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Analysis on the Treatment of Gray Matter Heterotopia Epilepsy

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ABSTRACT
This essay started off by giving a brief introduction about gray matter heterotopia and its classification. It is then followed by listing out the common genetic mutations that is associated with the disease including FLNA, ARFGEF2, C6orf70, FAT4, DCSH1 for periventricular nodular heterotopia (PNH), and DCX, LIS1, TUBA1A, TUBG1 for subcortical band heterotopia (SBH). Upon reviewing various literature, credible evidence regarding the possible molecular mechanism of the mutations were summarized as well. Due to the high prevalence of epilepsy involved with the disease, evidence regarding the pathophysiology of seizures were also discussed. Clinical aspects of the disorder including signs and symptoms, imaging findings leading to diagnosis, and management strategies were also highlighted.

Keywords: *Gray matter heterotopia, Epilepsy, Pathophysiology, Molecular mechanism*

1. INTRODUCTION

Heterotopia of the gray matter during the development of cortex is a common anomaly. There are two types of patients with this disorder clinically: those with nodular diseases (periventricular nodules and subcortical heterotopias), and those with diffuse diseases (band heterotopia) [1]. Most women with periventricular nodular heterotopia (PNH) develop partial epilepsy during their second decade of life; up to that time, development and neurologic examinations are typically normal. PNH in males differs according to whether it is an X-linked or an autosomal disorder. CNS and visceral defects are more common in X-linked men and their development is usually abnormal. Men with the autosomal variant have the same clinical history as women with the disorder [2]. In the second half of their first decade of life, men and women with subcortical heterotopia develop partial epilepsy and congenital fixed neurologic abnormalities. A large deficit leads to a greater degree of subcortical heterotopia; bilateral heterotopia will almost always indicate a significant mental retardation or developmental delay. In most cases, band heterotopia occurs in women, but in males with a mutation of genes XLIS or DCX, there are either severe brain abnormalities or death during pregnancy. There is a direct relationship between the severity of the disease and the thickness of the band of halted neurons. Women with this condition experience developmental delays or mental impairment ranging from mild to severe [3]. The most common types of epilepsy are partial complex and atypical absence epilepsy. Some patients who suffer from epilepsy also suffer from drop attacks [1].

2. GENETICS AND MOLECULAR MECHANISM

2.1 PNH

In adulthood, periventricular nodular heterotopia (PNH) is characterized by ectopic neuronal nodules lining the lateral ventricles. Families with X-linked bilateral PNH and those with sporadic PNH were both found to have mutations in the FLNA gene on Xq28 [4]. FLNA gene encodes a protein that binds actin and a range of cytoplasmic signaling proteins responsible for cell adhesion and migration [5]. As FLNA expression increases in the brain during pregnancy, neonatal periods, and adolescence, it declines to moderate levels during adulthood [6]. FLNA has been identified as a component of somatodendritic compartments within neocortical pyramidal neurons [7] as well. A recent study found that females with heterozygous heterozygotes had relatively normal level of intelligence and epilepsy [10]. Despite the existence of a few male patients with bilateral PNH caused by FLNA mutations, most of the male foetuses do not survive [8].

An ARFGEF2 gene mutation on 20q13.1, responsible for a rare recessive variant in two consanguineous families, has been identified [10]. BREFINDIN-inhibited guanine nucleotide exchange protein 2 (BIG2) is a protein encoded by ARFGEF2 found in the Golgi and recycling endosomes [11]. ARF-dependent vesicle trafficking through these subcellular compartments has been hypothesized to be mediated by BIG2 [12]. DCHS1 and FAT4 gene mutations, which produce the receptor-ligand cadherin pair, have recently been linked to a multisystem illness, including PNH [13]. PNH has also been observed in patients with chromosomal rearrangements and deletions on chromosomes 5 and 6. Another diagnostic breakthrough came from finding a de novo missense mutation in the C6orf70 gene that mapped the minimally critical deleted area of 6q27 in a sporadic patient with developmental delay, epilepsy, and PNH [15]. There are currently 13 different PNH diseases, although the majority of them have an unclear cause.

Even though it is well understood that PNH is caused by blocking of neural migration between the ventricular and subventricular zones, the mechanism behind its emergence remains a mystery. PNH caused by in utero FLNA mutations has been successfully reproduced in rats, and it is a suitable model to investigate pathogenetic processes underpinning PNH [16]. This study proposes that PNH is associated with a loss of radial glial integrity in the ventricle.

2.2 SBH

Dual cortex syndrome, or SBH, is an abnormality of cortical development that is less severe than lissencephaly. Bilateral smooth bands of grey matter in subcortical white matter are the key characteristics of SBH [17]. It often displays a normal gyration pattern with extensive circumvolutions and pronounced cortical thickening. Cortical malformations associated with SBH are hereditary. Most of the cases are caused by mutations in the DCX and LIS1 genes. Mutations of microtubule subunit genes (TUBA1A and TUBG1), although considerably less common, have also been found in SBH patients [18]. In addition, the microtubule-dependent motor protein KIF2A gene is also found to be related [19].

Genetic defects linked to DCX, an Xlinked gene, are more common in females; females with heterozygous DCX develop SBH, while men with hemizygous DCX develop isolated lissencephaly. Women who are DCX mutants are most commonly sporadic, however, family examples may account for up to a third of the affected women [20]. A DCX mutation or deletion in male SBH patients has been documented, although it is far less common than in females [21]. There is a possibility that they arise from a mild mutation that enables some residual DCX function, or they may result from a mosaic mutation or deletion that only affects a subset of neurons [22].

The DCX gene encodes a microtubule-associated protein (MAP), which binds to protofilaments and forms a nucleus. Immediately following the end of the cell cycle, it is strongly expressed in freshly formed neurons, from the VZ/SVZ to the cortical layer, but its expression is decreased during later stages of differentiation [23].

LIS1 binds to microtubule-minus-end directed motor cytoplasmic dynein [24]. LIS1/dynein controls the orientation of dividing neurons at the VZ, and decreased LIS1 levels result in lack of TUBA1 mutations in lissencephaly patients, but there is only one mutation in SBH patients [25]. Tubulin heterodimerizes with TUB1, which encodes a tubulin. The TUBG1 gene has also been associated with laminar heterotopia, posterior pachygyria, and dysmorphic corpus callosum [26].

Recent research suggests that SBH may result from abnormal cell events involving neuroprogenitors that can result in inappropriate neuronal development, abnormal neuronal migration, or a mispositioned neuron in the cortical wall [27].

3. PATHOPHYSIOLOGY OF EPILEPSY

3.1 PNH Patients

Study results utilizing intracranial EEG recordings in individuals with PNH indicate that epilepsy may be caused by a network of epileptogenic nodules that include heterotopic nodules and other cortical locations. One of two outcomes was apparent when deep electrodes were used for exploration of intracerebral nodules: either no ictal discharges were found, or at least one nodule contributed to ictal discharges [28]. There were seizures that originated from heterotopic nodules and cortical areas simultaneously, from heterotopic nodules alone, or from nodules that originated at a combination of locations including the temporal cortex and mesial structures [28]. Using EEG-fMRI, similar results have been produced, showing concurrent involvement of multiple locations far from the malformation, underscoring the possibility that a vast epileptogenic network is involved involving heterotopic nodules and additional cortical regions [29].

3.2 SBH Patients

SBH patients with a poor prognosis are rarely recommended for epilepsy surgery and therefore have depth recordings performed infrequently [30]. Epileptiform activity has sometimes been documented from both heterotopic and normotopic cortex independently or not, and it has sometimes spread to other brain areas as well [31]. Aside from the absence of epileptiform activity recorded from the heterotopic band, electrical discharges emanated from elsewhere and propagated to the heterotopic and normotopic cortices. In EEG or fMRI studies, there were shifts in fMRI signals across both the ictal and interictal bands during

epileptiform occurrences [32]. There is a possibility that a change in signal occurs in a particular section of the heterotopic band or that the whole double cortex is activated [33].

4. SIGNS AND SYMPTOMS

Grey matter heterotopia shows a clinical manifestation depending on the size, type, and location of the deformity, as well as if it is associated with other brain abnormalities or congenital defects. In 80-90 percent of patients, gray matter heterotopia results in epilepsy or seizures, which are usually resistant to treatment. Abnormalities in gray matter result in absence seizures most of the time [34]. Patients usually develop the condition in their late teens.

In addition to epilepsy, grey matter heterotopia can cause moderate intellectual disability, developmental delays, and motor impairments, which can lead to dyslexia, which hampers reading, information processing, and executive control. Although developmental delay is common, neurological impairments are frequently only visible in cases of severe grey matter heterotopias accompanied by mild motor, sensory, and visual issues [35]. Dyspraxia (problems with coordination) and fine motor skills issues have also been found. There are several factors that influence neurological impairments and developmental delay related to gray matter heterotopia, including its kind and intensity. A person can suffer from no symptoms to severe symptoms, with bilateral or widespread heterotopia or other neurologic abnormalities being the most severe. Gray matter heterotopia can also present without neurological impairments or developmental delays in patients with severe unilateral subcortical grey matter heterotopia [36].

5. DIAGNOSIS

Individuals with grey matter heterotopia generally suffer seizures, developmental delays, or behavioural issues. MRIs or CT scans are typically used to diagnose seizures resistant to medicine, which can result in heterotopia. Since heterotopic grey matter cannot always be seen on CT scans, MRI is the preferred method of investigation for the examination of heterotopic grey matter due to its capability to distinguish between grey and white matter [37].

A summary of typical findings in imaging is listed below:

5.1 Ultrasound

Ultrasonography has trouble distinguishing heterotopic grey matter from surrounding white matter because of the echogenicity of the grey matter [38].

5.2 CT

Whenever grey matter heterotopias are sufficiently large, they are able to be distinguished from their surrounding white matter by their density. However, thin or small areas may not show up as clearly [38].

5.3 MRI

Mri images show heterotopic tissue following grey matter. These images often have smudged margins. In order to detect related abnormalities, a complete evaluation of the remainder of the brain is necessary [38]. An MR spectroscope shows that in heterotopic grey matter, the NAA/Cr ratio is lower than that in normal control participants. A comparison with the 'apparent normal contralateral side' as a control is not always appropriate as metabolic abnormalities can result in individuals with cortical development defects [39]. EEG discharges associated with brain nodules can be associated with fMRI (BOLD imaging) signals [40].

6. TREATMENT OPTIONS

It is the same principle of treatment that applies to seizure diseases caused by recognized structural brain problems. Carbamezipine is the most commonly used medication in individuals with grey matter heterotopia and suffering from focal seizures. The choice of antiepileptic medication is, however, influenced by side effects, tolerance, and effectiveness [43]. Given the possibility of aortic or carotid dissection or other vascular abnormalities, persons with the X-linked variant of periventricular nodular heterotopia should have investigations examining the carotid artery and an abdomen ultrasound [42]. The lesion can also be removed surgically or with magnetic resonance-guided laser ablation [41]. A variety of other supportive treatments such as deep brain stimulation, medications that stop seizures, feeding techniques for infants not sucking enough, physiotherapy to promote movement, specialized equipment to enhance fine motor skills, as well as tailored schooling and educational programmes may help address seizures [44].

6.1 Surgery Efficacy

It is not possible to cure developmental problems with such surgery, but it is possible to remit epilepsy to some degree. Multiple case studies demonstrated the benefits of a radical surgical approach to patients with heterotopia based on post-operative stereo electroencephalography and drastically improved surgical outcomes. In individuals with certain cortical abnormalities, aggressive surgeries should result in comparable surgical outcomes. However, evidence suggested that patients with bilateral PNH should be warned that surgery may not completely eliminate their seizures [46].

7. CONCLUSION

Prior to the widespread use of MRI images, GMH was rarely recognized as a condition involving neuronal migration. Most often, seizures are associated with the disease, but there is also intellectual impairment to varying degrees. There is evidence that GMH is not just linked to schizophrenia, but also to an array of neuropsychiatric symptoms, some of which may coexist among the same patients [45].

After examining the pathophysiological basis of grey matter heterotopia, it was shown that grey matter heterotopia has important implications for brain cortical development and function, including epilepsy. There is evidence that cortical abnormalities cause up to 40% of drug-resistant epilepsy [27]. The cognitive abilities of individuals with epilepsy range from normal to severely impaired. Reviewing animal models and human data, it is clear GMH affect not just neuronal migration but also the proliferation of cortical progenitors, making grey matter heterotopias more complex than just abnormal neuronal migration, and it is too restrictive to confine them to such a classification.

Due to the rarity of the disease, the evidence for demonstrating the efficacy of aggressive surgical treatments for GMH is limited. The current management plan for GMH is still centered around the appropriate control of seizures by medication, however, due to the high rate of drug resistance, the underlying mechanism needs to be studied, for example by using animal models. Hopefully, through genetic studies and thus better understanding the molecular and cellular events of the disease, a curative therapy could be developed in the future, especially considering the reduction in quality of life brought by the disease and the difficulty of medication optimization caused by drug resistance and side effects.

REFERENCES

[1] Pridmore S, McInerney G, Rybak M, Archer S. Psychotic disorder NOS with heterotopia. J Pychiatr Intensive Care. 2007;2(2):118–21. 10.1017/S1742646407000386

[2] Abdel Razek AA, Kandell AY, Elsorogy LG, Elmongy A, Basett AA. Disorders of cortical formation: MR imaging features. AJNR Am J Neuroradiol. 2009;30(1):4-11. doi:10.3174/ajnr.A1223 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7051699

[3] Guerrini R, Dobyns WB. Malformations of cortical development: clinical features and genetic causes. Lancet Neurol 2014;13:710–726.

[4] Parrini E, Ramazzotti A, Dobyns WB, et al. Periventricular heterotopia: phenotypic heterogeneity and correlation with Filamin A mutations. Brain 2006;129:1892–1906.

[5] Robertson SP. Filamin A: phenotypic diversity. Curr Opin Genet Dev 2005;15:301–307.

[6] Stossel TP, Condeelis J, Cooley L, et al. Filamins as integrators of cell mechanics and signalling. Nat Rev Mol Cell Biol 2001;2:138–145.

[7] Noam Y, Phan L, McClelland S, et al. Distinct regional and subcellular localization of the actin-binding protein filamin A in the mature rat brain. J Comp Neurol 2012;520:3013–3034.

[8] Sheen VL, Dixon PH, Fox JW, et al. Mutations in the X-linked filamin 1 gene cause periventricular nodular heterotopia in males as well as in females. Hum Mol Genet 2001;10:1775–1783.

[9] Fox JW, Lamperti ED, Eksioglu YZ, et al. Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia. Neuron 1998;21:1315–1325.

[10] Sheen VL, Ganesh VS, Topcu M, et al. Mutations in ARFGEF2 implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex. Nat Genet 2004;36:69–76.

[11] Charych EI, Yu W, Miralles CP, et al. The brefeldin A-inhibited GDP/GTP exchange factor 2, a protein involved in vesicular trafficking, interacts with the beta subunits of the GABA receptors. J Neurochem 2004;90:173–189.

[12] Shin H, Shinotsuka C, Nakayama K. Expression of BIG2 and analysis of its function in mammalian cells. Methods Enzymol 2005;404:206–215.

[13] Cappello S, Gray MJ, Badouel C, et al. Mutations in genes encoding the cadherin receptor-ligand pair DCHS1 and FAT4 disrupt cerebral cortical development. Nat Genet 2013;45:1300–1308.

[14] Cardoso C, Boys A, Parrini E, et al. Periventricular heterotopia, mental retardation, and epilepsy associated with 5q14.3-q15 deletion. Neurology 2009;72:784–792.

[15] Conti V, Carabalona A, Pallesi-Pocachard E, et al. Periventricular heterotopia in 6q terminal deletion syndrome: role of the C6orf70 gene. Brain 2013;136:3378–3394.

[16] Carabalona A, Beguin S, Pallesi-Pocachard E, et al. A glial origin for periventricular nodular heterotopia caused by impaired expression of Filamin-A. Hum Mol Genet 2012;21:1004–1017.

[17] Guerrini R, Dobyns WB. Malformations of cortical development: clinical features and genetic causes. Lancet Neurol 2014;13:710–726.

[18] Poirier K, Keays DA, Francis F, et al. Large spectrum of lissencephaly and pachygyria phenotypes resulting from de novo missense mutations in tubulin alpha 1A (TUBA1A). Hum Mutat 2007;28:1055–1064.

[19] Poirier K, Lebrun N, Broix L, et al. Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. Nat Genet 2013;45:639–647.

[20] Bahi-Buisson N, Souville I, Fourniol FJ, et al. New insights into genotype-phenotype correlations for the doublecortin-related lissencephaly spectrum. Brain 2013;136:223–244.

[21] D'Agostino MD, Bernasconi A, Das S, et al. Subcortical band heterotopia (SBH) in males: clinical, imaging and genetic findings in comparison with females. Brain 2002;125:2507–2522.

[22] Leger P, Souville I, Boddaert N, et al. The location of DCX mutations predicts malformation severity in X-linked lissencephaly. Neurogenetics 2008;9:277–285.

[23] Gleeson JG, Lin PT, Flanagan LA, Walsh CA. Doublecortin is a microtubule-associated protein and is expressed widely by migrating neurons. Neuron 1999;23:257–271.

[24] Sapir T, Elbaum M, Reiner O. Reduction of microtubule catastrophe events by LIS1, platelet-activating factor acetylhydrolase subunit. EMBO J 1997;16:6977–6984.

[25] Keays DA, Tian G, Poirier K, et al. Mutations in alpha-tubulin cause abnormal neuronal migration in mice and lissencephaly in humans. Cell 2007;128:45–57.

[26] Poirier K, Lebrun N, Broix L, et al. Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. Nat Genet 2013;45:639–647.

[27] Watrin F, Manent JB, Cardoso C, Represa A. Causes and consequences of gray matter heterotopia. CNS Neurosci Ther. 2015;21(2):112-122. doi:10.1111/cns.12322.

[28] Dubeau F, Tampieri D, Lee N, et al. Periventricular and subcortical nodular heterotopia. A study of 33 patients. Brain 1995;118(Pt 5):1273–1287.

[29] Tassi L, Colombo N, Cossu M, et al. Electroclinical, MRI and neuropathological study of 10 patients with nodular heterotopia, with surgical outcomes. Brain 2005;128:321–337.

[30] [30] Bernasconi A, Martinez V, Rosa-Neto P, et al. Surgical resection for intractable epilepsy in "double cortex" syndrome yields inadequate results. Epilepsia 2001;42:1124–1129.

[31] Mai R, Tassi L, Cossu M, et al. A neuropathological, stereo-EEG, and MRI study of subcortical band heterotopia. Neurology 2003;60:1834–1838.

[32] Kobayashi E, Bagshaw AP, Grova C, Gotman J, Dubeau F. Gray matter heterotopia: what EEG-fMRI can tell us about epileptogenicity of neuronal migration disorders. Brain 2006;129:366–374.

[33] Tyvaert L, Hawco C, Kobayashi E, LeVan P, Dubeau F, Gotman J. Different structures involved during ictal and interictal epileptic activity in malformations of cortical development: an EEG-fMRI study. Brain 2008;131:2042–2060.

[34] Barkovich AJ, Kuzniecky RI. Gray matter heterotopia. Neurology. 2000;55:1603–8. 10.1212/WNL.55.11.1603

[35] Felker MV, Walker LM, Sokol DK, Edwards-Brown M, Chang BS. Early cognitive and behavioral problems in children with nodular heterotopia. Epilepsy Behav (2011) 22(3):523–6. 10.1016/j.yebeh.2011.08.010

[36] Fry AE, Kerr MP, Gibbon F, et al. . Neuropsychiatric disease in patients with periventricular heterotopia. J Neuropsychiatry Clin Neurosci. 2013;25:26–31. 10.1176/appi.neuropsych.11110336

[37] Bourgeois JA, Nisenbaum J, Drexler KG, Dobbins KM, Hall MJ. A case of subcortical grey matter heterotopia presenting as bipolar disorder. Compr Psychiatry. 1992;33(6):407–10. 10.1016/0010-440X(92)90063-V.

[38] Baxter GM, Allan PL, Morley P. Clinical diagnostic ultrasound. Wiley-Blackwell. (1999) ISBN:063203744X.

[39] Leite CC, Lucato LT, Sato JR et-al. Multivoxel proton MR spectroscopy in malformations of cortical development. AJNR Am J Neuroradiol. 28 (6): 1071-5.

[40] Kobayashi E, Bagshaw AP, Grova C et-al. Grey matter heterotopia: what EEG-fMRI can tell us about epileptogenicity of neuronal migration disorders. Brain. 2006;129 (Pt): 366-74.

[41] Esquenazi Y, Kalamangalam GP, Slater JD, Knowlton RC, Friedman E, Morris SA, Shetty A, Gowda A, Tandon N. Stereotactic laser ablation of

epileptogenic periventricular nodular heterotopia. Epilepsy Res. 2014 Mar;108(3):547-54.

[42] Sheen VL, Bodell A & Walsh CA. X-Linked Periventricular Heterotopia. GeneReviews. September 17, 2015.

[43] Epilepsy and Disorders of Consciousness. In: Ropper AH, Samuels MA, Klein JP, Prasad S. eds. Adams and Victor's Principles of Neurology, 11e. McGraw Hill; 2019.

[44] Hehr U, Uyanik G, Aigner L, et al. DCX-Related Disorders. 2007 Oct 19 [Updated 2019 Feb 7]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.

[45] Lippi G. Neuropsychiatric symptoms and diagnosis of grey matter heterotopia: A case-based reflection. S Afr J Psychiatr. 2017;23:923. Published 2017 Mar 28. doi:10.4102/sajpsychiatry.v23i0.923.

[46] Garcia PA. Surgery for heterotopia: a second look. Epilepsy Curr. 2005;5(5):197-199. doi:10.1111/j.1535-7511.2005.00063.x