Psychiatric Dysfunction in Temporal Lobe Epilepsy

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Why worry about psychiatric dysfunction in PWE?

	Controls	Epilepsy
Major depressive disorder	10·7 (10·2–11·2)	17·4 (10·0–24·9)
Mood disorder	13·2 (12·7–13·7)	24·4 (16·0–32·8)
Anxiety disorder	11·2 (10·8–11·7)	22·8 (14·8–30·9)
Mood disorder, anxiety disorder, or dysthymia	19·6 (19·0–20·2)	34·2 (25·0–43·3)
Panic disorder or agoraphobia	3·6 (3·3–3·9)	6·6 (2·9–10·3)
Suicidal ideation	13·3 (12·8–13·8)	25·0 (17·4–32·5)
Any mental health disorder	20·7 (19·5–20·7)	35·5 (25·9–44·0)

Figures quoted as prevalence (95% CI). Patients without epilepsy (n=36727); patients with epilepsy (n=253). Adapted with permission from Blackwell Publishing.[14]

Table: **Lifetime prevalence of psychiatric comorbidity in patients with epilepsy compared with the general population**

Unresolved issues?

- What is the bases of psychiatric comorbidities? Anatomical substrates, seizure burden, medication effects, behavioral fallout?
- At what stage does it start? Is there an evolutionary pattern? What is the role of chronicity?

Models of epilepsy

- JME the commonest paradigm of IGE in adult epileptology is associated with a burden of anomalous frontal lobe dysfunction that is corroborated by mesial and dorsal frontal atrophy on MRI
- TLE the commonest model of LRE offers a host of insights into associated psychiatric dysfunction

TLE and behavioral problems

- F/27 years presented to JHRC Epilepsy Clinic with a refractory epilepsy of 14 years duration.
- Clinical history, physical examination, EEG, and imaging confirmed a MTLE syndrome.
- MRI corroborated hippocampal sclerosis
- Was poorly controlled on CBZ and CLBZM
- Drug failures included VPA, PHT, PHB, LTG,GBPNTN.

TLE and behavioral problems

- Presurgical evaluation was concordant for left MTLE, and surgery was advised. (ATL)
- There were no psychiatric antecedents.
- Family asked for time and one more AED trial.
- Topiramate (TPM) started in a dose of 25mg/day and gradually increased to 150 mg/day over a span of 6 weeks. CBZ was continued.

TLE and behavioral problems

- 8 weeks later distraught parents, weepy mother and sister report to clinic.
- Patient had become paranoid, hallucinated frequently, developed sexual attraction towards father and brother, dreamed of sexual encounters with them, felt people watched when she bathed, refused to come out of the house
- Family consulted priest and then neurologist

MTS and acute psychosis

- Could hippocampal sclerosis itself lead to psychotic symptoms?
- Does acute psychosis reflect an epileptic process in patients with TLE?
- Was the psychosis triggered by aggressive counseling for a surgical Rx?
- Did topiramate induce the acute psychotic episode?
- TPM withdrawn & patient remits

The role of hippocampal sclerosis in topiramate-related depression and cognitive deficits in people with epilepsy.

Mula M, Trimble MR, Sander JW. Epilepsia. 2003 Dec;44(12):1573-7.

- We analyzed the data of 70 patients with TLE and HS and 128 patients with cryptogenic TLE matched for age, sex, starting dose, and titration schedule of TPM. They were selected from the first consecutive 431 patients started on TPM between 1995 and 1999.
- Patients with HS were more likely to develop cognitive adverse events (CAEs; $p = 0.002$) and depression ($p = 0.018$) and to be receiving a polytherapy regimen ($p = 0.007$).
- However, regression analysis demonstrated that only HS was a predictive factor for the occurrence of CAEs (OR = 2.4; $p < 0.001$) and depression (OR = 2.3; $p = 0.02$).

The role of hippocampal sclerosis in topiramate-related depression and cognitive deficits in people with epilepsy.

Mula M, Trimble MR, Sander JW. Epilepsia. 2003 Dec;44(12):1573-7.

Conclusions:

- Patients with TLE and HS were more prone to develop CAEs and depression than were patients with cryptogenic TLE, during TPM therapy, despite the same titration schedule.
- The presence of HS and not duration of epilepsy or polytherapy regimen represented the main risk factor.

TLE and psychiatric manifestations

- Does the pathological substrate of TLE and/or its chronicity determine personality and behavioral aberrations?
- Are specific pathological substrates particularly vulnerable?
- Does medical intervention (pharmacological and surgical) contribute to psychiatric manifestations?

Dostoevsky and Epilepsy: An Attempt to Look Through the Frame

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Abstract

Fyodor Mihailovich Dostoevsky, one of the greatest novelists of all times, had a unique ability to depict the social and moral conditions of 19th-century Russia, and anticipated with his writings many philosophical and scientific developments, such as existentialism and psychoanalysis. The study of auto- and hetero-biographic reports, as well as of his literary production, suggests that he suffered from epilepsy since his mid-20s. Most of his seizures were described as generalized convulsive; however, many features, such as the presence of an 'ecstatic' aura, a pallor preceding the generalization, and especially a postictal dysphasia, point to a dominant (mesio-) temporal lobe origin. Although Dostoevsky in his late years complained of progressive memory impairment, he was able to write with his usual cleverness until the end of his life, when he succumbed to a chronic lung disorder. From an epileptological point of view, this uncommon relatively benign evolution is noteworthy, and it offers an insight to the natural course of this illness. A natural course that is mostly unknown in our times, as the availability of antiepileptic drugs and surgery has biased our knowledge. The relationship between epilepsy and Dostoevsky's production is twofold. Firstly, as he had a tendency towards autobiographical descriptions not only of facts but also of thoughts, his novels represent a valuable source for the understanding of his illness. Secondly, his works contribute greatly to the de-stigmatization of patients with epilepsy.

Religious ecstasy and TLE: the realm of neuropsychiatry

lepsy Dostoevsky describes, the import of which, as it must be remembered, is not as a warning of impending seizure but as a focal seizure itself. Prince Myshkin's aura is described as follows:

"there was a moment or two almost before the fit itself... when suddenly amid the sadness, spiritual darkness, and depression, his brain seemed to catch fire at brief moments, and with an extraordinary momentum his vital forces were strained to the utmost all at once. His sensation of being alive and his awareness increased tenfold at these moments which flashed by like lightning... all his doubts and worries seemed composed in a twinkling, culminating in a great calm, full of sense and harmonious joy and hope[3]... a blinding *inner* light flooded his soul[3]... but those moments... were merely the presentiment of the last second... which preceded the actual fit. This second was, of course, unendurable."[3]

SHORT REPORT

Religiosity is associated with hippocampal but not amygdala volumes in patients with refractory epilepsy

J Wuerfel, E S Krishnamoorthy, R J Brown, L Lemieux, M Koepp, L Tebartz van Elst, M R Trimble

J Neurol Neurosurg Psychiatry 2004;**75**:640–642. doi: 10.1136/jnnp.2003.06973

Objective: To assess the relationship between the behavioural triad of hyper-religiosity, hypergraphia and hypo-sexuality in epilepsy, and volumes of the mesial temporal structures.

Method: Magnetic resonance images were obtained from 33 patients with refractory epilepsy and mesial temporal structure volumes assessed. Amygdala and hippocampal volumes were then compared in high and low scorers on the religiosity, writing, and sexuality sub-scales of the Neurobehavioural Inventory.

Results: Patients with high ratings on the religiosity scale had significantly smaller right hippocampi. Religiosity scores rated by both patient and carer showed a significant negative correlation with right hippocampal volumes in this group. There were no other differences in amygdala or hippocampal volumes between these groups, or between high and low scorers on the writing and sexuality sub-scales.

Conclusions: These findings suggest that right hippocampal volumes are negatively correlated with religiosity in patients with refractory epilepsy.

Geschwind Syndrome

- Hyper-religiosity
- Hyper-graphia
- Hypo-sexuality
- Aggression

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History

- M/15 yrs
- Referred for increasingly difficult behavioural changes resulting in disruption of familial harmony in 2016 June.
- In 2008 underwent surgical resection for right temporal lobe ganglioglioma at SCTIMST after an antecedent interval of six months of complex partial seizures.
- Seizures remitted after surgery and patient was maintained on 600 mg of OXC twice daily and could resume school.
- In 2014 patient started experiencing occasional complex partial seizures despite OXC and local neurologist added LVTCM

History

- Within three to four months patient's behaviour changed and started exhibiting obsessional ideas about Gods and temples. He demanded daily multiple visits to the temple and collected photographs of all Hindu Gods. He created a pantheon of these at home and had a whole room festooned with celestial photographs. If denied a visit to the temple he would become aggressive and physically assault all members including younger sibs and elder grandparents. On occasions they had to undergo suturing for CLWs. Parents unclear whether on his aggressive days he experienced seizures. His mother had to be hospitalized after one such grievous assault.

History

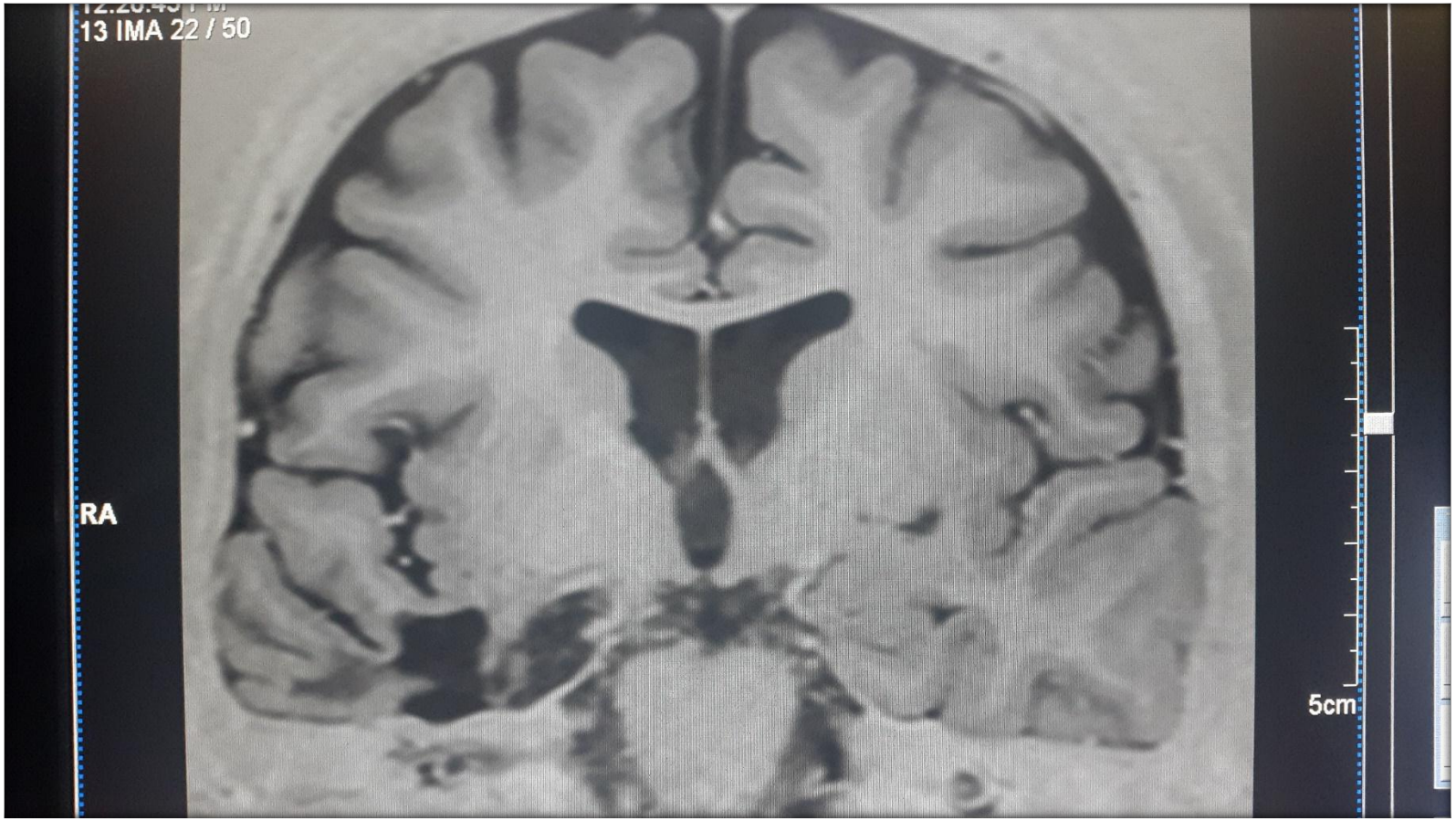
- In 2015 he was assessed by various psychiatrists and neurologists. Two inter-ictal EEGs were normal. MRI was done. It did not reveal any recurrence of gangliogioma. MR perfusion did not reveal any focal high perfusion zones in the right temporal lobe.
- He was hospitalized in Ahmedabad and was administered 7 sittings of ECT to no avail.
- Both parents were distraught enough to contemplate mass familial suicide and required counselling. Father was unable to attend to his shop due to incessant temple visit demands. Psychiatrist let loose a pharmacological war……

Antipsychotic Medication Therapy

- Sertraline 200 mg per day
- Haloperidol 30 mg per day
- Clozapine 75 mg per day
- Olanzepine 20 mg per day
- Clobazam 25 mg per day
- Lacosamide 200mg per day
- Oxcarbazepine 1200 mg per day
- Levetiracetam had been withdrawn

History

- The seizures escalated to daily one or two generalized tonic clonic events and multiple dialeptic events.
- In between seizures patient would exhibit obsession for Gods and temples. If denied access would swear and physically assault family members.
- All family members confessed to being terrorized by his bizzare behaviour.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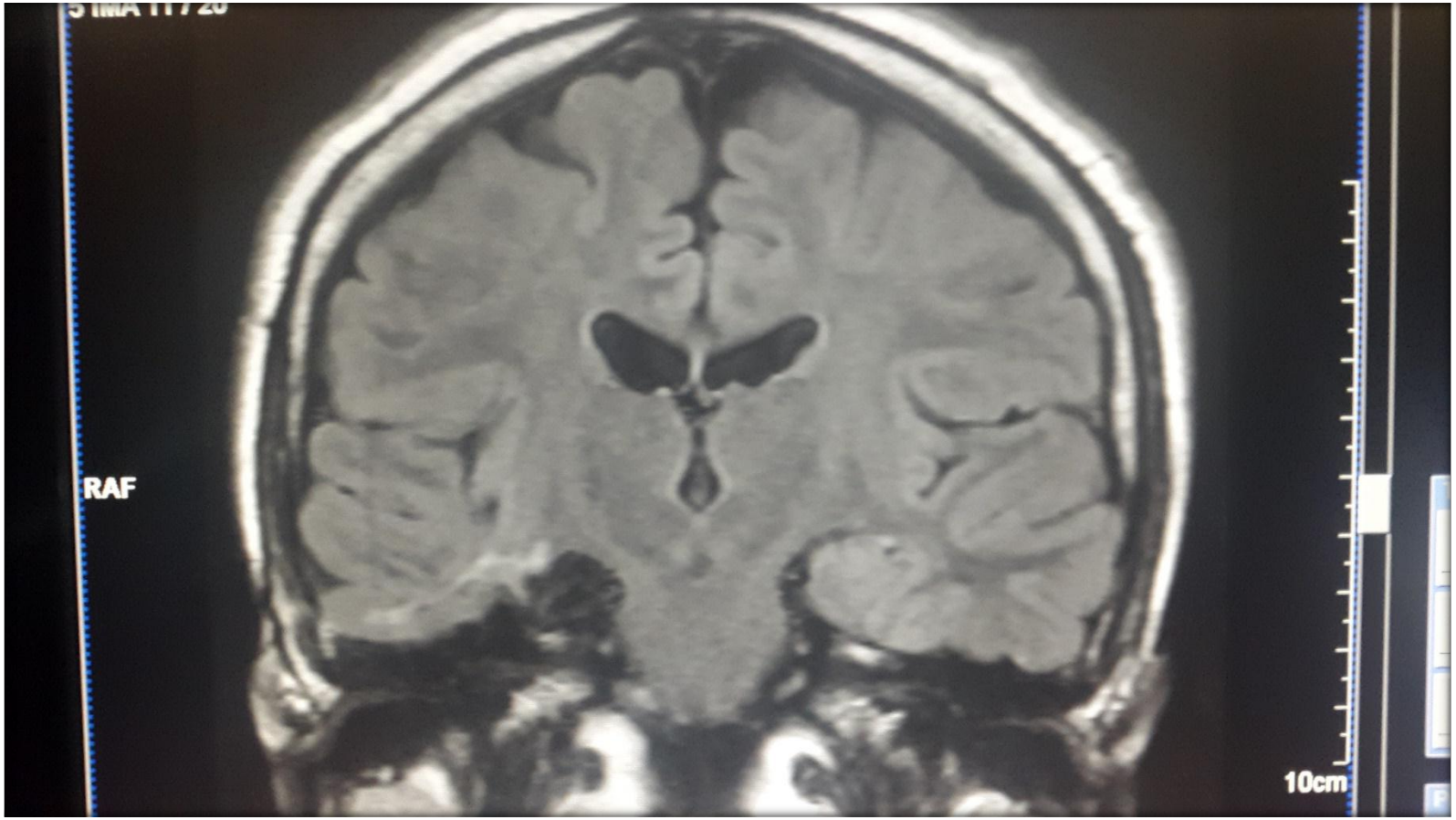
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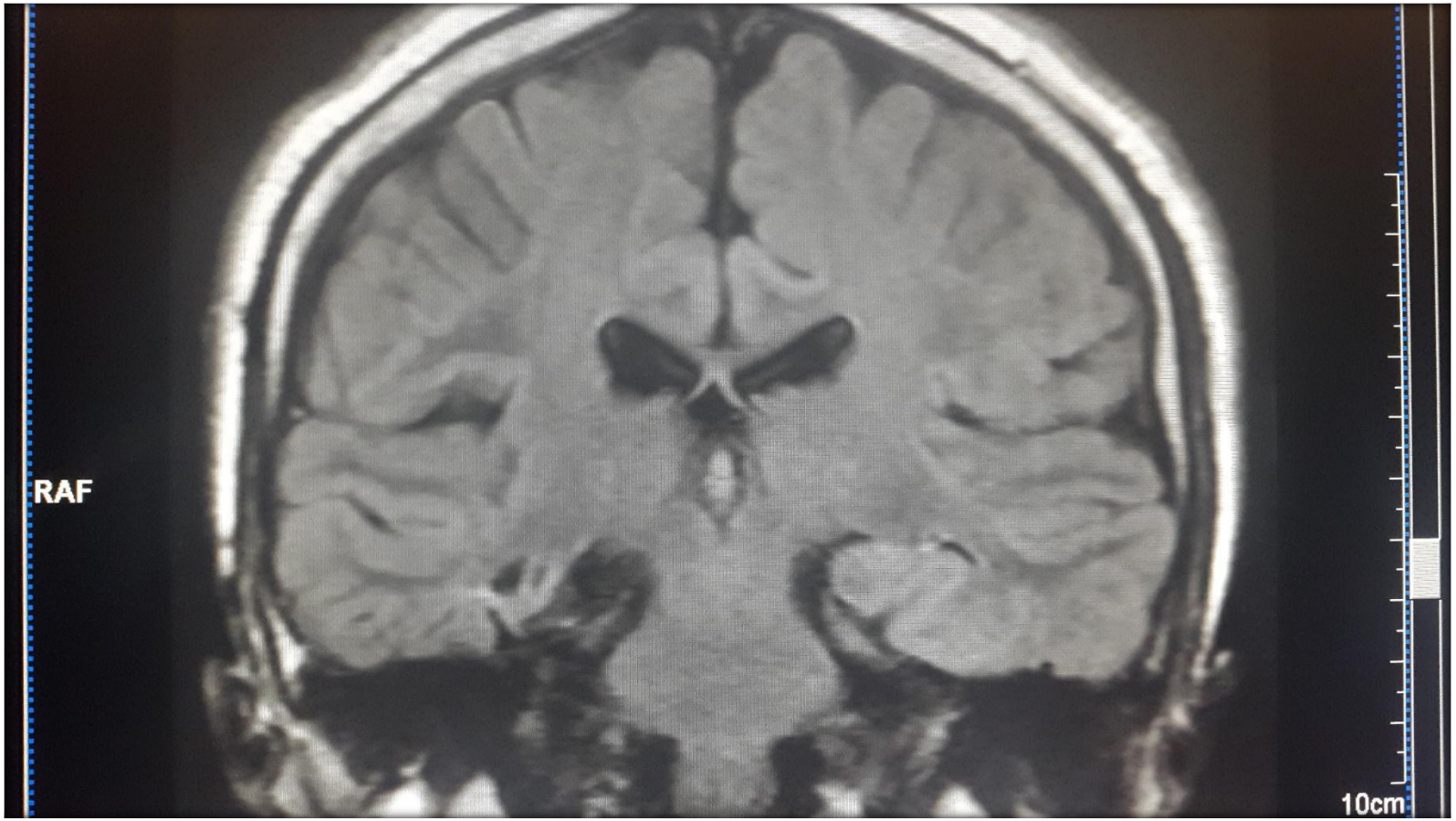
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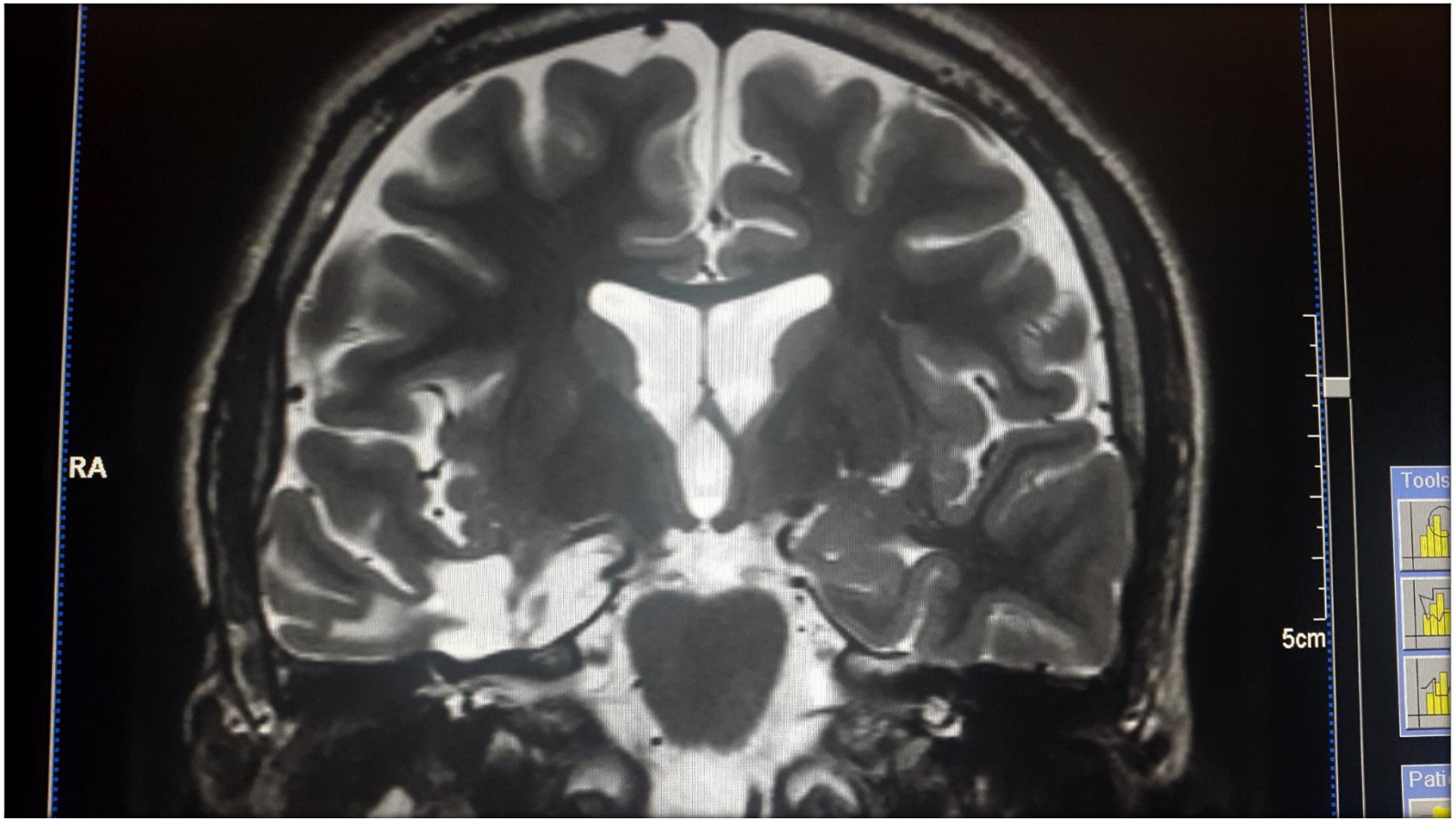
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History

- Patient was unwilling to undergo VEEG.
- Reluctantly allowed FDG brain PET scan which revealed right temporal lobe hypometabolism. Surround brain and other lobar perfusion was normal.
- Dilemmas in therapy:
  - Change of medications
  - Any prospect of surgery

The pathophysiology of hyperreligiosity is complex and not fully understood. Religiosity in epilepsy is thought to originate in the limbic system due to its association with the temporal lobe and its function in emotions. Kindling, which refers to an enhancement of seizure susceptibility due to repeated stimulation [8], might be one of the ways hyperreligiosity develops as it is believed activation and strengthening of limbic-cortical connections occur in these patients [9]. Imaging studies have not completely elucidated the underlying changes. Wuerfel evaluated hippocampal MRI volumes in patients with refractory epilepsy and found a smaller right hippocampus in patients with hyperreligiosity but not with other components of the Gastaut-Geschwind syndrome, suggesting that the right hippocampus may have a role in the development of religiosity but causality could not be determined [10]. Involvement of the Papez circuit in the limbic system may lead to ictal events and ictal religiosity is more common with a right temporal seizure focus [1]. Chronic stimulation of the amygdala due to seizure activity may lead to altered behavior and heightened emotionality during the interictal period. This behavior is what is known as epileptic personality or interictal behavior. Geshwind described this as the interictal behavioral syndrome, which he observed in subjects with temporal lobe epilepsy who had a chronic change in personality which became more striking as time passes [2]. Postictal religiosity may be associated with

TLE patients with postictal psychosis: Mesial dysplasia and anterior hippocampal preservation

Article abstract—The authors studied six patients with refractory temporal lobe epilepsy and postictal psychosis using quantitative MRI and histopathology, and compared the results with 45 patients with temporal lobe epilepsy without postictal psychosis. Total hippocampal volumes were not different between the two groups. However, patients with postictal psychosis had a relatively preserved anterior hippocampus, and temporal lobe dysplasia was more frequent ($p = 0.006$, chi-square test). These findings may be associated with the clinical symptoms.

NEUROLOGY 2000;55:1027–1030

R.S. Briellmann, MD; R.M. Kalnins, FRCPA; M.J. Hopwood, FRANZCP; C. Ward, FRANZCP; S.F. Berkovic, MD; and G.D. Jackson, MD

Schizencephaly associated with psychosis

Robert C Alexander, Ashwin A Patkar, Jocelyne S Lapointe, Sean W Flynn, William G Honer

Abstract

Schizencephaly is a rare disorder of brain development resulting in the formation of abnormal unilateral or bilateral clefts in the cerebral hemispheres. It is often accompanied by partial seizures, mental retardation, and hemiparesis. Two patients are described with clear psychotic symptoms with either unilateral or bilateral schizencephaly. The implications of the association between schizencephaly and psychosis in these patients for understanding the biology of the psychoses are discussed.

(*J Neurol Neurosurg Psychiatry* 1997;**63**:373–375)

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Temporal lobe pathologies and psychosis

- Cortical Dysplasia
  (Briellmann et al. Neurology 2000)
- Developmental Tumors: DNET & Gangliogliomas
  (Currie et al, Brain 1971; Taylor DC, Epilepsia 1972; Andermann et al, Epilepsia 1999)
- Schizencephaly
  (Alexander et al. JNNP 1997)

Therapy related psychosis

- Drug Induced Psychosis:
  - Topiramate
  - Vigabatrin
  - Levetiracetam
  - Zonisamide

Topiramate and psychosis

Arq Neuropsiquiatr 2002 Jun;60(2-A):285-7 Acute psychotic disorders induced by topiramate: report of two cases.

Stella F, Caetano D, Cendes F, Guerreiro CA.

We report on two epileptic patients who developed acute psychosis after the use of topiramate (TPM). One patient exhibited severe psychomotor agitation, heteroaggressiveness, auditory and visual hallucinations as well as severe paranoid and mystic delusions. The other patient had psychomotor agitation, depersonalization, derealization, severe anxiety and deluded that he was losing his memory. After interruption of TPM in one patient and reduction of dose in the other, a full remission of the psychotic symptoms was obtained without the need of antipsychotic drugs. Clinicians should be aware of the possibility of development of acute psychotic symptoms in patients undergoing TPM treatment.

TOPIRAMATE INDUCED MANIC EPISODE

Topiramate induced manic episode

Topiramate is a novel antiepileptic drug (AED) that has been in use for several years, mainly as add on treatment for partial and secondarily generalising seizures that are otherwise refractory to treatment.[1] Despite the good efficacy of topiramate, dizziness, ataxia, double vision, and somnolence have been noted as the main side effects. While older AEDs such as carbamazepine and sodium valproate are now routinely used for the treatment of mood disorders, recent studies suggest that novel AEDs, such as lamotrigine, gabapentin, tiagabine, and topiramate, have mood stabilising efficacy as well.[2] Exacerbation of psychotic symptoms has been reported but mostly in patients with pre-existing psychiatric disorders.[3 4] However, more patients than previously assumed may be affected by a broader range of side effects. We present a case of a patient taking topiramate who presented with an acute manic episode, lacking any previous history of affective disorders or episodes.

A 57 year old woman with a history of temporal lobe epilepsy was referred to our hospital by her local general practitioner due to suicidal ideation and the intention of killing her husband. In the preceding weeks, her relatives had noted a progressive change of personality with verbal attacks, lack of sleep, expensive purchases, and the recurrent desire to give her house to a distant acquaintance. On admission, she was fully oriented, agitated, restless, suspicious, and laughing inappropriately. She refused any medical help and in turn was convinced that her spouse was mentally ill and needed urgent medical advice. Her speech was hasty, with pompous, overbearing, and self important utterances, obvious "flight of ideas", and high "pressure of thoughts". She boastfully admitted ideas about a relationship with a younger man and her own irresistible attractiveness, and threatened the psychiatrist verbally and physically during the initial interview. She had partially lost coherence of thought and she was "talking past the point". She denied hearing voices or other hallucinations; nevertheless, it was impossible to complete a full psychiatric interview. At this time, the patient scored 37 out of 44 points on the young mania rating scale (YMRS).

The patient had a well documented history of seizures (including video encephalographic monitoring), which had started 18 years previously with 7–10 attacks per month (on average) and were classified as single and complex partial seizures without secondary generalisation. Neuropsychological testing showed a pattern of medial temporal lobe dysfunction, and brain magnetic resonance imaging showed left hippocampal sclerosis. According to both the referring physician and her relatives, she had never experienced any psychiatric symptoms in her life. Apart from hypertension there was no relevant medical or neurological history. Reviewing her medication, we noted that 12 weeks before her admission topiramate had been added to her antiepileptic regimen of tiagabine (40 mg/day

Psychiatric adverse events during levetiracetam therapy

M. Mula, MD; M.R. Trimble, MD, FRCP, FRCPsych; A. Yuen, MD, MRCP; R.S.N. Liu, MD, MRCP; and J.W.A.S. Sander, MD, MRCP, PhD

Abstract—The prevalence and psychopathologic features of psychiatric adverse events (PAE) in 517 patients taking levetiracetam (LEV) were investigated. Fifty-three (10.1%) patients developed PAE. A significant association was found with previous psychiatric history, history of febrile convulsions, and history of status epilepticus, whereas lamotrigine co-therapy had a protective effect. PAE were not related to the titration schedule of LEV, and certain patients seem to be biologically more vulnerable.

NEUROLOGY 2003;61:704–706

Table 2 *Logistic regression analysis of risk variables for PAE during LEV therapy*

Variables	Wald	OR (95% CI)	*p* Value
History of febrile convulsions	9.565	2.90 (1.48–5.84)	0.002
History of status epilepticus	5.78	2.56 (1.17–5.58)	0.018
Previous psychiatric history	10.18	1.19 (1.070–1.328)	0.001
Lamotrigine co-therapy	4.63	0.40 (0.17–0.92)	0.031

PAE = pychiatric adverse events; LEV = levetiracetam; OR = odds ratio.

Table 3 *Dose and prescription time of LEV in patients with PAE*

Variables	Affective disorder, n = 13	Psychosis, n = 6	Aggressive behavior, n = 19	Emotional lability, n = 12	Others, n = 3
Gender, M/F	6/7	4/2	10/9	5/7	3/0
Median (range) dose LEV, mg	1,000 (500–3,000)	750 (250–3,000)	1,000 (250–3,000)	2,000 (500–4,000)	250 (250–2,000)
Median (range) PAE onset, d	80 (18–180)	12.5 (7–18)	31 (10–250)	80 (15–180)	10 (2–180)
Psychotropic drug prescription	2	4	4	2	0

LEV = levetiracetam; PAE = psychiatric adverse events.

Discussion. In a multicenter, double-blind, placebo-controlled trial of LEV,[6] the prevalence of depression was 1.9% in patients taking 1,000 mg/day, 5.7% in patients taking 2,000 mg/day, and 2.7% in the placebo group. In controlled clinical trials,[2] the prevalence of depression was 4% in patients with epilepsy, whereas 0.5% displayed suicidal behavior. In our study, 2.5% developed depression and 0.7% of patients reported suicidal ideation, usually in the context of a mood disorder. Several reasons may explain the discrepancy in rates of depression between this and previous studies. The categorization of psychiatric events may not have been accurately reported in controlled clinical trials, owing to assessments by staff not trained in psychiatry. Further controlled studies are designed for regulatory approval and may not elicit a comprehensive profile of the drug. The clinical assessment is often not per-

A recent study[2] reviewed the rate of treatment emergent adverse events with LEV during placebo-controlled trials for epilepsy, cognition, and anxiety. Interestingly, patients with epilepsy experienced more behavioral problems, when treated with LEV, than those with cognitive impairment or anxiety, suggesting that patients with epilepsy were biologically more vulnerable to PAE. In our study, we demonstrated a significant association with a previous history of febrile convulsions or status epilepticus. Both are suspected of playing a role in epileptogenic processes, the main hypothesis regarding neuronal loss and synaptic reorganization within the limbic system.[8] Such mechanisms may explain the biological vulnerability of these subsets of patients to the development of psychopathology during LEV therapy.

A systematic review of the behavioral effects of levetiracetam in adults with epilepsy, cognitive disorders, or an anxiety disorder during clinical trials.

Cramer JA, De Rue K, Devinsky O, Edrich P, Trimble MR.

Epilepsy Behav. 2003 Apr;4(2):124-32.

- Assessment of psychiatric events in placebo controlled studies for epilepsy (1023) patients, cognitive disorders (719) and anxiety disorders (1510) patients, and 1393 epilepsy patients observed in long term follow up.
- Patients with cognitive and anxiety disorders had a lower incidence of all psychiatric symptoms compared to patients with epilepsy.
- This study in a surrogate manner demonstrates that the intrinsic pathology of refractory epilepsy especially within the temporal lobe predisposes these patients to experiencing psychiatric adverse effects of certain anticonvulsants.

PAPER

Schizophrenia-like psychosis arising de novo following a temporal lobectomy: timing and risk factors

P Shaw, J Mellers, M Henderson, C Polkey, A S David, B K Toone

J Neurol Neurosurg Psychiatry 2004;**75**:1003–1008. doi: 10.1136/jnnp.2003.022392

Objectives: To clarify risk factors for the development of schizophrenia-like psychotic disorders following temporal lobectomy, and to explore the possibility that the early postoperative period is a time of high risk for the onset of such chronic psychotic disorders.

Methods: Patients who developed schizophrenia-like psychosis were identified from a series of 320 patients who had a temporal lobectomy for medically intractable epilepsy. The relationship of their disorders to both the operation and subsequent seizure activity was examined. Using a retrospective case–control design, risk factors for the development of schizophrenia-like psychosis were established.

Results: Eleven patients who developed schizophrenia-like psychosis postoperatively were identified and compared with 33 control subjects who remained free of psychosis postoperatively. The onset of de novo psychotic symptoms was typically in the first year following the operation. No clear relationship between postoperative seizure activity and fluctuations in psychotic symptoms emerged. Compared with the controls, patients who become psychotic had more preoperative bilateral electroencephalogram (EEG) abnormalities, pathologies other than mesial temporal sclerosis in the excised lobe and a smaller amygdala on the unoperated side.

Conclusions: Temporal lobectomy for medically intractable epilepsy may precipitate a schizophrenia-like psychosis. Patients with bilateral functional and structural abnormalities, particularly of the amygdala, may be at particular risk for the development of such psychoses.

J Neurol Neurosurg Psychiatry 1998;64:601–604

A prospective study of the early postsurgical psychiatric associations of epilepsy surgery

H A Ring, J Moriarty, M R Trimble

Abstract

***Objectives*— To examine prospectively the frequency and nature of psychiatric symptoms seen in patients during the first three months after temporal lobe surgery for chronic intractable epilepsy and in addition to study the relation between presurgical mental state, laterality of surgery, and postsurgical seizure and psychiatric course.**

***Method*—A consecutive series of 60 patients being assessed for temporal lobe surgery for intractable epilepsy were studied. They were interviewed before surgery and at six weeks and again at three months after operation.**

***Results*—At six weeks after surgery half of those with no psychopathology preoperatively had developed symptoms of anxiety or depression and 45% of all patients were noted to have increased emotional lability. By three months after surgery emotional lability and anxiety symptoms had diminished whereas depressive states tended to persist. Patients with a left hemispheric focus were more likely to experience persisting anxiety.**

***Conclusion*—The early months after surgery for epilepsy are characterised by the relatively common presence of psychiatric symptoms. It is proposed that presurgical and early postsurgical neuropsychiatric involvement in programmes of surgery for epilepsy will help to improve the quality of the treatment package offered to patients.**

(*J Neurol Neurosurg Psychiatry* 1998;64:601–604)

J Neurol Neurosurg Psychiatry 2001;70:649–656

The "burden of normality": concepts of adjustment after surgery for seizures

S Wilson, P Bladin, M Saling

Abstract

***Objectives*—To conceptualise the process of adjustment provoked by the sudden alleviation of chronic epilepsy by temporal lobectomy. On being rendered seizure free, the process of adjustment primarily depends on the patient's capacity to discard roles associated with chronic epilepsy and to learn to become well. This can involve a reconceptualisation of the patient's identity from chronically ill to "cured", and can give rise to a constellation of psychological, affective, behavioural, and sociological features characterised as the "burden of normality".**

***Methods*—This is a theoretical inquiry that documents the clinical phenomenology of the burden of normality by classifying its key psychological and psychosocial features. The model of adjustment is presented in the context of previous outcome research on surgery for seizures, providing a conceptual link between practice based rehabilitation measures of outcome and multidimensional constructs, such as health related quality of life.**

***Results*—The model represents a process oriented, theoretical framework for comprehensively measuring outcome after life changing medical interventions. It has implications for clinical practice, including the identification of preoperative predictors of outcome and informing appropriate management and rehabilitation of patients.**

***Conclusion*—This model of outcome after temporal lobectomy may ultimately be applicable to the treatment of other chronic conditions.**

(*J Neurol Neurosurg Psychiatry* 2001;70:649–656)

Keywords: postperative adjustment: psychosocial outcome; seizure surgery; health related quality of life

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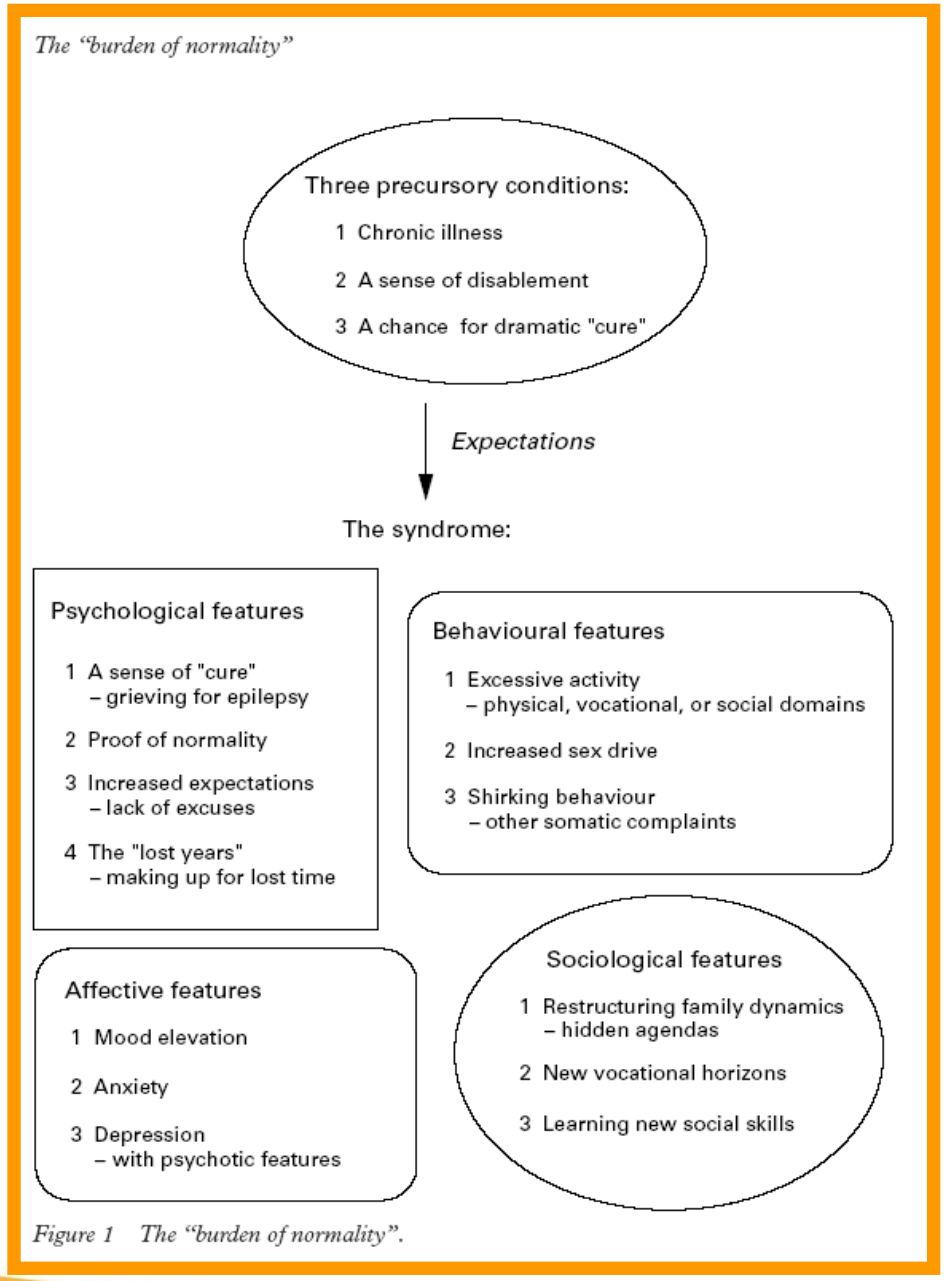

Figure 1 The "burden of normality".

Chronic epilepsy and cognition: a longitudinal study in TLE.

Helmstaedter C, et al.

Ann Neurol 2003; 54: 421-22. (Bonn)

- 147 surgically Rxed and 102 medically Rxed patients with TLE were assessed cognitively over 10 years
- 63% of surgically Rxed and 12% of medically Rxed patients were seizure free at 10 years
- 50% of medically Rxed and 60% of surgically Rxed patients showed significant memory decline at 10 years
- Surgery anticipated the decline seen in the medically treated group and exceeded it when surgery was performed on the left, or if seizures continued postoperatively.
- In addition, psychosocial outcome was better when seizures were controlled.

Chronic epilepsy and cognition: a longitudinal study in TLE

Helmstaedter C, et al.

Ann Neurol 2003; 54: 421-22. (Bonn)

In conclusion:

- Chronic temporal lobe epilepsy is associated with progressive memory impairment.
- Surgery, particularly if unsuccessful, accelerates this decline.
- However, memory decline may be stopped and even reversed if seizures are fully controlled.

The Role of Anatomy

OVERVIEW

Three-week-old Wistar rats underwent a rapid kindling to the ventral hippocampus.[1] Two to 4 weeks later, the rats were subjected to two tests developed to assess the presence of depression-equivalent phenomena in animal models: the forced swim test (FST) and the taste preference toward calorie-free saccharin or sucrose solutions. In the FST, a rat is placed in a situation of despair, which allows for assessment of its ability to adopt active strategies in an inescapable stressful situation. Failure to do so, as evidenced by increased immobility time during the FST, is interpreted as equivalent to a depression-like state. The second test tries to replicate the loss of an animal's ability to experience pleasure, as evidenced by loss of taste preference. Normal animals prefer sweetened to regular water; animals with suspected equivalent symptoms of depression do not exhibit such a preference. Kindled animals exhibited a sustained increase in immobility time in the FST and loss of taste preference toward calorie-free saccharin, as compared with controls.

Structural Abnormalities

Hippocampal atrophy

In 75% to 80% of patients with temporal lobe epilepsy (TLE), mesial structures (amygdala, hippocampal formation, entorhinal cortex, and parahippocampal gyrus) are the site of the epileptogenic area[25] and hippocampal atrophy caused by mesial temporal sclerosis is the most frequent cause of TLE. By the same token, the prevalence of depression is significantly higher in PWE who have involvement of mesial temporal structures. Furthermore, bilateral hippocampal atrophy has been demonstrated by several investigators in patients with recurrent major depressive disorders without epilepsy, including patients whose mood disorder is in remission.[26–28] In addition, a significant inverse correlation between the duration of depression and the magnitude of (left) hippocampal volume is documented, whereas lower verbal memory scores were associated with the hippocampal damage of these patients.[28]

Suicidality in Epilepsy

Suicidality in Epilepsy

In the general population in the United States, the lifetime prevalence rates of suicide are estimated from approximately 1.1% to 1.2%, whereas the suicide attempt rates range from 1.1% to 4.6%. Recent population-based studies have reported that PWE have a three times higher risk of committing suicide than controls.[67] The highest risk of suicide was identified in PWE and comorbid psychiatric disease, in particular those with a depressive disorder, who had a 32-fold higher risk of committing suicide. In a second population-based study (from Canada) that included a sample of 36,984 subjects, the lifetime prevalence of suicidal ideation was twice as high in PWE (25%; 95% CI, 17.4–32.5) compared with that of the general population (13.3%; 95% CI, 12.8–13.8).[12] From a review of 17 studies on suicidal behavior in PWE, Robertson suggested that the lifetime prevalence rates of suicide and suicidal attempts ranged between 5% and 14.3%.[68] Furthermore, patients with TLE had suicidal rates 6 to 25 times greater than the general population.

Post-ictal Suicidal Ideation

Suicidal ideation as a postictal phenomenon

Suicidal ideation can be a habitual postictal symptom. As stated previously, in a study of 100 consecutive patients with refractory partial epilepsy, Kanner and colleagues[58] identified postictal suicidal ideation in 13 patients (13%) after more than 50% of their seizures during the previous 3 months; their duration ranged from 0.5 to 108 hours with a median duration of 24 hours. Active and passive suicidal ideation was reported by five and eight patients, respectively. Ten of these 13 patients (77%) had a past history of major depression or bipolar disorder and this association was highly significant. Furthermore, the presence of postictal suicidal ideation was also significantly associated with a history of psychiatric hospitalization. Postictal symptoms of depression were accompanied by postictal symptoms of anxiety and postictal neurovegetative symptoms.

AEDs and suicidality

In January of 2008, the Food and Drug Administration (FDA) issued an alert regarding the association between suicidality and AEDs, which was based on results of a meta-analysis that included data from 199 randomized clinical trials of 11 AEDs[74]: carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide.[6] The meta-analysis encompassed a total of 43,892 patients treated for epilepsy, psychiatric disorders, and other disorders, predominantly pain. The FDA concluded that there was a statistically significant 1.80-fold increased risk of suicidality with exposure to AEDs. Suicidality occurred in 4.3 per 1,000 patients treated with AEDs in the active arm compared with 2.2 per 1,000 patients in the comparison arm. Of all the suicidality reported, suicidal ideation accounted for 67.6%, preparatory acts for 2.8%, attempts for 26.8%, and completed suicide for 2.8%. AEDs were associated with a greater risk for suicidality with epilepsy (odds ratio [OR] 3.53; 95% CI, 1.28–12.10) than with psychiatric disorders (OR 1.51; 95% CI, 0.95–2.45) or other disorders (OR 1.87; 95% CI, 0.81–4.76). However, the validity of the results of this meta-analysis recently has been questioned because of several methodologic problems, including[75]

Is the analysis flawed?

1. The assessment of suicidality was not gathered in a systematic prospective manner and was based on "spontaneous" reports of patients.
2. The FDA associated the increased risk of suicide with all AEDs, despite the fact that statistical significance was found in only two drugs (topiramate and lamotrigine) of the 11 AEDs studied.
3. Most epilepsy trials (92%) include patients on adjunctive therapy (compared with 14% of psychiatric trials and 15% of other medical trials). It is unclear whether or not the higher suicidality rates in the epilepsy trials were due to drug interactions, given the high proportion of epilepsy trials designed with polytherapy.
4. Suicidal behavior was greater in certain geographic regions. For example, the OR of suicidality was 1.38 in North American studies and 4.53 in studies done elsewhere. Such differences strongly suggest serious methodologic errors in data gathering.

Conclusions

- Psychiatric issues abound in the patient with TLE, especially when it is refractory.
- Atrophy of hippocampal structures on the right side seem to be associated with the development of the Geschwind Syndrome.
- Peri-ictal psychosis correlates with the occurrence of dysplastic neuroglial elements (e. g. FCD, DNET, ganglioglioma) within the temporal lobe epileptic substrate.
- Anxiety and depression are common comorbidites with TLE

Conclusions

- AEDs like TPM, VGBN, LVTCM, and ZNSM can lead to the development of psychosis in susceptible TLE patients.
- ATL as a therapy is associated with the precipitation of anxiety and depression in the early postoperative period.
- Psychosocial issues resulting from the 'burden of normality' require addressing in patient with successful seizure control after surgery.

Conclusions

- Following ATL, patients with bilateral mesial temporal lobe structural abnormalities are at risk of developing psychosis.
- Patients undergoing ATL require counseling about memory changes following surgery, especially those with dominant lobe abnormalities.
- Multidisciplinary care models are a pre-requisite to the initiation of a surgical program for refractory TLE.

Conclusions

- The risk of suicide amongst patients with epilepsy is determined by myriad comorbid factors including anomalies of anatomy, biochemistry, and AED administration
- The contribution of AEDs to the enhanced risk of suicide warrants further study as the existing data is debatable if analyzed purely on statistical grounds.

MISSING LINK