

Periventricular Nodular Heterotopia and Cardiovascular Defects

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Background: Periventricular nodular heterotopia (PNH) is a rare congenital anomaly of the brain presenting as nodular heterotopia along the paraventricular region. Ten cases of PNH complicated by aortic aneurysm have been reported in the literature, and 9 of them also had symptoms of Ehlers-Danlos syndrome (EDS). This study investigated the association of PNH and cardiovascular anomalies in Asians.

Methods: Patients with a diagnosis of brain heterotopia on magnetic resonance imaging at Chang Gung Memorial Hospital between 1994 and 2010 were screened for both typical PNH and cardiovascular anomalies. The family members of the index cases were also evaluated.

Results: One family (5 patients) and a sporadic case were found to have both typical PNH and cardiovascular anomalies. Two of them had aortic root aneurysm, one had aortic regurgitation, and one had minor valvular disease. Two patients had a history of seizures, but none of them had EDS.

Conclusions: Clinical heterogeneity exists in the patients with PNH. Overlap in the symptoms of PNH, cardiovascular anomalies, aortic aneurysm, and EDS were reviewed. EDS is unusual in Asians with PNH. Aortic aneurysm and other valvular heart diseases are common cardiovascular anomalies in PNH patients.

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Key words: periventricular heterotopia, neuronal migration disorder, cardiovascular anomalies, aortic aneurysm, Filamin A

Periventricular heterotopia (PH) is a congenital cerebral anomaly with a characteristic ectopic cerebral cortex. It is caused by failure of neuronal migration from the periventricular area to the developing cortex. Most familial cases have a mutation at the Filamin A (*FLNA*) gene in chromosome Xq28,⁽¹⁾ and some cases have mutations in the ADP-ribosylation factor guanine nucleotide-exchange factor 2

(*ARFGEF2*) gene located in chromosome 20q13.13.⁽²⁾

The function of filamin A protein is not yet fully understood, but is presumed to be involved in coagulation, angiogenesis, and cell migration.⁽³⁾ A gene knockout mouse model showed cardiac defects involving the ventricles, atria, and outflow tracts.⁽⁴⁾ In the central nervous system, the filamin A protein is

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important in maintaining the surface integrity of the ventricular zone, and its impairment may predispose to the development of periventricular nodular heterotopia (PNH).⁽⁵⁾

There are two categories of clinical presentations of *FLNA* gene mutations. Gain-of-function of filamin A protein results in the otopalatodigital (OPD) category which has various phenotypes, and loss-of-function leads to the non-OPD category presenting as PH and/or cardiovascular anomalies.⁽⁶⁾

According to the morphology and distribution of the heterotopia, PH syndrome is classified into 3 major groups (nodular, laminar, unclassified), and further subdivided into 15 subgroups by phenotype and genotype.⁽⁷⁾ The nodular group (PNH) accounts for the majority (89%) of PH cases. Common accompanying manifestations include aortic valve insufficiency, aortic aneurysm, thrombocytopenia, a malrotated or shortened intestine, epilepsy, and mental retardation. Other patients may have Ehlers-Danlos syndrome (EDS),^(8,9) ambiguous genitalia, limb abnormalities, microcephaly, cerebellar hypoplasia, frontonasal dysplasia, hydrocephalus, and fragile-X syndrome. Only ten cases of PNH with aortic aneurysm have been described in the literature, and 9 of them had EDS. EDS is a rare clinical diagnosis in Asians. This study investigated the relationship of PNH, aortic aneurysm, and EDS in Asians.

METHODS

We searched for outpatients and inpatients from 1994 to 2010 in the epilepsy department, and the database of the 24-hour video electroencephalography (EEG) monitoring unit at Chang Gung Memorial Hospital (CGMH). Patients with a diagnosis of cerebral heterotopia were retrospectively reviewed. Because this disease can be a hereditary disease, the proband's family members were also reviewed. Magnetic resonance imaging (MRI) of the head was evaluated by one radiologist and one neurologist. The morphology (nodules or bands), distribution (bilateral or unilateral, symmetric or asymmetric), and location (periventricular or subcortical) of the heterotopia were classified. PNH was defined as nodules of gray matter lining the lateral ventricles. Special attention was taken to identify associated congenital anomalies, including holoprosencephaly, schizencephaly, lissencephaly, pachygyria, and

polymicrogyria. The other common candidate conditions in the differential diagnosis procedure included tuberous sclerosis and cytomegalovirus (CMV) infection. To exclude these conditions, patients with heterotopic nodules not isointense to gray matter on MRI were excluded. Subependymal nodules with calcification on computed tomography or enhancement were presumed due to tuberous sclerosis. Patients with CMV infection had periventricular white matter lesions with calcification and clinical symptoms of encephalopathy, and they were excluded.

Transthoracic echocardiograms (TTE) and electrocardiography were used to evaluate cardiovascular function. Aortic root aneurysm was defined as a permanent localized dilatation of the sinuses of Valsalva with a diameter at least 1.5 times that of normal. Aortic regurgitation (AR) was diagnosed when abnormal diastolic flow originating from the aortic cusps was identified in the left ventricular outflow tract. The existence and severity of cardiac valvular diseases were assessed by the cardiologist performing the TTE. Patients were defined as having major cardiovascular anomalies if an aortic aneurysm or moderate to severe valvular disease was identified.

Patients with hyperelasticity and fragility of the skin or hypermobility of the joints were suspected of having EDS. The mobility of the thumb, index finger, elbow, knee, and waist was examined. Associated findings of EDS such as flat feet, a high, narrow palate, and easy bruising were identified.

All patients were interviewed to obtain their clinical history, and physical and neurological examinations were done. Most patients received blood tests (complete blood count and basic biochemistry), neuroelectrophysiological examinations (EEG, multimodality evoked potential studies), and gastrointestinal (GI) and renal surveys (abdominal and renal sonography). We enrolled patients with both cerebral heterotopia and cardiovascular anomalies.

RESULTS

We found 11 patients with a diagnosis of cerebral heterotopia. Five patients were excluded because cardiovascular anomalies were not found. Three of these 5 patients had bilateral PNH, one had left posterior trigonal heterotopia, and one had right subcortical heterotopia with right open-lipped schizen-

cephaly. A large family (5 cases) and one sporadic patient were identified with cerebral heterotopia and cardiovascular anomalies. All of them were women, and all had bilateral PNH without hydrocephalus, schizencephaly, lissencephaly, or other congenital cerebral anomalies. None of the patients had joint hypermobility. Two members in the family of 5 patients had aortic root aneurysm, and one had mild AR and mitral regurgitation. The sporadic patient had severe AR. No other cardiac valvular disease was found. Overall, 3 of these 6 PNH patients had major cardiovascular anomalies (50%), and 2 of them had aortic aneurysms (33%). Two of the 6 PNH patients had epilepsy (33%). The clinical data are summarized in the Table.

Family I

Family I was a big family which included 7 women in the second generation (Fig. 1). There were no male siblings in the second generation. Their mother (patient I:1) had PNH, but died of peritoneal carcinomatosis. Four of the 7 women in the second generation had PNH. MRIs of the head are shown in Fig. 1. The eldest sibling (patient II:1) had an aortic aneurysm (5.4 cm) and annuloaortic ectasia. The echocardiography of patient II:2 disclosed mild mitral and aortic regurgitation. Patient II:3 had generalized seizures and an aortic aneurysm. Patient II:4 died of heart disease in infancy. Family members other than patient II:3 did not have a history of seizures. The results of the neurological examinations were grossly normal except for patient II:7 who had mild impairment of verbal-conceptual intellectual function. Physical examinations did not show joint hypermobility, skin extensibility, facial dysmorphism, or digital anomalies. Laboratory examinations revealed thrombocytopenia and anemia in patient I:1. EEG, multi-modality evoke potential studies, and renal sonography were all normal.

Sporadic case

This woman had her first generalized tonic-clonic seizure at 24 years old. Episodes of déjà vu were another seizure pattern. She was seizure-free for 3 years with carbamazepine (600 mg/d) treatment, and then the antiepileptic drug was tapered off. However, seizures recurred 8 months later, and she resumed carbamazepine treatment. Video EEG revealed epileptiform discharges over the left fron-

totemporal area. MRI showed PNH (Fig. 1).

Her echocardiography disclosed severe AR, a dilated left ventricle, and borderline left ventricular systolic function. She received minimally invasive aortic valve replacement. Her laboratory data showed anemia and thrombocytopenia. The neurological examination was grossly normal. The patient was the only member in her family known to have PNH or a cardiovascular anomaly. Her mother's MRI of the head was negative for PNH.

DISCUSSION

The segregation pattern of family I suggests the inheritance of the disease was X-linked. Male siblings of the second generation in family I had died during gestation with spontaneous abortion. Male offspring of carrier women usually die prenatally. In fact, only 9% of sporadic male patients with PNH have a confirmed *FLNA* mutation.⁽¹⁰⁾ Families with PNH in Asia had been reported,⁽¹¹⁾ but our family I was the largest PNH family (5 patients) with associated cardiovascular defects reported in Asia. Sporadic PNH cases with an *FLNA* mutation have been reported. A large series confirmed various types of cardiac valvular diseases caused by *FLNA* mutation.⁽¹²⁾ Therefore, our sporadic patient's PNH and severe AR were presumed to result from this mutation.

Previous reports showed 72% to 90% of PNH patients have epilepsy;^(7,13) however, only one member of family I had seizures. The mechanism of the epileptogenesis in PNH patients is still unknown. It is suspected to be due to an imbalance between excitatory and inhibitory interneurons based on the finding that the messenger ribonucleic acid expression of γ -aminobutyric acid receptor subunits is reduced, and the expression of glutamate receptor subunits is increased.⁽¹⁴⁾ Although cerebral heterotopia usually leads to epilepsy, not all patients with a typical presentation of PNH and cardiovascular defects have seizures.⁽¹⁵⁾ The reasons for the low seizure frequency in our study, may have been the small case number, a seizure presentation which was too mild to be noticed by the patients, or deaths of some patients due to major cardiovascular anomalies before the onset of seizures.

Two of our 6 patients had thrombocytopenia (platelet counts of 96,000 and 128,000/ μ L). *FLNA*

Table Clinical Findings in Family I with 5 Cases and the Sporadic Case

	Patient I:1	Patient II:1	Patient II:2	Patient II:3	Patient II:7	Sporadic patient
Age at examination (year)	75	51	48	45	35	24
Gender	Female	Female	Female	Female	Female	Female
Family history	Yes	Yes	Yes	Yes	Yes	No
Seizures	Nil	Nil	Nil	GTCS	Nil	CPS and secondary GTCS
MRI	Bilateral PNH	Bilateral PNH	Bilateral PNH	Bilateral PNH	Bilateral PNH	Bilateral PNH
Cardiovascular examination						
Echo-cardiography		Aortic aneurysm (5.4 cm)	Mild AR, MR	Aortic aneurysm		Severe AR
ECG	Poor R progression V1-V4	Very frequent isolated VPCs	Normal	Normal	Normal	Sinus bradycardia
Neurological examination	Right trigeminal neuralgia (V ₂)	Normal	Normal	Normal	Mild intellectual impairment	Normal
Neuroelectrophysiological examination						
EEG		Normal	Normal		Normal	ED over left frontotemporal
EP studies	SSEP: conduction impairment below high cervical cord	VEP: P100 negative bilaterally	Normal		Normal	Normal
SSR/RRIV	Normal	Impaired SSR			Normal	
Systemic examination						
Blood	Hemoglobin: 7.4, platelet: 96000					Hemoglobin: 11.8 Platelet: 128000
Gastro-intestinal	Peritoneal carcinomatosis, gallstones, GU	Duodenal ulcer, hepatitis B virus carrier	Gallstones			
Renal sonography	Bilateral renal cysts	Parenchymal renal disease	Parenchymal renal disease		Parenchymal renal disease	

Abbreviations: GTCS: generalized tonic-clonic seizure; CPS: complex partial seizure; MRI: magnetic resonance imaging; PNH: periventricular nodular heterotopia; AR: aortic regurgitation; MR: mitral regurgitation; ECG: electrocardiography; VPC: ventricular premature complex; ED: epileptiform discharge; EEG: electroencephalography; EP: evoked potential; SSEP: somatosensory evoked potential; VEP: visual evoked potential; SSR: sympathetic skin response; RRIV: R-R interval; GU: gastric ulcer.

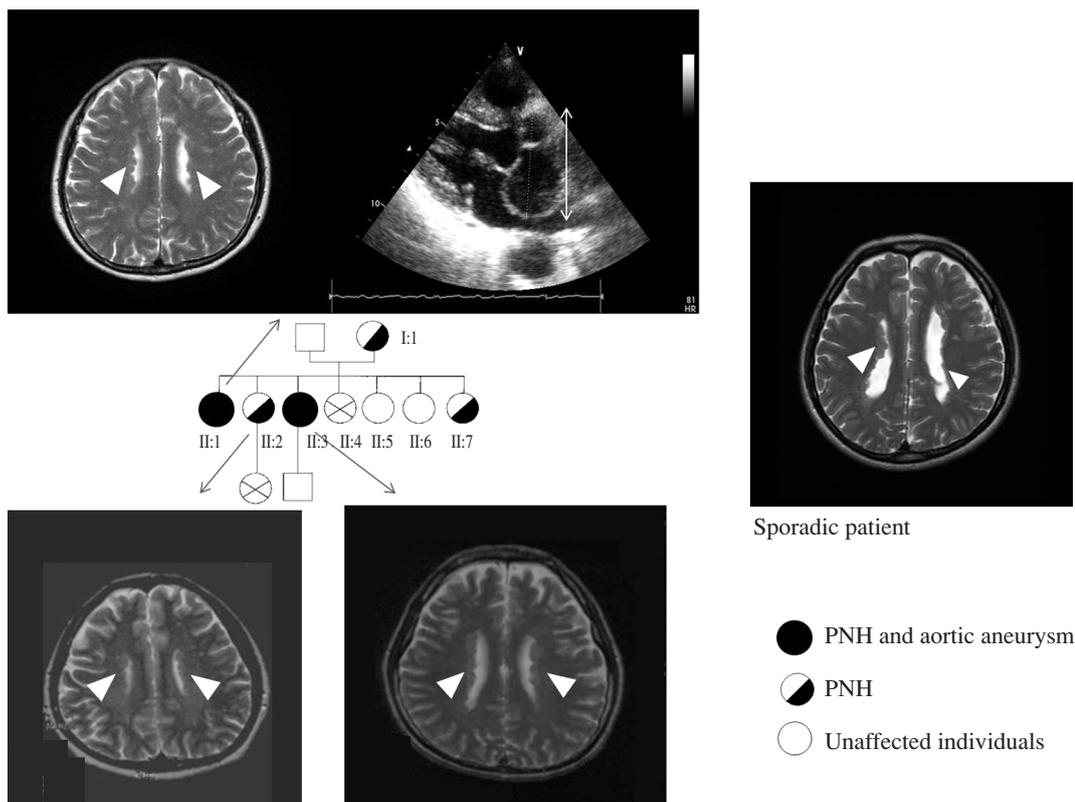


Fig. 1 Pedigree of family I and their image studies. All MRI studies reveal PNH. The eldest sibling's echocardiography (parasternal long axial view) discloses an aortic aneurysm with a diameter of 5.4 cm (delineated by the two-way arrow). The MRI of the sporadic case is also shown, and Doppler echocardiography (not shown) revealed severe AR. Abbreviations used: MRI: magnetic resonance imaging; PNH: periventricular nodular heterotopia.

protein plays some role in hemostasis. It binds to tissue factor and involves the extrinsic coagulation cascade. Its second role in hemostasis is to couple glycoprotein Ib α , a membrane receptor for von Willebrand's factor (vWF) in platelets, to the actin cytoskeleton. Binding of vWF to glycoprotein Ib α causes the earliest stage of thrombus formation.⁽¹⁾ The proportion of thrombocytopenia in PNH patients has not been reported. The thrombocytopenia in our 2 patients might have resulted from FLNA protein dysfunction, although the deficiency was mild. Their coagulation was normal.

EDS was recently reported linked to PNH.^(8,9) The mechanism for this relationship may be disruption in cell adhesion.⁽¹⁶⁾ EDS is caused by defects in collagen that alter the crosslinkage and adhesion of collagen fibrils in the extracellular matrix. The FLNA protein also mediates cell matrix adhesions. So, impaired cell adhesion can lead to EDS and the

neuronal migration disorder simultaneously. None of our patients displayed the clinical symptoms of EDS, and this might be attributed to the rare incidence of EDS in Asians.

The complex overlap of clinical symptoms of PNH, cardiovascular anomalies, aortic aneurysms, and EDS, are illustrated in Fig. 2. In the non-OPD category of *FLNA* mutation, PNH and cardiovascular anomalies are the two major clinical presentations. Almost all patients in this category have PNH, and only 5 reported families in this category with mitral or aortic valve disease did not present with PNH.⁽¹⁶⁾

In patients with classic bilateral PNH, 20% have cardiovascular anomalies.⁽⁷⁾ Aortic aneurysm is a rare presentation in PNH patients, and only 10 cases (3 familial and 7 sporadic) have been reported.^(10,17,18) EDS was a common presentation noted in 9 of 10 reported patients.^(10,18) Among these 9 patients, 5 patients had genetic identification, which revealed

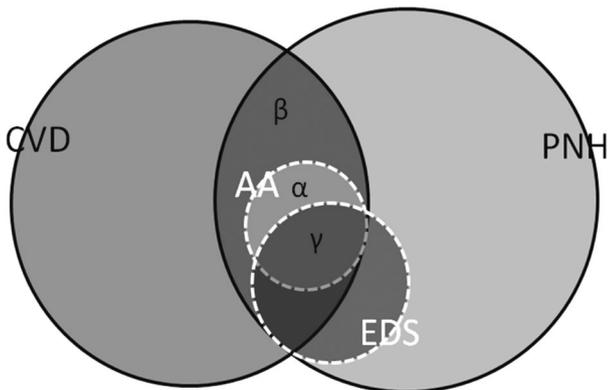


Fig. 2 Illustration of two major presentations (PNH and cardiovascular defects) and their association with EDS in patients with *FLNA* mutations. Circle AA: aortic aneurysm; circle CVD: cardiovascular defects; circle EDS: Ehlers-Danlos syndrome; circle PNH: periventricular nodular heterotopia; area α : patients in family I; area β : our sporadic patient; area γ : 9 patients with aortic aneurysm, EDS, and PNH in the literature.

mutations at the actin binding domain (ABD) of the *FLNA* gene in 4 patients, and at exon 25 in another sporadic case. The one patient without EDS symptoms had mutation upstream of exon 12.⁽¹⁷⁾ Including the 2 patients in family I in this study, only 3 cases of PNH and aortic aneurysm without EDS have been reported. The central area (α) in Fig. 2 represents these 3 patients.

All 5 familial cases with both PNH and aortic aneurysms mentioned above were identified to have mutations at the ABD. Parrini et al also suggested that ABD is a hotspot for *FLNA* mutations causing PNH.⁽⁷⁾ Further genetic study in family I might confirm the relationship of this phenotype (PNH and aortic aneurysm) and genotype (ABD mutation). The *FLNA* gene spans about 26 Kb and consists of 48 coding exons. The ABD is located at the N-terminus and is composed of two calponin homology domains (CHD1 and CHD2). The ABD is followed by 24 filamin repeats. Two filamin A proteins form a Y-shaped dimer,⁽¹⁹⁾ and bind the actin cytoskeleton through the ABD at the N-terminus.

Gene mutations were identified in 87.5% of familial PNH cases, but in only 19% of sporadic cases.^(10,20) We did not do *FLNA* gene analysis, but it was speculated that a mutation in the *FLNA* gene might be responsible for the clinical presentations of

PNH in family I.

Intestinal malrotation is a characteristic GI presentation in patients of PNH. Members of the current family I had several GI diseases including gallstones and gastric ulcers, and patient I:1 died of peritoneal carcinomatosis. These GI conditions were assumed to be a coincidence instead of a presentation of *FLNA* mutation.

Given the rare incidence of both PNH and EDS, this study was limited by the small number of the cases enrolled. A multi-center study must be carried out to increase the case number and limit bias.

Conclusions

There is clinical heterogeneity in patients with PNH. The overlap of symptoms of PNH, cardiovascular anomalies, aortic aneurysm, and EDS were reviewed. EDS is unusual in Asians with PNH. Patients with PNH should receive cardiovascular survey for aortic root aneurysm and other cardiac valvular diseases.

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腦室旁節結狀灰質異位與心臟血管異常

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- 背景：** 腦室旁節結狀灰質異位是一罕見先天性腦部病變。文獻中只有十個這樣的病人合併主動脈瘤，而其中有九個是 Ehlers-Danlos 綜合症患者。本研究探討腦室旁節結狀灰質異位，主動脈瘤，與 Ehlers-Danlos 綜合症在東方人身上彼此的相關聯性與表現。
- 方法：** 我們回溯性研究在 1994 年至 2010 年林口長庚紀念醫院同時有腦室旁節結狀灰質異位與心臟血管異常的病人。病人之家屬也同時納入研究。
- 結果：** 共有一個家族（五個病人）與一個偶發性個案同時擁有腦室旁節結狀灰質異位與心臟血管異常：兩人有主動脈瘤，一人有嚴重主動脈閉鎖不全，一人有輕微心臟瓣膜疾病。所有病人中兩人有癲癇，並且沒有人有 Ehlers-Danlos 綜合症。
- 結論：** 腦室旁節結狀灰質異位病人有廣泛的臨床表現。我們闡釋腦室旁節結狀灰質異位，心臟血管異常，以及 Ehlers-Danlos 綜合症之間的關連性。在東方人中，腦室旁節結狀灰質異位的病人很少有 Ehlers-Danlos 綜合症。所有腦室旁節結狀灰質異位的病人都應該接受心臟血管檢查以排除主動脈瘤或其他心臟血管異常。
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關鍵詞： 腦室旁節結狀灰質異位，神經元移行障礙疾病，心臟血管異常，主動脈瘤，肌絲蛋白 A

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