

Patients with epilepsy associated with schizophrenia: a descriptive study of patients investigated with magnetic resonance imaging (MRI) and standard electroencephalography (EEG)

Associazione di epilessia e schizofrenia: studio descrittivo di un campione di pazienti indagato con risonanza magnetica nucleare (RMN) ed elettroencefalografia standard (EEG)

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Summary

Objective

Psychiatric illnesses are generally considered to be more common among patients with epilepsy than in the general population. Several factors have been suggested to explain increased psychopathology in epilepsy, for example, temporal lobe pathology, antiepileptic medication, psychosocial difficulties, and disability associated with epileptic seizures.

Methods

Seven patients suffering from epileptic seizures followed by a schizophrenia-like state were examined. They all were men admitted at the ward of the III Psychiatric Clinic, Sapienza University, Rome, Italy. Psychiatric diagnoses were determined according to the DSM-IV criteria. Assessment of epilepsy and localization of seizure foci were determined by collaborating neurologists on the basis of routine surface electroencephalograms (EEG), using an 18-channel EEG monitoring device. Brain magnetic resonance imaging (MRI) were performed on a 1.5 Tesla Magnetom Siemens Operating Unit.

Results

Concerning neurological diagnosis, three patients received a diagnosis of temporal lobe epilepsy, two of partial epilepsy and two of generalized epilepsy. In all seven cases, a paranoid-hallucinatory symptomatology prevailed. Six epilepsy cases had their onset during infancy (average age $6.3 \text{ years} \pm 2.1 \text{ SD}$); onset preceded psychosis in all cases. The mean duration between the onset of seizures and the psychotic state was $14.4 \text{ years} \pm 3.4 \text{ SD}$. MRI abnormalities were present in four cases: right side ventricular asymmetry, cortical atrophy, hypoplasia of the stem of the corpus callosum, polymicrogyria, insular and parietal dysplasia in case 1 (Fig. 1); heterotopias in the right posterior periventricular area, abnormal thickening of the right posterior parietal cortex, polymicrogyria and left-to-right asymmetry of cerebral hemispheres in case 3 (Fig. 2); cortical atrophy with ventricular enlargement in case 6 (Fig. 3); and atrophy of left hippocampus in case 7 (Fig. 4).

Conclusions

EEG results contributed to confirm the laterality of the epilepsy, mostly in the left lobe, and its preferential association with temporal lobe epilepsy. In five patients, the electroencephalographic focus was initially located in the right lobe, with lateralization to the other side in four cases. In addition, in three cases, the EEG normalized over a period corresponding to the appearance of psychiatric disorder. With respect to antiepileptic drugs, all seven cases were on antiepileptic therapy since childhood. Only four cases are currently treated and three are in remission as regards epileptic symptomatology. Finally, four out of seven patients are treated with clozapine with an improvement of psychiatric symptomatology, and at the same time without worsening of the epileptic state. Possible mechanisms of epilepsy-related psychosis, including the common neuropathological substrate, the secondary effects of epilepsy and the exposure to antiepileptic drugs are discussed.

Introduction

Epilepsy and schizophrenia are both an expression of an altered cerebral functioning and their history is often connected. The first descriptions of cases showing coexistence of symptoms of both disorders can be traced back to Bouchet & Cazauvieilh (1825) who noted a loss of neurons as a common anatomical element to both conditions and located it in the Ammon's horn¹.

Despite extensive literature on this subject, a lot of aspects are still controversial and definitive conclusions are often hindered by methodological limitations such as definition of psychosis, sample size or inadequate control groups.

As we know so far, epidemiological data show a 6-12% greater incidence of psychosis in populations of patients with epilepsy, than in the general population. Among these, the most common are acute transient psychotic disorder and schizophrenia²⁻⁴. Epilepsy, in these cases, precedes psychosis, beginning at an early age and continuing through puberty⁵⁻⁶.

The time lapse between the beginning of epilepsy and the onset of psychosis is usually 10-14 years⁷⁻⁹. The frequency of seizures in that period is variable and the onset of epilepsy-related psychoses is associated, according to some authors, with an improvement of the epileptic symptomatology⁵ and according to others with a worsening of it¹⁰. The clinical history of the psychotic syndrome in epilepsy seems largely characterized by paranoid-hallucinatory symptoms⁸⁻¹¹ commonly associated with catatonia⁹, distinguishable from schizophrenia in the traditional psychiatric conception by a better premorbid personality and a more benign and variable course.

Lastly, many authors support the hypothesis of a preferential association with temporal lobe epilepsy¹²⁻¹⁵. The hypothesis of an association between psychosis and epilepsy is also supported by electroencephalography studies, in agreement to consider the electroencephalographic abnormalities as signs of an underlying structural pathology, a potential substratum for a subsequent development of psychosis⁸⁻⁹⁻¹¹. In the attempt to identify these peculiar aspects, the debate is also continuing on the importance of the laterality, with contrasting results. Since the earliest suggestive studies, some authors have identified an irrefutable evidence, represented by EEG abnormalities limited within the same area, mainly on the left side⁸⁻¹⁶; other authors, on the other hand, have pointed out that the laterality is not always present¹⁷⁻¹⁸.

More recently the application of new techniques of brain imaging has promoted new advances.

Earlier studies have emphasized medial and temporal lobe pathology¹⁹⁻²⁰, whilst subsequent neuroimaging investigations have also shown ventricle enlargement, frontal-parietal and hippocampus atrophy in both

epileptics and psychotic patients²¹. These preliminary statements, seen at the light of the more recent advances in the knowledge about the role of neurodevelopment alteration in the pathogenesis of psychosis, lead to revise the characteristics of the association between schizophrenia-spectrum disorders in epilepsy and epilepsy itself.

In this respect, we report seven case histories of patients, each diagnosed with epilepsy and schizophrenia. Psychotic features, magnetic resonance imaging (MRI) and standard electroencephalography (EEG) findings are reported.

Case Reports

CASE 1

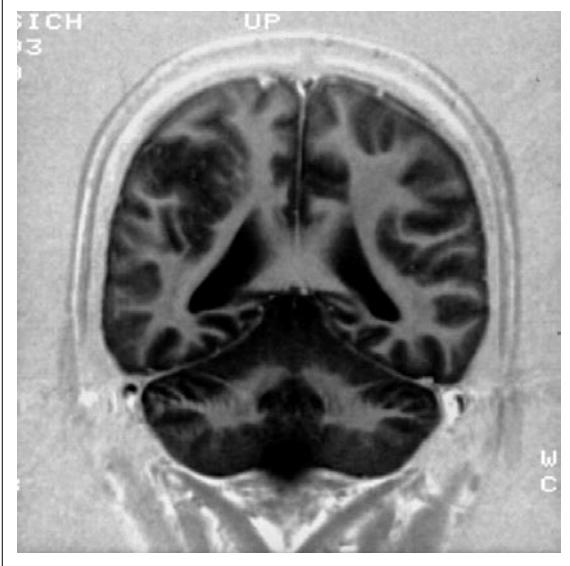
Age: 37. Family history was negative for neurological disorders, but positive for psychopathology; an uncle on his mother's side had committed suicide. Onset of epilepsy at age 9, with the first epileptic fit followed by multiple daily fits; an "epileptogenic encephalopathy" was diagnosed and phenytoin-based treatment was instituted. At age 26, temporal lobe epilepsy was diagnosed, followed by a new treatment with phenytoin, barbiturates and carbamazepine. By the age of 27 psychiatric symptomatology appeared, with a delusional episode of the persecutory type characterized by the patient's belief that some strangers had hidden microphones in his home to spy on him; auditory hallucinations were also present. Hospitalized in our ward, he was discharged with a clozapine-based therapy. The analysis of the electroencephalographic findings revealed an early presence of a right temporal focus (at age 13-14), which presents a gradual migration until it is transformed into a "left frontal-temporal focus" (30 aa). The EEG performed during hospitalization in our ward shows "spike wave discharges of modest degree located in bilateral temporal-frontal areas, alternatively more pronounced on one side". A brain MRI shows "right-side ventricular asymmetry, cortical atrophy, hypoplasia of the stem of the *corpus callosum*, polymicrogyria and insular and lower right parietal dysplasia" (Fig. 1).

CASE 2

Age: 44. Family history revealed that his brother had an epileptic disorder and an aunt on his father's side had suffered from psychosis. Neurological history of the patient started in infancy, at age 4, with febrile convulsions, while the first epileptic seizure dates back to the age of 11.

A diagnosis of generalized seizure was made, which was then followed by therapy based on carbamazepine. Psychiatric history (chronic schizophrenia, paranoid type) started at age 23; the patient gradually withdrew

Fig. 1. Right side ventricular asymmetry, cortical atrophy, hypoplasia of the stem of *corpus callosum*, polymicrogyria and insular and lower parietal dysplasia. *Asimmetria ventricolare per prevalenza destra, atrofia corticale diffusa, ipoplasia del corpo calloso, polimicrografia e displasia insulare e parietale inferiore destra.*

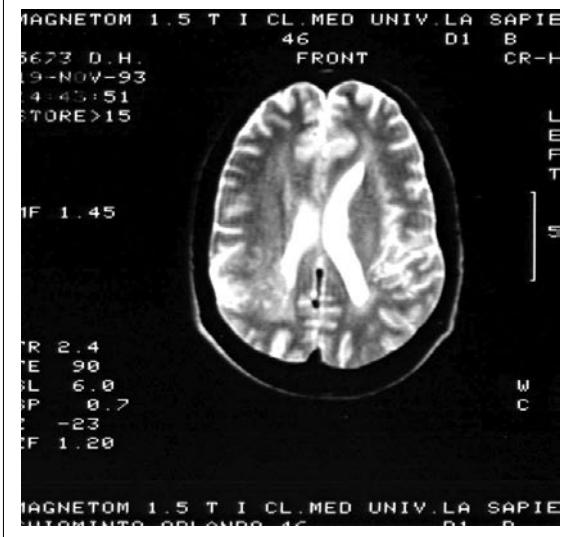


and developed a persecutory delusion, for which he was treated with antipsychotic agents and electroconvulsive therapy. At age 44 he was hospitalized in our ward, where he was treated with an atypical antipsychotic drug (quetiapine). EEG showed an "irregular and discontinuous base rhythm", with no evidence of an epileptic focus; brain MRI showed no gross abnormalities.

CASE 3

Age: 46. Family history was negative. The onset of epilepsy was at age 14, with initial seizures during sleep, and after a short period they were present also in daytime; the patient therefore received a diagnosis of partial seizure with secondary generalization. Until the age of 20 he followed an undefined treatment. He was afterwards started on phenytoin, barbiturates, carbamazepine and primidone. At age 38, an EEG recording showed "a mesial, central-posterior, active epileptogenic focus localized in right hemisphere", the diagnosis of partial epilepsy with secondary generalization was confirmed and the patient has been treated for 8 years with carbamazepine, barbexacalone and primidone. At age 42, persecutory symptoms appeared, with a delusion hinging on body transformation due, according to the patient, to antiepileptic therapy. He was then hospitalized in our ward receiving a diagnosis of chronic schizophrenia, paranoid type, and was treated with haloperidol and pimozide. During his hospitalization he performed an EEG

Fig. 2. Heterotopias in the grey matter, located in the right posterior periventricular area. Abnormal thickening of the right posterior parietal cortex in comparison with polymicrogyria and left-to-right asymmetry of the cerebral hemispheres. *Eterotopia della sostanza grigia in sede periventricolare posteriore destra, polimicrografia e asimmetria degli emisferi cerebrali per prevalenza sinistra.*



which showed the presence of "epileptiform activity of modest degree located in right frontal-temporal area", whereas brain MRI revealed "heterotopias in the grey matter, located in the right posterior periventricular area, an abnormal thickening of the right posterior parietal cortex, polymicrogyria and asymmetry of cerebral hemispheres" (Fig. 2).

CASE 4

Age: 19. Family history was negative. The first seizures appeared during sleep at age 4. Since then, after receiving a diagnosis of secondarily generalized partial epilepsy, he is treated with phenobarbital and valproic acid until the age of 11, when he interrupts the antiepileptic therapy. The onset of psychiatric symptomatology is at age 16; the patient interrupted school, became more withdrawn, with poorer social communication. At age 19 delusional thinking predominates, associated to auditory hallucinations with persecutory connotation, finally reaching a condition of catatonia, for which he is hospitalized with a diagnosis of epileptic psychosis. Transferred to our ward he underwent 6 sessions of ECT in combination with antipsychotic drugs and carbamazepine. He was then dismissed from hospital with a diagnosis of chronic schizophrenia, catatonic type, with acute exacerbation, and clozapine-based therapy. EEG history showed initial "nonspecific abnormalities associated with altered electrocortical organization attributable

to the left hemisphere" which were progressively transformed into paroxysmal phenomena "bilateral, left anterior and right posterior spike wave". EEG performed in our ward showed "spike wave discharges of a limited degree located in bilateral temporal-frontal areas with an occasional prevalence at the left hemisphere". Brain MRI is clinically normal.

CASE 5

Age: 37. Family history was negative. The patient did not remember data regarding the period and circumstances of the onset of epilepsy. However, at age 8 he received the diagnosis of temporal lobe epilepsy with a right focus, and a treatment based on valproic acid, ethosuximide, barbiturate and primidone. At age 20, psychiatric symptomatology emerged, and was characterized by delusions of body transformation, whose contents is linked to homosexual feelings, accompanied by auditory hallucinations; the patient was started on haloperidol and subsequently also phenothiazines, due to the emergence of hetero-directed aggressiveness. EEG which was performed during hospitalization in our ward, from which he was discharged with a diagnosis of chronic schizophrenia, undifferentiated type, showed "spike-waves in temporal-central areas of both hemispheres, slightly more prominent at the right side". Brain MRI was negative.

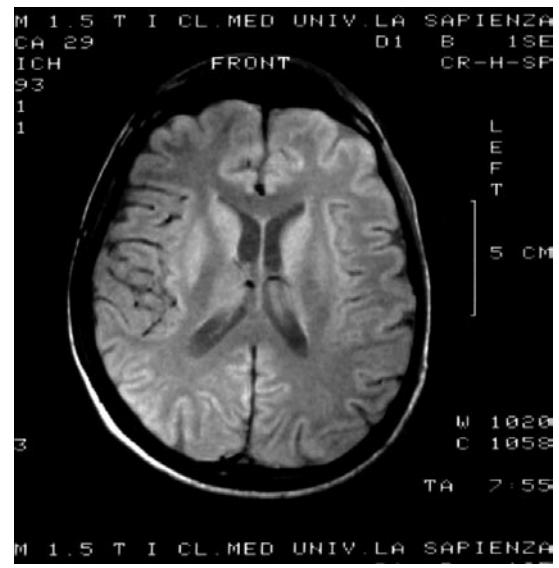
CASE 6

Age: 29. Family history was positive for psychiatric disorders since his mother suffered from depressive disorder. At age 7 the first partial epileptic seizure appeared. The patient underwent EEG, which showed "sharp spikes in right parietal-occipital area, sometimes bilateral" and a diagnosis of temporal lobe epilepsy was made. He was started on antiepileptic therapy which he was unable to recall, with seizures eventually disappearing. At age 16 his EEG recording normalized; this persisted for 1-2 years, until the onset of psychiatric symptomatology; the patient began to show social withdrawal, aggressiveness, even pantothenic crises. Hospitalized in our ward, he was discharged with a diagnosis of chronic schizophrenia, undifferentiated type, and with clozapine-based therapy. EEG, performed during hospitalization, revealed "slight discharge abnormalities located in temporal-frontal regions of the left side, with occasional propagation to the homologous counter lateral regions" and brain MRI showed "marked cortical atrophy with enlargement of the lateral ventricles" (Fig. 3).

CASE 7

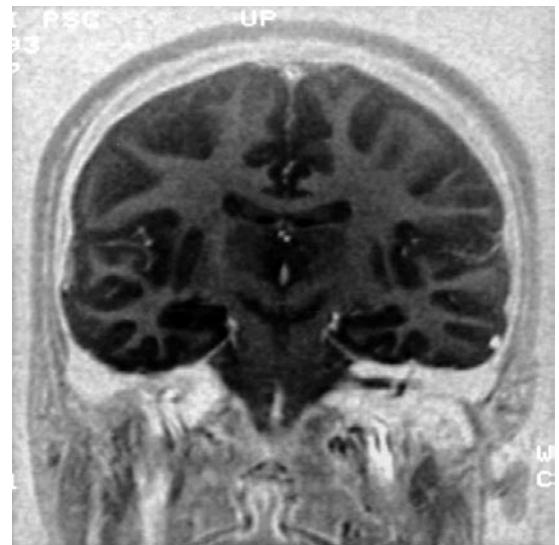
Age: 26. Family history was positive for affective disorders; an aunt on his mother side was suffering from depressive disorder. His family members did not remember the onset of neurological disorder, but an EEG performed at age 6 showed "discharges in-

Fig. 3. Diffuse cortical atrophy with supratentorial lateral ventricle enlargement. *Atrofia diffusa corticale con ampliamento del sistema ventricolare sovratentoriale.*



dicate of epileptic seizures, located in right central-posterior area, with a marked liability to hyperpnoea". A diagnosis of epilepsy is made and the patient was started on ethosuximide, phenytoin and phenobarbital. At age 18, valproic acid was also introduced. Through age 16 to 22, normalization of the electroencephalogram could be observed. Onset of psychiatric

Fig. 4. Atrophy of left hippocampus. *Atrofia dell'ippocampo di sinistra.*



symptomatology is at age 21, and is characterized by florid persecutory delusions and auditory hallucinations, thus the diagnosis of chronic schizophrenia, paranoid type, is made and a therapy based on haloperidol and phenothiazines was started, which did not bring however any benefit. He was then hospitalized in our ward, where he underwent electroconvulsive treatment in combination with antipsychotic drugs. He was discharged with a diagnosis of chronic schizophrenia, paranoid type, and clozapine-based therapy. EEG performed during hospitalization in our clinic showed "isolated waves in temporal areas of both hemispheres"; brain MRI revealed "atrophy of left hippocampus" (Fig. 4).

Conclusions

It is important to emphasise some aspects of similarity of the observed patients (all males, belonging to a limited age-group, all with DSM-IV diagnosis of chronic schizophrenia), that allow us to consider them to some degree as a group and to effect some common clinical considerations.

As in previous studies^{5-7,9}, a beginning of epilepsy in infancy is clear, always preceding psychosis, after a mean duration of epilepsy between 12 and 19 years; only in case 3 this latency lapse of time turned out to be longer, 28 years, but in this case epilepsy appeared later, at age 14.

In accordance with other authors^{8,11}, a paranoid-hallucinatory symptomatology prevails, associated only in case 4 to catatonia.

Consistent with MRI studies^{19,20}, 4 out of 7 patients are also characterized by the presence of anatomical abnormalities. Some of these findings could be related to malformation, linked to abnormal brain development; in particular, hypoplasia of *corpus callosum*, polymicrogyria, insular and parietal dysplasia in case 1, or polymicrogyria and heterotopias in case 3. Other results could be explained as developmental alterations, such as generalized cortical atrophy with ventricular enlargement (clear in cases 1 and 6) and interhemispheric asymmetry (case 3) or ventricular asymmetry (case 1). Case 7 is distinguished by the presence of atrophy of the left hippocampus, a condition being thoroughly investigated in literature. In fact, patients with sclerosis of hippocampus form a subgroup within those affected by temporal lobe epilepsy, being characterized by peculiar clinical implications, like earlier occurrence and increased severity of the epileptic seizures²².

The EEG data contribute to confirm the laterality of the epilepsy^{8,16}, mostly in the left lobe (cases 1, 4, 5, 6, and 7), and a preferential association with temporal lobe epilepsy^{12,14,15} (cases 1, 5, and 6). In as many as 5 of the 7 patients, the electroencephalographic focus

is initially localized in the right lobe, whereas in 4 patients a subsequent migration of the focus to the left can be observed, in the cases 5, 6 and 7 the EEG gets back to normal at a period corresponding to the onset of psychosis. Recent advances of cellular and molecular neurobiology have promoted the hypothesis that drugs acting at CNS level in chronic conditions are able to induce changes of cerebral functions, including the regulation of the gene expression of neuronal GABA-A receptors²³. In our sample, all 7 cases have followed an antiepileptic therapy since their childhood, whilst currently only 4 patients are being treated and in 3 a remission of epileptic symptomatology was seen.

Finally, 4 out of 7 patients were treated with clozapine with an improvement of psychiatric symptomatology, and at the same time, epilepsy did not appear to be activated by a drug which is known to have seizure-facilitating properties²⁴. Apparently, the manifestation of epilepsy-related psychosis has been followed by a stabilization of those changes of neural circuits which, along a continuum, may have initially given rise to the epilepsy, and subsequently to the schizophrenic psychosis.

Although the cause of psychopathological disorders in many of these patients is probably multifactorial, three hypothetical mechanisms might be advanced. The first hypothesis focuses on a common cerebral vulnerability to both epilepsy and schizophrenia, originating during the neurodevelopment (dysgenesis, heterotopy, and hypoplasia) or acquired in early post-birth period. The frequency with which atypical cerebral tissue can be observed and the precocity of the first manifestation of the seizures in these subjects suggest the possibility of developmental lesions at the level of mesial temporal structures. The neuronal damage underlying epilepsy, which most frequently regards limbic structures, could influence, in subsequent brain maturation stages, the development of the psychotic condition.

A second hypothesis suggests that the schizophrenia-like illness in epilepsy is of epileptic origin. Continuous and repetitive seizures may induce sub-cellular changes, which could characterize the neurochemical substrate which underlies the progressive development of psychosis. It is possible that frequent seizures give rise to aberrant neuronal responses (e.g. synaptic reorganization), above all in the medial temporal lobes and consequently to subsequent behavioural disorders²⁵. It has been assumed that a prolonged stimulation of hippocampus promotes abnormal axonal regenerative changes, particularly regarding the dentate granule cells, even before seizure onset²⁵. This model identifies the basis for the manifestation of epilepsy-related psychosis in aberrant regeneration, alone or associated with the underlying pre-existing neuropathology. The importance of limbic structures in schizophrenic

psychosis is also asserted by the analogy between the symptoms of temporal lobe seizures and numerous subjective symptoms referred by schizophrenic patients. These observations are confirmed by the appearance of schizophrenia-like symptoms as a result of stimulation of deep limbic structures²⁶.

The third hypothesis identifies a link between antiepileptic drugs and psychosis in epilepsy. All antiepileptic drugs have been associated with psychosis, either as idiosyncratic, dose-related effect or as a result of alternative psychosis with “forced normalization” of the

EEG, a rare phenomenon paralleling seizure control²⁷. When the EEG in psychotic patients is normalized, often with anticonvulsive medicines, the psychiatric problems worsen. The mechanism underlying these interesting phenomena is not yet understood.

New evidence could be further promoted by technological improvement of study methodology, development and greater accuracy of already proven techniques for the study of brain functioning or, even more recently, of immunocytochemistry and analysis of gene expression techniques.

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