Neurology Asia 2010; 15 (Supplement 1) : 70 – 71

Genetic testing for non-familial epilepsies

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Background and Objective: Recent studies have demonstrated that more than 80 genes are linked to monogenetic epilepsy. The common idiopathic epilepsy syndrome with simple inheritance include generalized epilepsy with febrile seizures plus (GEFS+), severe myoclonic epilepsy in infancy (SMEI), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), juvenile myoclonic epilepsy (JME), benign familial neonatal seizures (BFNS), benign familial neonatal-infantile seizures (BFNIS). Most of the causative epileptic genes are found from big epilepsy families. It is generally estimated that familial epilepsies account for about 5% of the whole epilepsy population. Although genetic epilepsies are characterized by inheritance, isolated cases is theoretically also important, because of the possibility of *de novo* mutations. Epilepsies with febrile seizure plus (EFS+) caused by mutations of voltage-gated sodium channel α subunit type 1 gene (*SCN1A*) may serve as an example to show genetic testing in non-familiar epilepsy patients.

Methods: All mutations of *SCN1A* published previously were summarized; the origins of the mutations in different phenotypes were analyzed. Additionally, we studied 220 patients with EFS+ in 4046 out-patients from the Epilepsy Center of the Second Affiliated Hospital of Guangzhou Medical College seen in the last 12 years. DNA was obtained from blood samples of the EFS+ patients and their parents. Mutations in *SCN1A* were screened by PCR amplification and denaturing high performance liquid chromatography (DHPLC) analysis, and were identified by subsequent sequencing. Parental DNA was examined to ascertain the origins of the mutations.

Results: 289 mutations in *SCN1A* gene were reported so far (Table 1). The most common phenotype is SME, i.e., the most severe phenotype of EFS+, including 197 cases (68.2%) of SMEI and 47 (16.3%) of SMEB. On the contrary, GEFS+, the mild phenotype of EFS+, is only 9 (3.1%). As regard to the origin of the mutations, 69.7% mutations are found in non-familiar epilepsy patients, and only 12.5% in familial patients. The *de novo* mutation is found in about 75% of SME and none of GEFS+ patients, suggesting that more severe form of genetic epilepsies may have higher possibility of *de novo* origin (non-familial). Only 6.6% (16/244) mutations in SME are familial. It should be emphasised that among the 16 inherited mutations 5 were from their parents who were asymptomatic or milder FS with mosaic mutations. In our study of screening *SCN1A* mutations in a general population of patients with EFS+, 20 mutations have been found. Nine (45%) mutations, including 7 *de novo* mutations and 2 familial mutations, are from SMEI or SMEB patients. The others include 9 (45%) from PEFS+, 1 from GEFS+, and 1 from an FS patient.

Conclusion: Most of the EFS+ patients with *SCN1A* mutations, especially those of severe phenotypes, appear as sporadic cases. It is thus suggested that except familial GEFS+, sporadic EFS+ cases should not be ignored in genetic testing. The challenge in practice is how to find candidates for different gene testing.

Acknowledgement

This work was supported in part by grants from the National Natural Science Foundation of China (No. 30600198 to Dr Yue-Sheng Long and No 30700247 to Dr Xiao-Rong Liu)

Table 1. The origins of *SCN1A* mutations in epileptic syndromes*

Syndromes	*De novo* mutation	Familial mutation	Undetermined	Total
SMEI	148 (75.1)	15 (7.6)	34 (17.3)	197
SMEB	35 (74.5)	1 (2.1)	11 (23.4)	47
PEFS+	4 (36.4)	7 (63.6)	0	11
GEFS+	0	9 (100.0)	0	9
ICEGTC	3 (33.3)	2 (22.2)	4 (44.4)	9
CGE	3 (60.0)	1 (20.0)	1 (20.0)	5
CFE	3 (75.0)	1 (25.0)	0	4
MAE	3 (100.0)	0	0	3
SIGEI	2 (100.0)	0	0	2
LGS	1 (100.0)	0	0	1
IS	0	0	1 (100.0)	1
Total	202 (69.7)	36 (12.5)	51 (17.6)	289

*Values expressed indicate no(%).
SMEI: severe myoclonic epilepsy in infancy; SMEB: borderland SME; PEFS+: partial epilepsy with febrile seizures plus; GEFS+: generalized epilepsy with febrile seizure plus; ICEGTC: intractable childhood epilepsy with generalized tonic-clonic seizures; CGE: cryptogenic generalized epilepsy; CFE: cryptogenic focal epilepsy; MAE: myoclonic-astatic epilepsy; SIGEI: severe idiopathic generalized epilepsy of infancy; LGS: Lennox- Gastaut syndrome; IS: infantile spasm