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Psychotic disorders induced by antiepileptic drugs in people with epilepsy

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Antiepileptic drug treatment can induce psychosis in some patients. However, there are no agreed definitions or diagnostic criteria for antiepileptic drug-induced psychotic disorder in the classification systems of either epileptology or psychiatry. In this study we investigated the clinical spectrum of antiepileptic drug-induced psychotic disorder in patients with epilepsy. The medical records of all patients with epilepsy who were diagnosed by a neuropsychiatrist as having a psychotic disorder at the Royal Melbourne Hospital from January 1993 to June 2015 were reviewed. Data were extracted regarding epilepsy and its treatment, psychotic symptoms profile and outcome. The diagnosis of epilepsy was established in accordance to the classification system of the International League Against Epilepsy while that of psychotic disorder was made according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition and the proposal on neuropsychiatric disorders in epilepsy. Patients with antiepileptic drug-induced psychotic disorder were compared to those with psychotic disorders unrelated to antiepileptic drugs assessed over the same period (non-antiepileptic drug induced psychotic disorder group). Univariate comparisons were performed and variables with a value of $P < 0.1$ were selected for the multivariate logistic regression analysis. The records of 2630 in-patients and outpatients with epilepsy were screened, from which 98 (3.7%) with psychotic disorders were identified. Among these, 14 (14.3%) were diagnosed to have antiepileptic drug-induced psychotic disorder. Excluding one patient who developed psychosis after valproate withdrawal, 76.9% in the antiepileptic drug induced psychotic disorder group were female and the percentage of temporal lobe involvement was higher in the antiepileptic drug induced psychotic disorder group (69.2% versus 38.1%, $P < 0.05$). Current use of levetiracetam was higher in antiepileptic drug-induced psychotic disorder group (84.6% versus 20.2%, $P < 0.01$) while use of carbamazepine was higher in the comparator group (15.4% versus 44.0%, $P < 0.05$). Multivariate logistic regression confirmed four factors associated with antiepileptic drug-induced psychotic disorder: female gender, temporal lobe involvement and use of levetiracetam, and a negative association with carbamazepine. Disorganized behaviours and thinking were more common in the antiepileptic drug-induced psychotic disorder group (100% versus 72.6% and 76.9% versus 38.1%, respectively; $P < 0.05$). The percentage of continuous treatment with antipsychotic drugs was lower in the antiepileptic drug-induced psychotic disorder group (15.4% versus 66.7%, $P < 0.01$). No patients experienced a chronic course in antiepileptic drug-induced psychotic disorder group whereas 40.5% did in non-antiepileptic drug induced psychotic disorder ($P < 0.05$). Our findings indicated that one in seven patients with epilepsy who developed psychosis had antiepileptic drug-induced psychotic disorder. In these patients, female gender, temporal lobe involvement and current use of levetiracetam were significantly associated with antiepileptic drug induced psychotic disorder compared to other types of psychosis, while carbamazepine had a negative association. Disorganized behaviours and thinking were predominant in antiepileptic drug-induced psychotic disorder. Patients with antiepileptic drug-induced psychotic disorder differed from non-antiepileptic drug-induced psychotic disorders in having better outcome.

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Abbreviations: AED = antiepileptic drug; AIPD = antiepileptic drug induced psychotic disorder; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

Introduction

Epilepsy is one of the most common neurological disorders and ranks as the second leading neurological cause of reduced disability-adjusted life-years (Murray *et al.*, 2012). Patients with epilepsy have increased vulnerability to psychiatric co-morbidity including psychotic disorders (Clarke *et al.*, 2012; Rai *et al.*, 2012), imposing additional disease burden. For instance, in a Danish population-based cohort study, the incidence of schizophrenia and schizophrenia-like psychosis in epilepsy patients was nearly 2.5 times and 3 times higher than in the general population, respectively (Qin *et al.*, 2005).

Among the various types of psychotic disorders in epilepsy, antiepileptic drug (AED)-induced psychotic disorder (AIPD) represents an iatrogenic, adverse drug reaction. Prevalence of AIPD has been reported to range from 1.0% to 8.4% in clinical trials of AEDs (Piedad *et al.*, 2012). However, detailed analysis of the clinical profile of the psychotic episodes was lacking in these studies, which tended to rely on screening questionnaires to ascertain psychiatric symptoms with few patients undergoing structured interview by psychiatrists (Clancy *et al.*, 2014). Few studies have reported long-term outcome of the psychotic episodes, as most randomized trials reported the psychiatric events within the 12–16 weeks of observation (de la Loge *et al.*, 2010).

Besides methodological limitations, advances in understanding AIDP have been further hampered by the lack of agreed diagnostic criteria in the existing classification systems (Lin *et al.*, 2012). Although substance/medication-induced psychotic disorder is defined in the Fifth Edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5), its applicability to AIPD may be questioned because the pharmacodynamic mechanisms of AEDs may be different from other substances or medications (American Psychiatric Association, 2013). The International League Against Epilepsy (ILAE) has published a classification scheme for AED-induced psychiatric disorders, but it is not specific for psychosis and covers other psychiatric manifestations, such as affective disorders, that show a different clinical course (Krishnamoorthy *et al.*, 2007).

As a result of these limitations in knowledge, the management of AIPD in clinical practice is extremely challenging and not evidence-based. By definition, the definitive diagnosis of AIPD can only be made retrospectively. In theory, the most valid way to determine whether a given AED is responsible in causing a particular adverse event would be to withdraw the culprit drug and observe the remission of symptoms, followed by rechallenging with the medication and observing symptom relapse (Edwards and Aronson, 2000). This approach, however, is rarely practical in the clinical epilepsy setting, particularly for psychiatric adverse effects. The diagnosis is further compounded by the predisposition towards AIPD in people with history of psychiatric illnesses (Trimble *et al.*, 2000; Weintraub *et al.*, 2007). In some cases the episode of AIPD can resemble recurrence of previous primary psychotic disorder. Therefore, when a patient with epilepsy develops psychotic symptoms, it is challenging to determine at presentation whether the psychosis is AED induced or not.

Misdiagnosing AIPD as primary psychotic disorder may lead to inappropriate management, including continuation of the culprit AED and additional treatment with antipsychotic drugs. Often, the psychotic symptoms of AIPD persist in a fluctuating manner as long as the AED is continued (Amerincan Psychiatric Association, 2013). The patient may endure both the adverse effects of the AED and potential exacerbation of epilepsy by antipsychotic drug therapy (Lin *et al.*, 2012). Therefore, identification of reliable factors at presentation that help to differentiate AIDP from other forms of psychosis in epilepsy is needed.

In this study we aimed to identify these factors by investigating the clinical spectrum of AIPD in patients with epilepsy who presented with psychotic symptoms, including the clinical features of the epilepsy, AED treatment, the psychotic symptoms and outcome.

Materials and methods

Patient sources

Eligible patients were identified from the Department of Neurology at the Royal Melbourne Hospital between January 1993 and June 2015. Patients were mainly identified from those admitted electively for a comprehensive epilepsy evaluation, which included prolonged (5 days or more) video EEG monitoring, clinical assessment by epileptologists, psychiatric evaluation by neuropsychiatrists, and review of neuroimaging by neuroradiologists. A minority (7.1%) of patients were identified from the epilepsy outpatient clinics. All patients had undergone formal psychiatric interview by a specialist neuropsychiatrist.

The inclusion criteria were: (i) onset of the psychotic disorders at 16 years or older; (ii) diagnosis of epilepsy; and (iii) admission to hospital or attendance at epilepsy outpatient

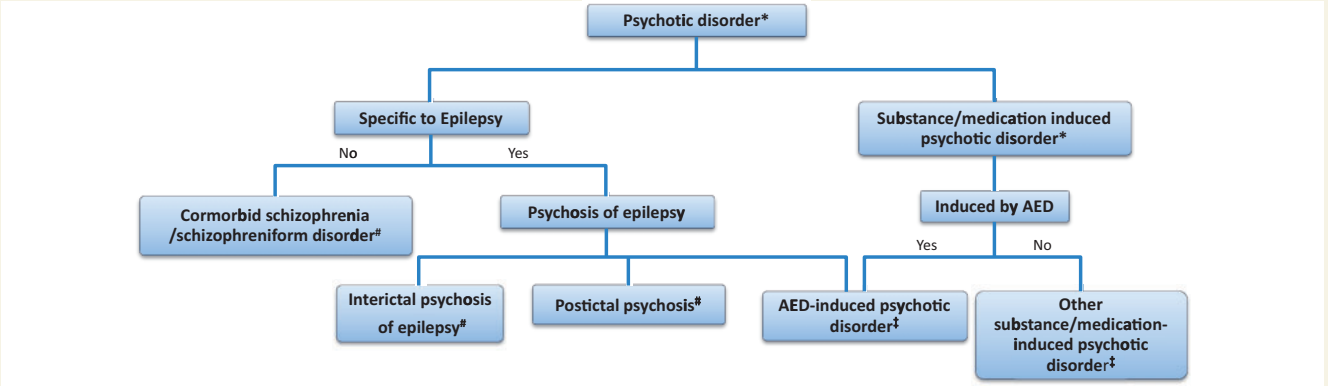

Figure 1 Diagnosis scheme of psychotic disorders related to epilepsy modified from DSM-5 and the proposal by ILAE Commission on Psychobiology of Epilepsy. *As per DSM-5 (American Psychiatric Association, 2013); #as per ILAE proposal (Krishnamoorthy *et al.*, 2007); ‡defined in this study.

clinic for psychotic symptoms. Patients were excluded if they had (i) psychogenic non-epileptic seizures; (ii) psychotic symptoms as part of the ictal semiology; or (iii) an organic illness with known psychiatric manifestations, e.g. Wilson's disease.

Study procedure and diagnostic approach

The study was approved by the Clinical Research and Ethics Committee of the Royal Melbourne Hospital (HREC No: 2002.232). Information regarding individual demographic data, the clinical manifestations of epilepsy and psychosis, prior psychiatric history, AED usage, and outcomes of epilepsy and psychosis was retrieved from the medical records using a standardized case report form. The data were reviewed by an epileptologist (Z.C.) and a neuropsychiatry fellow (A.L.) who jointly confirmed the diagnosis of epilepsy and psychotic disorder.

Figure 1 illustrates the diagnostic scheme for the various types of psychotic disorders in relation to epilepsy in the patients. First, the diagnosis of psychotic disorders was established. As per the ILAE proposal (Krishnamoorthy *et al.*, 2007), psychotic disorders specific to epilepsy were then classified as psychosis of epilepsy, including interictal psychosis of epilepsy, postictal psychosis, and AIPD. Psychotic disorders unrelated to the underlying epilepsy were classified as comorbid schizophrenia/schizophreniform disorder. As AIPD was not specifically defined in the ILAE proposal, its definition was adopted from the criteria for substance/medication-induced psychotic disorders in DSM-5, such that if the offending drug was an AED, the episode was classified as AIPD. Otherwise it was classified as other substance/medication-induced psychotic disorder.

Clinical assessments and definitions

According to the classification system of the ILAE, seizures were classified as generalized or focal. Focal seizures were further classified depending on whether there was impairment of consciousness or evolution to bilateral convulsion (Berg *et al.*, 2010). Epilepsy syndromes were broadly classified as genetic, structural/metabolic, and epilepsy of unknown cause. Specific structural abnormalities of interest were hippocampal sclerosis, brain tumour and malformations of cortical development. Temporal lobe involvement was defined as the epileptogenic lesion locating in temporal lobe with or without the involvement of other lobes. Drug resistance was defined as the failure of two appropriately chosen and tolerated AED schedules to maintain seizure freedom (Kwan *et al.*, 2010).

According to the classification system DSM-5, the diagnosis of psychotic disorders requires the presence of delusions or hallucinations, plus possible disorganized thinking and grossly disorganized or abnormal motor behaviour. Either delusions or hallucinations must be present and the duration of the psychotic episode must last at least 1 day. Delusions may be persecutory, referential, somatic, religious, or grandiose delusions. The characteristics of hallucinations, such as auditory, visual or tactile hallucinations were recorded in the medical notes. Disorganized thinking was characterized by derailment or loose associations, tangentiality, incoherence or 'word salad'. Grossly disorganized behaviours reported in our cohort consisted of aggressive behaviour and unusual social behaviours, such as socially or sexually inappropriate behaviours, e.g. talking to oneself in public, obscene language, or exposing oneself to others.

The relationship of the psychotic disorder to the patient's underlying epilepsy were established in accordance with the proposal by ILAE (Krishnamoorthy *et al.*, 2007). Interictal psychosis of epilepsy was defined as psychotic episodes in accordance with the criteria of psychosis in DSM-5 and independent from seizures (Table 1). Post-ictal psychosis was defined as psychotic episodes after a lucid interval (up to 48 h) following a cluster of seizures. Comorbid schizophrenia/schizophreniform disorder was diagnosed under DSM-5. In substance/medication-induced psychotic disorder, either delusions or hallucinations must be present and the psychotic symptoms develop during or soon after the exposure to a substance or medication or the withdrawal of that substance. The severity must impair the patients' social or occupational function. When the offending agents were AEDs, the disorder was classified as AIPD.

For the analysis of outcome, the clinical courses were categorized as following: (i) a single episode was defined as the duration of psychosis of longer than 1 day; (ii) a relapse was defined as recurrent episodes within 1 year after remittance of

Table 1 Diagnosis criteria of psychotic disorders in epilepsy used in this study

Groups	Diagnosis criteria
AIPD	Delusions, hallucinations, disorganized thinking and grossly disorganized or abnormal motor behaviour. At least delusion or hallucination must be present. The duration of the psychotic episodes lasted at least 1 day. The severity reached the level that impaired patients' social or occupational function. The psychotic symptoms developed during or soon after the exposure to an AED or the withdrawal.
Interictal psychosis of epilepsy	Delusions, hallucinations, disorganized thinking and grossly disorganized or abnormal motor behaviour. At least delusion or hallucination must be present. The duration of the psychotic episodes lasted at least 1 day. The severity reached the level that impaired patients' social or occupational function. Psychotic episodes are independent with seizures.
Post-ictal psychosis	Delusions, hallucinations, disorganized thinking and grossly disorganized or abnormal motor behaviour. At least delusion or hallucination must be present. The duration of the psychotic episodes lasted at least 1 day. The severity reached the level that impaired patients' social or occupational function. The psychotic episodes occur after a lucid interval following clusters of seizures.
Comorbid schizophrenia/ schizophreniform disorder	Delusions, hallucinations, disorganized thinking and grossly disorganized or abnormal motor behaviour. At least delusion or hallucination must be present. The duration of the psychotic episodes lasted at least 1 month. The severity reached the level that impaired patients' social or occupational function. No distinguishing features separate it from those seen in general population.
Other substance/medication-induced psychotic disorder	Delusions, hallucinations, disorganized thinking and grossly disorganized or abnormal motor behaviour. At least delusion or hallucination must be present. The duration of the psychotic episodes lasted at least 1 day. The severity reached the level that impaired patients' social or occupational function. The psychotic symptoms developed during or soon after the exposure to substance/medication or the withdrawal except AED.

longer than 2 months; and (iii) a chronic course was defined as duration of the psychotic state of over 1 year without remittance for more than 2 months (Matsuura *et al.*, 2000).

Statistical analysis

Data were presented as *n* (%) for categorical/qualitative variables or mean ± standard deviation (SD) or median (interquartile range, IQR) for continuous/quantitative variables. Cases were patients with AIPD. Controls were the patients with epilepsy and psychotic disorders unrelated to AEDs assessed over the same period (non-AIPD group). Clinical variables of epilepsy and psychotic disorder were compared between the AIPD group and the non-AIPD group. Univariate comparisons were performed with *t*-test, χ^2 test or Fisher's exact test, as appropriate. Univariate logistic regression analyses were performed to calculate the odds ratios of the variables. Variables with $P < 0.1$ were selected for multivariate logistic regression analysis. $P < 0.05$ was considered to be statistically significant. Statistical analyses were carried out using the statistical software package SPSS 20.0.

Results

Patient characteristics

A total of 98 patients (53 male) with epilepsy who had experienced psychotic disorders were identified, 22 of whom had been reported previously (Adams *et al.*, 2008). Six patients developed psychosis during hospitalization for video EEG monitoring while the remaining 92 experienced the psychotic episode at times separate from the monitoring admission. The median age of onset of epilepsy was 18.5 years (IQR 9–31) and the median age of onset of psychosis was 34.5 years (IQR 27–45). Seventy-nine (80.6%) patients had focal onset seizures and 19 (19.4%) had generalized onset seizures (Table 2). The epilepsy was classified as genetic in 16 (16.3%), structural/metabolic in 59 (60.3%), and of unknown cause in 23 (23.5%).

The psychosis was classified as AIPD in 14 (14.3%) patients and unrelated to AED therapy in the other 84 (85.7%). The latter included interictal psychosis of epilepsy in 33 (33.7%) patients, post-ictal psychosis in 25 (25.5%), comorbid schizophrenia/schizophreniform disorder in 19 (19.4%), and psychotic disorder induced by substances or medications other than AEDs in seven (7.1%).

Patients with antiepileptic drug-induced psychotic disorder

Table 3 shows the clinical features of the 14 patients with AIPD. The majority (10 of 14) of patients had temporal lobe involvement in their seizures with a variety of pathologies. In these patients the most common hallucinations were auditory and visual. Two patients reported tactile

Table 2 Diagnosis classification of epilepsy and psychotic disorders

Diagnosis	*n* (%)
Epilepsy	
Genetic epilepsy	16 (16.3)
Structural/metabolic epilepsy	59 (60.3)
Epilepsy with unknown cause	23 (23.5)
Psychotic disorders	
AEDs-induced psychotic disorders	14 (14.3)
Interictal psychosis of epilepsy	33 (33.7)
Post-ictal psychosis	25 (25.5)
Comorbid schizophrenia/schizophreniform disorder	19 (19.4)
Other substance/medication-induced psychotic disorder	7 (7.1)
Total	**98 (100)**

hallucinations. The most prevalent type of delusion was persecutory. Other delusions reported by the patients included referential, religious, grandiose and somatic. All patients presented with disorganized behaviours, such as aggressive and unusual social behaviours. Patient 1 had a previous history of psychosis induced by an overdose of weight-loss medication. A similar history was reported by Patient 4 after taking an antihistamine.

Levetiracetam was the most common AED taken by patients with AIPD, either as monotherapy or in combination with other AEDs, accounting for 8 (57.1%) of the 14 cases. Three (21.4%) were taking lamotrigine. Two (14.3%) patients experienced two episodes of psychosis associated with levetiracetam and topiramate separately. One (7.1%) case was induced by the withdrawal of valproate. The maximal dose of levetiracetam used in the AIDP patients varied from 500 mg/day to 3000 mg/day (median 2000 mg/day). Notably, relatively low doses (500 to 1000 mg/day) were used in the four patients who developed AIPD on monotherapy levetiracetam. Among the three cases with lamotrigine induced AIPD, the maximal doses ranged from 100 to 600 mg/day. For topiramate, one patient took 400 mg/day and the other developed psychosis while taking 150 mg/day.

In 11 patients the psychotic symptoms resolved after withdrawal of the culprit AEDs. Two patients and one patient in one of her episodes recovered after reducing the dosage of the culprit AEDs. The duration of the AIPD episodes was less than 7 days in nearly half of the patients. Although eight patients needed treatment with antipsychotic drugs to control the psychiatric symptoms, most of them did not require antipsychotic medication for longer than 1 month.

Patient 13 of AIPD associated with valproic acid withdrawal was established in accordance to diagnosis criteria by ILAE. It is possible this was a primary psychotic disorder, which relapsed because of the abrupt withdrawal of valproic acid therapy. Review of the record showed no previous history of psychosis in this patient. The time interval of drug withdrawal to onset of psychosis and that of re-prescription to symptom resolution fulfilled the diagnosis criteria. Furthermore, although antipsychotic treatment with olanzapine was prescribed, the psychotic symptoms resolved without continuous use of olanzapine. Hence, this case may be diagnosed as AIPD. As psychosis that develops after AED withdrawal is conceptually distinct from that induced by drug initiation or dose escalation, Patient 13 was excluded from the AIPD group in the following statistical comparisons.

Comparison between antiepileptic drug-induced and non-antiepileptic drug-induced psychotic disorder

Epilepsy and treatment related factors

The epilepsy and AED-treatment related factors are listed in Table 4. There were more females in the AIPD group (76.9%) compared with the non-AIPD group (41.7%; $P < 0.05$). There was no difference in age of onset of psychosis between the two groups, nor was there difference in seizure types.

In the analysis of aetiology classification, AIPD was more often associated with structural/metabolic epilepsy (84.6% versus 56.0% in non-AIPD group, $P < 0.05$). There was a trend of higher proportion of patients having brain tumour in the AIPD group but the difference did not reach statistical significance. In the AIPD group, two patients had craniopharyngioma and one had meningioma. In the non-AIPD group, there were two patients with astrocytoma and one with metastasis of ovarian cancer. Tumour type was unknown in the other two patients. Comparisons of other common causes, including hippocampal sclerosis, malformations of cortical development, brain traumatic injury and cerebral vascular disease, showed no significant differences.

There was no difference in lateralization of seizure focus between AIPD and non-AIPD patients. However, the percentage of temporal lobe involvement was higher in the AIPD group [69.2% versus 38.1% in non-AIPD group, odds ratio (OR) 4.063, $P < 0.05$].

Two (15.4%) patients in the AIPD group had a history of psychiatric disorder prior to epilepsy onset while 24 (28.6%) in the non-AIPD group did. Interestingly, both cases in the AIPD group were classified as substance/medication-induced psychosis (antihistamine and overdose of weight-loss medication, respectively) while only two cases in the non-AIPD group experienced prior substance/medication induced psychosis (marijuana and steroid, respectively). In the latter group, another two patients had depression, one had antisocial personality disorder and the remaining 19 had comorbid schizophrenia/schizophreniform disorder. The differences in prior psychiatric history in general or that specifically related to substance/medication between the two groups were not statistically significant. Besides epilepsy and psychotic disorders, four (23.1%) patients in the AIPD group had other medical comorbidities, including pan-hypopituitarism, liver

Table 3 Sociodemographic and clinical features of the 14 cases with AIPD

Sociodemographic and clinical features

Patient ID	Gender	Age at epilepsy onset	Age at psychosis onset	Seizure types	Cause of epilepsy	Localization of the lesion(s)	Seizures frequency before psychosis	Number of previous AEDs	Number of present AEDs
1	F	22	38	Focal seizure with impairment of consciousness or awareness	HS	R T	3–4/w	2	1
2	F	7	34	Myoclonus seizure, generalized tonic-clonic seizure	Presumed genetic	No	1–2/m	3	2
3	F	9	38	Focal seizure with impairment of consciousness or awareness, focal seizures evolving to a bilateral convulsive seizure	Porencephaly	L TPO	3/w	3	2
4	F	9	36	Focal seizure with impairment of consciousness or awareness, focal seizures evolving to a bilateral convulsive seizure	FCD	R T	1/m	7	3
5	F	10	36	Focal seizure with impairment of consciousness or awareness, focal seizures evolving to a bilateral convulsive seizure	HS	LT	2/m	2	2
6	F	28	28	Focal seizure with impairment of consciousness or awareness, non-convulsion status epilepticus	Craniopharyngioma	LF	1–2/w	4	4
7	M	55	55	generalized tonic-clonic seizure	Haemochromatosis	No	2/d	1	1
8	F	88	89	Focal seizure with impairment of consciousness or awareness	Infarction	L TFP	1 (3 m after stroke)	1	1
9	M	12	37	Focal seizure with impairment of consciousness or awareness, focal seizures evolving to a bilateral convulsive seizure	Craniopharyngioma	L TF	3/y	6	2
10	M	5	45	Myoclonus seizure, generalized tonic-clonic seizure	Motor vehicle accident	No	1/m	5	5
11	F	23	23	Focal seizure without impairment of consciousness or awareness, focal seizures evolving to a bilateral convulsive seizure	Cavernous malformation	R F	1/6–12 m	1	1
12	F	43	58	Focal seizure with impairment of consciousness or awareness	Melanoma	R TF	2–4/d	4	2
13	M	5	27	Atonic, focal seizures evolving to a bilateral convulsive seizure	Astrocytoma	R TFP	1–2/d	3	2
14	F	16	29	Focal seizure with impairment of consciousness or awareness, focal seizures evolving to a bilateral convulsive seizure	Unknown	L T	1/w	6	3

Psychotic symptoms and antipsychotic treatment

Patient ID	Hallucination	Delusion	Disorganized behaviour	Disorganized thinking	Previous psychotic history	Culprit AEDs	Interval to psychosis onset	D_{Max} (mg)	Adjustment of culprit AEDs	Combined AEDs	Duration index psychosis	APDs	Continuous APDs	Follow-up duration after AIPD	Outcome
1	Auditory	Persecutory	Aggressive, unusual social	+	Induced by overdose of diet pills	LEV	1 m	1000	Withdrawn	—	2	Olanzapine	—	32 m	2
2	Auditory, tactile	Referential	Aggressive	—	—	TPM,2004 LEV,2005	10 d 3 m	400 2000	400 mg to 100 mg Withdrawn	CLZ CLZ	1	Risperidone	—	10 m 1 m	2
3	Auditory, visual	Referential somatic	Aggressive	—	—	LMT,1996 LMT,2004	33 d 68 d	600	Withdrawn	PHT	2	Droperidol, haloperidol	—	8 y 1 m	2
4	Auditory	Persecutory	Aggressive	+	Induced by antihistamine	LMT	21 d	600	600 mg to 400 mg	PRM, CLZ	1	—	—	6 m	2
5	Tactile	Religious	Aggressive	+	—	LEV	54 d	3000	3000 mg to 2000 mg	CBZ	1	Olanzapine	+	34 m	2

(continued)

Table 3 Continued

Psychotic symptoms and antipsychotic treatment														
Patient ID	Hallucination	Delusion	Disorganized behaviour	Disorganized thinking	Previous psychotic history	Culprit AEDs	Interval to psychosis onset	D_{Max} (mg)	Adjustment of culprit AEDs	Combined AEDs	Duration index psychosis	APDs	Continuous APDs	Follow-up duration after AIPD	Outcome
6	Auditory	Persecutory, grandiose	Aggressive	—	—	LEV	13 d	2000	Withdrawn	VPA, CLB, PHT	2	Risperidone	—	2 m	1
7	—	Religious	Aggressive	+	—	LEV	2 d	1000	Withdrawn	—	2	Olanzapine	—	14 m	1
8	Visual	—	Aggressive	+	—	LEV	9 d	1000	Withdrawn	—	1	—	—	3 m	1
9	—	Persecutory	Aggressive	+	—	LEV,2008 TPM,2010	5 d 6 m	1250 150	Withdrawn	VPA VPA	1	—	—	6 y 4 y	2
10	Auditory	Persecutory	Aggressive, unusual social	+	—	LEV	10+ d	2000	Withdrawn	VPA, LMT, TPM, CLZ	3	Risperidone	+	6 y	1
11	Auditory	Persecutory	Aggressive	+	—	LEV	23 d	500	Withdrawn	—	2	—	—	5 y	1
12	Auditory	Persecutory, referential	Unusual social	+	—	LMT	21 d	100	Withdrawn	LEV	3	—	—	7 m	1
13	Visual	—	Unusual social	+	—	Cease of VPA	28 d	1000	Represcribed	CBZ, LMT	3	Olanzapine	—	11 y	1
14	Visual	—	Unusual social	+	—	LEV	30 d	2000	Withdrawn	CBZ, CLB	1	—	—	6 m	1

CBZ = carbamazepine; d = day; F = frontal; L = left; m = month; P = parietal; O = occipital; T = temporal; y = year; LMT = lamotrigine; LEV = levetiracetam; TPM = topiramate; VPA = valproic acid.
Patient 5 experienced the relapse of psychosis 2 years after the episode of AIPD. The relapse was caused by non-compliance of AEDs and her divorce, but no epileptic seizures had been observed before the relapse.
Duration of index psychosis: 1 = 1–7 d; 2 = 8–30 d; 3 = 1–6 m; 4 = > 6 m.
Outcome: 1 = a single episode; 2 = a relapse; 3 = a chronic course.

Table 4 Manifestations and treatment of epilepsy in the cohort of patients with AIPD compared with the cohort of patients with non-AIPD

Variables, *n*(%)	AIPD (*n* = 13)[a]	Non-AIPD (*n* = 84)	OR	*P*-value
Gender: F	10(76.9%)	35(41.7%)	4.667	0.033[b]
Age of onset of epilepsy	16(9–28)	19.5(10–31.5)	1.003	0.790
Seizure types				
Generalized seizures	3(21.6%)	18(21.4%)	0.909	0.569[c]
Focal seizure with impairment of consciousness or awareness	9(69.2%)	48(57.1%)	1.688	0.549[c]
Focal seizures evolving to a bilateral convulsive seizure	6(46.2%)	51(60.7%)	0.555	0.321
Aetiology				
Genetic	1(7.7%)	15(17.9%)	0.383	0.323[c]
Structural/metabolic	11(84.6%)	47(56.0%)	4.330	0.044[b,c]
Hippocampal sclerosis	2(15.4%)	17(20.2%)	0.717	0.510[c]
Brain tumour	3(23.1%)	5(6.0%)	4.740	0.072[c]
Malformations of cortical development	2(15.4%)	12(14.3%)	1.091	0.596[c]
Unknown cause	1(7.7%)	22(26.2%)	0.235	0.181[c]
Lateralization				
Left involved	6(46.2%)	33(39.3%)	0.755	0.638
Right involved	4(30.8%)	29(34.5%)	0.843	0.529[c]
Bilateral	3(23.1%)	22(26.1%)	0.441	0.187[c]
Localization				
Temporal lobe involved	9(69.2%)	32(38.1%)	3.656	0.035[b,c]
Febrile convulsion	2(15.4%)	4(4.8%)	3.636	0.183[c]
History of prior psychiatric disorders	2(15.4%)	24(28.6%)[d]	0.455	0.504[c]
History of prior medication/ substance-induced psychiatric disorders	2(15.4%)	2(2.4%)	7.455	0.086[c]
Family history of epilepsy	0(0%)	9(10.7%)	–	0.258[a]
Drug resistance	10(76.9%)	55(65.5%)	0.569	0.317[c]
Brain surgery	5(38.5%)	25(29.8%)	1.475	0.369
Number of previous AEDs	3(2–5)	2(1–3)	1.336	0.068
Number of present AEDs	2(1–3)	2(1–3)	1.415	0.148

[a]Excluding the patient who developed psychosis after withdrawal of valproate (Case 13 in Table 3).
[b]Statistically significant.
[c]Fisher's Exact Test.
[d]Among the 24 cases, two had marijuana- or steroid-induced psychotic disorder, two had depression, one had antisocial personality disorder and the remaining 19 had comorbid schizophrenia/schizophreniform disorder.

cirrhosis, hypertension and type 2 diabetes mellitus, while in the non-AIPD group, 31 (36.9%) had medical comorbidities including interstitial nephritis, non-Hodgkin's lymphoma, type 1 diabetes mellitus, asthma and myocardial infarction (OR = 0.722, $P = 0.429$).

A similar proportion of patients were drug-resistant in the two groups. However, patients in the AIPD group had been treated with a greater number of prior AEDs before the index episode of psychosis, compared to the non-AIPD group, although the difference was not statistical [3(IQR: 2–5) versus 2(IQR: 1–3), $P = 0.068$].

Table 5 lists the AEDs taken by the patients during the psychotic episodes. In the AIPD group, levetiracetam was the most commonly used AED, followed by lamotrigine and valproate. In the non-AIPD group, carbamazepine, valproate and phenytoin were most commonly used. Use of levetiracetam was higher in AIPD group (84.6% versus

Table 5 AEDs currently used during by the patients with epilepsy the episode of psychosis

Drug	AIPD (*n* = 13)[a]	Non-AIPD (n = 84)	OR	*P*-value
Valproic acid	4(30.8%)	29(34.5%)	0.843	0.529[b]
Carbamazepine	2(15.4%)	37(44.0%)	0.231	0.044[b,c]
Phenytoin	2(28.6%)	24(28.6%)	0.455	0.262[b]
Primidone	1(7.7%)	2(2.4%)	3.417	0.354[b]
Levetiracetam	11(84.6%)	17(20.2%)	21.676	0.001[b,c]
Lamotrigine	4(30.8%)	17(20.2%)	1.752	0.297
Topiramate	3(23.1%)	9(10.7%)	2.500	0.201[b]
Clonazepam	3(23.1%)	7(8.3%)	3.300	0.130[b]

[a]Excluding the patient who developed psychosis after withdrawal of valproate (Patient 13 in Table 3).
[b]Fisher's Exact Test.
[c]Statistically significant.

Table 6 Multivariate logistic regression of risk factors for AIPD[a]

Variables	OR	95% CI	*P*-value
Female gender	26.440	1.457–79.731	0.027
Structural/metabolic epilepsy	2.504	0.264–23.743	0.424
Brain tumour	1.118	0.066–19.069	0.938
Temporal lobe involvement	27.201	1.655–47.105	0.021
History of prior substance/ medication-induced psychotic disorder	5.314	0.090–14.974	0.423
Number of previous AEDs	1.093	0.664–1.797	0.727
Current use of levetiracetam	64.672	3.730–121.431	0.004
Current use of carbamazepine	0.030	0.002–0.454	0.011

[a]Excluding the patient who developed psychosis after withdrawal of valproate (Patient 13 in Table 3).
CI = confidence interval.

20.2%, $P < 0.01$) while use of carbamazepine was higher in the non-AIPD group (15.4% versus 44.0%, $P < 0.05$).

Eight factors with $P < 0.1$ from Tables 4 and 5 were selected for the multivariate analysis. Multivariate logistic regression confirmed four factors associated with AIPD: female gender, temporal lobe involvement and current use of levetiracetam, and a negative association with carbamazepine (Table 6).

Psychiatric manifestations and outcome

Table 7 summarizes the clinical manifestation of psychotic disorders and the outcome. There were no significant between-group differences observed with regard to age of onset of psychoses, or the prevalence of hallucinations or delusions. Disorganized behaviours and thinking were more common in the AIPD group compared to non-AIPD group (100% versus 72.6% and 76.9% versus 64.3%, respectively; $P < 0.05$ for both). There were no significant differences between the groups in co-morbid depressive mood, anxiety or cognitive function. The duration of psychotic

Table 7 Manifestations, treatment and outcome of psychotic disorders in the cohort of patients with AIDP compared with those with non-AIDP

	AIPD (*n* = 13)[a]	Non-AIPD (*n* = 84)	OR	*P*-value
Age of onset of psychosis, years	37(34–45)	34(23–46.5)	1.018	0.290
Interval of epilepsy to psychosis, years	16(1–27)	13.5(1.5–23)	1.020	0.365
Follow-up duration after psychotic episode, years	1.2(0.5–4.3)	2.7(1.4–7.3)	0.858	0.127
Hallucination	11(84.6%)	67(79.8%)	1.396	0.510[b]
Auditory hallucination	8(61.5%)	58(69.0%)	0.717	0.402
Visual hallucination	3(23.1%)	15(17.9%)	1.380	0.449[b]
Tactile hallucination	2(15.4%)	2(2.4%)	7.455	0.086[b]
Delusion	11(84.6%)	69(82.1%)	1.196	0.593[b]
Persecutory delusion	7(53.8%)	52(61.9%)	0.718	0.396
Referential delusion	3(23.1%)	21(25.0%)	0.900	0.594[b]
Somatic delusion	1(7.7%)	4(4.8%)	1.646	0.525[b]
Religious delusion	2(15.4%)	6(7.2%)	2.333	0.295[b]
Grandiose delusion	2(15.4%)	4(4.8%)	3.636	0.183[b]
Grossly disorganized or catatonic behaviour	13(100%)	61(72.6%)	–	0.034[b,c]
Aggressive	11(84.6%)	54(64.3%)	3.056	0.209[a]
Unusual social	4(30.8%)	7(8.3%)	4.889	0.038[c]
Disorganized thinking	10(76.9%)	32(38.1%)	5.417	0.014[b,c]
Depressive mode	2(15.4%)	22(26.2%)	0.512	0.509[b]
Anxiety	2(15.4%)	17(20.2%)	0.717	0.510[b]
Cognitive impairment	5(38.5%)	37(44.0%)	0.794	0.473
Duration of the index psychosis				
1:1–7 d	6(46.2%)	19(22.6%)	–	0.013[c]
2:8–30 d	5(38.5%)	13(15.5%)	–	–
3:1–6 m	2(15.4%)	23(27.4%)	–	–
4: >6 m	0	29(34.5%)	–	–
Family history of psychotic disorders	1(7.7%)	7(8.4%)	0.905	0.705[b]
APD	7(53.8%)	68(81.0%)	0.275	0.030[c]
More than one APD	1(7.7%)	22(26.2%)	0.235	0.131[b]
Continuous treatment with APDs	2(15.4%)	56(66.7%)	0.091	0.001[b,c]
Outcome				
1: A single episode	7(53.8%)	33(39.3%)	–	0.011[c]
2: Recurrent episodes	6(42.9%)	17(20.2%)	–	–
3: Chronic course	0	34(40.5%)	–	–

[a]Excluding the patient who developed psychosis after withdrawal of valproate (Patient13 in Table 3).
[b]Fisher's Exact Test.
[c]Statistically significant.
APD = antipsychotic drug.

episodes were less than 1 week in 42.9% of patients in the AIPD group compared with 22.6% in the non-AIPD group ($P < 0.05$).

Fewer patients with AIPD were treated with antipsychotic drugs compared with patients with other psychotic disorders (53.8% versus 81.0%, $P < 0.05$). Only one patient with AIPD was treated with more than one antipsychotic drug. The proportion of patients taking continuous antipsychotic treatment was lower in the AIPD group than in the non-AIPD group (15.4% versus 66.7%, $P < 0.01$). More patients in the AIPD group experienced a single episode (53.8% versus 39.3%) and fewer experienced

recurrent episodes (46.2% versus 20.2%, $P < 0.05$). No patient experienced a chronic course of psychosis in the AIPD group while 40.5% did in the non-AIPD group.

Discussion

In this study we report the detailed clinical profiles of AIPD in comparison with other psychotic disorders in patients with epilepsy. In a systematic review and meta-analysis, the pooled prevalence rate for psychosis in epilepsy patients was 5.6% (Clancy *et al.*, 2014). Although prevalence of AIPD has been reported to vary from 1.0% to 8.4% in drug trials (Piedad *et al.*, 2012), the percentage of AIPD in the population of psychosis in epilepsy has not been reported before. In this study, among epilepsy patients with psychotic disorders, one in seven could be attributed to AEDs. This highlighted the importance of considering the possibility of AIPD in patient with epilepsy who develops psychotic symptoms.

Antiepileptic drug-induced psychotic disorder is associated with female gender and temporal lobe involvement

Our findings showed that female gender and temporal lobe involvement were significant risk factors for AEDs-induced psychotic disorders. More than two-thirds of the patients with AIPD were female in this study. In previous studies on the psychiatric side effects of the new AEDs, a similar trend was reported (Trimble *et al.*, 2000; Mula *et al.*, 2003; Weintraub *et al.*, 2007).

Results from both univariate and multivariate analyses demonstrated that temporal lobe involvement was strongly associated with AIPD. Previous studies showed that the patients with temporal lobe epilepsy may be susceptible to develop psychosis (van der Feltz-Cornelis *et al.*, 2008; Mula and Monaco, 2009). The susceptibility of temporal lobe epilepsy to AIPD could be linked to the neuroanatomical anomalies, such as hippocampal sclerosis and the underlying abnormal connections to temporal and extratemporal cortices (Lin *et al.*, 2012). The epileptic aetiology within temporal lobe involvement varied and brain tumour was one of the risk factors for AIPD in the univariate comparison. The lesions of all three cases with tumours were located at both temporal and other lobes, which indicated complicated pathological mechanisms of intra/extratemporal connection for the relation of AED-induced psychotic disorder and temporal involvement.

The whole cohort with psychotic disorders shared some mutual epilepsy characteristics, such as focal seizures, cognitive impairment and drug resistance. It has been reported that a higher ratio of patients suffered from focal seizures with impairment of awareness than other epileptic seizure types in the population with psychiatric symptoms (Trimble *et al.*, 2000; van der Feltz-Cornelis *et al.*, 2008). In our observation, the percentages of this seizure type in both groups were higher that 50%, but no significant difference was demonstrated between them. Hence, focal seizures with impairment of awareness might be a predictor of psychiatric comorbidity but not specifically that of AED-induced psychosis.

Similarly, cognitive impairment has been reported to be related to psychosis in patients with epilepsy (Noguchi *et al.*, 2012). In our study nearly half the patients had intellectual disability but no statistically significant difference was found between the AIPD group and the comparator group. This suggests that intellectual dysfunction might be associated with psychosis in epilepsy in general but not with AED-induced psychosis.

Both groups had high percentage of drug resistance, an observation noted in previous reports. A population-based study in male adolescents reported that treatment-refractory epilepsy increased the risk of psychotic disorders (Fruchter *et al.*, 2014). We further analysed the AEDs used before the episodes of psychosis. The development of psychosis during the treatment with the culprit AED was associated with a higher number of previous AEDs used. This finding was perhaps not surprising given that the more AEDs were trialled to control seizures in patients with drug-resistant epilepsy, the higher the possibility of developing psychiatric adverse effects. However, this factor was not significant as an independent variable contributing to the development of AIPD in the multivariate logistic regression analysis.

Patients with a history of febrile convulsions (Mula *et al.*, 2003, 2007) and status epilepticus (Mula *et al.*, 2004) might be more vulnerable to develop psychiatric adverse effects, as suggested in post-marketing studies of levetiracetam. In our study, neither the history of febrile convulsions nor status epilepticus was a predictor of AIPD.

Association with specific antiepileptic drugs

In the multivariate logistic regression, levetiracetam was more commonly used among patients with AIDP compared to those with other types of psychosis. Levetiracetam targets the synaptic vesicle glycoprotein SV2A and presynaptic calcium channels (Shorvon and van Rijckevorsel, 2002; Lynch *et al.*, 2004). Previous studies concerning levetiracetam-induced psychotic adverse effects were contradictory (Mula *et al.*, 2003; Noguchi *et al.*, 2012). Many clinical trials of levetiracetam reported behaviour adverse effects, such as irritability, aggressive behaviour in both children and adults. However, patients in these studies were often not assessed by psychiatrists (Glauser *et al.*, 2006; de la Loge *et al.*, 2010). By analysing a cohort of patients who had developed psychosis, our findings suggest that when a patient with epilepsy presents with psychotic symptoms,

current usage of levetiracetam should raise the strong suspicion of AIPD.

Interestingly, logistic regression analysis demonstrated that the current use of carbamazepine was negatively associated with AIPD, compared with other types of psychosis, an observation reported by others (Piedad *et al.*, 2012). No literature has reported carbamazepine-induced psychosis, although possible psychotropic effects of carbamazepine, such as anxiety (Berg *et al.*, 1993) or depression (Pulliainen and Jokelainen, 1995), have long been recognized. Indeed, carbamazepine has been shown to reduce aggressive behavioural symptoms (Jones *et al.*, 2011). Hence, in case of AIDP, carbamazepine might be a safe substitution for the offending agent.

Antiepileptic drug-induced psychotic disorder characterized by disorganized behaviour and thought

In the proposal by ILAE, clinical features of psychotic disorders in epilepsy may include auditory hallucination and/or paranoid delusions (Krishnamoorthy *et al.*, 2007). In DSM-5, the diagnostic criteria of substance/medication-induced psychotic disorder consist of delusions and hallucinations. Disorganized speech and grossly disorganized behaviour are the diagnostic criteria of brief psychotic disorder but not specifically of substance/medication-induced psychotic disorder.

We reviewed all the four categories of symptoms in both groups and found no differences about the two core symptoms of psychotic disorders, i.e. hallucinations or delusions. However, the AIPD group showed higher occurrence of grossly disorganized behaviours and disorganized thinking compared with the non-AIPD group. This is consistent with previous reports of high incidence of aggression, agitation or irritability with certain AEDs, such as 2.7–24.4% with topiramate (Elterman *et al.*, 1999; Mula and Trimble, 2003; Weintraub *et al.*, 2007), 2.3–12.5% with levetiracetam (Mula *et al.*, 2003; de la Loge *et al.*, 2010), and 1.3–6.1% with lamotrigine (Weintraub *et al.*, 2007; Labiner *et al.*, 2009). In contrast, the prevalence of psychosis was relatively low, as 1.5–6.3% with topiramate (Mula and Trimble, 2003), 1.0–1.3% with levetiracetam (Mula *et al.*, 2003; Weintraub *et al.*, 2007) and 0.4% with lamotrigine (Weintraub *et al.*, 2007). Therefore, in case of psychosis with prominent abnormal behaviours in patients with epilepsy, AIPD should be taken into consideration. Disorganized thinking was seldom reported in previous studies. In a European multicentre parallel-group double-blind trial of zonisamide as add-on treatment, the presence of disorganized thinking was statistically significant compared with placebo (Schmidt *et al.*, 1993). Hence the presence of disorganized thinking or speech should raise the suspicion of AIPD.

Follow-up observation showed that AIPD had a generally better outcome than that of the other epileptic psychoses. Theoretically, AIPD should improve after the cessation of the culprit medication; hence, if treated properly, the cases with AIPD might have shorter duration of the psychotic episode than other types of psychosis. Furthermore none of the AIPD cases experienced chronic psychiatric course. For the cases with recurrent course, the main cause was resumption of the same or similarly acting culprit drugs. Therefore, the timely cessation of the offending drug and avoidance of prescription again would offer protection against further AIPD.

The limitations of this study included a relatively small sample size and its retrospective design without randomization or blinding. As such, it is possible that certain AEDs might have been preferentially chosen or not chosen in patients with prior psychiatric history. Patients were assessed by different epileptologists and psychiatrists. To minimize the heterogeneity in evaluation for the present study, the clinical information was jointly reviewed by a single epileptologist (Z.C.) and a neuropsychiatrist (A.L.) using a standardized approach, based on the combination of medical notes and clinic letters, to arrive at the final diagnosis.

Future research may seek to identify genetic predictors of psychosis in epilepsy (Helmstaedter *et al.*, 2013). In this study, the psychotic symptoms induced were not associated with high dose or fast titration of the offending agents, suggesting that there was individual susceptibility in terms of AIPD. Therefore investigation of genetic markers of AIPD should be the considered for the future studies.

Conclusion

AIPD was common among epilepsy patients who develop psychotic symptoms. In our study one in seven patients with epilepsy who presented with psychosis had AIPD. In these patients, female gender, temporal lobe involvement and current use of levetiracetam were significantly associated with AIPD compared to other types of psychosis, while carbamazepine had a negative association. Disorganized behaviours and abnormal disorganized thinking were predominant symptoms of AIPD. AIPD had an overall better outcome than that of other psychotic disorders in people with epilepsy.

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