

RAPID PUBLICATION

REPORT FROM THE WORKSHOP ON PALLISTER-HALL SYNDROME AND RELATED PHENOTYPES.

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A one day workshop was convened on the NIH campus on March 1, 1996, in Bethesda, Maryland to discuss emerging clinical and molecular information on Pallister-Hall syndrome (PHS) and related disorders. PHS is a pleiotropic autosomal dominant disorder comprising hypothalamic hamartoma, pituitary dysfunction, central polydactyly, and visceral malformations. The goals of the meeting were to update participants in the latest clinical and research findings in the disorder, review the history and evolution of the understanding of the phenotype, determine diagnostic criteria for PHS, and make recommendations for clinical evaluation of individuals affected by PHS. These topics were addressed by several speakers (Table I) and data were displayed

from several of the large pedigrees of autosomal dominant PHS.

Following these presentations, interim diagnostic criteria for PHS were developed (Table II). These criteria are intended to be used for research and for clinical studies. It was a consensus that the criteria should be as simple and as useful as possible given the current state of knowledge. The group acknowledged that these criteria may need to be revised after the gene or genes for these disorders are cloned and the mutations characterized.

The diagnosis of PHS is unlikely if the patient has preaxial duplication of the hallux, hamartomas of the tongue, or signs of skeletal dysplasia. The diagnosis is excluded if the patient has laboratory results consistent with a block in cholesterol metabolism. The inclusion of histologic evidence of a hypothalamic hamartoma in criterion A1 is not intended to imply that biopsy should be

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TABLE I. Formal Presentations at the Workshop

History and Evolution of PHS Judith Hall	Phenotypes Related to PHS Alain Verloes
The Overlap of Oral-Facial-Digital syndromes and PHS Giovanni Neri	Neurologic Evaluation and Management of PHS Daniel Lefton and Jeffrey Allen
Phenotype of PHS John M. Graham, Jr.	Genetic Analysis of Familial PHS Leslie Biesecker

TABLE II. Diagnostic Criteria for Pallister-Hall syndrome

A. Index case. Both of the following findings must be present in at least one person in a family (index case):

1. Hypothalamic hamartoma characterized on magnetic resonance imaging (MRI) as a non-enhancing, midline hypothalamic mass that is isointense to gray matter on all pulse sequences, or histologic confirmation of a hypothalamic hamartoma.
2. Central polydactyly, most commonly including skeletal polysyndactyly of the third or fourth digit.

B. First degree relatives of an index case. Both of the following must be present in the relative:

1. Either finding A1 or A2 alone*.
2. Inheritance of A1 or A2 in an autosomal dominant pattern or in a manner consistent with gonadal mosaicism.

*After confirmation of the diagnosis in an index case, postaxial polydactyly may be substituted for central polydactyly.

used to make or confirm the diagnosis of PHS. This criterion allows anatomic and/or histologic support for the diagnosis of the syndrome in patients who died before an MRI study could be performed or was available. Available clinical data suggest that hypothalamic hamartomas are benign lesions in many, if not all cases of PHS. Patients should be evaluated clinically and biopsied only if there is ambiguity about the MRI determination of hamartoma versus another central nervous system tumor or suspicion of compression of a critical brain structure.

Patients who have some signs of PHS but do not meet these diagnostic criteria should be investigated carefully for other signs of the disorder. The following signs and

symptoms should raise suspicion of PHS, especially when they are found with one of the two main diagnostic criteria listed above: precocious puberty, micropenis in males, buccal frenula, hand malformations other than central polydactyly (particularly brachytelephalangy with associated nail hypoplasia), and epiglottic and /or laryngeal clefts, renal anomalies, abnormal lung lobation, anorectal anomalies, small and rounded ears, and short nose.

In addition to these diagnostic criteria, recommendations for the evaluation of possibly affected individuals and apparently unaffected parents were also outlined by the participants (Table III). This list is intended to be a guide for clinicians managing a rare

malformation syndrome and reflect the best judgment of geneticists who have experience with this disorder. They are neither exhaustive nor mandatory and the clinician should be the final arbiter of tests to be performed.

The participants were convinced that MRI should be used in all cases where imaging to detect a possible hamartoma is indicated. Neither computed tomography nor ultrasound study would be expected to be particularly useful for the detection of a hypothalamic hamartoma.

The Smith-Lemli-Opitz syndrome has several signs in common with sporadic congenital cases of PHS. In addition, it is possible that there may be other defects of cholesterol metabolism than the block of 7-dehydrocholesterol to cholesterol that causes Smith-Lemli-Opitz syndrome. Interested geneticists should contact the cholesterol biosynthetic testing laboratories for their current protocol because the assay procedures

for evaluating cholesterol metabolic defects are evolving rapidly. Endocrinology evaluation should be performed urgently in sporadic cases of PHS, or when PHS is considered a likely diagnosis. The risk of endocrine dysfunction in sporadic cases of PHS is high and hypoadrenalism is thought to be a major contributor to the high neonatal mortality rate of sporadic PHS. The risk in mildly affected inherited cases is unknown but apparently low.

The participants delineated a different set of recommendations for the apparently unaffected parents of persons affected with PHS (Table IV). These are interim recommendations that may be modified when genetic testing becomes available. These recommendations are based on current clinical evidence that is inadequate to exclude significant degrees of variable expressivity. The imaging data are considered clinically important because the recurrence risk estimates may change drastically on the basis of these results.

TABLE III Clinical Evaluation of Persons Possibly Affected with Pallister-Hall Syndrome

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- A. Detailed medical and family history and physical examination.
 - B. Unenhanced cranial MRI examination with addition of gadolinium contrast if a mass is detected on the unenhanced scan.
 - C. Full skeletal survey to detect generalized skeletal dysplasia.
 - D. Giemsa-banded karyotype of at least 600 band resolution if the index case has multiple congenital anomalies.
- Other studies to consider if clinical need exists or if the diagnosis seems probable:
- E. Endocrinology evaluation.
 - F. Assay for cholesterol synthetic defects.
 - G. Indirect laryngoscopy.
 - H. Renal ultrasonography.
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TABLE IV. Clinical Evaluation of Apparently Unaffected Parents.

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- A. Detailed medical and family history and physical examination.
 - B. Unenhanced cranial MRI examination with addition of gadolinium contrast if a mass is detected on the unenhanced scan.
 - C. AP radiographs of hands and feet.
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The workshop participants also identified three areas for active investigation and development priorities and outlined approaches likely to address these priorities:

1. Mapping of the gene or genes that cause PHS and characterization of the causative mutation.

Positional cloning of the gene for familial PHS is necessary to investigate questions of heterogeneity and overlap with other phenotypes. Specifically, it is still unclear whether the wide spectrum of severity (from prenatal/perinatal lethal to minimally symptomatic) is attributable to mutational or locus heterogeneity. The existing clinical data describing the breadth and continuity of this spectrum are compatible with either hypothesis. In addition, cloning of the PHS gene will allow studies to assess whether overlapping phenotypes (e.g., oral-facial-digital syndrome type VI, McKusick-Kaufman syndrome, Greig syndrome, Beemer-Langer syndrome, familial holoprosencephaly) are due to allelic or locus heterogeneity.

2. Characterization of the natural history of PHS.

Until 1993, PHS was thought to be an extremely rare, sporadic malformation syndrome that was uniformly lethal in the neonatal period. The evaluation of affected individuals from a number of large kindreds has shown that this earlier assessment was subject to significant ascertainment bias. It is important to gather additional information about known and new cases of PHS in order to define the range of variability and penetrance of this disorder.

3. Development of resources for families, clinicians, and researcher.

Because PHS is a rare disorder (fewer than 100 patients are known to the workshop participants) accessibility to current information regarding the condition is limited. It was decided that a World Wide Web site for PHS would be established by the NCHGR to increase the availability of information for patients, families, and professionals. This site will include:

- A. A home page.
- B. The diagnostic criteria for PHS.
- C. A listing of consultants with expertise in the diagnostic evaluation and clinical care of persons with PHS.
- D. A description of the PHS support group with information about the support group, telephone number, and address.
- E. The recommended clinical evaluation of PHS.
- F. A description of current research into the cause and manifestations of PHS and contacts for persons who wish to participate.
- G. A PHS bibliography (Appendix)

The establishment of diagnostic criteria and recommendations for clinical evaluation of affected patients and their parents is intended to increase the identification of persons affected by this disorder. It is suspected that there are a significant number of undiagnosed cases of PHS due to the difficulty of diagnosing a disorder with such a wide range of variability. It is the hope and intent of this group to stimulate interest in this disorder, promote research, and improve the clinical care of the families with whom we are privileged to work.

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APPENDIX. Pallister-Hall Syndrome Bibliography

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