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Case Report

Childhood Juvenile idiopathic arthritis combined with Klinefelter syndrome: a case report and literature review

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Abstract: Klinefelter syndrome (KS) is a chromosomal karyotype abnormality, most commonly presenting with the 47,XXY karyotype, and it has been associated with a variety of autoimmune diseases (AD). Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disorder of unknown etiology that primarily affects the joints, with pathogenesis likely involving interactions among genetic predisposition, immune systems, and environmental exposure. Here we report the youngest known case of JIA complicated with KS to date, and the first pediatric case seen in China, who was hospitalized in the Pediatrics Department of Huizhou Central People's Hospital in February 2021. Clinical manifestations, physical signs, immunological indices, joint imaging findings, sex hormone levels, and chromosomal analysis were evaluated. Relevant literature was reviewed to explore potential mechanisms underlying the increased susceptibility of KS patients to autoimmune diseases. This predisposition may be related to X chromosome inactivation and sex hormone imbalance. Greater awareness of KS is warranted, and clinicians should recognize the elevated risk of autoimmune disorders in these patients. Chromosomal testing in young male children with autoimmune disorders is recommended.

Keywords: Klinefelter syndrome, juvenile idiopathic arthritis, autoimmune diseases

Introduction

Klinefelter syndrome (KS), a chromosomal abnormality with an incidence of approximately 1/500 to 1/1000 live births, was first described in 1942 by Klinefelter at Massachusetts General Hospital [1]. The 47,XXY karyotype accounts for 80-90% of KS cases [2, 3]. Typical clinical manifestations include dysgenesis of the external genitalia and secondary sexual characteristics, infertility, gynecomastia, learning and cognitive impairment, and social dysfunction, and the condition may be complicated by obesity, metabolic syndrome, diabetes, and osteoporosis. KS has also been associated with several autoimmune diseases (AID), possibly due to the presence of an additional X chromosome and sex hormone imbalance [4]. Previous studies [5] have suggested that individuals with KS are more likely to develop certain autoimmune disorders, particularly those with higher prevalence in females. To date, no pediatric cases of KS complicated by autoimmune diseases have been reported in China, which may be related to the atypical clinical manifestations in childhood. Juvenile idiopathic arthritis (JIA) is a chronic, idiopathic inflammatory disorder that most frequently occurs between the ages of one and three, with a higher incidence in girls than in boys [6]. Although the pathophysiology of JIA remains unclear, it is believed to result from a combination of genetic factors, immune systems, and environmental exposure [7]. To enhance clinical understanding of the association between KS and autoimmune diseases, and to inform future research, we present the diagnosis and management of a child with both JIA and KS, who was to our knowledge, the youngest such case reported to date and the first pediatric case in China.

Cases presentation

Basic case details

Physical examination: In February 2021, a 1-year-9 month-old boy was admitted to the Department of Pediatrics at Huizhou Central People's Hospital, with a complaint of swelling

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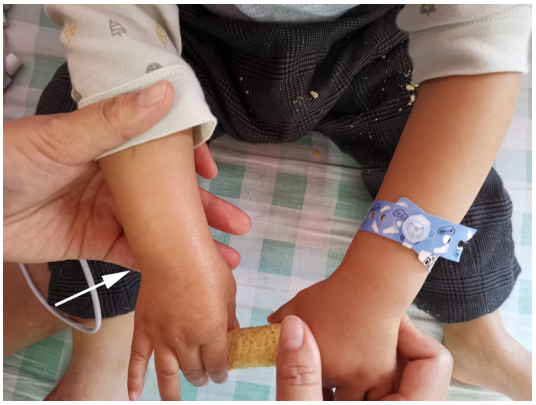

Figure 1. The right wrist joint of the child was noticeably swollen and painful at admission. The arrow shows the location of the injury.

and pain in the right wrist joint for more than 10 days and bilateral lower limb pain for 7 days. The right wrist swelling developed spontaneously without obvious cause, was most pronounced in the morning, and partially subsided by evening. The child avoided pushing or moving the wrist, and cried when asked to bend or touch it. Seven days prior admission, he developed difficulty walking, bilateral thigh tenderness and resistance to pressing. He also had a history of respiratory infection with fever one month earlier.

Medical and family history: Delivered prematurely at a gestational age of 35+5 weeks, the boy was hospitalized for neonatal asphyxia, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, and neonatal sepsis, requiring mechanical ventilation. He also had a history of infantile eczema and cow's milk allergy, as well as recurrent wheezing episodes following respiratory infections, which were controlled with prescribed nebulization therapy. Family history was unremarkable, and the parents were not consanguineous.

Findings on admission: the patient presented with no skin rash, no superficial lymphadenopathy, no abnormal findings on cardiac, pulmonary or abdominal examination. Physical examination revealed swelling and tenderness of the right wrist joint (**Figure 1**) without erythema or local temperature elevation, a positive four-character sign in bilateral hip joints, and no abnormalities or restriction of movement in other limb joints.

Auxiliary examinations

Laboratory results: Upon admission, the patient underwent comprehensive laboratory tests (reference ranges are shown in parentheses). Anti-streptolysin O (ASO) and anti-nuclear antibody (ANA) were within normal limits. Rheumatoid factor (RF) was markedly elevated at 561.70 IU/ml (14 IU/ml), anti-cyclic citrullinated peptide antibody (ACCP) was 42.104 RU/ml (0-5 RU/ml), and the erythrocyte sedimentation rate (ESR) was 42 mm/h (0-20 mm/h). These four measurements - ESR, CRP, RF, and ACCP - were all significantly above normal, with RF exceeding the reference value by approximately 40-fold (**Table 1**). Five ANCA vasculitis panels and eleven ANA profile tests were negative. Bone marrow smear revealed active proliferation. Routine blood, urine, stool tests, blood smear, serum biochemistry, liver and renal function, cardiac enzymes, lipid profile, coagulation studies, and humoral immune indices were unremarkable. Sex hormone panel (seven items) was within normal ranges. Human leukocyte antigen HLA-B27 was negative. Tuberculosis screening (PPD skin test, tuberculosis antibody), Epstein-Barr virus (EBV) nucleic acid, and mycoplasma pneumonia serological test were all negative. The results of the ophthalmologic examination were normal.

Imaging results: Ultrasound examination of major limb joints revealed no significant abnormalities in other extremity joints, but showed mild synovial thickening in the left wrist, a small effusion in the right knee, and minor effusions in both hip joints. Ultrasound findings on heart, liver, gallbladder, pancreas, spleen, mesenteric lymph nodes, retroperitoneum, and urinary tract were normal.

Chest CT showed (1) blurred lung texture, dispersed patchy, faint opacities in both lungs with indistinct margins; (2) several translucent foci were present in the upper lobe of the left lung, possibly reflecting small alveolar dilatation or localized hyperinflation.

Contrast-enhanced MRI of the right wrist revealed multiple patchy T2WI-weighted hyperintense lesions with blurred margins beneath the articular surfaces of the distal radius and ulna, part of the carpal bone, the 2nd-4th metacarpophalangeal joints, the 1st-5th proximal interphalangeal joints, and some distal inter-

Table 1. The patient's growth, development, and treatment course

Age	CRP (mg/L)	ESR (mm/h)	RF (IU/ml)	ACCP (RU/ml)	Height (cm)	Weight (kg)	Treatment
2 years	13.78	42	561.7	42.104	85	9.7	TNF-α receptor antibody fusion protein
2 years and 3 months old	2.5	8	1351.5	180.756	88	10.5	TNF-α receptor antibody fusion protein
2 years and 6 months old	16.03	45	1498.7	-	90.5	10.5	Adalimumab
2 years and 9 months old	4.25	6	2383.2	-	92	11	Adalimumab

Note: The CRP, ESR, RF, and ACCP stand for reactive protein, erythrocyte sedimentation rate, rheumatoid factor, and anti-cyclic citrullinated peptide antibody, respectively. "-" means not measured.

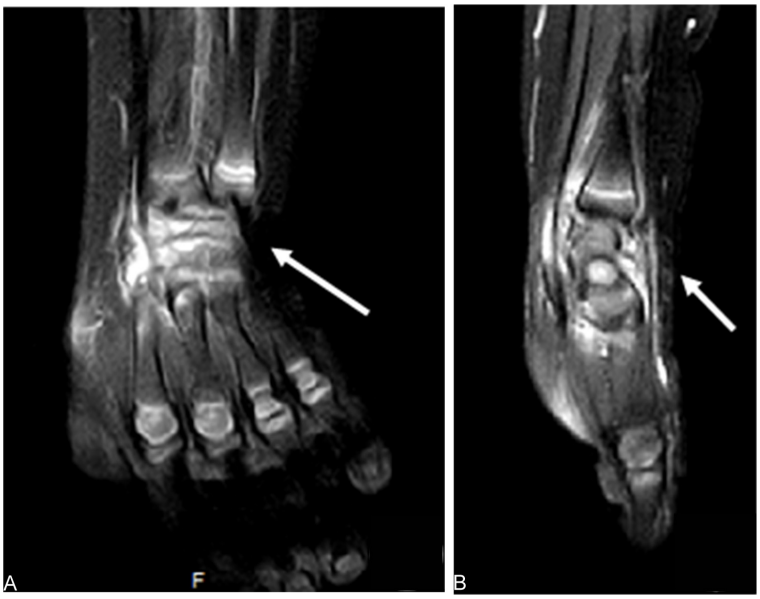

Figure 2. Enhanced MRI images of the right wrist joint of the child. A. Multiple patchy hyperintense lesions on T2WI seen observed beneath the distal articular surfaces of the radius and ulna, as well as portions of the carpal articular surfaces. B. Mild synovial thickening with patchy T2-weighted hyperintense lesions within the joint cavity. The arrow shows the location of the lesion.

phalangeal joints, with enhancement on post-contrast images. Patchy T2 hyperintensity was observed in the joint cavity with mild synovial thickening. Edema of the right wrist joint and spotty T2 hyperintense lesions with ill-defined borders were observed, along with a modest quantity of effusion (**Figure 2**).

Diagnosis and treatment

The child was diagnosed with: (1) suspected JIA; (2) preschool wheezing; (3) bronchopulmonary dysplasia. Treatment included oral ibuprofen (30 mg/kg/d), Taurine granules and calcium and vitamin D supplementation. The child was discharged after his arthralgia improved, with no movement restrictions in the lower limbs.

Genetic testing: With parental consent, whole-exome gene sequencing was performed for the patient and his parents, revealing no pathogenic mutations associated with the disease phenotype. Peripheral blood chromosome G-banding analysis revealed a karyotype of 47,XXY, with both X chromosomes derived from the maternal homolog (**Figure 3**).

Treatment process: after six weeks of treatment, the child continued to present with active arthritis. Based on the 2001 International League of Associations for Rheumatology (ILAR) diagnostic criteria for JIA [8] and karyotype results, the final diagnoses were (1) JIA and (2) KS. Methotrexate (MTX, 10 mg/m^2 once a week) was initiated, and recombinant human type II TNF-α receptor antibody fusion protein (0.8 mg/kg, subcutaneous injection once a week) was administered from the second week. The inflammatory markers normalized after 3 months of biological therapy (CRP 2.5 mg/L (0-6 mg/l), ESR 8 mm/h (0-20 mm/h)), although RF and ACCP remained significantly elevated at 1351.50 IU/ml (14 IU/ml) and 180.756 RU/ml (0-5 RU/ml), respectively. Right wrist joint swelling was lessened (**Figure 4**), with no signs of active arthritis, pain, or movement restriction in other joints. Enhanced MRI of the right wrist demonstrated a reduction in the original lesion.

Following 5 months of biologic treatment, the patient was readmitted with severe pneumonia and respiratory syncytial virus infection, neces-

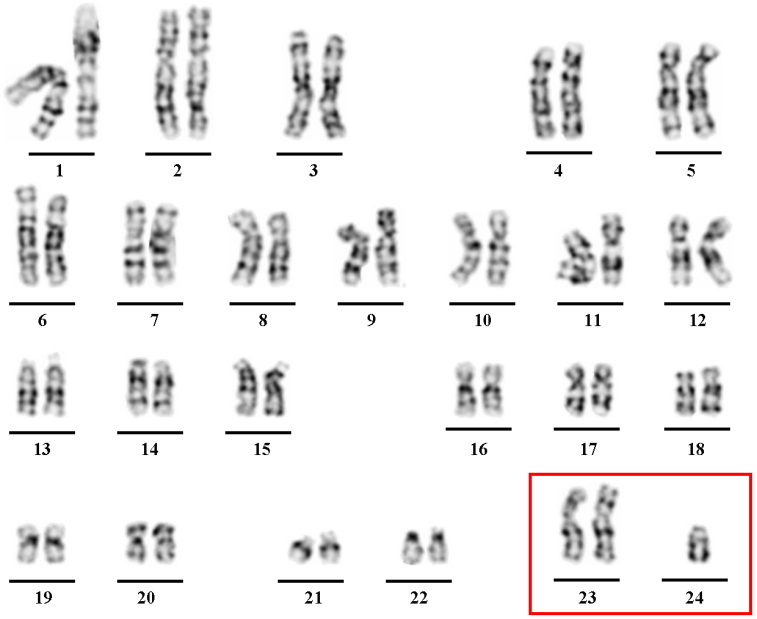

Figure 3. The child's peripheral blood chromosome results: karyotype 47, XXY. The sex chromosomes are in the red box.

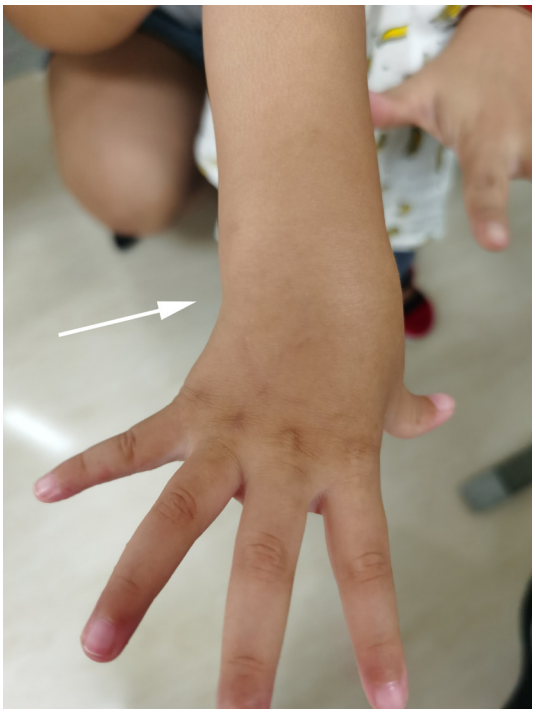

Figure 4. The child's right wrist joint swelling was significantly relieved after 3 months of MTX+biologic treatment. The arrow shows the location of the injured area.

sitating a 3-week treatment interruption. After discharge, joint pain and swelling recurred, and adalimumab (20 mg, subcutaneous injection every 2 weeks) was introduced as the biologic agent. Subsequent therapy led to gradual improvement of joint symptoms, with normalization of inflammatory parameters, including CRP of 4.25 mg/L (0-6 mg/l) and ESR of 6 mm/h (0-20 mm/h), although RF remained significantly elevated at 1498.7 IU/ml (14 IU/ml). The patient's growth, development, and treatment course are summarized in **Table 1**.

Literature review

An electronic search of the China National Knowledge Infrastructure (CNKI) (https://www.cnki.net/), Wanfang databases (https://www.wanfangdata.com.cn/), and PubMed (https://pubmed.ncbi.nlm.nih.gov/) was conducted without restrictions on time or language, up to January 31, 2022. The search terms used were "Klinefelter syndrome", "juvenile idiopathic arthritis", and "rheumatoid arthritis". No relevant reports were identified in CNKI or Wanfang databases. In PubMed, seven articles were retrieved [4, 9-14]. As summarized in **Table 2**, these included one adolescent case of JIA with KS and six adult cases of rheumatoid arthritis (RA) with KS.

The adolescent patient with JIA and KS was diagnosed with KS (47, XXY) at age 6 and commenced testosterone therapy at age 14. At age 16, he developed bilateral "claw hands" and generalized morning stiffness of the proximal and distal phalanges. The patient's examination reveal swelling across the proximal and distal phalanges, bilateral wrist and finger joints, bilateral shoulder joints, involvement of the left ankle joint, but no abnormalities in the thoracic, lumbosacral, and sacroiliac joints, negative RF, and positive HLA-B27. The final diagnosis was JIA (polyarticular, RF negative), and symptoms improved after oral non-steroidal anti-inflammatory drugs (NSAIDs) and methotrexate (MTX) [4]. The other six cases involved adult patients with RA and KS, aged 29-65 years, all presenting with elevated RF titers. Two cases

Table 2. Characteristics of previously reported cases

Case	Author/year	Sex	Age (years)	Diagnosis/karyotype	Treatment
1	Mirkinson et al., 2006	Male	16	Klinefelter's syndrome, 47XY	Non-steroidal anti-inflammatory (NSAID). Therapy, Methotrexate (MTX).
2	Bosmanský et al., 1979	Not provided.	Not provided.	Not provided.	Not provided.
3	Lamotie et al., 1965	Not provided.	Not provided.	Not provided.	Not provided.
4	Macsween et al., 1965	Not provided.	Not provided.	Not provided.	Not provided.
5	Tsung et al., 1974	Not provided.	Not provided.	Not provided.	Not provided.
6	Kobayashi et al., 1994	Male	Not provided.	Klinefelter's syndrome associated with rheumatoid arthritis (RA).	A mild clinical course.
7	Al-Arfaj et al., 2010	Not provided.	Not provided.	Klinefelter's syndrome.	Not provided.

were complicated by diabetes mellitus, and the other two by malignant lymphomas [9-14]. Taken together, the literature indicates that the child described in our study represents, to our knowledge, the youngest reported case of JIA with KS, and the first such case documented in China.

Discussion

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease of unknown etiology, characterized by chronic arthritis that may involve multiple systems and is a leading cause of childhood disability and blindness. Rather than being an isolated disease, JIA is considered a syndrome with heterogeneous etiologies [15]. Similar to most autoimmune disorders, its pathogenesis involves the interplay of genetic factors, immune dysregulation, and environmental exposure. According to the 2001 ILAR JIA diagnostic and classification criteria, JIA refers to arthritis of unknown origin that develops before the age of 16 and lasts for more than 6 weeks. JIA is categorized into seven subtypes. In 2018, the Pediatric Rheumatology International Trials Organization (PRINTO) revised these into six subtypes [8, 16, 17]. Globally, the estimated incidence ranges from 1.6 to 23.1 per 100,000 children, with a female predominance (male to female ratio 0.57:1), although sex distribution varies across subtypes [18]. For instance, males are more susceptible to enthesitis related arthritis (ERA) [19, 20]. The immunopathogenesis of JIA resembles that of adult RA, and the pathological changes are primarily chronic synovitis, which is characterized by infiltration of synovial tissue with T and B lymphocytes, monocytes, plasma cells, and proliferation of fibroblasts and macrophage-like synovial cells [21]. However, JIA differs from RA in several aspects, including the rarity of subcutaneous nodules and RF positivity as well as the absence of some subtypes' corresponding adult diseases. Although multiple autoantibodies can be detected in JIA, none of them are pathognomonic. RF and ANA are the most frequently assessed laboratory markers, useful for disease stratification and prognostic evaluation, though they lack specificity and sensitivity for diagnosis. In adult RA, ACCP is highly specific, and ACCP positivity in children is typically seen in RF-positive kids [22]. According to the 2001 JIA classification criteria, the present case was classified as RF-positive polyarticular JIA, with onset before the age of two years. Such subtype accounts for only 5-10% of JIA cases and occurs predominantly in female children, with a study reporting a male-to-female ratio of 5.7:12.8 [15].

KS, also known as congenital varicocele dysplasia and testicular hypoplasia syndrome, is the most common chromosomal disorder in males and results from the presence of an extra X chromosome (most frequently 47,XXY karyotype), which arises from meiotic nondisjunction in parental germ cells [23]. The likelihood of the extra X chromosome originating from either parent is approximately equal. Advanced parental age and genetic predisposition are recognized risk factors, whereas the contributions of radiation exposure and viral infection remain controversial [3]. Children with one or more extra X chromosomes are phenotypically male because the sex-determining region Y (SRY) gene resides on the Y chromosome. The clinical presentation of KS is highly variable and evolves with age, with severity influenced by the number of extra X chromosomes, CAG repeat polymorphisms in the androgen receptor (AR) gene, parental origin of the extra X chromosome, and mosaic karyo-

type [24]. Testosterone replacement therapy initiated at puberty remains the principal treatment strategy.

Patients with KS have significantly increased risks of multiple comorbidities, including metabolic syndrome and diabetes mellitus, likely related to genetic defects and chronic testosterone deficiency [25]. Similar to JIA, KS has also been associated with several autoimmune diseases, many of which show a higher prevalence in females [26]. In a cohort study of 2,208 KS patients, Seminog et al. [5] reported a significantly increased risk of seven autoimmune diseases, including Addison's disease, type 1 diabetes, multiple sclerosis, acquired hypothyroidism, RA, Sjogren's syndrome (SS), and systemic lupus erythematosus (SLE). Among these, diabetes, RA, SS, and SLE were most strongly associated with KS, consistent with prior reports. Mirkinson et al. [4] reported a 16-year-old boy with KS and JIA who received testosterone replacement, NSAIDs, and MTX, which alleviated his joint symptoms.

The mechanisms underlying the increased susceptibility of KS patients to autoimmune diseases (AID) remain incompletely understood. Current research has focused primarily on two factors: imbalance in the estrogen-to-androgen ratio and abnormalities in X-chromosome inactivation. Sex hormones are known to regulate immune responses, with androgens generally exerting immunosuppressive effects and estrogens enhancing immune activation. Hence, the high prevalence of AID in women may be related to the immunomodulatory effects of sex hormones. In KS patients, an imbalanced androgen/estrogen ratio may therefore contribute to the propensity for AID. Spector et al. [27], in a study of 276 men with RA and ankylosing spondylitis (AS), found that serum free and total testosterone levels were lower in RA patients compared to healthy controls. Similarly, Cutolo et al. [28] reported that serum testosterone concentrations were considerably reduced in RA patients compared with age-matched osteoarthritis patients. In the present case, however, the child had not yet entered puberty, and his sex hormone levels were within normal limits. The onset of JIA before the age of two indicates that mechanisms independent of sex hormone imbalance may be involved. Whether estrogen-related pathways contribute to early-onset disease in KS requires further investigation and long-term follow-up.

Dosage compensation is a genetic phenomenon ensuring that X-linked genes are expressed at comparable levels in both sexes, achieved through inactivation of one X chromosome in females [29]. In 1962, Lyon [30] proposed the concept of X chromosome inactivation (XCI), whereby one of the two X chromosomes undergoes transcriptional silencing during early embryogenesis, forming a "Barr body". This inactivation is stably maintained during mitosis and usually occurs randomly, and can be either paternally or maternally inactivated. However, XCI may sometimes be skewed, nonrandom, or incomplete [31]. Although the precise mechanisms remain unclear, aberrations in XCI have been implicated in human disease. For example, female carriers of X-linked recessive disorders may develop clinical manifestations if skewed XCI leads to preferential expression of the mutant allele [32, 33]. Studies have demonstrated that incomplete or biased inactivation of X-linked immune-related genes may increase susceptibility to systemic lupus erythematosus (SLE) [34, 35]. The presence of an additional X chromosome in KS may therefore predispose patients to autoimmunity [36, 37]. A rare case of a phenotypic male with a 46,XX karyotype who developed severe childhood-onset SLE has been reported [38]. Apart from KS and Turner syndrome, this remains the only known description of SLE in patients with sex chromosome abnormalities. Analogous to Turner syndrome, where specific chromosomal deletions or duplications have been linked to disease risk, mapping the critical X chromosome regions in KS may provide important insights into autoimmune pathogenesis [39].

To date, there are currently no reported data on prevalence of KS among male patients with other female-predominant autoimmune diseases. Further research is required to investigate the relationship between the 47,XXY karyotype and disorders such as multiple sclerosis, Sjögren's syndrome, rheumatoid arthritis, scleroderma, and autoimmune thyroid diseases. Such studies could be performed in large male cohorts with these conditions or at the population level. Notably, acquired sex chromosome abnormalities have also been described in autoimmune diseases. Patients with primary

biliary cirrhosis [40], scleroderma, and autoimmune thyroid disease [41] demonstrate increased frequencies of X chromosome monosomy in peripheral blood lymphocytes.

The association of KS with AID highlights the complex interaction between sex hormones and additional X chromosomes in disease development. This relationship, whether mediated directly or indirectly, warrants further investigation to identify more precise therapeutic targets. KS patients appear particularly susceptible to AIDs with higher prevalence in females, although the underlying mechanisms remain unclear and may involve extra X chromosomes or androgen imbalance. Clinicians should therefore recognize the increased autoimmune risk in KS and strengthen awareness and monitoring in affected individuals.

Conclusions

KS is a chromosomal defect that frequently remains undiagnosed until puberty or adulthood, and typically lacks distinctive clinical signs in childhood. When encountering a male child with early-onset autoimmune disease, clinicians should not only exclude congenital genetic disorders but also consider underlying chromosomal abnormalities.

Disclosure of conflict of interest

None.

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