 encodes type II collagen. Type II collagen is a large, homotrimeric protein with a triple-helical domain consisted of triplet repeat motifs Gly-X-Y. Variants identified in LCPD patients are in the triple-helical domain of the *COL2A1* and are highly conserved in various organisms. Although both serine and glycine residues are polar, a large hydroxymethyl group is added to the center of the superhelix due to the substitution. This change is expected to disturb the local protein domain and loosen the superhelix, leading to the pathological changes observed in LCPD cases.[75] Radiographic changes similar to LCPD were observed in affected individuals of the aforementioned families.[72,76] It is hypothesized that the collagen variants lead to the weakening of the cartilage matrix[76] and thus subsequently lead to a compromise in the integrity of the blood vessels within the cartilage. It is worth mentioning that variants in *COL2A1* only account for a small number of patients with bilateral familial LCPD. Screening of sporadic unilateral or non-familial bilateral cases of LCPD did not reveal *COL2A1* variants.[57]

CONCLUSION

LCPD is a rare hip condition of unknown etiology and is considered to be caused by temporary cessation of the blood flow to the femoral head resulting in venous occlusion and necrosis of the femoral head. The susceptibility to developing LCPD is determined by various environmental and genetic factors, while the nature and level of interaction between them are still not clear. Occurrence of multiple cases of LCPD in families and variability in the phenotype is well documented. Variations in genes that code for coagulation factors (*F5* and *F3*) and structural components of bones (*COL2A1*) might have a role in the etiology of LCPD but, so far, no strong candidate genes underlying increased risk have been identified. In conclusion, there is still much to learn about the etiology and the pathogenesis of LCPD. The overall pathogenesis of the deformity of the femoral head is complex, with multiple underlying factors. Therefore, an effective treatment should take into account the mechanical as well as biological factors involved in the pathogenesis of LCPD.

Need for detailed clinical phenotyping

Several studies have discussed the etiology, epidemiology, natural history, radiographic classifications, and treatment outcomes of LCPD. However, still many aspects of the disease are not clear. Detailed clinical phenotyping and examination of synovial joint and articular cartilage are missing due to the unavailability of human patient samples. Further analysis of bone remodeling in model organisms such as mice is essential to describe the dynamic changes of bone phenotype over time.

Delineation of genetic and epigenetic factors

LCPD is 4 times more common in boys.[4] The only plausible explanation is that the LCPD causative genetic variant is located on X-chromosome in families where the condition is more common in males. In an isolated population of the Faroe Islands, high incidence (29 affected cases in 100,000 individuals) and strong intrafamilial accumulation of the LCPD were found.[77] This has been attributed to a strong genetic drift or a huge founder effect. Although, the causative genetic variants underlying LCPD remain unknown, associations of LCPD with various factors have been described. The environmental factors may play a major role in the development of LCPD, and several factors (including inflammation, occlusion of vessels, hypercoagulability, maternal smoking, as well as exposure to smoke) may be associated with the occurrence of LCPD.[15,78,79] Most of the environmental factors have been shown to be controlled by epigenetic modifications.[80] In a preliminary finding, it has been shown that there is a significant change in genomic DNA methylation in children with LCPD.[80] However, the study was restricted to only LINE1 elements. Therefore, analysis of the genome-wide DNA methylation profile of LCPD patients is an appropriate first step to examine the epigenetic changes in the DNA of patients and its association with LCPD.

Since the genetic background is a determinant of LCPD and variants in a few genes (*F5, F2,* and *COL2A1*) have been associated with LCPD. However, almost all genetic studies on LCPD cases/families have focused on the analysis of a limited number of genes. Therefore, extensive genomics research is needed to detect polymorphic loci to reveal the pathogenesis. Moreover, a large-scale study on LCPD cases targeting the complete coding part of the DNA of LCPD patients is missing. Hence, the whole-exome sequencing strategy has the potential to identify a large effect variant underlying the LCPD phenotype. Detection of large-effect variants, haplotype, and analysis of the sequence of the targeted genes in LCPD cases can be used to detect carriers of mutant alleles before the onset of clinical features. This will allow the physician to initiate measures that may delay the progression of the disease. Furthermore, a deeper understanding of the associations between thrombophilia and LCPD might lead to improved treatments, both to shorten the acute phase of the childhood LCPD and probably reduce adult osteoarthritic sequelae.

The pathogenic process by which mutations in candidate genes confer risk of LCPD and the nature of the interaction between environmental and genetic factors are yet to be identified. The best approach forward for LCPD research, in our opinion, is a large scale combined efforts to perform single nucleotide polymorphism genotyping for copy number variation analysis and association analysis in sporadic cases, studies using exome sequencing followed by Sanger sequencing-based validation in families with multiple cases for the identification of potential sequence changes underlying LCPD. Moreover, whole-genome epigenetic studies to identify epigenetic signatures underlying LCPD phenotype might lead to interesting discoveries. In general, these studies are powerful enough to detect causative genes contributing to the LCPD phenotype. Detection and functional characterization of new genes for LCPD will certainly improve our understanding of the pathophysiology of LCPD and will help in delineating the molecular pathways involved in the development of osteonecrosis. Additionally, identification of the LCPD causative genes underlying will provide accurate genetic counseling for at-risk individuals, for prevention program development and better management.

Development of biological compounds for the treatment and biomarkers for diagnosis

Clinical features of LCPD were first reported almost a 100 years ago still, there is no effective clinical therapy or

treatment available for LCPD patients. The past 20 years have seen an influx of clinically relevant biomolecules that have been used in the treatment of diseases of bones, including osteoporosis, rheumatoid arthritis, and juvenile idiopathic arthritis. It might be helpful to develop several promising therapeutic agents for LCPD and establish comprehensive guidelines for patients based on the phase of the LCPD. Inflammatory cytokines (IL-1β and TNF-α) have been shown to be involved in the LCPD pathogenesis.[81,82] Therapeutic strategies for these cytokines may be valid for the development of effective clinical therapy for LCPD. Bisphosphonate therapy has shown promising results in animals. This shows that possibility does exist for the pharmacological treatments of LCPD in the future.[1]

A variety of substances is known to release in the extracellular space as a result of tissue damage and repair mechanism. Therefore, evaluation of the association between LCPD with those substances implicated in the pathogenesis of LCPD in the extracellular space may help in the identification of diagnostic biomarkers. Moreover, variation in global DNA methylome may serve as epigenetic biomarkers for the early detection of LCPD. Furthermore, delineating the epigenetic mechanisms involved in LCPD may offer opportunities for diagnosis and treatment of the disease.

AUTHORS' CONTRIBUTIONS

Both authors have contributed to the conception and design of the work, critically reviewed and approved the final draft and are responsible for the manuscript's content and similarity index.

ETHICAL APPROVAL

The authors confirm that this review had been prepared in accordance with COPE roles and regulations. Given the nature of the review, the IRB review was not required.

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Conflict of interest

There is no conflict of interest.

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