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H．知的財産権の出願・登録状況

特になし。

II-5 分担研究報告書

精神疾患の病態診断と治療評価のための
イメージングバイオマーカーの開発と臨床応用

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分担研究報告

精神疾患の病態診断と治療評価のためのイメージングバイオマーカーの開発と臨床応用

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研究要旨

脳の特定の部位に β アミロイドが沈着する事が、アルツハイマー病の発症・進行に大きく影響する事から、我々はアミロイド分子イメージングとして[^{18}F]florbetapir を用いてアルツハイマー型認知症患者、健常者、アルツハイマー病のハイリスクである軽度認知機能障害者に実施することで、アルツハイマー病の病態診断と治療評価についての有用性を検討した。また臨床で認知症診断に用いられている検査も実施し、アミロイド PET との関連を検討した。

アルツハイマー型認知症群 14 名におけるアミロイド陽性率は 85.7%であった。一方で軽度認知機能障害群では陽性率 39.1%、健常者群では陽性率は 8.3%であった。軽度認知機能障害およびアルツハイマー型認知症におけるβアミロイド沈着が陽性かどうかに対する感度、特異度は Mini-Mental State Examination（57.1%と 58.8%）、Alzheimer's Disease Assessment Scale-cognitive component 日本語版（76.2%と 47.1%）、および MRI による海馬萎縮（50.0%と 73.3%）であった。この事から、[^{18}F]florbetapir を用いたあアミロイド分子イメージングの手法はアルツハイマー型認知症の鑑別に有効である可能性が示された。

A. 研究目的

アルツハイマー病の原因は、完全には解明されていないが、神経病理学的所見から、脳の特定部位にβアミロイドが沈着する事が、発症・進行に大きく影響する事が明らかになってきている。また軽度認知機能障害などがアルツハイマー病のハイリスクと考えられており、治療などの臨床的見地からアルツハイマー病は早期発見が望ましいものの、現在の臨床診断は脳形態画像、症状、経過などから疑い診断に止まり、病態に基づいた確定診断は生体では行えていない。近年、分子イメージングの手法を用いる事で生体内でβアミロイドの存在の確認や評価が出来るとする報告がなされ、臨床利用に向けた研究と開発がされている。そこでわれわれは、AVID社が開発したアミロイド分子イメージングのための検査薬[^{18}F]florbetapirを導入し、アルツハイマー病を含む認知症患者群、健常者群、アルツハイマー病のハイリスク群である軽度認知機能障害群を対象に、アミロイド分子イメージングを実施し、有用性を検討した。

B. 研究方法

薬物試験審査委員会の承認を得たのち、本実験の内容を口頭で説明し、文書により同意の得られた健常者群ならびに軽度認知機能障害群では本人、アルツハイマー病を含む認知症患者群については、本人ならびに代諾者の同意を得られたものを対象とした。認知症の診断は国際疾病分類第10版に基づいた。アルツハイマー病の診断にはNINCDS-ADRDAのprobableADの臨床診断基準を用いた。ICD-10被験者は認知症の状態評価のためのミニメンタルステート検査（MMSE）、アルツハイマー病評価尺度（ADAS-Jcog）、周辺症状評価のためのNeuropsychiatric Inventory（NPI）、老年期うつ病評価尺度（GDS）、日常生活能力評価のための臨床認知症評価法（CDR）を実施した。脳器質性病変の鑑別、解析用の脳形態情報を得るために臨床用PHILIPS社製1.5テスラMRI装置Intera 1.5T Achieve Novaを用いて撮像した。[^{18}F]florbetapirを静脈内に注射し、注射後50分から10分間のPET画像を島津製作所製Eminence SET-3000GCT/Xを用いて撮像した。データの解析にはPMOD 3.1 (PMOD Technologies Ltd., Zurich, Switzerland）を使用した。

MMSEおよびADAS-Jcogの有意な低下としてのcut-off値はそれぞれ23点と10点とした。

βアミロイド沈着の評価には、脳剖検の知見を踏まえてFleisherらにより提唱されている定量化手法を用いた。これは標準脳ならびに統計処理ソフトを用いる事で、前頭葉眼窩野、側頭葉、前部および後部帯状回、頭頂葉ならびに楔前部の領域における集積を皮質ー全小脳比による standard uptake value ratio によりβアミロイド沈着を自動的に数値化するものである。この数字を脳剖検の結果から、アミロイド陰性(SUVRs≤1.08)、アルツハイマー病の病理呈

するレベル(SUVRs≥1.17)と 2 つの cut-off 値を示している。今回我々は、SUVRs>1.08 をアミロイド陽性として用いた。

MRI も同様に標準脳ならびに統計処理ソフトを用いる事で海馬における萎縮の程度を z-score に数値化した。z-score≥2 を有意な海馬萎縮とした。

（倫理面への配慮）

本研究は、ヘルシンキ宣言に基づき倫理面について十分な配慮の上で倫理委員会で承認された説明文書、同意書を用いて文書による説明と同意を得たうえで実施された。本研究で得られたデータは匿名化し、解析を行った。

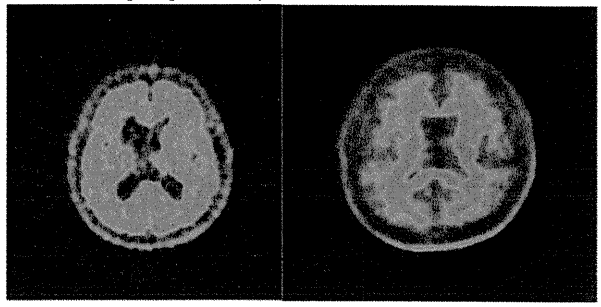
C. 研究結果

健常対照群 12 名、アルツハイマー型認知症患者群 14 名、軽度認知機能障害群 23 名に対して[^{18}F]florbetapir を用いたアミロイド分子イメージングを実施した。平均年齢、男女比、症状評価ならびに β アミロイド陽性率については以下に示す通りである。

	アルツハイマー型認知症群	軽度認知機能障害群	健常群
N	14	23	12
平均年齢	75.9±7.0	74.3±8.3	69.8±3.4
男女比	3:11	7:16	7:05
MMSE	18.1±4.6	25.0±3.2	29.0±1.1
ADAS-Jcog	21.6±11.6	9.6±4.5	4.1±2.4
NPI	10.5±11.7	11.3±16.1	1.0±1.6
CDR	1.4±0.7	0.5±0.2	0.0±0.0
MRI	2.9±1.0	1.4±0.8	1.4±1.5
PET	1．19±0.11	1.03±0.14	0.99±0.09
B アミロイド陽性	12(85.7%)	9(39.1%)	1(8.3%)

実際の[^{18}F]florbetapir の画像を下に示す。

[^{18}F]florbetapirによるPET画像



amyloid (+)　　amyloid (-)

軽度認知機能障害およびアルツハイマー型認知症におけるβアミロイド沈着が陽性かどうかに対する感度、特異度は Mini-Mental State Examination（57.1%と 58.8%）、Alzheimer's Disease Assessment Scale-cognitive component 日本語版（76.2%と 47.1%）、および MRI による海馬萎縮（50.0%と 73.3%）であった。

	βアミロイド陽性	βアミロイド陰性
N	21	16
MMSE		
陽性（23 点以下）	12	7
陰性(24 点以上)	9	9
ADAS-Jcog		
陽性（10 点以上）	16	9
陰性(10 点未満)	5	7
MRI		
陽性(z-score 2 以上)	9	4
陰性（z-score 2 未満）	9	10

D．考察

今回、我々はアルツハイマー型認知症、その他の認知症、アルツハイマー型認知症のハイリスク群、健常者を対象にアルツハイマー病の診断におけるアミロイド分子イメージングの有用性を検討した。

少数例での結果ではあるが、[^{18}F]florbetapir を用いた PET 検査では、アルツハイマー病の臨床診断とアミロイド陽性の一致率は 85.7%であり、健常者における

陽性率が 8.3%であった事から、アルツハイマー型認知症の診断に有用である可能性が示された。海外での研究では、アルツハイマー型認知症患者に対して行われたアミロイド分子イメージングでのアミロイド陽性率は 80 から 90%とされており、我々の結果と同等である。これは、我々の症例が少数である事が大きな要因であると考える。このことから[^{18}F]florbetapir を用いたβアミロイドの判定が、日本においても有用であり人種を問わずに有効である事が示せたと考える。また認知機能検査や MRI による萎縮の程度の結果などから、認知症と軽度認知機能障害の鑑別においては[^{18}F]florbetapir を用いた PET 検査はより有用であると考えられた。集積の程度を示す SUVR 値が海外の報告に比べると低めとなっている。これは対象者の違いを反映している可能性や収集条件の違いを反映しているかも知れない。これらの点に関して、今後より多くの症例を対象とすることで検討していきたいと考える。

E.結論

本研究により、アルツハイマー病の診断と[^{18}F]florbetapir を用いたアミロイド分子イメージングによるアミロイド陽性が高い割合で一致する事が示された。アルツハイマー病のハイリスク群においても陽性者がいた事から、長期的な予後追跡によるアルツハイマー病への移行についての検討も必要と考えられる。今後は症例数を増やす事でハイリスク群やその他の認知症群の下位分類を行い、より詳細な鑑別診断やハイリスク評価ならびに治療による変化などを検討する事が重要であると考えられた。

F. 健康危険情報 なし

G. 研究発表

１．論文発表

なし

２．学会発表

なし

知的財産権の出願・登録状況

III 研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

書籍
別紙４

研究成果の刊行に関する一覧表

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FULL-LENGTH ORIGINAL RESEARCH

Analogy between psychosis antedating epilepsy and epilepsy antedating psychosis

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Summary

Purpose: **Patients with recurrent epileptic seizures after the development of psychosis (Psychosis-Epilepsy) have been regarded as belonging to a different clinical entity from those with epilepsy antedating the development of psychosis (Epilepsy-Psychosis). However, clinical characteristics of patients with Psychosis-Epilepsy have not been well described, except for early German studies. We aimed to estimate the reliability of distinction between Psychosis-Epilepsy and Epilepsy-Psychosis by comparing their clinical characteristics.**

Methods: **Among 312 patients with epilepsy and psychosis enrolled in this multicenter study, 23 patients had Psychosis-Epilepsy and 289 patients had Epilepsy-Psychosis (i.e., interictal psychosis). Demographic (i.e., sex, age at time of evaluation, and intellectual functioning), psychiatric (i.e., age at onset of psychosis, subtype of psychosis, duration of psychotic episode, and a family history of psychosis), and epileptic (i.e., age at onset of epilepsy, subtype of epilepsy, seizure type, and a family history of epilepsy) characteristics of both groups were compared.**

Key Findings: **Clinical characteristics, either in their psychoses or epilepsies, except for age-related variables, were equivalent between patients with Psychosis-Epilepsy and those with Epilepsy-Psychosis. Time intervals between onset of psychosis and that of epilepsy in the two groups showed a normal distribution curve.**

Significance: **The presence of many common features and the linear distribution of the time intervals did not fully support that Psychosis-Epilepsy and Epilepsy-Psychosis were two distinctly different entities. Among certain patients who have genetic vulnerabilities to both psychoses and seizures, psychosis may develop either antedating or postdating the development of epilepsy. These findings may suggest a necessary reconceptualization of psychoses in epilepsy.**

KEY WORDS: **Psychosis, Epilepsy, Epilepsy psychosis, Organic psychosis, Classification of mental disorders in epilepsy.**

Comorbidity of psychoses has been described frequently in patients with epilepsy. Psychoses unrelated to ictal events can be classified according to the timing of the development of epilepsy (World Health Organization, 1992). Psychoses antedating recurrent epileptic seizures (Psychosis-Epilepsy) are generally regarded as functional psychosis (e.g., schizophrenia) and other psychoses after recurrent seizures (Epilepsy-Psychosis) are categorized as organic psychosis. Slater (1969) established the modern concept of "epileptic psychosis," in which chronic paranoid psychosis came on after years of epileptic fits. His concepts, similar to Epilepsy-Psychosis, were mainly based on three findings: (1) psychopathologies different from those commonly seen in patients with schizophrenia; (2) genetic predisposition of psychosis equivalent to that in the general population; and (3) occurrence of psychosis following the onset of psychosis with a mean interval of 14 years. In recent literature, Epilepsy-Psychosis has been vigorously studied as a condition likely associated with epilepsy-related processes (Trimble & Schmitz, 1997), whereas Psychosis-Epilepsy was often regarded as a consequence of iatrogenic factors such as side effects from antipsychotic drugs (APDs) (Itil & Soldatos, 1980; Hedges et al., 2003) or mere coincidence of the two conditions despite a comparatively high prevalence of spontaneous seizures in patients with schizophrenia in the period prior to the development of modern APDs (Esser, 1938; Yde et al., 1941). Interestingly, little attention has been paid to classical studies in that psychosis antedating epilepsy was

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considered as a variant of epilepsy-related psychoses (so called epilepsy psychoses) (Krapf, 1928; Glaus, 1931; Gruhle, 1935). Recent large studies have shown that not only epileptic factors but also nonepileptic factors are associated with the development of "Epilepsy-Psychosis" (Adachi et al., 2002; Qin et al., 2005; Adachi et al., 2010). In contrast, clinical features of Psychosis-Epilepsy, in particular its epilepsy-related phenomena, are not well characterized. This has raised a question as to the rationale of the dichotomy of psychoses in epilepsy patients according to the timing of the development of epilepsy. In the current study, we investigated clinical characteristics of patients with psychosis antedating epilepsy (Psychosis-Epilepsy) and those with epilepsy antedating psychosis (Epilepsy-Psychosis).

Methods

Subjects

Three hundred twelve patients with both epilepsy and psychosis unrelated to ictal symptoms (interictal) were consecutively registered for the study in December 2000, from a collaborative database specially designed for epilepsy and psychosis of five institutions in Tokyo with adult epilepsy clinics: the National Center Hospital for Mental, Nervous, and Muscular Disorders; Nihon University Hospital; Tokyo Medical University Hospital; Tokyo Medical and Dental University Hospital; and Komagino Hospital (Adachi et al., 2000, 2002, 2008, 2010). There were 23 patients who developed recurrent epileptic seizures after the development of psychosis (Psychosis-Epilepsy); a full set of data was available for 21 patients and some pieces of data were missing in two patients. Two hundred eighty-nine patients developed interictal psychosis after the development of epilepsy (Epilepsy-Psychosis). Psychosis was defined as the presence of hallucinations, delusions, or a limited number of severe abnormalities of behavior in accordance with the International Classification of Diseases (ICD10) (World Health Organization, 1992). Patients with a history of postictal psychotic episodes (i.e., postictal psychosis or bimodal psychosis where interictal and postictal psychoses occurred independently) (Adachi et al., 2000, 2002, 2008, 2010) were excluded. All the patients met diagnostic criteria for the International Epilepsy Classifications (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Other seizure-like conditions, such as syncope, panic attacks, tics, and migraines, were also excluded (Koutroumanidis et al., 2010). None of the patients enrolled had a history of substance misuse, evidence of dementing processes, a progressive mass lesion in the brain, or a neurodegenerative disorder.

Research variables

We investigated the following characteristics of the study patients: (1) age at the time of examination; (2) sex; (3) family history (first-degree relative) of psychosis (Kitamura et al., 1984); (4) family history (first-degree relative) of epilepsy; (5) intellectual functioning, that is, normal (full-scale IQ [FIQ] ≥85), borderline (70 ≤ FIQ < 85), mental retardation (IQ < 70); (6) age of onset of psychosis; (7) subtype of psychosis (i.e., schizophrenia, schizotypal disorders, delusional disorders, acute and transient psychotic disorders, schizoaffective disorders, and other psychosis), classified in accordance with the ICD10 criteria (although Epilepsy-Psychosis were formally classified as Organic Mental Disorders, psychiatric diagnosis was made with an exception of epilepsy for comparing the two groups) (World Health Organization, 1992); (8) duration of the longest psychotic episode, whether that lasted for 1 month or longer (Bruens, 1974; World Health Organization, 1992); (9) age at onset of epilepsy; (10) time interval between onset of psychosis and that of epilepsy; (11) type of epilepsy (i.e., partial epilepsy [PE], generalized epilepsy [GE], or unclassifiable epilepsy [UE]), determined on the basis of ictal symptoms, electroencephalography, and neuroimaging findings in accordance with the International Classification of Epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989); and (12) types of seizures, in accordance with the International Seizure Classification (Commission on Classification and Terminology of the International League Against Epilepsy, 1981).

In the Psychosis-Epilepsy patients, further variables were noted: (13) antipsychotic drugs (APDs) at the time of the first seizure, that is, first-generation (typical) APDs (e.g., butyrophenones, phenothiazines, benzamides, and thiepines) and second-generation (atypical) APDs (e.g., serotonin-dopamine antagonists, dibenzothiazepines, and multi-acting receptor-targeted antipsychotics) (Hedges et al., 2003); (14) a history of electroconvulsive treatment (ECT); and (15) a history of febrile seizure.

Procedures

Diagnoses and clinical evaluations were made by consultant neuropsychiatrists qualified in both epileptology and psychiatry. The psychiatric diagnosis was based on standard clinical interviews with any differences resolved by consensus; a formal psychiatric rating scale and structured interview were not used. This study was given approval by the hospitals' ethics committees.

Data analysis

Differences in linear variables were subjected to analysis of variance (ANOVA). Correlations between categorical variables were analyzed with a contingency table analysis, that is, chi-square test or Fisher's exact test. A p-value of <0.05 was considered significant. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) version 14.0 (SPSS Inc, Chicago, IL, U.S.A.).

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Results

Characteristics of all patients

The 312 patients with psychosis and epilepsy were composed of 157 men and 155 women. Age at the examination ranged from 15–72 years [mean 37.0, standard deviation (SD) 12.9]. Age at onset of epilepsy ranged from 0–53 years (mean 13.0, SD 9.4). Age at onset of psychosis ranged from 10–65 years (mean 25.6, SD 9.6). The time interval from the onset of epilepsy to that of psychosis showed a normal distribution curve (mean 12.7 years, SD 10.9, range 33–50, Fig. 1A).

Characteristics of patients with Psychosis-Epilepsy and those with Epilepsy-Psychosis

Main clinical characteristics of the 23 Psychosis-Epilepsy patients and the 289 Epilepsy-Psychosis are shown in Table 1. The other clinical characteristics of the main body of the Epilepsy-Psychosis patients (n = 285) were shown in detail elsewhere (Adachi et al., 2010). Whereas the number of unclassifiable epilepsy diagnoses was significantly greater in Psychosis-Epilepsy patients ($\chi^2 = 8.38$, $p = 0.014$), there was no difference in the distributions of partial and generalized epilepsies between the Psychosis-Epilepsy and the Epilepsy-Psychosis patients ($\chi^2 = 0.10$, $p = 0.760$). The time interval from the onset of epilepsy to that of psychosis in the Epilepsy-Psychosis patients ranged from 0–50 years (mean 14.2, SD 9.3, median 13, mode 10) (Adachi et al., 2010). The time interval from the onset of psychosis to that of epilepsy in the Psychosis-Epilepsy ranged from 1–33 years (mean 8.6, SD 8.6, median 6, mode 1, Fig. 1B).

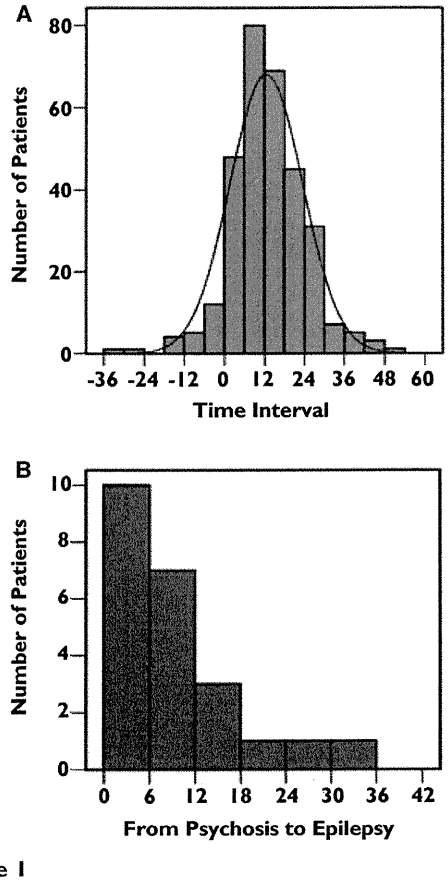

Figure 1
(**A**) The time interval (years) from onset of epilepsy to that of psychosis in both groups showed a continuous bell-curve shape. (**B**) The distribution of time interval (years) from onset of psychosis to that of epilepsy in the patients with Psychosis-Epilepsy was shown.
Epilepsia © ILAE

Additional information of the Psychosis-Epilepsy patients

Subcategories of the 18 schizophrenia patients were hebephrenic in nine, paranoid in eight, and unclassified in one. Three patients had atypical autism (World Health Organization, 1992) prior to the development of psychosis. At the onset of the first seizure, 11 of the 21 patients had taken various combinations of first-generation APDs (six patients were treated mainly with haloperidol, three mainly with phenothiazines, and two with APD unspecified); no patient took any second-generation APDs. Twenty-two patients were on different regimens of APDs between the time of their first and second seizures. The remaining one patient was on the same regimen of APDs (chlorpromazine 75 mg/day and levomepromazine 10 mg/day) when she developed her first and second seizures (complex partial seizures); however, her medication compliance was poor on both occasions. Three patients had conventional ECTs 5–16 (mean 11.0) years before the development of epilepsy. No patients had a distinct seizure-inducing condition preceding the first seizure, for example, central nervous system infection, head trauma, alcohol withdrawal, or overdose. Subcategories of partial epilepsy were temporal lobe epilepsy in six, frontal lobe epilepsy in six, occipital lobe epilepsy in one, and multi- or undetermined-lobular epilepsy in three. Fourteen of the 21 patients had infrequent seizures, with a frequency of less than yearly (total numbers of seizures were 10 or less after the first epileptic seizure). Seven of the 21 patients had febrile seizures in their infancy.

Discussion

Among 312 patients with epilepsy who had a history of ictus-unrelated psychosis, 23 (6.8%) patients had psychosis antedating the development of epilepsy. Our findings are comparable to those in early German studies (Krapf, 1928; Glaus, 1931; Gruhle, 1935) reporting that 8–17% of patients with a history of both epilepsy and psychosis exhibited psychosis first, although the prevalence from their multiple

Table 1. Clinical characteristics in the Psychosis-Epilepsy patients and the Epilepsy-Psychosis patients

	Psychosis-Epilepsy (n = 23)	Epilepsy-Psychosis (n = 289)	Statistics	p
Sex (men/women)	11/12	146/143	0.062	0.832
Age at the examination; mean (SD)	42.6 (13.2)	40.9 (12.9)	0.37	0.544
Family history of psychosis (positive/negative)	2/21	21/264	0.00	0.682
Family history of epilepsy (positive/negative)	3/20	19/266	1.36	0.214
Intellectual functioning (normal/borderline/mental retardation)	13/7/3	143/56/90	3.84	0.164
Age of onset of psychosis; mean (SD)	17.5	26.1 (9.6)	10.1	0.002
Subtype of psychosis (SC/SD/DD/AP/SAD/OTS)	18/0/2/2/1/0	213/7/29/27/5/8	2.06	0.863
The duration of psychotic episodes (>1 month/≤1 month/not available)	21/2/0	247/28/14	1.08	0.703
Age of onset of epilepsy; mean (SD)	28.2 (11.4)	11.8 (8.1)	80.8	0.000
Epilepsy type (GE/PE/UE)	4/16/3	49/236/4	8.38	0.014
[GE/PE]	[4/16]	[49/236]	[0.10]	[0.760]
Seizure type; GTC (exist/absent)	20/3	210/79	2.25	0.216
CPS [PE]	13/3	193/43	1.56	1.000
SPS [PE]	9/7	153/83	0.48	0.591
Other generalized [GE]	1/3	31/17	2.44	0.285

SC, schizophrenia; SD, schizotypal disorders; DD, delusional disorders; AP, acute-transient psychoses; SAD, schizoaffective disorders; OTS, other psychotic disorders; GE, generalized epilepsies; PE, partial epilepsies; UE, unclassifiable epilepsies; GTC, generalized tonic–clonic seizure; CPS, complex partial seizure; SPS, simple partial seizure; other generalized, other generalized seizures (absence, myoclonic, tonic, and so on).

case report approaches might not be totally accurate. Because the prevalence of Psychosis-Epilepsy may be higher than generally thought, it is worth clarifying its clinical characteristics.

When seizures occur in patients who have already been treated for psychosis, APDs (Itil & Soldatos, 1980) and ECT (Rasmussen & Lunde, 2007) can be considered as iatrogenic risk factors for seizures. Whereas seizures in psychotic patients taking APDs are often regarded just as APD-related events recently (Itil & Soldatos, 1980; Hedges et al., 2003), such assumption is not always supported by evidence. Recurrent partial seizures were rarely associated only with an APD-related condition (Devinsky & Pacia, 1994). Approximately 2–3% of patients with schizophrenia exhibited spontaneous convulsive seizures, even in the pre-APD period (Esser, 1938; Yde et al., 1941). Similarly, in terms of possible iatrogenic effects of ECT, several large studies have shown no significant causal association between ECT and newly developed epilepsy (Blackwood et al., 1980; Devinsky & Duchowny, 1983). In the current study, one half of our Psychosis-Epilepsy patients developed their first seizure while not taking an APD. The rest of them were on first-generation APDs, which have a lower risk of inducing seizures than second-generation APDs (Centorrino et al., 2002; Hedges et al., 2003). Most of the Psychosis-Epilepsy patients took different regimens of APDs at the time of their initial and second seizures. Furthermore, three patients exhibited spontaneous partial seizures long after ECT, which were unlikely to be typical ECT-induced phenomenon (Devinsky & Duchowny, 1983). All taken together, the development of seizures in our Psychosis-Epilepsy patients was not fully explained by the adverse effects from APDs and ECT.

Psychiatric characteristics of the Psychosis-Epilepsy patients were similar to those of the Epilepsy-Psychosis patients. Both groups tended to have long-lasting psychoses (Kanemoto et al., 2001). Whereas most of the Psychosis-Epilepsy patients had chronic schizophrenia, the majority of Epilepsy-Psychosis patients also met the ICD10 Schizophrenia Criteria (World Health Organization, 1992), with an exception of the presence of epilepsy. We did not carry out structured interviews for detailed psychopathologies to compare between the two groups in the current study; therefore, we could not depict the psychiatric features in the two groups against those described by Slater et al. (1963) that patients with epileptic psychosis retained emotional responses in comparison to those with schizophrenia. Three patients had atypical autism prior to schizophrenia. Children with autistic spectrum disorders showed increased risk for psychosis and epilepsy (Volkmar & Cohen, 1991; Craddock & Owen, 2010a). The onset of psychosis was earlier in age for Psychosis-Epilepsy patients than for Epilepsy-Psychosis patients. This may be partly due to the study design, as psychosis and epilepsy had already developed at the time of observation. The frequent family history of psychosis in both groups indicated that genetic vulnerability to psychosis was equivalent between them.

Types of epilepsy and seizure were similar between the Psychosis-Epilepsy patients and the Epilepsy-Psychosis patients. The majority of the patients in both groups had partial epilepsy and partial seizures, which indicated the presence of focal brain damage causing self-sustained repeated seizures, as opposed to condition-related events like APD overdose. Genetic predisposition to epilepsy was also equivalent between both groups of patients and comparable to that (9.1%) of our cohort of epilepsy patients without psychosis (Adachi et al., 2002). A history of febrile