Menstrual and hormonal alterations in juvenile dermatomyositis

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Abstract

Objective

To evaluate age at menarche, menstrual cycles and hormone profile in juvenile dermatomyositis (JDM) patients and controls.

Methods

Twelve consecutive JDM patients were compared to 24 age-matched healthy subjects. Age at menarche and age of maternal menarche were recorded. Menstrual cycle was evaluated prospectively for 6 consecutive months and the mean cycle length and flow were calculated. The hormone profile was collected on the last menstrual cycle. Demographic data, clinical features, muscle enzymes, JDM scores and treatment were analysed.

Results

The median of current age of JDM patients and controls was similar (18 vs. 17 years, p=0.99). The median age at menarche of the JDM patients was higher than in the control group (13 vs. 11 years, p=0.02) whereas the median age of maternal menarche was alike in both groups (12 vs. 13 years, p=0.67). Menstrual disturbances were not observed, except for one patient who had longer length of menstrual cycle. The median of follicle stimulating hormone (FSH) was significantly higher in JDM patients compared to controls (4.5 vs. 3.0 IU/L, p=0.02) and none of them had premature ovarian failure (POF). The median of progesterone was significantly lower in JDM patients (0.3 vs. 0.7 ng/mL, p=0.01) with a higher frequency of decreased progesterone compared to controls (75% vs. 29%, p=0.01).

Conclusions

Our study identifies in JDM patients delayed menarche with normal cycles and low follicular reserve. The decreased progesterone levels may suggest an underlying subclinical corpus luteum dysfunction in this disease.

Key words

Juvenile dermatomyositis, menstrual abnormalities, menarche, hormone

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Introduction

We have previously shown delayed menarche and a high frequency of menstrual and hormone alterations in juvenile systemic lupus erythematosus (JSLE) patients compared to controls (1-3). However, no study has prospectively evaluated menstrual cycle and hormonal status of juvenile dermatomyositis (JDM) patients. We have therefore performed a detailed evaluation of age at menarche, menstrual disturbances and hormonal profile in JDM patients and compared them with healthy adolescents.

Materials and methods

Twelve consecutive JDM female patients from the Paediatric Rheumatology Unit or the Rheumatology Division of University of São Paulo were evaluated. All patients fulfilled the Bohan and Peter criteria for JDM (4). The control group included 24 healthy female adolescents followed at the educational and preventive Adolescent Unit at our University Hospital. None of them had current pregnancy or was under hormonal contraceptive agents. The Brazilian socio-economic classes were classified according to *Associação Brasileira dos Institutos de Pesquisa de Mercados* (5). This study was approved by the local Ethics Committee and informed consent was obtained from all participants. Ages at menarche were registered based on recollection of JDM patients and controls, and their respective mothers. The age at menarche of the mother was also systematically recorded. Menstrual cycle was evaluated prospectively for 6 consecutive months and the mean cycle length and flow were calculated. Normal cycle was defined as length varying from 25 to 35 days with 3 to 7 days of duration of blood flow (1, 3). Menstrual disturbances were based on alterations in one or more of these parameters during evaluation. Amenorrhea and sustained amenorrhea were defined as the cessation of menstruation for more than 4 months after menarche and persisting for more than 12 months, respectively. Patients with sustained amenorrhea in whom menstruation did not resume and with follicle-stimulating hormone (FSH) levels >40 IU/L fulfilled the diagnosis of premature ovarian failure (POF) (6). Secondary sexual characteristics were classified according to pubertal changes (7). Body mass index (BMI) was defined by the formula: BMI (kg/m^2) weight in kilograms/height in square-metres.

Hormonal determinations were performed for all JDM patients and controls at the last evaluated menstrual cycle or randomly for those with amenorrhea. Serum levels of FSH, luteinizing hormone (LH), estradiol, prolactin, progesterone and total testosterone were measured by fluoroimmunoassay using kits from DELPHIA^R time-resolved fluoroimmunoassay (WALLAC Ou, Turku, Finland) on days 1, 2 or 3 of the menstrual cycle (or randomly for those with amenorrhea) according to pubertal changes (7) and age. Intra and inter-assay coefficients of variation recommended by the manufacturer were limited to 3.5% and 2.1%, respectively.

Clinical manifestations of JDM were defined as cutaneous lesions (heliotrope, Gottron's papules, vasculitis, calcinosis, ulcerative skin or malar rash), articular involvement (nonerosive arthritis), muscular involvement (muscle weakness), cardiopulmonary disease (serositis, myocarditis, restrictive lung disease or pulmonary hypertension) and gastrointestinal involvement (dysphagia or vasculitis). Disease activity was assessed at menarche, at diagnosis and at study entry by using disease activity score (DAS) (8), childhood myositis assessment scale (CMAS) (9) and manual muscle testing (MMT) (10). Data concerning the current dosage of prednisone, and the use of methotrexate, azathioprine, chloroquine and cyclosporine were determined at diagnosis and at study entry. In addition, cumulative doses of prednisone and disease duration until the first period were evaluated.

Statistical analysis

Results were presented as the median (range) for continuous variables and number (%) for categorical variables. Continuous variables were compared using the Mann Whitney test to evaluate differences between JDM patients and control group. For categorical variables differences were assessed by Fisher's

Table I. Demographic features, BMI, pattern of pubertal changes and menstrual cycle in JDM patients and controls.

Variables	JDM patients (n=12)	Controls (n=24)	*p*-value
Demographic features and socio-economic status			
Current age, years	18 (11–20)	17 (13–21)	0.99
Number of school years	10.5 (5–11)	10.5 (8–13)	0.32
Brazilian socio-economic class, C or D	9 (75)	16 (67)	0.71
Occupation	1 (8)	4 (17)	0.64
BMI, kg/m^2	22.1 (17.8–30)	21.1 (15–27.2)	0.36
Adult pubertal status (Tanner 4 or 5)	9 (75)	19 (79)	1.0
Menarche and menstrual cycle			
Age at menarche, years	13 (10–15)	11 (9–14)	0.02
Age at maternal menarche, years	12 (11–17)	13 (10–16)	0.67
Gynaecological age*, years	4 (1-8)	6 (2–10)	0.11
Menstrual disturbances	1 (8)	2 (8)	1.0
Flow duration, days	5 (3–6)	5 (3–8)	0.13
<3	0 (0)	0 (0)	1.0
>7	0 (0)	1 (4)	1.0
Length of cycle, days	28 (27–75)	30 (24–35)	0.14
<25	0 (0)	1 (4)	1.0
>35	1 (8)	0 (0)	0.33
Amenorrhea frequency	0 (0)	0 (0)	1.0

Values expressed in n (%) or median (range). JDM: juvenile dermatomyositis; BMI: body mass index; *time between menarche and current age.

exact test. Pearson's coefficient was used to evaluate correlations between age at menarche in JDM patients and cumulative doses of prednisone, disease duration and JDM scores until the first period. In all statistical tests significance was set at a *p*-value <0.05.

Results

Demographic features and BMI

The distribution of demographic features revealed that JDM patients and controls were comparable regarding median current age (18 *vs*. 17 years, *p*=0.99), number of school years (10.5 *vs*. 10.5, *p*=0.32), frequency of the two lowest Brazilian socio-economic classes (C or D) (75% x 67%, *p*=0.71), occupation (8% *vs*. 17%, *p*=0.64) and BMI (22.6 *vs*. 21.1 kg/m^2, *p*=0.22) (Table I). Median age at JDM onset was 10.1 (3–16) years and median of disease duration was 8.2 (3–11.2) years.

Age at menarche and menstrual cycles

The median age at menarche of JDM patients was higher than in control group (13 *vs*.11 years, *p*=0.02) whereas the median maternal age at menarche of JDM patients was similar to controls (12 *vs*. 13 years, *p*=0.67). The gynaecological age (time between menarche and current age) was also comparable (*p*=0.11) (Table I). Menarche occurred after JDM onset in 10 patients and before JDM onset in 2. In the former group, no correlation was found between glucocorticoid cumulative doses (until the first period) and menarche age (*p*=0.887) and between disease duration (until the first menstruation) and menarche age (*p*=0.698). Moreover, no correlation was found between muscle enzymes levels (at the first period) and menarche age (CPK, *p*=0.672; ALT, *p*=0.262; AST, *p*=0.502; aldolase, *p*=0.335; LDH, *p*=0.887) or JDM scores (at the first menstruation) and menarche age (DAS, *p*=0.342; CMAS, *p*=0.142; MMT, *p*=0.091).

The secondary sexual characteristics according to pattern of pubertal changes (7) were similar in JDM and controls, particularly Tanner 4 and 5 (75% *vs*. 79%, *p*=1.0). The frequency of menstrual alterations in JDM patients (8%) was similar to controls (8%) (*p*=1.0). Accordingly, the frequencies of menstrual abnormalities were comparable in both groups: flow duration [decreased (<3 days, *p*=1.0) or increased (>7 days, *p*=1.0)] and length of menstrual cycle [shorter (<25 days, *p*=1.0) or longer (>35 days, *p*=0.33)]. The median time of flow duration and length of cycle were also similar [5 (3-6) *vs*. 5 (3-8) days, *p*=0.13; 28 (27-75) *vs*. 30 (24-35) days, *p*=0.14] (Table I). None of JDM patients and controls had amenorrhea or POF.

Hormonal profile

The median level of FSH was significantly higher in JDM patients compared to controls [4.5 (2.0-8.8) *vs*. 3.0 (0.5-16.7) IU/L, *p*=0.02] whereas the frequency of elevated levels of FSH was comparable (*p*=1.0). The median of prolactin was lower in JDM patients than in controls [5.9 (1.7-9.4) *vs*. 8.9 (5.3-15.2) ng/mL, *p*=0.005], although both were within normal range. The median of progesterone was significantly lower in JDM patients *versus* controls [0.3 (0.3-4.2) *vs*. 0.7 (0.3-17.2) ng/mL, *p*=0.01] with a higher frequency of decreased progesterone compared to controls (75% *vs*. 29%, *p*=0.01). The median and frequencies of altered LH, estradiol and testosterone were comparable in both studied groups (Table II).

Demographic data, clinical features, muscle enzymes levels, JDM scores, hormone profiles and treatment of 12 JDM patients

The median age at disease onset was 10 (3-16) years, all of them with muscle enzymes above the upper normal limit. At diagnosis, seven patients had gastrointestinal symptom, two of them concomitantly with cardiac involvement. The evaluation at study entry revealed that none of them had JDM lipoatrophy with a median time of disease duration of 8.2 (2.3–11.2) years. At time of study entry, nine patients had low progesterone, only three of them were under glucocorticoid therapy. One JDM patient (Case 7) had decreased progesterone with increased menstrual cycle length. All other 11 patients had normal cycles (Table III).

Discussion

To our knowledge, this is the first study that evaluated menstrual cycle con-

comitantly to the hormonal evaluation in adolescents and young JDM patients compared to a healthy control population. We identified delayed menarche with normal cycles and low follicular reserve in JDM. The study also demonstrated a high prevalence of low progesterone in this disease without an association with menstrual abnormalities.

The great advantage of this study is prospective design which allows a more accurate definition of menstrual disturbances in adolescent population. In addition, the median gynaecological age over 4 years in both groups excludes menstrual abnormalities due to a physiologic phenomenon of puberty which has been described for the normal adolescent particularly in the first 24 months following the first period (1). In this study, menarche age was recorded by subject's recollection, as previously described in our JSLE population (1-3).

Table II. Hormonal profiles of patients with juvenile dermatomyositis (JDM) versus controls.

Hormones	JDM patients (n=12)	Controls (n=24)	*p*-value
FSH, UI/L			
Median (range)	4.5 (2–8.8)	3.0 (0.5–16.7)	0.02
Elevated levels, n (%)	1 (8)	2 (8)	1.0
LH, UI/L			
Median (range)	4.1 (2.1–7.3)	2.6 (0.5–71.5)	0.29
Elevated levels, n (%)	1 (8)	5 (21)	0.64
Estradiol, pg/ml			
Median (range)	38 (29–93)	51.7 (17–374)	0.13
Decreased levels, n (%)	0 (0)	1 (4)	1.0
Prolactin, ng/ml			
Median (range)	5.9 (1.7–9.4)	8.9 (5.3–15.2)	0.005
Elevated levels, n (%)	0 (0)	0 (0)	1.0
Progesterone, ng/ml			
Median (range)	0.3 (0.3–4.2)	0.7 (0.3–17.2)	0.01
Decreased levels, n (%)	9 (75)	7 (29)	0.01
Testosterone, ng/dl			
Median (range)	22 (11–75)	33 (1.2–134)	0.47
Elevated levels, n (%)	0 (0)	1 (4)	1.0

JDM: juvenile dermatomyositis; FSH: follicle stimulating hormone; LH: luteinizing hormone.

Table III. Demographic data, clinical features, muscle enzymes, scores, treatment and hormonal profile of 12 patients with juvenile dermatomyositis (JDM) at hormonal evaluation.

Patients	1	2	3	4	5	6	7	8	9	10	11	12
Demographic data												
Disease duration, years	5.0	11.2	3.7	3.0	8.1	8.4	2.3	8.5	8.3	9.7	9.3	7.2
Current age, years	11.2	14.2	14	14.8	15.1	17.5	18.3	17.5	18.4	19.7	19.3	20.2
Clinical features												
Cutaneous	–	+	+	+	–	–	–	–	–	–	–	+
Muscle	–	+	–	–	–	–	+	–	–	–	–	–
Articular	–	–	–	–	–	–	–	–	–	–	–	–
Cardiopulmonary	–	–	–	–	–	–	–	–	–	–	–	–
Gastrointestinal	–	–	–	–	–	–	–	–	–	–	–	–
Muscle enzymes												
CPK (39-308 IU/L)	55	602	96	158	96	70	657	109	33	87	77	125
ALT (24 – 49 IU/L)	14	60	19	26	20	22	23	22	13	17	18	10
AST (10 – 36 IU/L)	31	70	34	38	32	27	40	34	22	21	31	22
Aldolase (<7.6 IU/L)	6.7	17.2	5.9	7.3	5.8	4.0	8.1	3.5	3.4	2.8	5.0	3.2
LDH (240 – 480 IU/L)	137	305	129	168	158	102	203	135	107	336	96	385
Scores												
DAS (0-20)	0	5	3	3	0	0	12	0	0	0	0	6
CMAS (0-52)	52	44	51	52	52	52	51	52	52	52	52	52
MMT (0-80)	80	80	80	80	80	80	76	80	80	80	80	80
Treatment (previous use/current dose, mg)												
Prednisone	+/0	+/5	+/0	+/0	+/0	+/0	+/20	+/0	+/0	+/0	+/0	+/2.5
Cyclosporine	–	–	–	–	–	–	+/200	–	–	–	–	–
Methotrexate	–	+/50	–	+/25	–	–	+/30	–	–	+/0	–	–
Azatioprine	–	–	–	–	–	–	+/100	–	–	–	–	+/150
Chloroquine phosphate	–	+/250	–	–	–	–	–	–	–	+/0	–	+/250
Hormones												
Elevated FSH or LH	–	–	–	–	–	+	–	–	–	+	–	–
Low progesterone	–	+	+	+	–	+	+	+	+	+	–	+
Menstrual disturbance	–	–	–	–	–	–	+	–	–	–	–	–

+ positive; – negative; CPK: creatine phosphokinase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DHL: lactate dehydrogenase; DAS: Disease Activity Score; CMAS: childhood muscle assessment score; MMT: manual muscle testing; FSH: follicle stimulating hormone, LH: luteinizing hormone.

This data is considered reliable, since menarche is a historical moment in the women's life and remembered over 30 years after its occurrence (11). A possible weakness of our study is the small number of JDM patients, especially with menarche after disease onset.

We previously showed a late occurrence of the first period in JSLE compared with normal Brazilian adolescents (1-3), as observed herein in JDM patients. No clear etiology for the delay of menarche was determined but it is not attributed to the genetic background given that the menarche age of their mothers was similar in groups.

On the other hand, we have reported that adolescent JSLE patients have a remarkable high frequency of menstrual irregularities particularly with longer length of cycles not associated with disease activity or cyclophosphamide treatment (3). In contrast, only one JDM patient of the present study had menstrual alteration but disease activity does not seem to account for this finding since four other patients had cutaneous activity at study entry without menstrual irregularities.

Regardless of this almost uniform normal cycle, the majority of patients had inadequate or lower production of progesterone in early follicular phase of menstrual cycle as also reported for adults SLE (12) and JSLE (1, 3) suggesting a possible luteal dysfunction (13, 14) in this disease. In fact, a high frequency of decreased progesterone level and normal LH was observed in lupus patients with normal cycles (3). We are currently investigating the possible role of anti-corpus luteum antibodies in JDM population. Moreover, glucocorticoid may act directly on the hypothalamic-pituitary-ovarian axis and reduce gonadotropin-releasing hormone (GnRH) pulse frequency and pituitary LH and FSH secretion, as well as progesterone levels (15). This factor does not seem to be relevant in JDM since most patients with low progesterone levels were not under this therapy.

Of interest, FSH levels in JDM patients were within normal range but significantly higher than in controls, indicating a reduced ovarian reserve not explained by distinct patterns of puberty, as also observed in adolescent SLE patients (3). FSH increases throughout the reproductive years (16) and it is the most sensitive marker of ovarian function (6). Reinforcing this notion, we have demonstrated that this hormone was a marker for severe sperm abnormalities in male lupus population (17).

In spite of the small number of patients and the low disease severity diversity, we have identified in JDM patients delayed menarche with normal cycles and low follicular reserve. The decreased progesterone levels may suggest an underlying subclinical corpus luteum dysfunction in this disease. Larger prospective studies are essential to confirm the present data.

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