CURRENT TOPIC

The Prader-Willi syndrome

M D C Donaldson, C E Chu, A Cooke, A Wilson, S A Greene, J B P Stephenson

Since the original description by Prader, Labhart, and Willi in 1956,¹ there have been over 700 case reports of the Prader-Willi syndrome and by the end of 1991 the Prader-Willi Association were aware of 1595 affected individuals in North America.² Estimates of prevalence vary: one group has reported a consensus figure of one in 10 000 births,³ but with modern techniques for laboratory diagnosis this estimate will probably be shown to have been too high.

It is now known that the Prader-Willi syndrome results from abnormality or loss of a critical region on the proximal part of the long arm of the paternal chromosome 15. Clinically the condition is expressed as a dysmorphic syndrome that principally affects the central nervous system, and has a particular predilection for the hypothalamus.

In this paper we summarise the clinical features of the Prader-Willi syndrome and present the current understanding of its molecular basis. The laboratory and clinical approaches to diagnosis are discussed, as well as some issues concerning the management of the metabolic, dietary, and growth problems.

Clinical features

The classic concept of the Prader-Willi syndrome is that of a two stage disorder with an infantile hypotonic phase followed by a childhood obese phase.⁴ This has been extended by Whitman and Accardo to include a third, adolescent phase with particular behavioural features,⁵ and we would develop this model further to include a fetal and neonatal phase, as shown in the table.

FETAL AND NEONATAL STAGE

Decreased fetal movements presumably account for the increased incidence of breech delivery and there is also a higher incidence of delivery by caesarean section.³ At birth infants are described as hypotonic, with abnormal, weak, or absent cry⁶ and an almost invariable need for tube feeding. It is important to note that the hypotonia mainly affects the neck^{7 8}; the limbs commonly have normal tone or take up dystonic postures.⁸ Sticky saliva is a helpful and under recognised pointer to the clinical diagnosis.⁷ Genital hypoplasia is the rule in girls, but is subtle and easily missed⁸; scrotal hypoplasia and cryptorchidism are common in boys, while the penis is small but not tiny.^{6 8}

INFANT AND EARLY CHILDHOOD STAGE

After the neonatal period motor activity gradually increases and hypotonia becomes less marked, but the child remains difficult to feed with consequent failure to thrive. Development is delayed, particularly gross motor and speech.⁹ Subsequently expressive language and articulation difficulties become evident¹⁰ with a peculiar high pitched nasal quality extending into adolescence.¹¹ The narrow bifrontal diameter, almond shaped palpebral fissures, thin downturned upper lip, and narrow nose that may have been noted during the neonatal period⁶ become more pronounced. Classically, affected subjects are hypopigmented with fair hair and blue eyes.¹²

CHILDHOOD STAGE

This is marked by hyperphagia with consequent obesity (see below) and behaviour problems, with outbursts of temper in response to frustration (for example, the withholding of food) making parenting unusually difficult. A tendency to skin pick is noticed by parents at this stage, although it becomes much more pronounced later on, and this is combined with decreased sensitivity to pain.¹¹ The pigmentary and sensory disturbances observed raises the possibility of an abnormality in the peptides

*Clinical features in Prader-Willi syndrome***Fetal and neonatal**

Decreased fetal movements
Poor feeding/tube feeding
Abnormal/no cry
Axial hypotonia/limb dystonia
Sticky saliva
Genital hypoplasia and cryptorchidism

Infancy and early childhood

Failure to thrive
Developmental delay
Delayed speech
Typical facies
Fair hair/blue eyes

Childhood

Voracious appetite
Obesity
Short stature
Small hands and feet, straight ulnar border
Scoliosis
Easy bruising
Skin picking/other self abuse
Caries
Excessive daytime sleepiness
Temper tantrums
Squint

Adolescence

Cataplexy/pseudoseizures
Obsessional traits
Behaviour problems
Particular difficulties with handling money
Lack of independence
Delayed/incomplete secondary sexual development

Department of Child Health, Fraser of Allander Unit (Neurology and Child Development), and Duncan Guthrie Institute of Medical Genetics, Yorkhill, Glasgow G3 8SJ
M D C Donaldson
C E Chu
J B P Stephenson
A Cooke

Department of Child Health, Ninewells Hospital and Medical School, Dundee
A Wilson
S A Greene

Correspondence to:
Dr Donaldson.

Figure 1 Deletion of Prader-Willi/Angelman's (PW/AS) locus resulting in Prader-Willi syndrome (PWS) or Angelman's syndrome (AS) according to the parental origin of affected chromosome.

derived from pro-opiomelanocortin but studies to date have not supported this hypothesis.^{13 14} Other cutaneous manifestations include easy bruising, sometimes to an extent that child abuse is suspected, and marked erythema after a hot bath. Caries affecting primary dentition are common,⁹ and may be related to the viscous saliva. By school entry impairment of linear growth (see below), typical phenotype, obesity, and genital hypoplasia, complete the clinical picture. Scoliosis may be noted at this stage, but becomes more evident in adolescence.¹¹ Severe intellectual impairment is seldom seen, especially during the childhood years, and some subjects can attend normal school,⁷ although virtually all will require special education from secondary school level onwards.^{11 12} The cognitive impairment is uneven. Skill at jigsaw assembly is characteristically excellent, reading ability is often reasonable, but arithmetic is usually poor. Particular difficulty with short term memory processing has been demonstrated.¹⁵

ADOLESCENT STAGE

In adolescence, specific behaviour and learning difficulties become prominent.^{5 16} Adolescents with Prader-Willi syndrome have particular difficulty coping with the logistics of handling money, and fall asleep easily when sitting on journeys so that independent travel on public transport is rarely possible. The obsessional nature of the disorder is particularly evident so that trivial alterations in routine, such as the rescheduling of a favourite television programme, may provoke a tantrum. Cataplexy¹⁷ and pseudoseizures may occur and can be mistaken for true epilepsy (JBP Stephenson,

personal observation). Despite reasonable skills in selected areas that can be amplified by appropriate youth training, Prader-Willi subjects are unable to be completely independent as adults.^{11 15 18} Puberty is characteristically delayed, although precocious puberty has been reported.¹⁹ In subjects with pubertal delay the response to luteinising hormone releasing hormone is blunted,⁹ while stimulation with human chorionic gonadotrophin in boys may show an abnormally low testosterone response indicating an element of primary hypogonadism.²⁰ Girls will achieve secondary sexual development spontaneously but oligomenorrhoea is the rule, while most boys require testosterone treatment to achieve normal development. Fertility has not been reported in *bona fide* cases in either sex.

Molecular genetic aspects

(1) PRADER-WILLI SYNDROME DUE TO DELETION IN THE LONG ARM OF PATERNAL CHROMOSOME 15

Chromosomal abnormality was proposed as a possible cause in some patients as early as 1976 with translocations involving chromosome 15 being predominant.²¹ This led to studies of chromosome 15 in patients with Prader-Willi syndrome using high resolution banding techniques. In 1981 cytogenetic deletions involving the long arm of chromosome 15 were first described,²² and approximately 50% of patients have an interstitial deletion of 15q11-13 visible on high resolution banding. Five per cent of patients have duplications or translocations while the remainder have normal karyotypes.²³ By studying chromosome 15 heteromorphism the deleted 15q in patients Prader-Willi syndrome was found to be *paternal* in origin in most cases, although both parents had normal phenotypes and karyotypes.

At the same time, studies in individuals with Angelman's syndrome showed that affected subjects frequently showed deletions in the same 15q11-13 area, but that the affected chromosome was *maternal* in origin (fig 1).²⁴ The inference from these discoveries was that both maternal and paternal copies of 15q11-13 are required for normal development to occur. This phenomenon, whereby genetic material is expressed differentially depending on whether it is paternal or maternal, is called *genomic imprinting*.²⁵ In more recent years DNA probes specific for the 15q11-13 region have been isolated and used to physically map the area of interest²⁶ (fig 2). Kuwano *et al* in 1992²⁷ and Knoll in 1993²⁸ have defined a critical region and order of probes for Prader-Willi and Angelman's syndromes, by the use of fluorescence in situ hybridisation, and yeast artificial chromosomes clones. The minimum region of deletion for Prader-Willi syndrome has been shown to lie between the loci D15S13 and D15S10, and includes locus D15S63. Most individuals with Prader-Willi and Angelman's syndromes have deletions involving a common set of markers that include D15S9, D15S11, D15S13, and D15S10.

Figure 2 Diagram of Prader-Willi syndrome (PWS) and Angelman's syndrome loci on chromosome 15.

However, a family have been described by Hamabe *et al* where a small 15q deletion transmitted to a woman from her father resulted in a normal phenotype rather than Prader-Willi syndrome, while transmission to her children resulted in Angelman's syndrome.²⁹ This observation shows that the critical region for Prader-Willi syndrome must be separate from the critical region for Angelman's syndrome.

(2) PRADER-WILLI SYNDROME DUE TO MATERNAL DISOMY

In 1989 Knoll *et al* carried out DNA studies using probes and confirmed the paternal origin of the deleted chromosomes in some Prader-Willi subjects.²⁴ However, they also found that in some karyotypically normal patients *both* chromosomes were *maternal* in origin (uniparental maternal disomy). In some instances both apparently intact maternal chromosomes were present (heterodisomy) and in other instances two copies of the same maternal chromosome were present (isodisomy) (fig 3). In Angelman's syndrome the phenomenon of uniparental *paternal* disomy has been reported in 5% of cases.³⁰

(3) MECHANISMS FOR AND EXPRESSION OF THE MOLECULAR ABNORMALITIES IN PRADER-WILLI SYNDROME

Environmental factors have been postulated in the aetiology of deletions in the paternally derived chromosome. Strakowski and Butler in 1987 found that an increased incidence (21%) of fathers of children with Prader-Willi syndrome were employed in occupations where hydrocarbons were used at the time of conception compared with the fathers of children with Down's or fragile X syndromes (12%).³¹ Cassidy *et al* looked at 81 individuals with Prader-Willi syndrome and found that approximately half of the fathers were employed in jobs where they were exposed to hydrocarbons around conception.³² Whatever the specific cause, it seems likely that the 15q deletion occurs in the father's gametes at the stage of meiosis. Uniparental disomy presumably results from a sequence of non-disjunction and duplication events occurring at the time of gamete formation and conception.

As one would expect, the Prader-Willi

syndrome is sporadic in almost all cases. Indeed, the only mechanisms by which the disorder might be expected to have a familial basis are:

(A) In the very rare instances where a father carries a balanced translocation involving the critical area for Prader-Willi syndrome so that those of his children receiving unbalanced translocations will have the condition.³³

(B) When a father has inherited a deletion *specific* for Prader-Willi syndrome from his mother. This could explain the family described by Lubinsky *et al* who reported two brothers and two sisters in a single sibship with classic Prader-Willi phenotype and normal chromosomes on cytogenetic examination.³⁴

It is not known how the molecular abnormality (Snrpn) in Prader-Willi syndrome is translated into the predominantly neurological disorder seen clinically. It is of interest, however, that Ozcelik *et al* have mapped a gene encoding a small nuclear ribonucleoprotein polypeptide to the critical region for Prader-Willi syndrome between D15S13 and D15S10 (fig 2).³⁵ This is the first gene encoding a characterised protein to be mapped to this area. The protein is expressed predominantly in the brain and is thought possibly to affect alternative splicing of transcripts. Mutations in this gene may therefore have effects on the development or function of the nervous system. In the mouse, Snrpn gene is imprinted and only the paternally derived allele is expressed in the brain. If this gene is the Prader-Willi syndrome gene, there is a possibility that point mutations may be found in those rare non-deleted patients who appear to have Prader-Willi syndrome.

Diagnosis of Prader-Willi syndrome

(1) LABORATORY DIAGNOSIS

It is now known that deletions seen by microscopy do not necessarily correlate with molecular deletions. Hamabe *et al* described six patients with cytological deletions that were not demonstrable at the molecular level.³⁶ The explanation for this may be that these patients either had deletions outside the critical area for Prader-Willi syndrome, or that apparent cytogenetic deletions may in fact be normal variations, pericentric inversions, or balanced insertions. We suggest that conventional cytogenetic analyses are no longer appropriate in the diagnosis of Prader-Willi syndrome.

There are three approaches currently favoured in the molecular diagnosis of Prader-Willi syndrome. One is to use specific DNA probes for the region 15q11-13 together with restriction digests (which allow for detection of restriction fragment length polymorphisms) and Southern blotting, comparing the resulting bands with those of the parents and recording any absence of a paternal allele. Recently Dittrich *et al* have developed a more refined technique involving probe PW71 (which maps to locus D15S63) in conjunction with a double restriction digest using the enzymes *HindIII* and *HpaII*, the latter being methylation

Figure 3 Diagram showing maternal disomy.

sensitive.³⁷ As the locus D15S63 is methylated on maternally derived chromosomes, and unmethylated on paternally derived chromosomes, it is possible to screen patients using Southern blotting techniques. In 27 patients with Prader-Willi syndrome and 16 with Angelman's syndrome, Prader-Willi patients had only one 6 kilobase (kb) band indicating either deletion in the paternally derived chromosome or maternal disomy, and patients with Angelman's syndrome only one 4.4 kb band indicating either deletion in the maternally derived chromosome or paternal disomy. Normal subjects will have both the 6 kb and 4.4 kb bands. This method is currently the most efficient in diagnosing affected individuals without the need for parental samples, but does not definitely distinguish between deleted and disomic patients.

Rapid diagnosis of Prader-Willi and Angelman's syndromes has been described by Mutirangura *et al* using dinucleotide repeat markers and the polymerase chain reaction.³⁸ This method is quicker and less labour intensive than studies using DNA probes, but is only informative in 70% of cases and requires samples from both parents.

Fluorescent in situ hybridisation with mapping of cosmids to the 15q11-13 region is an alternative approach and gives fairly rapid results in deleted cases, but will not detect disomy.

(2) CLINICAL DIAGNOSIS

Despite advances in molecular genetics, the Prader-Willi gene has not yet been identified with certainty so that the diagnosis remains clinical. Holm *et al* have developed two scoring systems for the diagnosis in children aged 0 to 3 years and from 3 years to adulthood.³⁹ In a multidisciplinary Prader-Willi clinic held in Glasgow since the beginning of 1992, 24 subjects have been seen by a team consisting of a neurologist, clinical geneticist, endocrinologist, and dietitian. Sixteen patients satisfied the criteria for Prader-Willi syndrome both in the view of the Glasgow team and on the consensus criteria devised by Holm *et al*. Of these 12 were deleted, three disomic, while no abnormality could be detected in one girl with certain atypical features. The diagnosis of Prader-Willi syndrome was rejected on clinical grounds in eight of the other subjects and none of these showed any molecular genetic abnormality.

Reversing the diagnosis of Prader-Willi syndrome in these eight patients has inevitably resulted in considerable distress among some of the parents. This situation can be largely avoided by carrying out molecular genetic studies in all suspected cases and reconsidering the diagnosis if the results are negative. The consensus diagnostic criteria of Holm *et al* are useful and we would highlight the importance of tube feeding during infancy as well as sticky saliva and weak/absent cry (the latter two features are listed as minor criteria by Holm *et al*). By contrast, we consider the phenotype, especially the facies, to be more difficult to

assess objectively while the uncontrolled eating habits also lack specificity.

Metabolic and dietary aspects

Classically the obesity of Prader-Willi syndrome begins in the childhood phase, after the age of 1.5–2 years, although rarely it can become manifest from as early as 6 months of age.^{40–41} The deposition of excess fat may be severe in many subjects, especially in adolescence and adulthood.¹¹ Characteristically the subcutaneous fat is distributed mainly over the trunk, buttocks, and thighs.⁴² Untreated obesity is the most serious and common complication of Prader-Willi syndrome, contributing significantly to the morbidity and mortality.¹¹

Hyperphagia is the major cause of obesity. Prader-Willi subjects are notorious for their persistent and often ingenious ways of obtaining food. Common strategies include stealing, with night time raids on the kitchen and larder, finishing the uneaten lunches of classmates at school, and persuading carers to give food. Refusal to do so often leads to a tantrum. With unrestricted eating, energy intakes of $21\,736 \pm 209$ kJ (5200 ± 50 kcal)/day have been reported.⁴³

Increased intake is not the only factor in causing the obesity in Prader-Willi syndrome. Total energy expenditure, attributable to reduced activity, is reduced.⁴⁴ Body composition is abnormal with increased fat mass and percentage body fat.⁴⁵ However, in contrast to simple obesity, fat free mass is not increased so that there is a relative reduction in muscle mass.⁴⁵ Resting energy expenditure is normal when adjusted for the fat free mass content.⁴⁴ The composition of adipose tissue differs from simple obesity, with an increase in long chained polyunsaturated fatty acids.⁴⁵

Diabetes mellitus occurs in up to 20% of subjects with long standing Prader-Willi syndrome.^{11–46} The insulin resistance found is similar to that of simple obesity,⁴⁷ and clinically the diabetes behaves as type II non-ketotic diabetes responding to weight reduction and/or oral hypoglycaemic agents. If insulin is required a simple once daily long acting preparation is usually effective.

STRATEGIES FOR MANAGING THE OBESITY OF PRADER-WILLI SYNDROME

Constant supervision by parents, restriction of access to food by locking cupboards and refrigerator, and cooperation on the part of care givers (including the school and extended family) remain the cornerstone of management in preventing morbid obesity.^{48–49} With early diagnosis the obese phase of the disorder can be pre-empted.⁴⁸ In obese individuals, the energy intake must be adjusted to cause weight reduction, but success is more difficult to achieve in older subjects.⁴⁹ Guidelines have been given for the energy intakes required for weight loss ($29.3\text{--}33.4$ kJ (7.8 kcal)/cm height), and for weight maintenance ($41.8\text{--}58.5$ kJ ($10\text{--}14$ kcal)/cm height),^{42–48}

with 20% of energy from protein, 20–25% energy from fat, and the remaining 55–60% from carbohydrate. Other dietary approaches have been used including low carbohydrate diets,⁴⁰ very low energy diets,⁵⁰ and ketogenic diets,⁴⁵ with some success but their value lies largely in achieving control in the short term. Behavioural management approaches have proved helpful in weight reduction,^{45 50} and these techniques, combined with energy restriction under the guidance of an experienced dietitian, form the basis of conventional care.

The inevitable problems of achieving satisfactory weight control in some individuals has prompted the search for other forms of treatment. Surgical management with gastric bypass is a drastic but effective strategy in the treatment of morbid obesity.⁵¹ Various drug treatments have been tried with limited success. Appetite suppressants such as fenfluramine have been used with mixed results, and further studies of longer term treatment are required to determine their effectiveness.⁵² Naltrexone, a blocker of the endogenous opioids, has proved ineffective in reducing nutrient intake in Prader-Willi individuals,⁵³ although the possibility that other similar antagonists may be more successful remains to be tested.

Growth hormone, with its effect on protein synthesis and lipid metabolism might be expected to have a beneficial role in the Prader-Willi syndrome, especially given the abnormal body composition with increased fat and reduced muscle. In Dundee a recent study on 12 Prader-Willi subjects aged 5–16 years has shown an encouraging increase in fat free mass over a six week period using growth hormone in doses of 15 and 20 units/m²/week in children and adolescents respectively. However, all but one subject gained weight while a particularly obese 14 year old boy developed type II diabetes mellitus within three weeks of starting treatment, responding to dietary restriction and oral hypoglycaemic agents. There was also a subjective impression on the part of several parents that their children showed an increase in appetite on growth hormone treatment. A future role for growth hormone in preventing the obesity of Prader-Willi syndrome is doubtful, but further work is required to investigate its value in improving muscle mass.

Growth aspects

The growth pattern of children with Prader-Willi syndrome is characteristic with low or normal birth length and poor growth during infancy.⁵⁴ In contrast to simple obesity where children are relatively tall with enhanced height velocity and advance in bone age, obese Prader-Willi subjects are short, usually 10th centile and below, with normal or low height velocity for age, and bone age delay until late childhood. There is also a selective aspect to the reduced growth affecting the hands and feet particularly, while the lower body segment is relatively short compared with the sitting

height.⁵⁵ These factors, combined with poor growth at adolescence, contribute towards the low final adult height.^{11 56}

The existence of growth hormone deficiency in the Prader-Willi syndrome is debated. Several studies have demonstrated a subnormal growth hormone response to insulin induced hypoglycaemia,⁵⁷ but this response is similar to the blunting effect of simple obesity.^{58 59} However, one study has reported an abnormally low growth hormone response to clonidine stimulation in lean children with Prader-Willi syndrome suggesting that growth hormone deficiency is a genuine feature of the condition and not an artefact of the obesity.⁶⁰ In Glasgow, of 11 patients tested for growth hormone deficiency using insulin hypoglycaemia, peak concentrations were less than 10 mU/l in six patients, 10–20 mU/l in three, and greater than 20 mU/l in only two. Pituitary imaging was carried out in only one patient and showed marked pituitary hypoplasia on high resolution computed tomography that was subsequently confirmed by magnetic resonance imaging. Given the difficulties in interpreting dynamic tests of growth hormone stimulation in obese subjects, the value of detailed pituitary imaging in the Prader-Willi syndrome should be examined prospectively.

The role of growth hormone treatment in the statural management of Prader-Willi syndrome is undecided. While an improvement in short term height velocity has been documented⁶⁰ there are no satisfactory data on final height. In Glasgow our experience of final and near final height is limited, but cautiously optimistic. Three subjects aged 13·7, 16·3, and 17·6 years have received growth hormone for a minimum of three years with no additional sex steroid treatment and height SD scores have changed from –3·5 to 0·7, –5·2 to –2·7, and –4·3 to –1·5 respectively, with final height achieved in the latter two patients. Given the rarity of the condition, the effect of growth hormone on final height will be difficult to evaluate unless data from different centres are pooled, restricting analysis to patients in whom the diagnosis has been confirmed by molecular studies.

Conclusion

The Prader-Willi syndrome results from a disturbance of molecular arrangement in a critical area of 15q, with widespread effect on the central nervous system. Correct diagnosis is essential, and can be achieved by combining clinical diagnostic criteria with molecular genetic (as opposed to cytogenetic) techniques. Dietary supervision remains the mainstay in management of the obesity. Further work to explore a potential role for growth hormone in improving body composition is justified. Detailed studies of hypothalamo-pituitary function including high resolution imaging may clarify the endocrine pathology, and collaborative work is needed to examine the effect of growth hormone treatment on final height.

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