Syndrome of the month

Pallister-Hall syndrome

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A syndrome of hypothalamic hamartoma, polydactyly, panhypopituitarism, imperforate anus, and other visceral anomalies was delineated by Hall and colleagues in 1980.^{1,2} This syndrome has been most commonly designated Pallister-Hall syndrome (PHS) although some prefer the designation Hall-Pallister syndrome to parallel the authorship of that seminal description.³ The original report described six children, all of whom were sporadic cases and died with severe anomalies. Before that report, there are several descriptions of children who may have had the same disorder although the authors did not describe it as a distinct syndrome and did not thoroughly describe the anomalies.^{4,5} Because the cases of Hall *et al*.^{1,2} were severe and sporadic, the authors were cautious in their speculation about the range of severity that might be associated with this disorder and its inheritance pattern. There have been numerous case reports described in the 15 years following the report by Hall *et al*.^{1,2} These cases present a picture of an evolving phenotype with successively milder cases being assigned that diagnosis. In this summary we

Major manifestations of Pallister-Hall syndrome

Major manifestations	Frequency*
CNS	
Hypothalamic hamartoma	+++
Other CNS malformations	+
Limb	
Polydactyly	+++
Dysplastic nails	+++
Syndactyly	++
Endocrinological	
Pituitary dysplasia/hypopituitarism	++
Craniofacial (fig 1)	
Bifid epiglottis	++
Ear anomalies	++
Broad or flat nasal bridge	+
Short or anteverted nose	+
Visceral anomalies	
Imperforate anus	++
Renal anomalies	++
Congenital heart defects	+
Pulmonary segmentation anomalies	+

* Estimate of the frequency of the malformation or finding in patients with PHS: +++ very common, ++ frequent, + occasional. The characteristic malformations are in bold type.

provide a description of that evolving phenotype (table), discuss the inheritance of this disorder, and consider the clinical management for persons affected by PHS.

Key words: hypothalamic hamartoma; polydactyly; imperforate anus; hypopituitarism.

Figure 1 These four panels show facial views of the patient reported by Graham *et al*.²⁷ at birth and aged 4 years. In panels A and B note the presence of a short, upturned nose with depressed bridge, and small, round ears with overfolded superior helix. Panel C shows the small tongue and pointed chin at a later age. Panel D shows the child at 4 years with similar nasal features and a small, pointed chin.

Figure 2 (A) Inferior view of the brain from case 4 of Hall *et al*.¹ showing the protruding hypothalamic mass. (B) Sagittal section of that brain showing the extent of the hamartoma and relationship to the surrounding structures.

Figure 3 Sagittal cranial magnetic resonance image of the father reported by Topf et al.⁶ The open arrow indicates the hamartoma and the solid arrow indicates signals compatible with dysplastic pituitary tissue. Note the similarity of this lesion to that shown in the pathological specimen in fig 2B.

The evolving phenotype

As mentioned above, the original six cases of PHS were infants who died in the neonatal period with severe congenital anomalies.¹ The cause of death was thought to be a combination of the structural malformations and acute adrenal insufficiency secondary to pituitary hypoplasia. The adrenal hypoplasia is a severe manifestation of a sequence that begins with an abnormality of hypothalamic neural and glial proliferation or migration. This developmental anomaly results in an abnormal expansion of the hypothalamus (fig 2) and secondarily disrupts pituitary development (fig 3). The pituitary dysplasia then results in a spectrum of pituitary abnormalities ranging from asymptomatic pituitary displacement to pituitary hypoplasia with panhypopituitarism.

Prolonged survival in a child (now 11 years old) with all the major malformations associated with PHS was first documented in 1985.⁷ The oldest published survivor with the major malformations of PHS is a 33 year old

man with an affected son.⁶ Several other cases of prolonged survival have been reported recently,^{8,9} and it is clear that PHS should not be considered to be invariably lethal. In addition to the published cases of PHS there are two large pedigrees of families with autosomal dominant segregation of polydactyly and hypothalamic hamartoma.^{10,11} These two families include 22 and seven cases, respectively, of hypothalamic hamartoma and polydactyly with complete penetrance and excellent survival.

Differential diagnosis

The definition of PHS has evolved from a severe, lethal disorder to encompass a broader range of severity. Additionally, there has been much discussion about the relationship and possible overlap of PHS with several other disorders.¹²⁻¹⁴ Because the hand malformations of central or insertional polydactyly (figs 4 and 5) and the hamartomas are the most remarkable parts of the phenotype, we will focus on disorders that share those features with PHS.

Pallister-Hall syndrome shares a number of features with oral-facial-digital syndrome type VI (OFD VI). This condition was first described in an inbred gypsy family in Hungary and it is inherited in an autosomal recessive pattern.¹⁶ OFD VI has similar insertional polydactyly, but includes hamartomas of the tongue and cerebellar vermis hypoplasia. The report of a hypothalamic hamartoma in a case of OFD VI supports the notion of clinical overlap of this disorder with PHS.¹⁷ A second disorder that shares a similar type of polydactyly with PHS is the McKusick-Kaufmann or polydactyly-hydrometrocolpos syndrome.¹⁸ It also has an autosomal recessive inheritance pattern and was originally described in a clan of American Amish. In addition to the polydactyly, this disorder manifests hydrometrocolpos in females with other anomalies. McKusick-Kaufmann syndrome has also been associated with a hypothalamic hamartoma in a single case.¹⁹

Other overlapping disorders with more common types of polydactyly in combination with CNS malformations should be considered in the differential diagnosis of PHS. Smith-Lemli-Opitz syndrome (SLOS) includes variable CNS anomalies in association with postaxial polydactyly, and may also include the previously described entity of autosomal recessive polydactyly with holoprosencephaly or pseudotrisomy 13.²⁰ Smith-Lemli-Opitz syndrome has been associated with defects in cholesterol metabolism and the potential gene has been localised to 7q32.1 by physical mapping of a patient with SLOS and a de novo translocation.²¹ In spite of this clinical overlap, patients with PHS do not have a known abnormality of cholesterol metabolism.^{10,14} In addition, no patients with biochemically proven SLOS are known to have a hypothalamic hamartoma. Furthermore, familial PHS is not linked to 7q32.1.¹⁰

Other disorders that have clinical overlap with PHS include the hydrolethrus syndrome,²² Beemer-Langer syndrome,²³ Greig

Figure 4 Hand radiographs from the son reported by Topf et al.⁶ This radiograph shows asymmetrical hand malformations consisting of unilateral central or insertional polysyndactyly and contralateral postaxial polydactyly.

Figure 5 Panel A (from case 2 of Hall *et al*¹) shows tapered digits with clinodactyly and hypoplastic fingertips and nails. The fifth finger had two phalangeal rays with a single fifth metacarpal on radiographic examination. The fourth metacarpal was hypoplastic. Panel B (from case 1 of Iaffola *et al*¹⁵) shows a hand with severe distal digital and nail hypoplasia. The other hand shows three fingers and a thumb. Panel C (case 2 of Graham *et al*¹) shows a hand radiograph with an example of type b postaxial polydactyly with a Y shaped metacarpal. The distal digits are hypoplastic. Panel D is a photograph of the same hand as in panel C showing clinodactyly of the fifth digit and postaxial polydactyly.

cephalopolysyndactyly syndrome,²⁴ Meckel syndrome,²⁵ and Ellis-van Creveld syndrome.²⁶ These cases, and others, have led to the assertion that they are part of a malformation complex termed CAVE (cerebro-acro-visceral-early lethality) complex.¹² This concept addresses the variety of combinations of anomalies that comprise these syndromes and acknowledges the difficulty of making a single unifying diagnosis in some cases. However, it does not address the variability in prognoses, specifically that not all cases of PHS manifest early lethality. Nonetheless, it is reasonable to assume that hypothalamic hamartomas are aetiologically heterogeneous, and the acronym CAVE complex may still be useful, if the E is used for the endocrine abnormalities that frequently accompany hypothalamic hamartomas, rather than for early lethality.

Over the past 15 years, Pallister-Hall syndrome has evolved from a disorder that was originally considered to be severe and lethal, to a spectrum of anomalies that includes hypothalamic hamartoma and polydactyly with variable somatic malformations. As is true for many disorders, this evolution is the result of the initial identification of severely affected sporadic cases, with subsequent identification of more mild cases. We believe that much of this confusion is attributable to inconsistent and erratic ascertainment of a rare disorder

and that molecular analysis will allow the phenotypes to be properly categorised and distinguished.

Aetiological considerations

The original report by Hall *et al*¹ discussed a number of aetiological hypotheses for this disorder. As is prudent when faced with several cases of a sporadic disorder in the absence of consanguinity, the authors considered genetic and non-genetic causes. The genetic considerations included new mutations in a gene inherited in an autosomal dominant pattern, a gene inherited in an autosomal recessive pattern with a low population frequency of mutant alleles, or submicroscopic chromosomal alterations. In addition, they considered teratogenic or environmental causes although no consistent exposure could be identified.

The first insight into the aetiology of PHS was a case report of an affected proband (fig 5) who had a history of a maternal aunt who died at birth with similar features, including polydactyly.²⁷ This case was the first to suggest autosomal dominant inheritance of PHS and implied that penetrance of the mutant allele was less than 100%. Additional familial cases were described in 1993, when autosomal dominant inheritance was unambiguously shown by documentation of father to son transmission.⁶ Interestingly, that father was less severely affected than his son, suggesting that expressivity might be variable, or that mosaic founders could be less severe. Thomas *et al*²⁸ described two sibs affected with PHS who had a father with polydactyly of the feet. Penman-Splitt *et al*²⁹ described an affected mother with short limbs, polydactyly, a bifid epiglottis, and renal anomalies, who had two affected sibs (one of which died on day 1 with a hypothalamic hamartoma), and Löw *et al*⁹ described an affected mother with polydactyly and a hypothalamic hamartoma, who had a similarly affected son. All of these cases are compatible with an aetiological hypothesis of a mutation in a single gene inherited in an autosomal dominant pattern with either variable expressivity or founder mosaicism.

Several additional case reports described affected sibs with thorough evaluation and documentation of the absence of anomalies in both parents.^{30,31} These cases would suggest either that there are founder mosaics with normal phenotypes (gonadal mosaics or gonosomal mosaics with non-penetrance) or an autosomal recessive phenocopy. Larger pedigrees with features of PHS in an autosomal dominant inheritance pattern also exist. As described above, the larger families have milder manifestations, associated with normal reproductive fitness. These families range in size from four to 22 affected persons. In these pedigrees there are no instances of non-penetrance in the 15 persons who are obligate heterozygotes. Variable expressivity is shown and includes variation in the type of hand malformations and in the presence of the hypothalamic hamartoma.

One case report included a cytogenetic evaluation of a hypothalamic hamartoma.²⁷ This lesion showed absence of chromosome 17 in two of 43 cells. No other tumour cytogenetic analyses have been reported. Hypothalamic hamartoma associated with premaxillary agenesis and microphthalmia (but not with polydactyly) has been associated with an unbalanced translocation (46,XY,-7,+der7,t(3;7)(p25.4;q36) in one family.³² Such data can be helpful in delineating the cause of complex malformations by directing the search for linkage to specific areas of the genome. We have shown that familial PHS is not linked to 7qter, 7q32.1, or 3pter by linkage analysis.¹⁰ These data suggest that familial PHS is aetiologically distinct from the cause of hypothalamic hamartoma seen in this family, and that hypothalamic hamartoma is a malformation with aetiological heterogeneity. Alternatively, the translocation could be more complex than is appreciated by microscopic analysis and involve another area of the genome that includes the PHS locus.

Clinical considerations

Current issues with PHS patients include genetic counselling of sporadic and familial cases, variable expressivity, and management of the complications of the disorder. Genetic counselling of patients with PHS is complicated by the incomplete knowledge of the spectrum of severity, possible cases of incomplete penetrance and expressivity, and possible aetiological heterogeneity. Estimating recurrence risks for sporadic cases is very difficult and can be performed confidently only with extremely wide ranges of risk. The presence of subtle malformations in parents of children with PHS means that thorough evaluation of parents should be performed in all cases before genetic counselling. The existence of large families with polydactyly and asymptomatic hypothalamic hamartomas raises the question of the depth of evaluation that is indicated for persons and families with apparently isolated polydactyly. Given that this picture is known to exist, it seems prudent to consider cranial MRI examination in families with four limb polydactyly.

A careful history and targeted evaluation of the hypothalamic-pituitary axis are indicated in persons with PHS. Younger patients should be carefully evaluated for signs and symptoms of adrenal insufficiency because of its devastating consequences. This appears to be infrequent in large families with asymptomatic adults, but there are insufficient data to be confident about this conclusion.^{10,11} Ophthalmological evaluation with visual field testing is indicated in patients with hypothalamic hamartomas owing to their proximity to the optic chiasm. The presence of airway malformations in some affected people warrants careful evaluation before elective surgical procedures.

The management of hypothalamic hamartomas is problematical. Initially, these lesions were believed to be malignant or premalignant

and some patients have undergone biopsy or resection of the hamartomas. Later analyses showed the benign, developmental nature of these lesions.³³ Given the presence of these apparently stable lesions in older people and the rarity of hydrocephalus or other manifestations of an expanding CNS tumour, we urge conservative management of these lesions. A perplexing problem is that of severe headaches in patients with hamartomas (unpublished observations). It is difficult to determine the best management for a patient with severe headaches and a CNS lesion that is usually benign. In at least one patient with PHS, surgical reduction of the lesion did not result in any improvement in the headaches and led to endocrinological complications.

Future directions

Improved understanding of the differential diagnosis and developmental pathology of PHS, as well as discrimination of discrete entities within the malformation spectrum of PHS will ultimately be gained by molecular analyses of families with this and related disorders. The description of larger families with PHS will allow a whole genome linkage approach to be used for positional cloning of the gene that causes this disorder. The isolation of the gene for PHS will then allow dissection of the PHS spectrum to determine if the more severe sporadic cases are the result of new mutations in the same gene or other genes in a common morphogenetic pathway. Similarly, the related phenotypes of OFD VI, McKusick-Kaufmann syndrome, etc, can be analysed to determine if they are allelic to PHS or the result of other genes that interact within this common morphogenetic pathway.

The clinical needs of patients with PHS and related disorders will continue to be met by careful consideration of individual symptoms and findings in the context of an improved understanding of the full spectrum of these malformations. Major challenges will continue to include appropriate management of the hypothalamic hamartomas and secondary endocrine dysfunction that are seen in some families. Improved understanding of the pathogenesis of the endocrine dysfunction will most likely be accomplished by detailed study of affected humans. An integrated approach of careful clinical analysis and positional cloning with molecular analysis will result in an improved understanding of this perplexing group of disorders.

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