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Lower genital tract infections in young female juvenile idiopathic arthritis patients

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Abstract

Background: To evaluate human papillomavirus (HPV), *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) infections in juvenile idiopathic arthritis (JIA) patients.

Methods: After exclusion, 33 female adolescent and young JIA patients (ILAR criteria) and 28 healthy controls were selected for this study. Demographic data, gynecological, sexual function, cervical cytology and histological abnormalities were evaluated. JIA clinical/laboratorial parameters and treatment were also assessed. HPV-DNA, CT-DNA and NG-DNA testing in cervical specimens were performed by Hybrid Capture 2 assays.

Results: The mean current age was similar in JIA patients and controls (23.3 ± 6.24 vs. 26.1 ± 6.03 years, $p = 0.09$). The frequencies of sexual intercourse (76% vs. 89%, $p = 0.201$) and abnormal cervical cytology (24% vs. 11%, $p = 0.201$) were similar in JIA compared to controls. The higher frequency of HPV infection in JIA patients than controls (30% vs. 11%, $p = 0.155$) did not reach statistical significance. CT (0% vs. 7%, $p = 0.207$) and NG infections (0% vs. 4%, $p = 0.459$) were also alike in both groups. Further evaluation of JIA patients with abnormal and normal cervical cytology showed that the former group had a higher frequency of HPV infection (87% vs. 12%, $p = 0.0002$) with a low frequency of HPV vaccination (0% vs. 8%, $p = 1.0$). No differences were evidenced between these two JIA groups regarding demographic data, sexual function and clinical/laboratorial parameters. The frequencies of methotrexate ($p = 0.206$) and biological agent use ($p = 0.238$) were similar in both JIA groups.

Conclusions: To our knowledge, this was the first study to assess lower genital infections in JIA patients allowing the identification of HPV as main cause of cervical dysplasia. Methotrexate and biological agents do not seem to increase risk of lower genital tract infections in JIA patients.

Keywords: Human papillomavirus, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, Infection, Juvenile idiopathic arthritis

Introduction

Juvenile idiopathic arthritis (JIA) includes a heterogeneous group of diseases characterized by chronic arthritis [1–3]. This painful and disable disease occurs mainly in females during the adolescence and young adulthood. Patients may have a precocious sexual activity with a possibility of sexually transmitted infections (STI) [4].

Others and we have previously demonstrated that lower genital tract infections, such as human papillomavirus (HPV) and *Chlamydia trachomatis* (CT) [5–8] are relevant issues in sexually active adults with rheumatoid arthritis (RA). There are, however, no studies assessing these infections and *Neisseria gonorrhoeae* (NG) in female adolescent and young adults with JIA.

Therefore, the objective of the present study was to evaluate these STI infections in JIA patients. The possible associations among these infections with demographic

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data, sexual function, disease parameters and treatment were also analyzed.

Methods

A cross-section study was conducted from September 2014 to June 2016 and all 110 female JIA patients, aged between 15 and 40 years, were invited. JIA patients fulfilled the International League of Associations for Rheumatology (ILAR) classification criteria [9] and were followed at two services: Pediatric Rheumatology Unit and Rheumatology Division of our tertiary university hospital.

The exclusion criteria were other chronic diseases ($n = 10$), current gestation or lactation ($n = 3$) and refusal to participate in this study ($n = 64$). Thus, after the exclusion of 77 patients, 33 post-pubertal JIA patients were studied. The healthy age-matched control group included 28 community post-pubertal females adolescents or young adults, between 15 and 40 years of age, selected consecutively using the same exclusion criteria. The Local Ethics Committee of our tertiary service approved the study and an informed consent was obtained from all participants or their legal guardian. Treatments in JIA patients with abnormal and normal cervical cytology were included in Table 1.

Demographic data

The demographic data included current age, disease duration and ethnicity. Socioeconomic class according to Brazilian classification were divided in five categories: upper, upper-middle, middle, lower-middle and lower socioeconomic classes [10].

Sexual function and gynecological evaluation

The presence of vaginal discharge and sexual function (age of first sexual intercourse, number of sexual activity in the last month, number of sexual activity in the last year, number of sexual partners in the last month and number of sexual partners in the last year) were registered based on recollection [6]. A systematic clinical examination of the genitalia was performed by the same expert gynecologist at study entry and includes evaluation of vulva, hymen, vagina and cervix [11]. Previous quadrivalent HPV vaccination was also assessed.

Determination of HPV, CT and NG infections

All exams were carried out in patients and healthy controls and were blinded to JIA disease parameters. HPV DNA testing was performed using Hybrid Capture 2 (HC2 high-risk; Digene Corporation, Gaithersburg, MD, USA) by DNA of oncogenic group of probes. These probes were chosen to detect 13 high-risk types of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). CT DNA testing and NG testing were performed using Hybrid Capture 2 (HC2 CT-ID DNA; Digene Corporation, Gaithersburg, MD, USA). These HPV, CT and NG tests were performed following strictly the manufacturer's instructions and the results were presented as the ratio of the relative light units, which was considered positive when a relative light unit was greater than 1.0.

Cervical cytology and histological evaluations

The Pap smears were collected from virgin adolescents with *Cytobrush®*, the brush was inserted in the band of vaginal ostium and gently rotated 90° to 180°, and immediately rolled over the slide. In sexually active patients, the cervicovaginal cytology was collected with *Cytobrush®* and spatula Ayre, after insertion of the speculum [11]. The cervix was visualized and the spatula Ayre was inserted in the ostium and rotated 360° under gentle pressure, after inserting the *Cytobrush®* for two thirds in the endocervical canal and rotated 90° to 180°. The material of the *Cytobrush®* was rolled over the slide and the material on the spatula Ayre was spread on a thin layer in one movement over the middle third of the slide. After the fixation by immersion in 95% ethanol, the specimens were immediately transported to the laboratory [6]. All Pap smears were evaluated by the same cytopathologist blinded to gynecology examination in our University Hospital. They were performed according to the Bethesda Classification System in: 1) negative for intraepithelial lesions of malignancy with or without organisms (*Trichomonas vaginalis, Candida spp*, bacterial vaginosis, *Actinomyces spp,* herpes simplex virus), 2) other non-neoplastic findings (including inflammatory changes) and 3) epithelial cell abnormalities atypical [atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL) encompassing HPV/mild dysplasia/cervical intraepithelial neoplasia (CIN) 1, high-grade squamous intraepithelial lesion (HSIL) encompassing moderate and severe dysplasia, carcinoma in situ, CIN 1 and CIN 2] [12]. Colposcopically guided biopsies were obtained of the most severe visible lesions. Specimen slides were reviewed by a pathologist who had no knowledge of the other clinical or laboratorial data [13].

Clinical and laboratorial parameters

The following JIA parameters were systematically assessed: number of active and limited joints, patient and physician global assessment of arthritis activity measured in a 10 cm horizontal visual analogy scale (VAS), erythrocyte sedimentation rate (ESR) by modified Westergren and C-reactive protein (CPR) by nephelometric method.

Current and previous treatment

Use of non-steroidal anti-inflammatory drugs, corticosteroids, disease-modifying antirheumatic drugs - DMARDs (methotrexate, leflunomide, sulfasalazine and hydroxichloroquine) and biological agents (etanercept,

Table 1 Treatments in juvenile idiopathic arthritis (JIA) patients with abnormal and normal cervical cytology

Variables	Abnormal cervical cytology ($n = 8$)	Normal cervical cytology ($n = 25$)	p
Treatment			
Prednisone, current use	2 (25)	4 (16)	0.616
Current dose, mg/day	6.3 (5–7.5)	5 (5–9)	0.800
Cumulative dose, grams	2 (0–137.7)	10 (0–61.2)	0.785
Methotrexate, current use	1 (12)	11 (44)	0.206
Current dose, mg/week	15 (15–15)	20 (10–25)	0.383
Cumulative dose, grams	1.7 (0–16.7)	6.3 (0.3–20.5)	0.034
Biologic agents, current or previous use	3 (37)	16 (64)	0.238
Etanercept	1 (12)	6 (24)	0.652
Adalimumab	0 (0)	2 (8)	1.000
Golimumab	0 (0)	1 (4)	1.000
Certolizumab	0 (0)	1 (4)	1.000
Infliximab	1 (12)	0 (0)	0.242
Tocilizumab	1 (12)	4 (16)	1.000
Abatacept	0 (0)	2 (8)	1.000

Values expressed as n (%) or median (minimum - maximum value)

adalimumab, abatacept and tocilizumab) were systematically assessed.

Statistical analysis

The results for the continuous variables were presented by median (minimum and maximum values) or mean ± standard deviation (SD), and for categorical variables presented as frequency (percentage). The scores that had normal and abnormal distributions were compared by Student's t-test and Mann-Whitney test, respectively. The differences of categorical variables were calculated by Fisher's exact test. The adopted significance level in all analyses was set at 5%.

Results

The mean current age was similar in JIA patients and healthy controls (23.3 ± 6.24 vs. 26.1 ± 6.03 years, $p = 0.09$). No differences in Caucasians and in upper middle and lower middle socio-economic classes were observed in both groups ($p > 0.05$). The mean of JIA duration was 15.0 ± 7.3 years (Table 2).

The frequencies of sexual intercourses (76% vs. 89%, $p = 0.201$), vaginal discharge (30% vs. 18%, $p = 0.378$) and abnormal cervical cytology (24% vs. 11%, $p = 0.201$) were similar in JIA patients compared to healthy controls. No differences were evidenced in sexual intercourse and sexual partner in both groups (Table 2). Group sex was not reported by any JIA patients and healthy controls.

According to hybrid capture detections, CT (0% vs. 7%, $p = 0.207$) and NG infections (0% vs. 4%, $p = 0.459$) were also similar in JIA patients and healthy controls. The frequency of HPV infection was higher in JIA patients than in controls, however without statistical significance (30% vs. 11%, $p = 0.155$). Previous quadrivalent HPV vaccination was similar in both groups (6% vs. 21%, $p = 0.127$) (Table 2). None of them had condylomata acuminata.

Further evaluation of JIA patients with abnormal and normal cervical cytology showed that the former group had a higher frequency of HPV infection (87% vs. 12%, $p = 0.0002$). No differences were evidenced between two groups regarding demographic data, gynecologic history, sexual function, previous quadrivalent HPV vaccination and JIA clinical and laboratorial parameters ($p > 0.05$; Table 3). The frequencies of current methotrexate (12% vs. 44%, $p = 0.206$) and biological agent use (37% vs. 64%, $p = 0.238$) were similar in JIA patients with abnormal and normal cervical cytology.

Discussion

To our knowledge, this was the first study to assess lower genital infections in JIA patients allowing the identification of HPV as main cause of cervical dysplasia in this disease.

The strength of the present study was the systematic assessment of HPV, CT and NG infections in JIA patients and healthy controls with comparable age and sexual function. The use of hybrid capture test for HPV including the oncogenic group of probes is an additional advantage due to its high sensitivity and specificity [13, 14].

HPV infection identified in young JIA patients was subclinical, mild and significantly associated with cervical abnormalities and no evidence of cervical cancer. Contrasting with the reported increased risk of cervical dysplasia and persistent HPV infection in adults with RA

Table 2 Demographic data, sexual function, gynecological evaluation, Pap smears, genital infections and HPV vaccination in juvenile idiopathic arthritis (JIA) patients and healthy controls

Variables	JIA ($n = 33$)	Controls ($n = 28$)	p
Demographic data			
Current age, years	23.3 ± 6.24	26.1 ± 6.03	0.090
Disease duration, years	15 ± 7.3	–	–
Caucasian	20 (61)	23 (82)	0.092
Upper-middle and lower-middle SE classes	32 (97)	23 (79)	0.085
Sexual function and gynecological evaluation			
Vaginal discharge	10 (30)	5 (18)	0.378
Sexual intercourse	25 (76)	25 (89)	0.201
First sexual activity age, years	18 (14–30)	17 (10–24)	0.196
Sexual intercourse in last month	19 (57)	19 (68)	0.439
Sexual intercourse in last month, number	2 (0–15)	4 (0–30)	0.231
Sexual intercourse in last year	23 (70)	21 (75)	0.767
Sexual intercourse in last year, number	20 (0–180)	48 (0–360)	0.167
Sexual partner in last month, number	1 (0–1)	1 (0–2)	0.148
Sexual partner in last year, number	1 (0–2)	1 (0–5)	0.184
Pap smears and genital infections			
Abnormal cervical cytology	8 (24)	3 (11)	0.201
Inflammation	25 (76)	25 (89)	0.201
ASCUS	3 (9)	0 (0)	0.243
LSIL	5 (15)	3 (11)	0.715
HSIL	0 (0)	0 (0)	1.000
Gardnerella vaginalis	4 (12)	1 (4)	0.367
Candida sp.	0 (0)	1 (4)	0.459
Trichomonas vaginallis	0 (0)	0 (0)	1.000
Hybrid capture detection			
Chlamydia trachomatis	0 (0)	2 (7)	0.207
Neisseria gonorrhoeae	0 (0)	1 (4)	0.459
Human papillomavirus (HPV)	10 (30)	3 (11)	0.115
Previous quadrivalent HPV vaccination	2 (6)	6 (21)	0.127

Values expressed as n (%), median (minimum - maximum value) or mean ± standard deviation
SE socio-economic, *ASCUS* atypical squamous cells of undetermined significance, *LSIL* low-grade squamous intraepithelial lesion, *HSIL* high-grade squamous intraepithelial lesion

[5, 6, 15] and anogenital warts due to condyloma acuminatum in young systemic lupus erythematosus patients [11, 16]. In Sjögren syndrome, a disease with mean age of onset usually in the 4th to 5th decade, a very low prevalence of HPV infection was evidenced [17].

CT and NG infections are rare in sexually active Chilean adolescents and young adults [18] and adult RA patients [6]. Likewise, we have not observed these STI in JIA or health control groups.

A high rate of serious infections, including tuberculosis, herpes zoster and systemic mycosis, were reported in JIA patients under biologic therapy and methotrexate in a real-life setting [19]. On the contrary, anti-TNF does not seem to increase short-term risk of exacerbation and/or progression genital infections (HPV and CT) in RA patients [6]. Further prospective studies are necessary to determine if JIA patients with HPV will develop cervical cancer, and therefore a rigorous surveillance is recommended for this group of patients.

Only 6% of our JIA patients received previous HPV vaccination, in spite of prompt indication by our service for all adolescent and young JIA patients. In fact, HPV vaccines are efficacious and safe in patients with autoimmune diseases, including systemic lupus

Table 3 Demographic data, sexual function, gynecological evaluation, Pap smears, genital infections and HPV vaccination and disease parameters in juvenile idiopathic arthritis (JIA) patients with abnormal and normal cervical cytology

Variables	Abnormal cervical cytology ($n = 8$)	Normal cervical cytology ($n = 25$)	p
Demographic data			
Current age, years	26.2 ± 6.3	23.5 ± 6.3	0.730
Disease duration, years	13.5 ± 6.6	15.9 ± 7.5	0.427
Caucasian	4 (50)	16 (64)	0.681
Upper middle and lower middle SE class	8 (100)	24 (96)	1.000
Sexual function and gynecological evaluation			
Vaginal discharge	4 (50)	6 (24)	0.205
Sexual activity	7 (87)	18 (72)	0.649
First sexual activity age, years	19.5 (15–22)	17 (14–30)	0.779
Sexual intercourse in last month	4 (50)	15 (60)	0.695
Sexual intercourse in last month, number	1 (0–12)	2.5 (0–15)	0.85
Sexual intercourse in last year	6 (75)	17 (68)	1.000
Sexual intercourse in last year, number	12 (0–144)	20 (0–180)	0.813
Sexual partner in last month, number	1 (0–1)	1 (0–1)	0.849
Sexual partner in last year, number	1 (0–1)	1 (0–2)	0.776
Urogenital infections			
Gardnerella vaginalis	1 (12)	3 (12)	1.000
Candida sp.	0 (0)	0 (0)	1.000
Trichomonas vaginallis	0 (0)	0 (0)	1.000
Hybrid capture detection			
Chlamydia trachomatis	0 (0)	0 (0)	1.000
Neisseria gonorrhoeae	0 (0)	0 (0)	1.000
Human Papillomavirus (HPV)	7 (87)	3 (12)	**0.0002**
Previous quadrivalent HPV vaccination	0 (0)	2 (8)	1.000
JIA clinical and laboratory parameters			
JADAS 71 (0–101)	0	2 (0–5)	NA
DAS28 (0–7)	4.5 (1.36–2.66)	5.0 (1.05–5.21)	0.674
Number of active joints	0 (0–3)	1 (0–12)	0.514
Number of limited joints	1.5 (0–43)	5 (0–39)	0.425
Patient global VAS (0–10)	1.5 (0–8)	2 (0–9)	0.705
Physician global VAS (0–10)	0 (0–2)	1 (0–5)	0.344
ESR, mm/1st hour	12.8 ± 5.4	9.7 ± 6.9	0.268
CRP, mg/L	3.7 (0.4–77)	1.8 (0.2–14)	0.257

Values expressed as n (%), median (minimum - maximum value) or mean ± standard deviation
SE socio-economic, *JADAS71* Juvenile Arthritis Disease Activity Score, *DAS28* Disease Activity Score 28-Joint Counts, *NA* not applicable, *VAS* visual analog scale, *CRP* C-reactive protein (normal range method: < 5 mg/L), *ESR* erythrocyte sedimentation rate

erythematosus and JIA, and systematic use should be reinforced for all patients in clinical practice [20, 21].

In addition, methotrexate and biological agents do not seem to increase the risk of lower genital tract infections in JIA patients.

Conclusions

This study further reinforces the importance of vaccination in adolescent with chronic arthritis. It also showed a low frequency of STIs in spite of immunosuppressive and biological agents exposure. We further demonstrated that cervical dysplasia in JIA patients was highly associated with HPV, reinforcing the need of close observation and HPV immunization during childhood.

Abbreviations

ASCUS: Atypical squamous cells of undetermined significance; CIN: Cervical intraepithelial neoplasia; CPR: C-reactive protein; CT: *Chlamydia trachomatis*; DMARDs: Disease-modifying antirheumatic drugs; DNA: Deoxyribonucleic

acid; ESR: Erythrocyte sedimentation rate; HPV: Human papillomavirus; HSIL: High-grade squamous intraepithelial lesion; ILAR: International League of Associations for Rheumatology; JIA: Juvenile idiopathic arthritis; LSIL: Low-grade squamous intraepithelial lesion; NG: *Neisseria gonorrhoeae*; RA: Rheumatoid arthritis; SD: Standard deviation; STI: Sexually transmitted infections; VAS: Visual analogy scale

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Authors' contributions
All authors analyzed and interpreted the patient data. GVRF, RBT, EB and CAS were the major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Not applicable.

Ethics approval and consent to participate
This study was approved by our Ethics Committee. The Local Ethics Committee of our tertiary service (CAPPesq - Comissão de Pesquisa e Ética do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo) approved the study and an informed consent was obtained from all participants or their legal guardian. The Local Ethics Committee of our tertiary service (CAPPesq - Comissão de Pesquisa e Ética do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo) approved the study and an informed consent was obtained from all participants or their legal guardian.

Consent for publication
All JIA patients and healthy controls signed the consent for publication.

Competing interests
The authors declare that they have no competing interests.

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