

The Changing Purpose of Prader-Willi Syndrome Clinical Diagnostic Criteria and Proposed Revised Criteria

Meral Gunay-Aygun, MD*; Stuart Schwartz, PhD‡; Shauna Heeger, MS‡; Mary Ann O'Riordan, MSS‡; and Suzanne B. Cassidy, MD||

ABSTRACT. *Background.* Prader-Willi syndrome (PWS) is a complex, multisystem disorder. Its major clinical features include neonatal hypotonia, developmental delay, short stature, behavioral abnormalities, childhood-onset obesity, hypothalamic hypogonadism, and characteristic appearance.^{1,2} The genetic basis of PWS is also complex. It is caused by absence of expression of the paternally active genes in the PWS critical region on 15q11-q13. In approximately 70% of cases this is the result of deletion of this region from the paternal chromosome 15. In approximately 28%, it is attributable to maternal uniparental disomy (UPD; inheritance of 2 copies of a chromosome from the mother and no copies from the father, as opposed to the normal 1 copy from each parent) of chromosome 15, and in <2%, it is the result of a mutation, deletion, or other defect in the imprinting center.³⁻⁸

Clinical diagnostic criteria were established by consensus in 1993.¹ Subsequently, definitive molecular genetic testing became available for laboratory diagnosis of PWS. However, identification of appropriate patients for testing remains a challenge for most practitioners because many features of the disorder are nonspecific and others can be subtle or evolve over time. For example, hypotonic infants who are still in the failure to thrive phase of the disorder often do not have sufficient features for recognition of PWS and often are not tested. Initial screening with these diagnostic criteria can increase the yield of molecular testing for older children and adults with nonspecific obesity and mental retardation. Therefore, the purpose of clinical diagnostic criteria has shifted from assisting in making the definitive diagnosis to raising diagnostic suspicion, thereby prompting testing.

We conducted a retrospective review of patients with PWS confirmed with genetic testing to assess the validity and sensitivity of clinical diagnostic criteria published before the widespread availability of testing for all affected patients¹ and recommend revised clinical criteria.

Methods. Charts of all 90 patients with laboratory-confirmed PWS were reviewed. For each patient, the presence or absence of the major, minor, and supportive features listed in the published diagnostic criteria was

recorded. The sensitivity of each criterion, mean of the total number of major and minor criteria, and mean total score for each patient were calculated.

Results. There were 68 patients with a deletion (del 15q11-q13), 21 with maternal UPD of chromosome 15, and 1 with a presumed imprinting defect. Age range at the time of the most recent evaluation was 5 months to 60 years (median: 14.5 years; del median: 14 years; range: 5 months-60 years; UPD median: 18 years; range: 5-42 years).

The sensitivities of the major criteria ranged from 49% (characteristic facial features) to 98% (developmental delay). Global developmental delay and neonatal hypotonia were the 2 most consistently positive major criteria and were positive in >97% of the patients. Feeding problems in infancy, excessive weight gain after 1 year, hypogonadism, and hyperphagia were all present in 93% or more of patients.

Sensitivities of the minor criteria ranged from 37% (sleep disturbance and apneas) to 93% (speech and articulation defects). Interestingly, the sensitivities of 8 of the minor criteria were higher than the sensitivity of characteristic facial features, which is a major criterion.

Fifteen out of 90 patients with molecular diagnosis did not meet the clinical diagnostic criteria retrospectively.

Conclusion. When definitive diagnostic testing is not available, as was the case for PWS when the 1993 criteria were developed, diagnostic criteria are important to avoid overdiagnosis and to ensure that diagnostic test development is performed on appropriate samples. When diagnostic testing is available, as is now the case for PWS, diagnostic criteria should serve to raise diagnostic suspicion, ensure that all appropriate people are tested, and avoid the expense of testing unnecessarily. Our results indicate that the sensitivities of most of the published criteria are acceptable. However, 16.7% of patients with molecular diagnosis did not meet the 1993 clinical diagnostic criteria retrospectively, suggesting that the published criteria may be too exclusive. A less strict scoring system may ensure that all appropriate people are tested.

Accordingly, we suggest revised clinical criteria to help identify the appropriate patients for DNA testing for PWS. The suggested age groupings are based on characteristic phases of the natural history of PWS. Some of the features (eg, neonatal hypotonia, feeding problems in infancy) serve to diagnose the syndrome in the first few years of life, whereas others (eg, excessive eating) are useful during early childhood. Similarly, hypogonadism is most useful during and after adolescence. Some of the features like neonatal hypotonia and infantile feeding problems are less likely to be missed, whereas others such as characteristic facial features and hypogonadism (especially in prepubertal females) may require more careful and/or expert examination.

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The issue of who should have diagnostic testing is distinct from the determination of features among confirmed patients. Based on the sensitivities of the published criteria and our experience, we suggest testing all newborns/infants with otherwise unexplained hypotonia with poor suck. For children between 2 and 6 years of age, we consider hypotonia with history of poor suck associated with global developmental delay sufficient criteria to prompt testing. Between 6 and 12 years of age, we suggest testing those with hypotonia (or history of hypotonia with poor suck), global developmental delay, and excessive eating with central obesity (if uncontrolled). At the ages of 13 years and above, we recommend testing patients with cognitive impairment, excessive eating with central obesity (if uncontrolled), and hypogonadotropic hypogonadism and/or typical behavior problems (including temper tantrums and obsessive-compulsive features). Thus, we propose a lower threshold to prompt diagnostic DNA testing, leading to a higher likelihood of diagnosis of this disorder in which anticipatory guidance and intervention can significantly influence outcome. *Pediatrics* 2001;108(5). URL: <http://www.pediatrics.org/cgi/content/full/108/5/e92>; Prader-Willi syndrome, diagnostic criteria, 15q deletion, uniparental disomy, microdeletion, fluorescence in situ hybridization, methylation analysis, chromosome 15, obesity, mental retardation, imprinting.

ABBREVIATIONS. PWS, Prader-Willi syndrome; UPD, uniparental disomy; FISH, fluorescence in situ hybridization; RFLP, restriction fragment length polymorphisms.

Prader-Willi syndrome (PWS) is a complex, multisystem disorder. Its major clinical features include neonatal hypotonia, developmental delay, short stature, behavioral abnormalities, childhood-onset obesity, hypothalamic hypogonadism, and characteristic appearance.¹⁻² The genetic basis of PWS is also complex. It is caused by absence of expression of the paternally active genes in the PWS critical region on 15q11-q13. In approximately 70% of cases this is the result of deletion of this region from the paternal chromosome 15. In approximately 28%, it is attributable to maternal uniparental disomy (UPD; inheritance of 2 copies of a chromosome from the mother and no copies from the father, as opposed to the normal 1 copy from each parent) of chromosome 15, and in <2%, it is the result of a mutation or deletion in the imprinting center³⁻⁸ or other imprinting defect.

Following the clinical availability of methylation analysis and UPD studies for standardized analysis of parent-of-origin for genes in this region, these tests and fluorescence in situ hybridization (FISH) became the gold standard for diagnosing PWS.⁹ Methylation analysis detects all 3 groups of molecular defects described above. If biparental inheritance is identified, then PWS is ruled out. If the methylation pattern is abnormal, FISH can be used to document a deletion and/or microsatellite probes can be used to confirm maternal UPD. Abnormal methylation and negative FISH and UPD studies indicate an imprinting defect.

Although the definitive diagnosis of PWS is currently made by genetic testing, clinical diagnostic

criteria continue to have importance, especially for selection of appropriate patients for testing. Diagnostic criteria for PWS were first proposed by Holm in 1981.¹⁰ In 1993, clinical diagnostic criteria for PWS were developed through a consensus process¹ (Table 1). At the time the consensus criteria were developed, deletions had been seen microscopically, but FISH was not yet widely available, nor were methylation or microsatellite analysis available clinically. The goal of these diagnostic criteria was to help practicing clinicians confirm or rule out the diagnosis of PWS on a clinical basis. Now that definitive diagnosis of PWS is made by genetic testing, clinical diagnostic criteria should be used more often to raise diagnostic suspicion and prompt testing.

To determine the accuracy and validity of the previously published criteria, we conducted a retrospective review of patients with molecular confirmation of PWS to see whether the 1993 criteria represented the optimally sensitive characteristics and to determine how well they performed in selecting the most appropriate patients for testing.

METHODS

Subjects and Clinical Findings

Charts of the approximately 300 patients followed by one of us (S.B.C.) in the PWS Management Clinics at University of Arizona (1988–1994), University of Connecticut (1981–1999), and University Hospitals of Cleveland (1993–1999) were reviewed to identify those who had a laboratory-confirmed diagnosis. Of the 300 total patients, the 90 with completed definitive molecular confirmation at the time were included in the study. Other patients followed in these clinics for many years have not had complete molecular testing either because of lack of available financial reimbursement for these tests or because of decision by their parents or guardians not to test without management implications. Others have not been seen since molecular testing became available and standardized. All chart reviews were done by a single author (M.G.A.) so that differences in identification of subjective findings were minimized.

Laboratory Methodology

Most patients had been initially studied with high-resolution chromosome analysis, and the presence or absence of a deletion was determined using FISH. The FISH studies performed before 1994 involved a combination of probes D15S11 and GABRB3, whereas after the commercial release of the SNRPN FISH probe, this probe was used alone. If initial studies with D15S11 and GABRB3 were negative, the cases were then studied with the SNRPN probe. If FISH studies detected a deletion, no additional studies were performed. If FISH did not show a deletion, UPD and methylation studies were undertaken simultaneously in 16, methylation analysis alone was performed in 3 (because of lack of availability of 1 or both parents), and only UPD studies with restriction fragment length polymorphisms (RFLP) were performed in 2 of the 21 UPD patients.

Cytogenetic analysis, DNA extraction, microsatellite analysis for UPD, and methylation analysis were performed according to standard methods, as previously described.⁹ RFLP analysis was also performed using standard methodology as previously described.¹¹

Statistical Analysis

For each patient, the presence or absence of the major, minor, and supportive features listed in the published diagnostic criteria was recorded. For each criterion, the number of patients for whom that criterion was documented was divided by the number of total patients to calculate the percentage of documentation for each criterion. The sensitivity of each criterion except for the abnormal genetic test criterion was calculated by dividing the number of

TABLE 1. Published Diagnostic Criteria for PWS

Major Criteria

1. Neonatal and infantile central hypotonia with poor suck, gradually improving with age
2. Feeding problems in infancy with need for special feeding techniques and poor weight gain/failure to thrive
3. Excessive or rapid weight gain on weight-for-length chart (excessive is defined as crossing two centile channels) after 12 months but before 6 years of age; central obesity in the absence of intervention
4. Characteristic facial features with dolichocephaly in infancy, narrow face or bifrontal diameter, almond-shaped eyes, small-appearing mouth with thin upper lip, down-turned corners of the mouth (3 or more are required).
5. Hypogonadism—with any of the following, depending on age:
 - a. Genital hypoplasia, (male: scrotal hypoplasia, cryptorchidism, small penis and/or testes for age (<5th percentile); female: absence or severe hypoplasia or labia minora and/or clitoris
 - b. Delayed or incomplete gonadal maturation with delayed pubertal signs in the absence of intervention after 16 years of age (male: small gonads, decreased facial and body hair, lack of voice change; female: amenorrhea/oligomenorrhea after age 16)
6. Global developmental delay in a child <6 years of age; mild to moderate mental retardation or learning problems in older children
7. Hyperphagia/food foraging/obsession with food
8. Deletion 15q11–13 on high resolution (>650 bands) or other cytogenetic molecular abnormality of the Prader-Willi chromosome region, including maternal disomy

Minor Criteria

1. Decreased fetal movement or infantile lethargy or weak cry in infancy, improving with age
2. Characteristic behavior problems—temper tantrums, violent outbursts, and obsessive-compulsive behavior; tendency to be argumentative, oppositional, rigid, manipulative possessive, and stubborn; perseverating, stealing, and lying (5 or more of these symptoms required)
3. Sleep disturbance and sleep apnea
4. Short stature for genetic background by age 15 (in the absence of growth hormone intervention)
5. Hypopigmentation—fair skin and hair compared with family
6. Small hands (<25th percentile) and/or feet (<10th percentile) for height age.
7. Narrow hands with straight ulnar borders
8. Eye abnormalities (esotropia, myopia)
9. Thick viscous saliva with crusting at corners of the mouth
10. Speech articulation defects
11. Skin-picking

Supportive Findings

1. High pain threshold
2. Decreased vomiting
3. Temperature instability in infancy or altered temperature sensitivity in older children and adults
4. Scoliosis and/or kyphosis
5. Early adrenarche
6. Osteoporosis
7. Unusual skill with jigsaw puzzles
8. Normal neuromuscular studies

To score, major criteria are weighted at 1 point each, and minor criteria are weighted at ½ point each. Supportive findings increase the certainty of diagnosis but are not scored. For children 3 years of age or younger, 5 points are required, 4 of which should come from the major group. For children >3 years of age and for adults, a total score of 8 is required and major criteria must comprise 5 or more points of the total score.

patients who are positive for that criterion by the number for whom that criterion was documented.

RESULTS

Of the 90 patients with molecularly confirmed diagnosis, 68 had deletion and 21 had maternal UPD. The remaining patient was a 6-year-old who had abnormal methylation analysis with biparental inheritance, presumably attributable to an abnormality in the imprinting process. Age range at the time of most recent evaluation was 5 months to 60 years (median: 14.5 years; del median: 14 years; range: 5 months–60 years; UPD median: 18 years; range: 5–42 years).

The percentages of documentation and sensitivities of the major and minor criteria are summarized in Table 2. The percent documented for major criteria ranged from 51.1% to 98.9%. The sensitivities of the major criteria ranged from 49.4% to 97.8%. Global developmental delay and neonatal hypotonia were the 2 most consistently positive major criteria, being positive in >97% of the patients. Feeding problems in infancy, excessive weight gain after 1 year, hypo-

gonadism, and hyperphagia were all present in 93% or more of patients. Characteristic facial features was the least sensitive major criterion, being positive in only 49.4% of the patients.

The percent documented for minor criteria ranged between 62.2% and 88.9% (Table 2). The most frequently positive minor criterion was speech and articulation defects, with a sensitivity of 93%, followed closely by several others.

Fifteen (16.7%) of the 90 patients with molecular diagnosis did not meet the clinical diagnostic criteria of Holm et al,¹ retrospectively. (See the end of Table 1 for an explanation of scoring of diagnostic criteria for a clinical diagnosis of PWS). All were above 3 years of age. Fourteen had deletion and 1 had UPD. Mean total score of these 15 patients was 6.9 (range: 5–7.5; 8 required). Five of these 15 patients had <5 points of the total score from the major criteria (at least 5 required from the major criteria).

When the sensitivity of each criterion was compared between patients with deletion and UPD, the difference between sensitivities was significant only

TABLE 2. Sensitivities and the Percentages of Documentation of the Published Criteria

	% Documented	Sensitivity
Major criteria		
Neonatal hypotonia	87.9	97.5
Feeding problems in infancy	77.8	95.7
Excessive weight gain	66.7	95.0
Facial features	88.4	49.4
Hypogonadism	51.1	95.6
Developmental delay	98.9	97.8
Hyperphagia	84.4	93.4
Minor criteria		
Decreased fetal activity	62.2	89.3
Behavior problems	86.7	82.1
Sleep disturbance/sleep apnea	75.6	36.8
Short stature	63.3	86.0
Hypopigmentation	73.3	47.0
Small hands and/or feet	87.8	74.7
Narrow hands/straight ulnar borders	82.2	69.0
Eye abnormalities	67.8	49.2
Thick viscous saliva	88.9	82.5
Articulation defects	80.0	93.1
Skin-picking	83.3	61.3

for hypopigmentation (18.8% in UPD; 56.0% in del; $P = .01$) and almond-shaped eyes (55.0% in UPD; 80.7% in del; $P = .04$) (data not shown).

DISCUSSION

Although diagnostic molecular testing for PWS is currently available, clinical identification of patients for testing remains a challenge because many features of PWS are nonspecific and others evolve over time or can be subtle. Hypotonic infants who are still in the failure to thrive phase of the disorder do not have sufficient features to prompt recognition of PWS and often are not tested. On the other hand, initial screening with clinical diagnostic criteria can increase the yield of molecular testing for older children and adults with nonspecific obesity and mental retardation.

In this study, the sensitivities of the major criteria ranged between 93% and 98% (Table 2) except for characteristic facial features, which was present in only 49% of the patients. Interestingly, only 3 of the 11 minor criteria were lower in sensitivity than the major criterion characteristic facial features. The fact that all the patients included in the study were examined by the same individual (S.B.C.) minimizes

the variability of this assessment and makes it more likely that this lower sensitivity reflects real differences in the facial features among people with PWS. Higher likelihood of difficulty in recognizing facial features among practitioners who rarely see affected individuals with PWS further decreases the value of characteristic facial features as a diagnostic criterion. In general, the sensitivities of the minor criteria were lower than those of the major criteria (Table 2). One would expect the sensitivities of the criteria decreased fetal activity and neonatal hypotonia to be similar as they are etiologically related. Variability in the mothers' perception of decreased fetal activity may explain the relatively lower sensitivity of this criterion.

When the sensitivity of each criterion was compared between genotypes, the difference between sensitivities was significant only for hypopigmentation and almond-shaped eyes. Sensitivity of hypopigmentation was 19% in the UPD group and 56% in the deletion group. The hypopigmentation difference is a good test of our methodology because there is a pigmentation gene, the P gene, which codes for a tyrosine transporter within the common deleted region that is not imprinted.¹² Thus, this difference in hypopigmentation may be associated with hemizygosity for this gene in the deletion group. The sensitivity of almond-shaped eyes was 55% in the UPD and about 80% in the deletion group. This finding is consistent with our group's previous study suggesting that patients with UPD may not have typical facial features.¹³

The major limitation of our study is that documentation was available for <100% of the patients for each criterion, because it was a retrospective chart review. Specificity of the criteria could not be calculated because of a lack of sufficient data on patients with clinical findings suggestive of PWS and negative molecular tests. Finally, bias of referral may have influenced our results.

When definitive diagnostic testing is not available, as was the case for PWS when the 1993 criteria were developed, diagnostic criteria are important to avoid overdiagnosis and ensure that diagnostic test development is performed on appropriate samples. When diagnostic testing is available, as is now the case for PWS, diagnostic criteria should serve to raise diag-

TABLE 3. Suggested New Criteria to Prompt DNA Testing for PWS

Age at Assessment	Features Sufficient to Prompt DNA Testing
Birth to 2 y	1. Hypotonia with poor suck.
2 y–6 y	1. Hypotonia with history of poor suck. 2. Global developmental delay.
6 y–12 y	1. History of hypotonia with poor suck (hypotonia often persists). 2. Global developmental delay. 3. Excessive eating (hyperphagia; obsession with food) with central obesity if uncontrolled.
13 y through adulthood	1. Cognitive impairment; usually mild mental retardation. 2. Excessive eating (hyperphagia; obsession with food) with central obesity if uncontrolled. 3. Hypothalamic hypogonadism and/or typical behavior problems (including temper tantrums and obsessive-compulsive features).

nostic suspicion, ensure that all appropriate people are tested, and avoid the expense of testing unnecessarily. Our results indicate that the sensitivities of most of the published criteria are acceptable. However, 16.7% of patients in this study with molecular diagnosis did not meet the 1993 clinical diagnostic criteria retrospectively, suggesting that the published criteria may be too exclusive. A less strict scoring system may ensure that all appropriate people are tested.

Accordingly, we suggest revised clinical criteria to help identify the appropriate patients for DNA testing for PWS (Table 3). The suggested age groupings are based on characteristic phases of the natural history of PWS. Some of the features (eg, neonatal hypotonia, feeding problems in infancy) serve to diagnose the syndrome in the first few years of life, whereas others (eg, excessive eating) are useful during early childhood. Similarly, hypogonadism is most useful during and after adolescence. On the other hand, some of the features like neonatal hypotonia and infantile feeding problems are less likely to be missed, whereas others such as characteristic facial features and hypogonadism (especially in prepubertal females) may require more careful and/or expert examination.

The issue of who should have diagnostic testing is distinct from the determination of features among confirmed patients. Based on the sensitivities of the published criteria and our experience, we suggest testing all newborns/infants with otherwise unexplained hypotonia with poor suck (Table 3). For children between ages 2 and 6 years of age, we consider hypotonia with history of poor suck associated with global developmental delay sufficient to prompt testing. Between 6 and 12 years of age, we suggest testing those with hypotonia (or history of hypotonia with poor suck), global developmental delay, and excessive eating with central obesity (if uncontrolled). At the ages 13 years and above, we recommend testing

patients with cognitive impairment, excessive eating with central obesity (if uncontrolled), and hypogonadotropic hypogonadism and/or typical behavior problems (including temper tantrums and obsessive-compulsive features). Thus, we propose a lower threshold to prompt diagnostic DNA testing.

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