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Exploring Correlation of PSEN1 E280A Mutation with Clinical Features in Patients with Glioma Related Seizures

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ZQG conceived the idea and designed the study. DDZ and QGQ analyzed the data. XXL, LL, YZX and SG contributed to literature review. ZQG wrote the manuscript. All authors read and approved the final manuscript.

Key words
Presenilin-1 E280A, Dysembryoplastic neuroepithelial tumors, Glioneuronal tumors, Gangliogliomas, Seizures

ABSTRACT

The correlation between Presenilin-1 (PSEN1) E280A mutation and clinical characteristics of glioma-related seizures (GRS) was explored. For this purpose, brain tissue samples were collected from 40 patients diagnosed with glioneuronal tumors (GNTs), including 25 cases of gangliogliomas (GGs) and 15 cases of dysembryoplastic neuroepithelial tumors (DNTs). Then, the DNA of GNTs tissues was extracted, and the PSEN1 E280A mutation was detected by sequencing. Finally, the correlation of PSEN1 E280A mutation with clinical characteristics was analyzed. PSEN1 E280A mutation was detected in 16 GNTs patients (44% in GGs (11/25) and 33.3% in DNTs (5/15)). PSEN1 E280A mutation was obviously elevated in females (10/16, 62.5%) versus in males (6/24, 25%) (P = 0.025). Meanwhile, more extensive seizure types were present in GNTs with PSEN1 mutations versus wilds (P = 0.001), but there was no clear correlation between PSEN1 and clinical manifestations like age of seizure, operative age, duration and absence of seizures after surgery. To conclude, PSEN1 E280A mutation is present in GNTs seizures patients, and greatly associated with multiple types of seizures and gender. The requirement of larger sample studies and long-term follow-up is implemented for further confirmation.

INTRODUCTION

In line with the European Epileptic Brain Bank's data, a quarter of patients undergoing epilepsy surgery suffer from brain tumors (Blumcke *et al*., 2014). Glioneuronal tumor (GNTs), consisting of gangliogliomas (GGs) and dysembryoplastic neuroepithelial tumors (DNTs) are extremely familiar histological kind. The location of slow growing tumors is the neocortex, and the linked symptoms will be manifested at a young age, among which, epilepsy is a greatly salient, and frequently the only neurological symptom. Under the microscope, the symptoms manifest as the differentiation of neurons and glial cells, revealing as the hybrid neural epithelium cell types, including malformed neurons and glial elements (Delev *et al*., 2020). Cortical dysplasia frequently coexist, suggesting an advanced mechanism of these lesions (Prabowo *et al*., 2014). As epilepsy surgery is advancing, GNTs are gaining much more attention.

Presenilin-1 (PSEN1) is believed to mediate amyloid precursor protein (APP) processing through its influence on gamma-secretase (an enzyme cutting APP). Abnormal PSEN1 has been observed in various cancers (Ma *et al*., 2018; Gou *et al*., 2020). In the meantime, studies have clarified that PSEN1 mutations occupy 95% of familial autosomal dominant early-onset *al*zheimer's disease (AD) cases (Hunter and Brayne, 2018), whereas PARK-DJ1 mutations, PARK-Parkin or PARK PINK1 are extremely familiar single-gene reasons of early-onset Parkinson's disease (Niemann and Jankovic, 2019). Up to now, over 280 pathogenic mutations of PSEN1 have appeared (Shen *et al*., 2019), characterized by ataxia, globular symptoms, spastic paraplegia and extrapyramidal symptoms (dystonia, myo clonus, Parkinson's disease and tremors), and been associated with neuropsychiatric and neurobehavioral disorders, neurocognition and rapid cognitive decline of varying degrees of severity (Carecchio *et al*., 2017). Studies have affirmed that point mutations in codon 280 of PSEN1 cause the change of glutamate to alanine (Alzheimer's Disease Collaborative Group, 1995), which has been characterized in antioquia, colombia (Lalli *et al*., 2014; Ochoa *et al*., 2017; Fleisher *et al*., 2012). Moreover,

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PSEN1 E280A has been demonstrated to change the proteolytic process of Aβ C-terminal AβPP through prosenectin/γ-secretase, thereby augmenting the deposition mechanism (Sisodia, 2001; Sisodia and George-Hyslop, 2002) of amyloid β (Aβ(1-42/43)) (Lemere *et al*., 1996). Nevertheless, the correlation between PSEN1 E280A mutation and clinicopathological features in patients with seizures was hardly explored.

In this study, clinical and pathological data were gained from 40 patients with epileptic GNTs. The purpose was verification of the presence of PSEN1 E280A mutation in epileptic GNTs and explore its association with clinical features.

MATERIALS AND METHODS

Subjects

From September 2014 to March 2018, brain tissue samples were collected from patients undergoing epileptic surgery in Linyi Central Hospital, of which 40 cases were diagnosed as GNTs (including 25 GGs and 15 DNTs) in line with the tumor classification in central nervous system revised by WHO in 2007. A detailed history manifested clinical features like demographic data, age of seizures, duration of seizures, and type of seizures, previous history (i.e., head trauma, hypoxic-ischemic brain injury, encephalitis), epilepsy, and family history of brain tumor, etc. All patients (n = 40) were received with noninvasive long-term Video-Electroencephalography (VEEG), postoperative seizure time, medication, seizure and magnetic resonance imaging (MRI) results. Multiple seizure kinds were regarded as two or over two kinds, consisting of partial seizure evolving into secondary systemic seizure, simple partial seizure, complex partial seizure, etc. Follow-up was over 3 months. The approvement of this study was via the Ethics Committee of Linyi Central Hospital.

Tissue immunofluorescence

The brain tumor specimens were fixed with 10% buffered formalin and embedded in paraffin, and 4 μm sections were cut for immunostaining. Incubation of the sections was with primary anti-PSEN1 antibody (1: 1000, Abcam) and second antibody. Immunofluorescence images were obtained with a Zeiss LSM 710 confocal microscope. Staining of the nucleus was via 4', 6-diamidino-2-phenylindole.

DNA extraction and PSEN1 E280A mutation analysis

DNA was extracted from tissues with the QIAamp DNA FFPE Tissue Kit (QIAGNE Cat No: 56404, Germany) under manufacturer's instructions. PCR amplification and sequencing of PSEN1 E280A was done accourding to Fleisher *et al*. (2015). The purified PCR products were sequenced vis an ABI3730xl sequencer (Applied Biosystems, Foster City, CA).

Statistical analysis

All analyses were done via Prism software. Description of continuous variables was via means and ranges. Categorical variables having proportions and percentages were manifested. The Student's t test was employed for assessment of differences of groups (duration of epilepsy, age of seizure, and age at surgery), but two-tailed chi-square or Fisher's exact tests for evaluation of the correlation between PSEN1 E280A mutation and other clinical manifestations (multiple seizure type, site, drug-resistant epilepsy, tumor location, post-operation seizure-free, etc.). $P < 0.05$ was considered statistically significant.

RESULTS

Study characteristics

Forty patients (24 males, 16 females) with mean duration of seizures 5.4 years, and the mean age of seizures 21.0 years. Approximately 75% of the patients were under age of 35, and the mean age of surgery was 25.4 years (Table I). In 40 patients, 28 (70%) owned a drug-resistant seizures history. Partial seizures were an extremely familiar kind of seizures, accounting for 85% of the sample. Presence of two or more seizure types was in seventeen patients (42.5%). GNTs patients were with complex partial seizures (plant-based or affective aura, psychosensory aura, autosomia and epileptic seizure) and partial seizures evolving into secondary systemic seizures. Only 3 patients were affirmed with a prior history of febrile seizures. The patients had no previous encephalitis, cerebral trauma, hypoxic-ischemic brain injury, and none of the patients reported a family history of brain tumors. Among the 32 patients diagnosed by non-invasive long-term VEEG examination, 26 patients presented with slow wave, and 30 patients presented with epileptic discharge. The lesions could be clearly displayed in the 40 patients implemented with MRI examination, and the extremely familiar sites of GNTs were the temporal and the frontal lobes (Table I). In GGs, major of the lesions were cystic or solid in nature, with full-bottomed T1 and T2 signals. MRI of DNTs manifested as clear edges of the lesions, with long T1 and T2 signals. Most were concomitant with one or more cysts or septations, with occasional triangular or gyrus appearance. Moreover, MRI features of PSEN1 E280A mutant and wild-type (WT) patients were similar. Surgical treatment was implemented in all patients, containing lesionectomy and resection of epileptogenic

focus, and 25 GGs and 15 DNTs were present. The performance of focal cortical dysplasia (FCD), also known as FCD IIIb, was detected in 9 GGs. Follow-up must be for at least 3 months. Luckily, 80% (32/40) of the patients were seizure-free, and the other 10 patients assured a clear decline in seizure frequency (Table I).

Table I. Summary of clinical manifestations of patients.

Feature	GNTs (n = 40)	GGs (n = 25)	DNTs (n = 15)
Male/female	24/16	15/10	9/6
Mean age of seizures years (range)	21.0 (0.5-54)	19.6 (0.5-55)	23.2 (3-52)
Duration of epilepsy years (range)	5.4 (0.4-32)	5.6 (0.2-34)	3.9 (0.3-15)
Mean age at surgery years (range)	25.4 (3.5-50)	23.6 (2.5-52)	24.3 (4-51)
Febrile convulsion (positive/ negative)	3/37	2/23	1/14
Past history (positive/negative)	0/40	0/25	0/15
Family history (positive/negative)	0/40	0/25	0/15
Multiple seizure types (yes/no)	17/23	12/13	5/10
VEEG at diagnosis			
Negative	0	0	0
Slow wave	26	18	8
Epileptiform discharge	30	20	10
NA	10	7	3
Drug-resistant seizures (yes/no)	28/12	18/7	10/5
Location			
Temporal lobe	28	20	8
Frontal lobe	8	5	3
Parietal lobe	4	3	1
Coexisting with FCD (yes/no)	9/31	9/16	0/15
Postoperative seizure-free (yes/no)	32/8	20/5	12/3

PSEN1 E280A mutation is found in GNTs

DNA sequencing revealed PSEN1 E280A mutation in 16 patients (Fig. 1A-D), including 11 GGs (44% mutation frequency), 5 DNTs (33.3% mutation frequency), and 6 males and 10 females. In the mutant, there were the mean age of seizures 20.0 years; the mean duration of seizures 5.3 years; the mean surgical age 24.2 years; 75% (12/16) was drug-resistant epilepsy, which was one of multiple seizure types. Location of major of the GNTs of PSEN1 E280A mutations was in the temporal lobe (Fig. 2). Among them, 3 cases were related to FCD and 75% of patients were with PSEN1 E280A mutation had no seizures after surgery, lasting over 3 months (Table II).

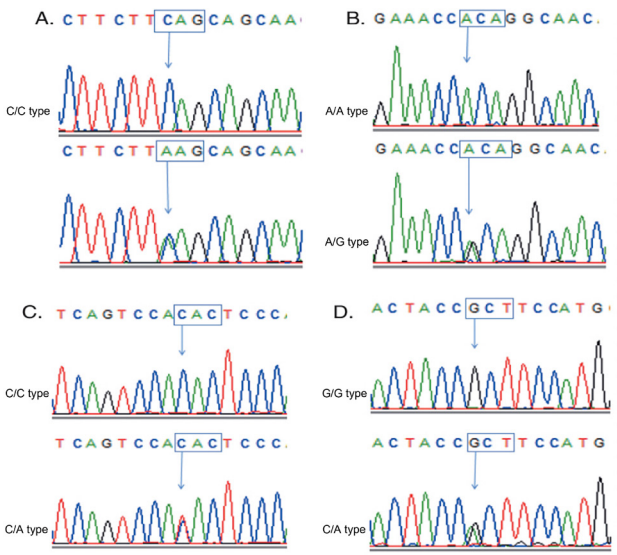

Fig. 1. PSEN1 sequencing peak figures. A, Exon 2 (c. 211 c > A); B, Exon 6 (c. 733A > G); C, Exon 6 (c.852C > T); D, Exon 15 (c.1762G > A).

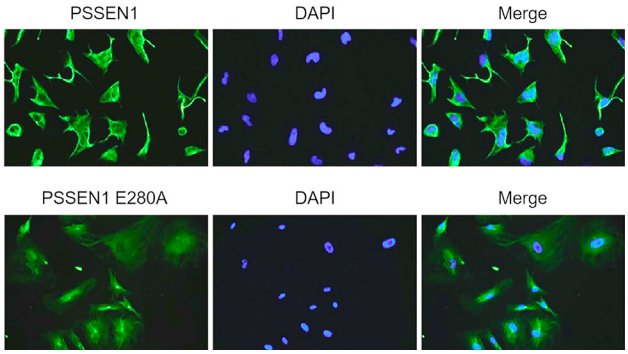

Fig. 2. PSEN1 location figures. Immunofluorescence test for PSEN1 expression in the brain tissue.

Correlation between PSEN1 E280A mutation and clinical characteristics in GNTs

The possibility of PSEN1 E280A mutation in females (10/16, 62.5%) was greatly elevated versus that in males (6/24, 25%) (P = 0.025). Meanwhile, more extensive seizure types were in GNTs with PSEN1 mutations versus WT (P= 0.001). Nevertheless, PSEN1 status was not greatly linked with a number of clinical features, like seizure age, duration of seizures, surgical age, febrile convulsion, drug-resistant seizures, tumor location and seizure-free time after surgery (Table II). Moreover, 28 patients with drug-resistant epilepsy (12 with PSEN1 E280A mutation) were chosen for further evaluation. Within this subgroup, consistence of the results of PSEN1 mutation and WT was with the above analysis (gender P =

0.020; multiple seizure kinds $P = 0.019$) (Table III).

Table II. Correlation between PSEN1 E280A mutation and clinical characteristics in GNTs.

Parameter	PSEN1 E280A mutation	PSEN1 wild type	P
Gender (male/female)	6/10	18/6	0.025
Age of seizures years (range)	20.0 (2-51)	20.6 (1.5-54)	0.758
Duration of seizures years (range)	5.3 (0.2-20)	5.0 (0.5-30)	0.866
Age at surgery years (range)	24.2 (5-52)	27.5 (2.5-50)	0.673
Febrile convulsion (positive/ negative)	1/15	2/22	1.000
Multiple seizure kinds (yes/no)	12/4	5/19	0.001
Drug-resistant seizures (yes/no)	12/4	16/8	0.729
Location (temporal/other)	13/3	15/9	0.297
Coexist with FCD (yes/no)	4/12	5/19	1.000
Postoperative seizure free (yes/no)	12/4	20/4	0.691

Table III. Correlation of PSEN1 E280A mutation with clinical characteristics in drug-resistant epilepsy.

Parameters	PSEN1 E280A mutation	PSEN1 wild type	P
Gender (male/female)	3/9	12/4	0.020
Age of seizures years (range)	21.2 (1.4-51)	22.6 (0.6-54)	0.668
Duration of seizures years (range)	5.1 (0.3-18)	5.0 (0.4-32)	0.769
Age at surgery years (range)	25.6 (4-50)	26.5 (2.7-53)	0.578
Febrile convulsion (positive/ negative)	1/11	1/15	1.000
Multiple seizure types (yes/no)	8/4	3/13	0.019
Drug-resistant seizures (yes/no)	9/3	12/4	1.000
Location (temporal/other)	10/2	11/5	0.662
Coexisting with FCD (yes/no)	3/9	4/12	1.000
Postoperative seizure free (yes/no)	8/4	11/5	1.000

The correlation of PSEN1 E280A mutation and clinical features in DNTs and GGs

GGs subgroup analysis manifested that PSEN1 state with various epilepsy types had apparent correlation ($P < 0.001$), but no statistical significance ($P = 0.116$) exhibited in gender differences (Table IV). Similar results were indicated in the DNTs subgroup (Table V).

Table IV. Correlation between PSEN1 E280A mutation and clinical characteristics in GGs.

Parameter	PSEN1 E280A mutation	PSEN1 wild type	P
Gender (male/female)	4/7	10/4	0.116
Age of seizures years (range)	24.0 (3-54)	22.1 (1.5-55)	0.534
Duration of seizures years (range)	5.5 (0.4-19)	5.3 (0.2-33)	0.476
Age at surgery years (range)	24.0 (5.5-53)	25.4 (2.8-54)	0.603
Febrile convulsion (positive/ negative)	0/11	2/12	0.487
Multiple seizure kinds (yes/no)	10/1	2/12	< 0.001
Drug-resistant seizures (yes/no)	7/4	10/4	1.000
Location (temporal/other)	9/2	11/3	1.000
Coexisting with FCD (yes/no)	3/8	5/9	1.000
Postoperative seizure free (yes/no)	8/3	12/2	0.623

Table V. Correlation between PSEN1 E280A mutation and clinical characteristics in DNTs.

Parameter	PSEN1 E280A mutation	PSEN1 wild type	P
Gender (male/female)	2/3	8/2	0.251
Age of seizures years (range)	20.5 (1-52)	21.8 (0.5-53)	0.322
Duration of seizures years (range)	5.2 (0.3-21)	5.4 (0.6-31)	0.549
Age at surgery years (range)	25.8 (4.7-50)	22.5 (2.5-51)	0.428
Febrile convulsion (positive/ negative)	0/5	1/9	1.000
Multiple seizure kinds (yes/no)	5/0	0/10	< 0.001
Drug-resistant seizures (yes/no)	3/2	7/3	1.000
Location (temporal/other)	3/2	5/5	1.000
Coexisting with FCD (yes/no)	0/5	0/10	1.000
Postoperative seizure free (yes/no)	4/1	8/2	1.000

DISCUSSION

GNTs are frequently defined as a low-grade glioma with mixed neuron-glioma. The seizure frequency of DNTs is up to 100%, and that of GGs is up to 80%-90% (van Breemen *et al.*, 2007). Seizures linked with GNTs

are usually not mediated via antiepileptic drugs, so GNTs are also grouped as long-term seizures related tumors, but additionally, highly responsive to surgical treatment (Luyken *et al*., 2003).

In this study, 40 epileptic patients with GNTs were collected. Additionally, its clinical and pathological characteristics are greatly coincident with former studies (Bonney *et al*., 2015, 2016; Chassoux *et al*., 2013). The study manifested that GNTs were widespread in men (male: female = 3: 2) and consistently presented as early occurrence but long duration seizures, coincident with plenty of former studies (Blümcke, 2009; Thom *et al*., 2011). Meanwhile, in line with this study, most frequent location of GNTs is the temporal lobe (Thom *et al*., 2012; Martinoni *et al*., 2015). Moreover, partial seizures (chiefly complex) were the extremely familiar kind of seizures, with about 50% patients having two or more seizures kinds.

At present, PSEN1 E280A mutation is widely present in various central nervous system diseases, particularly in AD, stimulating wide attention (Lanoiselée *et al*., 2017; Qiu, 2020; Jiang, 2020; Raut *et al*., 2021). Here, it was demonstrated PSEN1 E280A mutation in 16 of 40 patients (40%), with 44% mutation rate in GGs and 33.3% in DNTs. It was acknowledged that this study is the first case in patients with GRS.

PSEN1 E280A mutation and its clinical relevance were evaluated in GNTs in the study, which has rarely been previously reported. In this study, the frequency of PSEN1 E280A mutation in female patients was greatly elevated versus male, particularly in patients with drug-resistant seizures. This result might be directly or indirectly implicated with sex hormones with ambiguous mechanism. This association with gender is interesting and deserves further confirmation.

In the meantime, clear association of PSEN1 E280A mutation was manifested with multiple seizure types. The semiotic characteristics of epileptic seizure are associated with epileptogenic area and transmission network (Chauvel and McGonigal, 2014). It was hypothesized that there was a complex interaction between PSEN1 E280A mutation and seizures, and the mutation may be influential in neural networks, resulting in ictal discharge of different kinds of neurons in various parts, further leading to different types of seizures. Nevertheless, further research is required to confirm this. Noticeably, drug-resistance was present in nearly all patients with multiple seizure kinds. Thus, this could mean that PSEN1 E280A mutation could induce multiple kinds of seizures, which could make drug therapy difficult in these patients. No association was found between PSEN1 E280A mutation and age of seizure or clinical variables like age at surgery, tumor location, duration of epilepsy, etc. Unlike previous Alzheimer's studies, the subjects in this study were patients with seizures. Therefore, postoperative seizures were focused. However, a surprising result was obtained that the incidence of postoperative seizures was not linked with PSEN1 E280A mutation. Owing to the limited follow-up time, further confirmation of the connection of PSEN1 E280A mutation together with postoperative prognosis of seizures is required.

Some limitations are present in the study. Owing to limited follow-up time of some cases, changes of the seizure-free findings with time advancing, and not large sample size, the ability to further subgroup analysis and providing for more accurate results was limited. Large sample explorations and long-term follow-up are needed to testify the validity of the findings.

Statement of conflict of interest

The authors have declared no conflict of interest.

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