

Heritable syndromes with hypothalamic hamartoma and seizures: using rare syndromes to understand more common disorders

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ABSTRACT – Manifestations of non-syndromic hypothalamic hamartomas are different from those of the syndromic hamartomas, and the syndromic ones are rare. In spite of the rarity of the syndromic hamartomas, they can be a powerful biological tool to help us understand the pathophysiology of these heritable disorders. Several disorders that include hypothalamic hamartomas are reviewed here and the current understanding of the biology of the lesions is summarized.

KEY WORDS: hypothalamic hamartoma, gelastic epilepsy, multiple abnormalities, developmental biology, heritable diseases, Pallister-Hall

There is a group of heritable syndromes that includes hypothalamic hamartoma (HH) as a manifestation. It is important for neurologists who care for patients with HH to be sufficiently familiar with these syndromes to allow proper evaluation and treatment of these patients, because in general, syndromic hypothalamic hamartomas have different manifestations compared to non-syndromic ones. The second part of this paper summarizes recent data on the molecular etiology of syndromic HH to highlight opportunities to advance our understanding of the molecular pathology of HH in general.

Heritable syndromes that include hypothalamic hamartoma

Pallister-Hall syndrome

Nearly all patients with Pallister-Hall syndrome (PHS) have a HH [1]. The disorder is well characterized and in-

cludes HH, polydactyly, laryngeal malformations including bifid epiglottis or laryngeal cleft, imperforate anus, pulmonary segmentation anomalies, and other less common manifestations. There is a striking range of severity of PHS, with some patients presenting with severe, life-threatening manifestations in the nursery [2] and others presenting with excellent health, normal intellect and malformations that are sufficiently subtle that many non-geneticists would miss the fact that the patient has a syndrome of any kind. Pallister-Hall syndrome is inherited in an autosomal dominant pattern [3]. Some patients (generally mildly affected), are members of families with many affected members, whereas others may be the first affected in their family, and are more likely to be severe.

The most surprising finding in PHS is that many of the patients have no

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symptoms arising from the HH. Although biased ascertainment precludes accurate estimates, probably fewer than half of the patients have symptoms that are definitely or possibly caused by the hamartoma. In many cases, it is difficult to know if a particular symptom in a particular patient is or is not directly attributable to the hamartoma. In any pleiotropic malformation syndrome that involves the central nervous system, there may be a combination of obvious and subtle or cryptic anatomic or functional abnormalities. Current imaging and diagnostic technology cannot detect a number of important CNS abnormalities, so although it may be tempting to attribute all symptoms to the identifiable abnormality, this may not be true.

A major distinction of PHS-associated CNS manifestations is that when they are present, they are generally mild and treatable. We estimate that 20-25% of patients with PHS have gelastic or other forms of epilepsy. Again, these are generally mild with most patients having infrequent seizures that are responsive to carbamazepine, lamotrigine, or gabapentin. Some patients have other types of seizures, and although they are also generally treatable, they are more difficult to control than the simple gelastic seizures. Another 15-20% of patients have learning disabilities, developmental delay, or mental retardation. Again, at the mild end of this spectrum it is very difficult to know if the dysfunction is attributable to the HH, because the symptomatology is so common in the general population.

Behavioral disorders may be present in about 5% of patients and therefore do not appear to be elevated compared to background rates. An additional medical complication of HH in patients with PHS is disruption of the neuroendocrine axis. Some newborns with PHS present with panhypopituitarism in the nursery, which is a medical emergency. More commonly, they may present in childhood with short stature, as the result of growth hormone deficiency, or precocious puberty. The former is readily treated with exogenous growth hormone and the latter is treated with GnRH antagonists.

The medical diagnostic evaluation of the HH should be limited to magnetic resonance imaging. There are a variety of MRI modalities that can be used to distinguish the HH from other lesions in this region of the brain. The claim has been made that the HH is isointense to gray matter on all pulse sequences, but that is now out of date. The HH of PHS can have a distinct or non-homogenous signal on T2 or FLAIR sequences. The size and position of the HH can vary. Most are within the hypothalamic floor and expand supero-laterally into the hypothalamus. Some displace the optic chiasm anteriorly and/or the midbrain or midbrain and pons posteriorly. In the context of other typical PHS malformations and typical MRI imaging characteristics, the HH should not be biopsied or removed. There have been no patients in the NIH series where biopsy or removal has altered management or improved symptoms. Removal of an HH can cause endocrine deficiency.

As can be seen from this description, the typical PHS patient has no symptoms attributable to the hamartoma, or mild to moderate symptoms that are generally responsive to treatment. This description encompasses most, but not all patients with PHS, as we have recently identified one family with two siblings affected by PHS who have intractable seizures, severe mental retardation, and behavioral difficulties. So the typical (but not every) PHS patient is very different from the typical non-syndromic HH patient who may manifest high frequency, complex seizures that are refractory to treatment, severe and progressive mental deficiency, and moderate to severe behavioral disturbances.

Oral-facial-digital syndromes

The oral-facial-digital syndromes (OFD) are themselves a group of disorders with overlapping manifestations [4]. There are presently 12 subtypes of this group and the boundaries that separate these subtypes are not well-defined. Furthermore, there are patients described in the literature who do not fit any defined subtype or who have features of more than one subtype. The main features of the OFD include oral manifestations (cleft palate, tongue hamartomas, buccal frenulae), facial dysmorphic features, and limb anomalies (polydactyly and limb reduction defects). Central nervous system malformations including hypothalamic hamartomas are uncommon, but have been recognized in a number of published and unpublished cases [5, 6]. There are very little data on the neurological or endocrine manifestations of these hamartomas, so generalizations cannot be made.

Bardet-Biedl syndrome

The Bardet-Biedl syndrome (BBS) comprises polydactyly, obesity, diabetes, pigmentary retinopathy, cystic renal dysplasia, and learning disability or mental retardation [7]. It is inherited in an autosomal recessive pattern and can be caused by mutations in at least seven different genes, four of which have been identified [8]. There is one published and one unpublished case of BBS with hypothalamic hamartoma [9]. Neither of these patients had symptoms directly referable to the hamartoma, which was detected when an MRI scan was performed for other reasons.

Unclassifiable syndromes

There are a number of patients with HH and other malformations where the malformations do not match a recognizable pattern. These include patients who have features that partially overlap with the above noted syndromes and patients whose features appear unique. These are individually, extremely rare occurrences.

Pathophysiology of syndromic hypothalamic hamartomas

Although the syndromes that include an HH are phenotypically distinct from isolated or non-syndromic HH, they

can be exploited to understand the developmental biology of the normal and abnormal hypothalamus, and ultimately the hamartoma. The heritable nature of these disorders means that the genes that are mutated in affected patients can be determined. The identification of genes that, in the mutant state, cause hypothalamic hamartomas, suggests that the normal function of these genes are important for the normal development and function of the hypothalamus. In addition to the individual genes that are identified as mutated in patients with HH, the genes function in genetic pathways or genetic networks that jointly determine the molecular homeostasis of the cell. Furthermore, since these syndromes can each manifest HH and have substantial overlap in addition to HH, the hypothesis can be made that the genes that are mutated in these disorders interact with each other during development. The understanding of a perturbation of a genetic, developmental or homeostatic pathway provides opportunities for therapy, as all of the gene products of that pathway are potential therapeutic targets. It is reasonable to hypothesize that perturbation in the same genetic pathway that can cause a syndromic HH can also cause a non-syndromic HH. For these reasons, the molecular genetic analysis of syndromic HH may be a very fruitful pathway for understanding the etiology and treatment of sporadic, non-syndromic HH.

Molecular pathology of syndromic hypothalamic hamartomas

The disorder for which the most is known in this regard is the Pallister-Hall syndrome. This syndrome is caused by mutations in the *GLI3* zinc finger transcription factor gene [10]. *GLI3* is a transcription factor that regulates the expression of a number of other genes, which are considered to be downstream of *GLI3* (that is, they are regulated by *GLI3*). *GLI3* is known to be a part of the sonic hedgehog (SHH) pathway, which is an extracellular signaling ligand important in central nervous system morphogenesis [11]. The presence or absence of the SHH ligand is the primary trigger of this pathway, and binds to the patched receptor, which in turn signals to the smoothed cell membrane protein. The patched protein triggers a cytoplasmic protein complex that includes *GLI3*. In the presence of SHH, the *GLI3* transcription factor is released intact and migrates to the nucleus to activate downstream genes. In the absence of SHH, *GLI3* appears to be processed by a protease into a shorter form that represses downstream genes. In patients with PHS, all mutations in the gene cause the production of a truncated version of the protein, which is functionally identical to the processed, repressor form of the protein [12]. Thus, the mutations in patients with PHS remove the ability of SHH to switch *GLI3* between the repressor and activator state.

The SHH/*GLI3* pathway is composed of more than 13 gene products or proteins. This suggests that these 13 gene products all have a role in hypothalamic development or function. Indeed, although mutations in SHH do not cause HH, SHH has been shown to be necessary for the regulation of proliferation of some types of neural cells [13].

As noted above, patients with the Bardet-Biedl syndrome can occasionally have an HH and in addition, the obesity phenotype of BBS may be attributable to hypothalamic dysfunction. There are four genes that have been found to be mutated in patients with BBS. These include *BBS1*, *BBS2*, *BBS4*, and *BBS6/MKKS*. Current understanding of these genes is limited, being much less specific than that of *GLI3*. However, *BBS6* appears to be a chaperonin on the basis of sequence comparisons [14]. Chaperonins are proteins that function to fold polypeptide strands as they emerge from the synthesizing ribosome and can refold proteins that have become denatured or unfolded from chemical or physical effects. This suggests that there are proteins involved in the formation of an HH that are susceptible to these environmental stressors and that interventions to reduce these stressors or increase the ability of the cells to tolerate such stressors may effect the pathogenesis of the HH.

The only genes that are known to cause the oral-facial-digital syndromes are *CXORF5* (which causes OFD type I [15]) and *GLI3*, which can cause atypical forms of OFD (L. Biesecker, unpublished results). OFD type 1 patients are not known to have HH, so that gene may not be part of the pathogenesis of HH. Again, since *GLI3* mutations can cause OFD with HH, this supports the importance of the SHH/*GLI3* pathway in this process.

Conclusion

Hypothalamic hamartomas can be isolated, or part of a multiple malformation syndrome. Syndromic HH generally have milder symptoms than do non-syndromic (isolated) HH, but likely arise from similar pathogenetic mechanisms. Because the molecular pathogenesis of syndromic HH is a tractable scientific problem, the study of these lesions may lead to insights into all forms of HH. Neurologists and geneticists should be aware of the similarities and differences among these types of HH for research and clinical purposes. Modern molecular genetics allows for rapid and detailed molecular study of syndromic HH as they are often heritable. In the clinic, the differences between syndromic and isolated HH are important for accurate diagnosis, optimal management, and proper assessment of recurrence risks. Ultimately, the goal is to understand the pathophysiology of all HH, but the path to that understanding may lie with the rarer, syndromic lesions. □

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