PRADER-WILLI SYNDROME - GUIDE 2005

A GUIDE FOR FAMILIES AND PROFESSIONALS

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What is Prader Willi syndrome (PWS)?

PWS is a genetic condition first described in 1956 by 3 Swiss Doctors, Prader, Labhart, and Willi. They described a small group of children with obesity, short stature, undescended testicles and mental impairment with history of hypotonia (decreased muscle tone) in the neonatal period. Many other features of PWS have since been described. Understanding of this condition has grown substantially thanks to the clinical diagnostic criteria developed by Dr. Holm in 1993 and the advances of molecular biology. PWS is, nowadays, considered as the most frequently occurring genetic cause of obesity with prevalence between 1:10,000 and 1:15,000 live births. This syndrome occurs equally in both males and females and is seen in individuals of all races. Individuals with PWS will share some but not all of the same features and symptoms. Many of their features are believed to arise from a dysfunctional region in the brain, known as the hypothalamus. In addition to its role in controlling temperature, behavior, appetite and satiety the hypothalamus controls the release of a number of hormones from the anterior pituitary gland (master gland) including growth hormone (GH), gonadotropins (FSH/LH), thyroid stimulating hormone (TSH), prolactin and adrenocorticotropic hormones (ACTH). Normal pituitary hormonal secretion is necessary to achieve appropriate growth, sexual maturation and other vital functions in the body (Figure 1).

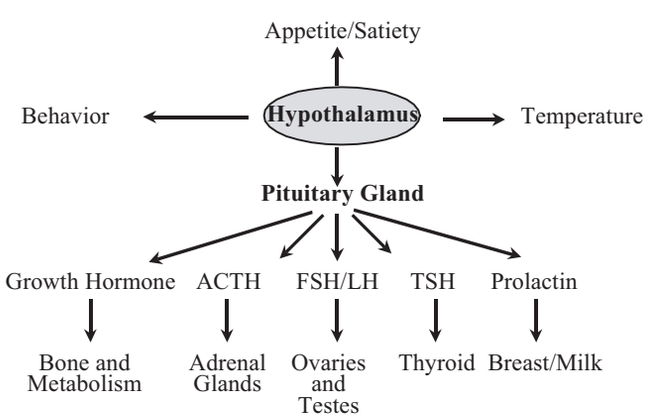

Figure 1. Hypothalamic functions and its links with pituitary function

What are the common features?

Individuals with PWS have generally similar features but the number and degree of severity of them may vary. The clinical picture changes with age.

Neonatal Period: Babies born with PWS are described as being "Floppy", with a weak or absent cry. This neonatal hypotonia seems to be a nearly universal finding. Infants show little facial expression, and the low muscle tone leads to feeding difficulties that last for weeks or months and most of them require special assistance with feeding. This hypotonia is manifested even before birth by decreased fetal movements (80%-90%) and this inactivity may account for the high number of breech presentation (20%-30%) associated with the syndrome. Other neonatal features of PWS may include increased head/chest circumference ratio, narrow forehead, almond-shaped eyes, and thin upper lips with down-turned angles of the mouth, a small penis with undescended testicles as well as hypoplasia (small) clitoris and labia minora in female infants. The saliva is characteristically thick, sticky and may be seen as a string between the lips which can be a helpful diagnostic pointer in hypotonic infants. Although hands and feet may be normal in size, the ulnar borders of hands and inner side of legs are usually straight (Fig 2)

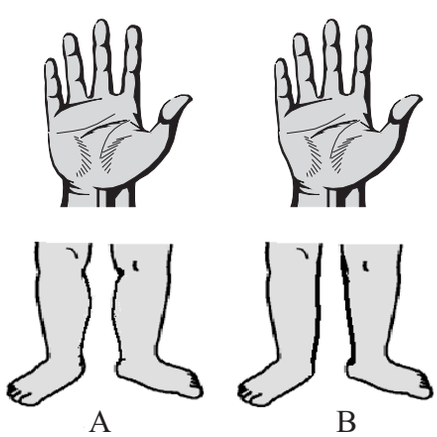

Figure 2. Comparison of hand and leg borders in normal (A) and PWS individuals (B)

Infant Period: Many of the above clinical features are easier to recognize during this period. Typically, the infant shows some degree of failure to thrive. The hypotonia gradually improve to the point that assisted feeding (such as gavage or gastrostomy tube) may not be necessary anymore in most affected infants. Motor activity increases but gross motor development is delayed compared with otherwise normal infants. Difficulties with articulation and expressive language lead to delayed speech and high-pitch voice.

Childhood Period: Begins between 2 and 3 years of age and it is characterized by increased appetite and excessive weight gain. Children may start talking during this period and begin to exhibit behavioral problems with outburst of temper-tantrums in response to frustrations mostly centered on the constant craving for food. PWS infants and children have excessive adiposity (body fat content) and low muscle mass, regardless of their weight. Speech articulation problems may persist and a small number of these children may have autistic personality. Unmotivated sleepiness decreased pain sensitivity, skin-picking habits, and decreased growth velocity may manifest during this period.
Although 5% of children with PWS can attend regular school until secondary level, cognitive dysfunction is nearly always present. Specific academic weakness in arithmetic, writing, sequential processing and short term memory are common, whereas reading and art skills are considered strengths.

Adolescence and Adulthood: The inactivity associated with obesity leads to sleeping and respiratory abnormalities such as hypoventilation and oxygen desaturation. These problems however, can be seen from childhood through to adulthood. Behavioral problems, learning difficulties, and temper tantrums may become more prominent in the teenage years. The normal growth spurt and complete sexual development is absent in most of these individuals due to the lack of normal amount of sex hormone production. Final adult height in males with PWS is about 155 cm (61.3 inches) and 148 cm (58.5 inches) in females. Growth hormone deficiency has been found recently in most PWS children and prolonged periods of growth hormone therapy may exceed that estimated final adult height. Other features include a high incidence of scoliosis (40 - 80%) which seems to worsen with age from childhood to adulthood. Regardless of their IQ, these individuals still need strict 24-hour supervision for their caloric intake. Persistent food-seeking behavior and cognitive impairment may preclude normal adult independent living.
Adults with PWS and especially those with marked weight loss may be prone to osteoporosis and increased risk of fractures.

Who should be evaluated for PWS?

Any infant with unexplained hypotonia and a child with obesity, associated with short stature, sexual infantilism and mental impairment should be evaluated for PWS. Obesity is cardinal feature in PWS during the childhood and becomes the most significant health problem during adulthood. Obesity secondary to increased caloric intake (Exogenous obesity) in a normal child is commonly associated with normal or tall stature. Children with obesity, short stature, and intellectual impairment on the other hand, need complete genetic and endocrine evaluation. Overlapping between genetic and endocrine conditions is not that uncommon. The following chart (Fig. 3) may help parents and physicians in the initial evaluation of the obese child.

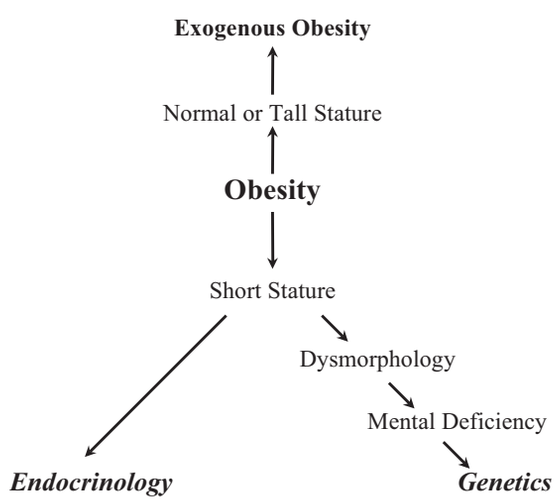

Figure 3. Clinical Evaluation of Obesity in Childhood

Genetics and Diagnostic Testing in PWS

Evaluation and diagnosis of PWS was based merely on clinical criteria for many years. Due to the variety of clinical features many children were undiagnosed and the incidence therefore was considered less common than nowadays. It was not until 1981 that the genetic region involved in this multisystemic condition was mapped to the proximal region of the long arm of chromosome 15 (15q11-q13). PWS results from the lack of expression of genes on the paternally derived PWS region of chromosome 15 q11-q13 by one of several genetic mechanisms. PWS was one of the first human genetic conditions attributable to a microdeletion and to be associated with genomic imprinting.

The advent of high-resolution chromosome analysis in the 1980's provided a method capable to detect small de-novo interstitial deletion in the long arm of chromosome 15q11-q13 in 60%-70% of affected individuals with PWS. It was found later on that the microdeletion in PWS occurs only on the chromosome 15 inherited from the father and that 25% of cases had received both copies of chromosome 15 from the mother (uniparental disomy 15) and none from the father. A very small number of PWS cases are caused by other mechanisms such as a defect in the paternally inherited region of the PWS/AS region that affect the imprinting process as well as chromosome translocations involving the PWS region on paternal chromosome 15q11-q13 (Fig. 4).

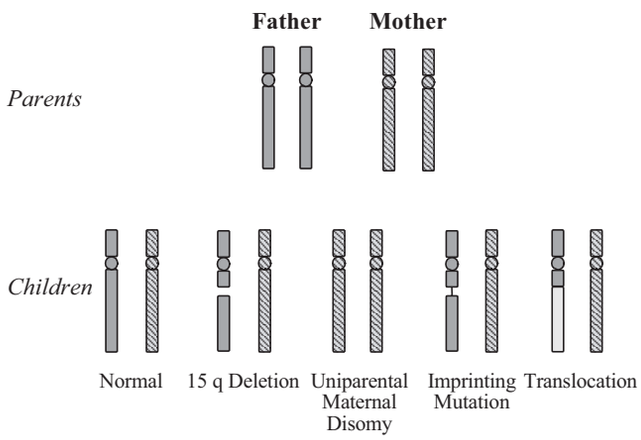

Figure 4. Chromosome 15 abnormalities resulting in Prader-Willi syndrome

The paternally expressed genes in the 15q11-q13 region are particularly important in the hypothalamic development. In contrast to the classical Mendelian inheritance, the imprinted genes have differential expression depending upon their parental origin.

Genes are the fundamental units of heredity and consist of DNA (Deoxyribonucleic acid).

The genes belonging to each cell are arranged on chromosomes, which are simple giant molecules of DNA. The DNA molecule carries the original copies of the genetic information but it uses RNA (Ribonucleic acid) known as messenger RNA (mRNA) to transfer the actual genetic information for the protein synthesis (Fig 5).

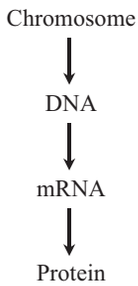

Figure 5. Protein Synthesis

Absence or changes of vital DNA known as mutations will alter the normal cascade from DNA to RNA and protein. DNA methylation (overmethylation) at the beginning of genes is known to affect gene expression under normal circumstances. Either overmethylation in the mother and undermethylation in the father germ cells will modify several genes in the PWS region through genomic imprinting during or after gametogenesis (egg and sperm formation) This imprinting will lead to activation of genes in PWS/AS region of all sperms, whereas the maternal genes will be inactive in the same region in all of mature germ cells (eggs). It is expected therefore, that every child is born with one active and one inactive PWS region in chromosome 15q11-q13 inherited from the father and mother respectively. The candidate genes for PWS including *SNURF-SNRPN* are imprinted and silenced on the maternally inherited but activated in the paternally inherited chromosome 15q11-q13. PWS therefore develops if paternal alleles in the region 15q11-q13 are missing, defective or silenced (Fig 6).

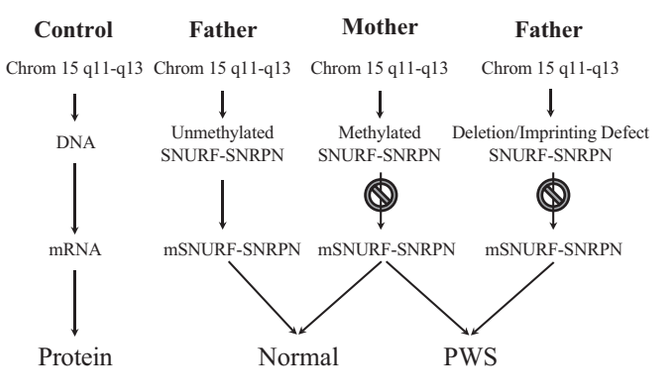

Figure 6. Methylation and Gene expression using SNRPN probe. Presence of only methylated DNA-*SNURF-SNRPN* or absence of RNA-*SNURF-SNRPN* expression confirms the diagnosis of PWS.

Diagnostic Testing

1. High-resolution chromosome analysis (HRCA) in the 1980s provided a method capable of showing that in many patients with PWS there was a small de novo deletion within chromosome 15q11-q13 in 50-60%. However, recently developed molecular analysis techniques demonstrated that both false-negative and false-positive results occur with this technique.

2. Fluorescence in situ hybridization (FISH) technique was developed later on after cloning several genes in the PWS region of chromosome 15q11-q13. This technique uses a fluorescent-tagged probe to detect the presence of a gene (DNA) on chromosome 15. FISH analysis is scientifically and clinically valid for detection of the 15q11-15q13 deletion found in 70% of people with typical PWS.

3. DNA methylation. This technique is the best known process of imprinting and uses restriction digests with methyl-sensitive enzymes such as HpaII and HhaI and probing Southern blots with several genomic and cDNA probes (e.g. *SNURF-SNRPN* and *PW71B* probes). The methylation pattern varies according to the parent of origin, providing further evidence for the association of methylation with genomic imprinting. DNA methylation analysis in a normal individual will reveal methylated and unmethylated DNA fragments from maternal and paternal origin, respectively. The presence of only methylated DNA fragments (maternal pattern) indicates inactive genes that could result from paternal deletion, uniparental maternal disomy or a defect in the PWS imprinting centre (IC). DNA methylation analysis is the single most sensitive test and will detect over 99% of cases. If DNA methylation analysis is normal, it is highly unlikely that the individual has PWS.

4. RNA expression. This technique uses reverse-transcriptase and polymerase chain reaction (RT-PCR) to detect the presence or absence of gene expression such as *SNURF-SNRPN* or any other gene in the PWS region. Based on the fact that DNA methylation inactivates the genes and their expression, the absence of *SNURF-SNRPN* expression indicates inactive genes that could result from paternal deletion, uniparental maternal disomy or imprinting defect.

Both, DNA methylation and RNA expression testing detect all cases of PWS caused by deletions, uniparental disomy (UPD), and imprinting defects, the molecular mechanism that account for 99% of PWS cases. Positive analysis for PWS using DNA methylation or RNA expression however, will not distinguish the molecular class of mutation. Deletions can be detected using FISH analysis with the *SNRPN* probe. Chromosome analysis may be necessary in those patients with clinical features of PWS and normal biparental inheritance of the PWS region by methylation.

Subtypes of deletions (I and II) based on their size have been recently reported. The larger deletion, type I involves more genes that could result in some differences in expressing phenotype and behavior, larger studies however will be necessary to identify the incidence and difference among these two or any other new recognized deletion subtype.

Risk to family members:

Most cases of PWS are known to occur sporadically. The risks, however, to siblings and family members of a child with PWS depend on the genetic mechanisms causing loss of the paternally contributed PWS region:

Table 1. Risks to siblings of PWS patient based on genetic mechanism.

% of Patients	Genetic Mechanism	Risk
70%	Deletion PWS/ AS region	Less than 1%
25%	Uniparental Disomy (UPD)	Less than 1%
<5%	Imprinting defect	up to 50% *
<1%	Balanced chromosome translocation or abnormality	up to 25% for PWS up to 25% for other defects

*If the healthy parent carries the imprinting mutation.

Is There a Cure or Any Management of Persons with PWS?

Prader-Willi syndrome is a multisystemic condition for which no cure is available at the present time. Recognition and early intervention, however, may improve the prognosis.
Hypotonic infants are now evaluated not only by neonatologists and neurologists, but also by geneticists. Through this team approach, larger numbers of individuals with PWS are expected to be diagnosed early in life and prevent further complications of adulthood obesity.

Hypotonia: Neonatal hypotonia makes sucking difficult, and a special feeding method such as gavage (placing a tube into the stomach through the mouth) during the first days of life is not unusual. Decreased caloric intake as a result of feeding difficulties may lead to failure to gain weight. To keep the child's weight under control, supervision by a professional nutritionist or dietitian who understands the syndrome may be necessary. Physical therapy is strongly recommended to improve muscle tone.
Severe neonatal hypotonia in a 5-month old girl was initially attributed to a mitochondrial myopathy due to a defect in Complex III, confirmed by muscle biopsy. She was started on coenzyme Q10 supplementation at age 7.5 months with improvement of her motor development. Based on her excessive weight and other clinical features, by age 2, she was diagnosed as Prader-Willi Syndrome due to UPD. Her muscle tone has improved but still subnormal.
Based on this case and other isolated reports, parents are using coenzyme Q10 supplementation in their children without professional supervision and variable results. Although this is a provocative observation, additional studies are required to verify if this mitochondrial defect is part of the Prader-Willi Syndrome complex picture or just a coincidental association, as well as the efficacy of coenzyme Q10.

Hypogonadism: Signs of incomplete sexual development may be present at birth and characteristically the male infant may have small penis and scrotum with undescended testicles, whereas the female infant has small clitoris and vaginal folds. The hypogonadism is thought to be due to hypothalamic dysfunction. The hypothalamus is the region in the brain that controls the pituitary gland to produce gonadotropins (FSH and LH) which stimulate the gonads (ovaries and testicles).
The gonadotropins act to maintain gonadal function, including germ cell formation in males, ovarian cyclicity in females, and steroid (androgens, estrogens and progestins) and gonadal peptide (activins and inhibins) production in both sexes.

The incidence of cryptorchidism in normal full term newborns is about 3.4% and present in 0.7% of children after 1 year of age and in adults, whereas in PWS it is present in 88%. Spontaneous testicular descent is unlikely to occur after the age of 1 year in PWS and non-PWS children. Patients with untreated intra-abdominal cryptorchidism or those who underwent surgical correction during or after puberty may have increased risk to develop testicular tumors.
The gonadotropins are important during the 3rd trimester of gestation for testicular descent and production of sex hormones for further enlargement of the penis. Low concentration of gonadotropins may explain the undescended testicles and small genitalia characteristic of PWS individuals.
Hormonal treatment with human chorionic gonadotropins (hCG) or luteinizing hormone releasing hormone (LH-RH) is effective in about 30% of those children with true undescended testicles.
Medical management does not replace surgical intervention but a course of hCG might facilitate surgery for undescended testicles and circumcision.
Testosterone concentration increases after hCG treatment and it may help to increase the size of penis and scrotum as well as to improve the low muscle tone and mass.
Medical management before surgery seems

to be most appropriate in PWS children with undescended testicles. Figure 7.

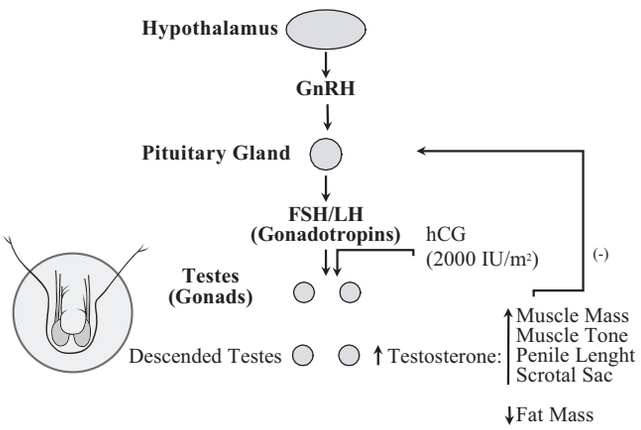

Figure 7. Hypothalamus-Pituitary-Gonadal axis and effects of hCG on undescended testicles.

Testosterone administration under an endocrinologist's supervision may also be used in treating males with sexual infantilism. Testosterone administration to adult obese PWS may result in peripheral aromatization in adipose tissue and therefore further breast enlargement. The use of aromatase inhibitors adjunct with testosterone could give better results.

Infertility is characteristic of PWS individuals. A case report at the end of the century of normal pregnancy and delivery in a PWS female however, brought some concern in terms of counseling to parents and their children. Spontaneous development of normal secondary sexual characteristics including breast, axillary and pubic hair as well as normal menstrual cycle in a PWS female, should be considered as a marker of normally functioning hypothalamus-pituitary-gonadal axis and therefore at risk for pregnancy. Estrogen action is critical for normal bone fusion and mineralization in both men and women. Estrogen replacement, especially in those PWS adult females who have already achieved significant weight loss may be necessary to prevent osteoporosis.

Obesity: Unless food intake is controlled, most children begin rapid weight gain by age 2 to 5 years. PWS children have low metabolic rate and energy expenditure; therefore they need fewer calories than normal children to maintain normal weight for height. To assure adequate nutrition, dietary restriction should be based on well balanced-hypocaloric diet. The goal is to prevent obesity and its complication such as diabetes, heart disease, and respiratory problems. Children that have lost weight must be kept on caloric intake averaging about 60% of the normal for their age in order to maintain their reduced weight. 8 to 9 Kcal/cm of height can achieve slow and adequate weight loss, whereas 10 to 11 Kcal/cm of height are sufficient for weight maintenance.

Leptin, a protein produced by the adipose cells, discovered in the mid 90s was a great hope for researchers. A strain of monumentally obese mice lacking this protein as result of a genetic defect lost their appetite and wasted away to normal weight in a short period of time after leptin administration. In human obesity with or without PWS, leptin levels are increased in proportion to their body fat. Studies in human obesity show that leptin failed as an appetite suppressant and weight-loss drug. At this time we can state that leptin is not a signal to loose weight but a reflection of the amount of adipose tissue in the body. Ghrelin, a novel hormone, was identified and purified from the rat and human stomach in 1999 because of its ability to increase growth hormone (GH) secretion from the pituitary gland. Independent from the ability to stimulate GH secretion, ghrelin induces adiposity by increasing food intake and decreasing fat utilization in animal models and humans. Opposite to leptin, serum levels of ghrelin are lower in obese than normal weight individuals. Although ghrelin levels are inversely related to body weight in humans, ghrelin concentrations are higher during starvation and increase with weight loss. In normal weight as well as obese individuals, circulating ghrelin levels increase during fasting and decreases after food intake. Therefore, ghrelin may signal conservation of energy to prevent further weight loss and restore usual body weight.

Preliminary reports show that PWS individuals have higher fasting ghrelin levels and lack the normal decrease in circulating ghrelin after food intake. At the present time significant research is

being conducted to find a way either to decrease or block the ghrelin effect, and eventually use it in the management of uncontrollable appetite characteristic of PWS.
A recent report in small number of adult individuals with PWS, show significant decrease in plasma levels of ghrelin after administering somatostatin, but not decrease in appetite. Studies with larger number of subjects and long-term effects however, will be necessary to evaluate substances that decrease or block the effect of ghrelin in PWS.
Another peptide involved in the control of energy balance is peptide YY (PYY) which is secreted by the intestine and released post-prandially (after meals), acting at the brain level, particularly the hypothalamus to inhibit appetite.
Children and adult with PWS have lower levels of plasma PYY. Preliminary studies have shown that PYY decreases appetite in about 30% in normal obese and non-obese individuals. The effect of PYY in subjects with PWS however, has not been reported at the time of this publication.
Appetite suppressant drugs such as Diethylpropion (Tenuate), Phendimetrazin (Melfiat), and Sibutramine (Meridia) have been used in rare cases of extreme obesity but they only work partially for short periods of time and are not recommended before age 12 years. Other class of anti-obese drugs includes Xenical (Orlistat) which interferes with lipase function, decreasing intestinal fat absorption by 30%. This class of drugs, known as fat blockers can cause adverse effects such as urge to go the bathroom and deficiency of liposoluble vitamins.

Somnolence: Patients with PWS appear to have an intrinsic sleep disorder leading to hypersomnia (sleepiness) and abnormalities of REM (rapid eye movement) sleep; probably due to hypothalamic dysfunction. Excessive daytime sleepiness (EDS) is a common feature of PWS, often beginning in early childhood. Snoring and breathing difficulty during sleep are commonly reported by caregivers. EDS is a primary feature and occurs despite increased quantity or quality of nocturnal sleep in patients with PWS. Most studies at this point have failed to demonstrate a relationship between sleep-disordered breathing and EDS. People with PWS are at risk of a variety of sleep-disordered breathing patterns for a number of reasons. Obesity of any cause is associated with sleep-disordered breathing in children and adults, specifically obstructive sleep apnea (OSA) and alveolar hypoventilation. The incidence and severity of alveolar hypoventilation during sleep are related to degree of obesity. Restrictive lung disease due to muscle weakness or scoliosis is also a risk factor for sleep-related hypoxemia and hypoventilation. In addition, ventilatory response to hypercapnia (increased CO2 and hypoxia (decreased O2) are reduced during sleep and wakefulness in PWS, and this may compound sleep-related hypoventilation of any cause.
Among the types of sleep disorders that have already been described in PWS are: disturbance to the sleep wake cycle, obstructive sleep apnea (OSA), hypoventilation syndromes, and narcolepsy. Although patients with PWS fall asleep rather quickly, their sleep architecture is significantly disrupted with frequent awakenings and abnormal patterns of rapid eye movements sleep.
Obstructive sleep apnea occurs in association with increased upper airways resistance, either from enlarged tonsils and adenoids, relaxation of the upper airway musculature, or from structural airway anomalies. Narcolepsy, which involves sleep attacks and occasional loss of muscle tone, precipitated by strong emotions, has also been described in these patients. Alveolar hypoventilation during sleep may occur in PWS due in part to an increased load on weak respiratory muscles. Hypoventilation is strongly correlated with degree of obesity which is associated with desaturation during sleep.
Patients' questionnaires alone underestimate the incidence and severity of these symptoms. These disorders are diagnosed with sleep studies, known as overnight Polysomnogram and daytime sleep studies, called the Multiple Sleep Latency Tests (MSLT). Sleep disordered breathing, characterized by obstructive hypoventilation or episodes of apnea that occur primarily during rapid eye movement sleep, may improve with weight reduction.
A significant number of PWS individuals have persistent daytime sleepiness despite weight reduction, suggesting a primary disturbance of sleep. Various therapies are available for the

treatment of sleep-related problems and are individualized to meet the patient's needs. Early identification of sleep-disordered breathing and appropriate management may delay or prevent the development of cor-pulmonale, a common cause of death in patients with PWS. Treatment of OSA in children with PWS does not differ from that in general population. Adenotonsillar hypertrophy in children with OSA should be treated with adenotonsillectomy. Polysomnogram before and after surgery should be considered to ensure resolution of obstructive events and hypoventilation, as patients with obesity, hypotonia, and other contributing factors are less likely to have complete resolution of OSA after surgery.

Individuals with PWS can safely undergo anesthesia. Risks are related to their general health before the procedure. The majority of complications do not appear to come from general anesthesia, but form poorly monitored conscious sedation. Drowsiness after anesthesia may be due to the underlying somnolence and a component of central apnea. Post surgery complications are unpredictable in children and adults with PWS, consideration should be given to an overnight observation after outpatient procedures. Tracheostomy or continuous positive airway pressure (CPAP) via nasal mask may be indicated in adults, or in children without adenotonsillar hypertrophy, or for whom adenotonsillectomy fails to lead to resolution of OSA. CPAP has been demonstrated to be effective in controlling obstructive events, but nonobstructive REM-related desaturation may not resolve, and treatment may be poorly tolerated. Improvement in central respiratory drive and resting energy expenditure after growth hormone (GH) therapy, accompanied by an increase in ventilatory response to hypercapnia has been reported. These reports suggest that GH therapy may contribute to better sleep quality and pulmonary function. Further studies however, will be necessary to evaluate the benefits of long-term GH therapy in sleep and pulmonary function.

Intellectual Development/Behavior: Delay in attaining early developmental milestones is common in PWS. While the full-scale IQ testing around 70 indicates that individuals with PWS are at the mild to borderline range of learning disabilities, the range varies from severely retarded to no retarded, with 40% having borderline retardation or low normal intelligence. Most affected children, regardless of their IQ, will have multiple, severe learning disabilities, with poor academic performance in relation to their mental abilities.

Children with PWS often exhibit distinct behavioral abnormalities (70-100%) linked to the frustrations associated with the syndrome. These behaviors may begin as early as two years of age. They may manifest a variety of deviant eating behaviors such as foraging for food, secretly consuming large amounts of food, and other attempts to continue eating. Other problems include verbally and physically aggressive behaviors such as lying, stealing, scratching and skin picking. Tantrums and unprovoked outbursts are common among children and youths with PWS. They are likely to be short but intense. Behavior management of the child with PWS should be included as an integral part of the child's individualized education plan (IEP). All who come in contact with the child should have knowledge of the techniques used to assist in managing those behaviors that may interfere with learning or enjoyment of activities in school or home. Behavioral problems may worsen in adolescence and adulthood. No medication has been documented to be beneficial in managing behavior in all PWS patients. Serotonin reuptake inhibitors and Buspirone however, have been used in the largest proportion of patients to manage the behavioral problems with variable response. Selective serotonin reuptake inhibitors (SSRIs) are not likely to cause weight gain if used for 6 months or less. Opinions vary as to whether they cause weight gain when used for 1 year or longer. PWS individuals are somehow susceptible to water intoxication which may lead to bizarre behavioral or neurological symptoms. Anticonvulsant drugs such as valproic acid (Depakote) and oxcarbazepine (Trileptal) are commonly used for different behavioral problems in PWS individuals.

These two drugs however, can cause severe reactions including hyponatremia (low sodium) and inappropriate secretion of antidiuretic hormone which result again in behavioral and neurological symptoms. It is recommended therefore to monitor

periodically their serum electrolytes and urine analysis while taking those anticonvulsant drugs. Restricted fluid intake is recommended in the presence of water intoxication. Affected adult individuals with PWS generally require a sheltered employment environment. Issues of guardianship, wills, trust and advocacy should be investigated.

Short Stature: Short stature is also a common feature of PWS individual (80-100%), while birth length is usually normal. Children with PWS typically have a gradually declining linear growth velocity beginning in early childhood, and most adults are significantly below their mid-parental height. The cause of short stature in PWS was initially unknown. Clinical studies in the early 1970s indicated already that these children might have a deficiency of GH (Growth Hormone) secretion.
The known association of obesity itself with low GH secretion however complicated the interpretation of these results. Subsequent large number of reports indicated that GH secretion as well as other GH-dependent proteins, such as Insulin Like Growth Factor 1 (IGF-1), Insulin-like Growth Factor Binding Globulin (IGFBP3) and Growth hormone binding globulin (GHBG) was also low in PWS children regardless of their weight. Overall, the clinical picture, body composition, and biochemical markers seem to be similar to those children with Isolated GH deficiency (IGHD). See Table 2.

	Simple Obesity	GH Deficiency	PWS
Growth Velocity	Normal or ⇧	⇩	⇩
Bone Maturation	⇧	⇩	⇩
IGF-I	⇧	⇩	⇩
GH-BP	⇧	Normal or ⇩	Normal or ⇩
Body Fat (%)	⇧	⇧	⇧
Sexual Development	Normal or ⇧	⇩	⇩
GH Secretion	⇩	⇩	⇩

Table 2. Comparison of PWS with Obese and Isolated Growth Hormone Deficiency (IGHD) Children

This data indicates that decreased GH secretion in PWS children is not secondary to their obesity but to true GH deficiency from hypothalamic dysfunction. Several USA and international studies have been conducted on GH replacement therapy in children with PWS and documented GH deficiency by standard testing. Children with isolated GH deficiency (IGHD) and PWS children with documented GH deficiency have similar growth velocity after four years of GH therapy. Fig 8.

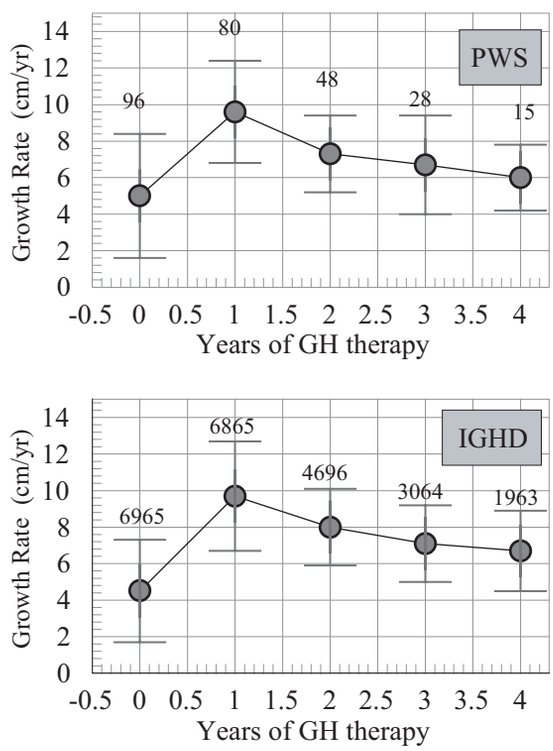

Figure 8. Growth Velocity in PWS and Isolated Growth Hormone Deficiency (IGHD) Children.

Other anabolic actions of growth hormone have been reported in the literature such as improvement of muscle mass, muscle strength, energy expenditure, bone mineral density, and sexual development, in addition to decrease in body fat mass.
Physical and body composition changes vary in each child, most significant changes however occur during the first two years of GH therapy. Fig. 9 shows the physical and body composition changes in a 9 years old child with PWS before and after 2 years of GH therapy.

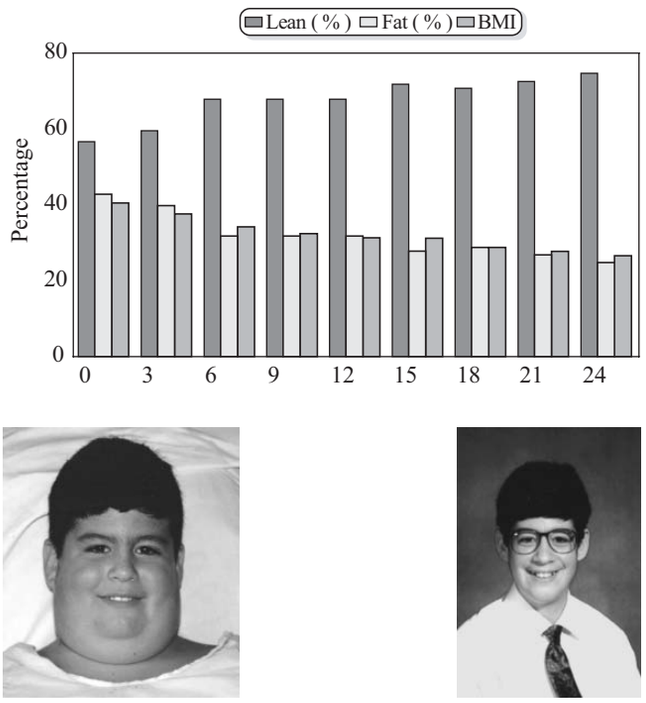

Figure 9. Body composition and BMI changes after 2 years of GH therapy

Preliminary results in 20 of 21 children, who completed GH therapy, revealed a final adult height on the growth chart for normal individuals. A larger study however will be necessary to draw conclusions regarding the final adult height.

Possible adverse effects of GH treatment in children with PWS are currently being studied. PWS is thought to be associated with an increased risk for scoliosis in part related to the low muscle tone, and scoliosis is known to be exacerbated by rapid growth in children without PWS, regardless of GH status or treatment. Therefore, all children with PWS should be carefully monitored for scoliosis regardless of GH treatment.
GH treatment is known to decrease insulin sensitivity, which may further increase the risk of non-insulin-dependent diabetes mellitus (NIDDM) seen in obese individuals. Although PWS does not appear to be associated with NIDDM *per se*, all children with PWS and obesity should be carefully monitored with plasma glucose and insulin levels regardless of GH treatment.

Based on current information suggesting GH deficiency as nearly universal occurrence in PWS, the FDA approved the use of GH treatment in PWS children with growth failure without the need of testing for GH deficiency on June 20th 2000. Due to a few recent fatalities reported in individuals with PWS during GH therapy, a controversy arose concerning the safety of GH therapy in these children. The possibility (that is currently unproven) that GH could increase the growth of lymphoid tissue in the airway, thus worsening already the existing hypoventilation and/or OSA, was mentioned.

The report of 13 children with PWS that died while receiving GH treatment revealed that they were obese, and 10 (77%) of them died in the context of respiratory insufficiency. Twenty seven children with PWS reported to the PWSA-USA, died without GH therapy in USA up to June 2004. As in the GH treated group fatalities, most of these untreated children were obese (85%) and died of respiratory compromise (77%). Similar results were reported by European investigators in 23 untreated children. Irrespective of GH treatment, children with PWS suffer more frequently and more seriously from respiratory problems than healthy children.

The pathogenesis of such respiratory problems in children and adults with PWS is multifactorial in origin but, mainly related to insufficiency of respiratory muscles and pharyngeal narrowness. There is currently no definitive data demonstrating that GH causes or worsens sleep disordered breathing. We should be aware that mortality rate is somehow increased in PWS due to higher baseline obesity and respiratory compromise.
Early diagnosis and close monitoring of hypotonia, respiratory problems and sleep-disordered breathing in infants and prevention of obesity in childhood, could decrease morbidity and mortality rate in children with PWS regardless GH therapy. Sleep apnea studies should be done if indicated, not necessarily to consider GH treatment.

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