



Game-related seizures presenting with two types of clinical features

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Summary We evaluated 22 patients with epileptic seizures in which the seizures were triggered by various games or game-related materials. Based on whether spontaneous seizure coexisted or not, these 22 patients were divided into two groups. Ten patients who experienced seizures exclusively while playing or watching specific games were referred to as Group I, while 12 patients that had both game-induced and spontaneous seizures were classified as Group II. The patients in Group I had a middle-age onset (39.1 years) with a male predominance (90%). The electroencephalogram (EEG) or brain magnetic resonance imaging revealed non-specific abnormalities in 60%, and the partial onset seizure was recognized in 30% of patients. Antiepileptic drugs had uncertain benefits in this group. In Group II, patients had a male predominance (67%), with onset during adolescence (16.3 years). Most of them had generalized tonic–clonic seizures, myoclonic seizures, and absences, and 42% showed epileptiform discharge on EEG. These 12 patients were categorized into idiopathic generalized epilepsies. Although photosensitivity was an important factor, higher mental activity seemed to be significant precipitants of seizures in Group II. Antiepileptic drugs were necessary and valproic acid alone or combined with clonazepam was effective in this group. The results showed that game-related seizures are not a unique and homogeneous syndrome and may consist of different mechanisms. Teenage onset, coexistent spontaneous seizure, and associated idiopathic generalized epilepsies were crucial factors in the determination of antiepileptic drug therapy. Moreover, avoiding the related games altogether may be a more productive preventive measure.

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Introduction

Activation of epileptic seizures by game playing has been delineated as early as the late 1950s.¹ Since then, a number of cases have been reported in neurological literature.^{2–6} These games include card games,^{2–4} Mah-Jong,⁶ chess,³ draughts,^{2,4} checkers,⁵ and other similar games.^{3,7} Furthermore, in 1981, Rushton⁸ described the first case of epileptic seizures induced by video games. There are more than 200 documented cases of epileptic seizures thought to be associated with playing video games.⁹ Although game-related seizures are not new, the nature of the link between the various games and the epileptic seizures is uncertain. Many investigators consider the seizure induced by video games to be an extension of photosensitive epilepsy.^{10–13} Other reports, however, point to some mechanisms other than photosensitivity in relation to game-induced seizures.^{3,14,15}

Recent advances in the information technology has ushered “gaming” into a new era, with vast amounts of novel computerized games available worldwide, including small hand-held games, video or television (TV) games, newly special game consoles (e.g. Xbox, Microsoft and PlayStation, Sony Computer Entertainment Inc.), personal computer (PC) games, and online games. These new computerized games are even more popular, more graphic, more complex, and more violent than earlier games.¹⁶ Playing computerized or non-computerized games has been a preferred leisure activity not only for children and adolescents, but also for adults in the new century. While the prevalence of game-related epilepsy is unknown, it may be more common than is generally recognized. However, the reported cases of epileptic seizures associated with these novel entertainments are infrequent.

Few reports concerning video game-related seizures or other game-induced seizures discussed their cases with reviewed cases from literature and always concluded that game-induced epilepsy is a homogenous syndrome.^{3,15,17} To our knowledge, seizures can occur while game playing or independently of them in a patient with game-induced seizures.^{3,15,17} A previous report³ delineated the related epileptic syndrome in which seizures not induced by reflex activation were present in 76% of patients. However, they did not analyze the difference between the two groups. In this study, we investigated the clinical manifestations of 22 patients with game-related seizures. Our results suggest that game-related seizures are not a unique syndrome and it presents with two distinctive types of clinical features.

Patients and methods

Between January 1998 and June 2004, 22 patients with various game-induced epileptic seizures were evaluated at the Epilepsy Outpatient Clinic of Chang Gung Memorial Hospital-Kaohsiung, Taiwan. Clinical information obtained retrospectively from the clinical records and interviews included the age at onset, gender, personal and family history, specific game of seizure activation, clinical pattern and frequency of seizures associated with or without the game, and antiepileptic drug therapy and clinical outcome. Evaluation of the age at onset included the age at onset of the first attack of game-induced seizure and the age at onset of unprovoked spontaneous seizure. The inquiry of the specific game of seizure activation included Mah-Jong game, chess, card game, board game, online game, video or TV game, PC game, and special game consoles.

Game-induced seizures were defined as seizures precipitated exclusively by playing the related games, and where the possibility of sleep deprivation-induced seizures and medical causes (such as fever, drug use, toxin exposure, infection, or alcohol) were excluded. Patients who had at least three attacks of game-induced seizures were included in this study. “Spontaneous seizure” was defined as an epileptic seizure that occurred independently of the related games.

All of the patients underwent physical and neurological examinations, electroencephalogram (EEG) studies, brain magnetic resonance imaging (MRI) studies, and intelligence assessment. EEG recordings were carried out in 12 or 16-channel machines taken during wakefulness and sleepiness, hyperventilation, and intermittent photic stimulation (IPS) but not during the actual playing of the games. IPS was routinely performed by using a photostimulator at a distance of 30 cm from the nasion. Flash frequencies of 1–24 Hz were tested with eyes closed and eyes open. The seizure type and epileptic syndrome were categorized according to the International League Against Epilepsy (ILAE) classification of epilepsies and epileptic syndromes.¹⁸

The length of clinical follow-up ranged from 15 months to 6 years. Based on the coexistence of spontaneous seizures during the follow-up period, 22 patients were divided into two groups. Patients who experienced seizures exclusively by playing or watching the specific games were referred to as Group I. Otherwise, patients with epileptic seizures related to particular games and independent of games were classified as Group II.

Results

Based on the criteria set, 10 patients (Patients 1–10) were classified under Group I and 12 patients (Patients 11–22) in Group II. Their clinical and laboratory characteristics of the 22 patients are summarized in Tables 1 and 2.

Age and gender

The mean age at onset of the first game-related seizure was 39.1 years in Group I (range: 25–51 years) and 16.3 years in Group II (range: 13–25 years). Among 22 patients, there were 17 males and 5 females. Group I included 9 males (90%) and 1 female (10%), while Group II consisted of 8 males (67%) and 4 females (33%).

Specific games of seizure activation

Related games that evoked seizures in Group I included Mah-Jong in 8 patients, Chinese chess in 2, card game in 2, and board game in 1. Interestingly, 2 patients (Patients 1 and 3) experienced seizures while watching a Mah-Jong game, even though they did not personally play. Moreover, after usually playing the traditional Mah-Jong tiles, Patient 1 had seizures after playing a computer version of Taiwan Mah-Jong. The seizure latency ranged from 30 min to 10 h.

In Group II, the most frequently related games included online game in 6 patients, video or TV game in 7, PC game in 6, and playing game console in 4. Except for computer-related games, Patient 16 had a previous history of seizure while playing card games, and Patient 22 had seizures while playing a board game. In addition, 2 patients (Patients 18 and 19) in Group II also experienced seizures while watching TV. The seizure latency during playing online games ranged from 1 to 7 h. Moreover, the seizure latencies for playing PC games, video games or game consoles ranged from 30 min to 2 h.

Relevant medical and family history

In Group I, an associated medical history of hypertension was noted in 4 patients (Patients 1, 3, 6 and 10), hyperlipidemia in 2 (Patients 1 and 10), and diabetes mellitus in 1 (Patient 1). In Group II, 2 patients (Patients 13 and 16) had a history of febrile convulsion and 6 patients (Patient 16–21) had a history of seizures independent of game-playing before the first game-induced seizure. A family history of juvenile myoclonic epilepsy (JME) was noted in Patient 17.

Table 1 Clinical characteristics of the 10 patients with game-related seizures without spontaneous seizures (Group I)

Patients	Sex	Age at onset	Seizure patterns	Interictal EEG	Brain MRI	Specific games of seizure activation	Therapy	Effect of therapy
1	M	40	Partial seizure with secondary generalization	Rare right frontal sharp waves	Old right basal ganglia hemorrhage, pituitary adenoma	Mah-Jong game	CBZ	Ineffective
2	M	36	GTCS	Normal	Negative	Mah-Jong game, Chinese chess	VPA	Ineffective
3	M	50	GTCS	Normal	Mild brain atrophy	Mah-Jong game	VPA	Ineffective
4	M	37	GTCS	Normal	Negative	Mah-Jong game	Refused	—
5	F	34	GTCS	Normal	Negative	Mah-Jong game	Refused	—
6	M	51	Partial seizure with secondary generalization	Slightly slow background	Mild brain atrophy	Mah-Jong game, card game	Refused	—
7	M	44	GTCS	Normal	Negative	Mah-Jong game	PHT	Ineffective
8	M	34	Partial seizure with secondary generalization	Few right frontal theta activity	Negative	Mah-Jong game	VPA	Ineffective
9	M	25	GTCS	Normal	Negative	Board game	VPA	Controlled
10	M	40	GTCS	Diffused slow activity	Bilateral frontoparietal subcortical small infarcts	Chinese chess, card game	PHT	Ineffective

Table 2 Clinical characteristics of the 12 patients with game-related seizures and coexisting spontaneous seizures (Group II)

Patients	Sex	Age at onset	Seizure patterns	Epileptic syndrome	Interictal EEG	Brain MRI	Specific games of seizure activation	Therapy	Effect of therapy
11	F	19	GTCS	GTCS alone	Normal	Negative	Online game	VPA	Seizure-free
12	M	21	GTCS	GTCS alone	Normal	Negative	Video/TV game, game console	VPA	Lost follow-up
13	M	14	GTCS	GTCS alone	Normal	Negative	Online game	CBZ VPA	Ineffective Seizure-free
14	M	18	GTCS	GTCS alone	Bilateral frontal sharp waves	Negative	Online game, video/TV game, PC game, game console	VPA	Effective
15	F	13	GTCS	GTCS alone	Normal	Negative	PC game	GBP	Controlled ^a
16	M	25	GTCS	GTCS alone	Slow background	Negative	Card game, online game	VPA	Seizure-free Controlled
17	M	15	MS, GTCS	JME	Polyspike-and-waves	Negative	PC game, online game	VPA	Seizure-free
18	M	13	MS, GTCS	JME	Normal	Negative	Video/TV game, PC game, game console	CBZ + LTG	Aggravated
19	F	14	MS, GTCS	JME	Polyspike-and-waves, photoparoxysmal response	Negative	Video/TV game	VPA CBZ	Seizure-free Ineffective
20	F	14	MS, GTCS	JME	Polyspike-and-waves	Negative	Video/TV game, PC game	VPA + CNP CBZ, PHT	Seizure-free Ineffective
21	M	15	ABS, MS	JAE	Generalized spike-and-waves	Negative	Online game, video/TV game, PC game, game console	VPA GBP	Seizure-free Aggravated ^b
22	M	14	GTCS ABS, GTCS	JAE	Normal	Negative	Video/TV game, PC game, board game	VPA + CNP VPA	Controlled Seizure-free

M: male; F: female; GTCS: generalized tonic–clonic seizure; MS: myoclonic seizure; ABS: absence; JME: juvenile myoclonic epilepsy; JAE: juvenile absence epilepsy. PC: personal computer; TV: television; CBZ: carbamazepine; VPA: valproic acid; GBP: gabapentin; CNP: clonazepam; PHT: phenytoin; LTG: lamotrigine.

^a Shifted to gabapentin therapy due to hepatitis C and elevated plasma transaminases.

^b Gabapentin therapy aggravated ABS and MS.

EEG, brain MRI and other examinations

The physical and neurologic examinations showed unremarkable results for all of the patients in both groups. Except for Patient 8, who had borderline intelligence, the other 21 patients had an average or above average intelligence. Brain MRI studies revealed positive findings in 4 patients (40%) in Group I, but no similarly abnormal findings in Group II. Interictal EEG studies revealed that the background activities were normal in 12 patients (55%). Intermittent slow sharp waves, not clearly epileptiform, were recorded from the right frontal in Patient 1 and from bilateral frontal in Patient 14. Generalized epileptiform discharges were found in 4 patients (Patients 17 and 19–21) in Group II, and intermittent photic stimulation evoked a photoparoxysmal response in Patient 19.

Clinical seizure patterns

All of the patients experienced generalized tonic–clonic seizures. Partial onset seizures were recognized in 3 patients (Patients 1, 6 and 8) in Group I. The seizures of Patient 1 began with a jerking of the left face and staring, which could progress to generalized tonic–clonic seizures. Patient 6 experienced a tonic–clonic seizure followed by a short period of clouding of consciousness and head turning. Patient 8 noted repeated jerking of the left forearm while playing Mah-Jong. Occasionally, he lost consciousness and had a generalized convulsive seizure.

Six patients (Patients 17–22) in Group II had experienced coexistent myoclonic seizures and/or absences with generalized tonic–clonic seizures. Based on the seizure semiology and EEG findings, 12 patients in Group II were classified into idiopathic generalized epilepsies (IGE) by the ILAE classification of epilepsies and epileptic syndromes.¹⁸ The clinically recognizable subtypes¹⁹ included other IGE with generalized tonic–clonic seizures alone in 6 patients (Patients 11–16), JME in 4 patients (Patients 17–20), and juvenile absence epilepsy (JAE) in 2 patients (Patients 21 and 22).

Therapy and clinical outcome

Eighteen patients had regular antiepileptic drug therapy and consecutive follow-up. In Group I, three patients refused medication while seven other patients received regular treatment of anti-epileptic drugs. Six patients were unable to effectively control their game-induced seizures. One patient (Patient 9), controlled by valproic acid therapy, had a decrease in seizure frequency.

In contrast, all of the patients in Group II were treated with antiepileptic drugs. Carbamazepine was given to four patients (Patients 13 and 18–20), but it was ineffective in controlling game-induced and spontaneous seizures. Patient 18 had been receiving a combined therapy of carbamazepine and lamotrigine that aggravated his seizures. Moreover, in Patient 20, phenytoin therapy could remit generalized tonic–clonic seizures, but was ineffective in myoclonic seizures. Gabapentin monotherapy had been given to Patient 21 but was ineffective and aggravated absences and myoclonic seizures.

All of the patients in Group II had been receiving valproic acid therapy. Except for Patient 12 who was lost follow-up, valproic acid alone or combined with clonazepam showed an effective control on all types of game-induced and spontaneous seizures. Eight patients (Patients 11, 13, 15, 17–20, and 22) were seizure-free during the follow-up period. Patient 14 who had chronic hepatitis C received valproic acid alone had elevated plasma transaminases, and later shifted to gabapentin therapy also had controlled seizures.

Discussion

Reflex epilepsy comprises a group of syndromes characterized by seizures that predictably occur in response to specific stimuli, either simple or complex.²⁰ Undoubtedly, epileptic seizures induced by games or game-related materials are a particular form of reflex epilepsy.^{3,6} The major finding of this study is that game-related seizures could be divided into two significantly different types of reflex epilepsy by clinical features. Coexistent spontaneous seizure is a crucial factor in this categorization. Our observations provided the awareness of associated IGE in Group II patients and the different therapeutic consideration in each group.

Game-related seizures appear to have a predominance of males compared with females, and this gender difference is especially manifest in Group I. The mean age at onset is significantly older in Group I (39.1 years) than in Group II (16.3 years). In Group I, most experienced generalized tonic–clonic seizures, but focal onset was recognized in 30%. EEGs or brain MRI revealed non-specific diffused or focal abnormalities in 60% of patients. Taken together, these features are attributable to certain aspects of focal or diffused pathologic changes of the cerebral cortex in patients in Group I. There was no special epileptic syndrome presented in Group I.

On the other hand, the events in Group II were primary generalized tonic–clonic seizures, myoclonic seizures and absences. Coexistent myoclonic

seizures and/or absences with generalized tonic-clonic seizures are common in Group II. The EEGs always show generalized epileptiform discharge, and brain MRI revealed negative results. Based on the seizure semiology, 12 patients in Group II were related to adolescent-onset IGE syndromes, including other IGE with generalized tonic-clonic seizures alone, JME and JAE.¹⁹ These findings suggest that game-related seizures in Group II could overlap with IGE syndromes. Of particular importance, patients are often diagnosed only when a game-induced generalized tonic-clonic seizure supervenes and myoclonus or absences may be ignored.

The pathophysiologic mechanisms underlying reflex epilepsy induced by game playing has not yet been well established. Various circumstances acting either singly or in combination may lead to the occurrence of epileptic seizure in a subject playing a game.¹⁴ Photosensitivity and pattern sensitivity to the physical characteristics of a display and the visual content of the game are the most important factors.^{10–13,21} Another reflex mechanism is seizure precipitation by specific cognitive activities, decision-making, thinking, spatial task or hand movements.^{3,14} Moreover, certain non-specific factors, including anxiety, emotional excitement, stress, fatigue, prolonged play, and sleep deprivation may contribute to the genesis of game-induced seizures or act as independent risk factors.^{14,15}

From our results, two types of game-related seizures presenting with different clinical features suggest that distinct mechanisms take part in the epileptogenicity between the two groups. We recognized that Group I patients had seizures precipitated by involving higher mental activities. This type of game-related seizures is an extension of Mah-Jong-induced epilepsy in our previous report.⁶ Taiwanese Mah-Jong is a rather complicated game. Players continually exchange their tiles with other players, sorting and arranging their own tiles into desired spatial sequences. One wins or loses the game based on a special assembly of tiles. It takes about 30 min to play one round. Usually, people play Mah-Jong for at least 4 rounds (2 h), and it is common to play up to 40 rounds (more than 20 h). No doubt, thinking, memory, intuition and decision-making are important factors for winning in the long run. In our patients in Group I, photosensitivity and pattern sensitivity might play a minor role in the epileptogenicity. We postulate that complex factors while playing games may have a reciprocal relationship in the epileptogenic activation of the specific pathological cortex, including spatial tasks, action-programming, thinking, decision-making and related stress, particularly among the Chinese people.⁶

According to previous studies on video game- and TV-induced seizures, photosensitivity, pattern sensitivity, chromatic sensitivity and stimulus frequency were emphasized.^{10–13,22} In this study, pattern sensitivity was not tested on the patients. Only one patient with photo-paroxysmal response to IPS was noted. The relatively old age of our patients and the fact that most patients were tested while they were being treated with valproic acid, may explain the low-rate of photosensitivity of the EEG. In addition, the limited frequencies (1–24 Hz) used during the IPS procedure may have missed some patients who are only sensitive to high frequencies (30–60 Hz) of IPS possibly resulting in the low-rate of photosensitivity.

However, in Group II, some patients had experienced seizures while watching TV and all of the patients had seizures in front of the computer monitor while playing computerized games. Consequently, clinical photosensitivity plays an important role in the generation of game-related seizures in Group II patients. Nevertheless, two patients also experienced seizure during card or board games. While a higher frequency of males was found in Group II, two thirds of photosensitive patients were female.^{21,23} Therefore, the observation of male predominance further supported the hypothesis that factors other than photosensitivity may contribute to the pathophysiologic mechanism in Group II. Thus, we propose that the reflex mechanism involving higher mental stimuli during game playing triggering generalized epileptogenicity is another important mechanism in the genesis of game-related seizures in Group II. In fact, higher mental activities can precipitate generalized spike-and-wave discharges, which may be accompanied by myoclonic seizures or absences. This is suggestive of the relation to IGE syndrome, including JME and JAE.^{24,25}

Sleep deprivation has been mentioned as a contributing factor in a proportion of patients with game-induced seizures.¹⁴ In our patients, the seizure latency after playing related games is highly variable. In Group I patients, the seizure latency ranged from 30 min to 10 h. In Group II patients, the seizure latency during playing online games ranged from 1 to 7 h. However, seizure latencies for playing PC games, video games or game consoles is relative shorter than other games that ranged from 30 min to 2 h. Since these games are more graphic and intense than the other games, stress-related factors and photosensitivity may take part in the shorter latency of reflex seizure. According to the seizure history of each patient, we found a notable absence of clinical triggers related to startle stimuli, prolonged game playing, and sleep deprivation in our patients. We

suggest that the variable and rather long latency for the occurrence of game-related seizures may be involved in a reflex mechanism while the specific scenario presented during the course of the game coincides with the activation of the areas of cortical hyperexcitability during higher mental activities. These specific scenarios may be particular to each individual player, especially in the Mah-Jong and on-line games. This particularity plays an important role in the highly variable latency of game-related seizures.

In our study, seven patients in Group I received antiepileptic drug therapy, which was ineffective in controlling game-induced seizures. As no spontaneous seizure occurred in these patients and that the seizure attacks were only related to a specific game, we suggest that antiepileptic drug therapy in Group I has uncertain benefits. Instead, perhaps an abstinence from the related games would be more effective in preventing seizures. On the other hand, the response to medication is generally good in Group II. Except for avoiding the related game playing, antiepileptic drug therapy is necessary. Valproic acid alone or combined with clonazepam is effective in controlling all types of game-induced seizures and spontaneous seizure in Group II. However, monotherapy should be used whenever possible. Based on our observation, carbamazepine, lamotrigine, phenytoin, and gabapentin are not suggested for this group of patients.

On the other hand, we found the presentation of clinical features in our patients is distinct from the reported cases of game-induced seizures. We propose that some associated factors might precipitate the different clinical presentations, including the pop games in special society, lifestyle under cultural background, different cortical organization in populations, and particularities of ethnic and genetic factors. Furthermore, the fact that different age groups preferred different games contributes to the age difference and characteristic clinical features in the two groups of our patients. However, the exact mechanism of game-related seizures is not completely elucidated. Hence, further studies are mandatory in the future to confirm these observations.

In conclusion, our results demonstrated that game-related seizures are not a unique and homogenous syndrome that was divided into two significantly different types of reflex epilepsy by clinical features. It may consist of distinct pathophysiologic mechanisms in these two types of game-related reflex seizures. Teenage onset, coexistent spontaneous seizure, and associated IGE are crucial factors in the determination of antiepileptic drug

therapy. Moreover, avoiding the related game altogether may be more productive in preventing seizure.

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