Clinical Status and Cardiovascular Risk Profile of Adults with a History of Juvenile Dermatomyositis

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Objective A pilot study of adults who had onset of juvenile dermatomyositis (JDM) in childhood, before current therapeutic approaches, to characterize JDM symptoms and subclinical cardiovascular disease.

Study design Eight adults who had JDM assessed for disease activity and 8 healthy adults (cardiovascular disease controls) were tested for carotid intima media thickness and brachial arterial reactivity. Adults who had JDM and 16 age-, sex-, and body mass index-matched healthy metabolic controls were evaluated for body composition, blood pressure, fasting glucose, lipids, insulin resistance, leptin, adiponectin, proinflammatory oxidized high-density lipoprotein (HDL), and nail-fold capillary end row loops.

Results Adults with a history of JDM, median age 38 years (24-44 years) enrolled a median 29 years (9-38 years) after disease onset, had elevated disease activity scores, skin (7/8), muscle (4/8), and creatine phosphokinase (2/8). Compared with cardiovascular disease controls, adults who had JDM were younger, had lower body mass index and HDL cholesterol ($P = .002$), and increased intima media thickness ($P = .015$) and their brachial arterial reactivity suggested impairment of endothelial cell function. Compared with metabolic controls, adults who had JDM had higher systolic and diastolic blood pressure, $P = .048$, $P = .002$, respectively; lower adiponectin ($P = .03$); less upper arm fat ($P = .008$); HDL associated with end row loops loss ($r = -0.838$, $P = .009$); and increased proinflammatory oxidized HDL ($P = .0037$).

Conclusion Adults who had JDM, 29 years after disease onset, had progressive disease and increased cardiovascular risk factors. *(J Pediatr 2011;159:795-801)*.

Juvenile dermatomyositis (JDM) is characterized by symmetric proximal muscle weakness, a typical rash, and objective evidence of muscle inflammation.[1] The hallmark of JDM is systemic microvascular injury to arterioles and capillaries, reflected in a decrease in the number of nail-fold capillary end row loops (ERL),[2] the development of prominent cutaneous telangiectasia, as well as histologic evidence of intravascular and perivascular inflammation.[1] The pathophysiology of JDM includes genetic susceptibility, environmental factors, and infectious triggers, with associated activation of complement and the cellular and humoral immune systems.[1]

The course of JDM can be either unicyclic or chronic, and the activity of persistent inflammation can be assessed by an elevated disease activity score[3] and by quantitation of the number of nail-fold capillary ERL, which drop out with chronic inflammation.[2] Risk factors for less-favorable outcomes and continued disease activity include a longer duration of untreated disease,[4] younger age at presentation, and an A vs G polymorphism in the tumor necrosis factor-α (TNF-α)-308 promoter region.[5]

Cardiovascular involvement has rarely been documented in JDM, and most commonly includes cardiac arrhythmias in the child,[6] or reports of myocardial infarction in adults.[7] The physiology of the disease itself, with its metabolic abnormalities,[8] as well as the treatment of JDM, which includes prolonged corticosteroid administration, may predispose to accelerated cardiovascular disease (CVD).

The presence of cardiovascular disease in adults who had JDM in childhood and, according to the standards of the time, were treated less aggressively at diagnosis, has not been evaluated. In this study, we tested the oldest patients who had been diagnosed with definite JDM for whom we had inception data. We

BAR	Brachial arterial reactivity	HDL	High-density lipoprotein
BMI	Body mass index	HOMA-IR	Homeostasis model assessment of insulin resistance
BP	Blood pressure		
CMH	Children's Memorial Hospital	IMT	Intima media thickness
CPK	Creatine phosphokinase	JDM	Juvenile dermatomyositis
CVD	Cardiovascular disease	Met-C	Metabolic controls
CVD-C	Cardiovascular disease controls	TNF-a	Tumor necrosis factor-a
ERL	End row loops	vWF:Ag	von Willebrand factor antigen

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recruited 8 adults diagnosed with JDM in childhood to evaluate the extent of disease activity and to assess their cardiovascular risk profiles.

Methods

All research complied with the Helsinki Declaration and was approved by the institutional review boards at Children's Memorial Hospital (CMH), Chicago, Illinois (nos. 2002-12345, 2007-12974, GCRC 1037) and Northwestern University, Chicago, Illinois (STU00009196 to R.R-G.).

Twenty-five subjects of the more than 400 patients in our database qualified for the study. We sought adults who had JDM, who were 25-45 years old, and who had a definite or possible JDM diagnosis without overlap syndrome (such as antibody to UI-ribonucleoprotein or polymyositis-scleroderma antigens), or polymyositis. Of the 25 potential candidates, 8 were eligible and agreed to participate in this pilot study (JDM). Their previous CMH records were extracted for disease presentation. Adults who had JDM were assessed for disease activity, ERL, cardiovascular risk, and metabolic function. Two of the 8 smoked cigarettes (1 pack a week). Seven were not taking medications for the treatment of JDM or any other medications that interfere with glucose metabolism. Subject no. 7 was noncompliant in taking 5 mg/d (0.06 mg/kg) of oral prednisone for the 2 months preceding the study.

Sixteen healthy, nonsmoking participants (metabolic controls [Met-C]), matched 2:1 to adults who had JDM based on age, sex, and body mass index (BMI) enrolled. Historical data, anthropometric measurements, physical examination, blood sample (after an 8-hour fast), and ERL studies were obtained. A convenience sample was identified of 8 healthy subjects who had cardiovascular testing identical to the adults who had JDM in a concurrent rheumatologic research project (cardiovascular disease control [CVD-C]).

Disease Assessment

Adults who had JDM were evaluated by using a validated disease activity score of skin and muscle involvement,[3] which were developed for children and used for comparison with previous diagnostic data. Eight fingers for each subject were studied for ERL, as previously described.[2] Muscle enzymes were determined by standard methodology (aldolase, ultravoilet kinetic assay; creatine kinase, alanine aminotransferase, aspartate aminotransferase by enzymatic rate method), Neopterin by immunoassay (DRG international, Mountainside, New Jersey), and von Willebrand factor antigen (vWF:Ag) in citrated plasma by using a turbidimetric assay.

Metabolic Assessment

Weight (kg) and height (cm) were rounded to the nearest tenth. BMI z score and height z score were calculated (Epi Info 2000; wwwn.cdc.gov/epiinfo/html/downloads.htm). Adult height z score were based on z scores for 20 year olds. Skinfold data obtained by 1 of 2 experienced nutritionists (mid arm circumference, waist, and hips measured to 0.1 cm; triceps and subscapular to 0.1 mm) were compared with reference percentiles.[9] Fasting glucose was determined by the hexokinase method, and insulin was determined by radioimmunoassay (cat. no. H1-14K; Millipore/Linco Research Inc, Billerica, Massachusetts). Cholesterol and triglycerides were determined by the timed-endpoint method, and high-density lipoprotein (HDL) was determined by the direct HDL-cholesterol method. Low-density lipoprotein–cholesterol was calculated by using total cholesterol – HDL – (triglycerides/5). Leptin and adiponectin were analyzed by radioimmunoassay (Millipore/Linco Research). Proinflammatory oxidized HDLs were evaluated in the laboratory of Navab and Fogelman by using previously published methodology.[10]

Fasting insulin and the homeostasis model assessment of insulin resistance (HOMA-IR: [glucose (mmol/L) × insulin (μU/mL)]/22.5) were used as markers of insulin resistance.[11] Higher HOMA-IR reflected more insulin resistance. An approximate value of 4 represents insulin resistant state.[12] The 75th percentile HOMA-IR in 5900 adults without diabetes >20 years of age was 2.86.[13] Features of metabolic syndrome were based on the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute consensus.[14]

Subclinical Cardiovascular Assessment

The subjects underwent measurement of carotid intima media thickness (IMT) with a 8L5 linear transducer attached to a Sequoia 256 (Accuson Siemens, Mountain View, California) machine by using standard positioning and long-axis imaging planes. The B-mode imaging gain was set to allow optimal visualization of the intima-luminal interface.[15] Images were obtained from the common carotid artery, carotid bulb, and internal carotid artery bilaterally, and measured (Image J [a public domain, Java-based image processing program developed at the National Institutes of Health]). The IMT was determined to be the largest value to the far wall of each segment.

Supine, fasting subjects for brachial arterial reactivity (BAR) were studied with a 8L5 linear transducer attached to an Sequoia 256 (Accuson Siemens) in a temperature-controlled environment between 7:30-9:30 a.m. A blood pressure cuff was placed distal to the elbow, and an imaging window for the brachial artery in long axis was obtained. The brachial arterial lumen equals the trailing edge of the intima to the leading edge of the opposite intima. The blood pressure cuff was inflated to 30 mm Hg over the systolic blood pressure, held for 5 minutes, and released. Images were reobtained in the same location at 60 and 90 seconds after cuff deflation and were measured offline by using Image J (www.rsbweb.nih.gov/ij/). The percentage change equals the greater of the percent changes from the 60 second or 90 second timepoints compared with baseline; values for a change less than 5% are considered abnormal, and 7%-10% change is normal.[16] After a 5-minute rest, the adults who had JDM and the Met-C subjects had manual blood pressure