Periventricular nodular heterotopia: pathogenesis, epileptogenesis and implications in higher cerebral functions

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Periventricular nodular heterotopia (PNH) is a neuronal migration disorder characterized by nodules of gray matter located along the lateral ventricles, which can range from isolated single nodules to bilateral confluent nodules. This malformation of cortical development can be related to genetic or extrinsic factors. Reading dysfluency, epilepsy and normal intelligence are main hallmark. PNH and overlying cortex integrate a (dys)functional network. In this review, we discuss the recent progress about pathogenesis and epileptogenesis on PNH, and their participation in the processing of higher cortical functions.

Keywords: periventricular; heterotopia; pathogenesis; epileptogenesis; dyslexia


Introduction

Nodular heterotopia is a neuronal migration disorder characterized by nodules of gray matter that can be located in various regions from the lateral ventricles (periventricular nodular heterotopia – PNH) to the cortical mantle (e.g. subcortical nodular heterotopias), and range from isolated single nodule to bilateral confluent nodules [1]. This malformation of cortical development can be related to genetic mutations (e.g., FilaminA, ARFGEF2), or extrinsic factors (e.g., irradiation, infection, injury) [2].

There are complex interactions between PNH and allo- or neocortex [3], which shows that PNH is part of a network, connects to the overlying cortex taking part in epileptogenesis [4] and acting in higher cortical functions [5].

The prevalence of PNH in the general population is unknown, although some reports suggest that it represents 15-20% of the various forms of cortical malformations [6,7].

In addition, there is a broad spectrum of clinical presentation in PNH. Epilepsy is the most common manifestation, it is estimated that up to 90% of patients with PNH develop epilepsy at some time in life [8]. A significant proportion of patients present with refractory epilepsy [7] and surgical treatment with good outcome may be achieved after careful MRI and electroclinical evaluation to precisely identify the epileptogenic zone [3,4,9]. However, this procedure may have considerable limitations (e.g. epileptogenic zone involving functional eloquent cortex) and alternative therapies may be required [10,11,12].
This review discusses the recent progress on PNH knowledge, including pathogenesis, epileptogenesis and contribution in higher cerebral functions.

**Pathogenesis**

**Genetics in PNH**

Abnormalities in genes related to beginning of neuronal migration seem to be the genetic basis for the development of PNH. Mutations in filamin A (FLNA) and adenosine diphosphate- ribosylation factor guanine exchange factor 2 (ARFGEF2) genes are the main genetics causes. Approximately 80% of familial cases of PNH are related to FLNA mutation, gene located on the long arm of the X-chromosome inherited in a dominant fashion. Heterozygous females with bilateral and symmetrical PNH usually are intellectually normal, present focal epilepsy, frequently refractory. Mutations in males are thought to be lethal, usually with intrauterine death.

FLNA is a cytoskeleton molecule that plays an important role in the initiation and progression of neuronal movement in the process of migration, possibly by maintaining these cells attached to supporting cells until they receive the signal for locomotion. FLNA is a rare cause of PNH. PNH has also been associated with duplication 5p15, deletion 6q26-q27 or 7q11.33, fragile X syndrome, Williams syndrome, 22q11 microdeletion syndrome and 6q terminal deletion syndrome, demonstrating that PNH is a genetically heterogeneous disorder.

Individuals affected by ARFGEF2 mutations develop heterotopic nodules, microcephaly, and severe developmental delay. The inheritance pattern is autosomal recessive and the gene is located in chromosome 20. Fortunately, this mutation is a rare cause of PNH. PNH has also been associated with duplication 5p15, deletion 6q26-q27 or 7q11.33, fragile X syndrome, Williams syndrome, 22q11 microdeletion syndrome and 6q terminal deletion syndrome, demonstrating that PNH is a genetically heterogeneous disorder.

**Extrinsic factors**

Unilateral PNH is usually sporadic, commonly associated with risk factors for prenatl brain damage, and is frequently located in watershed areas, suggesting that acquired factors acting in restricted areas of the developing brain, may provoke the genesis of unilateral nodules, although it cannot be ruled out contribution of genetic factors.

Thus, Bataglia et al. formulated the following hypothesis: “the selective ablation of a subpopulation of dividing neuroblasts is sufficient per se to disturb the migration and differentiation of subsequently neurons, which in turn set the base for the formation of heterotopias”.

**Reelin**

Reelin is a large extracellular matrix glycoprotein secreted by Cajal-Retzius cells, the oldest neurons of the cortex. It has been proposed that Reelin play a crucial role in correct positioning of migrating cortical neurons in horizontal layers, sending a “stop signal” for migrating cortical neurons process.

Recently, an experimental study using an animal model demonstrated that Reelin expressed ectopically is able to induce the formation of heterotopic nodules very similar to those observed in patients.

Regardless of the etiology, size, number (single or multiple) or topography, heterotopic nodules present similar features and organization, suggesting that there is a final common pathway involved in the formation of the nodules. According to some authors, ectopically expressed Reelin is the key factor in this process.

**Epileptogenesis**

**Heterotopic nodules and the overlying cortex: a neuronal network**

Heterotopic nodules consist of well-delimited groups of neurons highly differentiated, that emit and receive large sprouts and elaborate dense synaptic terminals, without presenting laminar organization.

Tractography and functional MRI (fMRI) studies have suggested anatomic and functional connections between heterotopic nodules and overlying cortex, as well as connections between nodules and regions of contralateral cortex, other heterotopic nodules and ipsilateral cortex. In agreement, a recent in vitro physiologic study demonstrated functional connection between heterotopic nodules and overlying hippocampus resected from a man with refractory mesial temporal lobe epilepsy.

**Epileptogenicity of heterotopic nodules**

Li et al. reported poor outcome in seizures control after temporal lobe resection in patients with PNH presenting electroclinical evidence of involvement of the temporal lobe in seizures onset, suggesting that such electroencephalographic correlation can be misleading in PNH.

Later, a series of 10 patients undergoing nodule (partial or total) and overlying cortex resection presented good outcome. In these cases, surgical strategy was defined by invasive EEG (iEEG) which demonstrated seizures originating in the overlying cortex or simultaneously in the cortex and nodule.

In 2005, Scherer et al. described a case of a woman with refractory epilepsy and a single periventricular nodule. She was submitted to iEEG that recorded seizures starting in the nodule with subsequent propagation to the
overlying cortex. Nodule resection resulted in excellent outcome [9], indicating that heterotopic nodules can be epileptogenic lesions. In agreement, several other authors reported good prognosis in seizures control with therapeutic approach targeting only PNH [10,11,12], including cases in which iEEG recorded seizures onset on the overlying cortex [26].

However, others studies have questioned the epileptogenicity of heterotopic nodules: 1) report of dual pathology (PNH and mesial temporal sclerosis) with good outcome after surgical approach targeting only mesial temporal sclerosis [27]; 2) EEG/fMRI studies during seizures showing the maximum BOLD responses always in the overlying cortex and not in heterotopia [28]; 3) an animal model study demonstrating that heterotopic nodules were unable to initiate or spread epileptiform activity [29].

Recently, Schmitt et al. reported the case of a man with a heteropic nodule and refractory epilepsy, characterized by unspecific auras, daily clonic, aphasic seizures and one bilateral tonic-clonic seizure per week. Invasive monitoring recorded auras with ictal correlate restricted to nodule, indicating that heterotopic nodules can be sintomatogenic areas [10].

Thus, the role of PNH in epileptogenesis remains controversial, and surgical planning in patients with refractory epilepsy should be based on individual assessments of structural imaging and electroclinical studies, including iEEG.

Mechanisms of epileptogenesis in PNH

In the context of PNH, knowledge of the mechanisms involved in the genesis of seizures is very limited. A pathological study of heterotopic nodules resected from children with epilepsy identified changes in GABAergic pathways. These changes indicate that intranodular GABAergic pathways are more excitatory than inhibitory in PNH [30]. However, additional studies are necessary to confirm the relevance of these findings.

Higher cerebral functions

Implications in higher cerebral functions

fMRI studies demonstrated coactivation of heterotopic nodules and the overlying cortex during the performance of reading related tasks, reinforcing the hypothesis that PNH and overlying cortex integrate a functional network [23].

Wagner et al. described the cases of two patients in whom language and complex visual and acoustic processing was elicited during electrical stimulation of PNH, demonstrating the involvement of heterotopic nodules in higher cortical functions [5].

In the case described by Scherer et al. in 2005, fMRI showed activation of both the heterotopic tissue and the overlying cortex during language tasks, however resection of the nodule did not caused language deficits, suggesting that the role of heterotopic nodule was not essential for adequate functioning of the language [9]. Other authors also reported no cognitive decline following resection of heterotopic nodules [4].

PNH seem not to be essential in the processing of cortical functions, although it plays some role. Further studies are necessary to confirm that resection of heterotopic nodules is not associated with increased risk of cognitive decline.

Dyslexia

Dyslexia, epilepsy and normal intelligence are frequent aspects in PNH [23, 24, 31].

A majority of individuals with PNH has a singular form of dyslexia in which reading fluency is the primary deficit and not phonological awareness (which is impaired in most individuals with developmental dyslexia) [23, 31].

Chang et al. conducted neuropsychological evaluations in 10 patients with PNH, eight presented normal intelligence and impairment in reading skills, not correlated with epilepsy severity or antiepileptic medication use [31].

Recent studies have demonstrated that PNH disrupt cortico-cortical tracts that normally connect regions of brain that are important for reading fluency. Such circuit changes may be the underlying anatomical basis for difficulties with reading fluency [24].

Conclusions

Important advances in PNH knowledge were done in the last decade, influencing therapeutic strategies, especially in refractory epilepsy.

PNH and overlying cortex are part of a functional and epileptogenic network, with the nodules playing multiple roles, such as in generate, amplify and spread ictal activity. Additionally, nodules may participate in higher cortical functions and lead to dysfunctions in cortical reading process.

Further studies will try to provide more information necessary to bridge the gaps in our understanding about the molecular pathways involved in the pathogenesis and epileptogenesis of PNH. The identification of these molecular pathways may lead to targets that can guide the
References


