Title: Exploring the relationship between Legg-Calvé-Perthes disease (LCPD) and Attention Deficit Hyperactivity Disorder (ADHD)

Principal Investigator (PI): Dr. César García Fontecha, head of Orthopaedics and Traumatology Service (O.T.S) at the Hospital Sant Joan de Déu (HSDJ)

Purpose

Legg-Calvé-Perthes disease (LCPD) is defined as an idiopathic necrosis of the proximal epiphysis of the femur in children between 2 and 12 years of age. Although the aetiology is unknown, a relationship with microtrauma, genetic factors or hypercoagulability has been described, suggesting a multifactorial pathogenic process. Treatments lead to a restriction of the child's physical activity and a change in daily habits for children and parents, which could have psychological consequences. Biochemical and genetic alterations have been described in this pathology.

Attention Deficit Hyperactivity Disorder (ADHD) is currently defined by difficulties in maintaining attention and is accompanied by problems of impulsivity, and permanent and uncontrolled hyperactivity that leads to excessive body movement for their age.

A relationship between LCPD and ADHD has been described, either because hyperactivity favours LCPD due to a repetitive traumatic effect, or because the restriction of activity due to LCPD favours the appearance of ADHD due to severe changes in lifestyle, or because both entities belong to a more global disorder [8-12].

We propose to study the relationship between both diseases, studying the prevalence of ADHD in patients with LCPD, as well as the prevalence of LCPD in patients with ADHD in patients monitored in our corresponding Traumatology and Mental Health services.

Main Objective of the project: Analyse the possible correlation between the LCPD and ADHD and the possible causal relationship or concomitance.

Secondary objectives:

- To analyse the emotional distress of parents when diagnosed with LCPDdisease and to compare it with the emotional distress of parents of children with ADHD.

Hypothesis

There is an association between the occurrence of Legg-Calvé-Perthes disease and the presence of Attention Deficit Hyperactivity Disorder.

Methodology

Design:

Observational study with two groups, one with LCPD and one with ADHD.Two a priori independent diseases where we will observe the incidence of ADHD in patients with LCPD and the incidence of LCPD in patients with ADHD. For this project, the O.T.S will count with the collaboration of the Mental Health Service of the HSJD.

Study subjects:

LCPD Group: all patients with a diagnosis of LCPD (already known or new cases in the study period) at the HSJD aged between 4 and 12 years.

Inclusion criteria:

- Patients between 4 and 12 years old.
- Diagnosed or in control of LCPD at the HSJD

Exclusion criteria

- Patients out of the range 4-12 years old

ADHD Group: all new patients diagnosed with ADHD without previous pharmacological treatment attended for ADHD at the ADHD Unit of the HSJD and at the Centre De Salut Mental Infanto Juvenil (CSMIJ) Mollet, both centres belonging to the Mental Health Service of the HSJD during a period of 18 months.

Inclusion criteria:

- Patients between 4 and 12 years old
- Diagnosed of ADHD at the HSJD and without previous pharmacological treatment

Exclusion criteria

- Patients age out of the range 4-12 years old
- Patients diagnosed of ADHD in other centres
- Patients who have been pharmacological treated before.

The estimated n of the LCPD group is about 100 patients in 18 months of recruitment. In the ADHD group, the estimated number of cases is 150 in 18 months of recruitment.

Variables:

1. Mental health questionnaires to be administered to all patients in both groups (LCPD and ADHD).

- ADHD symptoms:
  - ADHD RS du Paul
  - Conners parents
  - CBCL
- Quality of life through the KIDSCREEN 27
- Anxiety via the SCARED, parent version and child version
- Depression through the CDI completed by child
- Assessment of emotional distress in parents GHQ-28 Goldberg items
- Constants: weight, height, heart rate, BP, BMI
- Problems with sleep using the BEARS scale

2. Ksads in LCPD patients with an ADHD RS version IV total score greater than or equal to 28 points in order to confirm the diagnosis and evaluate possible comorbidities.

3. Hip pathology history questionnaire to be administered to all patients with ADHD.

- Ad hoc questionnaire

4. Demographic variables

- Date of birth
- Age (calculated) at entry into the study
- Sex

Data collection:

The project involves the collection and processing of personal data. The collection and processing of personal data of all participating subjects shall comply with the provisions of the General Data Protection Regulation (GDPR 2016/679) and the applicable national legislation-Organic Law 3/2018 of 5 December on Personal Data Protection.

The data collected will be accessible by medical and care staff responsible for the patient. The data will be pseudo-anonymised. Information obtained in the course of the study will only be used for these study purposes.

Data analysis

Descriptive and statistical analysis will be carried out using R3 (R Core Team, 2019) and IBM SPSS Statistics 27.

For the analysis of socio-demographic variables, descriptive statistics of absolute value (n) and percentage (%) will be used. For the exploitation of the ADHD, SCARED, CDI questionnaires, a direct score will be obtained, which will later be translated into scores typed according to age and gender. Quantitative data will be expressed with measures of central tendency (mean, median) and dispersion (standard deviation and interquartile range). To assess the presence or absence of indicators of psychopathology according to the different questionnaires used, the Chi-square test will be used.

We will work with a confidence level of 95% and the difference between the variables will be considered to be significant when the degree of significance (p) is less than or equal to 0.05.

Correlation study between variables presence of LCPD and ADHD.

Chi-square for categorical variables and T student for continuous variables in comparison of biological markers in LCPD and ADHD.

To analyse possible causality, logistic regression will be carried out.

Sample size. The prevalence of LCPD is 1/10,000 and the expected n in the 18 months of recruitment in the SJD hospital is about 100 patients. The prevalence of ADHD in our setting is 6.8%. To estimate the prevalence of ADHD within the LCPD population, assuming a prevalence of 30%, with the expected sample of 100 LCPD patients, using a 95% confidence interval, will have an accuracy of 8.98%.

Study development:

This study is divided in four work packages (WP):

WP_1: Preparatory work for the execution of the study

Duration: 2 months

Tasks:

- Prepare and submit documentation for ethics committee approval (month 1)
- Data base design (month 2)

WP$_2$: Recruitment and data collection

Duration: 18 months

Tasks:

- Recruitment and measure of variables (both tasks are simultaneous during the 18 months, months 3-20)
- Registration in database (both tasks are simultaneous during the 18 months, months 3-20)

WP$_3$: Statistical Analysis

Duration: 1 month

Task:

- Statistical analysis of data extracted from the database (month 21)

WP$_4$: Dissemination of results

Duration: 2 months

Tasks:

- Write manuscript and send it to a peer-reviewed journal. (month 22)
- Dissemination of result in the Scoliosis Research Society Conference (month 23)

We estimate that the total duration of the study will be approximately 23 months.

	Months 1-2	Months 3-20	Month 21	Months 22-23
WP1: Preparatory work				
WP2: Recruitment and data registration				
WP3: Statistical Analysis				
WP4: Dissemination of results				

Short literature review

Arthur T. Legg, Jacques Calvé and Georg Perthes independently described Legg-Calvé-Perthes disease in 1910 after the advent of radiology as an osteonecrosis of the proximal epiphysis of the femur. Although it can occur between the ages of 2 and 12 years, it is most common between the ages of 5 and 8 years. The incidence varies according to population group, being highest in Europe (10:100,000) and less prevalent in Asian (0.2-5:100,000) and African (0.45:100,000 South Africa) populations. It is the most frequent cause of lameness between 4 and 10 years of age together with transient synovitis[1,2].

On the other hand, attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood and adolescence. The worldwide prevalence is around 7-11%, although there is a wide variability depending on the type of sample and the criteria used [3-6]. Prevalence studies in Spain indicate a prevalence of 6.8% in children and adolescents [7].

Loder, Swartch & Hensinger [8] established the existence of a correlation between the LCPD and ADHD, finding a prevalence of ADHD of 30% in their clinical sample. It should be noted that the sample of this study was 24 participants, which is a small n number. In a cohort study carried out by Hailer & Nilsson [9] where they evaluated 4057 people with LCPD, they found an increased likelihood of ADHD, with a hazard ratio of 1.5 (95% CI: 1.2-1.9). Differentiating by gender, women had an increased risk (HR= 2.1, CI: 1.3-3.5), while in men it was HR= 1.4, CI: 1.1-1.8). Some authors such as Berman [10] are of the opinion that ADHD may be one of the causes of LCPD by a repetitive trauma-type mechanism. However, Hailer [9] suggests that both entities may be manifestations of a systemic condition.

Other authors such as Türkmen [11] who carried out a comparative study between patients with LCPD (n=60), trauma patients (n=60) and orthopaedic patients (n=60) found no statistically significant differences between the two groups, concluding that there was no relationship between ADHD and LCPD.

In conclusion, it is necessary to deepen the study of both pathologies in order to understand the complex multifactorial genesis of the vascular necrosis that characterises LCPD, the relationship with ADHD disorder and the possible presence of genetic or humoral markers between both pathologies.

1. Kessler JI, Cannamela PC. What are the demographics and epidemiology of legg-calvé-perthes disease in a large Southern California integrated health system? Clin Orthop Relat Res [Internet]. 2018 [cited 2021 Mar 5];476(12):2344–50. Available from: https://pubmed.ncbi.nlm.nih.gov/30211706/

2. Hailer YD, Hailer NP. Is Legg-Calvé-Perthes Disease a Local Manifestation of a Systemic Condition? Clin Orthop Relat Res [Internet]. 2018 May 1 [cited 2021 Jan 26];476(5):1055–64-. Available from: https://pubmed.ncbi.nlm.nih.gov/29481348/

3. Polanczyk G V, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int J Epidemiol. 2014 Apr;43(2):434–42.

4. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. Vol. 135, Pediatrics. American Academy of Pediatrics; 2015. p. e994–1001.

5. Gnanavel S, Sharma P, Kaushal P, Hussain S. Attention deficit hyperactivity disorder and comorbidity: A review of literature. Vol. 7, World Journal of Clinical Cases. Baishideng Publishing Group Co; 2019. p. 2420–6.

6. Wolraich ML, McKeown RE, Visser SN, Bard D, Cuffe S, Neas B, et al. The Prevalence of ADHD: Its Diagnosis and Treatment in Four School Districts Across Two States. J Atten Disord. 2014 Oct;18(7):563–75.

7. Catalá-López F, Peiró S, Ridao M, Sanfélix-Gimeno G, Gènova-Maleras R, Catalá MA. Prevalence of attention deficit hyperactivity disorder among children and adolescents in Spain: a systematic review and meta-analysis of epidemiological studies. BMC Psychiatry. 2012 Oct;12:168.

8. Loder RT, Schwartz EM, Hensinger RN. Behavioral characteristics of children with Legg-Calvé-Perthes disease. J Pediatr Orthop. 1993;13(5):598–601.

9. Hailer YD, Nilsson O. Legg-Calvé-Perthes disease and the risk of ADHD, depression, and mortality A registry study involving 4,057 individuals. Acta Orthop. 2014 Sep 1;85(5):501–5.

10. Berman J, Aran A, Berenstein-Weyel T, Lebel E. Exploring the Association between Legg-Calvé-Perthes Disease and Attention Deficit Hyperactivity Disorder in Children. Isr Med Assoc J. 2016 Nov;18(11):652–4.

11. Türkmen I, Poyanli O, Ünay K, Kemah B, Akan K, Ulusan S. Association between attention deficit and hyperactivity disorder and Perthes disease. Acta Orthop Traumatol Turc [Internet]. 2014 [cited 2021 Jan 26];48(1):67–72.