Syndrome of the month

Prader-Willi syndrome

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Abstract

Prader-Willi syndrome is a complex disorder affecting multiple systems with many manifestations relating to hypothalamic insufficiency. Major findings include infantile hypotonia, developmental delay and mental retardation, behaviour disorder, characteristic facial appearance, obesity, hypogonadism, and short stature. Obesity and the behavioural problems are the major causes of morbidity and mortality.

Prader-Willi syndrome is caused by abnormalities of the imprinted region of proximal 15q and results from absence of the normally active paternal genes in this region. Such absence results from paternal interstitial deletion, maternal uniparental disomy, or a mutation or other abnormality in the imprinting process.

Diagnostic identification of all causes has become available in recent years, permitting early detection and institution of appropriate management. This testing has permitted recent identification of some phenotypic differences among affected subjects of different race and between those with deletions and uniparental disomy as a cause.

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Prader-Willi syndrome (PWS) is a complex, multisystem disorder first described in 1956.¹ Twenty-five years later it captured the interest of geneticists because it was the first recognised microdeletion syndrome identified by high resolution chromosome analysis.² PWS is now known to be one of the most common microdeletion syndromes, one of the most frequent disorders seen in genetics clinics, and the most common recognised genetic form of obesity. It is also the first recognised human genomic imprinting disorder and the first recognised as resulting from uniparental disomy.³ PWS thus occupies an important place in the contemporary history of human genetic disorders. It is, in addition, distinguished by being a syndrome caused by several different genetic alterations of proximal

15q (genetic heterogeneity) and it is typified by a distinctive behavioural phenotype.⁴⁻⁷

Approximately 1 in 10 000-15 000 subjects is diagnosed with PWS⁸ and it occurs in both sexes and all races. Unfortunately, diagnosis is still delayed in many cases despite the availability of clinical diagnostic criteria.⁵ Appropriate management can have a significant positive impact on health and quality of life, but controlling the characteristic obesity and difficult behaviour constitutes a major challenge, requiring cooperative input from geneticists, primary care physicians, endocrinologists, nutritionists, psychologists, psychiatrists, and teachers, as well as families and other care givers.

Clinical findings and natural history

Although many of the manifestations of PWS are related to functional hypothalamic deficiency, the clinical appearance in infancy differs considerably from that in childhood and adulthood.^{4,5}

HYPOTONIA

Hypotonia of prenatal onset is nearly uniformly present and is probably the cause of decreased fetal movement, frequent abnormal fetal position, and difficulty at the time of delivery often necessitating caesarean section.⁴ The neonatal central hypotonia is almost invariably associated with poor sucking, with consequent failure to thrive and the necessity for nasogastric or other special feeding techniques. Infantile lethargy, with decreased arousal and weak cry, are also prominent findings, leading to the necessity to awaken the child to feed. A gastrostomy tube is rarely necessary since this problem is transient. Reflexes may be decreased or absent. Neuromuscular electrophysiological and biopsy studies are normal or non-specific and the hypotonia gradually improves. Motor milestones are delayed and average age of sitting is 12 months and walking is 24 months. Adults remain mildly hypotonic with decreased muscle bulk and tone.

HYPOGONADISM

Hypogonadism is prenatal in onset⁹ and is evident at birth as genital hypoplasia. It is manifested by cryptorchidism, scrotal hypoplasia (small, hypopigmented, and poorly rugated), and sometimes a small penis in males,

Figure 1 Evolution of the phenotype of PWS in a patient with a 15q deletion: (A) 11 months, (B) 2½ years, (C) 3½ years, (D) 7 years, (E) 13 years, (F) 27 years. See text for description of phenotypic findings. (All photographs reproduced with permission.)

and by hypoplasia of the labia minora and clitoris in females. These findings persist throughout life, though spontaneous descent of testes has been observed up to adolescence.

Hypogonadism is also evident in abnormal pubertal development. While pubic and axillary hair may develop early or normally, the remainder of pubertal development is delayed and usually incomplete. Adult males only occasionally have voice change, male body habitus, or substantial facial or body hair. In females, breast development generally begins at a normal age, but there is usually amenorrhoea or oligomenorrhoea. Menarche may occur as late as the 30s, particularly in association with significant weight loss. In both males and females, sexual activity is rare and infertility is the rule.

The hypogonadism is hypothalamic in origin and gonadotrophins, oestrogen, and testosterone are generally deficient.⁴⁻⁹ Since the pituitary gland and gonads are normal but under-

stimulated, treatment with pituitary or gonadal hormones can improve secondary sex characteristics.⁴⁻⁹

HYPERPHAGIA AND OBESITY

The proportion of fat mass to lean body mass is high even in thin infants with PWS,^{10,11} presumably because of hypotonia and the subsequent decreased muscle bulk. However, significant obesity generally begins after hyperphagia has its onset, often between the ages of 1 and 6 years. Food seeking behaviour, with hoarding of or foraging for food, eating of unappealing substances such as garbage, pet food, and frozen food, and stealing of food or money to buy food, are common. A high threshold for vomiting may complicate bingeing on spoiled food from the garbage or such items as boxes of sugar or frozen uncooked meat, and toxicity from ineffective Ipecac used to induce vomiting has occurred. The obesity is central in distribution with relative sparing of

Figure 2 A 41 year old with PWS. See text for description of phenotypic findings.

the distal extremities, and even subjects who are not overweight tend to deposit fat on the abdomen, buttocks, and thighs (figs 1 and 2).

Obesity is the major cause of morbidity and mortality in PWS and longevity may be nearly normal if it is avoided.¹²⁻¹³ Cardiopulmonary compromise results from excessive obesity, as can type II diabetes mellitus, hypertension, thrombophlebitis, and chronic leg oedema. Sleep apnoea occurs at increased frequency.

The hyperphagia is the result of a hypothalamic abnormality resulting in lack of satiety.¹⁴⁻¹⁵ In addition, there is a decreased caloric requirement,¹⁶ probably related to hypotonia and decreased activity.

DYSMORPHIC APPEARANCE

Characteristic facial features, including narrow bifrontal diameter, almond shaped palpebral fissures, narrow nasal bridge, and downturned mouth with a thin upper lip, are either present from birth or evolve over time¹⁷ (figs 1 and 2). Small, narrow hands with a straight ulnar border and sometimes tapering fingers, and short, often broad feet are usually present by the age of 10, with an average adult foot length of 20.3 cm in females and 22.3 cm in males.¹⁸ African-Americans are less likely to have small hands and feet.¹⁹ A characteristic body habitus, including sloping shoulders, heavy mid section, and genu valgum with straight lower leg borders, is usually present from toddlerhood (figs 1 and 2). Hypopigmentation for the family, manifested as fairer skin, hair, and eye colour, occurs in about a third of affected subjects.²⁰ Strabismus is often present.²¹ Scoliosis/kyphosis are common, the former occurring at any age, and the latter developing in early adulthood (fig 2).

SHORT STATURE

Birth weight and length are usually within normal limits, but the early period of failure to thrive may result in both weight and length being below the 3rd centile. Short stature, if not apparent in childhood, is almost always present by the second half of the second decade, associated with lack of a pubertal growth spurt. Average height is 155 cm for males and 148 cm for females. African-Americans tend to be taller.¹⁹ Growth hormone deficiency has been shown in most tested patients with PWS, and treatment with growth hormone increases height and lean body mass, often resulting in decreased body mass index.⁹⁻²²

DEVELOPMENTAL DELAY/MENTAL RETARDATION

In addition to the gross motor delay described above, language development is also delayed. Verbal skills are an ultimate strength in most patients, though speech is often poorly articulated, having a nasal/slurred character. Cognitive abnormalities are evident and most patients are mildly retarded (mean IQ 60s-low 70s).⁶⁻²³ Approximately 40% have borderline retardation or low normal intelligence and about 20% have moderate retardation. Academic performance is poor for cognitive ability. Specific patterns of cognitive strength and weakness have begun to emerge, frequently with relative strength in reading, visual-spatial skills, and long term memory, and weakness in arithmetic, sequential processing, and short term memory.⁷ Coming to clinic with a book of word search puzzles can almost be considered a diagnostic sign for PWS and unusual skill with jigsaw puzzles is common.

BEHAVIOURAL PROBLEMS

A characteristic behavioural profile becomes evident in early childhood, with temper tantrums, stubbornness, controlling and manipulative behaviour, obsessive-compulsive characteristics, and difficulty with change in routine.⁶⁻⁷⁻²⁴ Lying, stealing, and aggressive behaviour are common. True psychosis is evident in young adulthood in approximately 5-10% of patients. Behavioural and psychiatric problems interfere the most with quality of life in adulthood.

MISCELLANEOUS CHARACTERISTICS

A variety of more minor findings are unique to this condition, including thick, viscous saliva that may predispose to dental caries and contribute to articulation abnormalities, high pain threshold, skin picking and high threshold for vomiting. Sleep disturbances, especially excessive daytime sleepiness and oxygen desaturation in REM sleep, are common even in the absence of obesity.²⁵ Osteoporosis is frequent.

Management

Management of PWS is largely problem oriented. Early intervention and special education, followed by supportive employment, are appropriate to address the developmental disabilities. Physical, occupational, and speech

Figure 3 Genetic map of the 15q11-q13 region. Jagged lines indicate the two common proximal and one common distal breakpoints, circles indicate genes and reference markers, and bars indicate critical regions involved in PWS, Angelman syndrome (AS), and the imprinting centre (IC), the centromere (cen), and telomere (tel). See text for details of genes and the IC function. (Map contributed by Robert D Nicholls, PhD and Nancy Rebert, Case Western Reserve University).

therapies can be beneficial at all ages. The obesity can be controlled with a well balanced low calorie diet of about 1000-1200 kcal/day, regular exercise (30 minutes per day is an appropriate goal), and environmental modification, such as locking kitchen cabinets and close supervision to avoid access to food. So far, no medication has had long term effectiveness in controlling appetite. Recent evidence shows great benefit from growth hormone replacement. Sex hormone replacement will improve secondary sex characteristics and theoretically will improve osteoporosis, but testosterone treatment is sometimes associated with an increase in aggressive behaviour. Products to increase saliva production have proved of benefit in treating the dry mouth and probably improve dental hygiene. Behaviourally, strict reinforcement of behavioural limits, clear delineation of behavioural expectations, and establishment of regular routines often lead to improved behaviour. Medications such as specific serotonin reuptake inhibitors (for example, fluoxetine) often improve behaviour. The optimal living situation for adults with PWS in terms of behaviour and weight management has been documented to be a group home specially designated for this condition.^{13 26}

Aetiology and genetics

Although many of the manifestations of PWS result from hypothalamic insufficiency, no structural defect of the hypothalamus has been documented on postmortem examination. Therefore, the deficiency must be functional, but its nature has not yet been identified. On the other hand, the genetic basis for PWS has been intensively investigated.

Prader-Willi syndrome is caused by the absence of normally active paternally inherited genes at chromosome 15(q11-q13); the maternally inherited genes are normally inactive owing to genetic imprinting.²⁷ In approximately 75% of patients with clinically typical PWS, there is a deletion of the paternally contributed chromosome 15q11-q13.² In the vast majority of cases, the same 4 Mb deletion has occurred. Most of the remaining patients have maternal uniparental disomy (UPD) for chromosome 15.^{3 28 29} Approximately 5% of patients with PWS have a translocation or other structural abnormality involving chromosome 15 which has caused either a deletion or maternal UPD for the critical region.

Genomic imprinting in proximal 15q is the explanation for the parent of origin influence on the clinical outcome of deletion 15q or UPD. In fact, at least 1% of patients, including

virtually all families studied in which there has been a recurrence of PWS, have neither deletion nor UPD, but rather have a very small deletion in the centre controlling imprinting within 15q11-q13, the imprinting centre (IC).^{6 7 30-34} Methylation is one mechanism by which genomic imprinting can occur, and methylation has been shown for several genes identified within the PWS/AS region.²⁷

It is of interest that a clinically very different disorder, Angelman syndrome, is the result of an oppositely imprinted gene in the same region of chromosome 15.^{35 36} Thus, approximately 60% of patients with Angelman syndrome have the same 15q11-q13 deletion, but occurring in the maternally derived chromosome. Paternal uniparental disomy is seen in 3-5%. In approximately 10% there is an imprinting mutation and the remaining cases, a category that has not been reported in PWS, have a presumed single gene mutation. Recently, mutations in the UBE3A gene have been identified in a small number of these patients.^{37 38}

A number of genes have been mapped within the PWS/Angelman syndrome region and others that are not maternally imprinted have been mapped between the common deletion breakpoints (fig 3). The first mapped gene, considered an important candidate gene, is SNRPN (small nuclear ribonucleoprotein N). This gene is expressed from the paternally inherited chromosome only³⁹⁻⁴¹ and is expressed abundantly in brain. Other genes in the PWS/AS region include ZNF127, a zinc finger gene, and two additional non-coding genes (the IC transcript and IPW). All these exclusively paternally expressed genes and transcripts are inactivated in patients with PWS with an imprinting mutation, including those patients with a small (7-25 kb) deletion or without detected deletions.³³ The non-imprinted P gene, which also resides in this region, codes for tyrosinase positive albinism, and its deletion probably causes the hypopigmentation seen in 1/3 of patients with PWS.⁴²

Recently, some clinical differences have been reported between patients with PWS resulting from deletion and UPD.⁴³⁻⁴⁶ Perhaps the most clinically significant of these is that patients with UPD may lack the typical facial phenotype⁴⁵ and may have delayed diagnosis.⁴⁶ In addition, African-Americans with PWS are often of normal height, have normal sized hands and feet, and may also lack the typical facial phenotype.¹⁹

Diagnosis, differential diagnosis, and diagnostic testing

Diagnostic criteria were developed by consensus before the availability of complete sensitive and specific laboratory testing.⁵ These are still extremely valuable in suggesting the diagnosis and indicating the need for diagnostic testing (table 1).

The differential diagnosis for PWS in infancy includes many causes of neonatal hypotonia, particularly neuromuscular disorders. Later in childhood and adulthood, a number of conditions in which mental

Table 1 Summary of the clinical diagnostic criteria for Prader-Willi syndrome (adapted from Holm *et al*⁵). The diagnosis should be strongly suspected in children under 3 years of age with five points, three from major criteria, or in those above 3 years with eight points, four from major criteria. The original diagnostic criteria, developed before the availability of sensitive and specific genetic testing, included a major criteria of chromosome 15 deletion or other chromosome 15 anomaly

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, pubertal deficiency
Developmental delay/mental retardation
Minor criteria (1/2 point each)
Decreased fetal movement and infantile lethargy
Typical behavioural problems
Sleep disturbance/sleep apnoea
Short stature for the family by age 15 years
Hypopigmentation
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
Decreased vomiting
Temperature control problems
Scoliosis/kyphosis
Early adrenarche
Osteoporosis
Unusual skill with jigsaw puzzles
Normal neuromuscular studies

retardation/developmental delay is associated with obesity are included in the differential diagnosis, including Bardet-Biedl syndrome, Albright hereditary osteodystrophy, and Cohen syndrome.⁴⁷ Mental retardation disorders in which obesity is an occasional finding, such as fragile X and Angelman syndromes, may also be confused with PWS. Acquired hypothalamic injury from accidents, tumours, or surgical complications can closely mimic PWS.

Currently, the most efficient molecular diagnostic test for PWS is determination of the parent specific methylation imprint within the PWS/AS region using Southern hybridisation and methylation sensitive probes (SNRPN and PW71).^{34 41 48-52} If the methylation pattern is characteristic of maternal only inheritance, PWS is confirmed, and if not, PWS resulting from deletion, UPD, or an imprinting mutation is ruled out. Newer techniques using PCR to detect the methylation status of SNRPN⁵³ or SNRPN expression⁵⁴ have been developed, but are not yet in widespread use. Determination of whether the PWS is the result of deletion, UPD, or an imprinting mutation is important primarily for genetic counselling purposes and to identify those few cases with a translocation or inherited microdeletion.

High resolution cytogenetic analysis can often detect the 15q11-q13 deletion; however, there is an unacceptably high false negative and false positive rate using this technique, and it is no longer considered sufficient for diagnostic purposes.^{49 50 52 55} Fluorescence in situ hybridisation (FISH) using probes within the PWS/AS critical region (SNRPN or D15S11) is the definitive diagnostic test for the common sized deletion causing PWS. It is best accomplished in conjunction with a probe outside the critical region, optimally a 15 centromeric

(alpha satellite) probe which can serve as a control, and a method to detect a cryptic translocation involving chromosome 15 (which would predispose to unbalanced rearrangements or UPD, and thus increase the chance of recurrence).⁵²

Uniparental disomy can be detected with PCR using informative microsatellite markers from the PWS/AS region by studying both parents and the child.^{52 56} Using additional markers from other chromosomes can confirm correct paternity.

Prenatal detection is possible. FISH is indicated when a cytogenetic 15q deletion is suspected on chorionic villus sampling (CVS) or amniocentesis. If trisomy 15 is detected on CVS and the fetus survives, parent of origin (methylation analysis or microsatellite marker) studies are indicated and validated.⁵⁶⁻⁵⁹ FISH and parent of origin studies are also indicated if an inherited or de novo translocation involving chromosome 15 is detected prenatally.

Parents should be studied in cases with an identified imprinting mutation, since a healthy parent can carry this abnormality and be at increased risk for recurrence.³⁴ Prenatal detection through identification of the mutation or maternal only methylation pattern in a fetus is possible.⁵⁹

The American Society of Human Genetics/American College of Medical Genetics Test and Technology Transfer Committee has developed and published a statement regarding the status of genetic testing for PWS and Angelman syndrome.⁵²

Recurrence risk

PWS resulting from either the common large deletion in the absence of a structural chromosome abnormality or from UPD has not been reported to recur. However, a paternal balanced insertion or gonadal mosaicism is possible, and therefore a recurrence risk of approximately 1% or less is appropriate for genetic counselling purposes. UPD is caused by non-disjunction, as evidenced by advanced maternal age in this group,^{28 29} and by documentation of trisomy 15 on CVS and maternal UPD at birth.^{60 61} Since non-disjunction can recur, a recurrence risk of 1% is appropriate for genetic counselling purposes.^{56 62} In those families with a detected imprinting mutation (small deletion) or with a presumed imprinting mutation based on maternal only methylation pattern when other testing fails to indicate deletion or uniparental disomy, a recurrence risk of up to 50% pertains, as this is likely to be an imprinted dominant mutation, occurring in the paternal grandmother's germline.³⁴

Conclusion

In summary, PWS is a multisystem disorder with considerable clinical variability. It is caused by absence of expression of as yet unelucidated genes within 15q11-q13 from the normally active paternal copy, with cases resulting from paternal interstitial deletion, maternal uniparental disomy, and imprinting mutations. Recently, testing through detection of parent of origin of SNRPN has allowed

diagnostic confirmation in virtually all cases. Continued analysis of known but anonymous genes within this region, and search for additional genes, will probably provide information about genes contributing to normal hypothalamic function or regulation. Although symptomatic management is available, more definitive treatment will probably await reversal of imprinting in this region.

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