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Original Article

ORIGINAL ARTICLE

Risk factors for steroid-induced osteonecrosis of the femoral head in children with immune kidney disease

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ABSTRACT

Objective. To investigate the risk factors for steroid-induced osteonecrosis of the femoral head (SONFH) after glucocorticoid (GC) therapy in children with immune kidney diseases.
Methods. This retrospective study included patients (1–18 years) diagnosed with immune kidney disease treated with GCs from January 2012 to July 2022 in our hospital. Data, such as sex, age and body weight at the first GC treatment, and the GC dose, were collected. Patients were divided into SONFH and non-SONFH groups based on the occurrence of SONFH. According to the International Classification of Diseases, Tenth Revision, the disease diagnosis was searched on the clinical data webpage of our hospital. The descriptive statistics and binary logistic regression analyses were performed. A nomogram was constructed to predict the risk of SONFH in children with immune kidney disease after GC treatment. The predictive ability of the nomogram was evaluated using the concordance index and calibration plots.
Results. The SONFH and non-SONFH groups included 18 and 90 patients, respectively. Age at first GC treatment, 6-month cumulative [oral (po) plus intravenous (iv)] GC dose, total cumulative prednisone (po) dose, total cumulative methylprednisolone (iv) dose for pulse therapy and total cumulative GC (po plus iv) dose significantly differed between the two groups. Age at the initial GC treatment, total cumulative prednisone (po) dose and total cumulative methylprednisolone (iv) dose for pulse therapy were independent risk factors for SONFH in the multivariate analysis.
Conclusions. This study identified specific risk factors for developing SONFH during GC treatment. Thus, children with immune kidney disease undergoing GC treatment should be monitored closely based on these risk factors, with the aim to avoid irreversible damage to the femoral head.

Keywords: children, immune kidney diseases, risk factors, steroid-induced osteonecrosis of the femoral head

INTRODUCTION

Steroid-induced osteonecrosis of the femoral head (SONFH) results from pathophysiological changes in the bone tissue and blood vessels after long-term and high-dose glucocorticoid (GC) treatment. Consequently, the femoral head receives an insufficient blood supply, causing bone tissue necrosis, repair and changes to the femoral head structure [1]. Osteonecrosis of the femoral head (ONFH) caused by long-term high-dose GC use was

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KEY LEARNING POINTS

What was known:

- At present, there are few studies on the occurrence of steroid-associated femoral head necrosis in children with immune kidney disease.

This study adds:

- Through this study, we analysed the independent risk factors for steroid-associated femoral head necrosis in children with immune kidney disease, including: the age at initial GC treatment, total cumulative prednisone dose (oral) and total cumulative dose of methylprednisolone (intravenous) for pulse treatment.
- Based on this, we constructed a nomogram model that can be used to assess the risk of steroid-induced osteonecrosis of the femoral head (SONFH) for children with immune kidney disease.

Potential impact:

- The results of this study can help in the screening of children at high risk of SONFH for early detection, diagnosis and treatment.

first reported in 1957 [2]. Since then, studies have confirmed that GCs can cause ONFH in adults [3, 4] and that GC is the most significant risk factor for SONFH in adults [5, 6]. However, relatively few reports exist on SONFH in children [7, 8].

Immune kidney disease is a chronic glomerular disease caused by autoantigens and antibodies from an abnormal immune response. As a result, immune complexes are deposited in the kidneys, which damages the structure and causes functional disorders, including lupus nephritis, nephrotic syndrome, Henoch-Schönlein purpura nephritis (HSPN) and immunoglobulin A nephropathy [9–11]. GC treatment is fundamental to controlling the progression of kidney damage in patients with immune kidney diseases [9, 12].

Presently, the causal relationship between GC and ONFH remains controversial mainly because studies on the occurrence of SONFH after GC treatment have been conducted in adults with diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis, or in those who underwent kidney transplantation [13, 14]. Shigemura *et al.* [15] and Nakamura *et al.* [16] hypothesized that once the GC dose reaches a certain threshold, the risk of ONFH increases. However, Ono *et al.* [14] and Zizic *et al.* [17] reported no causal relationship between GC treatment and SONFH.

Given the lack of studies regarding the occurrence of SONFH in children and the causal relationship between GC treatment and SONFH, this study assessed the risk factors for SONFH in children with immune kidney diseases who undergo GC treatment.

MATERIALS AND METHODS

Patients

This retrospective study included patients (1–18 years) diagnosed with immune kidney disease treated with GC at our hospital between January 2012 and July 2022. The diagnosis of immune kidney disease and ONFH were searched on the clinical big data webpage of our hospital according to the International Classification of Diseases, Tenth Revision. Confirmed diagnosis of immune kidney disease based on renal puncture pathological examination. ONFH was diagnosed by the orthopedic surgeon using a combination of physical examination and imaging. Patients diagnosed with immune kidney diseases who underwent GC treatment for ≥3 months were included. Patients with non-GC induced ONFH, with unclear data on the GC dosage, who underwent <3 months of treatment, with a history of GC use, and lacking complete clinical data or follow-up information were excluded.

The Children's Hospital of Chongqing Medical University Ethic Committee approved this study (approval number 2024YAN261). Written informed consent was obtained from all patients' guardians. Written informed consent for publication of photographs was obtained from all subjects' guardians.

GC dosages

The GC dosage was converted using the equivalent prednisone dosage (i.e. 4 mg methylprednisolone is equal to 5 mg prednisone). The total cumulative prednisone dose [oral (po) GC] includes all po prednisone doses from enrolment to the SONFH diagnosis or the end of the follow-up period. The total cumulative methylprednisolone dose {intravenous (iv) GC] includes all iv methylprednisolone doses used during the same period. The total cumulative GC dose is the sum of the equivalent prednisone doses for all GC (po and iv) administered from enrolment to the SONFH diagnosis or the end of the follow-up. Pulse therapy is the iv infusion of a large dose (≥0.2 g/day) of methylprednisolone in a short period (continuously for ≥3 days).

The following data were collected: the cumulative prednisone dose (po) at 1, 3 and 6 months and the total cumulative prednisone dose (po); the courses of methylprednisolone (iv) pulse therapy and total cumulative methylprednisolone dose (iv); and the cumulative GC dose (po and iv) at 1, 3 and 6 months, and the total cumulative GC dose (po and iv).

Statistical analyses

Statistical analyses were performed using the SPSS software (version 27.0; IBM Corp., Armonk, NY, USA) and R statistical software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). The Kolmogorov–Smirnov method was used to test the normality of the quantitative data, which are expressed as means ± standard deviations or medians with interquartile ranges (IQR). Categorical data are expressed as percentages.

The risk factors for SONFH were analysed using univariate logistic regression. Factors with *P*-values of <.05 in the univariate analysis were included in a multivariate analysis to identify independent risk factors. *P*-values of <.05 were considered statistically significant.

Table 1: Patient demographic and clinical data.

Variable	ONFH ($n = 18$)	Non-ONFH ($n = 90$)
Sex, *n* (%)		
Female	15 (83)	63 (70)
Male	3 (17)	27 (30)
Age at first GC therapy (years)	12.54 (11.12, 13.9)	11.5 (10.25, 13.08)
Weight at first GC therapy (kg)	39.5 (33.25, 45.75)	38.5 (29.25, 45)
Duration of GC therapy (years)	1.71 (0.92, 3.27)	1.25 (0.92, 2)
1-month cumulative prednisone (po GC) dose (g)	1.39 (1.12, 1.52)	1.28 (0.97, 1.64)
3-month cumulative prednisone (po GC) dose (g)	3.74 (3.35, 4.51)	3.84 (3.27, 4.37)
6-month cumulative prednisone (po GC) dose (g)	6.60 (5.61, 7.72)	6.57 (5.37, 7.30)
1-month cumulative GC dose (g)	3.34 (3.06, 5.32)	3.2 (1.86, 4.49)
3-month cumulative GC dose (g)	6.14 (5.15, 9.19)	5.75 (4.36, 7.67)
6-month cumulative GC dose (g)	10.88 (8.12, 13.00)	8.24 (6.85, 10.44)
Total cumulative prednisone (po GC) dose (g)	12.30 (9.10, 21.00)	10.20 (8.10, 12.90)
Courses of methylprednisolone pulse therapy	1.5 (1.00, 2.00)	1.00 (1.00, 2.00)
Total cumulative methylprednisolone (iv GC) dose (g)	2.48 (1.54, 4.50)	1.5 (0.79, 2.68)
Total cumulative GC (po and iv) dose (g)	18.00 (14.00, 25.00)	13.00 (10.00, 17.00)

Data are presented as *n* (%), median (IQR) or mean ± standard deviation.

A nomogram was constructed based on the results of the multivariate logistic regression to predict the risk of SONFH in children with immune kidney disease after GC treatment. The predictive ability of the nomogram was evaluated using the concordance index and calibration plots. These were performed by R statistical software.

RESULTS

Patient characteristics

The study included 108 patients; 18 and 90 patients were in the SONFH and non-SONFH groups, respectively (Table 1). The age range of the subjects included in this study was 4.75–16.5 years. The sex did not differ between the SONFH and non-SONFH groups.

GC treatment conditions

The GC treatment duration, weight at first GC therapy, cumulative prednisone doses at 1, 3 and 6 months, the cumulative GC dose at 1 and 3 months, and the courses of methylprednisolone pulse therapy did not differ between the groups. However, the age at first GC therapy, the cumulative GC dose at 6 months, the total cumulative prednisone dose, the total cumulative dose of methylprednisolone pulse treatment and the total cumulative GC dose were significantly higher in the SONFH group than in the non-SONFH group (Table 2).

Logistic regression analysis and nomogram model

The multivariate logistic regression analysis indicated that age at the initial GC treatment [$P = .011$, odds ratio (OR) = 1.56, 95% confidence interval (CI) 1.14–2.27], the total cumulative prednisone dose ($P = .006$, OR = 1.12, 95% CI 1.04–1.23) and the total cumulative dose of methylprednisolone pulse treatment ($P = .032$, OR = 1.48, 95% CI 1.04–2.15) were independent risk factors for SONFH in children with immune kidney diseases (Table 3).

A nomogram was constructed to predict the risk of SONFH after GC treatment in this patient population, which was based on the results of multivariate logistic regression (Fig. 1). The area

Table 2: Univariate analysis of factors associated with SONFH.

Variables	OR	95% CI	*P*-value
Sex			
Female	1.00	Reference	
Male	2.14	0.57–8.01	.257
Age at first GC therapy (years)	1.44	1.09–1.90	.011*
Weight at first GC therapy (kg)	1.01	0.97–1.05	.645
Duration of GC therapy (years)	1.20	0.89–1.64	.235
1-month cumulative prednisone (po GC) dose (g)	1.18	0.34–4.12	.792
3-month cumulative prednisone (po GC) dose (g)	1.04	0.57–1.89	.898
6-month cumulative prednisone (po GC) dose (g)	1.16	0.80–1.69	.433
1-month cumulative GC dose (g)	1.21	0.93–1.57	.153
3-month cumulative GC dose (g)	1.17	0.95–1.45	.133
6-month cumulative GC dose (g)	1.22	1.00–1.49	.049*
Total cumulative prednisone (po GC) dose (g)	1.07	1.01–1.14	.025*
Courses of methylprednisolone pulse therapy	1.65	0.97–2.82	.065
Total cumulative methylprednisolone (iv GC) dose (g)	1.59	1.15–2.19	.005**
Total cumulative GC (po and iv) dose (g)	1.09	1.02–1.16	.008**

*$P < .05$; **$P < .01$.

Table 3: Multivariate analysis of factors associated with SONFH.

Variables	OR	95% CI	*P*-value
Age at first GC therapy (years)	1.56	1.14–2.27	.011*
Total cumulative prednisone (po GC) dose (g)	1.12	1.04–1.23	.006**
Total cumulative methylprednisolone (iv GC) dose (g)	1.48	1.04–2.15	.032*

*$P < .05$; **$P < .01$.

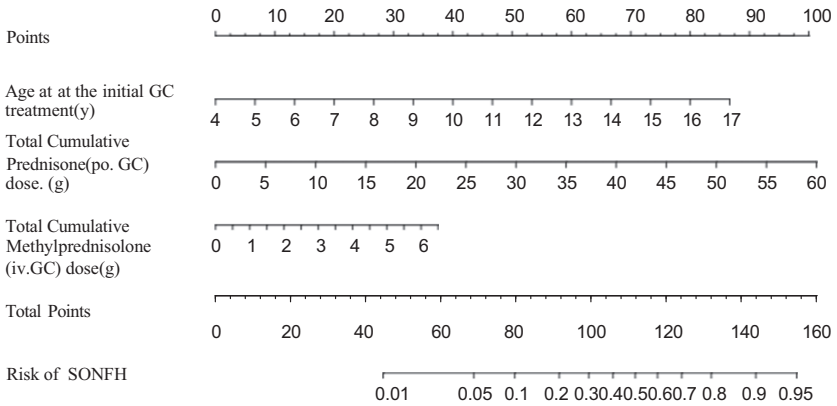

Figure 1: Nomogram for predicting the occurrence of SONFH in children with immune kidney after GC therapy. To estimate the probability of SONFH, mark the patient's values at each axis, then draw a straight line perpendicular to the point axis. Sum the points for all variables. Finally, mark the sum on the total point axis and draw a straight line perpendicular to the probability axis.

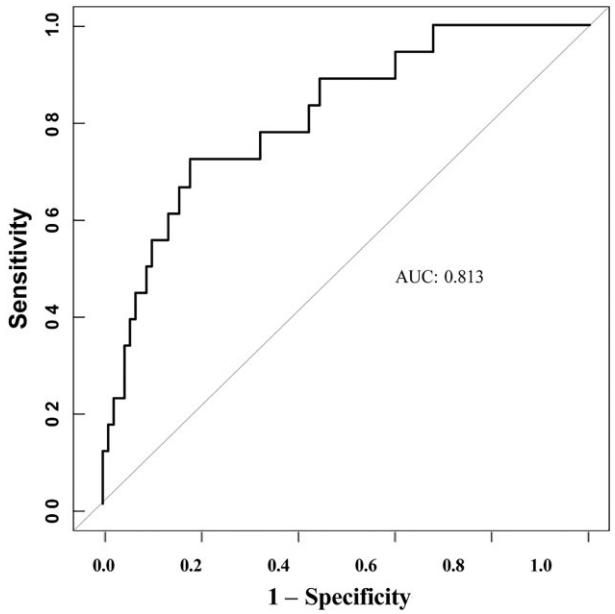

Figure 2: Receiver operating characteristic curve for the nomogram prediction model. The AUC was 0.813 (95% CI 0.705–0.921). AUC, area under the curve.

under the curve (AUC) was 0.813 (95% CI 0.705–0.921) (Fig. 2). The nomogram had a concordance index of 0.813 and it was well-calibrated (Fig. 3), indicating that the predictive model had good accuracy.

DISCUSSION

We found that the age at the initial GC treatment, the total cumulative prednisone (po) dose, and the total cumulative dose of methylprednisolone (iv) pulse treatment were independent risk factors for SONFH in children with immune kidney disease. Furthermore, we constructed a nomogram to predict the risk of SONFH development after GC treatment in this patient population.

The causal relationship between GC and ONFH remains controversial [13, 14]. Several studies have reported a significant correlation between GC treatment and ONFH onset [18]. For instance, Felson *et al.* [19] conducted a meta-analysis of ONFH after GC treatment for diseases such as SLE, kidney transplantation, asthma and inflammatory bowel disease, finding close associations between ONFH and the cumulative GC dose, GC treatment duration and the average daily dose. Koo *et al.* [20] also analysed the risk of ONFH after GC treatment in 22 patients who underwent kidney transplantation and who had aplastic anaemia and nephrotic syndrome. They found that the average cumulative GC dose from treatment initiation to magnetic resonance imaging (MRI)-confirmed ONFH was 5928 mg (1800–15 505 mg), and the average time from the initial GC treatment to the occurrence of ONFH was 5.3 months. In our study, the total cumulative GC dose (po and iv) was a risk factor for SONFH in children with immune kidney disease, but the GC treatment duration did not differ between the SONFH and non-SONFH groups. The total cumulative GC dose from the initial treatment to the SONFH diagnosis was 18.00 (14.00, 25.00) g, and the time from the initial GC treatment to the occurrence of SONFH was 1.71 (0.92, 3.27) years, which is much longer than that previously reported. Previous studies primarily focused on adult-onset SONFH, which may explain this result. Children have more severe kidney involvement and a more prolonged disease course than adults, which requires a higher GC dose [21]. Children also have an abundant blood supply from the red bone marrow and epiphyseal plate [22]. Thus, patients with early asymptomatic SONFH did not undergo imaging examinations, and conventional X-rays could not detect early lesions until the children presented with severe clinical symptoms, which may also explain the discrepancy between our results and previous studies.

Prospective studies by Shigemura *et al.* [15] and Nakamura *et al.* [16] suggested that when GC treatment exceeds a specific dose, the risk of ONFH increases accordingly. In this study, the total cumulative GC dose was also a risk factor for SONFH in children, consistent with the above-mentioned studies. Leventhal and Dorfman [23] hypothesized that the occurrence of SONFH in patients with SLE was related to the GC dose at 1, 3 and 6 months, and that the correlation was stronger than that of the cumulative GC dose. We found that the cumulative GC dose at 6 months and the total cumulative GC dose were risk factors for SONFH. Notably, the risk of SONFH associated with

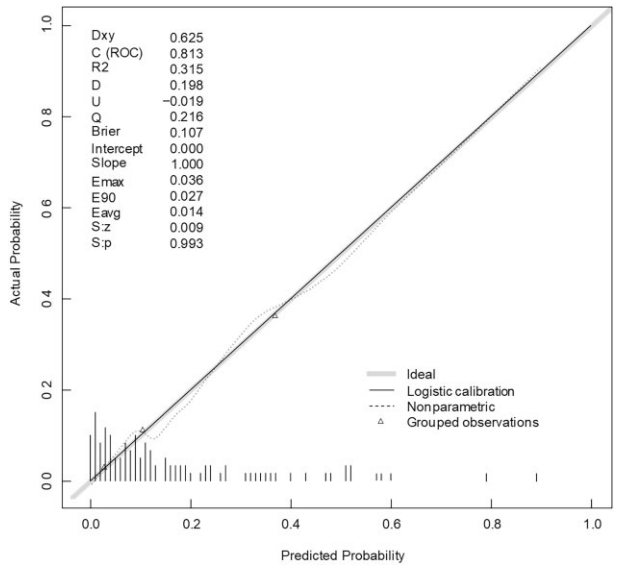

Figure 3: Calibration of the nomogram for SONFH. The x- and y-axes show the predicted and observed probabilities of SONFH, respectively.

the cumulative GC dose at 6 months was higher than that of the total cumulative GC dose. However, correlations between SONFH and the cumulative GC dose at 1 and 3 months did not exist.

Some reports have indicated that the affinities of various GCs to their receptors are related to the risk of osteonecrosis [24, 25] and the risk was higher in the pulse treatment group than in the non-pulse treatment group. The result of our study also proved that the total cumulative dose of methylprednisolone pulse treatment ($p = 0.032$, OR = 1.48, 95% CI: 1.04–2.15) was an independent risk factor for SONFH.

In contrast, other studies have reported that ONFH is not associated with GC treatment. Studies by Ono *et al.* [14] and Zizic *et al.* [17] suggested no causal relationship between total GC dose, GC treatment duration and SONFH. Our results also found no association between SONFH and GC treatment duration. However, total cumulative GC dose was a risk factor for SONFH in the univariate analysis. Sayarlioglu *et al.* [26] found no correlation between GC (iv) pulse treatment and SONFH. In contrast, we found that the total cumulative dose of methylprednisolone (iv) pulse treatment was an independent risk factor for SONFH. Furthermore, SONFH has been associated with age at the initial GC treatment [5, 27], and Kawedia *et al.* [28] hypothesized that children with SONFH had a relatively higher average age (6–14 years). Some studies have reported that age >10 years at the GC treatment is an independent risk factor for ONFH [29–31], and our results align with these studies; age at the initial GC treatment was an independent risk factor for the occurrence of SONFH ($P = .011$, OR = 1.56, 95% CI 1.14–2.27). This result could be due to the growth and development of bones in children. As children age, the epiphyseal plate gradually ossifies, and red bone marrow transforms into yellow bone marrow. Additionally, the collateral blood supply of the yellow bone marrow is relatively low and more sensitive to ischaemic injury [22]. Therefore, it is reasonable to conclude that the older the child, the higher the risk of SONFH after GC treatment.

Some studies indicate that the first 3 months of GC treatment increase the risk of SONFH [13], but others, such as that by Zizic *et al.* [32], indicate the incidence of SONFH is higher after 3 and 6 months of GC treatment. The shortest time to the occurrence of SONFH after GC treatment was 6 months in our study. Therefore, routine MRI examinations are recommended for high-risk children with renal lesions caused by immune responses, such as SLE, nephrotic syndrome and HSPN, who undergo GC treatment for 3 months, even if there are no clinical symptoms. MRI is the gold standard for the early diagnosis of ONFH [31, 33]; thus, regular re-examinations should be conducted for the early detection, diagnosis and treatment of SONFH (Figs 4 and 5).

This study had some limitations. First, this was a retrospective, single-centre study with a small sample size; prospective and multicentre studies are required. Secondly, the follow-up period for children with SONFH in this study was short.

CONCLUSION

Age at the initial GC treatment, total cumulative prednisone dose (po) and total cumulative dose of methylprednisolone (iv) pulse treatment were independent risk factors for SONFH in children with immune kidney disease. Therefore, close attention should be paid to the above-mentioned risk factors when treating this patient population, and they should be recommended to have MRI examinations routinely. Finally, we constructed a nomogram model that can be used to assess the risk of SONFH after GC treatment in children with immune kidney disease. The higher the points, the higher the risk of developing SONFH for children with immune kidney disease.

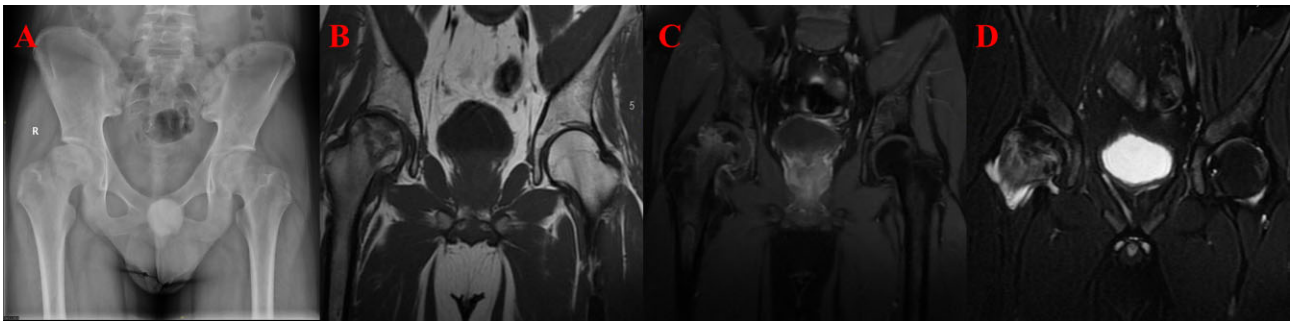

Figure 4: Representative case of a 16.5-year-old boy at the initial GC treatment who underwent one iv methylprednisolone pulse treatment due to HSPN (cumulative dose 2.25 g), followed by continuous po prednisone (cumulative dose 9.4975 g). After 0.83 years of continuous GC treatment (cumulative GC dose 15.635 g), the patient underwent imaging examinations due to right hip pain and was diagnosed with bilateral SONFH. (**A**) Radiograph shows that the right femoral head is slightly flatter than the left side, and uneven densities of the femoral head and neck are visible. (**B**, **C**) Uneven signals are observed in the right femoral head, mainly long T1 and T2 signal changes. (**D**) Obvious heterogeneous enhancement of the femoral head is visible, indicating avascular necrosis.

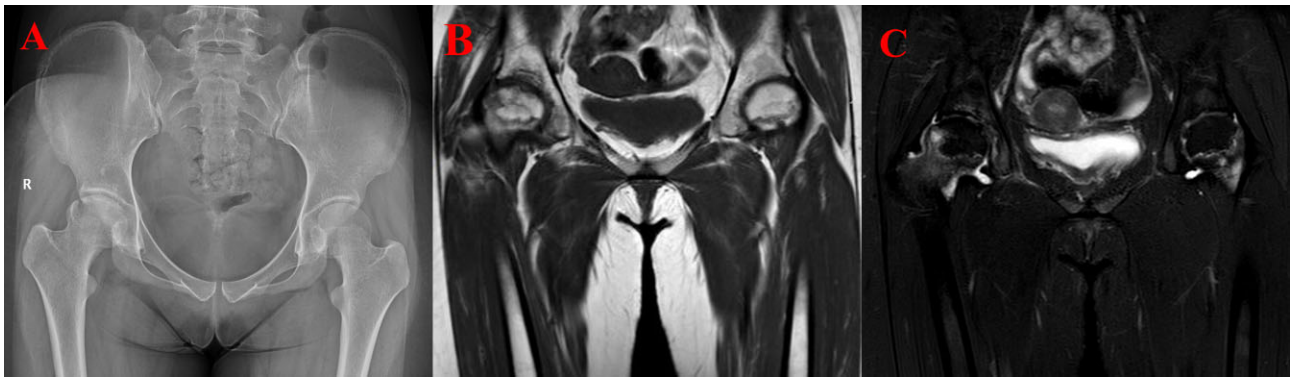

Figure 5: Representative case of a 14.8-year-old girl at the initial treatment who underwent two iv methylprednisolone pulse treatments due to SLE (cumulative dose 4.5 g), followed by continuous po prednisone (cumulative dose 11.625 g). After 1.17 years of continuous GC treatment (cumulative GC dose 17.475 g), the patient underwent imaging examinations due to bilateral hip pain and was diagnosed with bilateral SONFH. (**A**) X-ray radiograph shows an uneven density of the right femoral head. (**B**, **C**) Both femoral heads have a map-like change, mainly slightly low T1 and slightly high T2 signals, with low T1 and low T2 signals at the edges and slightly low T1 and slightly high T2 signals at the outer edges.

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None.

AUTHORS' CONTRIBUTIONS

J.L. and S.H.L. participated the study and drafted the manuscript. Y.X.S. conceived this study and helped draft the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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