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Juvenile idiopathic arthritis and Turner's syndrome[☆]



Artritis idiopática juvenil y síndrome de Turner

To the Editor:

Turner syndrome (TS), which is associated with complete or partial monosomy of the X chromosome, is one of the most frequent and best-known chromosomal disorders. In addition to the typical features, such as short stature and amenorrhoea, affected girls are at higher risk of having other diseases compared to the general population, including autoimmune disorders. The association of TS with autoimmune thyroiditis, type 1 diabetes and inflammatory bowel disease has been solidly established, but its association with juvenile idiopathic arthritis (JIA) is not as well understood. We present the cases of 3 girls with TS and JIA managed in our hospital whose diagnosis elicited uncertainty or unnecessary treatments and the results of a literature review that confirms that while the association is infrequent, it is nevertheless well established.

The 3 patients had a 45 × 0 karyotype. In 2 cases, the diagnosis was made in the neonatal period, and in 1 case it was made antenatally by means of amniocentesis. All 3 patients started growth hormone replacement therapy at age 3–4 years. All 3 received the diagnosis of TS years before JIA was diagnosed, and the history of TS had not been considered significant in any of them for the purpose of referral to rheumatology.

A girl aged 7 years was referred for evaluation of monoarthritis in the left knee identified a month prior. In December 2016, the patient underwent arthrocentesis for obtention of a synovial fluid sample that had fea-

tures consistent with inflammation (13 500 white blood cells [WBCs]/mm³; 80% mononuclear cells; glucose concentration, 49 mg/dL, protein concentration, 4.8 g/dL). The patient received a diagnosis of JIA and treatment with intraarticular corticosteroids. Three months later she had a relapse in the same knee, leading to initiation of treatment with subcutaneous methotrexate (MTX), with a good response. The girl remained in remission for the following 12 months, so MTX was discontinued. After 5 months without treatment, in January 2019 the patient experienced a relapse in the left knee, leading to resumption of treatment with MTX. She is currently in remission.

The second case corresponded to a girl that had undergone surgical correction of tetralogy of Fallot that was haemodynamically stable and presented at age 5 years with arthritis in the right knee concurrent with a streptococcal infection (scarlet fever). Two weeks later she presented with arthritis in the contralateral knee and was admitted to receive intravenous antibiotherapy. She did not improve with treatment, so she was referred to the department of rheumatology for evaluation. Given the history and course of disease, with persistence of mild synovitis in the right knee, the patient received a diagnosis of oligoarticular JIA. She underwent arthrocentesis in both knees, with examination of synovial fluid revealing inflammatory features (WBC count, 9500 cells/mm³; 80% polymorphonuclear cells; glucose, 52 mg/dL, protein concentration, 5.3 g/dL). The patient received intraarticular corticosteroids and exhibited a partial response, which prompted initiation of subcutaneous MTX. She is currently in remission. The third patient was a girl aged 6 years with a personal history of monoarthritis in the right knee and a previous arthrocentesis that had revealed inflammatory features in the synovial fluid (WBC count, 8700 cells/mm³; 60% mononuclear cells; glucose concentration, 66 mg/dL, protein concentration, 5.2 g/dL). She was referred to the department of rheumatology and given a diagnosis of oligoarticular JIA in January 2019. She has been treated with intraarticular corticosteroid injections and is currently in remission without treatment.

All 3 patients had negative results of tests for detection of antinuclear antibodies (ANA), rheumatoid factor (RF) and HLA-B27 antigen. None had associated uveitis or other autoimmune disorders.

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Table 1 Published cases of patients with Turner syndrome and juvenile idiopathic arthritis.

Author (year of publication)	N	Karyotype	Age at diagnosis of TS	Age at diagnosis of JIA	Age at onset of joint symptoms	JIA oligo/poly	ANA	RF	HLA-B27	Affected joints	Bone erosion	Other autoimmune diseases
Kohler et al (1981)	2	46Xi (Xq)	14 years	15 years	15 years	Oligo	NA	NA	Pos	Knees and 2 MCPs	NA	Crohn disease
		45X/46XX mosaicism	15 years	15 years	15 years	Oligo	NA	NA	NA	Left knee	NA	Crohn disease
Balestrazzi et al (1986)	1	45X/46XX mosaicism	8 years	8 years	6 years	Oligo	1/160	NA	NA	Left knee., right 2nd finger, left 3 rd finger.	NA	No
Foeldvari et al (1997)	1	45X/46XX mosaicism	10 years	16 years	8 years	Poly	NA	NA	Pos	Hands, wrists, elbows, knees and hips	No	No
Zulian et al (1998)	18	11 Oligo, 45X (n=6), 45X/46XX (n=2), other (n=3)	1 month-17 years (mean 5 years and 5 months)	1,7–12 years (mean 5 years and 8 months)	NA	Oligo	Pos 8/11	Neg 8/8	Neg in 5/5	Knee (11/11), ankle (4/11), MCP/PIP (2/11), elbow (1/11)	No	NA
		7 Poly, 45X (n=6) and 45X/46XX	8 months-16 years (mean 6 years and 1 month)	15 months-4.6 years (mean 3 years and 3 months)	NA	Poly	Pos 1/7	Pos 1/7	Neg in 1/1	Knee 6/7, hip 6/7, ankle 5/7, wrist 3/7, cervical spine 1/7	Yes	NA
Wilhborg et al (1999)	3	45X/46X (Xq) mosaicism	9 years	12 years	3 years	Poly	Neg	Neg	NA	Hands, wrists, knees, cervical and lumbar spine	Yes (feet)	No
		45X/46X (Xq) mosaicism	6 years	15 months	15 months	Poly	Neg	Neg	NA	Hands, elbows, knees and feet	yes (carpals, ulna, elbows, metatarsals)	No
		45X	1 month	9 years	9 years	Poly	Neg	Neg	NA	MCP, PIP, carpal bones, wrists, elbow, knees	Yes	No
Inamo et al (2000)	1	45X/46XX mosaicism	NA	14 years	14 years	Poly	Neg	Neg	NA	bilateral PIPs, right elbow, wrists, right knee and ankle	NA	Diabetes mellitus, Hashimoto disease

ANA, antinuclear antibodies; MCP, metacarpophalangeal joint; NA, data not available; Neg, negative; Oligo: oligoarticular; PIP, proximal interphalangeal joint; Poly: polyarticular; Pos, positive; RF, rheumatoid factor; TS, Turner syndrome.

There are previous descriptions of the association between X monosomy and JIA in the literature (Table 1). Most articles on the subject correspond to single case reports,¹⁻³ although there are also case series^{4,5} of up to 18 patients.⁶ The largest case series corresponds to a multi-centre study with participation of 28 rheumatology centres in Europe and North America and followup of approximately 15 000 patients with JIA. Based on the number of identified patients, the authors estimated that the prevalence of the association of TS and JIA was six times greater than expected.⁶ A more recent study using the Danish Cytogenetic Central Register that reviewed a cohort of 798 women with TS followed up for 12,461 person-years concluded that these patients had double the risk of developing an autoimmune disease compared to the general population, with a standardized incidence ratio for JIA (ratio of the observed number of cases to the expected number of cases) of 4.4 (Jørgensen et al., *Arthritis Rheum.* 2010;62:658–666).

The presentation of arthritis in JIA may be oligoarticular (up to 4 affected joints) or polyarticular (5 or more affected joints), with variability in the detection of ANA and HLA-B27 antigen and the presence of bone erosion. Additional autoimmune disorders are frequently reported, especially inflammatory bowel disease in HLA-B27-positive patients.

In conclusion, the prevalence of JIA in girls with TS is greater than expected for a random association. This must be taken into account in the evaluation of patients with TS that develop musculoskeletal manifestations suggestive of arthritis (joint swelling, limping or morning stiffness).

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Replacing “Apparent Life Threatening Event” (ALTE) with “Brief Resolved Unexplained Event” (BRUE). A retrospective review of the ALTEs that meet the criteria of a BRUE[☆]



Sustitución de ALTE por BRUE: revisión retrospectiva de los ALTE que cumplen criterios de BRUE

To the Editor:

In 2016, the American Academy of Pediatrics (AAP) published a guideline recommending replacing the term *apparent life-threatening event* (ALTE) with the term *brief resolved unexplained event* (BRUE) with the aim of identifying lower-risk patients (with a low probability of a repeat event or of severe underlying disease) that do not require hospital admission or further investigation.¹

The authors of the guideline considered that a more specific term was necessary because ALTE is a concept

that encompasses a broad range of disorders (from periodic breathing to sepsis), which can generate a feeling of uncertainty in the clinician and thus compel performance of unnecessary tests.² The alternative term, BRUE, is intended to reflect the transient nature and lack of clear aetiology of such events and remove the “life-threatening” notion that is the source of such anxiety. The guideline proposed that the evaluation of each infant should be based on the level of risk of the event and established recommendations for the management of low-risk cases.³

Based on this change, we carried out a study with the aim of retrospectively reviewing the cases of patients admitted with a diagnosis of ALTE that met the criteria for BRUE.⁴ Then, we determined which cases in the group meeting the criteria for BRUE would qualify as higher or lower risk, which would allow us to determine the number of infants in who performance of tests and hospital admission may have been deemed unnecessary. Until May 2018, our hospital had a protocol for management of ALTE that called for admission of all patients with ALTE.^{5,6}

Between January 2013 and December 2017, there were 194 patients with an admitting diagnosis code of ALTE. During this period, there was no diagnosis code for BRUE. We excluded 52 infants for who we did not find data allowing us to determine whether the event would qualify as a BRUE. The final sample included 142 patients, 68 female and 74 male, with a median age at admission of 37 days (range, 2–461 days), 95 of who were aged less than 2 months.

Of the 142 patients, 68 (48%) did not meet the criteria for BRUE because a cause for the event had been identified during the history-taking or physical examination (cold symptoms, fever, vomiting, abnormal breath sounds on aus-

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