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Psychosis in epilepsy patients and other chronic medically ill patients and the role of cerebral pathology in the onset of psychosis: A clinical epidemiological study

C.M. van der Feltz-Cornelis [a,b,e,*], A.P. Aldenkamp [c,d], H.J. Adèr [b], A. Boenink [g], D. Linszen [f,g], R. Van Dyck [b,g]

[a] *Netherlands institute of Mental Health and Addiction, PO Box 725, 3500 AS Utrecht, The Netherlands*
[b] *VU University Medical Centre Institute for Research in Extramural Medicine, Program for Common Mental Disorders, The Netherlands*
[c] *Kempenhaeghe Behavioural Science Department, Heeze, The Netherlands*
[d] *University of Maastricht, The Netherlands*
[e] *Sein epilepsy Clinic, Heemstede, The Netherlands*
[f] *Department of Psychiatry, AMC, Amsterdam, The Netherlands*
[g] *Department of Psychiatry, VU Medical Centre, Amsterdam, The Netherlands*

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Summary

Background: In a 3-year epidemiological survey (*N* = 2623) prevalence of psychosis in epilepsy patients as compared with other chronic medically ill patients is assessed.
Aim: To explore the role of cerebral pathology as compared to the role of chronic burden of disease in the onset of psychosis.
Method: One thousand seven hundred fifty two patients with chronic medical disorders admitted to an Academic Hospital and 901 patients with epilepsy admitted to a tertiary care epilepsy clinic were assessed by CIDI, MINI and clinical psychiatric interview in a two stage screening survey. Medical files were searched for MRI scans about cerebral pathology. Poisson regression analysis was performed to estimate the relative risk for psychosis in both groups.
Results: In total, 52 patients with prevalent psychosis were found: 49 (5.4%) in the epilepsy clinic and 3 (0.17%) in the Academic Hospital. Age range (18—88), mean age

* Corresponding author at: Research Program: Diagnosis and Treatment of Common Mental Disorder Trimbos-Instituut/Netherlands Institute of Mental Health and Addiction, PO Box 725, 3500 AS Utrecht, The Netherlands. Tel.: +31 30 29 71126; fax: +31 30 29 71111.
E-mail address: cfeltz@trimbos.nl (C.M. van der Feltz-Cornelis).

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(42) and gender distribution (equal) were similar in both samples. RR is 8.37 (2.74, 25.52). In 16 of the 49 epilepsy patients, cerebral pathology existed with mainly temporal and frontal localisation and of childhood-onset vascular or infectious origin. *Conclusions:* This finding suggests that in the onset of psychosis in epilepsy patients, the role of cerebral pathology, especially localized left temporal and frontal, is of strong etiological importance. The following epilepsy endophenotypes should be explored as factors in vulnerability for psychosis as well: frequent and severe epileptic activity; and psychotic reactions to certain AEDs, such as Topiramate and Lamotrigine. Burden of disease does not seem to play an important role.

Introduction

An association between epilepsy and psychotic symptoms, and a cerebral origin for psychotic symptoms, has been suggested for centuries.[1–4] On the other hand, it has been suggested that psychosis could be the result of social burden or trauma that chronic medical disorders pose on the individual with epilepsy. The concept of burden of disease has been described in such terms by the WHO.[5] If this should be the case, psychotic symptoms should be more prevalent in epilepsy patients than in the general population, but similarly prevalent in patients with other chronic medical disorders. This study seeks to establish the prevalence of psychotic symptoms in epilepsy patients as compared to patients with other chronic medical disorders, and to explore the possible role of cerebral pathology versus burden of disease in the development of psychosis in epilepsy. Possible implications of the findings will be discussed.

Method

Data assessment

Data were collected in 2623 patients from two sources:

(I) A sample of all 1752 patients with medical disorders admitted to an Academic Hospital setting from 2002 to 2005 for whom psychiatric consultation was requested. The sample was taken from all 7762 patients who in that period were admitted to the internal medicine and neurology wards. Patients admitted to traumatology wards or the emergency room were not taken into consideration in this study, as the focus was on patients with chronic medical disorders. From all referred patients, from the files those with chronic medical disorders were selected, who were diagnosed with psychotic disorder after screening with the MINI screening instrument[6,7] and standardised clinical psychiatric interview by CL psychiatrists from the CL service in the hospital. If the patients had been too psychotic to perform MINI screening at the time of the consultation, the MINI criteria were checked retrospectively from the interview and files.

(II) A sample of all 901 patients that visited a tertiary care epilepsy clinic and outpatient ward in a three-year period from 2002 to 2005, who were diagnosed with epilepsy and evaluated by a two stage screening method involving CID[8] administered by trained research assistants and standardised psychiatric interview by a consultant psychiatrist in order to establish DSM-IV diagnostic classification of symptoms[9] present at the time of the study. If the patients had been too psychotic to perform CIDI screening at the time of the interview, the CIDI criteria were checked retrospectively from the interview and files. In this sample, data were taken from the clinical reports for the history of DSM-IV classification,[9] seizure classification[10] and MRI scan for cerebral pathology, as well as EEG reports indicating lateralisation of seizure activity. Mental retardation was recorded if established by psychological test according to a validated preset protocol for cognitive functioning in epilepsy patients.[11] Existing data concerning DSM-IV diagnosis and seizure classification were collected. Psychotic symptoms occurring within a week time span around a seizure or cluster of seizures were classified as seizure related (peri-ictal). Psychotic symptoms that occurred within one week after a stressor had occurred were classified as stressor related.

Data analysis

The data were compared and analysed using SPSS-10 Chi-square tests, and Poisson regression analysis to estimate the relative risk to develop psychosis in both groups. Poisson analysis was chosen because this is a method fit as a model for seldom occurring

events. Following this method, risks were estimated to develop psychosis in the epilepsy group versus the chronic medically ill group. Age and gender in both groups were compared in a random sample of both settings.

Results

Age and gender distribution in both samples

Age and gender were compared in random samples of both groups: *N* = 119 in the epilepsy clinic sample and *N* = 67 in the Academic Hospital sample. In the epilepsy clinic sample, gender distribution was 53% male, 47% female. Mean age was 38, skewness .431 and kurtosis −.592, indicating a rather flat, symmetric, normal age distribution around the mean. In the Academic Hospital sample, gender distribution was 52% male, 48% female. Mean age was 51 years, skewness .352 and kurtosis ¯.258, indicating a flat, symmetric, normal age distribution around the mean as well. The random sample of the Academic Hospital population was therefore a mean 13 years older than the random sample from the epilepsy clinic. The gender distribution was equal and similar in both random samples.

In the patients diagnosed with psychosis in the Academic Hospital sample, gender distribution was

Table 1 Main ICD-10 diagnosis during admission on internal medicine and neurology wards in the Academic Medical Centre 2002—2004 (*N* = 7762), including specific prevalence rates for the most prevalent disorders

ICD-10 chapter	Blocks	Title	2002, N (%)	2003, N (%)	2004, N (%)
I	A00-B99	Certain infectious and parasitic diseases	83 (3.7)	125 (4.9)	150 (4.9)
II	C00-D48	Neoplasms	519 (23.4)	554 (21.9)	660 (21.8)
	C33-C34	- Malignant Neoplasm of trachea, bronchus and lung	295 (13.3)	329 (13.0)	368 (12.2)
III	D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	46 (2.1)	39 (1.5)	44 (1.4)
IV	E00-E90	Endocrine, nutritional and metabolic diseases	76 (3.4)	96 (3.9)	118 (3.9)
	E10-E14	- Diabetes mellitus	35 (1.6)	30 (1.2)	37 (1.2)
V	F00-F99	Mental and behavioral disorders	26 (1.2)	29 (1.2)	35 (1.2)
VI	G00-G99	Diseases of the nervous system	328 (14.8)	355 (14.1)	320 (10.7)
	G35	- Multiple sclerosis	184 (8.3)	164 (6.5)	166 (5.5)
	G20	- Parkinson disease	30 (1.4)	32 (1.3)	18 (0.6)
IX	I00-I99	Diseases of the circulatory system	421 (18.9)	544 (21.6)	664 (22.1)
	I27	- Primary pulmonary hypertension	110 (4.9)	166 (6.6)	267 (8.8)
	I63-I64	- CVA	91 (4.1)	126 (4.9)	138 (4.6)
X	J00-J99	Diseases of the respiratory system	268 (12.1)	285 (11.4)	360 (11.9)
	J40-J47	- Chronic lower respiratory disease	77 (3.5)	72 (2.9)	86 (2.8)
XI	K00-K93	Diseases of the digestive system	245 (11.0)	266 (10.6)	351 (11.7)
	K50	- Enteritis regionalis (M. Crohn)	22 (0.9)	26 (1.0)	23 (0.8)
	K51	- Colitis ulcerosa	9 (0.4)	2 (0.07)	11 (0.4)
XII	L00-L99	Diseases of the skin and subcutaneous tissue	13 (0.6)	11 (0.5)	22 (0.8)
XIII	M00-M99	Diseases of the musculoskeletal system and connective tissue	115 (5.2)	123 (4.9)	190 (6.3)
	M32	- SLE	26 (1.2)	15 (0.6)	23 (0.8)
	M05	- Reumatoid arthritis	29 (1.3)	16 (6.3)	38 (1.3)
XIV	N00-N99	Diseases of the genitourinary system	79 (3.6)	84 (3.5)	98 (3.2)
Total			2219 (100)	2525 (100)	3018 (100)

equal as well, mean age 44 years and age range 18—88 years. In the patients diagnosed with psychosis from the Epilepsy Clinic sample, mean age was 41 years, range 19—77, and 25 were male, 24 female.

This shows that patients with prevalent psychosis in both samples have similar age range and gender, although the mean age in the random sample of the Academic Hospital group is 13 years older than in the random sample of the Epilepsy Clinic.

Academic Hospital sample

Description of chronic disorders in the Academic Hospital sample. In this three-year period, in total 7762 patients were admitted to the internal medicine and neurological wards from which the sample was taken. ICD-10 classification[12] of the chronic disorders for which they were admitted is shown in Table 1.

As can be seen, the most prevalent chronic diseases in this patient group are Malignant neoplasm of trachea, bronchus and lung (mean prevalence 12.8%); primary pulmonary hypertension (6.8%); multiple sclerosis (6.7%); cerebro vascular accident (4.5%); COPD (3.1); rheumatoid arthritis (3.0%); diabetes mellitus (1.3%); Parkinson's disease (1.1%); SLE (0.9%); M. Crohn (0.9%) and colitis ulcerosa (0.3%).

Prevalence of psychotic symptoms. In this three-year period from 2002 to 2004, from the 7762 patients admitted to the internal medicine and neurological wards for treatment of somatic disorders, a sample of 1752 patients was seen consecutively by the consultation-liaison service of an Academic Hospital for evaluation of possible mental disorder. In 4 cases (0.2%) actual psychotic syndromes were diagnosed: One case of a 40-year-old woman with AIDS and a psychotic disorder with delusions due to AIDS; 1 case of a 88-year-old woman with hyperthyroidism and psychotic disorder with delusions due to hyperthyroidism; 1 case of an 18-year-old man with sickle cell crisis, B thalassaemia, and diabetes insipidus with psychotic disorder with hallucinations due to sickle cell crisis and a 30-year-old man with epilepsy with generalized tonic clonic seizures. The latter case was excluded, thus reducing the prevalence level to 0.17%.

Tertiary care epilepsy clinic sample

Prevalence. Of the 901 consecutive patients admitted to the diagnostic and treatment ward (574) or visiting the outpatient clinic of the long stay residency of the clinic (327), 126 patients with epilepsy scored positively for mental disorder after CIDI screening. Of these 126 patients, in a standardised clinical psychiatric interview performed by a consultant psychiatrist, 49 patients (5.4% of 901 and 38.9% of the 126 with comorbid mental disorder) were diagnosed with a psychotic disorder. Of those 49 patients, 16 were admitted at the ward, and 33 visited the outpatient clinic of the long stay department.

Table 2 Classification of seizures in the epilepsy patients' sample ($N = 49$)

Classification of seizures	*N*	%
Generalised tonic clonic seizures	26	53.1
Partial complex seizures	7	14.2
Partial complex seizures, secondarily generalising tonic clonic seizures	9	18.3
Multifocal partial complex seizures, myoclonus, secondarily generalising tonic clonic seizures	6	12.2
Myoclonic seizures	1	2.2
Total	49	100.0

Seizures. In all cases, the epileptic seizures existed before start of the psychotic symptoms, with a range of 1—10 years. The seizure classification of the 126 patients, based on the International League Against Epilepsy classification of seizures[10], is shown in Table 2.

As can be seen, 26 (53.1%) of patients suffered from Generalised tonic clonic seizures, 7 (14.2%) partial complex seizures, 9 (18.3%) partial complex seizures, secondarily generalising to tonic clonic seizures, 6 (12.2%) multifocal partial complex seizures, myoclonus, and secondarily generalising tonic clonic seizures; and 1 (2.2%) myoclonic seizures. Over 50% of the patients suffered from tonic clonic seizures. The frequency of seizures was high enough to warrant admission in a tertiary care epilepsy clinic, but unfortunately the exact frequency could not be established structurally from the charts. In 67.4% of cases the seizures were idiopathic; in 32.6% of cases cerebral pathology was considered to be of etiological relevance as will be reported further on.

Psychiatric diagnosis. The DSM-IV classification of the main diagnosis on Axis I is shown in Table 3.

The main number of psychoses in these patients is schizoaffective disorder, that is, psychotic disorder with a strong affective component in terms of mood swings, strong irritability, and psychotic symptoms concomitant with euforia. The psychotic symptoms generally consisted in hallucinations and paranoid delusions. Also, disturbed sleep was a common phenomenon. Phenomenology could range from moderate to serious severity. The symptoms would generally take a chronic fluctuating course.

Table 3 Classification DSM IV Axis I, main diagnosis ($N = 49$)

Diagnosis	*N*	%
Schizoaffective disorder 295.70	13	26.5
Bipolar type 295.70	3	6.1
Mood disorder with manic features due to frontal cerebral trauma 293.83	1	2.0
Psychotic disorder with delusions due to epilepsy 293.81	8	16.4
Psychotic disorder with hallucinations due to epilepsy 293.82	5	10.2
Psychosis due to antiepileptic drug: Topiramate 292.12	1	2.0
Psychosis due to antiepileptic drug: Lamictal 292.12	1	2.0
Chronic psychosis		
Paranoid type 295.30	7	14.4
Disorganised type 295.10	1	2.0
Residual type 295.60	1	2.0
Psychotic disorder NOS 298.9	4	8.2
Brief psychotic disorder with marked stressor 298.8	4	8.2
Total	49	100.0

The second set of syndromes is that of psychosis clearly related to frequency or severity of seizures. That is, the psychotic symptoms occurred within less than 5 days after the last seizure or cluster of seizures. In general they would last about one week in case of appropriate treatment. However, in some patients interictal treatment would be needed to achieve full remission of symptoms. The symptoms consisted of disintegrated, bizarre behavior, i.e. walking naked around the ward while masturbating, or suddenly slashing one's wrists without any apparent reason, and talking effusively and incoherently. Attention could be drawn, but patients would be easily distracted. Also, severe sleep disturbances would occur.

Less than 20% consists of chronic psychosis. These patients display classic schizophrenia-like psychotic symptoms that would last for months or years with hallucinations and paranoid delusions. Impulsive aggressive outbursts with seriously dangerous behavior occurred from time to time. However, contrary to schizophrenia patients without epilepsy, these patients generally experienced their aucoustic hallucinations ego-dystonic, in other words they experienced their hallucinations with a certain distance, as an odd but inevitable phenomenon that nevertheless controlled their overall behavior.

Chronicity and recurrence of symptoms was the rule. Fourteen patients had a history of psychiatric admission, 22 had a history of psychiatric outpatient treatment, so 36 of those 49 patients (72%) had a history of psychiatric treatment for psychotic symptoms.

Chi-square analysis revealed no association between classification of seizures and psychotic syndromes as described above.

Comorbid mental disorder. In 11 cases (22.5%) a comorbid diagnosis was made. These are shown in Table 4.

Most comorbid Axis I disorders were pervasive developmental disorder. In 20 cases, comorbid Axis II disorders were found, mainly mental retardation or impaired intellectual functioning. Chi-square analysis revealed that seizure related psychosis occurred mostly in non-retarded patients. The other psychotic syndromes showed no association with mental retardation (Chi-square 26.16, d.f. 12 and $p = .010$).

Cerebral pathology. Of the 49 patients suffering from psychotic symptoms, 16 (32.6%) had cerebral pathology, established from the medical charts and by MRI scan, as shown in Table 5. All these patients suffered from tonic clonic seizures, in three cases after secondary generalisation of partial complex seizures.

Six cases showed left sided temporal cerebral involvement: four CVA of the a. cerebri media sinistra during childbirth, one left temporal arteriovenous malformation, and one left hippocampal mesiotemporal sclerosis for which the patient underwent surgical extirpation of the hippocampus. In one case with atrophia cerebri sinistra, the localisation was left-sided frontotemporal. Thus, 7 out of 16 cases showed left sided pathology. The MTS patient had psychotic disorder due to seizures.

Three other cases had bilateral frontal localisation: two with childhood encephalitis and one with extirpation of a frontally localized ependymoma. All cases of frontal cerebral pathology except the ependymoma had existed from childhood on. In these three cases, schizoaffective disorder including manic episodes was diagnosed. The ependymoma

Table 4 Classification DSM-IV Axis I and II co-morbidity ($N = 31$)

	N	%
DSM-IV Axis I comorbidity		
Pervasive developmental disorder, NOS 299.80	4	36.5
Amnestic syndrome 294.8	1	9.0
Amnestic syndrome due to ependymoma surgery and radiation therapy 294.84	1	9.0
Dementia due to epilepsy 294.1	1	9.0
Obsessive Compulsive Disorder 300.3	2	18.25
Panic Disorder without agoraphobia 300.01	2	18.25
Subtotal Axis I	11	100
DSM-IV Axis II comorbidity		
Moderate mental retardation 318	6	30
Mild mental retardation 317	8	40
Borderline Intellectual Functioning V62.89	5	25
Personality Disorder NOS 301.9	1	5
Subtotal Axis II	20	100

Table 5 Localisation of cerebral pathology and psychotic disorder ($N = 16$)

Cerebral pathology	Schizo-affective disorder	Chronic psychosis	Psychotic disorder NOS	Brief psychotic disorder	Psychotic disorder due to epilepsy	Total
Left temporal						
CVA a. cerebri media sinistra at birth	0	1	2	1	0	4
Left temporal arteriovenous malformation	0	1	0	0	0	1
Left hippocampal surgery mesiotemporal sclerosis	0	0	0	0	1	1
Left frontal temporal						
Atrofia cerebri sinistra	1	0	0	0	0	1
Frontal bilateral						
Frontal childhood encephalitis	2	0	0	0	0	2
Extirpation frontal ependymoma	0	0	0	0	1	1
Bilateral						
Posttraumatic hydrocephalus	0	1	0	0	0	1
Childhood meningo-encephalitis	0	2	0	1	1	4
Surgery meningeoma Th12	0	0	0	0	1	1
Total	4	4	2	2	4	16

patient was diagnosed with psychotic disorder due to seizures.

Six patients showed cerebral pathology widely extended over both hemispheres that in all but one case originated from childhood. Half of them were diagnosed with chronic psychosis.

No cerebral pathology was localized uniquely right sided.

Comparative data

In 1751 patients admitted to the Academic Hospital for chronic medical disorders other than epilepsy, 3 (0.17%) were established to have a prevalent psychotic disorder. The epilepsy case in the Academic Hospital setting has been excluded. In the 901 patients admitted to the Epilepsy Clinic, 49 (5.4%) were established to have prevalent psychotic disorder. RR (Poisson GLM) to develop psychosis in the epilepsy group as compared to other chronic medical disorders is 8.37 (2.74, 25.52).

Discussion

Psychotic phenomena have often been considered the equivalent of epileptic activity.[13–19] Hill[20] and Pond[21] described paranoid psychosis in association

with temporal lobe epilepsy. The term 'schizophrenia-like psychosis of epilepsy' has been introduced by Slater and Beard[13] and Flor-Henry.[4] In a population of patients with epilepsy they found a higher percentage of patients who developed schizophrenia later on than could be expected on the basis of the incidence of schizophrenia. The patients showed temporal lobe phenomena such as lateralisation of a cerebral lesion in the left temporal lobe and partial complex seizures and a variant of schizophrenia with intact affect and a lack of personality deterioration that clustered together with psychotic symptoms. A review by Mace[22] reaffirmed the importance of this work and stated that research was needed to confirm the association of the two interrelated disorders.

An alternative explanation of the co-existence of the two disorders has been that mental disorders including psychosis could be the result of the burden that chronic medical disorders poses on the individual with epilepsy. Burden of disease in this respect could be conceptualised as burden of the chronic medically ill individual to cope with an invalidating chronic medical disorder. The other aspect of burden of disease is the conceptualisation of obtaining a chronic medical disorder as a trauma for the afflicted individual. In the literature, a relation between early childhood trauma and the onset of psychosis, and also between a burden of more recent trauma and psychosis[23] has been described in a stress-coping-vulnerability model.[24] If burden of disease, conceptualised this way, should play a role in the onset of psychosis, psychotic symptoms should be more prevalent than in the general population, but similarly prevalent in patients with other chronic medical disorders. However, if a cerebral factor would play a role, prevalence should be higher in patients with epilepsy compared to other non-cerebral chronic medical disorders. Both aspects of stress elicited psychosis in chronic disorders do not appear to apply in this study.

In this study, two samples were compared: 1752 patients with chronic medical illness admitted to an Academic Hospital; and 901 epilepsy patients admitted to an Epilepsy Clinic. The fact that patients with prevalent psychosis in both samples have similar age range and gender, although the mean age in the random sample of the Academic Hospital group is 13 years older than in the random sample of the Epilepsy Clinic, suggests that confounding factors such as age and gender do not explain the differences in prevalence of psychotic disorder established in both groups.

Limitations of the study

Limitation of the study is that in the Academic Hospital setting, consultation might not have been requested for all patients with psychopathology. Some psychotic patients might have been presented at the emergency room and not admitted to the hospital because they were admitted to a mental hospital instead. However, this would not have been the case if the patient would be seriously ill. In this study, it is presumed that if a patient was both psychotic and chronic medically ill, (s)he would have been admitted to the Academic Hospital and psychiatric consultation would have been requested: such severe psychopathology would not go unnoticed and support by the CL service would be needed. This is presumed because the consultation rates in general are high in the relevant wards of the hospital, because the medical wards from which the patients were referred use a screening method for all their patients that pinpoints all patients with possible mental disorder and selects them for psychiatric consultation. This is an established method because this hospital is well equipped to treat medically ill patients with comorbid mental disorder by way of a well functioning CL service.[25–27] However, replication of this finding in a greater study with a systematic screening and monitoring procedure as used in the Epilepsy Clinic sample would be desirable.

Another limitation of the study is that we do not have systematically reported data on the frequency of the seizures in the patient group and therefore, although this factor might very well be relevant in the development of psychosis, we cannot report on that issue. A similar case can be held for the chronic medical disorders patients, as we cannot report on the severity of their symptoms and their level of impairment. Therefore, in future prospective studies, it would be desirable to assess the severity of the disorders in both groups.

Another limitation of the study is that the two samples had different tests to screen for psychosis, that is CIDI and MINI. The reason was that in the different settings, personnel had been trained in using these different instruments. In the literature, CIDI as well as MINI are found to be reliable instruments that can be used to screen for mental disorders, if assessed by trained personnel. Therefore, both methods were considered usable. Moreover, because in both settings the screening was followed by a clinical diagnosis by a psychiatrist, it was considered acceptable in this study to use the two different screening instruments in the first step.

In the study, indications are found that left sided and frontal localisation of cerebral pathology might

play a role in the onset of psychosis. However, the numbers were too small to test statistically for significance levels. Another limitation of the study is that in the Epilepsy Clinic sample, as several conditions predisposing to psychotic symptoms, namely cerebral pathology, mental retardation, and PDD-NOS, cluster together in this complex cerebral disorder, their specific role in the aetiology of the psychotic symptoms could not be explored. Both should be attempted in further research into the aetiology of psychosis.

Prevalence and relative risk of psychosis in the respective samples

In the cross-sectional NEMESIS study[28–29] in which a random sample of 7076 patients between 18 and 40 years of age was taken from the general population in 1996 and screened by CIDI, the prevalence of schizophrenia and other non-affective psychoses was low, 0.4%. A comparison of prevalence in the two samples in this study shows that the chronic medical disorders excluding epilepsy sample shows a similar prevalence rate of psychotic disorder (0.17%) as found in the general population. But in case of epilepsy, prevalence of psychotic syndromes is 5.4%. The RR is 8.37. In 16 of these 49 patients, the combination exists with cerebral pathology as established by MRI scan. Also, it turns out that half of the patients with psychotic symptoms admitted to the Academic Hospital setting suffered from cerebral disease, including one patient with epilepsy (!) and one with diabetes insipidus. As higher levels of psychosis were expected in medically ill patients i.e. with Parkinson or on immunosuppressant regime, patients with such diagnostic categories were taken from the files and double checked. It was found that in such cases, delirium was the generally established diagnosis, as consciousness was often impaired in that patient group.

This finding, combined with the finding that the prevalence of psychosis in the patients with chronic medical disorders admitted to the hospital is similar to the prevalence found in the general population, supports the hypothesis that although chronic medical disorders might pose a burden that in some cases might play a role in the onset of transient psychotic symptoms, no indication can be found as such in this study. The role of cerebral pathology is of etiological importance in the onset and persistence of psychosis. The indications in literature that psychosis might be more prevalent in epilepsy patients, and that epilepsy and psychosis are somehow related disorders[29,30], are supported by this finding.

The role of seizures in the onset of psychosis

In all patients, the seizures preceded the psychosis with up to 10 years. This finding is similar to that of Slater and Flor-Henry. In former research, a high prevalence of psychotic disorders is especially suggested in patients with complex partial seizures.[32] In this study, almost half of the patients indeed suffer from complex partial seizures, but only 14.2% without secondary generalisation. More than half has tonic clonic seizures and if secondary generalisation is counted as well, 83.6% of the patients suffer from tonic clonic seizures. The patients visiting this setting often have treatment refractory seizures and a chronic course of the epilepsy despite polytherapy with two or more other anti-epileptic drugs (AEDs). In one case, psychosis occurred after lamotrigine was administered and subsided after withdrawal of the drug. In another case, the same occurred on topiramate. The seizure related psychosis shows psychotic symptoms associated with seizure frequency and severity, often after clusters of seizures. Seizure related psychosis occurs mostly in non-retarded patients. No clear-cut cases of forced normalisation, as described by Wolf[33] were found. These findings suggest that seizures play a significant role in the onset of psychosis, but this is linked to severity — treatment refractory seizures, tonic clonic seizures and clusters of seizures — as well as to certain AEDs, and not to partial complex seizure classification.

The role of affective psychosis in epilepsy patients

Systematic research in this field involving DSM-IV classification is scarce so far, or did not focus on psychotic symptoms.[34–35] In this study, psychotic symptoms were classified by DSM-IV criteria. The value of this classification method might be that this way, the vast amount of affective psychotic symptoms in epilepsy patients is clearly established by a psychiatric classification method. The DSM-IV is a classification method that relies mostly on description of symptom clusters. In epilepsy research, often etiological presumptions have been taken into account for description of symptoms. Use of the DSM-IV classification may be a valid method to establish uniformity in description while enabling researchers to explore possible etiological factors.

Although Wolf[36] stated that mania is seldom seen in epilepsy patients, in this study a considerable amount of schizoaffective disorder, including psychosis with elevated mood, is found. The high number of schizoaffective disorder and of depressive

disorder with psychotic features in this study confirms the vision of Blumer et al.[37] that psychotic symptoms in epilepsy patients are preceded or accompanied by mood disorder. Blumer coined the term Interictal Dysphoric Disorder and suggested that a long course of this disorder can culminate in psychotic symptoms.[38] Flor-Henry also mentioned the affective psychotic syndromes. This illustrates that although AEDs are widely used as mood stabilisers in general psychiatry, affective psychosis can persist in epilepsy patients despite this same treatment. In this study, almost 40% of the patients with psychotic symptoms suffer from serious concomitant mood disorder despite treatment with moodstabilizing anti epileptic drugs. This finding warrants further research into the treatment possibilities for this kind of psychotic disorder in epilepsy patients, such as the possible role of antidepressants.

The role of social deterioration in the onset of psychosis

Schizophrenia-like psychosis of epilepsy has been described as a chronic psychosis without the lack of affect and withdrawn attitude that is typical of the schizophrenic patient. In two surveys using PSE examination, the absence of personality deterioration as claimed by Slater could not be supported.[39,40] In this survey, in the group with chronic psychosis, patients experienced psychotic symptoms on a daily basis, for years. In the other psychotic syndromes established in this study, chronicity of impaired general functioning existed, and chronic recurrence of seizures, culminating in serious social impairment; but the psychotic symptoms in themselves could subside and relapse. Data from the psychiatric history revealed that 72% of the patients had a history of psychiatric treatment and 67% lived in a residency setting, both a strong indicator of chronicity. Lack of personality deterioration as found by Slater cannot be confirmed in the chronic psychosis group, as most of these patients had to live residential; but it is found in the patients with schizoaffective psychosis.

By the different methodology in this study, the lack of deterioration as described by Slater can be traced back to the high number of affective psychotic disorders. In this study, the course and features of several DSM-IV psychotic syndromes was established and compared. This is a way to establish control groups. It explains why the findings can suggest that the old concept of schizophrenia-like psychosis of the 1960s needs differentiation. For example, in schizoaffective disorder, mania-like symptoms are found. If schizoaffective disorder and chronic psychosis were all taken together in the concept as formulated by Slater, of course a less obvious display of negative symptoms could be found in the whole group, as lack of negative symptoms is a known feature of schizoaffective disorder. In this study, these syndromes are distinguished and studied separately and thus this differentiation can be made. This confirms Slaters point that many of the patients that he studied had affective symptomatology.

The role of temporal and frontal lesion in the onset of psychosis

According to Slater and Beard, schizophrenia-like psychosis of epilepsy would be linked with treatment refractory complex partial seizures, and Flor-Henry described the link with temporal lesions. Ferguson and Rayport[41] found structural lesions in the temporal region. In this study, as shown in Table 3, six cases are found of temporal lesion, and one of frontotemporal lesion. Five of these are of vascular origin (CVA and arteriovenous malformation), one case of mesiotemporal sclerosis, and one of atrofia cerebri sinistra. All these cases except the MTS suffered these conditions from early childhood.

A finding in this study is indeed that about half of the chronic psychosis patients suffer from cerebral pathology in the left temporal region. Also, all of them have tonic clonic seizures. They display a chronic course of the symptoms and chronic impairment in general functioning with strong social impairment. Therefore one may suggest that apparently temporal lesions play a substantial, but not an exclusive role in chronic psychosis in epilepsy patients.

Another finding in this study is that not only temporal but also frontal lesions are present in a substantial amount of cases: four out of 16 cases with cerebral pathology show frontal localisation. All existed since early childhood. All early onset frontal lesions in this sample were associated with schizoaffective disorder. In this study, the frontal lobe is associated with affective psychosis.

Conclusions

The main finding of this study is that the risk to develop psychosis in epilepsy is eighth fold when compared to other chronic medical disorders. This finding supports the hypothesis that psychosis in epilepsy should be attributed rather to brain pathology than to stress related to other chronic disorders. For the first time the relative risk to develop psychosis in epilepsy patients as compared to patients

with other chronic medical disorders has been established and has turned out to be high, i.e. >8. Another major finding is that the prevalence of psychosis in chronic medically ill patients admitted to the Academic Hospital setting is similar to the prevalence in the general population.

To some extent these findings might be explained by the sample. Patients in the tertiary epilepsy service are quite likely to have been referred there not just because their epilepsy is difficult to treat but also because they have comorbidity complicating its treatment. On the other hand, there is a similarity in the chronic medically ill sample as the same type of patients — with difficult to treat medical disorders and psychiatric comorbidity — tend to be refered to the CL service and included in the sample.

Also, as a more general link between cerebral disorder and psychosis is suggested in this study, it would be most interesting to investigate the role of the temporal and frontal lobe structure and function in psychosis in patients with other cerebral disease. Most cerebral pathology in this study existed from childhood and was acquired; however, the possible role of left frontotemporal cerebral pathology predisposing for psychotic states should be explored in further research as well. Patients with epilepsy can be considered to be at high risk for developing psychotic disorder[31] and therefore a population fit for attempts to identify factors concerning vulnerability for psychosis. The following epilepsy endophenotypes[42,43] that could be explored as factors in vulnerability for psychosis could be distinguished by the results from this study: left temporal or frontal cerebral pathology; frequent and severe epileptic activity; and psychotic reactions to certain AEDs, such as Topiramate and Lamotrigine.

Another important factor in the aetiology might be the high amount of co-morbidity, namely mental retardation and other mental disorder, such as PDD-NOS, found in this study. Mace[22] suggests that such aspects might have been explored not enough until now. This is confirmed in this survey. The main question remains whether the association between epilepsy and psychosis is due to having seizures per se, or to having the brain disease that may predispose to these seizures. What would be needed in order to establish the role of the temporal and frontal lobe in psychosis in epilepsy would be neurophysiological studies combined with a neurological and DSM-IV classification of patients. Another question that might be interesting and that has not been addressed in this study is whether cerebral pathology might play a role as well in patients with epilepsy and i.e. affective disorders. Further research should shed light not only on the onset of psychosis in epilepsy, but on cerebral causes of the onset of psychosis in general.

Declaration of interest

There is no conflict of interest for this paper for the authors involved.

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