Premature Pubarche in Children with Pompe Disease

Queenie K.-G. Tan, MD, PhD[1], David W. Stockton, MD[2], Eniko Pivnick, MD[3], Asim F. Choudhri, MD[4], Stacy Hines-Dowell, DNP, APNG[3], Loren D. M. Pena, MD, PhD[1], Melissa A. Deimling, MD[5], Michael S. Freemark, MD[6], and Priya S. Kishnani, MD[1]

Pompe disease (PD), or glycogen storage disease type II, results from deficiency of acid α-glucosidase. Patients with infantile-onset PD die by early childhood if untreated. Patient survival has improved with enzyme replacement therapy. We report a case series of 8 patients with infantile-onset PD on enzyme replacement therapy with premature pubarche. *(J Pediatr 2015;166:1075-8).*

Pompe disease (PD), or glycogen storage disease type II, is caused by a deficiency of acid α-glucosidase (GAA), a lysosomal enzyme. This enzyme deficiency leads to accumulation of lysosomal glycogen in cardiac, skeletal and smooth muscle, and other tissues. Classic infantile PD (IPD) is characterized by a complete deficiency of GAA, and patients usually die of cardiorespiratory complications by age 2 years if untreated. Patients with atypical IPD also usually present in infancy but have less severe or no cardiac involvement. Nevertheless, untreated patients with atypical IPD also have rapid clinical deterioration and early mortality.[1]

The development of enzyme replacement therapy (ERT) with recombinant human GAA has increased the lifespan of patients with IPD. New complications have been observed among long-term survivors that pose new challenges for management.[2]

Here we describe 8 patients with IPD on ERT who developed premature pubarche. Our findings suggest the need for ongoing monitoring of sexual development and function in children and adolescents with IPD because premature pubarche may be associated with subsequent development of glucose intolerance, insulin resistance, and/or ovarian hyperandrogenism.

Methods

Forty-nine patients with IPD were seen and clinically managed at 3 centers (Duke University, Wayne State University, and University of Tennessee). Retrospective chart review was completed on all cases following a finding of premature pubarche in 1 case (patient 2). Chart review for all patients was completed as part of a Duke Institutional Review Board-approved natural history study of IPD (Pro00010830). Written informed consent was obtained from the parents or guardians of the children.

We evaluated all IPD cases at Duke University, Wayne State University, and University of Tennessee. We found precocious pubarche in 8 of 41 patients enrolled in the study and whose puberty status is known (8 other patients with IPD were lost to follow-up, and their puberty status is unknown). **Table I** is a summary of these patients' sex/race, age at PD diagnosis, *GAA* mutations, age at ERT initiation, current age, as well as gastrointestinal, cardiopulmonary, and motor status. **Table II** is a summary of their body mass index (BMI), ages of presentation of pubarche and/or axillary hair, as well as studies or lab work.

In a cohort of 41 children with IPD, we found 8 who developed precocious pubarche (19.5%). There were 4 males and 4 females (4 Caucasians, 3 African Americans, 1 Hispanic). Of the 8 patients, 5 had classic IPD (patients 1-5) and 3 had atypical IPD (patients 6-8). The earliest onset of premature pubarche was 14 months (patient 2); the age range for onset of pubarche was 14 months to 4 years 2 months for patients with classic IPD, and 7 years for the 3 patients with atypical IPD. Of the 41 total patients with IPD, 5 are younger than age 14 months or died before age 14 months; thus, the

BMI	Body mass index
DHEA	Dehydroepiandrosterone
ERT	Enzyme replacement therapy
GAA	Acid α-glucosidase
IPD	Infantile PD
PCOS	Polycystic ovary syndrome
PD	Pompe disease

From the [1]Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center, Durham, NC; [2]Division of Genetic and Metabolic Disorders, Departments of Pediatrics and Internal Medicine, Wayne State University and Children's Hospital of Michigan, Detroit, MI; [3]Division of Medical Genetics, Department of Pediatrics, University of Tennessee; Le Bonheur Children's Hospital, [4]Departments of Radiology, Ophthalmology, and Neurosurgery, University of Tennessee Health Science Center; Le Bonheur Neuroscience Institute, Le Bonheur Children's Hospital, Memphis, TN; and Divisions of [5]Primary Care and [6]Endocrinology, Department of Pediatrics, Duke University Medical Center, Durham, NC

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Table I. Summary of characteristics of the cases, including feeding, cardiorespiratory, and mobility status

Pt	Sex/race	Age at PD diagnosis	*GAA* mutations	Age at ERT initiation	Dose of ERT (at onset premature pubarche)	Current age	Gastro intestinal symptoms	Cardio pulmonary status	Motor status
1	Male African American	6 mo	Maternal c.*2560C>T* p.Arg854X Paternal c.*1933G>A* p.Asp645Asn	9 mo	40 mg/kg IV alglucosidase alfa every other wk	10 y	G tube dependent	Biventricular and septal hypertrophy at diagnosis, now with normal left ventricular size and function. Completely ventilator dependent	Wheelchair dependent
2	Female Hispanic	5 mo	Homozygous for c.*1195-18_2190-20del* (p.Asp399Valfsx6)	6 mo	20 mg/kg IV alglucosidase alfa per wk	4 y	GJ tube dependent	Severe biventricular hypertrophy at diagnosis, now RVH resolved, LVH improved, normal biventricular function. Completely ventilator dependent	Wheelchair dependent
3	Female African American	5 mo	Homozygous for c.*2560C>T* (p.Arg854X)	6 mo	20 mg/kg IV alglucosidase alfa every other wk	Died at age 21 mo	GJ tube dependent	Severe LVH and moderate RVH at diagnosis, prior to death had improved RVH and LVH and normal biventricular systolic function. Ventilator dependent but tolerated 2 h per day off ventilator	Wheelchair dependent
4	Female Caucasian	2 mo	Compound heterozygous for c.*1210G>A* (p.D404N) and c.*2227C>T* (p.Q743X)	4 mo	20 mg/kg IV alglucosidase alfa every other wk	4.5 y	G tube dependent	Moderate RVH and LVH at presentation. Completely ventilator dependent	Wheelchair dependent
5	Female Caucasian	2 mo	Compound heterozygous for c.*1210G>A* (p.D404N) and c.*2227C>T* (p.Q743X)	4 mo	20 mg/kg IV alglucosidase alfa every other wk	4.5 y	G tube dependent	Moderate RVH and LVH. Completely ventilator dependent	Wheelchair dependent
6	Male Caucasian	16 mo	Compound heterozygous for c.*307T>G* (p.C103G) and c.*1583G>C* (p.G528A)	17 mo	20 mg/kg IV alglucosidase alfa every other wk	7 y	G tube dependent	Mild LVH, normal cardiac function at diagnosis. Completely ventilator dependent	Wheelchair dependent
7	Male Caucasian	3.5 y	Homozygous for c.*1655T>C* (p.L552P)	3.5 y	20 mg/kg IV alglucosidase alfa every other wk	8 y	G tube dependent	Normal echocardiogram and ECG at diagnosis. Completely ventilator dependent	Wheelchair dependent
8	Male African American	15 mo	Compound heterozygous for c.*-32-17_-32-10delinsT CCCTGCTGAGCCTCCTACA GGCCTCCCGC* and c.*1447G>A* (p. G483R)	16 mo	20 mg/kg IV alglucosidase alfa every other wk	8 y	Eats fully by mouth	Normal echocardiogram since diagnosis. Hypertension. On room air.	Ambulates independently with ankle-foot orthotics over short to moderate distances.

ECG, electrocardiogram; *G tube*, gastrostomy tube; *GJ tube*, gastrostomy-jejunostomy tube; *IV*, intravenous; *LVH*, left ventricular hypertrophy; *Pt*, patient; *RVH*, right ventricular hypertrophy.