Slipped Capital Femoral Epiphysis Associated With Hypogonadism: A Case Report And Literature Review

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Abstract

Background: Slipped capital femoral epiphysis (SCFE) is a displacement of the femoral head epiphysis that is sometimes associated with endocrinopathies. We report the case of a 12-year-old girl with hypergonadotropic hypogonadism (HH) who developed SCFE during growth hormone therapy (GHT). We also performed a systematic review of the cases of SCFE and hypogonadism in the literature.

Case presentation: The patient was diagnosed with HH based on the absence of ovaries and a uterus. Her medical history included GHT for 9 years as she was small for gestational age. Chromosomal and genetic analyses revealed no pathogenic abnormalities. Radiographs revealed a left SCFE with a 28.7° posterior tilt angle. GHT was discontinued, and bilateral *in situ* screw fixation was performed. Sex hormone therapy (SHT) was initiated. Two years later, the patient recovered.

Methods: We reviewed the cases of hypogonadism complicated with SCFE. The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement were followed. Case reports of patients were retrieved using PubMed on November 17, 2021.

Results: A total of 44 cases of SCFE and hypogonadism were identified, including this case. Endocrinological complications included growth hormone deficiency (n = 18), being overweight (n = 9), and hypothyroidism (n = 25). Hormone replacement was administered before (SHT, n = 6; GHT, n = 12) and after surgery (SHT, n = 21; GHT, n = 11). SCFE surgery was invasive (minimal, n = 19; moderate, n = 10; high, n = 8). Orthopedic complications were observed in four cases.

Conclusions: If hypogonadism occurs during GHT, SCFE should be noted. Hypogonadism should be studied to determine the effects of hormonal replacement on SCFE.

Introduction

Slipped capital femoral epiphysis (SCFE) is a rare disease in which the femoral head epiphysis is displaced at the growth plate[1]. The prevalence of SCFE varies from 2.98 to 10.8 per 100,000 children, depending on the country[2] and ethnicity[3]. SCFE predominantly occurs in obese adolescent boys; however, SCFE is also associated with endocrine disorders, including hypogonadism, growth hormone deficiency (GHD), hypothyroidism, and growth hormone therapy (GHT)[1]. According to Harris's hypothesis, SCFE is due to an imbalance between the excess effects of growth hormone and the decreased effects of sex hormones[4]. Although the associations of SCFE with endocrine disorders[5-7], GHT[8], hypothyroidism[9,10], and panhypopituitarism[11] have been reviewed, no reviews describe the relationship between SCFE and hypogonadism.

Patients with SCFE usually present with limping and poorly localized pain in the hip, groin, thigh, or knee[1]. The delayed diagnosis of SCFE may result in a poor prognosis. The goals of treatment are preventing slip progression and avoiding orthopedic complications, such as avascular necrosis (AVN). *In situ* screw fixation is the usual treatment for stable SCFE, while more invasive surgery, such as osteotomy, is required for unstable SCFE. Prophylactic contralateral surgery may be effective, but the efficacy of hormonal replacement on SCFE is not clear.

We report a case of hypergonadotropic hypogonadism (HH) with the development of SCFE during GHT. In addition to the case description, SCFE cases associated with hypogonadism were reviewed to investigate the relationship of hypogonadism and GHD with SCFE.

Methods

Case presentation

A 12-year-old girl presented with pain in her left thigh and hip. She was born at the gestational age of 33 weeks and 5 days with a height of 33.0 cm (−4. 28 SD) and weight of 960 g (−3. 90 SD) and was small for gestational age (SGA). She was treated with levothyroxine for transient hypothyroidism, which was discontinued at 9 months of age. At the age of 3 years, GHT was initiated for short stature due to SGA. She was diagnosed with HH based on increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and decreased estradiol at the age of 9 years (LH 3.7 IU/L, normal range for prepuberty: 0.01–0.09; FSH 35.8 IU/L, normal range: 0.54–2.47; E2 < 10 pg/mL, normal range: <10). Magnetic resonance imaging revealed no uterus and ovaries. Turner syndrome was suspected, but multiple tests for G-banding in the blood and fluorescence *in situ* hybridization of buccal mucosa showed the 46 XX karyotype. Analysis of 4813 genes, including those responsible for known sex-linked diseases and Mayer–Rokitansky–Küster–Hauser syndrome, microarray analysis, and whole exome analysis using next-generation sequencers did not identify any pathogenic mutations that could explain the clinical manifestations.

Her height and weight at the onset of SCFE were 140.9 cm (−1.95 SD) and 38.7 kg (−0.77 SD), respectively. She had a body mass index (BMI) of 19.5 kg/m^2 and was not obese. She had no breast development and pubic hair corresponded to Tanner stage 1. The bone age (11 years and 4 months), assessed by the radius, ulna, and short bone method, was mildly delayed compared to her calendar age (12 years and 6 months). Bone mineral density was mildly decreased in the lumbar spine at 0.740 g/cm^2 (81% of the age-equivalent standard), but normal in the forearm at 0.576 g/cm^2 (94%) on the right and 0.590 g/cm^2 (97%) on the left. She had normal thyroid function, increased gonadotropins, decreased estradiol, and normal insulin-like growth factor-1 (IGF-1) (TSH 1.276 μIU/mL, normal range: 0.61–4.23; free T4 1.47 ng/dL, normal range: 0.75–1.45; LH 19.2 IU/L, normal range for puberty: 1.61–3.53; FSH 88.1 IU/L, normal range: 1.21–8.22; E2 < 20 pg/mL, normal range: 28.8–196.8; IGF-1 454 ng/mL, normal range: 188–654).

Radiographs showed a posterior displacement of the left femoral head with a posterior tilt angle of 28.7° (**Fig 1A, 1B**). The right femoral head was intact. Computed tomography showed a widening of the left femoral epiphysis (**Fig 1C**). Based on these findings, she was diagnosed with SCFE. GHT was immediately discontinued. Prophylactic pinning of the right femoral head was considered necessary due to the HH and GHT. Thus, bilateral *in situ* screw

fixation was performed (**Fig 1D**). After the surgery, sex hormone therapy (SHT) with transdermal estradiol (0.09 mg every 2 days) was initiated, according to the protocol recommended by pediatric endocrinologists of the Turner Syndrome Research Collaboration in Japan[12]. Two years after the surgery, her recovery was satisfactory, with no SCFE complications.

Literature review

We reviewed cases of hypogonadism complicated with SCFE. The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement were followed[13]. Case reports of patients were identified in PubMed on November 17, 2021. We searched across all dates from inception. The following search terms were used: “slipped capital femoral epiphysis” AND “hormone” (128 results), “slipped capital femoral epiphysis” AND “endocrine disorders” (119 results), “slipped capital femoral epiphysis” AND “endocrine” (79 results), “slipped capital femoral epiphysis” AND “hypogonadism” (21 results), “slipped capital femoral epiphysis” AND “hypopituitarism” (20 results), and “slipped capital femoral epiphysis” AND “Turner syndrome” (11 results). Articles that described patients with hypogonadism complicated with SCFE were retrieved and the phenotypic descriptions were analyzed.

No restrictions on language or date were imposed. Due to the rarity of the condition, all study designs were accepted for inclusion, including clinical and radiological studies. After deletion of duplications, one reviewer (HI) checked all retrieved titles followed by abstract screening. The full manuscripts were retrieved for articles with potentially relevant abstracts. Information related to the clinical background, comorbidities, surgical procedures, and treatment outcomes was extracted for analysis from the included articles.

Analysis was performed using descriptive statistics and narrative synthesis. BMI > 25 was considered overweight. The surgical procedures were classified as minimally invasive (*in situ* pinning, internal fixation), moderately invasive (reduction and internal fixation), and highly invasive (hip dislocation and osteotomy). Postoperative AVN and chondrolysis were considered complications. Data were shown as medians (interquartile range).

Results

Search result

The electronic search generated 388 records (**Fig 2**). After deleting 166 duplicates and 1 article having 2 records, the initial abstract screening led to 221 potentially relevant articles. The number of articles and reasons for exclusion were as follows: 148 were not related to hypogonadism, 23 lacked detailed case information, 12 were reviews, and 3 reported animal-related research. In total, 34 studies were included in the analysis.

Demographic results of the pooled samples

The pooled samples consisted of 44 patients with SCFE associated with hypogonadism (with our case), including 9 bilateral, 14 right, 20 left, and 1 unknown SCFE (Table 1)[5,6,11,14-44]. Of the 44 cases, 24 were male, 18 were female, and 2 were of unknown sex. All patients had hypogonadism, 9 patients were overweight, 18 patients had GHD, and 25 patients had hypothyroidism. The median age and BMI at presentation were 19.7 (14.3–22.8) years and 22.9 (19.8–25.5), respectively. Before the onset of SCFE, 6, 12, and 8 patients were on SHT, GHT, and thyroid hormone therapy (THT), respectively. After the surgery for SCFE, 21, 11, and 20 patients were on SHT, GHT, and THT, respectively.

Surgical procedures and orthopedic complications

Information on surgical procedures was available for 37 cases. A total of 19 cases were minimally invasive, 10 cases were moderately invasive, and 8 cases were highly invasive. Of the 34 unilateral SCFE cases, 11 patients received prophylactic surgery for the intact hip and 4 patients developed contralateral SCFE. During a median observation period of 18 (8–32) months, 30 patients had no orthopedic complications and 4 patients developed complications, including AVN (n = 3) and AVN with chondrolysis (n = 1).

Discussion

We describe the case of a patient with HH who developed SCFE during GHT for short stature as she was SGA. The patient underwent *in situ* screw fixation and SHT with no complications. SCFE may have developed due to the combined effects of GHT and HH. In addition to the case description, we reviewed 44 previously reported cases of SCFE associated with hypogonadism.

Although SCFE predominantly occurs in obese adolescent boys, our patient was nonobese and prepubescent. Although endocrine disorders, such as GHD, hypothyroidism, hypogonadism, or delayed puberty, are associated with SCFE[1-3], endocrine disorders did not appear to be involved in our case. The thyroid function was normal for a 12-year-old and the growth hormone levels were sufficient due to growth hormone administration since the age of 3 years. On the other hand, excess growth hormone might be the cause of SCFE according to Harris’s hypothesis[4]. The patient was treated with GHT for SGA. Although her IGF-1 levels were within the normal range for her age, an imbalance between sex hormones and growth hormones could have caused the SCFE. Thus, hypogonadism and GHT were possible causes of SCFE in this case.

Information on SHT or GHT before the onset of SCFE was available for 44 patients; 6 had SHT and 12 had GHT. However, due to the lack of information on hypogonadism cases without SCFE, we could not clarify the association between SHT or GHT and the development of SCFE. In addition, complications such as Turner’s syndrome, obesity, and hypothyroidism could cause SCFE. Thus, the effects of SHT and GHT on SCFE development are unclear. High-quality randomized trials or observational studies on hypogonadism with or without hormonal replacement are needed to answer these clinical questions.

Based on Harris's hypothesis[4], initiation of SHT and/or discontinuation of GHT may be associated with the severity of SCFE and prevention of orthopedic complications. In our patient, GHT was discontinued and SHT was initiated to induce closure of the proximal femoral epiphysis. Our literature review could not show whether SHT or GHT before and after surgery was associated with SCFE severity or complication. In two of the four patients with AVN, SHT was not replaced after surgery. In our case, estradiol was supplemented from the early postoperative period, and AVN did not occur. These results suggest that SHT may prevent SCFE complications in patients with hypogonadism. However, various factors may contribute to the severity and complications of SCFE, such as instability, time from onset to treatment, and forcible manipulation. Therefore, this review could not ascertain whether initiation of SHT or discontinuation of GHT affected SCFE development.

There were several limitations to this study. First, this study was conducted retrospectively, which may introduce bias. A prospective study is necessary to determine the effects of hormonal replacement. Second, the studies in our literature review were conducted in different eras, and surgical techniques may have varied substantially. Third, the varied follow-up periods in the different studies may have affected the prevalence of surgical complications.

Conclusion

If hypogonadism occurs during GHT, SCFE should be noted. Prospective studies of hypogonadism are necessary to determine the effects of hormonal replacement on SCFE.

Declarations

Ethics approval: The study was approved by the ethics committee of Aichi Medical University (2021-H124).

Consent to participate and for publication: The parents of the study subjects provided consent to participate and for publication after full explanation of the purpose and nature of all the procedures used in this study.

Availability of data and material: The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available because of privacy and ethical restrictions.

Competing interests: The authors declare no competing interests.

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Author contributions

HI contributed to study design and data interpretation and was a major contributor in manuscript writing. SK, YA, HK, KT, and TY contributed to data acquisition and analysis. KW, KK, JT, and OA critically revised the manuscript for important intellectual content. HI contributed to the final approval of the version to be published. All authors read and approved the final manuscript.

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Data Availability: The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available because of privacy and ethical restrictions.

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Table

Table 1. The cases of hypogonadism complicated with SCFE in the literature.

Author, year	Original disease	Onset of SCFE	Sex	BMI	Side	HG	GHD	HT	Replacement						Treatment	Ortho progr (Follo
									pre-surgery			post-surgery				
									SH	GH	TH	SH	GH	TH		
Ihlenfeldt, 1950[14]	unknown	17	NA	NA	B	+	−	+	−	−	−	NA	NA	NA	NA	NA
	unknown	15	NA	NA	L	+	−	−	−	−	−	NA	NA	NA	unloading	right mo)
	unknown	14	F	NA	B	+	−	+	−	−	−	NA	NA	NA	NA	NC (N
	pituitary tumor	23	M	NA	R	+	−	+	−	−	−	NA	NA	NA	NA	NA
Primiano, 1971[15]	Klinefelter syndrome	19	M	not obese	R	+	−	−	−	−	−	NA	NA	NA	NA	NA
Rennie, 1974[16]	unknown	17	F	not obese	L	+	+	−	−	+	−	NA	NA	NA	*in situ* pinning*	NA
Hirsch, 1976[17]	"retarded puberty"	17	M	21.4	R	+	−	−	+	−	−	NA	NA	NA	reduction and internal fixation	NA
Reeves, 1978[18]	acromegaly	13	F	23.4	R	+	_a	−	−	−	−	+	−	+	*in situ* pinning	left S mo)
McCafee, 1983[5]	hypoestrogenism	19	F	NA	R	+	−	−	−	−	−	−	−	−	osteotomy	degen joint ((9 yrs
Prasad, 1990[19]	TS	15	F	not obese	L	+	+	−	−	+	−	−	+	−	*in situ* pinning	NC (N
Vanek, 1991[11]	panhypopituitarism	39	M	18.7	L	+	+	+	−	−	−	+	−	+	osteotomy	NC (3
Schmid, 1993[20]	pituitary insufficiency	21	M	23.9	L	+	+	−	+	−	−	+	+	−	osteotomy*	NC (1
Wells, 1993[6]	CP	26	M	25.4	B	+	+	+	−	+	+	−	+	+	*in situ* pinning	NA
	histiocytosis	22	M	23.4	L	+	+	+	−	+	+	−	+	+	*in situ* pinning	right (28 m
	TS	15	F	25.0	R	+	−	−	+	−	−	+	−	−	*in situ* pinning	left S mo)
Sakano, 1995[21]	TS	12	F	18.4	R	+	−	−	−	+	−	−	+	−	*in situ* pinning	NC (4
Takahashi, 1997[22]	KS	22	M	23.6	R	+	−	−	−	−	−	−	−	−	internal fixation	AVN (
Feydy, 1997[23]	acromegaly	20	M	20.5	B	+	_a	−	−	−	−	NA	NA	NA	open reduction and osteotomy	NA
Unnikrishnan, 2002[24]	acromegaly	17	M	NA	R	+	_a	+	−	−	−	−	−	+	*in situ* pinning	NC (1
Nabhan, 2006[25]	TS[2]	14	F	30	R	+	−	−	+	+	−	+	+	−	*in situ* pinning*	NC (2
	TS[2]	14	F	29.2	R	+	−	−	+	+	−	+	+	−	*in situ* pinning*	NC (2
Wang, 2007[26]	pituitary hypoplasia	20	M	25.6	L	+	+	+	−	+	+	−	−	+	reduction and internal fixation	NC (7
	CP	14	F	17.1	L	+	+	+	−	+	+	−	+	+	reduction and internal fixation	chon AVN (
	Prader-Willi syndrome	13	M	26.5	R	+	+	−	−	+	−	+	−	−	reduction and internal fixation	NC (3
Bowden,	pituitary hypoplasia	17	F	26	B	+	+	+	−	−	−	+	+	+	hip	NC (1

2009[27]															dislocation and osteotomy	
Brady, 2010[28]	CP	22	M	23.7	L	+	+	+	−	−	−	+	−	+	*in situ* pinning*	AVN (
Koteles, 2010[29]	hyperprolactinemia[c]	19	M	25.6	B	+	−	+	−	−	−	−	−	+	open reduction internal fixation	NC (3
Abaci, 2010[30]	delayed puberty	13	F	16.7	L	+	−	+	−	−	+	NA	NA	NA	NA	NA
Hu, 2011[31]	CP	29	M	21.8	L	+	+	+	−	−	−	+	−	+	*in situ* pinning	NC (1
Nasrallah, 2012[32]	TS	12	F	25.3	B	+	−	+	−	+	+	−	−	+	*in situ* pinning	NC (2
Soleymanha, 2015[33]	CP	28	M	not obese	L	+	+	+	−	−	−	NA	NA	NA	*in situ* pinning*	NC (4
Song, 2015[34]	CP	34	M	NA	L	+	−	+	−	−	−	NA	NA	NA	*in situ* fixation	NC (3
	KS	29	M	NA	L	+	−	+	+	−	+	+	−	+	*in situ* fixation	NC (9
Shetty, 2015[35]	pituitary adenoma	18	M	20.2	L	+	−	+	−	−	−	+	−	+	surgery	NA
Kotoura, 2017[36]	septooptic dysplasia	17	M	24.3	R	+	+	+	−	−	+	−	−	+	*in situ* pinning*	NC (1
Sankar, 2017[37]	germinoma	11	F	NA	L	+	+	+	−	−	−	+	+	+	*in situ* pinning*	NC (3
Singh_2018[38]	xanthomatous	18	M	18.7	L	+	+	+	−	−	−	+	−	+	open reduction percutaneous fixation*	NA
Yang, 2019[39]	CAH (17-OHD)	27	F	24.5	B	+	−	−	−	−	−	+	−	−	internal fixation	NC (7
Huang, 2019[40]	pituitary hypoplasia	29	M	NA	L	+	−	+	−	−	−	+	−	+	hip dislocation open reduction (Dunn's procedure)	NC (6
Ouyang, 2021[41]	congenital adrenal hypoplasia (DAX-1)	22	M	19.9	NA	+	−	−	−	−	−	+	−	−	open reduction internal fixation	NC (1
Harris, 2021[42]	pituitary adenoma	16	M	29.9	R	+	+	+	−	−	−	+	−	+	open reduction and pinning*	NC (1
Rosen, 2021[43]	panhypopituitarism	31	F	17.5	B	+	+	+	−	−	−	+	+	+	osteotomy	AVN (
Sawicka-Gutaj, 2021[44]	GNRHR mutation	25	M	22.1	L	+	−	−	−	−	−	+	−	−	hip dislocation open reduction (Dunn's procedure)	NC (2
Kitagawa, 2021 (This study)	hypergonadotropic hypogonadism	12	F	19.5	L	+	−	−	−	+[d]	−	+	−	−	*in situ* pinning*	NC (2

AVN, avascular necrosis; B, bilateral; BMI, body mass index; CAH, congenital adrenal hyperplasia; CP, craniopharyngioma; DAX-1, dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1; F, female; GH, growth hormone; GHD, growth hormone deficiency; GNRHR, gonadotropin-releasing hormone receptor; HG, hypogonadism; HT, hypothyroidism; L, left; M, male; NA, not available; NC, no complication; OHD, hydroxylase deficiency; R, right; SCFE, slipped capital femoral epiphysis; SH, sex hormone; TH, thyroid hormone; TS, Turner syndrome; KS, Kallmann syndrome; a, increased GH; 2, monozygotic

twins; c, hyperprolactinemia due to primary hypothyroidism; d, Growth hormone replacement therapy was performed for short stature due to small for gestational age.; *, prophylactic surgery was performed.

Figures

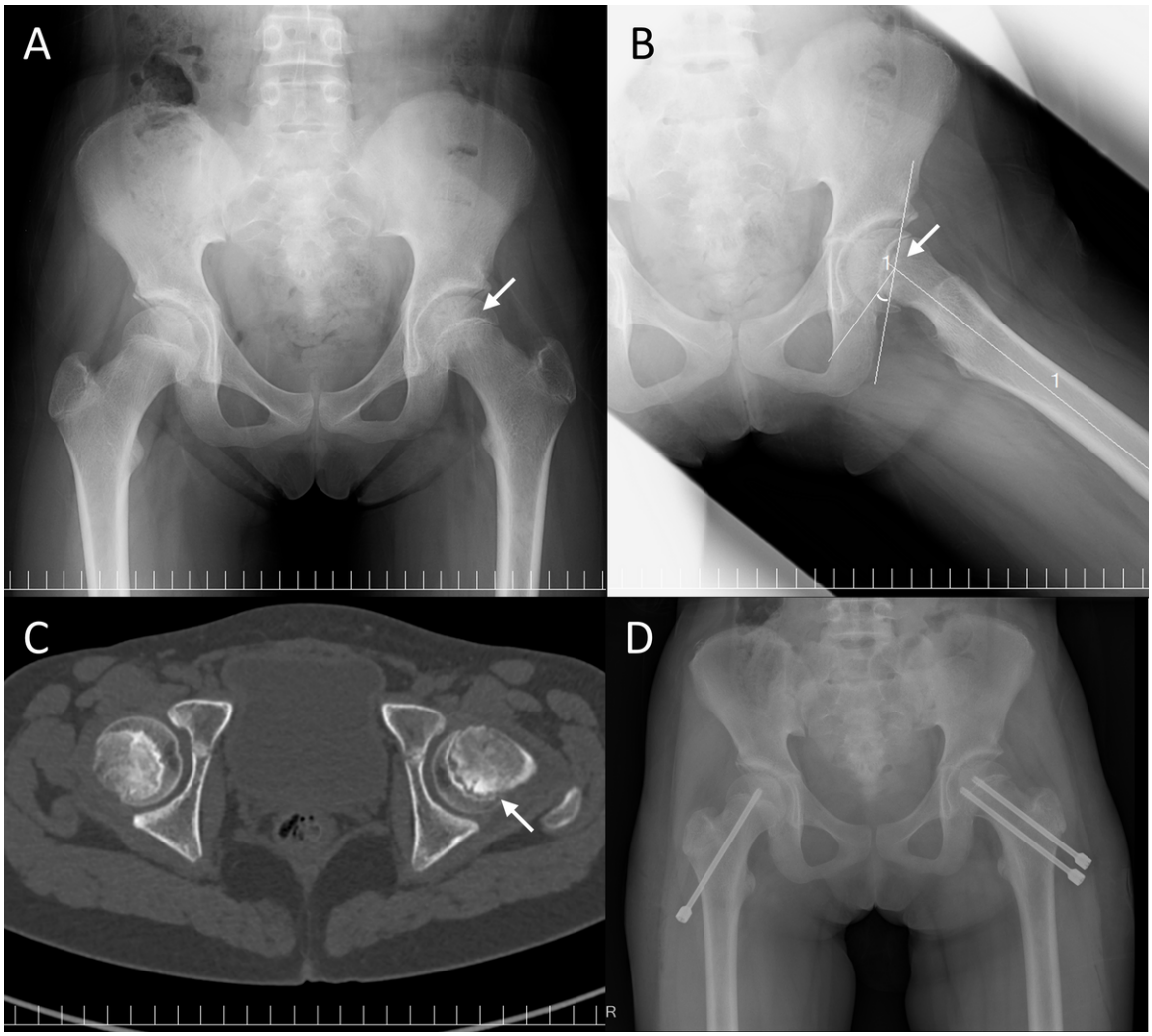

Figure 1

Imaging studies in the patient with slipped capital femoral epiphysis (SCFE). (A) Anteroposterior radiograph at the onset of SCFE. The arrow indicates a widening of the epiphysis in the affected hip (left) compared to the intact hip (right). (B) Lateral radiograph at the onset of SCFE. The arrow indicates the posterior displacement of the left femoral head with a posterior tilt angle of 28.7°. (C) Computed tomography at the onset of SCFE. The arrow indicates epiphysis widening in the left hip. (D) Radiograph after the surgery for SCFE. *In situ* pinning was performed with two screws on the affected hip and with one screw on the intact hip for prophylaxis.

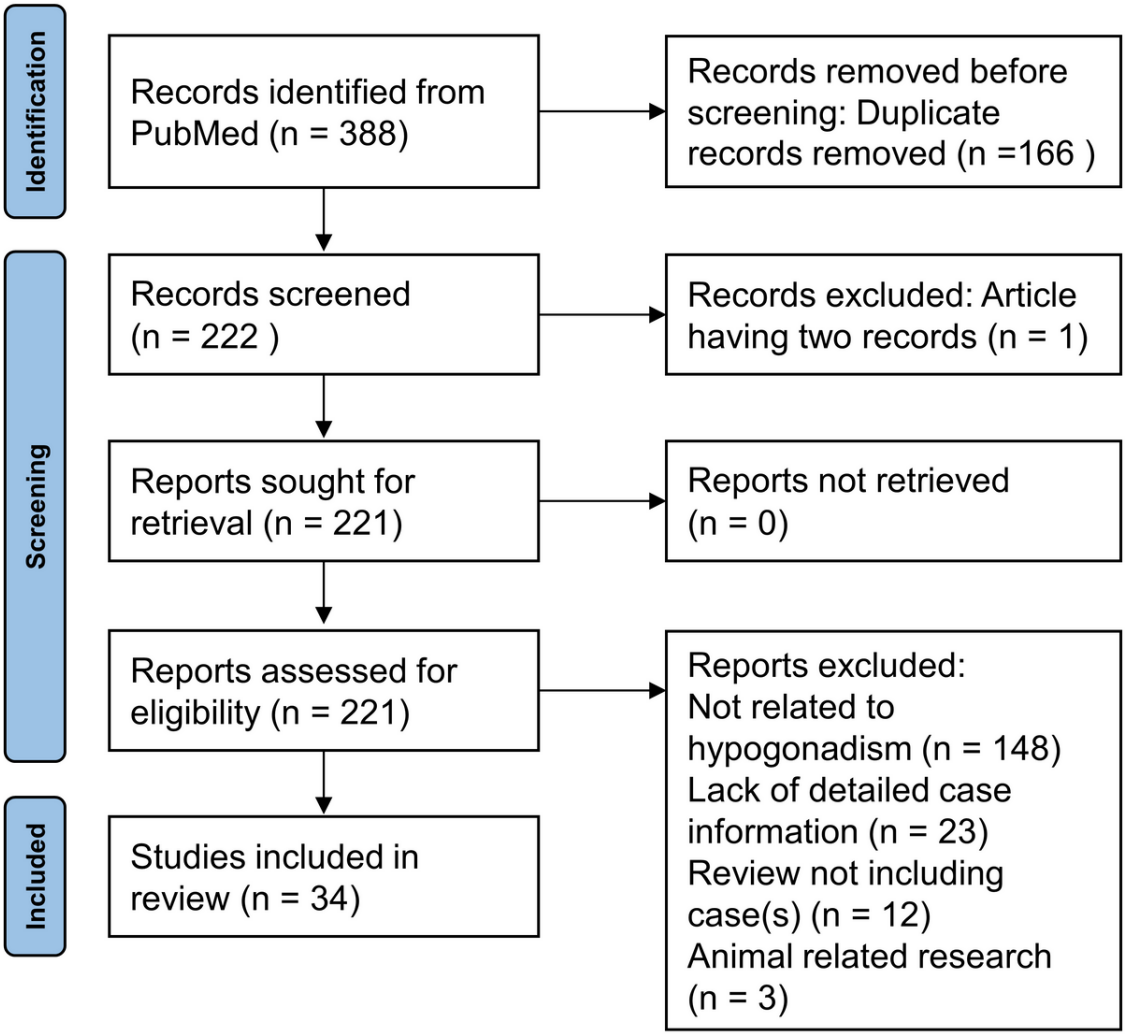

Figure 2

Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for this review.