PROTOCOLS

Prader-Willi syndrome

Principal investigator

Glenn B. Berall, BSc, MD, FRCPC

Chief of Paediatrics, North York General Hospital, 4001 Leslie St., Toronto, ON M2K 1E1; tel.: 416-756-6222; fax: 416-756-6853; e-mail: gberall@nygh.on.ca

Co-investigators

Judith Allanson, MD, FRCP, FCCMG, DABMG, Chief, Department of Genetics, Children's Hospital of Eastern Ontario

Maria Virginia Desantadina, MD, Paediatrician, Research Fellow, Department of Nutritional Sciences, University of Toronto, The Hospital for Sick Children.

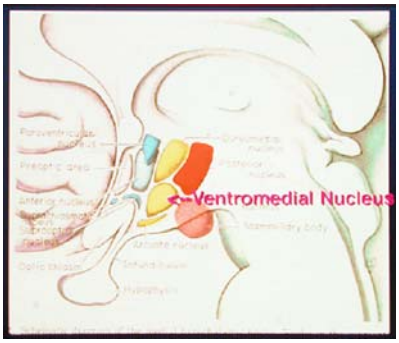
Consultant

Nita Goldband, Executive Director, Ontario Prader-Willi Syndrome Association

Background

Prader-Willi syndrome (PWS) is a rare genetic disorder with a hypothalamic dysfunction that leads to hyperphagia and obesity and has secondary consequences of diabetes, heart disease, stroke and sleep apnea, and to behavioral and psychiatric comorbidity. As information on the frequency of PWS is not currently well documented in Canada, incidence is estimated to be between 1/10,000 and 1/15,000 or 21 to 31 new cases per year. Prevalence of PWS with its consequential obesity and sequelae carries a much higher burden to the health-care system.

This genetic disorder is caused by an abnormality of chromosome 15. About 70% of the cases have deletion of a piece of chromosome 15 donated by the father; 30% have uniparental disomy, a condition where both chromosomes 15 are inherited from the mother. DNA testing is now commonly used to identify this abnormality and confirm the clinical diagnosis of PWS.



Studies have demonstrated a high prevalence of growth hormone deficiency in PWS patients with short stature, leading some experts to take the view that growth hormone treatment should be accepted in this syndrome without the necessity of

testing. This view is supported in PWS outcome studies demonstrating marked improvements in stature, weight for height, and even behaviour, without significant consequential side effects to growth hormone replacement therapy.

Knowing the Canadian PWS incidence and clinical status on diagnosis will allow for a better understanding of the challenge to be faced and will help with future health-care planning, both on an individual level (intervention strategies) and on a population basis (resource planning), regarding socio-economic support, design and obesity prevention strategy programming.

Despite the availability of both clinical diagnostic criteria and genetic testing, many diagnoses of PWS have been delayed even well into adulthood. Timely management, as a result of early and appropriate diagnosis, can have a positive impact on the patient's health and quality of life, particularly with respect to the prevention and treatment of morbid obesity and its treatable consequences (the common cause of mortality in PWS). Since many manifestations can be managed, decreased in intensity or prevented, preliminary data suggests that the earlier the diagnosis and medical intervention, the better the outcome.

Methods

Paediatricians who participate in the CPSP monthly survey will be asked to report all newly seen cases of PWS (as outlined in the case definition) where the diagnosis was confirmed clinically and/or genetically. Reporting physicians will be asked to complete a detailed report for each new case identified.

Objectives

1. To determine the incidence and the mean age of PWS diagnosis in Canada.
2. To ascertain the method of PWS diagnosis: clinical and/or genetic.
3. To create an awareness in the scientific community of PWS.

Case definition

Report any child up to and including 18 years of age with newly diagnosed PWS confirmed clinically and/or genetically (methylation and/or FISH [fluorescent *in situ* hybridization] test).

A diagnosis of PWS should be strongly suspected in children less than three years of age with a score of five points (four from major criteria) or in patients over three years of age with eight points (five from major criteria).

PWS clinical score:

< 3 years: 5 points (4 from major criteria)
> 3 years: 8 points (5 from major criteria)

Prader-Willi syndrome (continued)

A clinical diagnosis of PWS relies on a score derived from the following major and minor criteria:

Major criteria (1 point each)

- Infantile central hypotonia
- Infantile feeding problems/failure to thrive
- Rapid weight gain between 1 and 6 years
- Characteristic facial features
- Hypogonadism: genital hypoplasia, abnormal sexual development
- Developmental delay
- Hyperphagia/obsession with food
- Cytogenetic/molecular abnormality of Prader-Willi chromosome region

Minor criteria (1/2 point each)

- Decreased fetal movement and infantile lethargy
- Typical behavioral problems (temper tantrums, stubbornness, stealing/begging for food, anxiety regarding food, food seeking, perseverance about food)
- Sleep disturbances/sleep apnea
- Short stature for the family by 15 years of age
- Hypopigmentation for family
- Small hands and feet for height age
- Narrow hands with straight ulnar border
- Esotropia, myopia
- Thick, viscous saliva
- Speech articulation defects
- Skin picking

Supportive criteria (no points)

- High pain threshold
- Infrequent vomiting
- Temperature control problems
- Scoliosis/kyphosis
- Osteoporosis
- Unusual skill with jigsaw puzzles
- Normal neuromuscular studies

Duration

January 2003 to December 2004

Expected number of cases

Based on the annual birth rate in Canada of 400,000 and on the current estimates of PWS incidence as being 1 case in 10,000 to 15,000 births, the expected number of confirmed new cases is 21 to 31 per year.

Ethical approval

Research Ethics Board, North York General Hospital

Analysis and publication

Data will be analyzed regularly by the principal investigator for inclusion in quarterly updates and annual reports that will be distributed to all participants.

Study results will be presented at meetings and conferences, and upon completion of the study, published in a peer-reviewed journal.

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