# 2017 APS Membership Application Form

Application must be received by: **July 31, 2016** *(or first following business day)*

## Applicant Information

<table>
<thead>
<tr>
<th>Active Member Nomination</th>
<th>Honorary Member Nomination (International Applicants Only)</th>
<th>Applicant’s Name (First/M.I./Last)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Daniel G. Glaze</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Academic Degree(s) (MD, PhD)</th>
<th>Academic Title</th>
<th>Department or Division</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.D.</td>
<td>Professor</td>
<td>Department of Pediatrics, Section of Neurology</td>
<td>Baylor College of Medicine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Street Address</th>
<th>Room/Building/Suite</th>
<th>City, State, Zip</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>6701 Fannin Street</td>
<td>CCC D.1250</td>
<td>Houston, TX 77030</td>
<td>United States of America</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phone</th>
<th>Fax</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>832-822-7388, or toll-free at 1-888-430-7388</td>
<td>832-825-7388</td>
<td><a href="mailto:dglaze@bcm.edu">dglaze@bcm.edu</a></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Subspecialty Training</th>
<th>Date &amp; Name of Board Certification</th>
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<tbody>
<tr>
<td>Sleep</td>
<td>May, 1980 American Board of Pediatrics</td>
</tr>
<tr>
<td></td>
<td>April, 1981 American Board of Neurology</td>
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<tr>
<td></td>
<td>June, 1997 Special Competency in Child Neurology</td>
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<tr>
<td></td>
<td>May, 1999 American Board of Neurology, Special Competency in Neurophysiology</td>
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<tr>
<td></td>
<td>American Board of Sleep Medicine</td>
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<tr>
<th>Gender</th>
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<td>Female</td>
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<tr>
<th>Is the applicant of Hispanic, Latino/a, or Spanish origin?</th>
<th>Yes</th>
<th>No</th>
<th>X</th>
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<tbody>
<tr>
<td>If Yes (1 or more categories may be selected):</td>
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<tr>
<td>Yes, Mexican, Mexican American, Chicano/a</td>
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<td>Yes, Puerto Rican</td>
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<tr>
<td>Yes, Cuban</td>
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<tr>
<td>Yes, Another Hispanic, Latino/a or Spanish Origin</td>
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<th>What is the applicant’s race/ethnicity? (1 or more categories may be selected)</th>
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<tbody>
<tr>
<td>White</td>
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<tr>
<td>Black or African American</td>
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<td>American Indian/Alaska Native/First Nations</td>
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<tr>
<td>Asian Indian</td>
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<tr>
<td>Korean</td>
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<tr>
<td>Vietnamese</td>
</tr>
<tr>
<td>Other Asian</td>
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<tr>
<td>Native Hawaiian</td>
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</table>
Daniel G. Glaze, M.D. is a professor in the Department of Pediatrics and Neurology at Baylor College of Medicine. He has served as Medical Director of the Children’s Sleep Center at Texas Children’s Hospital over 30 years. In this capacity, he has been responsible for the development of a pediatric sleep medicine program known nationally and internationally for its excellence of care. Additionally, he has played a leadership role in the development of the sleep medicine fellowship at Baylor College of Medicine which is now recognized for its excellence in teaching and experience in pediatric sleep medicine. This year, four of the five sleep medicine fellowship positions are filled by pediatric-trained physicians. On a national level, he has served on the Board of the American Academy of Sleep Medicine and has served as the Chairperson of the Committee for Continuing Medical Education. He is known for his special interest in sleep disorders of children with neurological and developmental disorders.

Dr. Glaze is responsible for the sleep training at Baylor College of Medicine that is required by the ACGME for all residency programs. He is known for his excellence in teaching, clinical care, research and publications.
**National/International Recognition.** Indicate peer recognition of the candidate as an acknowledged leader or contributor to the advancement of child health. Clear and precise delineation of a candidate’s stature within pediatrics (academia or the pediatric community at large) is essential. (Expand area provided for answer as needed.)

Dr. Glaze also serves as the medical director of the Blue Bird Circle Rett Center at the Texas Children’s Hospital. He created and developed this center, and he and the Center are recognized nationally and internationally for the excellence of care of individuals with Rett syndrome and clinical research which has defined the clinical phenotype of Rett syndrome. He and the Rett Center have set the standard for care of individuals with Rett syndrome, resulting in improved quality of life and extending survival beyond the fifth decade for these individuals. His particular area of expertise regards the neurophysiology of this disorder as well as epilepsy and sleep problems. Recently, he and the members of the Rett Center have successfully completed the initial study of a novel medication, Trofinetide, which represents the first potentially efficacious treatment for Rett syndrome and the first successful trial in a neurogenetic developmental disorder.

**Anticipated Engagement in the American Pediatric Society and History of Engagement in the Pediatric Academic Societies.** Indicate in what way(s) the candidate will most likely contribute to the APS and describe the candidate’s previous engagement in PAS activities, including other PAS organizations and the PAS meeting. (Expand area provided for answer as needed.)

Dr. Glaze will bring expertise in Pediatric Sleep and in Neurodevelopmental disorders to the APS. Neurology has not had a strong representation at APS apart from neonatal neurology, and I would argue that Dr. Glaze will bring much needed expertise to the society.

**Seconder’s Letter.** The Seconder’s Letter should be brief comments on the particular strengths of the applicant for APS membership. No specific format is required for this letter.
Dr. Glaze is a senior member of the Department of Pediatrics in the Division of Neurology and Developmental Neuroscience. He is one of the hardest working faculty in the Department. Not only is he a busy clinician, but he has been quite prolific in publishing his clinical research, achieving extramural funding, and developing a sleep medicine program for Pediatrics within our Department. He serves as a tenured Professor within the Department, the director of our Rett Center, and the head of the Sleep Center within the Department. I am confident that given his leadership track record that he will make positive contributions to APS.
CURRICULUM VITAE

Daniel G. Glaze, M.D.

BORN: January 3, 1948; Phoenix, Arizona

ADDRESS: 1747 Northshore Drive, Missouri City, Texas 77459

TELEPHONE: (281) 499-1631

MARRIED: Sharon B. Glaze (10-18-46)
Associate Professor, Department of Radiology, Baylor College of Medicine

CHILDREN: Geoffrey M. Glaze, (Birthdate April 23, 1977)
Emily Elizabeth Glaze, (Birthdate May 10, 1983)

EDUCATION: B.A., Yale University, New Haven, CT, 1970
M.D., Baylor College of Medicine, Houston, TX, 1974

PROFESSIONAL EXPERIENCE:
1974-1977 Resident in Pediatrics, Baylor College of Medicine, Houston, Texas
1977-1980 Resident in Neurology, Baylor College of Medicine, Houston, Texas
1980-1981 Fellowship in Neurophysiology, Baylor College of Medicine, Houston, Texas
1981-Present Assistant Professor, Department of Pediatrics, Baylor College of Medicine
1981-Present Instructor, Department of Neurology, Baylor College of Medicine
1983-1990 Assistant Professor, Department of Neurology, Section of Neurophysiology, Baylor College of Medicine
1990-2009 Associate Professor, Department of Pediatrics and Department of Neurology, Section of Neurophysiology, Baylor College of Medicine
1990-Present Texas Children's Hospital Sleep Clinic
1992-Present Medical Director, The Blue Bird Circle Rett Center, Baylor College of Medicine
1997-2006 Director, The Methodist Hospital Sleep Laboratory
1997-Present Director, Texas Children's Hospital Sleep Laboratory
1997-present Director, Texas Children's Hospital Children’s Sleep Center
1997-2015 Chairman, Bioethics Committee, Texas Children’s Hospital, Houston, TX
2006-Present Director, St. Luke’s Episcopal Hospital Sleep Disorders Center, Texas Medical Center
2007-Present Chief, Texas Children's Hospital Sleep Clinic
2007-Present Chief, Texas Children's Hospital Rett Clinic
2009-Present  Professor, Department of Pediatrics and Department of Neurology, Section of Neurophysiology, Baylor College of Medicine

CERTIFICATION:

May, 1980  American Board of Pediatrics
April, 1981  American Board of Neurology, Special Competency in Child Neurology #460, #24182
June, 1997  American Board of Neurology, Special Competency in Neurophysiology
May, 1999  American Board of Sleep Medicine

HONORS:

1997-present  Chairman, Bioethics Committee, Texas Children’s Hospital, Houston, TX
2005-2006  Best Doctors in America, selected by peers
2005-2006  Section Editor, Neurology Section, UpToDate
2006-2007  Achievement in Teaching, Faculty Teaching Award, Department of Pediatrics, Baylor College of Medicine
2007-2010  Board of Directors, American Association of Sleep Medicine (AASM)
2007-2009  President, Epilepsy Foundation of Southeast Texas
2008  Received Baylor Pediatrics Award of Achievement in Teaching, Department of Pediatrics, May 2008
2008  Received Art of Caring Award, International Rett Syndrome Foundation, May
2008  Received Outstanding Contribution to the Sleep Medicine Fellowship Program Award, Baylor College of Medicine Pulmonary, Critical Care and Sleep Medicine Department, May
2009-2011  Advisor, Medical Advisory Board, International Rett Syndrome Foundation (IRSF)
2009  Recognized for active contributions to the peer-reviewed, online eMedicine Clinical Knowledge Base
2009  2009 Honoree, honored by the Blue Bird Circle for continued work in the Blue Bird Clinic towards Rett syndrome and sleep
2010  Distinguished Service Award, Received June 7, 2010, for outstanding dedication, commitment, and personal leadership to the AASM Board of Directors, 2007-2010.
2010  Selected to be included in the 65th edition of Who's Who in AMERICA 2011
2011  Awarded Certificate of Appreciation from Alvin Community College Polysomnography Program for clinical instruction to their students.
The Alvin Community College Polysomnography Program created the Dr. Daniel Glaze Foundation Scholarship program for Dr. Glaze’s dedication to the field of sleep medicine because of his dedication to the ACC students involved in the sleep medicine program.

Outstanding Educator Performance—awarded by the Sleep Medicine Fellows

MEMBERSHIPS:
Child Neurology Society
American Society of EEG Technology
American Clinical Neurophysiology Society
American Neurological Association
American Academy of Sleep Medicine
American Academy of Sleep Medicine, Task Force
American Academy of Sleep Medicine, Polysomnographic Technologist Training and Issues Committee
Sleep Medicine Fellowship Training Program Committee

HOSPITAL PRIVILEGES:
Texas Children's Hospital

TEXAS LICENSE #: E 2575 (original date of issue: 08/17/1974)

PUBLICATIONS


127. Glaze, D.G.  The Role of sTNF-gRI in asthma.  Letter to the Editor.  Pediatric Asthma, Allergy, and Immunology 2002, 15:233-234.


MEETINGS/PRESENTATIONS


Glaze, D.G.  Advanced Pediatric Sleep Medicine Faculty, Atlanta, GA, Nov. 6-8, 1998.

Glaze, D.G.  Faculty, National Pediatric Sleep Course, November 6-9, 1998, Atlanta, Georgia.


Glaze, D.G. “New Anticonvulsant Medications”, presented at the Epilepsy Update 1999 seminar, May 8, 1999, at Baylor College of Medicine, Houston, TX. Sponsored by Baylor College of Medicine Department of Pediatrics-Neurology and the Epilepsy Foundation of Southeast Texas.

Glaze, D.G. “Sleep Research: Fruit flies, dogs and humans”, Houston, TX, June 29, 1999 at the Summer Research Program Seminar, sponsored by The University of Texas at Houston, Health Science Center.

Glaze, D.G. Pediatric Sleep Medicine Course, Atlanta School of Sleep Medicine, Atlanta, GA, November 5th-7th, 1999.

Glaze, D.G. Pediatric Neurology: Update for the the Clinician, Houston, TX, March 18, 2000. Baylor College of Medicine Office of Continuing Medical Education seminar.

Glaze, D.G. Geriatric Sleep Disorders, Methodist Hospital, Houston, TX, May 4, 2000. Multidisciplinary Geriatrics Conference.


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Glaze, D.G. Marvin Fishman, M.D. Presented slide presentation honoring Dr. Marvin Fishman for his 25 years at Baylor College of Medicine and Texas Children’s Hospital. Held at Baylor College of Medicine, March 2004.


Glaze, D.G. Problem-based Sleep Medicine Course for the Primary Care Practitioner: Establishing a Differential Diagnosis and Treatment Plan. Title: “Why Pat Can’t Concentrate”. Saturday, September 18, 2004, J.W. Marriott in the Houston Galleria, Houston, TX, sponsored by The Houston Sleep Consortium.


Glaze, D.G.  M.D. Anderson Cancer Meeting, presentation: “What’s Sleep Got to do With It? Impact and Management of Sleep Problems in Patients with Cancer”, held in Houston, TX, September 10-12, 2005.

Glaze, D.G.  Sleep Problems in Children with Neurological Disorders. Presented at “Dreaming of a Good Night’s Sleep: Evaluation and Management of Sleep Disorders in Children. Sponsored by The University of Texas Health Science Center at San Antonio, Texas, September 30, 2005; held at CHRISTUS Santa Rosa Center for Children and Families, San Antonio, Texas.

Glaze, D.G.  “BEARS” and Beyond: Childhood Sleep Disorders and ADHD. Presented at “Problem Based Sleep Medicine Course for the Primary Care Practitioner: Establishing a differential diagnosis and treatment plan”. Sponsored by The Houston Sleep Consortium, Houston, Texas, February 24 2006; held at J.W. Marriott in the Houston Galleria.


Glaze, D.G.  Autism Treatment Network Clinical Committee Meeting held at the New England Research Institutes (NERI), Watertown, MA, May 8-10, 2006. Served as committee member.


Glaze, D.G. The Ethical, Psychosocial, and Spiritual Dimensions of a Neonatal Futility Case. Chaired session with Diane Treadwell-Deering, M.D., Baruch Brody, Ph.D., and Pamela Taylor, M.Div., BCC. Presented at the Baylor College of Medicine Psychiatry Grand Rounds, Menninger Department of Psychiatry and Behavioral Sciences. Broadcast at The Menninger Clinic and The Michael E. DeBakey Veterans Affairs Medical Center. Session held at Baylor College of Medicine, Houston, Texas, December 6, 2006.

Glaze, D.G. The Association of Childhood Sleep Disordered Breathing and ADHD. Presented at the Pediatric Grand Rounds, Texas Children’s Hospital, January 12, 2007.


Asthana, S. E. Lipshultz, W. T. Shearer: IL-1β and IL-6 Levels and Sleep Patterns in HIV-Infected Children with Viremia, being submitted for presentation at the American Academy of Allergy, Asthma and Immunology meeting, 2008.


Foster SB, Reuben J, Cohen E, Asthana, D, Lu, M, Thompson B, Glaze D, Shahzeidi S, Colin A, Miller T, Lipshultz S, Shearer W: Circadian Regulation of IL-6, IL-1β and IL-1RA Levels is Disrupted in HIV-Infected Children. Abstract to be submitted to the Federation of Clinical Immunology Societies 2009 Annual Meeting.


Poster presentation at SLEEP 2014, the 28th Annual Meeting of the Associated Professional Sleep Societies, LLC, on May 31-June 4, 2014, at the Minneapolis Convention Center in Minneapolis, Minnesota. Abstract with control ID #787 entitled, “A Pilot Study Exploring a Relation between Video Games, Sleep Quality, Quality of Life, and Depression in Teenagers” will be presented on Monday, June 2, 2014.


GRANTS/AWARDS


Effect of High Dose vs Low Dose ACTH on Infantile Spasms Grant. Support: NINCDS #NS25884. Period of Grant 4-1-88 to 3-31-93. Principal investigator: Richard A. Hrachovy, M.D.; Co-investigator: Daniel Glaze, M.D.

Rett Syndrome: A Program Project. Support NICND #2 PO2 HD24234. Period of grant 4-1-93 to 3-31-96. Director and Principal Investigator Daniel G. Glaze, M.D. Project 1 Clinical Aspects, Project Leader Daniel G. Glaze, M.D. Project 2 Nutrition, Project Leader Kay Motil, Co-Investigator Daniel G. Glaze, M.D.

National Institutes of Health: NIH 5PO1HD24234-08; Rett Syndrome: Program project. PI: Daniel G. Glaze, M.D.

Blue Bird Circle, Rett Center Grant, 1997-1998. Principal Investigator Daniel G. Glaze, M.D.


Blue Bird Circle, Rett Center Grant, 1999-2004. Principal Investigator Daniel G. Glaze, M.D.


Foster S and Glaze DG: IL-1β and IL-6 Levels and Sleep Patterns in HIV-Infected Children with Viremia, accepted for presentation at the AAAAI Annual Meeting in Philadelphia in March, 2008.

goal of this study is to study the relationship between melatonin and sleep problems in children with autism spectrum disorder. This research project has the following specific aims: Specific Aim 1: Characterize the endogenous MT profiles in children with ASD with and without sleep problems. Specific Aim 2: Determine the efficacy of MT used as a hypnotic for improving sleep directly and secondarily improving daytime behavior in children with ASD and sleep problems. Data from this study will provide important information concerning circadian rhythm dysregulation in ASD and will support the development of future studies using MT to modify and correct abnormal circadian rhythms. 09/01/07 - 8/31/10.


IRSF - ANGEL GRANT supplement - $184,408 – March 1, 2014– Sept 30, 2014


GORMAN DONATION - $11,000 TO PURCHASE PUPILOMETER FOR HeART STUDY

IRSF – SLEEP IN RARE DISEASE - $50,000 – JUNE 1, 2011 – MAY 31, 2014

NIH UAB U54HD061222 – RETT NATURAL HISTORY - $97,000 – AUG 1 2012 – JULY 31 2013

ANGELMAN FOUNDATION - SLEEP IN RARE DISEASE SUPPLEMENT - $17,000 – SEPT 1, 2012 – AUG31, 2013

NEUREN PHARMACEUTICALS NNZ-2566 IN ADULT RETT - $1,265,065.00– MARCH 1, 2013 – FEB 28, 2014

BLUE BIRD CIRCLE 2016
BLUE BIRD CIRCLE FOUNDATION
BLUE BIRD CIRCLE RETT CENTER GRANT 2016
Annual funding to support the clinical research operations of the BCM Rett Center.
Role: PI (for BCM site)

NEU-2566-RETT-001
NEUREN PHARMACEUTICALS LTD
NEUREN 002 - A DOUBLE-BLIND, RANDOMIZED, DOSE-RANGING STUDY OF THE SAFETY AND PHARMACOKINETICS OF ORAL NNZ-2566 IN PEDIATRIC RETT SYNDROME. Role: PI (for BCM site)
Establish a phenotype-genotype correlation over a broad spectrum of Rett syndrome phenotypes including the longitudinal pattern of progression that is the natural history of clinical features across this cohort including assessment of quality of life and longevity.

Role: PI (for BCM site)

IRSF Clinical Study Agreement
INTERNATIONAL RETT SYNDROME FOUNDATION
RETTSYNDROME.ORG - CLINICAL STUDY AGREEMENT - RETT NATURAL HISTORY STUDY. Funding on a per visit basis in support of the NIH funded Rett Natural History study. Role: PI (for BCM site)

BLUE BIRD CIRCLE 2016
BLUE BIRD CIRCLE FOUNDATION
BLUE BIRD CIRCLE RETT CENTER GRANT 2016
Annual funding to support the clinical research operations of the BCM Rett Center. Role: PI (for BCM site)

COMMITTEES

1986 to present  Member of the Admissions Committee, Baylor College of Medicine


1992 to present  American EEG Society Committee on Sleep Disorder, Children

1993 to present  Medical Advisory Board, The Research for Rett Syndrome Foundation, Inc.
<table>
<thead>
<tr>
<th>Year</th>
<th>Position and Affiliation</th>
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<tbody>
<tr>
<td>1995 to present</td>
<td>Medical Advisory Board, Gulf Coast Epilepsy Foundation of America</td>
</tr>
<tr>
<td>1996 to present</td>
<td>Member, Bioethics Committee, Texas Children's Hospital</td>
</tr>
<tr>
<td>1997</td>
<td>NIH General Clinical Research Center Review Committee. Hyatt Regency, Bethesda, Maryland.</td>
</tr>
<tr>
<td>1998-2004</td>
<td>Chairman, AASM Committee on Continuing Medical Education</td>
</tr>
<tr>
<td>2001-present</td>
<td>Member, Scientific Advisory Committee, Texas Children’s Hospital General Clinical Research Center</td>
</tr>
<tr>
<td>2001-2002</td>
<td>Member, The Methodist Hospital Bylaws and Rules Committee</td>
</tr>
<tr>
<td>2001-present</td>
<td>Associate Editor (CME), Journal of SLEEP</td>
</tr>
<tr>
<td>2004-present</td>
<td>Member, AASM Committee on PSG Tech Training Program</td>
</tr>
<tr>
<td>2004-present</td>
<td>Member, AASM Sleep Medicine Fellowship Training Program Committee</td>
</tr>
<tr>
<td>2006-present</td>
<td>Member, AASM Medical Education Committee</td>
</tr>
<tr>
<td>2007-2009</td>
<td>Reviewer, FDA Grant Review Committee</td>
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<tr>
<td>2007-2010</td>
<td>President, Professional Advisory Board, Epilepsy Foundation of Southeast Texas</td>
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<tr>
<td>2007-present</td>
<td>Member, Medical Staff Committee, Department of Ambulatory, Texas Children’s Hospital</td>
</tr>
<tr>
<td>2008-present</td>
<td>Member, Executive Board of RettSearch, an International Committee</td>
</tr>
<tr>
<td>2007-2015</td>
<td>Chair, Bioethics Committee of the Medical Staff, Texas Children’s Hospital</td>
</tr>
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</table>

Revised 8/1/2016
Gastrointestinal and Nutritional Problems Occur Frequently Throughout Life in Girls and Women With Rett Syndrome

Kathleen J. Motil, Erwin Caeg, Judy O. Barrish, Suzanne Geerts, Jane B. Lane, Alan K. Percy, Fran Annese, Lauren McNair, Steven A. Skinner, Hye-Seung Lee, Jeffrey L. Neul, and Daniel G. Glaze

ABSTRACT

Objective: We conducted a nationwide survey to determine the prevalence of common gastrointestinal and nutritional disorders in Rett syndrome (RTT) based on parental reporting and related the occurrence of these problems to age and methyl-CpG-binding protein 2 (MECP2) gene status.

Methods: We designed a questionnaire that probed symptoms, diagnoses, diagnostic tests, and treatment interventions related to gastrointestinal and nutritional problems in RTT. The International Rett Syndrome Foundation distributed the questionnaire to 1666 family-based members and forwarded their responses for our review. We interrogated the Rare Disease Clinical Research Network database to supplement findings related to medications used to treat gastrointestinal problems in RTT.

Results: Parents of 983 female patients with RTT (59%) responded and identified symptoms and diagnoses associated with gastrointestinal dysmotility (92%), chewing and swallowing difficulties (81%), weight deficits or excess (47%), growth deficits (45%), low bone mineral content or fractures (37%), and biliary tract disorders (3%). Height-for-age, weight-for-age, and body mass index z scores decreased significantly with age; height- and weight-, but not body mass index-for-age z scores were significantly lower in female subjects with MECP2 mutations than in those without. Vomiting, nighttime awakening, gastroesophageal reflux, chewing difficulty, and choking with feeding were significantly less likely to occur, whereas short stature was significantly more likely to occur in female subjects with MECP2 mutations than in those without. Diagnostic evaluations and therapeutic interventions were used less frequently than the occurrence of symptoms or diagnoses in the RTT cohort.

Conclusions: Gastrointestinal and nutritional problems perceived by parents are prevalent throughout life in girls and women with RTT and may pose a substantial medical burden for their caregivers. Physician awareness of these features of RTT may improve the health and quality of life of individuals affected with this disorder.

Key Words: cholelithiasis, constipation, gastroesophageal reflux, gastroparesis, gastrostomy, growth, low bone mineral content, MECP2

(RPGN 2012;55: 292–298)
features of RTT. The paucity of evidence-based information led us to design the present study to determine the prevalence of common gastrointestinal and nutritional problems in RTT based on parental reporting. We hypothesized that gastrointestinal and nutritional problems frequently affect girls and women with RTT, depending on their age and MECP2 status. Our goal in reporting this information is to increase awareness among physicians and health care providers regarding the burden of gastrointestinal and nutritional problems in this disorder.

**METHODS**

**Subjects**

The International Rett Syndrome Foundation (IRSF) maintains the North American RTT database, which contains the demographics, diagnosis, and mutation status of individuals in the United States and Canada affected with this disorder (11). Girls and women who fulfill the clinical criteria for RTT, either classic or one of the variant forms, or those who do not meet criteria but have a mutation in the MECP2 gene, populate the North American RTT database. The parents of individuals listed in the North American RTT database served as the participants for the present study.

**Methods**

**Survey Questionnaire**

We developed a structured questionnaire based on our experience with the gastrointestinal and nutritional problems associated with RTT (online-only Appendix, http://links.lww.com/MPG/A92). IRSF mailed the questionnaire to 1666 families within its membership in the United States and Canada whose daughters were diagnosed as having RTT. Because the mailings were conducted via bulk rate routing, IRSF did not have an accurate count of questionnaires not received by families due to faulty addresses. IRSF subsequently distributed the questionnaire 6 months later to families who attended the annual family conference and had not responded previously. Upon receipt of all responses, IRSF deidentified the questionnaires and forwarded the forms to us for data analysis.

The questionnaire included demographic items related to age, MECP2 status, and estimates of height and weight; clinical symptoms and diagnoses related to common gastrointestinal and nutritional complaints; diagnostic procedures performed in response to symptoms; and medical, nutritional, and surgical interventions for each individual. The questionnaire was designed such that the parent provided a “yes,” “no,” or “don’t know” response to all categorical questions (symptom/diagnosis present or absent, procedures performed or not performed, intervention applied or not applied). Exceptions included the age of each individual, which was categorized as 1 of 6 age-specific groups, and parental estimates of height and weight, which were used to calculate height-, weight-, and body mass index (BMI)-for-age z scores based on standard reference data (12). Parental estimates of height, weight, and BMI measurements of female subjects older than 20 years were assigned z scores obtained at 20 years of age, based on the assumption that these individuals had achieved adult body size.

**RDCRN Database**

We also interrogated the Rare Diseases Clinical Research Network (RDCRN) database, a programmatic component of the National Center for Research Resources, to supplement the survey data with additional medications used to treat gastrointestinal problems. The database contains information related to the clinical spectrum and natural history of individuals affected with RTT preparatory to the initiation of anticipated clinical trials. The data were collected by members of the RTT consortium from three primary centers and four satellite sites across the United States and entered electronically into the RDCRN database managed by the Data Technology Coordinating Center at the University of South Florida. The subset of data related to medication use was retrieved from the RDCRN database to complement data obtained from the questionnaire. Girls and women who were enrolled in the natural history study also were included in the North American RTT database.

This research study was designated exempt from institutional review and approval by the institutional review board for human subject research at Baylor College of Medicine. Informed consent was implied based on the return receipt of the questionnaire.

**Data Analysis**

Responses categorized as “yes” or “no” were considered to be an evaluable response to the questions; responses categorized as “don’t know” or left blank were considered to be indeterminate and excluded from data analysis. All of the evaluable responses were coded and entered into a statistical database (MiniTab Inc, version 11.0, State Park, PA). The frequency of positive or negative responses to individual questions constituted a conservative estimate of prevalence based on the total number of survey responses.

Descriptive statistics were applied to characterize the age groups, MECP2 status, and height-, weight-, and BMI-for-age z scores of the female subjects with RTT. One-way analysis of variance was used to detect differences in height-, weight-, and BMI-for-age z scores across the age groups of the RTT cohort. General linear modeling was applied to detect differences in height-, weight-, and BMI-for-age z scores between female subjects with and without MECP2 mutations when adjusted for age. One- and 2-sample t tests were applied to determine differences in height-, weight-, and BMI-for-age z scores between the RTT cohort and the reference standard and between female subjects with and without MECP2 mutations, respectively.

Descriptive statistics were applied to determine the prevalence of gastrointestinal and nutritional problems in terms of clinical symptoms and diagnoses; diagnostic procedures; and medical, nutritional, and surgical interventions in the RTT cohort. The classification of clinical problems was based on groups of, as well as individual, symptoms and diagnoses as follows: gastrointestinal dysmotility, including gastroesophageal reflux, gastroparesis, vomiting or regurgitation, nighttime awakening with irritability, constipation, straining with bowel movements, and passage of hard stools; feeding problems, including chewing difficulty, swallowing dysfunction, prolonged feeding time (>30 min-minutes), and choking or gagging with meals; nutritional problems, including underweight, defined as BMI-for-age less than the fifth percentile, and overweight, defined as BMI-for-age greater than the 85th percentile (12); short stature, defined as height z scores < -2 SD of the reference standard (12); skeletal abnormalities, including low bone mineral content (BMC) and fractures; biliary tract disorders, including choleslithiasis and biliary dyskinesia; and seizures. Diagnostic procedures included videofluoroscopic swallow function, upper gastrointestinal series, upper endoscopy, gastric emptying scan, abdominal ultrasound, colonoscopy, and bone density scan. Medical interventions included H2-receptor and proton pump inhibitors, prokinetic medications, laxatives, and anticonvulsants. Nutrition interventions included the use of commercial formulas as primary or supplemental food sources, the ketogenic diet, and multivitamin and mineral or herbal supplements. Surgical
interventions included fundoplication, gastrostomy, cholecystectomy, general abdominal surgery, and vagal nerve stimulator placement. Binary logistic regression was used to determine differences in the frequency of clinical symptoms and diagnoses, diagnostic tests, and medical, nutritional, and surgical treatments between females with and without MECP2 mutations when adjusted for age group within the RTT cohort.

**RESULTS**

**Demographics**

The rate of parental response to the questionnaire was 59% (n = 983). The age distribution of the RTT cohort was: 0 to 5 years, 12%; 6 to 10 years, 22%; 11 to 14 years, 12%; 15 to 19 years, 17%; 20 to 29 years, 24%; and 30+ years, 13%. MECP2 mutational analysis was performed in 659 (67%) and a mutation was found in 573 (87%) individuals.

The mean height-, weight-, and BMI-for-age \( z \) scores for each age group with RTT decreased significantly with advancing age and were significantly lower than the reference standard (Table 1). The mean height \(-1.9 \pm 2.2 \) vs \(-1.6 \pm 1.8, P < 0.001\)) and weight \(-2.1 \pm 3.0 \) vs \(-1.8 \pm 2.3, P < 0.001\) but not BMI-for-age \(-0.9 \pm 2.3 \) vs \(-1.0 \pm 1.8\), \( z \) scores were significantly lower in female subjects with MECP2 mutations than those without, respectively. Parental perceptions of underweight, normal weight, and overweight were associated \((P < 0.001)\) with calculated BMI-for-age \( z \) scores.

**Prevalence of Symptoms, Diagnoses, Procedures, and Interventions**

Symptoms and diagnoses associated with gastrointestinal dysmotility and feeding difficulties were reported to occur in the majority of the Rett cohort (Table 2), whereas a number of other gastrointestinal and nutritional symptoms were reported in some individuals. Straining with bowel movements, passage of hard stools, or constipation and prolonged feeding time or chewing difficulty were reported in more than half of the RTT cohort, whereas biliary tract disease, including cholelithiasis and biliary dyskinesia, occurred in only a small number of affected individuals.

Of the diagnostic procedures performed for gastrointestinal and nutritional problems, videofluoroscopic swallow function studies and upper gastrointestinal series were most commonly reported, but were performed only in approximately one-third of the RTT cohort (Table 3).

Laxatives were the medications most commonly used in nearly half of the RTT cohort. Commercial formulas and multivitamin and mineral supplements were the nutrition therapies most commonly used in approximately half of affected individuals. Gastrostomy placement was the surgical intervention most frequently performed in approximately one fourth of the group.

**Effect of Age on Symptoms and Diagnoses**

To assess the effect of age on the presentation of various symptoms or diagnoses, we calculated the odds ratio (OR) of having these features by age (Table 4). Features such as vomiting or regurgitation, nighttime awakening with irritability, gastroesophageal reflux, chewing difficulty, and choking or gagging with feeding were significantly less likely to occur in older than in younger individuals. In contrast, short stature, low BMC, fractures, and gastrostomy placement were significantly more likely to be

### TABLE 1. Height-, weight-, and BMI-for-age \( z \) scores for each age group of girls and women with Rett syndrome (n = 983)*

<table>
<thead>
<tr>
<th>Age group, y</th>
<th>N</th>
<th>Height-for-age ( z ) score</th>
<th>N</th>
<th>Weight-for-age ( z ) score</th>
<th>N</th>
<th>BMI-for-age ( z ) score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>90</td>
<td>(-0.6 \pm 2.5)</td>
<td>111</td>
<td>(-0.8 \pm 2.2)</td>
<td>90</td>
<td>(-0.5 \pm 2.3)</td>
</tr>
<tr>
<td>6–10</td>
<td>172</td>
<td>(-1.6 \pm 2.2)</td>
<td>217</td>
<td>(-1.3 \pm 2.1)</td>
<td>173</td>
<td>(-0.5 \pm 2.1)</td>
</tr>
<tr>
<td>11–14</td>
<td>91</td>
<td>(-2.1 \pm 1.6)</td>
<td>112</td>
<td>(-1.9 \pm 2.0)</td>
<td>91</td>
<td>(-0.9 \pm 1.9)</td>
</tr>
<tr>
<td>15–19</td>
<td>153</td>
<td>(-2.7 \pm 2.0)</td>
<td>168</td>
<td>(-3.5 \pm 3.6)</td>
<td>152</td>
<td>(-1.2 \pm 2.3)</td>
</tr>
<tr>
<td>20–29</td>
<td>216</td>
<td>(-2.7 \pm 1.6)</td>
<td>234</td>
<td>(-3.6 \pm 3.2)</td>
<td>215</td>
<td>(-1.5 \pm 2.2)</td>
</tr>
<tr>
<td>30–40*</td>
<td>121</td>
<td>(-2.5 \pm 1.9)</td>
<td>123</td>
<td>(-3.1 \pm 3.1)</td>
<td>121</td>
<td>(-1.3 \pm 2.5)</td>
</tr>
<tr>
<td>0–40*</td>
<td>844</td>
<td>(-2.2 \pm 2.1)</td>
<td>965</td>
<td>(-2.5 \pm 3.0)</td>
<td>842</td>
<td>(-1.0 \pm 2.3)</td>
</tr>
</tbody>
</table>

* BMI = body mass index.

* Data expressed as absolute values and \( z \) scores (mean ± SD).

\(^{\dagger} P < 0.001\), difference among age groups across time.

\(^{\ddagger} P < 0.001\), difference between Rett syndrome cohort and reference standard (11).
TABLE 3. Frequency of procedures and medical, nutritional, or surgical interventions reported by parents (n = 983) of girls and women with Rett syndrome on a structured survey questionnaire

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Proportion of cohort, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures</td>
<td></td>
</tr>
<tr>
<td>Videofluoroscopic swallow function</td>
<td>39</td>
</tr>
<tr>
<td>Upper gastrointestinal series</td>
<td>30</td>
</tr>
<tr>
<td>Upper endoscopy</td>
<td>23</td>
</tr>
<tr>
<td>Gastric emptying scan</td>
<td>11</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>20</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>6</td>
</tr>
<tr>
<td>Bone density scan</td>
<td>19</td>
</tr>
<tr>
<td>Medical†</td>
<td></td>
</tr>
<tr>
<td>H₂-receptor inhibitors</td>
<td>7</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>22</td>
</tr>
<tr>
<td>Prokinetics, and laxatives</td>
<td>3</td>
</tr>
<tr>
<td>Laxatives</td>
<td>47</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>68</td>
</tr>
<tr>
<td>Nutritional</td>
<td></td>
</tr>
<tr>
<td>Commercial formulas</td>
<td>48</td>
</tr>
<tr>
<td>Primary food source</td>
<td>16</td>
</tr>
<tr>
<td>Supplemental food source</td>
<td>32</td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>7</td>
</tr>
<tr>
<td>Multivitamin/mineral supplement</td>
<td>55</td>
</tr>
<tr>
<td>Herbal supplement</td>
<td>19</td>
</tr>
<tr>
<td>Surgical</td>
<td></td>
</tr>
<tr>
<td>Fundoplication</td>
<td>11</td>
</tr>
<tr>
<td>Gastrostomy</td>
<td>28</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>3</td>
</tr>
<tr>
<td>General abdominal surgery</td>
<td>5</td>
</tr>
<tr>
<td>Vagal nerve stimulator placement</td>
<td>5</td>
</tr>
</tbody>
</table>

*Medical therapies, including H₂-receptors, proton pump inhibitors, prokinetics, and laxatives, derived from the Rate Disease Clinical Research Network for Rett syndrome database (n = 647).

Feeding problems were reported frequently in the present study, although the prevalence varies across studies (7,8,15). Parents describe their daughters as having excellent appetites, but girls and women with RTT have greater difficulty eating solid foods than drinking thickened liquids because chewing difficulty prevails over swallowing dysfunction (8,15,16). Bruxism, involuntary tongue movements, and ineffective mastication contribute to prolonged feeding time (17,18). Hypersalivation and hyperventilation may interfere with eating (16–18). Videofluoroscopy demonstrates universal delay in time between spoon feeding and swallowing solid food because of oropharyngeal dysfunction (7,18,19). The correlation between the delay in time to first swallow and advancing age implies a gradual deterioration of oromotor function, although parental perception in the present study did not corroborate this finding (18,20).

Short stature and altered body composition characterize the natural history of growth disturbances in RTT (3,6). In the present study, the pattern of height-for-age and weight-for-height deficits was consistent with that previously reported (3,8). A small proportion demonstrated weight-for-height excess, similar to the prevalence of overweight in children with ASD (14). Weight deficits in RTT have been attributed to alterations in energy balance (21). In the present study, supplemental formula use and a feeding gastrostomy supported the nutritional needs of these individuals, presumably preventing a decline in their BMI-for-age (22). Although undernutrition may be causally related to linear growth deficits, the difference in height z scores between individuals with and without MECP2 mutations in the present study underscores a genetic basis, in part, for growth failure in RTT (22).

Altered bone health, characterized as reduced bone mass, bone mineral deficits, and increased fracture rate, typifies RTT across a broad spectrum of MECP2 mutations (6,24–29). The prevalence of low BMC and bone mineral density reported in previous studies is higher than that found in the present study, presumably because of infrequent testing outside the research setting. Altered bone health is of concern because low bone mineral density is associated with increased fracture risk in RTT (6,24,29). The prevalence of fractures in the present study is similar to that observed in most other RTT cohorts (6,24,25,29–31) and is estimated to be 3- to 4-fold higher than in healthy children (6,30,31).

Despite the increased prevalence of gastrointestinal and nutritional complaints, diagnostic procedures were performed less frequently throughout life in girls and women with RTT. In the present study, the majority of parents of a large RTT cohort reported ≥1 symptoms or diagnoses associated with gastrointestinal dysmotility and feeding difficulties in their affected daughters. Gastroesophageal symptoms and diagnoses were less likely to persist, whereas short stature and attention to bone health and alternative feeding methods were more likely to be present, with advanced age. Diagnostic evaluations and therapeutic interventions were used less frequently than the occurrence of reported symptoms or diagnoses. Increased physician and health care provider awareness of the gastrointestinal and nutritional manifestations of RTT, as well as the changing course of these problems as affected individuals grow older, may reduce the burden of care and improve the quality of life of girls and women affected with this disorder.

The gastrointestinal manifestations of RTT in the present study were protean and mirrored those reported by parents of children with other neurodevelopmental conditions such as autism spectrum disorders (ASD) (13,14); however, the prevalence of lower gastrointestinal symptoms such as constipation was 2- to 9-fold more frequent, and upper gastrointestinal symptoms were 1.2 to 2.5 times more frequent in the RTT cohort than in children with ASD (13,14). As in ASD, gastroesophageal reflux and biliary tract disease may present with nongastrointestinal symptoms such as nighttime awakening and unexplained irritability (14).

The prevalence of fractures in the present study is similar to that reported in previous studies (6,24–29). The prevalence of fractures in the present study is similar to that reported in previous studies (6,24–29). Bone mineral deficits, and increased fracture rate, typifies RTT across a broad spectrum of MECP2 mutations (6,24–29). The prevalence of low BMC and bone mineral density reported in previous studies is higher than that found in the present study, presumably because of infrequent testing outside the research setting. Altered bone health is of concern because low bone mineral density is associated with increased fracture risk in RTT (6,24,29). The prevalence of fractures in the present study is similar to that observed in most other RTT cohorts (6,24,25,29–31) and is estimated to be 3- to 4-fold higher than in healthy children (6,30,31).

Despite the increased prevalence of gastrointestinal and nutritional complaints, diagnostic procedures were performed less frequently throughout life in girls and women with RTT.
often and medications and nutrition supplements were administered less frequently than the occurrence of symptoms or diagnoses. Videofluoroscopic swallow function studies were performed in only 48% of individuals with feeding difficulties, and upper gastrointestinal series, upper endoscopy, and gastric emptying scans were obtained in 59% to 79% of individuals reported to have gastroesophageal diagnoses. We previously documented that the scope and severity of some gastrointestinal problems may become apparent only when diagnostic studies are performed (7). In contrast, the 7-fold increase in abdominal ultrasounds reflects early screening for unexplained irritability or apparent abdominal pain because of reported adverse outcomes when the diagnosis of

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Age group, y</th>
<th>P</th>
<th>Odds ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting or regurgitation</td>
<td>656</td>
<td>6–10</td>
<td>ns</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11–14</td>
<td>ns</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15–19</td>
<td>0.01</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20–29</td>
<td>0.01</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–40+</td>
<td>0.06</td>
<td>0.30</td>
</tr>
<tr>
<td>Nighttime awakening with irritability</td>
<td>660</td>
<td>6–10</td>
<td>ns</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
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<td>0.03</td>
<td>0.43</td>
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<td></td>
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<td>0.36</td>
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<td></td>
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<td>0.01</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–40+</td>
<td>ns</td>
<td>—</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>571</td>
<td>6–10</td>
<td>ns</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11–14</td>
<td>0.01</td>
<td>0.39</td>
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<td></td>
<td></td>
<td>30–40+</td>
<td>ns</td>
<td>—</td>
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<tr>
<td>Chewing difficulty</td>
<td>650</td>
<td>6–10</td>
<td>ns</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11–14</td>
<td>ns</td>
<td>—</td>
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<td>15–19</td>
<td>0.01</td>
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<td></td>
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<td>0.42</td>
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<tr>
<td></td>
<td></td>
<td>30–40+</td>
<td>ns</td>
<td>—</td>
</tr>
<tr>
<td>Choking or gagging with feeding</td>
<td>657</td>
<td>6–10</td>
<td>0.01</td>
<td>0.54</td>
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<tr>
<td></td>
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<td>11–14</td>
<td>0.001</td>
<td>0.31</td>
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<td>15–19</td>
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<td></td>
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<td>20–29</td>
<td>0.02</td>
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<td>30–40+</td>
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<td>0.15</td>
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<td>Short stature</td>
<td>555</td>
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<td></td>
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<td>11–14</td>
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</tr>
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<td></td>
<td></td>
<td>30–40+</td>
<td>0.001</td>
<td>5.96</td>
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<td>Low bone mineral content</td>
<td>377</td>
<td>6–10</td>
<td>0.01</td>
<td>15.4</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>0.001</td>
<td>30.4</td>
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<tr>
<td></td>
<td></td>
<td>15–19</td>
<td>0.001</td>
<td>36.3</td>
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<td></td>
<td></td>
<td>20–29</td>
<td>0.001</td>
<td>67.5</td>
</tr>
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<td></td>
<td></td>
<td>30–40+</td>
<td>0.001</td>
<td>140.3</td>
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<tr>
<td>Bone fracture</td>
<td>647</td>
<td>6–10</td>
<td>0.001</td>
<td>4.28</td>
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<tr>
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<td></td>
<td>11–14</td>
<td>0.001</td>
<td>5.83</td>
</tr>
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<td></td>
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<td>0.001</td>
<td>10.95</td>
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<tr>
<td></td>
<td></td>
<td>30–40+</td>
<td>0.001</td>
<td>13.06</td>
</tr>
<tr>
<td>Seizures presently</td>
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<td>0.001</td>
<td>2.41</td>
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<td>3.63</td>
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</tr>
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</tr>
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<td>30–40+</td>
<td>ns</td>
<td>—</td>
</tr>
<tr>
<td>Gastrostomy placement</td>
<td>658</td>
<td>6–10</td>
<td>0.001</td>
<td>2.96</td>
</tr>
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<tr>
<td></td>
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<td>30–40+</td>
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<td>—</td>
</tr>
</tbody>
</table>

NS, not significant.
* Odds ratio for each age group relative to the youngest age group, 0–5 years.
cholelithiasis is delayed. We estimated that proton pump inhibitors, prokinetic medications, and laxatives were used by only 56%, 21%, and 59% of individuals affected with gastroesophageal reflux, gastroparesis, or constipation, respectively, and formulas and multivitamins were administered to 59% and 68%, respectively, of individuals affected with oropharyngeal dysfunction. Whether the use of medications and nutrition supplements was not attempted or was ineffective and abandoned is unknown.

Physician visits represent the largest component of health care use for most clinical conditions. Gastroesophageal reflux and functional bowel disorders comprise the highest number of physician visits annually in the ambulatory care setting and 2 of the 5 diagnoses with the largest outpatient physician charges (32,33). Proton pump inhibitors represent 77% of total cost for medications in the United States (32,33). The burden of gastrointestinal disease on the quality of life of patients is substantial, with functional disorders such as reflux and irritable bowel imposing a high level of disruption to individuals’ lives (34). Although we did not provide a formal estimate, we assume that the physical, psychological, and economic burden of gastrointestinal disease in Rett is substantial based on the type and magnitude of gastrointestinal symptoms and diagnoses reported.

The limitations of our study included a partial response rate of 59%, which may result in selection bias, as well as the absence of an unaffected control group with which to compare prevalence, duration, and severity of symptoms. We were unable to perform phenotype-genotype comparisons because specific Rett mutations were not obtained. The natural history study of Rett in progress will afford this opportunity in the future. In addition, the symptoms and diagnoses that we reported were based on parental perceptions rather than on direct physician evaluation or review of medical records. Nevertheless, we found good agreement between parental perceptions of nutritional status and estimates of BMI, an observation that supports the reliability of parental reporting. Our list of symptoms and diagnoses was not all-inclusive in that complaints such as aerophagia and abdominal distention pose significant management issues in some individuals with Rett (35). Aerophagia, in conjunction with abnormal breathing patterns (36), contributes to gastric dilatation and perforation (9,10,37), findings that may be causally related to morbidity and mortality in individuals with mental and physical disabilities (38,39). In our experience, gastric and intestinal perforations in females with Rett have been found alone or in conjunction with volvulus and intussusception. These entities concern us because they may occur more frequently and with fewer signs and symptoms in cognitively impaired individuals, particularly in the setting of chronic constipation and megalocolon (40).

CONCLUSIONS

Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett and pose a significant medical burden to their caregivers. Physician and health care professional awareness of these problems may improve the health and quality of life of girls and women affected with Rett.

Acknowledgments: The authors thank the administrative staff of the IRSF for their support in processing the survey forms; the families of girls and women with Rett for their participation in completing the survey; J. Kennard Fraley for providing z score values; E. O’Brien Smith, PhD, for statistical consultation; Jeffrey P. Kirsches, PhD, professor and division chief, Data and Technology Coordinating Center, University of South Florida, for providing data analysis support; and Mary Lou Oster-Granite, PhD, who provided invaluable guidance, support, and encouragement for this rare disease initiative.

REFERENCES

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Sleepiness and Sleep Disordered Breathing in Prader-Willi Syndrome: Relationship to Genotype, Growth Hormone Therapy, and Body Composition

Korwyn Williams, M.D., Ph.D.1; Ann Scheimann, M.D., M.B.A.1,2; Vernon Sutton, M.D.4; Elizabeth Hayslett, R.N.2; Daniel G. Glaze, M.D.5

1Division of Neurology, Phoenix Children’s Hospital, Phoenix, AZ; 2Division of Gastroenterology and Nutrition, Department of Pediatrics, Johns Hopkins University, Baltimore, MD; 3Division of Pediatric Gastroenterology and Nutrition, Texas Children’s Hospital, Houston, TX; 4Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX; 5Division of Pediatric Neurology, Department of Pediatrics, Division of Neurophysiology, Department of Neurology, Baylor College of Medicine, Houston, TX

Study Objectives: Patients with Prader-Willi syndrome (PWS) suffer from excessive sleepiness and sleep disordered breathing (SDB). We reviewed the polysomnograms (PSGs) and multiple sleep latency tests (MSLTs) in a cohort of PWS patients to determine the relationship of BMIz scores, daytime sleepiness, growth hormone (GH) treatments, and SDB.

Methods: Attended overnight PSGs were performed for PWS patients referred for concern for SDB between January 2000 and January 2005. Age at time of study, genotype, use and dose of GH, sleepiness scale, normalized body-mass index (BMIz), total sleep time, latency to stage I and REM sleep, sleep stage percentages, apnea-hypopnea index (AHI), central apnea (CA) frequency, oxygen saturation nadir, maximum carbon dioxide tension, periodic limb movement index, presence of snoring, normality of EEG, and, in several patients, mean sleep latency testing were determined.

Results: All patients exhibited some form of SDB. There was a positive correlation between the BMIz and AHI. The BMIz was significantly different between GH–treated and –untreated groups, but there was not a significant difference between AHI, CA, oxygen nadir, or maximum carbon dioxide tension of the GH–treated and –untreated groups. There was no significant correlation between the MSLT and the sleepiness score or AHI. There was also no significant difference between the AHIs of patients with different genetic defects.

Conclusions: There should be a low threshold for obtaining PSG to evaluate SDB, but the type and severity of SDB were not predictable based on a sleepiness scale score, BMIz, or underlying genetic defect.

Keywords: Prader-Willi syndrome; breathing, sleep-disordered; polysomnography; obstructive sleep apnea; snoring; growth hormone

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Prader-Willi syndrome (PWS) is an uncommon syndrome whose diagnosis is based on clinical criteria and confirmed by genetic studies demonstrating a functional loss of paternally expressed genes (i.e., deletion of paternal DNA, maternal uniparental disomy [UPD], or imprinting) from chromosomal region 15q11-13.1 The clinical criteria include major criteria such as hypotonia, initial poor feeding and later childhood-onset obesity, a global developmental disorder, hypogonadism, and characteristic facial features; minor criteria include behavior disturbances and such features as small hands.2 Some of these features are thought to be related to an underlying hypothalamic dysfunction.3

Sleep disturbance and apnea are also minor criteria in the diagnosis of PWS. A retrospective chart review of the frequency of the major and minor criteria in genetically confirmed cases of PWS revealed that 76% of these patients had abnormal sleep.2 Given their childhood obesity, these patients are at risk for obstructive sleep apnea; however, polysomnographic (PSG) studies have demonstrated other sleep disturbances, such as blunted peripheral sensitivity to carbon dioxide and paradoxical responses to hypoxemia.4-10

PWS is a multisystem disorder, requiring multidisciplinary management and treatment. One mainstay of the management is growth hormone (GH) supplementation because of its proven benefits on reduction of adipose tissue, increase in lean body mass, and taller final height.11-14 GH replacement may have other indirect, beneficial effects as well. Haqq and colleagues noted changes in overall pulmonary function (e.g., increase in peak flow, increased vital capacity, trends towards decreased numbers of apneic/hypopneic events) with weekly injections.15 More ominously, however, several case reports have questioned whether a link exists between GH therapy and subsequent fatal sleep apnea.16-18

The role, if any, of GH in improving sleep disturbances is unclear, especially since sleep apnea due to obesity is not the only sleep abnormality. We report the PSG findings of a retrospective cohort of PWS patients, some of whom have been treated with daily GH supplementation. In addition, we assessed the

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Address correspondence to: Korwyn Williams, MD, PhD, Division of Neurology, 1919 E. Thomas Rd., Phoenix, AZ 85016; Tel: (602) 546-0970; Fax: (602) 546-0469; E-mail: kwilliams@phoenixchildrens.com

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prevalence of SDB in this cohort, the relationship between SDB and readily available clinical measures, and the difference in the prevalence of SDB between GH–treated and GH–untreated groups.

METHODS

Selection Criteria

This retrospective study was approved by the Baylor College of Medicine Affiliated Institutional Review Board and performed at 15m above sea level. The patient cohort was identified from patients followed by one of the authors (AS) at Texas Children’s Hospital PWS Clinic and from review of PSG records by the medical director (DG) of TCH Children’s Sleep Center. Only patients who had their initial PSG during the study period of January 2000 through January 2005 were included in the cohort. Patients were referred for PSG if there was any concern for SDB. Patients were prescribed GH replacement based on the following criteria: confirmation of genetic diagnosis of Prader–Willi syndrome and either evidence of growth failure or documentation of GH deficiency by provocative testing (prior to FDA approval of GH treatment in June 2000).

Genetic Testing

The molecular basis of PWS was established for all patients in the study. A variety of commercial labs that are both CAP- and CLIA-certified performed methylation studies, fluorescence in situ hybridization (FISH) studies, testing for uniparental disomy and sequencing of the 15q11.2 imprinting center. For those found to have a deletion by FISH, no further molecular testing was performed. When the first test performed was DNA methylation study of the PWS region, subsequent FISH analysis was performed. In families where recurrence risk was a concern, analysis for uniparental disomy was performed. In those with abnormal methylation studies, no deletion by FISH and biparental inheritance of 15q11.2, the PWS/AS imprinting center was sequenced.

PSG Evaluation

A sleepiness score was determined from a modified Epworth Sleepiness Scale (see appendix) and was completed by a proxy (parent) for each patient. Score range is 0-24 (score >10 suggests a tendency for daytime sleepiness in adults). All patients underwent overnight PSG of at least 8 hours duration. The patients were put to bed at their usual bedtimes. No hypnotic was given.

MSLT studies consisted of 5 nap sessions, beginning 2 hours after getting out of bed in the morning; nap sessions were at least 20 minutes and were timed two hours apart. These studies were completed in the sleep laboratory of the TCH Children's Sleep Center.

The following parameters were recorded using a MedCare Rembrandt digital system and software: 6 channels electroencephalography (EEG); eye movements; chin electromyography; airflow (nasal pressure transducer; oral thermocouple); respiratory effort (chest and abdominal piezo-strain gauges); oxygen saturation (pulse oximeter with recording of pulse waveform to verify values); end-tidal carbon dioxide (ETCO₂) levels (nasal catheter), but not percentage of total sleep time or occurrence during which stage of sleep; electrocardiogram (one channel); extremity movement (accelerometers); observations by sleep technologist in constant attendance; and time-synchronized video recording for characterization of behaviors. Respiratory monitors were not used during MSLT. Scoring of the sleep studies, MSLT, and EEG were interpreted by a board-certified sleep medicine physician (DG); computerized scoring was not utilized. Sleep staging was scored using standard methodology.¹⁹ Total sleep time and sleep efficiency were calculated based on the time from lights out to lights on during the overnight study. Sleep latency was calculated by the first epoch of any stage of sleep. Minimum oxygen saturation values and maximum ETCO₂ values were recorded. All obstructive apnea events (respiratory effort and no airflow for the duration of two or more breaths) and obstructive hypopnea events (two or more breaths’ duration with 30% decrease in airflow by nasal pressure transducer and ≥ 3% drop of oxygen saturation values from baseline oxygen saturation values) were scored. Central apneic events (no respiratory effort and no airflow ≥ 20 sec, or shorter events with ≥ 3% drop in oxygen saturation values from baseline values) were scored. For obstructive respiratory events and central apneic events, an index (number per hour of sleep) was calculated. Periodic limb movements (PLMs) were scored according to the American Academy of Sleep Medicine guidelines, and significant values were considered to be ≥ 5 PLMs per hour of sleep.²⁰

An MSLT was not obtained if: AHI was > 30; AHI was ≥ 20 and oxygen saturation fell below 75% (in which case a split-night study was performed); the patient required admission to the hospital for severe OSA; or if the patient was unable or unwilling to stay. The latency to any REM episode, the mean sleep latency to the first 30 second epoch and stage of sleep, the latency to any REM episode, and number of sleep-onset REM episodes were recorded.

PSG parameters were recorded into a spreadsheet for further analysis (Microsoft Excel 2003, Redmond, WA), including: sleep duration, REM and NREM sleep latency, sleep architecture, apnea/hypopnea or respiratory distress index, frequency of central apneas, arousal index, oxygen saturation nadir, peak ETCO₂ level, periodic limb movements, presence of snoring, MSLT findings, and visual analysis of the electroencephalogram.

Normalized Body Mass Indices (BMI)

Normalized body mass indices corrected for age, sex, and ethnicity (BMI) were obtained using the BMI z-score calculator from the body composition lab at the Children’s Nutrition Research Center (Shyapalo RJ, Carter J [2005] Children’s BMI-percentile-for-age Calculator. Retrieved 1/27/2006 from the Baylor College of Medicine, Children’s Nutrition Research Center website: www.kidsnutrition.org/bodycomp/bmi2z.html) and were obtained within 6 months of the PSG, so that patients of different ages could be compared; for children less than 2 years of age, the BMI was determined using weight-height measurements.
Statistical Analysis

All statistical analyses were performed using Microsoft Excel 2003 (Redmond, WA) and Prism 4 for Windows (Graphpad Software, San Diego, CA) with $p < 0.05$ considered significant.

RESULTS

Thirty-seven patients met the inclusion criteria for this review; the population data are detailed in Table 1. The average age was 9 years (standard deviation [SD] 6 yr; range 15 mo–24 yr). Fifty-four percent of the patients were male. Several genetic defects have been described for PWS; the frequency of these defects in this cohort were roughly similar to published prevalences: 59% with a deletion; 32% with maternal UPD; and 8% with imprinting.\(^2\) The mean BMI\(_s\) was 1.9 (SD 1.4), a value highly correlated with the percent body fat in this cohort (Spearman correlation coefficient $r^2 = 0.36$, $p < 0.001$).

Selected PSG data are described in Table 2 (apnea-hypopnea index, central apnea index, oxygen saturation nadir, peak ETCO\(_2\) tension, multiple sleep latency). Other data are not shown but are available, including weight, lean body mass, and fat percentage, arousal index, and normality of EEG.

Of note (data not shown): mean total sleep time was 408 min (SD 142); sleep efficiency was 85% (SD 12); sleep latency was 17 minutes (SD 16); REM latency was 84 minutes (SD 57); percentage of total sleep time in stage 1, 2, slow wave, and REM sleep was 12%, 40%, 26%, and 21%, respectively; arousal index was 12/h (SD 9). These findings are in keeping with published normative data.\(^21\) Six percent of the electroencephalograms (2/31) were considered abnormal. The patients’ families completed a sleepiness scale to assess subjective daytime sleepiness: a score above 10 (16 of 30 completed questionnaires) is considered to signify a tendency for daytime sleepiness in adults. Fifty-four percent (20/37) of the patients underwent a MSLT during the daytime following their overnight study. Twenty-two percent (8/37) of the patients underwent split-night studies with continuous positive pressure titration.

Some form of SDB (as defined by: snoring, greater than one obstructive apnea or central apnea per hour, ETCO\(_2\) tension, multiple sleep latency) was observed in all 37 patients (see Table 3).\(^21\) The most common SDB abnormality (86% of patients) was oxygen desaturation to less than 93%; of those, the mean desaturation was 78%. The next most common abnormality (70%) was elevated AHI; of those, the mean AHI was 20/h and the median was 8. Twenty-three patients (62%) exhibited hypercarbia; of those the mean ETCO\(_2\) was 62 mm Hg. Five patients had only one abnormality, 8 exhibited two abnormalities, 17 exhibited three abnormalities, and 7 exhibited four abnormalities. Half of the patients (17/33) snored. Notably, three patients (patients 25, 31, and 33) who had undergone tonsillectomy/adenoidectomy before the study and were found to have significant PLMs (38/h of sleep); all others had <5 PLM/h of sleep.

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<th>Male (%)</th>
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<th>Receiving growth hormone</th>
<th>Dose, mg/kg/wk (SD)</th>
<th>Sleepiness score (SD)</th>
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Sixteen patients in the cohort were receiving daily GH injections at the time of their initial PSG (mean dose = 0.22 mg/kg/week) and had been treated for an average of 4.8 years (range 1.5–12 years). There was no significant difference in age (106 ± 52 months treated, 111 ± 82 months untreated, $p = 0.8$) between groups. Sixty-two percent of the untreated group were male compared with 44% of the treated group (Fisher exact test, $p = 0.33$). The mean BMI\(_s\) scores (1.4 and 2.5 for the treated and untreated groups, respectively) were significantly different (unpaired $t$-test, $p = 0.005$). However, there were no statistically significant differences of the AHI, central apnea, oxygen nadir, or maximum ETCO\(_2\) between the treated and untreated groups (Table 4). In the entire cohort, there was a positive correlation between the AHI and BMI\(_s\) (Pearson correlation coefficient $r^2 = 0.16$, $p = 0.01$). None of these patients receiving GH, followed between 1.5 and 12 years, has died (AS, personal communication).

Additionally, 20 patients underwent an MSLT, an objective measure of daytime sleepiness. Five of the 20 MSLTs were consistent with narcolepsy and were characterized by 2 or more sleep-onset REM episodes and an average MSLT latency of 5.9 minutes. Cataplexy was not reported or recorded in any patient. There was no correlation between the sleepiness scale score and average MSLT sleep latency (Spearman correlation coefficient $r^2 = 0.03$, $p = 0.48$); AHI and MSLT sleep latency ($r^2 = 0.008$, $p = 0.72$); or the BMI\(_s\) and MSLT sleep latency ($r^2 = 0.004$, $p = 0.80$).

Lastly, we considered whether the type of underlying genetic abnormality (e.g., deletion) was associated with sleep disordered breathing. We therefore compared the AHI with the underlying genetic abnormality (i.e., deletion, uniparental disomy, or imprinting), but found no significant difference between the groups (one-way ANOVA, $F = 0.32$, $p = 0.72$; Table 4).

DISCUSSION

PWS is a syndrome with an estimated incidence of 1:10,000–25,000 births marked by neonatal hypotonia, mental retardation, and evidence of hypothalamic dysfunction (e.g., infertility, childhood obesity).\(^1,22\) Although SDB is a minor criterion for the diagnosis, several series have found a high prevalence of SDB in these patients.\(^22,24,25\)

From a PWS population study from England, 20% of pediatric and adult patients reported sleep disturbances.\(^26\) In small
Others have posited a central cause for sleep disturbances. One study reported low cerebrospinal fluid hypocretin levels in 4 patients with PWS without a history of narcolepsy/cataplexy relative to 10 controls and postulated that daytime sleepiness may be due in part to hypothalamic dysfunction; hypocretin is synthesized in the hypothalamus, promotes wakefulness, and suppresses REM sleep.

Other authors have reported blunted responses to hypoxia or hypercapnia and paradoxical responses to hypoxia in non-obese PWS patients. In our series, the most common PSG abnormality was oxy- gen desaturation, followed by elevated AHIs, hypoventilation, snoring, and elevated central apneas. However, PSG abnormalities do not fully explain sleep disturbances. Patients with three or even four PSG abnormalities did not necessarily have abnormally short multiple sleep latencies, an objective measure of daytime sleepiness. Patients who had undergone tonsillectomy and adenoidectomy still had elevated AHI, oxygen desaturations, and/or hypventilation. A third of the patients also had

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GH, growth hormone; SS, sleepiness score; $BMI_z$, normalized body mass index; del, deletion; UPD, uniparental disomy; impr, imprinting; AHI, apnea-hypopnea index; ETCO$_2$, end tidal carbon dioxide.

*snorers; **patient on 0.5 L/m supplemental oxygen; ***split-night study patient; +status post tonsillectomy/adenoidectomy; 0 bilevel positive airway pressure 6/3 cm H$_2$O

The basis of the sleep abnormalities is controversial. Given the obesity associated with this syndrome, many have postulated obstructive sleep apnea as the basis. Apneas and oxygen desaturations have been found in some series to be the predominant PSG abnormality, and one study suggested a correlation between the BMI, apneas, and oxygen desaturation. In our series, the most common PSG abnormality was oxygen desaturation, followed by elevated AHIs, hypventilation, snoring, and elevated central apneas. However, PSG abnormalities do not fully explain sleep disturbances. Patients with three or even four PSG abnormalities did not necessarily have abnormally short multiple sleep latencies, an objective measure of daytime sleepiness. Patients who had undergone tonsillectomy and adenoidectomy still had elevated AHI, oxygen desaturations, and/or hypventilation. A third of the patients also had...
evidence of central apnea. These data do not allow differentiation between the various proposed pathophysiological bases for the sleep disturbances (i.e., tonsillar hypertrophy and obesity, neurohormonal abnormalities, or blunted central chemoreceptors), but do not exclude any either. Approximately half of the 37 patients were receiving GH supplementation at the time of the initial PSG. One impetus for this study was publication of several case reports suggesting a link between initiation of GH supplementation and death two to six months later, raising the question of differences in PSG findings between the two groups.16-18 This study did not identify differences in PSG parameters between the two groups, and there have been no deaths in the cohort.

Several studies have demonstrated the benefit of GH supplementation, and none of these larger series have reported any deaths in their patient series.11-14,32 Eiholzer and colleagues mentioned in their case report that the patient who died following initiation of GH supplementation had a lifelong history of pulmonary problems. The remaining case reports made note of other underlying physiological abnormalities (e.g., increased pulmonary artery pressure, tonsillar and/or adenoidal hypertrophy, sleep apnea) following initiation of GH supplementation; given the small numbers and comorbidities, it would be difficult to ascribe the deaths solely to the hormonal supplementation.17,18

Studies of a small series of PWS patients not receiving GH supplementation reported deaths from the neonatal period to adulthood. Although while many of the causes of death were not well characterized, hypoventilation, upper respiratory tract infections, fever and/or gastroenteritis were thought to play a role in the pediatric deaths; other studies have also associated respiratory infections and/or high fever with sudden death in PWS.23,33,34

GH supplementation has several benefits for this patient population: increased final height, less adipose tissue, and increased lean muscle mass. In keeping with these findings, GH–supplemented patients in this cohort had significantly smaller BMI compared with untreated patients. There were no statistically

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SE, sleep efficiency; SL, sleep latency (to stage 1), MSLT, multiple sleep latency test
'split-night study patient;' status post tonsillectomy/adenoidectomy; ‘bilevel positive airway pressure 6/3 cm H2O

Table 2b—Sleepiness Scale Scores, Treatment Status, Weight, Genetic Abnormality, and Polysomnographic Data
significant differences between AHI, central apnea, oxygen nadir, or maximum ETCO$_2$ between the 2 groups, suggesting that GH does not directly affect these parameters. There was a correlation between the BMI$_{IGH}$ and AHI, in keeping with results from small case series demonstrating a reduction in obstructive apneas/hypopneas with weight loss. As noted above, this finding was not statistically significant, which could represent an underpowered sample. An alternative interpretation might be predictive of underlying SDB. Our cohort did not yield evidence for a correlation, echoing the findings of a relatively small number of patients were reviewed, although the rarity of this syndrome makes larger studies uncommon. The primary limitation of this study is its retrospective nature, as well as the multiple comparisons increasing the risk of type I statistical error. However, much of the statistically significant differences were in line with findings from other small series of these patients. Most of the comparisons were not significant, which could represent an underpowered sample. Another limitation of this study was the lack of serial PSGs identifying changes in SDB with therapy. Due to its retrospective nature, very few of the patients had serial studies, and not all were treated with GH therapy. Future larger, prospective, formalized studies could better define the incidence of SDB even in patients not suspected of SDB, the severity of SDB, and as importantly the benefits of clinical intervention.

We also considered whether the underlying genetic abnormality might affect SDB. Some reports have mentioned certain facial features more commonly associated with certain genetic abnormalities, and there are reports of differences in intelligence and risk for psychosis depending on the genetic subtype. As mentioned earlier, all patients exhibited some form of SDB (a finding in agreement with other studies suggesting a high prevalence of SDB in this population), so that the underlying genetic abnormality did not appear to affect this phenomenon. We considered whether the genetic abnormality might correlate with one particular aspect of SDB (i.e., AHI), but our cohort did not yield evidence for a correlation, echoing the findings of a small case series.

The physiologic benefits of GH supplementation have already been demonstrated. This study was undertaken to identify markers (BMI$_{IGH}$, genetic abnormality, and/or questionnaires) which might be predictive of underlying SDB. Our cohort did not yield evidence for markers with good predictive ability for SDB. However, a larger BMI$_{IGH}$ is correlated with a higher AHI. While both GH–treated and –untreated patients exhibited SDB, this does not necessarily imply that GH supplementation does not have a positive effect on SDB. This retrospective study did not follow most of these patients with serial studies to document any individual changes with therapy.

In summary, these findings underscore the importance of having a low threshold for obtaining PSG in PWS, when there is a suspicion of SDB—e.g., snoring, apnea, headaches, or worsening behavior problems. It was particularly worrisome that there were no clues to the severity of the SDB before PSG evaluations—some cases were abnormal enough to warrant immediate hospital admission for urgent pulmonary medicine consultation.

A relatively small number of patients were reviewed, although the rarity of this syndrome makes larger studies uncommon. The primary limitation of this study is its retrospective nature, as well as the multiple comparisons increasing the risk of type I statistical error. However, much of the statistically significant differences were in line with findings from other small series of these patients. Most of the comparisons were not significant, which could represent an underpowered sample. Another limitation of this study was the lack of serial PSGs identifying changes in SDB with therapy. Due to its retrospective nature, very few of the patients had serial studies, and not all were treated with GH therapy. Future larger, prospective, formalized studies could better define the incidence of SDB even in patients not suspected of SDB, the severity of SDB, and as importantly the benefits of clinical intervention.

**ABBREVIATIONS**

<table>
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<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>AHI</td>
<td>apnea-hypopnea index</td>
</tr>
<tr>
<td>BMI$_{IGH}$</td>
<td>normalized body mass index</td>
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<tr>
<td>EEG</td>
<td>electroencephalogram</td>
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<tr>
<td>FISH</td>
<td>fluorescence in situ hybridization</td>
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<tr>
<td>MSLT</td>
<td>multiple sleep latency test</td>
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<td>PLM</td>
<td>periodic limb movements</td>
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**Table 3**—Polysomnographic Evidence of Sleep Disordered Breathing

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<th>Criterion</th>
<th>Entire Cohort</th>
<th>Abnormal PSG criterion</th>
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<td>Mean AHI</td>
<td>17 (n = 37)</td>
<td>20 (n = 30)</td>
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<td>Central apnea</td>
<td>1.7 (n = 37)</td>
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<td>Minimum O$_2$ saturation</td>
<td>79 (n = 37)</td>
<td>77 (n = 32)</td>
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<tr>
<td>Maximum ETCO$_2$</td>
<td>56 (n = 37)</td>
<td>61 (n = 23)</td>
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<tr>
<td>MSLT latency</td>
<td>9 (n = 20)</td>
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AHI, apnea-hypopnea index; ETCO$_2$, end-tidal carbon dioxide; MSLT, multiple sleep latency test

---

**Table 4**—Comparisons between Polysomnographic and Clinical Data

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<th>Comparison</th>
<th>p-value</th>
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<td>BMI$_{IGH}$: GH–treated vs –untreated</td>
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<tr>
<td>AHI: GH–treated vs untreated</td>
<td>p=0.6*</td>
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<td>CA: GH–treated vs untreated</td>
<td>p=0.2*</td>
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<td>Oxygen nadir: GH–treated vs untreated</td>
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<td>Maximum CO$_2$: GH–treated vs untreated</td>
<td>p=0.4*</td>
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<tr>
<td>SS vs MSLT latency</td>
<td>p=0.5*</td>
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<td>AHI vs MSLT latency</td>
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<td>BMI$_{IGH}$ vs MSLT latency</td>
<td>p=0.8*</td>
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<tr>
<td>AHI: del vs UPD vs impr</td>
<td>p=0.7*</td>
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</table>

*p-statistically significant differences are in bold

---

As mentioned earlier, all patients exhibited some form of SDB (a finding in agreement with other studies suggesting a high prevalence of SDB in this population), so that the underlying genetic abnormality did not appear to affect this phenomenon.
### REFERENCES


29. Vgontzas AN, Kales A, Seip J, et al. Relationship of sleep ab-


### Appendix—Sleepiness Scale (age >4 years)

How likely is the child to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to the usual way of life in recent times. Even if the child has not done some of these things recently, try to work out how they would have affected him (or her). Use the following scale to choose the **most appropriate number** for each situation:

- 0 = would never doze
- 1 = slight chance of dozing
- 2 = moderate chance of dozing
- 3 = high chance of dozing

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<td>Watching TV</td>
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<td>Sitting, inactive in a public place (e.g., a theater)</td>
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<tr>
<td>As a passenger in a car</td>
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<tr>
<td>Lying down to rest in the afternoon</td>
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<tr>
<td>Sitting and talking to someone</td>
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<tr>
<td>Sitting quietly after a lunch</td>
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<tr>
<td>During class at school</td>
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